MULTI-SCALE FLUID MECHANICS OF NUTRIENT ABSORPTION IN THE SMALL INTESTINE ANALYZED WITH 2D AND 3D LATTICE BOLTZMANN MODELS

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by
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ABSTRACT

The primary roles of the small intestine (gut) are nutrient absorption and transport of digestive material (chyme). Two basic motility patterns (modes) exist to control these transport phenomena: propulsive wave-like propagations (peristalsis) for axial transport, and rhythmic contractions of short segments of the gut (segmentation) for radial transport to the surface for absorption. Once nutrients are advected to the surface, however, they must diffuse through a low-velocity fluid layer known as the “unstirred (water) layer (UL).” The thickness of this layer has been reported up to \( \sim 1000 \, \mu m \) [19], which, however, is physiologically unrealistic [23]. More realistic studies have reported thicknesses of less than 50\( \mu m \), suggesting that a “highly efficient stirring mechanism” may be present \textit{in vivo} to produce such small UL thicknesses [21].

We hypothesize that finger-like projections (villi) on the intestinal surface, under active muscular control, generate a “micro-mixing-layer (MML)” which, when coupled with macro-scale mixing, can provide highly efficient stirring. We develop a physiologically accurate computational model to investigate the hypothesis. We use the lattice Boltzmann framework (LBM) to predict fluid and scalar motions, with moving boundary conditions, and zero-passive-scalar concentration at the epithelial surface to model rapid nutrient absorption.

Using simpler gut models of flow generated by peristaltic and segmental motility (developed to establish technology needed for the combined multi-scale model), we show that the fluid mechanics-driven absorption dynamics of the small intestine is much more complex and interesting than has been previously reported. Contrary to common wisdom,
over the physiological range of occlusion ratios \( R_{\text{min}}/R_{\text{avg}} \), where \( R_{\text{min}} \) and \( R_{\text{avg}} \) are minimum and average radius, respectively), both peristalsis and segmentation significantly promote nutrient absorption. Segmentation has long been associated with the absorption process, but peristalsis has been generally explained as only necessary for axial transport. We show that the propulsive mechanisms generated by peristalsis for axial transport also create high nutrient gradients near the surface. These nutrient gradients lead to absorption characteristics of peristaltic motility that can be comparable to, or even exceed those of segmental motility. However, we also show that to maximize absorption while minimizing the power required by the muscle contractions necessary for gut motility, segmentation is optimal over the range of physiologically relevant occlusion ratios.

A three-dimensional, multi-scale lattice Boltzmann model was developed to study the effects of coupled macro-scale deformations and pendular villous motility on absorption. We show that active movements of the villi can enhance absorption by \( \sim 25\% \) beyond passive villous movements induced by macro-scale motility patterns alone. Increasing the length or the frequency of oscillation enhances the effect. Consistent with the findings of our simplified 2D and 3D villous motility models, we show that the presence of coordinated counter-oscillating groups of villi is a key mechanism in generation of the MML, and significantly promotes absorption. Azimuthally moving counter-oscillating groups of villi provide the most advantageous absorption characteristics. Because the azimuthal movements are perpendicular to the fluid patterns induced by the macro-scale motility, the interaction produces 3D fluid motions that further enhance mixing and increase the absorption in the gut.
# Table of Contents

List of Figures ........................................................................................................ix

List of Tables ..........................................................................................................xx

Acknowledgements ...............................................................................................xxi

CHAPTER 1: Background and Motivation ...............................................................1
  1.2 The Physiology of the Small Intestine .........................................................4
  1.3 Description of the Study Aims and Methods ..............................................9

CHAPTER 2: Review of the Relevant Literature ....................................................20
  2.1 Intestinal Motility ..........................................................................................20
  2.2 Intestinal Modeling .......................................................................................25
  2.3 Unstirred Layer (UL) Measurement .............................................................31
  2.4 Villous Motility ............................................................................................34
  2.5 The Lattice Boltzmann Method (LBM) .......................................................38

CHAPTER 3: Two-Dimensional Intestinal Model Simulations .................................46
  3.1 Macro-Scale Intestinal Model .......................................................................48
    3.1.1 The Numerical Method .........................................................................49
    3.1.2 Boundary Conditions ..........................................................................52
    3.1.3 Collection and Parameterization of Motility Data ...............................54
    3.1.4 The Geometry Model ..........................................................................58
    3.1.5 Code Validation ...................................................................................60
    3.1.6 Numerical Experiments .......................................................................61
    3.1.7 Results ..................................................................................................68
3.2 Multi-Scale 2D Cavity Flow Villous Motility Model

3.2.1 The Numerical Method

3.2.2 Boundary Conditions

3.2.3 The Geometry Model: A Lid-Driven Cavity Flow with 2D “Villi”

3.2.4 Numerical Experiments

3.2.5 Results

3.2.6 Discussion

CHAPTER 4: Three-Dimensional Intestinal Model Simulations

4.1 Macro-Scale Intestinal Model

4.1.1 The Numerical Method

4.1.2 Boundary Conditions

4.1.3 Physiological Data

4.1.4 The Geometry Model

4.1.5 Code Parallelization

4.1.6 Numerical Experiments

4.1.7 Results

4.1.8 Discussion

4.2 Multi-Scale 3D Cavity Flow Villous Motility Model

4.2.1 The Numerical Method

4.2.2 Boundary Conditions

4.2.3 The Geometry Model: A Lid-Driven Cavity Flow with 3D Finger-Like Villi
A.5 Discussion……………………………………………………………………………221

References…………………………………………………………………………………236
LIST OF FIGURES

Figure 1-1: The gastrointestinal (GI) tract. Source: [24]............................................................13

Figure 1-2: The three sections of the small intestine. .................................................................14

Figure 1-3: Illustration of the five primary layers of the intestinal wall (mucosa,
submucosa, circular and longitudinal muscularis, and serosa) and the
folds of Kerckring.................................................................15

Figure 1-4: A single, finger-like, human villus showing the strands of smooth muscle
that extend upward from the muscularis mucosae................................................16

Figure 1-5: Electron microscopy images of finger-like villi. (a): side view, (b): top
view. Unknown animal. Source: Prof. Jack Wood, Ohio State University........17

Figure 1-6: Electron microscopy images of leaf-like villi. Unknown animal. Source:
Kevin Haley, Bend Research.................................................................18

Figure 1-7: Electron microscopy images of the capillary networks within (a): finger-
like villi (white rabbit) and (b): leaf-like villi (guinea pig). Source:.........................19

Figures 3-1: The geometry used for the macro-scale intestinal motility model: (a) the
sinusoidal peristalsis model, (b) the alternating segmentation model. The
black, blue, and red geometries represent t=0, t=0.25 periods, and t=0.5
periods respectively. The geometry is periodic in both space (axial
direction) and time.................................................................87

Figure 3-2: Three initial condition/boundary conditions used on passive scalar
(nutrient) concentration shown for the equally weighted 50% peristalsis-
50% segmentation case: (a) “blob”, (b) “inlet”, and (c) “line”. The
colored isocontour represents scalar concentration: red indicates high values; blue indicates low values................................................................. 88

Figure 3-3(a): Total absorbed scalar versus number of time for systematically varied Sc for the “blob” case (pure peristalsis)................................. 89

Figure 3-3(b): Total absorbed scalar (scaled by N*) versus time (scaled by \( \tau_{\text{adv}} \)) for systematically varied Sc for the “blob” case (pure peristalsis)......................... 90

Figure 3-4(a): Total absorbed scalar (normalized by total initial amount of scalar) as a function of macro-scale period (time normalized by contraction period) for nine motility mode combinations for the “blob” case. Note: See the following page for Figure 3-4(b)................................................................. 91

Figure 3-4(b): Zoomed in view of Periods 0-8 showing the transition between Phase I and Phase II of absorption for the 87.5% Segmentation, 12.5% Peristalsis motility mix for the “blob” case. The transition occurs at roughly four periods................................................................. 92

Figure 3-5: Maximum average absorption rate (normalized) versus percent peristaltic contribution for the “blob” (blue) and “line” (red) cases................................................................. 93

Figure 3-6: UL (diffusion barrier) thickness versus percent peristaltic contribution for the “blob” (blue), “line” (red), and “inlet” (green) cases................................. 94

Figure 3-7: Axial component center of mass versus time (number of macro-scale motility periods) for nine motility mode combinations for the “blob” case................................................................. 95

Figure 3-8(a): Transverse component of “scalar spread parameter” versus time (number of macro-scale motility periods) for pure segmentation (red),
pure peristalsis (blue) and an equally weighted 50%/50% mix of both (black) for the “blob” case. Note: See the following page for Figure 3-8(b).

Figure 3-8(b): Axial component of “scalar spread parameter” versus time (number of macro-scale motility periods) for pure segmentation (red), pure peristalsis (blue) and an equally weighted 50%/50% mix of both (black) for the “blob” case.

Figure 3-9: A typical multiple-grid lattice with overlapping coarse (top) and fine grids (bottom). The white circles denote coincident nodes that lay both on the coarse and fine grids. The black circles are “hanging nodes” (fine grid nodes that lie in between coarse grid nodes). Source: [135].

Figure 3-10: Flow chart of multiple-grid scheme. Source:

Figure 3-11: Computational setup for the 2D villous motility model: lid-driven cavity flow with “villi” lining the lower surface. (a): The initial distribution of scalar concentration (red band at the top of cavity). The blue arrow indicates the direction of lid motion. The white curved arrow represents the macro-scale eddy generated by the lid-driven flow. (b): The multiple-grid setup as applied to 2D villous motility model. The red grid is the coarse grid; the green grid is the fine grid. Source: Dr. Yanxing Wang (modified from the originals).

Figures 3-12: Absorption rate versus villous length (height). Frequency ratio is held constant at $f_v/f_L = 10$ for all cases. Source: Dr. Yanxing Wang.
Figure 3-13: Absorption rate versus frequency ratio. The height of the villi was held at $l_v = 300\mu m$ for all cases. Source: Yanxing Wang .............................................. 102

Figure 3-14: The effect of villous grouping on absorption rate. (a): Streamlines generated by four groups of five villi oscillating $180^\circ$ out-of-phase. (b): Streamlines generated by one group of 23 villi oscillating in unison. (c): Absorption rate versus time (number of lid-driven circulation periods) for five grouping cases. The villous height and frequency ratio were held constant at $l_v = 300\mu m$, and $f_v/f_L = 10$ respectively for all cases. Source: Dr. Yanxing Wang ................................................................. 103

Figure 3-15: Absorption rate versus time (number of lid-driven circulation periods) is plotted for two cases: fixed villi with no oscillation (red) and pure cavity flow with no villi (blue). Source: Dr. Yanxing Wang ........................................... 104

Figure 3-16: Evidence of a “micro-mixing layer” (MML). (a): Isocontours of the magnitude of the vertical component of the “oscillation velocity”. (b): The magnitude of the vertical component of the oscillation velocity along lines 1 (red) and 2 (blue) as marked in white in Figure 3-17(a). Source: Dr. Yanxing Wang ................................................................. 105

Figure 3-17: Further evidence of the micro-mixing layer (MML). (a): Streamlines averaged over one period of micro-scale villous motion. (b): Pathlines of three fluid particles over several periods of micro-scale villous motion. The isocontours represent scalar concentration (red is high concentration; blue is low concentration). Source: [163] .......................................... 106
Figure 3-18: Spatio-temporal maps of (a): peristalsis, and (b): segmentation. Analysis conducted on MRI acquired during our companion study of motility in the rat intestine. Source: Dr. Amit Ailiani ............................................................... 107

Figure 4-1: Two examples of the 3D domain decomposition technique: (a) 48 subdomains, (b): 96 subdomains .............................................................................. 145

Figure 4-2: The two initial conditions, “blob” and “uniform”, on passive scalar concentration for the peristalsis, segmentation, and equally weighted (50/50) mix cases. Colored isocontours represent initial distribution of scalar concentration as depicted by the legend. Black lines represent isocontours of the stream function. O.R. = 0.5 for all cases shown. ..................... 146

Figure 4-3: Flow patterns and nutrient (scalar) distribution for segmentation over one period (Periods 20-21) for the “uniform” initial condition case. Colored isocontours represent the nutrient concentration distribution: blue corresponds to low concentration; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines). O.R. = 0.5 ................................................................................................................. 147

Figure 4-4: (a)-(e): Flow patterns and nutrient distribution for segmentation for various occlusion ratios for the “uniform” initial condition case after 20 periods of motility. (f): Local nutrient flux for each of the occlusion ratios in (a)-(e). Colored isocontours represent the nutrient (scalar) distribution: blue corresponds to low concentrations; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines) .................................................................................................................. 148
Figure 4.5: (a-d): Percent of scalar absorbed after five (a-b) and 20 (c-d) periods of
motility versus occlusion ratio. (e-f): Number of time periods for 90% absorption versus occlusion ratio. Left column is the “blob” initial
condition case; right column is the “uniform” case.................................149

Figure 4.6: Scalar (nutrient) absorption rate in the central straight portion of
segmental motility over one contractile period (20-21) for the: (a)
“uniform” and (b) “blob” initial conditions..............................................150

Figure 4.7: (a)-(e): Flow patterns and nutrient distribution for peristalsis for various
occlusion ratios for the “uniform” initial condition case after 20 periods
of motility. (f): Local nutrient flux for each of the occlusion ratios in (a)-(e). Colored isocontours represent the nutrient (scalar) distribution: blue corresponds to low concentrations; red corresponds to high
collision. Black lines represent isocontours of the stream function (streamlines).................................................................................................151

Figure 4.8: (a)-(e): Flow patterns and nutrient distribution for the 50/50 mix case for
various occlusion ratios for the “uniform” initial condition case after 20
periods of motility. (f): O.R. = 1.0: control case, pure diffusion in a fixed
tube. Colored isocontours represent the nutrient (scalar) distribution:
blue corresponds to low concentrations; red corresponds to high
concentration. Black lines represent isocontours of the stream function (streamlines).........................................................................................152

Figure 4.9: Average power requirement versus occlusion ratio for peristalsis (blue),
segmentation (red), and 50/50 mix (black)....................................................153
Figure 4-10: Schematic of the 3D multi-scale cavity-flow/villous motility model. The arrow indicates the direction of the lid driving the flow (although the lid is stationary in this particular figure). The isocontours indicate scalar (nutrient) concentration on an arbitrarily selected x-z plane, blue indicates low concentrations; red indicates high concentrations. .................................................. 154

Figure 4-11: Top view of 3D villous motility model for four different villous spacings: (a) $\Delta x = \Delta y = 2D_v$, (b) $\Delta x = \Delta y = 4D_v$, (c) $\Delta x = 4D_v$, $\Delta y = 2D_v$, and (d) $\Delta x = 2D_v$, $\Delta y = 4D_v$. Source: Dr. Yanxing Wang.................................................. 155

Figure 4-12: Absorption rate versus villous height. The frequency ratio was held constant at $f_v/f_L = 40$ for all cases............................................................... 156

Figure 4-13: A zoomed-in view of streamlines formed by the interaction between the flows generated by villous motility and macro-scale circulation. Blue arrows point to sites where the streamlines wrap around the villi, indicating fluid movement into the intravillous space. $\Delta x = \Delta y = 2D_v$. Source: Dr. Yanxing Wang............................................................... 157

Figure 4-14: Absorption rate versus frequency ratio. The height of the villi was held at $l_v = 200\mu m$ for all cases............................................................... 158

Figure 4-15: Profiles of average scalar concentration (averaged over one micro-scale villous motility period) versus vertical distance (z-direction) showing the effects of: (a) villous spacing, (b) villous height (length), and (c) villous frequency............................................................... 159
Figure 5-1: The combined multi-scale model of both macro-scale intestinal motility and micro-scale oscillatory villous motility. The case of segmental intestinal motility with 960 villi is shown. ................................. 185

Figure 5-2: Schematic of pre- and post-streamed distribution functions according to the: (a) the “bounce-back” boundary condition for the no-slip condition at a solid wall (black line), and (b) the symmetry boundary condition at a plane of symmetry (dot-dash line). Black circles are nodes within the computational domain; white circles are “phantom” nodes outside the domain. Black arrows indicate pre-streamed distribution functions; red arrows indicate post-streamed distribution functions if the phantom nodes were “normal” (black) nodes within the fluid domain; blue arrow indicate post-streamed distribution functions at the nodes where they are actually streamed according to the respective boundary conditions; green arrows indicate the effective pre-streamed distribution functions that become the blue post-streamed distribution functions........................................ 186

Figure 5-3: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus villous height. The frequency ratio was held constant at \( \frac{f_v}{f_m} = 50 \) (20Hz) for all cases. No macroscopic motility. Villi are in a single group (960 villi)................................. 187

Figure 5-4: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus villous oscillation frequency for various cases. The villous length was held constant at \( l_v = 300 \mu m \); the villous grouping was held constant at a single group of
villi, with the exception of the orange curve, which had four groups of villi. No macroscopic motility. Villi are in a single group (960 villi). Note: To convert from “frequency” to “frequency ratio”, the frequencies can be divided by the macro-scale motility frequency (0.4 Hz).

Figure 5-5: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus number of groups of villi. The villous length was held constant at $l_v = 300\mu m$; the villous frequency ratio was held constant at $f_v/f_m = 50$ (20Hz). No macroscopic motility. Villi move axially.

Figure 5-6: Instantaneous absorption rate at three equivalent periods of macro-scale motility (7.5 seconds) versus number of villi axial direction for axial villous motility. The villous length was held constant at $l_v = 300\mu m$; the villous frequency ratio was held constant at $f_v/f_m = 50$ (20Hz). The black curve shows the total absorption rate; the red curve shows the absorption rate through the intravillous space on the macroscopic inner gut surface; the blue curve shows the absorption rate through the villous surfaces. No macroscopic motility. Villi are in a single group.

Figure 5-7: Instantaneous absorption rate at three equivalent periods of macro-scale motility (7.5 seconds) versus number of villi axial direction for azimuthal villous motility. The villous length was held constant at $l_v = 300\mu m$; the villous frequency ratio was held constant at $f_v/f_m = 50$ (20Hz). The black curve shows the total absorption rate; the red curve shows the absorption rate through the intravillous space on the macroscopic inner gut surface;
the blue curve shows the absorption rate through the villous surfaces. No macroscopic motility. Villi are in a single group. .......................................................... 191

Figure 5-8: Percent of initial amount of scalar (nutrients) absorbed after three macro-scale motility periods (7.5s) for various cases. The black bars represent cases with no macro-scale motility; the blue bars represent cases with peristaltic macro-scale motility; the red bars represent cases with segmental motility. The bar groups represent different cases of villous motility, as indicated by the labels below the groups. For all cases with active villous motility, the villous length was held constant at \( l_v = 300 \mu m \); the villous frequency ratio was held constant at \( f_v / f_m = 50 \) (20Hz). The occlusion ratio for all cases with macro-scale motility is held constant at \( O.R. = 0.65 \)................................................................................................................... 192

Figure A-1: Log-log plot of drag coefficient (CD) versus Reynolds number (Re) for cross flow over smooth circular cylinders and spheres. Source: [156].................. 228

Figure A-2: Streamlines for 2D (top) and Axisymmetric/3D (bottom) right traveling peristalsis in the wave frame for \( Re = 1 \). Source: [158]............................................ 229

Figure A-3: Example geometries for (a) segmentation, (b) 50%/50% mix of segmentation/peristalsis, and (c) peristalsis from the 2D model. (The 3D geometries are identical, but axisymmetric). The isocontours show the initial scalar (nutrient) concentrations for each simulation. Blue denotes low concentrations; red denotes high concentrations. ........................................ 230

Figure A-4: Average absorption rate (normalized) versus percent peristaltic contribution (2D)........................................................................................................ 231
Figure A-5: Average absorption rate (normalized) versus percent peristaltic contribution (3D) ................................................................. 232

Figure A-6: Comparison of pressure fields (colored isocontours: blue indicates low pressure, red indicates high) for 2D (left) and 3D (right) flow fields for peristalsis (top) and segmentation (bottom): (a) 2D peristalsis, (b) 3D peristalsis, (c) 2D segmentation, (d) 3D segmentation. Black lines are streamlines for the 3D cases (b,d) ............................................................... 233

Figure A-7: Comparison of scalar concentration fields (colored isocontours: blue indicates low concentration, red indicates high concentration) for peristalsis (top) and segmentation (bottom): (a) 2D peristalsis, (b) 3D peristalsis, (c) 2D segmentation, (d) 3D segmentation. Black lines are streamlines for the 3D cases (b,d) ............................................................... 234

Figure A-8: Normalized absorption rate versus occlusion ratio for the (a) 2D model, and the (b) 3D model. Peristalsis is shown in blue; segmentation is shown in red ................................................................. 235
LIST OF TABLES

Table 3K1: Motility parameters for segmentation and peristalsis. The first column under each motility pattern contains the values obtained from analysis of the MRI images; the second column contains the values that were used as input into the computational model simulations. Source (for the values extracted from the MRI imaging): Dr. Amit Ailiani.......................... 108

Table 5K1: Base motility parameters used as input for combined multi-scale model of intestinal/villous motility............................ 193
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CHAPTER 1: BACKGROUND AND MOTIVATION

1.1 The Anatomy of the Small Intestine

The gastrointestinal (GI) tract (Figure 1-1) is responsible for ingestion, digestion, absorption, and defecation. This sequence of processes begins with ingestion, when food enters the mouth. Digestion begins immediately thereafter with chewing and mixing with saliva, which softens the food and starts to break down fats and starches at the molecular level. The food is then swallowed, the process by which a food “bolus” is forced through the pharynx and into the esophagus, where it is propelled to the stomach by a combination of gravity and active peristaltic contractions of the muscles (muscularis propria) within the esophageal walls. In the stomach, the food is churned and mixed with digestive enzymes and gastric acid, converting it into an approximately homogenous, highly viscous fluid (chyme). The chyme is then passed from the stomach to the small intestine (gut) during metered, periodic openings of the pyloric sphincter. Nearly all nutrient absorption takes place within the gut. The gut mixes the chyme with digestive secretions (primarily bile and pancreatic fluids) and transports the nutrient molecules to its absorptive interior surface. The nutrient-depleted chyme is then passed to the large intestine (colon). In the colon, water is removed from the chyme while being mixed with bacteria and converted into feces. The feces is stored in the colon until being moved to the rectum for defecation, the process through which waste is evacuated from the body through coordinated changes in muscle tone within the rectum, pelvic floor, and anal sphincter.

In this study we focus on the gut, the long, continuous, tube-shaped, muscular organ between the stomach and the colon. Although the gut has a single inlet and single outlet, it is
anatomically and physiologically separated into three sections (Figure 1-2): the duodenum, the jejunum, and the ileum. The duodenum begins at the outlet of the stomach at the pyloric sphincter. Of the three sections, it has the largest diameter (4 to 5 cm when filled), but the shortest length (25 to 30 cm in the adult human). The duodenum receives secretions from the pancreatic and bile ducts and contains intestinal receptors that regulate gastric emptying. While some absorption takes place in the duodenum, specifically iron and calcium, which are absorbed only in the duodenum, most nutrient absorption takes place in the jejunum [1]. The jejunum lies between the duodenum and the ileum and is structurally similar to both. It has a slightly smaller diameter than the duodenum (3 to 4 cm when filled), but is significantly longer (roughly 2 m). Over 95% of the nutrients in the chyme are absorbed in the jejunum [1]. The final section, between the jejunum and the colon is the ileum. The ileum has the smallest diameter (2 to 3 cm when filled), but is the longest (roughly 3 m) of the three sections. Bile salts and vitamin B$_{12}$ are absorbed in the ileum. However, chyme that enters the ileum is largely nutrient depleted, so it serves primarily as a “backup” section that absorbs any leftover nutrients [1].

The anatomical structure of the intestinal walls is basically consistent throughout the three sections. The walls are comprised of five distinct layers (see Figure 1-3): the mucosa, submucosa, circular muscularis, longitudinal muscularis, and the serosa [2]. The mucosa is closest to the inner open space (lumen) of the gut and is composed of a loose coat of connective tissue (the lamina propria) and a thin layer of smooth muscle (the muscularis mucosae) consisting mostly of longitudinal muscle fibers. The submucosa lies between the mucosa and the outer muscle layers, and houses a rich network of blood vessels, lymphatic, and an enteric nerves plexus. Adjacent to the submucosa is the innermost muscle layer (the circular
muscularis), a relatively thick circular layer of smooth muscle. The outermost layer of muscle, the longitudinal muscularis, is thinner than the circular muscularis and is comprised of longitudinal muscle fibers. Together, these two layers are called the \textit{muscularis propria}. A serosa encases the entire gut, except for a narrow region on the posterior wall where the mesentery tissue that suspends the jejunum and ileum from the abdominal wall attaches [2].

Although the outer gut surface is smooth, the inner lumenal surface has an intricate structure. In the human small intestine, there exist thin circular ridges known as “folds of Kerckring.” These folds (shown in Figure 1-3) are generally aligned transverse to the longitudinal axis of the gut. The folds vary in height from 3 to 10 mm and can extend half to two-thirds of the circumference or extend even farther to form nearly complete rings. Some folds have been observed to spiral and circumvent the lumen as many as two to three times. The folds begin just aft (2.5 to 5 cm) of the duodenal inlet and increase in size and number until the region between the lower duodenum and mid-jejunum where they are largest and most numerous. Beyond the mid-jejunum, the folds decrease considerably in size and number until the lower ileum, where they are essentially absent. It is generally accepted that the primary purpose of the folds is to passively increase the absorptive surface area of the intestine, by roughly a factor of three [1,2].

Lining the entire inner lumenal surface of the gut, over and between the folds of Kerckring, is a series of closely packed micro-scale projections known as villi. The villi (see Figures 1-4 through 1-8) tend to be roughly circular in cross-section, known as “finger-like” villi (see Figure 1-5), or wide, thin, and roughly rectangular in cross-section, known as “leaf-like” villi (see Figure 1-6). Carnivores generally have finger-like villi, while herbivore villi are
more often leaf-like. Omnivores may have either type or both [3]. Humans have mostly finger-like villi, ranging in height from roughly 500µm to 1000µm [2,4].

The villi are blanketed by a single layer of cylindrical absorptive epithelial cells (enterocytes) collectively known as the epithelium. Under the epithelium, in the intra-villous space (part of the lamina propria), there exists a network of capillaries and a central longitudinal lacteal for transporting absorbed nutrients to the bulk bloodstream. Whereas some simple molecules (e.g. sugars) are transported directly from the villous capillaries into the bloodstream, the lacteal carries lipids to the lymphatic system. Surrounding the lacteal are thin strands of smooth muscle fiber that extend up from the muscularis mucosae (see Figure 1-4) [2]. As with the folds of Kerckring, it is often asserted that the purpose of the villi is to passively increase the surface area of the gut, by roughly a factor of 10 in humans [1]. However, because the villi are so tightly packed, absorption along the sides is likely much less than over the tips. Furthermore, this explanation does not account for the presence of the muscle fibers that extend into the villi from the muscularis mucosae. We hypothesize that the existence of muscle fibers within the villi suggest the existence of active villous motions and that such motions may indicate a neurophysiologically-controlled enhancement of nutrient absorption.

1.2 The Physiology of the Small Intestine

For nutrients to be absorbed through the epithelium, they first must be transported to the inner lumenal surface. Analogous to the reduction of temperature of warm flow through circular rigid tubes with cool walls, the concentration of nutrients near the surface is depleted by absorption, creating a concentration gradient in the radial direction [5]. In the
absence of wall motion, the only mechanism for nutrient transport from the more highly-concentrated bulk flow to the nutrient-depleted surface is radial molecular diffusion. Diffusion can be a relatively slow process, especially for larger, more massive molecules. Advection, in general, is a more effective transport mechanism. As such, time scales for diffusive transport are often much longer than those for advective transport (the ratio of the two time scales is the Péclet number, $Pe$). For this reason, the gut induces wall deformations (motility) to generate advective fluid motions that mix the chyme and carry nutrients to the surface for absorption.

Intestinal motility is a result of coordinated local contractions of the circular muscularis and longitudinal muscularis. However, the relative contributions of these two muscle layers to gut motility patterns are unclear, and the details of the stimuli that induce the movements are not fully understood [6]. It is well known that the enteric nervous system of the gut is sensitive to local stimuli, and that motility differs with the caloric content of the ingested meal and that mechanical stretching of the gut diameter can generate propagating contractions [7]. Thus, it is clear that various external stimuli can induce certain patterns of motility.

However, motility has also been observed in the fasting state, when no apparent stimulus is present [7]. The patterns are controlled by the enteric nervous system, sometimes referred to as a “second brain,” and can be stimulated in gut segments that have been completely separated from the body [6]. The emotional state of the individual, however, is also known to alter gut motility through stimulation of the central nervous system [6]. This inherent complexity highlights the difficulty in studying the small intestine.
The motility patterns generated by the muscle layers within the gut walls can also be complex in spatial-temporal composition. Motility varies with location (duodenum, jejunum or ileum) as well as phase of digestion and caloric content of the food. Further variability is introduced by pharmaceutical and/or nutritional stimuli and the emotional state of the individual as previously noted [6,7]. With such complexity and variability, it can difficult to accurately describe and quantify the specific motility patterns that occur in the gut. In a general sense, however, two qualitatively distinct types of motility patterns (modes) are distinguished and classified in the literature: segmentation and peristalsis [e.g. 4,6,8].

Segmentation is characterized by rhythmic, repetitive radial contraction of short segments of the gut. Neighboring contractions entrap portions of chyme, creating a series of well formed segments. As these contractions relax, new contractions appear at the center of the previous segments, dividing them in two, and creating new segments. This pattern continues in a temporally periodic manner during the fed state, creating the visual appearance of the chyme “sloshing” back and forth between neighboring segments.

In the literature, segmentation is generally associated with mixing of the luminal content. That is, homogenization of the chyme by exchanging fluid between the relatively nutrient-rich centerline and the relatively nutrient-depleted region near the epithelial surface [4,6]. Relative to peristalsis, segmentation is essentially a stationary motility mode. However, Grivel and Ruckebusch [9] describe observations in which a small propagating component is present. Other studies describe segmental-type contractions with propagatory components that appear to “sway” back and forth [10,11]. We have observed a similar local back and forth patterning superposed over a standing motility pattern in a partner study of the motility in the rat gut (see Section 3.1.3) [55].
Peristalsis is characterized by propulsive wave-like propagations, and is similar to other propagatory contractile patterns found throughout the GI tract (the esophagus, for instance, is purely peristaltic). Peristaltic contractions vary substantially in the gut. There are peristaltic contractions that propagate relatively rapidly (a few cm/s) [7]. Other contractions propagate much slower (a few cm/min) [8]. The much larger, highly occlusive “migrating motor complex” (MMC) phase III (see Section 2.1) contractions sweep over long segments of the gut. Sometimes referred to as “housekeeper” contractions, they serve to clean the gut, evacuating the remaining contents during the fasting state [12].

A few analytical and computational models have been developed to study the fluid motions generated by the motility modes of the gut [13-16]. Such models, although necessarily simplified, can provide valuable qualitative information pertaining to the transport and absorption in the gut. Peristalsis as a general means of mechanically pumping fluid has been well-studied [17,18,55-64]. Segmentation, however, has been only scantly studied from a fluid mechanical perspective. Macagno et al. [15] provide only a brief qualitative description of flow phenomena resulting from a segmenting type motility pattern. It is suggested in the literature, that this mode of motility may generate advective fluid motions that promote mixing of the chyme, countering the depletion of nutrients that would exist without wall motions [e.g. 4,6].

After transport from the centerline of the gut to the near-surface region, nutrients must traverse a final absorption barrier, a diffusion-dominated region adjacent to the surface where advective fluid motions are suppressed. This diffusion dominated region, or boundary layer, is formed in wall-bounded flows where the relative fluid velocity is low from friction
and the no-slip condition. When a nutrient molecule reaches this barrier, transport becomes dominated by diffusion, a much slower process on which to reach the absorptive surface.

Several studies have investigated the effects of the diffusion dominated region, known in the literature as the “unstirred (water) layer” (UL) [e.g. 19,20]. In the 1970s and early 1980s, both in vitro and in vivo techniques were applied to humans and various animal models to estimate the thickness of the UL (see Section 2.3). Effective thicknesses were inconsistent and ranged from \(~100\mu m\) to over \(600\mu m\) [20]. However, an UL on the order of \(600\mu m\) is physiologically unrealistic. A diffusion barrier of this thickness would be the rate limiting step in absorption, and would reduce the maximal absorption rate of glucose to 1% of the lumenal content per minute [21]. This low absorption rate contradicts studies which show that 30% to 50% of ingested glucose is absorbed within the first few minutes after chyme is passed to the gut from the stomach [21].

In the late 1980s and early 1990s, Levitt, Strocchi and colleagues [e.g. 22,23] conducted several studies using a different approach to measure the UL thickness had produced measurements an order of magnitude less than what had been previously claimed. These measurements suggested that UL thicknesses of \(30\mu m\) to \(40\mu m\), which is much more consistent with anatomical considerations and physiological absorption rates. Interestingly, thicknesses of this order have not been measured in vitro, even with vigorous stirring induced by a magnetic bar. This suggests the existence of a mechanism in vivo that provides a much more effective mixing of the lumenal contents near the epithelial surface.

It has been difficult to study this mixing mechanism, largely due to the difficulty of observing micro-scale gut function without intrusive methods that disturb the natural state of the gut. Thus, essentially no details of the in vivo mechanism are known with certainty. It
has been suggested, however, that local mixing might be generated by active movements of the villi [e.g. 21]. The smooth muscle fibers that run along the central axis of each villus provide a possible means for movement. While no \textit{in vivo} data exists to confirm or refute this assertion, \textit{ex vivo} experiments have been performed in which suggest the existence of active villous movements in various animals [3].

Segments of gut (rabbit, dog, cat, etc.) have been exteriorized, cut open, placed in holding devices, exposed to a variety of stimuli, and observed under a microscope. The observed villous movements have been classified into three distinct types: (1) axial contractions in which individual villi shorten in height, (2) whip-like or pendular side-to-side motions of one or more villi, and (3) tonic contractions of groups of villi [3]. All three of these motions could, from a fluid mechanics perspective, generate fluid motions that could enhance nutrient transport in the diffusion-dominated region. However, there have been no data provided in the literature on \textit{in vivo} villous motion to support this claim.

1.3 Description of Study Aims and Methods

Although macro-scale deformations of the gut are necessary to efficiently transport nutrients from the nutrient-rich regions near the centerline to the less concentrated regions near the epithelium, this advective mechanism is less effective in transporting nutrient molecules through the diffusion-dominated UL adjacent to the surface. We hypothesize that active controlled movements of the villi (villous motility) play a critical role in the efficient mixing observed in the gut, reducing the thickness of the UL and enhancing the rate of absorption through the surface. We further hypothesize that the macro- and micro-scale mixing and transport mechanisms are strongly coupled, and that this coupled, multi-scale
motility is necessary to produce the physiologically observed absorption rates and UL thicknesses in the gut.

To develop a more complete understanding of the influence of macro- and micro-scale intestinal motility, as well as the interplay between the micro-macro interactions on the efficacy of gut function, we developed a multi-scale computational model of a simplified, physiologically relevant intestine that includes both macro-scale motility of the gut walls and micro-scale villous motility. We break the model development down into several simpler models, elements of which are incorporated into the final complete model. To this end, we have applied the lattice Boltzmann method (LBM) to predict the fluid motions in two separate, simplified, two-dimensional (2D) models relating to gut function: (1) a simplified small intestinal segment that includes peristaltic and segmental motility, but no villi (Figure 3-2a,b,c), and (2) a stationary lid-driven cavity flow with moving “villi” on the bottom surface (Figure 3-11a,b). Both models include a passive scalar as a model of nutrient concentration suspended within the bulk flow of chyme such as to simulate the gut in the fed state. We parameterize the models using magnetic resonance imaging (MRI) data of the in vivo, fed-state, rat intestine acquired by our research group in a companion study. We use these 2D models to gain preliminary understanding of small intestinal function, as discussed in Chapter 3. The 2D models are then extended to three dimensions (3D) to obtain further insight relevant to the true physiological system. Findings and corresponding discussion from the 3D models are presented in Chapter 4.

This interdisciplinary research program was funded by the National Science Foundation (NSF) through grant CTS-056215. Professor James G. Brasseur in mechanical engineering was the principal investigator and lead on the modeling and computer
simulation aspects of the program, while Professor Andrew G. Webb in bioengineering was a co-principle investigator and lead on the MRI imaging and animal model studies. Professor Brasseur is joined on the modeling side by post-doctoral researcher Dr. Yanxing Wang and doctoral candidate Gino Banco. Dr. Wang has developed the simplified computational models (2D and 3D) of villi motion in lid-driven cavity flow mentioned in the previous paragraph. Gino Banco, the author of this dissertation, has developed the macro-scale intestinal motility model (2D and 3D) as well as the combined multi-scale 3D model of both macro-scale gut motility and micro-scale villous motility. Professor Webb was joined by Dr. Thomas Neuberger, a research associate and scientist in the Huck Institute MRI Center, and Dr. Amit Ailiani, who received his doctoral degree on his work with this study. Dr. Neuberger conducted the MRI experiments, while Dr. Ailiani carried out the image analysis to extract anatomical and physiological parameters for the simulations. We were also assisted in the care of the animals by the late Professor Nadine B. Smith from the bioengineering department, who was a valued co-investigator. We mourn her untimely loss earlier this year.

In the coming chapters, the details of simulations carried out with each of our computational models are presented. Chapter 2 is a thorough review of the literature, covering each facet of the project and highlighting the gaps we seek to close with this work. The work completed with each of the simplified models (2D and 3D macro- and micro-scale models) are discussed in Chapters 3 and 4 respectively, with each set of results discussed with respect to physiological relevance. In Chapter 5, we discuss the combined multi-scale model of the physiologically relevant gut and the numerical experiments through which we provide insight into the complex absorptive mechanisms present in the gut. This dissertation concludes in Chapter 6 with a global summary and suggestions for continued research. The
appendix contains what we refer to as a “cautionary tale”, in which we provide an introspective examination of interpretive errors that were uncovered during the application of our simplified 2D models the complex 3D physics underlying gut function (see Appendix A).
Figure 1-1: The gastrointestinal (GI) tract. Source: [24]
Figure 1-2: The three sections of the small intestine. Source: [25]
Figure 1.3: Illustration of the five primary layers of the intestinal wall (mucosa, submucosa, circular and longitudinal muscularis, and serosa) and the folds of Kerckring. Source: [2]
Figure 1-4: A single, finger-like, human villus showing the strands of smooth muscle that extend upward from the muscularis mucosae. Source: [25]
Figure 1-5: Electron microscopy images of finger-like villi. (a): side view, (b): top view.

Unknown animal. Source: Prof. Jack Wood, Ohio State University.
Figure 1-6: Electron microscopy images of leaf-like villi. Unknown animal. Source: Kevin Haley, Bend Research.
Figure 1-7: Electron microscopy images of the capillary networks within (a): finger-like villi (white rabbit) and (b): leaf-like villi (guinea pig). Source: [165]
CHAPTER 2: REVIEW OF RELEVANT LITERATURE

This chapter provides a thorough review of the relevant literature. The multi-disciplinary nature of this program warrants several areas of otherwise unrelated literature to be covered. In other parts of this dissertation, readers are referred back this chapter to supply background information.

2.1 Intestinal Motility

The anatomy and physiology of the GI tract has been studied for centuries. Early work focused mostly on observation and inspection of the surgically exposed intestine. At the turn of the 20th century, Bayliss and Starling [26-28], and Cannon [8,29] pioneered the study of intestinal motility. In 1899, Bayliss and Starling published the first in a series of classic papers on the movements and innervations of the small intestine. The authors measured deformations of the gut walls in various anesthetized animal models (dog, rabbit, cat) using either a rubber tube connected to a manometer or through a device they dubbed an “enterograph”, which graphed changes in height of a specified point on the outer surface [26]. They reported both peristaltic waves and “pendular” movements, which appear to be the first mention of segmental motility, that were generated in response to various stimuli [27]. A major conclusion of their work was the notion that “excitation at any point of the gut excites contraction above, inhibition below,” which they asserted was “the law of the intestine” as a description of how chyme is transported axially along the length of the gut [28]. In 1902, Cannon [29] published his first findings of intestinal motility using radiographic technology to follow the progression of bismuth through the gut of the cat. He
noted similar motility patterns, and in a publication in 1912, used the specific names “peristalsis” and “segmentation” [8]. In the 1912 paper, he also reports the same behavior as the law of the intestine put forth by Bayliss and Starling, but used the term “myenteric reflex”. Interestingly, he showed that this reflex could also be induced in the stomach under certain circumstances [8]. The highly regarded physiologists’ findings, and the “law of the intestine” were rapidly adopted into widespread textbook use [30].

However, as first asserted by Alvarez in 1924 [31] and then more recently in the separate works of Hodgkiss [32] and Spencer et al. [33], the law of the intestine may not be uniformly applied across species. Alvarez notes that even the authors in their original communications admit that their results were not repeatable in all cases. Furthermore, the experiments were conducted on animal models anesthetized with morphine, which effectively detaches the intestine from the central nervous system [26]. Trendelenburg, who is among the most famous researchers in the field of intestinal motility research for his development of a device for studying deformations in exteriorized segments of the gut walls in vitro, showed in his classic 1917 paper that morphine inhibits intestinal motility [34]. Both Hodgkiss and Spencer et al. present data obtained using modified Trendelenburg devices on the domestic fowl and the guinea pig respectively that contradict the law of the intestine, local stimuli did induce motility, but the motility propagated orally (backward, or retrograde, toward the stomach rather than forward, or antigrade, toward the colon). Although not directly related to the focus of the study presented in this dissertation, even more compelling contradictions were reviewed by Wingate in 1981 [30]. Wingate describes spontaneous, migrating motility patterns that occur in the complete absence of stimuli, usually in fasted models [30]. The notion of simple, locally driven, forward propagating motility was likely
influenced by the work of the “founder of digestive physiology” William Beaumont, who in 1933 wrote that the stomach remained quiescent until stimulated by food or other local means [30,31]. While the law of the intestine is still described in physiology textbooks [e.g. 4], it is clear that gut movements are more complex than the simple explanation of propulsive motility.

Throughout the 20th century, many further advances on the description of gut motility were made. While the enterograph employed by Bayliss and Starling appears to have been passed on as a reasonable means of studying gut motility, advances in manometry allowed pressure measurement to emerge as a major technique to study muscle contraction. In 1940, Ingelfinger and Abbott presented the Miller-Abbott tube, a double-channel rubber tube with a balloon affixed to the end, designed to be inserted through the nose and routed into the gut [36]. Although this device was used primarily for treatment of intestinal obstructions rather than as a manometry instrument [37], the improvement of this device by adding multiple balloons by Chapman and Palazzo in 1949 [38] proved useful for research purposes. Chapman and Palazzo replicated the experiments of Ingelfinger and Abbott, correlating pressure readings with barium tracings to confirm a direct relationship between measured wave patterns and actual gut motility patterns. Their multi-ballooned probe provided them with simultaneous spatial and temporal information, which they were able to use to distinguish between rhythmic segmental contractions and propagating peristaltic movements in the human [38].

Although they reverted to a single balloon technique, in 1954 Foulk et al. [39] were the first to show that intestinal motility patterns were periodic, alternating between periods of activity and periods of quiescence. By the end of the 1960s, numerous investigators using
manometric probes had reported an interesting phenomenon present in the fasting state, a migrating motility pattern that rhythmically sweeps through the intestine at regular intervals [e.g. 38-40]. The pattern was not well described, however, until 1969 when Szurszewski [41] showed conclusively that the contractions migrated from the beginning of the duodenum to the end of the ileum in the dog, with a new wave beginning when the previous terminated. He used the term “complex” for this pattern, which became commonly known as the migrating motor complex (MMC). While much effort has been directed toward the study of MMCs, it is of little direct interest to our research as it is a fasting state phenomenon. Our work is focused on the fed state, during which nutrient absorption occurs after normal ingestion of a meal.

With the development of the personal computer, advancements were made that were not previously possible. In 1982, Ehrlein and Hiesinger [42] implanted extra-lumenal strain gauge transducers on the duodenum, near the gastroduodenal junction, of dogs and output the data to a computer for analysis. The experiments were conducted on unanesthetized models so that the data provided were close to the undisturbed case. Ehrlein [43] published similar work two years prior, but analysis of the data was limited without a computer. The same year, the authors published a study simultaneously using transducers and radiographic data collection [44]. In 1987, Ehrlein et al. [7] used videofluoroscopy in combination with the closely spaced transducers to identify a plethora of specific patterns in the unanesthetized dog under both fed and fasting conditions. The authors described propulsive, as well as non-propulsive motility, the non-propulsive activity consisting of individual or clusters of stationary contractions, and the propulsive activity consisting of standard propagating contractions (peristalsis), “propagating power contractions”, phase III of the MMC and
other clusters of migrating contractions. They also found retrograde transport of chyme produced by two motility patterns: retrograde propagating contractions (peristalsis) and retrograde “power” contractions, which were accompanied by reflux of chyme back into the stomach. In later papers, Ehrlein [45-47] and his colleagues provided direct quantitative data, such as propagation speed (wave speed), contraction frequency, and contraction incidence and spread of the motility they had observed in the conscious dog. In addition, the authors have made their videofluoroscopy data available to the public in the form of a set of two DVDs that are freely available for download on the world wide web, providing a wealth of very clear image data on not only the small intestine, but the stomach, large intestine, and colon, in the dog, pig and guinea pig [48,49].

Imaging modalities provide not only direct visual aids for understanding the complex motility of the gut, but with the use of computers and image analysis techniques, unbiased quantitative data can be extracted from still or dynamic image datasets [50]. Using versions of the Trendelenburg method (still in wide use nearly a century after its invention), several groups have mounted exteriorized segments of various parts of the intestine ex vivo and captured stimulated movements with high resolution optical video cameras. [e.g. 51,52] With the help of computers, image data have been digitized and parameters extracted (wave speeds, contraction frequencies, etc.) such as those provided by Ehrlein and his colleagues [42]. In 1997, Benard et al. [52] compiled data from an entire time sequence of images into a single spatio-temporal map as a powerful tool to visualize and analyze a dynamic system of such complexity as the intestine. Two recent studies by Furness and colleagues [53,54] have applied the spatio-temporal map technique to images acquired using the Trendelenburg
method “*in vivo*” on rat models. However, the intestine is still exteriorized, just still attached to the mesentery and blood system.

Over the last five years, our research group at Penn State has used MRI to obtain dynamic image sequences of the fed jejunum. In a paper by Ailiani *et al.* [55], we describe the experimental procedures for undisturbed, *in vivo* data acquisition on anesthetized rat models. Details of this part of the study are discussed further in Section 3.1.3.

### 2.2 Intestinal Modeling

Although motility studies discussed in the previous section have achieved a great deal over the past century in the understanding of complex intestinal motility patterns, experimental procedures have limits to their ability to provide information on intra-lumenal phenomena. Fluid flow patterns, details of nutrient and drug absorption, and mixing are difficult to measure without significantly disturbing the physiological state of the intestine. For such information, physics based mathematical and computational models of the physiological phenomena must be used.

Modeling of the intestine has its roots in the mathematical study of the flow patterns generated by peristaltic motion of the walls of channels and pipes or tubes. The first such published study was by Burns and Parkes in 1967 [55]. Using a perturbation technique, the pair predicted the flux of fluid through pipes and channels under continuous sinusoidal peristaltic motions of the walls of both, modeling the fluid as Newtonian and sufficiently viscous as to use the Stokes equations. A similar study of peristaltic motion in tubes was published by Barton and Raynor [57] the following year, with an attempt to correlate their results with experimental data of the intestine. Their predicted average flow rates differed
from experiment by 28%, which is not surprising since gut motility is much more complex
than simple continuously moving sinusoidal peristalsis. In 1968, Hanin [58] published a
study in which he used a boundary layer type approximation to predict flow constrained
within two peristaltically moving walls with a phase lag, finding that the results were not
significantly different until a lag of at least 20º. This, arguably, provides evidence that a
minor lack in symmetry with respect to the axis may not be important for the intestine, and
axisymmetric models may be a reasonable approximation [11].

Reflux, or flow in the oral direction, was first predicted by Shapiro, who along with
colleagues published a series of at least six papers from 1966 to 1971 on the subject of
peristalsis, which are widely considered the classical foundation of the subject [17,59-63].
Shapiro and Jaffrin [60] were also the first to show the phenomenon of “trapping” by which
a fluid bolus can be carried along with a wave in a region of internal circulation under
relatively highly occlusive peristalsis. In 1971, Lew et al. [14] used sharp, infinitely thin
protrusions extending from the walls into the fluid as the propagating peristaltic waveform,
and provided numerical solutions that interestingly showed the same type of net forward,
internally circulated flows predicted by Shapiro and colleagues [e.g. 60]. In 1987, Li and
Brasseur [18] modeled peristaltic waves with arbitrary geometry and number of waves in
finite length tubes and showed that a peristaltic pump in finite length tubes, as is obviously
the case in biological systems, is inherently unsteady. They note that retrograde pumping
(reflux) is greater with single peristaltic waves as opposed to infinite waves.

In 1972, Raju and Devanathan [64] studied peristaltic pumping of non-Newtonian
fluids described by a power law function, showing flow fields similar to those of the
Newtonian results discussed previously for the zero-pressure-difference case. Although Raju
and Devanathan did not explicitly mention the gut as an application, intestinal chyme most likely does exhibit non-Newtonian behavior [65]. Srivastava and Srivastava [66] published a study of peristaltic transport of a non-Newtonian fluid in tubes of non-uniform diameter in 1985 with the application to the intestine. They found that the non-Newtonian behavior of the fluid caused an increased pressure throughout the domain as compared with the Newtonian case in simulations with a non-zero pressure difference. The quantitative difference of pressure with axial distance, however, remains qualitatively similar between Newtonian and non-Newtonian fluids [66]. A conclusion from these two studies is that if the need for accurate, absolute (rather than relative) values of the flow parameters, such as pressure, etc., exists, then non-Newtonian effects may need to be considered. Qualitative behavior, however, is similar between the Newtonian and non-Newtonian cases in intestinal models [62,66]. A recent study published in 2007 by Reddy et al. [67] supports this conclusion. However, an even more recent 2008 study by Teran et al. [68] on complex, viscoelastic, non-Newtonian fluids reports that while the flow patterns are similar to those generated in Newtonian fluids, the monotonic increase in flow rate that occurs in Newtonian fluids as peristalsis becomes more occlusive is lost in viscoelastic fluids. As there is some indication that chyme may be viscoelastic [65], care should be taken to keep this in mind when approximating the fluid as Newtonian. A more potentially relevant issue to the current work is that fact that viscosity in the gut may be significantly inhomogeneous, especially in the near-wall region. That is, possible mucus secretions may locally alter the viscosity. Nutrient depletion near the surface could also have an impact on the viscosity. More study is needed to quantify the fluid mechanical properties of the chyme.
One last segment of the peristalsis literature is focused on the study of transport of solid, non-deformable material in the intestine. Although not especially physiologically relevant to the small intestine as its contents are rarely solid and non-deformable, the studies do exhibit some applicability to the rectum where relatively solid feces must eventually be evacuated. In 1983, Bertuzzi et al. [69] published the first study of such a case, investigating a deformable, cylindrical membrane peristaltically transporting a rigid sphere using a mathematical model. Two decades later Miftahof and Fedotov [70] published a similar model, but incorporated an intrinsic nervous motility control system and electrochemical coupling (synaptic neurotransmission) that together generate the peristaltic reflex. In 2007, Miftahof, working with Akhmadeev, [71] published a paper in which they used this model to assert that propulsion of the solid bolus is only possible under coordinated activity of both the circular and longitudinal muscle layers.

Although peristalsis has been significantly studied, and is fairly well understood, other types of motility, such as segmentation, have been only scantily studied. In 1974, Singerman [72] published a doctoral dissertation, titled “Fluid Mechanics of the Human Duodenum”, in which he developed a computational model of four types of simplified motility in the upper gut. Macagno (Singerman’s advisor) and Christensen [11] described the model and their findings in detail in a review paper on the fluid mechanics of the duodenum in 1980. Using a triangle-shaped waveform, he modeled both a stationary contraction in which the opposing waveforms rise out of opposing rigid walls and then subsequently collapse back to zero amplitude, and one that has the same instantaneous shape and maximum amplitude as the stationary contraction but with the waveform rising on one side and then collapsing on the other, giving the boundary an axial component of velocity. The
authors admit that these contraction patterns are “hypothetical but not without some observational basis”, due to a lack of sufficient quantitative geometric motility parameters available at the time [11].

In the same paper, they also discuss a model of a segmental-type contraction in which the central sections of two opposing walls collapse toward each other and then revert back to zero amplitude. This simple model was to our knowledge (until our current work) the only published attempt to simulate a segmental contraction for the purpose of predicting fluid flow, despite segmentation being the dominant pattern under normal conditions. The fourth motility pattern was a propagative longitudinal contraction, as described in previous work from the same authors in 1975 [73]. They propose that this type of contraction may be what Cannon [29] and others described as “pendular movements” [11].

In a book chapter published the following year, Macagno and Christensen [15] provide streamline plots of the flow generated from the propagative contraction and the segmental type contraction. For the segmental contraction, they also provide pressure and volume flux diagrams. They go on to present an interesting discussion on laminar mixing, and show the spread of initially thick adjacent layers of marked fluid into convoluted thin layers as caused by the propagative longitudinal contractions. The mixing results are basic, as they do not incorporate a solution of the advection/diffusion equation, but the work in general represented a very significant advance in the understanding of intestinal fluid mechanics as generated by deformations of gut walls.

None of aforementioned studies incorporate a key and necessary element of intestinal function: nutrient absorption. Not many models involving fluid mechanics and absorption exist in the literature. The first seems to be from Kristensen and Skadhauge [74]
in 1974, in which they model the absorption of salt in the fish intestine. The model is crude and does not include any wall movements. A more notable example is the model of Macagno et al. [75], published in 1982, in which they developed an analytical model of fluid and mass transfer in a compliant tube. They included three types of motility: stationary contractions, “asymmetric progressive contractions,” and “symmetric progressive contractions.” They also developed a physical mechanical model and conducted similar experiments with both models to investigate the effect of wall movement on the absorption of salt. Both models show that a 30-35% increase in absorption occurs with wall deformations as compared with the quiescent-walls case. In the model, using parameters not able to be replicated experimentally, they showed up to a 100% increase in absorption with the symmetric progressive contractions. A recent study published in 2005 by Mishra and Rao [16] describes a model of the intestine that employs sinusoidal peristalsis in a two-fluid system similar to that studied by Brasseur et al. in 1987 [76], but with the addition of porous walls. The paper reports the effect of porosity on the flow patterns, but does not include any mass transfer, and thus does not predict nutrient absorption.

After the work of Macagno et al. [75], no studies appear to have been published describing models combining fluid flow/absorption models in the gut. Two recent studies have used advanced computational techniques to solve coupled fluid flow, mass transport models, but with non-absorptive walls. In 2003, Jeffrey et al. [13], described a study in which peristalsis in the guinea pig ileum was recorded in experiment. Using image analysis, geometric parameters have been extracted to parameterize a two-dimensional computational model. They plot isocontours of axial velocity, pressure, and fluid mixing, as well as fluid particle paths for three distinct peristaltic motions. The authors argue that even with low
Reynolds number laminar flow there are fluid flow events that likely “promote digestion and absorption” but do not offer results from their model to support this conclusion. More recently, in a study published in 2007, Dillard et al. [77] model the antroduodenal junction, the connection between the stomach and the duodenum, with advanced computational methods. The two-dimensional model uses a speculative geometry model to predict the fluid motions and coupled mass transfer of the stomach emptying into the upper gut. The study was largely academic, with model parameters varied with little connection to the physiology.

2.3 Unstirred Layer (UL) Measurement

In the place of more complex models, non-motile models such as that of Kristensen and Skadhauge [e.g.78-80] have been implemented over the past few decades to study various aspects of absorption in the gut. Using such models for absorption, the permeability characteristics of the walls for various nutrients must be known [81]. However, as noted in a review by Barry and Diamond in 1984 [20], it can be difficult to obtain accurate measurements of those characteristics. One difficulty is the presence of a region, or layer, of relatively low velocity fluid adjacent to the wall, historically referred to as the “unstirred water layer.” The term “water” can be misleading, as the layer is comprised of intestinal fluid under physiological conditions. Therefore, we drop the term “water” to remove any confusion, and refer to the layer simply as the “unstirred layer” (UL). The UL is, more accurately, a high-resistance layer adjacent to the inner luminal surface across which the rate of transport of nutrient molecules is suppressed as a result of the suppression of advective motions by friction between the fluid and the wall. The layer acts as a barrier through which nutrients must be transported by diffusion. For highly permeable nutrients, such as glucose,
the rate limiting step is diffusion through the UL, rather than absorption through the epithelium. In such cases, experimentally measured permeability parameters can differ from the actual permeability parameters by orders of magnitude [20].

Dietschy and colleagues published a series of classic papers on the subject of the UL in the 1970s [e.g. 82-85], which were summarized in a review published in 1984 by Thomson and Dietschy [19]. The authors sought to identify this source of error, and develop procedures with which the experimentally measured parameters can be corrected to actual values. In this work, substantial effort was made to quantify the effective resistance of the UL through an equivalent “UL thickness.” This thickness, which was used as a correction factor, is simply a reformulation of the mathematical expressions for calculating the membrane parameters, such as the permeability coefficient, to account for the presence of the UL. While the correction is straightforward, it assumes that the thickness of the UL is known [84]. In the review by Thomson and Dietschy [19], the authors tabulate inconsistent thickness measurements represented in the literature ranging from ~100µm to over 600µm.

Dietschy and colleagues actually provided the first in vitro measurements of the UL in the intestine, in the rat (~200µm) in 1973 [82] and in the rabbit (~150µm) in 1974 [83], using a technique developed by Diamond [86] in 1966. Diamond proposed correlating the potential difference measured across a membrane, a rabbit gallbladder, to the increase of nutrient concentration at the surface, asserting that the time required for the value of the surface concentration to reach half of its bulk value is directly proportional to the square of the thickness of the UL. Interestingly, when Dietschy and colleagues applied the same technique in vivo in the rat jejunum in 1986, they reported much higher values ranging from ~300µm to well over ~600µm [85]. Rats have a gut diameter of ~5 mm [55], so a 600µm
would imply that over 40% of the lumen would be diffusion dominated. If that were the case, nutrient absorption would be too slow for normal function.

In 1988, Levitt [22] and colleagues questioned the findings of Dietschy’s group, reporting that the \textit{in vivo} UL in the conscious rat was no more than 100\(\mu\)m. The authors proposed a different method for determining UL thickness, in which the only unknown parameter is the nutrient absorption rate, and no correlations are necessary. The experiments were conducted on conscious, anesthetized, and both anesthetized and laparotomized rats. UL thickness increased by two and six fold in each of the latter two cases respectively. They conclude that the previous measurements published by other groups had been gathered under non-physiological conditions and are thus not relevant to the actual gut [22]. Levitt \textit{et al.} used the same technique to measure the maximal thickness of the UL in the dog jejunum, reporting UL thicknesses of \(\sim 35\mu\)m to 50\(\mu\)m [23]. In the same paper, the authors used previously published glucose absorption rate data to calculate the mean maximal UL thickness in humans to be only 40\(\mu\)m. In 1991, Strocchi and Levitt [21] published a formal argument that the thickness of UL should be reappraised. The authors criticize the methods used in previous studies, providing several arguments that thicknesses of several hundred micrometers are physiologically unrealistic.

One major argument is that nearly all previous studies were either done \textit{in vitro}, \textit{or in vivo} on anesthetized, laparotomized rats, a situation in which the jejunum is virtually amotile [21]. A logical hypothesis is that the deformations of the walls are a mechanism for reducing the UL thickness to physiologically observed values. However, the Strocchi and Levitt [21] state: “Surprising, the normally functioning intestine maintains a much thinner unstirred layer than apparently can be achieved with vigorous stirring with a magnetic bar, \textit{in vitro}.
Presumably, the intermittent contractions of the longitudinal and circular muscle could not induce this excellent mixing.” Strocchi and Levitt [21] then propose a controversial idea that lies at the center of our current study: “Although speculative, it seems possible that the thin, in vivo unstirred layer results from the contractions of the villi, a unique stirring mechanism that functions at the absorptive surface rather than in the center of the lumen”. In the next section, a segment of the literature is reviewed to summarize what is known about the movements of the villi to investigate this theory further.

2.4 Villous Motility

In a 1914 paper, Hambleton [87] states “The structure of the villi of the small intestine is such that one would naturally infer that they possess the property of motion.” In the same paper, he reports “lashing-like movements in various directions” and “alternating shortening or retraction, and extension of various villi in the field” using a binocular microscope to examine an opened loop of the anesthetized dog intestine. Hambleton was actual the first to make the assertion that these motions might be present to enhance mixing of the near wall chyme [87].

The first study of villous motility in live animals was actually reported 74 years earlier in 1843 by Gruby and Delafond [88], who reported shortening, lengthening, and lateral movements. King and Arnold [89] published a study in 1922 investigating villous motility in the dog and cat. They experimented with various stimuli, such as exposure to various nutrients, drugs, and mechanical agitation, finding the dog intestine to be more responsive than the cat intestine. The authors report similar motions to those reported by Hambleton, but present the first quantified parameters of villous motility, observing that the average time
between contractions was roughly three seconds, but with significant irregularity. They state that any given villus executes its cycle at somewhat regular intervals, but that while one villus could contract regularly, an adjacent villus could complete several cycles and abruptly stop, remaining quiescent for a significant time [89]. In 1934, Wells and Johnson [90] reported contraction frequencies of up to 20 to 30 per minute for short periods, and slower frequencies for “many minutes” in the anesthetized dog. The authors also point out that: “all observers agree that there are three types of villous movements.” The three motions are described as (1) “whipping, swaying movements of individual villi”, (2) sudden retraction, followed by sudden or gradual relaxation, and (3) “tonic retraction”, usually of several villi in unison [3].

While most studies have focused on the dog [3], Hooper and Schneider [91] observed the aforementioned three types of motion in the pigeon, although the villi were reportedly much less active as compared with previous studies of the dog. In 1932, Mahler et al. [92] reported villous contractile activity in conscious humans, although there seems to be little mention of any more data to either support or refute these findings.

It was not until 1987, when Womack et al. [93] performed their study of the moving dog villi, that a reasonably detailed description of villous motility, with quantification of the motility parameters (such as frequency of contraction occurrence), was published. The authors used a videomicroscope to observe opened, exteriorized loops of all three sections of the intestine. Although tonic contractions were not observed, both “piston-like” and “whipping”/“pendular” type motions were quantified in terms of rate of occurrence and duration of contraction. Piston-like contractions were found to be the predominant motion observed in all three sections of gut, comprising over 80% of the total number of
contractions observed [93]. The average rates of occurrence of the piston-like contractions were 7.3 ± 0.1/min, 4.0 ± 0.1/min, and 2.0 ± 0.1/min, in the duodenum, jejunum, and ileum respectively. The corresponding contraction durations, the total time of a single villus contraction, showed similar axial variation, with average durations of 2.6 ± 0.1 s, 2.1 ± 0.1 s, and 1.8 ± 0.1 s in each of the three sections, respectively. Pendular contractions were found to be much rarer, with rates of occurrence of only 0.06 ± 0.03/min, 0.93 ± 0.14/min, and 0.35 ± 0.07/min, in the duodenum, jejunum, and ileum, respectively. In contrast to the piston-like contractions, no significant difference was found to exist in the duration of pendular contraction among the three sections, the contractions lasting an average of 2.3 s.

The authors found that the presence of amino acids and solubilized free fatty acids substantially increased the rate of contraction, up to 92% for a mixture of taurocholic acid, monoolein, and oleic acid. In a review paper Womack et al. [3] published two years after the aforementioned study, the authors compile a rather extensive table of neuroeffectors and humoral factors that either increase or decrease the rates of occurrence, or generate a tonic contraction with or without rhythmic activity. In the final section of the review paper, the authors highlight the fact that although the subject of villous motility had been studied for over 150 years at the point of publication, the functional implication(s) still remained uncertain. Nearly 20 years later, our level of understanding has seemingly not improved.

Although there is some mention in the literature of the role of villous motility as a local mixing agent that enhances absorption, no direct evidence to support this notion has been presented [e.g. 21,89]. The in vivo studies by Levitt et al. [94] suggest that the existence of an efficient mixing mechanism. The augmented rates of glucose absorption with villi motion (as reported by Kokas and Ludany in 1938 [166], and Mahler et al. in 1933 [92]) and
add support to the hypothesis. Another study published by Strocchi et al. in 1996 [95], in which measurements of the UL in humans were seven times higher in patients affected with celiac disease (a disorder characterized by villous atrophy) versus healthy patients also supports this hypothesis. A study published in 1990 by Mailman et al. [96] (including Womack), however, concludes that villous contraction does not contribute to mixing of the UL based on a lack of correlation between absorption rate and villous motility. However, the invasive methods used to observe the villous motility in this study (same as those used by Womack [93]) have questionable relevance to the normal undisturbed in vivo situation.

Other hypotheses have been proposed to explain the physiological role of villous motility. One such explanation is a role of the villus as a lymph pump. This concept, in which a piston-like contraction facilitates propulsion of intestinal lymph out of the central lacteal, was first proposed by Brücke in 1851 [97]. Wells and Johnson [90], in 1934, argued against this hypothesis, reporting observations that the lacteals remain filled with lymph, even after many contractions. Another study, published in 1969 by Lee [98], however, suggests that this hypothesis may have some merit. The author injected mineral oil containing a dying agent into the central lacteal of dog villi, and observed that each time a contraction occurred, the oil had been transported toward the base of the villi.

Perhaps the reason for a relative lack of advancement of the field is the technical difficulty of observing the villi, and measuring pertinent parameters, in the natural, undisturbed in vivo state. All the previous studies have been conducted in exteriorized, opened segments of the intestine with varying degrees of invasiveness. One can question the relevance of any of the previously published data to the physiological conditions of the actual undisturbed intestine. Even if significant advances were made in non-invasive medical
imaging techniques, and villous motility was able to be quantified, the important parameters necessary to evaluate its purpose (such as rate of absorption) would still require invasive measurement. Computational models, however, can be employed to provide insight difficult to obtain experimentally.

2.5 The Lattice Boltzmann Method (LBM)

We include a review of the lattice Boltzmann method (LBM) literature, as we have chosen this framework as the basis for our computational models. The review includes papers pertinent to the current study, as well as a history of the development of the method. The review concludes with studies not directly related to the current study to demonstrate the robustness and versatility of the method for those readers who may be unfamiliar with the LBM.

In 1973, Hardy et al. [99] described a “cellular automaton,” a model in which space, time, and all state variables are discretized, with finite Boolean populations on each node of the discretized space, and analyzed fundamental questions in the field of statistical mechanics. The essential concepts are: (1) “streaming”, in which the populations “hop” to neighboring nodes, and (2) “collision”, in which the populations collide based on specified rules. This was the first “lattice-gas” model, but due to a lack of sufficient symmetry, it could not predict complex phenomena such as fluid dynamics [100].

In 1986, Frisch et al. [101] published a groundbreaking paper in which a cellular automaton set to a hexagonal lattice, obeying pure conservation laws at the microscopic level, was able to reproduce real, macro-scale, complex fluid flows. Much excitement was generated in the fluid mechanics community, the model presented hopes of an unusually
simple, intrinsically parallel model, free of round-off error. Soon after, however, several problems with the model became apparent, most notably statistical noise, causing significant velocity and density fluctuations that accompany the phase-space discretization [100].

While some worked to address the issues with the lattice-gas model, only two years later, McNamara and Zanetti [102] pointed out that if one used ensemble averaging of the Boolean populations to convert them to real numbers between 0 and 1, and then controlled the time evolutions with a Boltzmann equation derived directly from the lattice-gas model, then the problem of noise is resolved. As a side benefit, another one of the problems with the lattice-gas model is also solved using this new method, the ability to simulate 3D flows [100]. Some problems still did exist, however, (for instance an upper limit on achievable Reynolds number) because of a non-linear collision operator. Several linearizations were suggested, but the independent recommendations of Qian in 1990 [103] and Chen in 1991 [104] to use the Bhatnagar-Gross-Krook (BGK) collision operator, which used a linear operator involving a single relaxation parameter [105], was nearly universally accepted as an elegantly simple, very efficient model, and the now standard lattice-BGK (LBGK) model was born [100].

The basis for the LBM is statistical mechanics notion that the continuum level dynamics of a system is the result of the collective behavior of the molecular-level interactions that underlie the system, but that the continuum level dynamics are not sensitive to the details of the underlying interactions [106]. Thus, the method involves the construction of simplified kinetic equations such that the averaged mesoscopic interactions of particle distribution functions properly obey the continuum level governing equations (the Navier-Stokes equations for incompressible flow of a Newtonian fluid). In 1992, Chen et al.
formally proved that the Navier-Stokes equations can be recovered from the lattice Boltzmann equation (LBE) with the BGK collision operator. In 1997, He and Luo [108], as well as Abe [109], proved that although the LBE grew directly out of lattice-gas methods, the equation is a specially discretized form of the Boltzmann equation and is fundamentally different from its lattice gas predecessor.

As with all numerical methods, the LBM requires boundary conditions to handle such situations as flow bounded by a solid wall (no-slip), or flows in which inlet/outlet conditions need to be specified. In 1986, Wolfram [110] argued that a no-slip boundary condition could be simulated for lattice-gas simulations if a population “hopping” into the wall is bounced back along its original path, to return to its original location (the “bounce-back” scheme). In 1993, attempting to apply the no slip condition in LBM, Ziegler [111] pointed out that the bounce-back scheme was only first-order accurate, which degrades the accuracy of the simulation since LBM is second order accurate in the fluid domain. In the same paper, Ziegler notes that if the solid boundary is located half-way between two consecutive nodes, then the bounce-back scheme is second order accurate. This phenomenon arises because of the nature of streaming of the distribution functions, which must “stream” to the next neighboring node in a single time step. The only way a distribution function can stream to a wall and subsequently bounce back to its exact starting position (but facing the opposite direction) in a single time step is if the wall is located half-way in between the nodes, the first half of the time step the distribution function is streaming away from its starting node, the second half it is streaming back after hitting the wall. If the wall is anywhere other than half-way between nodes, the distribution function will not stream back to its exact original position and cause inaccuracy. This classical
bounce-back scheme works well for stationary walls, but does not handle the momentum exchange that must take place when the boundary is moving.

In 1994, Ladd [112] considered the interaction between moving rigid particles suspended in a flow and the flow itself using the LBM. He added a forcing term to the standard bounce-back scheme to transfer momentum to the fluid according to the boundary velocity and the fluid density. Ladd’s method can handle interactions with any arbitrary type of moving boundary condition [100]. However, because this method relies on the bounce-back scheme, it still suffers from inaccuracy when the wall is not located half-way between consecutive nodes. With arbitrarily moving boundaries, it is obvious that boundary being located at the exact half-way point is rarely the case. Several papers [e.g. 113,114] have proposed methods of obtaining second order accuracy for arbitrarily located walls. A common technique is to use an interpolation scheme, such as that proposed by Lallemand and Luo in 2003 [114]. The authors show their scheme to be second-order accurate. For the case of the wall located half-way between two nodes, the equations collapse to the formation of Ladd [112]. This scheme can also be used on arbitrarily located stationary geometry for a robust way of handling complex geometry (one of the strengths of the LBM itself) [100].

Schemes for prescribing inlet/outlet conditions, such as those often required for simulating flow in a channel or pipe have been provided by several papers [e.g. 115-117]. The simplest boundary condition is the periodic condition. The LBM is particularly well-suited periodic boundary conditions, as the distribution functions that would normally stream out of the computational domain are simply streamed back into the other side of the domain as if the inlet and outlet nodes were adjacent columns or rows of nodes. Periodic
boundary conditions are also the most stable treatment of the boundary conditions as there is no inherent source of error [100].

Two independent, but concurrently published 1997 schemes are the most popular methods of specifying a fixed boundary condition on a continuum-level quantity at an inlet/outlet. Chen et al. [115] proposed a simple, reasonably effective extrapolation of the pre-streamed distribution functions in the last two rows/columns of nodes in domain to a virtual row/column of nodes. The continuum-level velocity and/or density/pressure is then specified via the equilibrium distribution function. The authors show that the post streaming result is a second-order accurate solution of the continuum-level fields. The other method, published by Zou and He [116], directly specifies one of the two continuum-level quantities (velocity or density/pressure), and then solves for the other continuum-level quantity and the unknown components of the distribution function using the moment equations used for calculating continuum-level quantities. Any further unknown components of the distribution function are then solved by bouncing back the non-equilibrium parts of the distribution function. The Zou and He method is also reported to be second-order accurate. An interesting newer method published in 2006 by Zhang and Kwok [117] describes a method for which a pressure gradient is prescribed along with periodic boundary conditions. This is certainly not generally applicable to all flow conditions and geometries, but the results seem to show that the scheme provides a means of specifying a pressure difference without introducing any non-physical disturbances, and while maintaining periodicity.

In the current study, we incorporate a solution of the passive scalar advection/diffusion equation into the fluid simulation. There are several methods available to handle this situation within the LBM framework. The LBE itself can be used to solve for
the scalar concentration simultaneously with the flow domain by advancing a second
distribution function, and running two simulations concurrently. In one 1997 study, Shan
[118] proposed the use of a second distribution function, incorporating a buoyancy body
force to simulate Rayleigh-Bénard convection. Other similar studies also solve dual LBEs,
one for fluid, one for scalar concentration, but use various simpler formulations of the scalar
equilibrium distribution function [e.g. 119,126]. A unique method, originally developed by
Ernst [120], was published by Merks et al. in 2002 [121], who modified the method to
increase its applicability. Known as the “modified moment propagation method”, the
scheme provides a means for a scalar to propagate with the standard fluid distribution
functions. The authors report that within a maximum Péclet number limit, the method
provides excellent agreement with the advection/diffusion equation while saving
substantially on memory usage and computational expense. We have employed this method
in our models, and have shown it to perform very well for our applications.

The standard LBM requires a uniform, square/cubic lattice. This can be a problem if
disparate physical scales exist in the flow structure or geometry. In such cases, a uniform
lattice dictates that either the smallest scale features are not adequately resolved or the large
scale features are over-resolved, resulting in either inaccuracy or excessive computational
expense, respectively. In traditional computational methods, such as finite-difference or
finite-volume Navier Stokes solvers, the grid can be non-uniform, and stretched or skewed
as to provide locally refined region of interest, and lesser refined regions where the flow
structure is less complex. The standard LBM cannot take advantage of such techniques.
However, multiple-grid strategies can be used to achieve the same objective. In 1998,
Filippova and Hänel [122] proposed a method in which a finer grid(s) can be nested within a
coarse grid that spans the entire computational domain. At each time step, the coarse grid
distribution functions are used as boundary conditions for the fine grid calculation. Several
time steps (equivalent to a single coarse grid time step) are then carried out on the fine grid.
The resulting information is then passed back to the coarse grid. In 2002, Yu et al. [123]
published similar method, but argued that it was unnecessary for the coarse grid to span the
entire domain, and presented a means of overlapping the domains by one coarse grid node
instead, reducing computational expense and resources. Dupuis and Chopard [124] pointed
out in a 2003 paper that the method used by the two former groups has a singularity with a
unit value of the relaxation parameter in the BGK operator, and proposed revised method
without the singularity. Their method uses Filippova and Hänel’s concept of a domain-
spanning coarse grid.

While most of the following studies are beyond the scope of the current work, they
are mentioned to demonstrate the versatility of LBM in its ability to simulate a wide variety
of complex flows [e.g. 50,100,125]. The LBM is particularly well suited for multi-phase
and/or multi-component flows [e.g. 127-129] and complex geometries [e.g. 125], and can
simultaneously solve for energy along with mass and momentum upon reformulation of the
LBE [e.g. 130,131]. Its inherent particle-like properties allow it to interact naturally with
molecular dynamics simulations [e.g. 130,131]. The LBM can simulate 2D and 3D turbulent
flows at high Reynolds number [e.g. 134,135], as well as flow through micro-channels and
porous media when continuum descriptions may break down [e.g. 125]. Often, the
restriction to a square/cubic element lattice is considered a downfall of the LBM, but recent
work has described the development of axisymmetric models [e.g. 136,137], and even the use
of arbitrary curvilinear lattices [e.g. 138]. A 2006 paper [139] demonstrates the ability of
LBM to simulate power-law-model non-Newtonian fluids with second-order accuracy. LBM’s algorithmic simplicity, ability to easily incorporate additional physics, and its inherent inclination toward parallelism make it a viable alternative to traditional numerical techniques for certain classes of fluid flow [e.g. 140,141].
CHAPTER 3: TWO-DIMENSIONAL INTESTINAL MODEL SIMULATIONS

Our hypothesis is that highly-coupled, multi-scale interactions between macro-scale mixing/transport from intestinal motility and micro-scale mixing/transport from villous motility is important in normal gut function. To investigate this hypothesis, it is necessary to accurately simulate both the relevant physics and neurophysiologically-controlled intestinal motility at the macro- and micro-scales. With the inherent complexity of the gut, this is non-trivial. Therefore, we begin with simple models and add complexity in incremental steps.

Our starting point is a computational model of a circular tube with the diameter of the intestine. The tube is filled with a viscous fluid to model the chyme. The walls of the tube are specified to deform in a manner that models the complexity of intestinal motility. The LBM-based model predicts fluid motions driven by the complex moving boundaries. Although the LBM (see Section 2.5) is particularly well suited for complex geometry, accurate modeling of moving boundaries is a current research topic. The treatment of such boundary conditions is especially an issue when high accuracy is necessary at the fluid-solid interface. Since the mixing motions are driven by the deforming walls and nutrient absorption occurs at the surface of the gut, particular attention is paid to the wall boundary conditions in our models.

Concentrations of nutrients within the chyme must also be modeled. We use a continuum-level passive scalar to model the nutrient concentrations. Simple nutrients are small with respect to the fluid and do not significantly affect the flow. Thus, a simultaneous solution of the advection-diffusion equation can be incorporated. Several methods exist to do this within the LBM framework [e.g. 118,119,121]; however, no literature (to our
knowledge) exists on the subject of specifying accurate scalar concentration boundary conditions on moving boundaries. Therefore, we develop a second-order method of specifying such boundary conditions.

To incorporate villi into the model, the height of which are two orders of magnitude less than the gut diameter, grid resolution becomes an issue. The flow patterns around the villi require a much finer grid resolution than do the bulk fluid motions. Such fine resolution is computationally expensive and memory intensive. The LBM generally requires a uniform lattice, and therefore standard grid stretching for local mesh refinement cannot be used. Instead, multiple grids are used, with different resolutions, in the same computational domain. Information is then passed between them [e.g. 134]. Although such techniques have been shown to work well for simple geometries [135], the intestinal geometry is very complex, and would require a series of grids for the application to sufficiently reduce computational expense. Furthermore, a method for handling communication of the scalar concentration field on multiple grids is absent from the literature and is thus developed. Even with an adequate multiple-grid strategy, practical application of the model requires parallelization and use with high performance computing resources.

To overcome these technological challenges while gaining preliminary insight into the mixing and absorption mechanisms in the gut, we have developed two 2D models. This first is a 2D macro-scale intestinal model with moving boundaries and a scalar concentration field to model nutrient flow, mixing, and absorption, but without the complexity of villi (see Figures 3-1 and 3-2). This model provides information on the effects of various motility patterns on mixing and absorption. The second model is a 2D lid-driven macro-scale cavity flow with micro-scale moving villi on the bottom surface and a scalar concentration field to
model the nutrients. It incorporates a multiple-grid lattice, with higher resolution in the region around the villi. This model was developed by Dr. Yanxing Wang with in collaboration with Gino Banco and Professor Brasseur. We use the model to study the coupling between the macro- and micro-scale mixing processes, and its effect on absorption without the complexities of intricate moving macroscopic geometry (see Figures 3-11(a,b)).

While each of these models provides useful information, differences exist with the real gut. The first model does not consider the influence from villous motility. The second model is designed to create a macro-scale eddying flow similar to that found with occlusive peristalsis [e.g. 18] to preliminarily investigate macro-micro-scale interactions. The 2D geometry creates villi that are effectively infinite in one direction, which are in contrast to the actual 3D villi found in the gut. The models are building blocks, which are followed by more complex, physiologically relevant models of the intestine (see Chapters 4 and 5). The relationship between the results of the simple 2D models and the corresponding, more complex 3D models turns out to be interesting and insightful, as discussed in detail in Appendix A.

3.1 Macro-Scale Intestinal Model

Using the simplified 2D macro-scale intestinal motility model, we investigate the influence of two modes of motility, peristalsis and segmentation, on absorption and transport. We hypothesize that the small intestine can actively control the absorption process by strategically employing these two modes. In the coming sections, we present the details of the macro-scale motility model, discuss the results of the numerical experiments, and conclude with a discussion of the physiological implications.
3.1.1 The Numerical Method

We applied the LBM (see Section 2.5) to predict the fluid motions in chyme generated by contractile motility patterns of the intestinal walls. We chose the LBM as an algorithmically straight-forward, yet powerful technique for simulating biological flows of this type, where complex deformations of the boundaries drive the flow [e.g. 50,142]. To investigate the mixing, transport, and absorption characteristics of nutrient concentrations with the fluid motions, we include a passive scalar concentration field to model nutrient concentrations suspended within the bulk intestinal flow. The computational model was parameterized using physiological motility data extracted from magnetic resonance imaging (MRI) of the in vivo rat intestine [55]. The interface between the motility parameters and the computational simulations is a simplified, time-dependent geometry model of peristaltic and segmental motility patterns.

Fluid flow model: the lattice Boltzmann method. The standard LBM (see Section 2.5) solves a variation of the Boltzmann equation, discretized in space and time, as well as velocity. Particle distribution functions are tracked as they evolve on a uniform lattice. We apply the 2D, nine-speed model (D2Q9) version as given by Qian et al. [143]. The basic LBGK equation, with the collision operator, is given by Chen [104]:

\[
f_i(x + e_i \delta t, t + \delta t) = f_i(x, t) - \frac{1}{\tau} \left[ f_i(x, t) - f_i^{eq}(x, t) \right],
\]

where \( f_i(x, t) \) is the particle distribution function at discretized location \( x \) at discretized time \( t \), with discretized velocity \( e_i \), and \( f_i^{eq}(x, t) \) is the equilibrium distribution, toward which the
distribution functions relax with time scale $\tau$. In the low Mach number limit, the equilibrium distribution function is given by:

$$f_{i}^{eq}(x,t) = w_{i} \rho(x,t) \left[ 1 + 3 \frac{e_{i} \cdot u}{c^2} + \frac{9}{2} \left( \frac{e_{i} \cdot u}{c^2} \right)^2 - \frac{3}{2} \left( \frac{u}{c} \right)^2 \right],$$  \hspace{1cm} (3.2)

where $\rho$ and $u$ are the continuum-level density and velocity, $w_{i} = \frac{4}{9}, \frac{1}{9}, \frac{1}{36}$ are direction-specific weighting coefficients for center, off-diagonal, and diagonal directions respectively, and $c = \delta x / \delta t$ (usually of unit value in “lattice units”) is the basic speed on the lattice, where $\delta x$ and $\delta t$ are the lattice spacing and time step respectively. As shown by Equation 3.1, the two basic operations of LBM are “streaming”, during which the distribution functions at each node propagate to all neighboring nodes, and “collision”, during which the distribution functions relax toward equilibrium according to with time scale, $\tau$. Since collision represents intermolecular interactions, the relaxation parameter, $\tau$, defines the lattice kinematic viscosity, $\nu$, according to $\nu = c_{s}^{2} \delta t(\tau - 1/2)$, where $c_{s}$ is the “lattice speed of sound.” The LBM is inherently compressible in nature. The lattice speed of sound is proportional to the basic speed, $c_{s}^{2} = c^2 / 3 = RT$, where $R$ and $T$ are the gas constant and temperature respectively, but bear no physical significance in this low-Mach-number isothermal formulation.
The LBM is based on statistical mechanics, where continuum-level density and velocity fields, $\rho(x,t)$ and $u(x,t)$, respectively, are obtained from moments of the distribution function as follows:

$$\rho(x,t) = \sum_i f_i(x,t), \tag{3.3}$$

$$u(x,t) = \frac{\sum_i f_i(x,t)e_i}{\rho(x,t)}, \tag{3.4}$$

In the LBM, the pressure is locally calculated by an ideal gas equation of state:

$$P(x,t) = \rho(x,t)RT = \rho(x,t)c_i^2 \tag{3.5}$$

**Nutrient (passive scalar) concentration model.** To quantify the effectiveness of nutrient absorption, we incorporate a passive scalar concentration field, $\phi(x,t)$, into the LBM fluid flow model. Advection and diffusion of the concentration within the chyme are predicted as a result of fluid motions generated by the deforming walls. Nutrient concentration is evaluated with the “modified moment propagation method”, as described by Merks *et al.* [121]. Unlike other methods, where the LBM is used to concurrently calculate the evolution of a second distribution function for the scalar [e.g. 118], the moment propagation method evolves the continuum level scalar concentration field directly with fluid flow LBM distribution functions, according to the following equation:

$$\phi(x,t + \delta t) = \sum_i \left( \frac{f_i}{\rho} - w_i \Delta \phi \right)_{x-e_i\delta_t,t} + \Delta' \phi(x,t), \tag{3.6}$$

where $\phi(x,t)$ is the continuum level concentration, in molecules per unit volume (area for 2D), of scalar at location $x$ at time $t$. At each time step, $\phi(x,t)$ is recalculated as the sum of scalar advected from each $i$th neighboring node (first RHS term of Equation 3.6), and the
portion remaining at the node according to the molecular diffusivity-dependent \( (D_m) \) parameter: \( \Delta^* = 1 - 6D_m \) (second RHS term of Equation 3.6). By avoiding a second LBM distribution function for scalar, the method has a lower computational expense and reduced memory demands, yet maintains accurate prediction of the evolution of scalar concentration within the domain.

3.1.2 Boundary Conditions

In the small intestine, the fluid motions and resulting nutrient advection are induced by the deformation of the intestinal walls. Accurate simulation of these phenomena is therefore limited by the accuracy of the boundary conditions at the moving boundaries. In the current study, are careful to properly account for momentum transfer to the fluid from the deforming walls with second-order-accurate boundary conditions. Nutrient concentration also requires a reasonable boundary condition at the moving surface to model absorption through the epithelium. We apply a zero-scalar concentration condition at inner luminal surface, implying effectively immediate nutrient absorption at the epithelium. This “immediate absorption” assumption is a reasonable model for most nutrient molecules since resistance to absorption is typically small compared to the time scale associated with the transport of nutrients from the bulk flow to the surface [144]. The inlet and outlet of the intestine are modeled using periodic boundary conditions, taking advantage of the inherently periodic nature of the geometry and the numerical stability of this boundary condition [100].

**Boundary Conditions at the Moving Surfaces.** The momentum of the fluid in the near-wall region is affected by deformations of the surface. To properly capture the transfer of momentum from the surface to the fluid, we apply the second-order-accurate boundary
condition of Lallemand et al. [114]. This method extends the moving boundary bounce-back formulation of Ladd [112] to include interpolation for more accurate location of complex boundaries. The method employs one of two expressions according to the relative distance from the nearest fluid node to the solid boundary, \( q \):

\[
f_i (x, t) = q(1+2q)\left[ f_i^-(x, t) \right] + (1-4q^2)\left[ f_i^-(x, t) \right] - q(1-2q)\left[ f_i^-(x, t) \right] + 6w_i \rho (e_i \cdot u_b) \\
(3.7)
\]

\[
f_i (x, t) = \frac{1}{q(2q+1)}\left[ f_i^-(x, t) \right] + \frac{(2q-1)}{q}\left[ f_i^-(x, t) \right] - \frac{(2q-1)}{(2q+1)}\left[ f_i^-(x, t) \right] + \frac{6w_i \rho}{q(2q+1)} (e_i \cdot u_b) \\
(3.8)
\]

Equation 3.7 is used when \( q < \frac{1}{2} \), while Equation 3.8 is used when \( q \geq \frac{1}{2} \). Both equations collapse to the original formulation of Ladd [112] when \( q = \frac{1}{2} \) [114]. The last term in each expression accounts for the momentum induced by the moving surface, where \( u_b \) is the velocity of the moving boundary.

**Zero-scalar-concentration Boundary Condition.** With the complex boundaries moving through the stationary lattice, the walls seldom coincide directly with a lattice node. Therefore, the specification of the conditions for the scalar concentration at the walls is a non-trivial task, as the zero-scalar concentration value cannot be set directly. The scalar concentration at the wall must be specified indirectly by setting the concentration at each fluid node directly adjacent to the wall at each time-step. We employ an interpolation/extrapolation method developed by our research group (Dr. Yanxing Wang), as summarized in the following paragraph [144].

Denoting a node adjacent to the wall as \( A \), the method involves the definition of a corresponding virtual node, \( A^* \), located directly on the boundary, and a series of subsequent
virtual nodes, the number of which depends on the desired order of accuracy. Here we discuss the first-order scheme, requiring two virtual fluid nodes, $B^*$ and $C^*$, defined at one and two lattice spacings into the fluid domain from the wall respectively (a second-order scheme is applied in practice). The distribution functions, densities, and scalar concentrations at $B^*$ and $C^*$ (at time $\mathcal{t}$) are found by direct interpolation of the values of all neighboring nodes. The density and distribution function are then be extrapolated from $B^*$ and $C^*$ to find the values at $A^*$. The scalar concentration need not be extrapolated as it is set to zero at $A^*$ to reflect the boundary condition. Once the distribution function, density, and scalar concentration at time $t$ have been calculated at $A^*$, $B^*$, and $C^*$, the appropriate concentrations are updated to time $t + \delta t$ using Equation 3.6 as usual. The updated scalar concentrations are then extrapolated from $B^*$ and $C^*$, knowing relative distance, $q$, to determine the appropriate scalar concentration at the adjacent node $A$ that reflects the zero-scalar concentration condition at wall node $A^*$.

3.1.3 Collection and Parameterization of Motility Data

Several quantitative studies of peristaltic motility have been presented [e.g. 52,53,145]. However, there have been very few quantitative motility studies of segmentation [147,148]. Furthermore, what studies do exist have been conducted using various invasive techniques to surgically isolate and extract segments of the intestine from either dead or anesthetized animals. While this scenario allows for use of higher quality (higher resolution), more easily implemented optical imaging modalities, its relevance to the undisturbed *in vivo* gut is questionable (see Section 2.1).
To obtain anatomically and physiologically accurate motility parameters for our computational model, we performed a companion study of the motility in the undisturbed *in vivo* rat intestine using dynamic MRI [55]. This experimental aspect of the research was conducted by Dr. Amit Ailiani (former doctoral student) and Dr. Thomas Neuberger (current director of the Huck MRI Center at Penn State) under the direction of Professor Andrew Webb (formerly Penn State bioengineering). The image analysis and parameter extraction, as discussed in this section was conducted by Dr. Ailiani under Professor Webb's direct supervision and with interactions with Professor Brasseur and Gino Banco. Although this work was the primary portion of Dr. Ailiani's doctoral dissertation, it is included here because of its importance to the model parameterization and for continuity of the overall research study presented in this dissertation, namely the macro-scale intestinal models (see Sections 3.1 and 4.1), and the multi-scale combined model (see Chapter 5).

Our study is the first quantitative, *in vivo* motility study of both peristalsis and segmentation. Rats were chosen for convenience, being small enough for the bore of the magnet, yet possessing sufficiently large intestinal structure to be imaged within the resolution limitations of the equipment. Furthermore, the aforementioned peristaltic studies [52,53,145] were conducted on rat models and thus establish a sufficient base for comparison.

In the experimental study, the following protocol was applied. Eight rats weighing 200-300g were allowed to feed as they would under normal circumstances. Subsequently, they were then given an oral gavage of contrast agent (Gd-DPTA - 1 ml/kg) approximately 50 minutes before imaging. A second identical gavage of contrast agent was given immediately prior to imaging. This sequence ensured that the rats were in a normal fed state
and that the contrast agent had been appreciably transported with the chyme along the length of the intestine. The rats were anesthetized using a gaseous mixture of isoflurane (1.5%) and oxygen in one set of experiments and inactin in another (inactin was used to reduce possible impact on motility patterns) before being placed in the magnet where their vital signs were monitored continuously during the image acquisition.

The MRI was conducted using a 12cm diameter, horizontal bore, 7T magnet with a diameter gradient set and a Varian DirectDrive™ console. Two types of scans were conducted. Initially, a static volumetric scan was performed on the abdominal cavity to identify suitable gut segments for subsequent dynamic imaging. The volumetric scans were comprised of a T_1-weighted spin-echo sequence of 16 1mm-thick slices with an in-plane resolution 0.6mm x 0.4mm. The dynamic imaging was a gradient-echo sequence. Targeted locations in the jejunum, chosen to maximize the visible length, were scanned in series of up to 1000 consecutive images per location to capture the gut motion over significantly long time periods. The dynamic scans used the following parameters: TE = 1.6ms, TR = 3.13ms, data matrix: 96 x 72 (3/4 Fourier), 1mm slice thickness, field-of-view: 2.5cm x 2.5cm, in-plane resolution: 312µm x 416µm, and time per image: ~168ms. A quadrature transmit/receive coil (Varian) with diameter 6.9cm was used. The complete experimental protocol was approved by The Pennsylvania State University’s Institutional Animal Care and Use Committee (IACUC), IACUC Protocol #21347.

To extract the desired quantitative data from the dynamic image sequences, custom MATLAB™-based image analysis software was developed (Dr. Ailiani). Advanced edge detection techniques were used on each image to delineate the intestinal wall boundaries from the rest of the surroundings, resulting in a binary image where the intestinal area within
the boundaries is assigned a unit pixel intensity, while the surroundings are assigned zero intensity. A thinning algorithm was then applied to the binary images to determine the curvilinear centerline (medial axis) of the gut segments. Equally spaced points were placed on the medial axis, and diameter of the gut calculated for each of the points. Once this preliminary preparation was completed on each time sequence of images, it was possible to construct “spatiotemporal maps” which consolidate geometric data from each set of hundreds of images into a corresponding single image where one axis is time and distance along the medial axis are the axes of the image, and diameter is expressed as relative pixel intensity. Larger diameters appear brighter, and smaller diameters (contractions) appear darker. An example of spatio-temporal maps of for peristalsis and segmentation are shown in Figure 3-18.

In utilizing this type of analysis, distinct patterns emerge in the maps which directly correspond to the presence of the two distinct classes of gut motility. Peristalsis (see Figure 3-18(a)) is manifested as a dark, continuous diagonal streak, consistent with axial propagation of a contraction wave. Segmentation (see Figure 3-18(b)) manifests itself much differently. Because these are standing contractions, the dark regions are not continuous, and a checkerboard-like pattern emerges. The maps provide a useful means of obtaining information often not clearly discernable when observing the actual time sequences of images.

Quantification of geometric parameters was obtained from one-dimensional signals describing the diameter at particular spatial locations as functions of time. Minimum, maximum, and mean diameters were then computed from individual experiments for peristaltic and segmental motility. A discrete Fourier transform was applied to the signal to
determine the dominant frequencies. The average frequency of peristaltic and segmental contraction were then calculated, the inverse of which is the time period of contraction, the time taken for a point along the relaxed gut to contract fully and return to the relaxed state. Peristaltic wave speeds were determined from the slopes of the diagonal streaks in the spatiotemporal maps, and the wavelengths were calculated as the product of the wave speed and the period of contraction. The wavelength for segmentation was defined as the mean distance between two neighboring contractions. The results of the quantitative and statistical are given in Table 3-1. The average values for occlusion ratio, wavelength, wave speed, and contraction period were used to parameterize the geometry model as discussed in the next section.

### 3.1.4 The Geometry Model

The data extracted from the MRI experiments were used to parameterize a mathematical model of the wall geometry of the moving intestine. The model encompasses both modes of intestinal motility, peristalsis and segmentation, where the modes can be activated independently or in any desired weighted linear combination of the two. That is, the position of the intestinal wall, \( h(x,t) \), at axial location, \( x \), and time, \( t \), is determined as follows:

\[
h(x,t) = w_p h_p(x,t) + w_s h_s(x,t)
\]  

(3.9)

where \( h_p(x,t) \) is the contribution to the overall intestinal wall position from peristalsis, and \( h_s(x,t) \) is the contribution from segmentation. The weighting coefficients, \( w_p \) and \( w_s \), the sum of which must be unity, control the relative influence of peristalsis and segmentation respectively on the overall geometry.
The geometry is modeled as symmetric about the centerline, and is periodic in both space (axial direction) and time. We neglect the curvature of the gut, modeling a straight segment is for simplicity. While the small intestine is anatomically tubular, the 2D model is advantageous in numerical simplicity and reduced computational expense. While, as previously discussed, this model has been developed as a building block for the more complex model discussed in Chapter 5, previous studies of peristaltic transport have shown that the fluid motions generated by 2D and axisymmetric geometries are qualitatively similar, and share the same parametric trends [e.g. 18,60,149]. Nevertheless, conclusions drawn from the results of the 2D models should be taken cautiously, as discussed in the appendix. Incorrect conclusions are possible without careful consideration of differences between 2D and 3D axisymmetric mixing motions and scalar transport.

Peristalsis is modeled as an infinite train of continuous sinusoidal waves propagating along the upper and lower walls from left to right with constant velocity (see Figure 3K1(a)). The actual peristaltic motions in the gut are less ideal, both in shape and temporal continuity. However, the objective is to capture the average characteristics of propagating contraction waves. The sinusoidal model is consistent with previously presented studies [16,18] (see Section 2.2), and is parameterized by true motility data extracted from the MRI experiments on the rat intestine (see Table 3K1).

Segmentation is modeled as a series of alternating 180° out-of-phase contractions. That is, as one particular segment contracts, the neighboring segments expand, and vice versa. This trend continues periodically in time. The time-changing geometry was constructed using straight piecewise sections for the contracting segments, and quarter sine waves connecting the straight sections for spatial continuity (see Figure 3K1(b)). As with
peristalsis, the actual segmenting contractile patterns present in the intestine are more complex. In particular, a minor backwards-forwards axial motion at the contracting segments has been observed that is not included in the geometry model under the assumption that the dominant mixing motions within the chyme are generated by the radial displacement of the lumenal surface. Our segmental model is otherwise qualitatively similar to the actual observed motions and to the simpler model presented by Macagno, et al. [11] and is parameterized using the values derived from the MRI data given in Table 3-1.

3.1.5 Code Validation

Significant effort has been put into validating and verifying our computational methods and applications. We conducted a thorough comparison of computational predictions with solutions derived from an analytical model of peristaltic transport using lubrication theory in the low Reynolds number limit [17]. Unfortunately, the quantitative results of these validation tests were lost in disk failure in our computer lab. However, Dr. Anupam Pal, a previous doctoral and post-doctoral student in our lab, also conducted a comprehensive validation study between the lattice-Boltzmann simulations and the lubrication-theory model of peristaltic transport. As described in his PhD thesis (add reference), Dr. Pal showed excellent correlation between lattice Boltzmann computational results, both in the velocity and pressure fields, and the analytical solutions from the lubrication model [17]. The largest deviation in any variable was that of pressure at the centerline, which only deviated a maximum of 5% from the analytical solution [142].

Perhaps more importantly, we recently published a book chapter that specifically describes the computational methods we have applied and validation of each component of
our lattice-Boltzmann model [145]. The publication specifically addressed the accuracy of the moving boundary conditions, the fixed (zero) scalar boundary condition, and the multiple-grid technology (see Section 3.2.1). We showed excellent agreement between comparison cases for all methods, both in the velocity and in the pressure fields [145]. In addition, we demonstrated the accuracy of the transition in velocity and pressure across multiple grids.

3.1.6 Numerical Experiments

In this part of the study, we investigate the possible strategic utilization of peristalsis and segmentation as a means of controlling the absorption processes. We hypothesize that the intestine can potentially utilize the two motility modes, either independently or in some combination, to optimize the absorption and transport processes. We define this optimization as a minimization of the time scale of scalar absorption through the walls and/or the time scale of axial transport along the length of the gut.

We use our numerical method to predict the fluid motions and associated nutrient (scalar) advection/diffusion in a series of experiments where the relative contributions of peristalsis and segmentation are systematically investigated. A series of nine numerical experiments are presented, across which the contribution ratio of percent segmental contribution to percent peristaltic contribution is varied between the two single-mode cases.

We applied three different initial conditions for scalar concentration as shown in Figure 3-2(a-c) for the 50:50 case: “blob,” “line,” and “inlet.” The “blob” case is an initially normalized 2D Gaussian distribution of scalar concentration with a spread of three standard deviations in the center of the computational domain. The “line” case uses a similar normalized 1D Gaussian radial distribution of scalar concentration, but set at the centerline.
The concentration at the centerline is held constant at $\phi = 1$ for the duration of the simulation. The line case evolves to a stationary state, in which the scalar concentration averaged over one period is independent of time. The “inlet” case uses the same initial 1D Gaussian axial distribution of scalar concentration as the line case, but is set vertically at the inlet. The concentration is held constant at $\phi = 1$ for the duration of the simulation. While the line case evolves to a stationary state that is periodically homogeneous in both spatial directions, the inlet case evolves to a stationary state in which the scalar concentration decreases in the axial direction, as would be expected in vivo where nutrients are passed from a previous section of gut. Once initially specified, the scalar concentration distributions are allowed to evolve temporally as prescribed by the fluid motions resulting from the modeled motility patterns.

To investigate the effects of motility on absorption, we quantify the flux of scalar through the epithelial surfaces. The flux can be integrated over the surface area (per unit depth for 2D) for each instant in time to determine the instantaneous absorption rate, which is a particularly useful measure for the cases in which a stationary state is reached. The total absorbed scalar at any point in time is found by integrating the absorption rate from the initial to current times. The total absorbed scalar is a useful measure for the blob case, where there is a finite number of nutrient molecules to be absorbed.

A measure of mixing effectiveness is the thickness of the UL (see Section 2.2). We use the method of Levitt et al. [e.g. 23] to calculate the average diffusion barrier resistance (per unit depth), $\overline{R_d}$, as given by:

$$
\overline{R_d} \equiv \frac{\phi_b - \phi_s}{\overline{J_d}},
$$

(3.10)
where $\bar{\phi}_b$ is the average concentration of scalar in the bulk flow (at the centerline), $\phi_s$ is the surface concentration (zero for our case), and $\bar{J}_d$ is the average absorption rate (per unit depth). The UL thickness, $d$, is related to the resistance as follows:

$$d \equiv R_d D_m$$  \hspace{1cm} (3.11)

The thickness, $d$, may also be thought of as an effective diffusion layer thickness. The average scalar concentration at the centerline is readily calculated and the surface concentration is specified as a boundary condition. The molecular diffusivity is also specified. Thus, this method depends only on measurement of the average absorption rate.

To determine the axial transport effectiveness, we compute the center of mass vector of the scalar concentration distribution as it evolves with time according to:

$$\mathbf{X}(t) = \frac{\sum_{i=1}^{N} \phi(\mathbf{x}_i, t) x_i}{\sum_{i=1}^{N} \phi(\mathbf{x}_i, t)},$$  \hspace{1cm} (3.12)

where $\mathbf{X}(t) = (X(t), Y(t))$. We define axial and transverse “scalar spread parameters” which are a measure of the stretching of the scalar concentration distribution, given by:

$$S_x^2(t) = \int_A \left[ x_i - X(t) \right]^2 \phi(\mathbf{x}_i, t) dA / \int_A \phi(\mathbf{x}_i, t) dA, \text{ and}$$  \hspace{1cm} (3.13)

$$S_y^2(t) = \int_A \left[ y_i - Y(t) \right]^2 \phi(\mathbf{x}_i, t) dA / \int_A \phi(\mathbf{x}_i, t) dA$$  \hspace{1cm} (3.14)

The Schmidt number, $Sc = \nu/D_m$, a measure of the relative diffusion rates of momentum to mass concentration, is required as input for the simulations to accurately represent the conditions in the real intestine. The Schmidt numbers for nutrient molecules in intestinal chyme are typically in the thousands. This translates to a relative lack of diffusive
smoothing of the nutrient concentration gradients during advection by the macro-scale motions.

To numerically capture the high concentration gradients at high Schmidt numbers, simulations require substantially more grid resolution than is necessary to capture the fluid motions themselves. In addition, because absorption is directly proportional to molecular diffusivity, $D_m$ (see Equation 3.16), the time scale for absorption increases with increasing Schmidt number, requiring longer simulation runtimes. These two effects cause a simulation using a realistic Schmidt number to require excessive computational expense. Therefore, one must determine a reasonable value of $Sc$ that is practical in terms of computational expense while maintaining transport physics representative of nutrient transport in the gut.

Figure 3K3(a) shows the total number of absorbed nutrient molecules, $N\phi$, versus time, $t$, for various $Sc$, for the blob initial condition with pure peristalsis. The time required for the entire initial number of molecules to be absorbed increases as $Sc$ increases, reflecting the proportionality between nutrient concentration flux at the surface and $D_m$ as evidenced in Equation 3.16. (In all the simulations of Fig. 3K3, $\nu$ is held fixed.) To more clearly understand the effect of $Sc$ on the simulated nutrient transport within the bulk flow, the direct influence of $D_m$ in molecular flux at the surface must be removed from the results of Figure 3K3(a). To do this, we scale total absorption, $N\phi$, appropriately.

Molecular diffusivity, $D_m$, influences nutrient transport in the bulk flow through the advection-diffusion equation, given in vector form as:

$$\frac{\partial \phi}{\partial t} + \mathbf{u} \cdot \nabla \phi = D_m \nabla^2 \phi . \quad (3.15)$$
At the boundaries, $D_m$, influences nutrient absorption directly through the scalar concentration flux, $J'_\phi$:

$$J'_\phi = D_m \frac{\partial \phi}{\partial n},$$  \hspace{1cm} (3.16)

where $n$ is the direction normal to the surface, and $s$ indicates that the scalar concentration gradient is taken at the surface.

To scale Equation 3.15, we introduce the following nondimensional variables, denoted by tildes:

$$\tilde{\phi} = \frac{\phi}{\Phi_0}, \hspace{0.5cm} \tilde{u} = \frac{u}{\omega}, \hspace{0.5cm} \tilde{\nabla} = \frac{\nabla}{a}, \hspace{0.5cm} \tilde{t} = \frac{t}{\tau_{adv}},$$  \hspace{1cm} (3.17)

where $\Phi_0$ is the initial average scalar concentration, $\omega$ is the characteristic velocity of contraction driving the flow, $a$ is the average radius of the gut (see Figure 3.1), and $\tau_{adv} = a / \omega$ is the advection time scale for advection in the bulk flow. The characteristic contraction velocity is either the wave speed for peristalsis, or the average collapse velocity (distance traveled by the center of the segment/period of collapse) for segmentation. Introducing the normalized variables in Equation 3.17 into Equation 3.15 and simplifying, we obtain:

$$\frac{\partial \tilde{\phi}}{\partial \tilde{t}} + \tilde{u} \cdot \tilde{\nabla} \tilde{\phi} = \frac{D_m}{\omega a} \tilde{\nabla}^2 \tilde{\phi},$$  \hspace{1cm} (3.18)

where the nondimensional group on the right-hand side of Equation 3.18, $\frac{D_m}{\omega a}$, is the inverse of the Péclet number, $\frac{1}{Pe}$. With only these characteristic velocity and time scales driving the dynamics, the transport of nutrients in the bulk flow is governed directly by a
single parameter, the Péclet number, $Pe$. For sufficiently large $Pe$, Equation 3.18 becomes independent of $Pe$ and the transport dynamics is governed purely by advection.

Indirectly, the Reynolds number also appears in Equation 3.18 through the velocity in the advective derivative. Therefore it is useful to rearrange $Pe$ in the following two ways:

$$Pe = \frac{\omega a}{D_m} = \left(\frac{\omega a}{\nu}\right) \left(\frac{\nu}{D_m}\right) = (Re)(Sc), \quad \text{and} \quad (3.19)$$

$$Pe = \frac{\omega a}{D_m} = \left(\frac{a^2}{D_m}\right) \left(\frac{\omega}{\nu}\right) = \frac{\tau_{\text{diff}}}{\tau_{\text{adv}}} \quad (3.20)$$

The $Pe$ is the product of Reynolds number $Re$ and $Sc$, as shown in Equation 3.19. Under the single length and velocity scale assumption, only $Re$ appears in the momentum equation as the governing nondimensional parameter, as shown below. Equation 3.20 shows that $Pe$ is the ratio of the timescales for diffusion and advection, where the diffusion time scale, $\tau_{\text{diff}} = a^2/D_m$, is the characteristic time for molecular diffusion from the bulk flow to the surface. The Reynolds numbers for gut transport are $\sim O(1)$ ($Re \leq 4$ for our simulations). Thus, Equations 3.19 and 3.20 show that with the high $Sc$ in gut transport, the appropriate time scale upon which to scale the equations is the advection time scale.

As mentioned, the $Re$ is obtained through nondimensionalization of the Navier-Stokes equation:

$$\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\frac{1}{\rho} \nabla P + \nu \nabla^2 \mathbf{u}.$$

(3.21)

Using the nondimensional variables in Equation 3.18, normalizing pressure for a friction-driven flow:
\[ \tilde{p} = \frac{p}{\rho v \omega / a}, \]  
(3.22)

and simplifying, Equation 3.21 becomes:

\[ \left( \frac{\alpha \nu}{\nu} \right) \left( \frac{\partial \tilde{u}}{\partial t} + \tilde{u} \cdot \nabla \tilde{u} \right) = -\nabla \tilde{P} + \nabla^2 \tilde{u}, \]  
(3.23)

where the nondimensional group on the left-hand side of Equation 3.23 is \( Re \), which is a ratio of the inertial effects to the diffusive effects in the flow. For our simulations the Reynolds number remains moderately low: \( Re \leq 4 \). Therefore, inertial effects are relatively weak. We have observed no suggestion of boundary layer type behavior or separation in our simulations, and only mild inertia-induced asymmetry. We therefore argue that \( Re \) is sufficiently low that there is not a strong separate Reynolds number effect in the advection-diffusion dynamics in the gut described by Equation 3.18. Thus \( Pe \) is the dominant influence in the bulk transport of nutrient concentrations. \( Pe \) varies through a combination of \( Sc \) and \( Re \), within the lower \( Re \) range of our simulations.

Consider now the direct influence of \( Sc \) at the absorbing surfaces. Figure 3-3(a) shows total absorption through the boundary, \( N_\phi \), by integrating the absorption boundary condition equation (Equation 3.16) over space and time as follows:

\[ N_\phi = \int_{A_0} \int_{D_m} \left. \frac{\partial \phi}{\partial n} \right|_{n=0} dt dA. \]  
(3.24)

where \( A \) is the absorptive area. Using the nondimensional variables in Equation 3.18, and introducing more nondimensional variables as follows:

\[ \tilde{n} = \frac{n}{a}, \quad \tilde{A} = \frac{A}{\lambda} \]  
(3.25)

and simplifying, Equation 3.24 becomes:
\[
N_\phi = \left( \frac{\Phi_0 D_m \lambda}{\omega} \right) \left( \int_0^T \frac{\partial \tilde{\phi}}{\partial n} \right) d\tilde{t} d\tilde{A}.
\]

The variable group, \( N^* = \frac{\Phi_0 D_m \lambda}{\omega} \), is therefore the proper characteristic scale for \( N_\phi \) to remove the influence of \( D_m \) and to discern the influence of \( Sc \) on the bulk flow simulations.

Scaling \( N_\phi \) by \( N^* \) and \( t \) by \( \tau_{adv} \), the data in Figure 3-3(a) becomes Figure 3-3(b). In Figure 3-3(b), the total molecules absorbed becomes independent of \( Sc \) as \( Sc \) increases. Ideally, we would have liked to use a \( Sc \sim 100 \) or greater, to be near the collapsed curves in Fig. 3-3(b). However, we were limited by practical concerns. Given the computational expense and the number of the wide range of computational experiments we planned, we were limited to \( Sc=50 \). Although Figure 3-3(b) shows that \( Sc=50 \) produces a more similar curve to the higher \( Sc \) cases than to the lower \( Sc \) cases, a higher \( Sc \) would have been more desirable, and we must note that our simulations have more of an influence from diffusion than is likely the case in the real gut.

3.1.7 Results

By systematically varying the relative contributions of peristalsis and segmentation in linear weighted combinations, several interesting phenomena emerge. In Figure 3-4(a), total absorbed scalar is plotted as a function of time (number of macro-scale motility periods) for each of the nine cases for the blob case. We find that the absorption process occurs in two distinct time phases. The initial phase (Phase I) for each case is sensitive to the degree of the segmental component present for each case, and is characterized by a period of relatively high absorption rate. Figure 3-4(b) shows the initial phase more clearly. Both the absorption
effectiveness, quantified as the amount of total scalar absorbed, and the length of time that
Phase I lasts increase with increasing relative contribution of segmentation. That is, pure
peristalsis is least effective in absorption, while pure segmentation is most effective. The
mixed modes then vary systematically between the two pure cases.

The second phase is marked by a shift each curve with a non-zero peristaltic
component toward the pure peristaltic case. For example, for the 87.5%:12.5%
(segmentation:peristalsis) case (see Figure 3-4(b)), the transition from the first phase to the
second phase occurs at about four periods. The second phase is characterized by relatively
lower absorption rates, and lasts for the remainder of the absorption process. The time scale
for which a particular case shifts toward the purely peristaltic case increases with decreasing
peristaltic component, yet even with only 5% peristalsis (95% segmentation), this transition
still occurs (at roughly seven periods). Only pure segmentation does not shift toward pure
peristalsis. This suggests that pure segmentation is the most effective means of promoting
the absorption of nutrients through the intestinal surface, and that any peristaltic component
interferes with this maximum effectiveness.

The maximum (average) absorption rate (normalized) versus percent peristalsis is
plotted in Figure 3-5 for the blob and line cases. The inlet case is omitted due to spurious
effects from a lack of transport in cases with high segmental contributions (discussed in
more detail later in this section). The percent peristalsis ranges from zero (pure
segmentation) to one (pure peristalsis). The maximum absorption rate results from the pure
segmentation case for both the blob and line initial conditions. The absorption rate quickly
drops with any addition of peristalsis, supporting the results for total absorbed scalar
described in the previous paragraph. The disparity in values between the blob and line cases is due to the different amounts of total scalar (nutrient molecules) present in the domain.

UL thicknesses for all three initial conditions are shown in Figure 3-6 as a function of peristaltic contribution. The minimum UL thickness (maximum degree of mixing) results from the pure segmentation case for all three initial conditions. The UL thickness rises quickly with any addition of peristalsis. This result demonstrates that pure segmentation case provides the best mixing characteristics, as well as the best absorption characteristics (as shown in Figures 3-4 and 3-6). As in the absorption rate result, the disparity in UL thicknesses among the different initial condition cases is due to the different amounts of scalar inherent with the different cases.

Figure 3-7 shows the axial component of center of mass vector of scalar concentration, given by Equation 3.12, as a function of the number of periods of contraction for the blob case. The plot quantifies the relative effectiveness of axial transport of scalar concentration for the different types of motility. We find that the concentration distribution with pure peristalsis case has propagated farthest in the axial direction. This is consistent with the role of peristalsis as a pumping mechanism. With increasing segmental contribution, this propagation distance is reduced. Pure segmentation, as modeled, produces no net transport component since it is a series of standing contractions.

These aforementioned results suggest a tradeoff between the intestinal functions of nutrient absorption (requiring radial transport) and bulk axial transport. To better understand this tradeoff, we analyze the axial and transverse components of the scalar spread parameter as a function of time. In Figure 3-8(a), the transverse component of the spread parameter is shown for pure segmentation and peristalsis and the 50:50 case. Overall,
pure segmentation produces the highest spread in the transverse direction, and pure peristalsis produces the lowest. This suggests that the concentration is stretched in the transverse direction more by segmentation than by peristalsis. In Figure 3-8(b), the corresponding axial component is shown for the same cases. In contrast to the transverse direction, pure peristalsis produces the highest axial spread, and pure segmentation produces the lowest, indicating that the scalar concentration distribution is stretched more in the axial direction by peristalsis than by segmentation.

The spread parameter analysis points to the cause of the tradeoff between absorption and transport. With diffusive effects playing a limited role, the scalar concentration distribution is largely attached to the fluid. That is, in the limit of zero diffusion, the scalar concentration is carried purely by the movement of the fluid particles and cannot move across streamlines. For two-dimensional, incompressible flows, the conservation of mass principle dictates that for a change in one component of the velocity in its own direction, there must be a corresponding equal but opposite change in the perpendicular component in its respective direction. Thus, if the concentration of scalar is spread in one direction, it must be condensed in the other direction. Peristalsis not only transports the scalar axially, but stretches it in the axial direction as well, causing a corresponding reduction in the transverse spread an inhibition of nutrient transport and absorption. Segmental motility is therefore necessary to compensate for the apparent inhibition of radial transport by peristalsis.

3.1.7 Discussion

The primary functions of the small intestine are the absorption of nutrients from the bulk intestinal flow, and the transport of the material axially along its length for eventual
evacuation. These roles are accomplished by the two intestinal wall contractile motility patterns, segmentation and peristalsis. The two modes are distinctly different, both in geometrical description and physiological function. Peristalsis has been well studied and described in previous studies as a pumping mechanism used in the body as well as in various mechanical systems applications [e.g. 16-18]. It is characterized by its propagatory nature. Segmentation, conversely, is an essentially stationary pattern. It has been attributed to mixing, and fluid exchange between the bulk flow and the near flow regions [10,11,150].

Previously presented intestinal models rely solely on fluid motion calculations, without nutrient absorptions models, to make the assertions that deformations of the walls affect mixing, transport, and/or absorption in the gut [11,13,14,16] (see Section 2.2). By including a model for scalar advection/diffusion and absorption our model, we can draw more applicable, physiological conclusions pertaining to the relative impacts of both motility modes on the absorption process.

As discussed in the Section 3.1.6, and supported by Figures 3K8(a,b), there is a tradeoff between the effectiveness of absorption/mixing and the effectiveness of axial transport in the small intestine. Peristalsis, while an effective means of transporting fluid along the length of the gut, also stretches the nutrient concentration distribution in the axial direction in the processes. This axial stretching requires a corresponding compression of the transverse spread of the nutrient concentration distribution, inhibiting the absorption process. Our 2D results suggest that segmentation is more effective than peristalsis for absorption and mixing than (see Figures 3-4 through 3-6), but at the expense axial transport (see Figure 3-7). For mixtures of the two modes, we find here that any non-zero peristaltic component causes a significant degradation in the absorption and mixing effectiveness.
relative to the case of pure segmentation. However, as discussed in more detail in the appendix, the dynamics of the actual gut are more complex than the 2D model captures. Upon extending the 2D model to 3D, we find the case to be less simplistic, with peristalsis being as or even more effective than segmentation for absorption under certain conditions.

The results of our 2D simulations suggest that it may be possible for the gut to utilize the motility modes to control the absorption and axial transport processes. Evidence of such active control of gut function by motility utilization exists upon consideration of the times during which these two modes are generally active. Peristalsis is often observed after a meal of non-caloric content, while segmentation is the dominant contractile pattern observed after a nutrient-containing caloric meal [e.g. 4,6-7]. This suggests that the gut has enteric responses to the content of the chyme, and may deploy motility modes as needed to accomplish the necessary functions. For a non-caloric meal, the absorption process is unnecessary and peristalsis is utilized to evacuate the content from the gut. For a caloric meal, segmentation is utilized to promote absorption of the present nutrients [e.g. 7].

For any normal caloric meal, both modes of motility are necessary. The lack of a significant propagatory component in the pure segmentation case requires peristalsis to be present in some respect to transport the chyme axially for additional epithelial exposure and eventual evacuation. This suggests that to optimally utilize the two modes, interference should be minimized.

Some observations of actual gut motility indicate that this optimal this minimal interference hypothesis. In our companion MRI study of the rat intestine (see Section 3.1.3), segmentation was the primarily observed contractile pattern with caloric meals [55]. Peristalsis, was much rarer despite extensive searching. In over 50 collected datasets of eight
separate animals, peristalsis was only captured twice. This phenomenon may be explained by a reduction in peristalsis from the administered anesthesia [151,152]. It is also possible that peristalsis is simply utilized less frequently under the experimental conditions (caloric meal), allowing segmentation to maximize the effectiveness of absorption without interference from peristaltic patterns for most of the digestive process. If this assertion is true, peristalsis would optimally be utilized intermittently to transport the content axially to further locations. After such a transport event, segmentation would resume, with the process repeating until the available nutrients have been absorbed.

Although these results provide preliminary insight on gut function at the macroscopic level, we note that this model is simplified and has not been fully analyzed. The difference in qualitative information provided between the 2D and axisymmetric cases was assumed to be minimal [18,149], however, the corresponding 3D model discussed in Section 4.1 produced significantly different results in many respects (see Appendix A for a reflection of our use of 2D models in analysis of the gut).

### 3.2 Multi-Scale 2D Cavity Flow Villous Motility Model

The development of this model and the corresponding simulations were conducted by Dr. Yanxing Wang, a postdoctoral researcher in our group. While the design of the model and the numerical experiments, analysis of the results, and conclusions were drawn a team, we wish to make it explicitly clear that this work, most notably the technological advances in modeling, was carried out by Dr. Wang [163]. It is discussed here because of its importance and relevance to this research as a whole, especially its integral part in the full combined computational model (see Chapter 5).
To gain insight into the potential effects of villous motility on absorption and mixing in the gut, we developed the multi-scale lid-driven cavity flow model shown in Figure 3-11 to investigate macro-micro interactions between a macro-scale eddy generated by the moving lid and micro-scale fluid motions generated by 2D “villi” lining the lower surface of the cavity. A qualitative description of the model is given in this section. We hypothesize that the movement of villi will substantially increase absorption as compared to the case of stationary villi, and that parametric variations of villous motility will significantly affect absorption. Intuitively, as villous height or oscillation frequency increase, so should absorption rate since increasing the height increases the absorptive surface area and increasing the frequency should increase advective transport in the diffusion layer (the UL) near the absorptive surfaces and enhance transport of nutrients from the bulk flow to the surface. In the coming sections, the details of the model, numerical experiments, and associated results are presented. The section concludes with a discussion of the preliminary physiological implications suggested by the results of the simulations.

3.2.1 The Numerical Method

The numerical methods used in the villi model are largely the same as those used in the macro-scale intestinal model (see Section 3.1.1) with the added application of multiple computational grids of different resolutions and minor variations of the boundary conditions. The LBM (see Section 2.5) was used to predict the fluid flow generated by the moving cavity lid and the villous motility [e.g. 100]. The modified moment propagation method was applied within the LBM framework to predict the evolution of the passive scalar concentration field to simulate nutrient transport and absorption [121]. The multiple-grid
strategy was implemented to locally increase the resolution in the near-villi region without over-resolving the bulk flow elsewhere, reducing computational expense and memory requirements.

**Multiple-grid Strategy.** We employ the multiple-grid strategy for LBM of Yu et al. [135]. Here we describe the application of two grids, one coarse grid and one fine grid, as an example of the approach. Each sub-grid is uniform, the shape, location, and resolution of which is chosen according to the requirements of the local flow structure. At the interface of neighboring sub-grids, an overlap of one coarse-grid spacing, two rows of coarse grid nodes, is used.

To ensure consistent lattice viscosity and basic lattice speed across the entire domain (ensuring a consistent $Re$), the fine grid relaxation parameter must satisfy the following relation (found by equating $\nu = c\delta x(2\tau - 1)/6$ for the two grids):

$$\tau_f = \frac{1}{2} + m \left( \frac{\tau_c - \frac{1}{2}}{2} \right),$$

(3.27)

where $m = \delta x_c / \delta x_f$ is the ratio of the lattice spacings. To conserve mass and momentum, and maintain continuity in continuum level density, velocity, and deviatory stresses at the interface, it the following equations are used to transfer information between grids [135]:

$$\hat{f}_i^c = f_i^{eq,f} + m \frac{\tau_c - 1}{\tau_f - 1} \left( \hat{f}_i^f - f_i^{eq,f} \right),$$

(3.28)

$$\hat{f}_i^f = f_i^{eq,c} + \frac{\tau_f - 1}{m(\tau_c - 1)} \left( \hat{f}_i^c - f_i^{eq,c} \right),$$

(3.29)
where $\hat{f}_i$ denotes the post-collision distribution function. As is apparent in Equations 3.28 and 3.29, care must be taken to avoid values close to one for the relaxation parameters, $\tau_c$ and $\tau_f$, as a singularity occur, causing numerical instability.

Figure 3-9 shows a typical interface between two grids. The overlap is such that each of the two overlapping rows of coarse grid nodes coincides with a fine grid node. However, there are $m-1$ “hanging” fine grid nodes in the outermost row of the fine grid, so spatial interpolation of the known coarse grid post-collision distribution functions to the hanging fine grid nodes is required. Temporal interpolation at each of the outermost fine grid boundary nodes is also required because a constant basic lattice speed across the entire domain requires $m$ sub-time-steps on fine grid for each full time step on the coarse grid.

The algorithmic procedure is illustrated in Figure 3-10. Streaming of post-collision distribution functions is carried out on the coarse grid, meaning that the overlapping nodes of both grids have updated distribution functions at the new (coarse grid) time step. These values are then used to spatially interpolate new values to the hanging nodes on the fine grid. However, because the fine grid sub-time-steps occur between each full time step, the updated distribution functions streamed from the coarse grid are actually from the future and must be used in combination with the current distribution functions to interpolate the distribution functions at each of the fine grid boundary nodes, for each of the $m$ fine grid sub-time steps. These interpolated values are used as boundary conditions for $m$ LBM time steps on the fine grid. Upon completion of the collision step of the $m^{th}$ sub-time step, the post-collision distribution functions at the overlapping nodes of both grids are streamed on the coarse grid and the method is repeated for the next full time step.
We developed a generalization of the multiple-grid algorithm for the passive scalar concentration field into the multiple-grid scheme required the development of such. The modified moment propagation method, as described in Section 3.1.1, is only valid for a single-grid system. Merks, et al. [121] show that the molecular diffusivity on a single grid is given by $D_m = (1 - \Delta^*) / 6$, where $\Delta^*$ is the proportion of scalar remaining on each lattice node after streaming. Warren [154] reported that $D_m = c_x^2 (1 - \Delta^*) / 2$. Comparing the two equations, it is clear that they are equivalent since $c_x = 1 / \sqrt{3}$. Both expressions implicitly contain the choice that $c = \delta x = \delta t = 1$. Substituting this more general information, the first expression for diffusivity becomes:

$$D_m = c \delta x (1 - \Delta^*) / 6,$$

which is analogous to the expression for the lattice kinematic viscosity. Requiring continuity in diffusivity and basic lattice speed, the parameter, $\Delta^*$, must be modified on the fine grid as follows:

$$\Delta_f^* = 1 - m \left( 1 - \Delta_c^* \right),$$

With this modification, the scalar concentration can be calculated during each streaming step on both the fine and coarse grids according to Equation 3.6. When the scalar concentration information is transferred from the coarse grid to the fine grid, spatial and temporal interpolations are needed at the fine grid boundary of both scalar concentration and the distribution function.
3.2.2 Boundary Conditions

**Fluid Boundary Conditions.** To specify the no-slip condition, we employ the standard bounce-back scheme to the stationary walls of the domain, the left and right sides, and in between the moving villi on the lower surface of the domain (see Figure 3-11). The walls are placed half-way in between rows of nodes to maintain second order accuracy [111]. Since the upper lid moves, driving the bulk flow, momentum must be transferred from the lid to the fluid. The lid is also placed half-way between two rows, and moves parallel to the rows, so we apply a simple extension given by Ladd [112] to the standard bounce-back scheme. The villi, however, move such that their surfaces can lie in arbitrary locations relative to the computational nodes that make up the lattice. Thus, on the villous surfaces, we apply the same method as is used for the macro-scale intestinal model for the complex moving boundaries, the interpolated version of Ladd’s method, given by Lallemand and Luo [114] (see Section 3.1.2).

**Scalar Concentration Boundary Conditions.** As described in Section 3.1.2 for the macro-scale intestinal model, we specify a zero-scalar concentration condition along and in between the villi to model rapid nutrient absorption at the lumenal surface. At all other surfaces we apply zero-flux boundary conditions. Merks *et al.* [121] indirectly points out that a bounce-back scheme analogous to the standard bounce-back of the distribution functions can be used to implement a zero-scalar-flux boundary condition. We apply this method where non-absorptive walls are present.
3.2.3 The Geometry Model: A Lid-driven Cavity Flow with 2D “Villi”

The geometry model specified for the micro-scale villous motility model is illustrated in Figures 3-11(a,b). The domain is 2D and rectangular, with dimensions consistent with the lower half of a single wavelength as observed in the rat gut. The upper lid moves with constant velocity from left to right, driving a clockwise macro-scale eddy within the cavity to roughly emulate an eddy generated by peristaltic motility [17].

The villi are modeled as rectangular protrusions with rounded tips located along the bottom wall as shown in Figures 3.11(a,b) and have dimensions typical of what is reported in the literature for the rat (see Section 2.4). Rat villi are sometimes of the “leaf-like” variety, thin and wider than they are high (see Figure 1-6). While the geometry of the real gut is inherently 3D and complex, the 2D representation effectively creates geometry that representative of the basic characteristics of the leaf-like villi of the rat.

Womack et al. [3] states that leaf-like villi are restricted in their motility as compared with finger-like villi. Whereas finger-like villi have been observed to exert contractile pumping motions, side-to-side whipping or pendular motions, and tonic contractions, in which several or all villi move together, observations of leaf-like villi have been limited to the latter two motions. Therefore, we model the villous motility as an oscillatory side-to-side motion, in either a single group or multiple smaller 180° out-of-phase counter-rotating groups (see Figure 3.11).

3.2.4 Numerical Experiments

In all numerical experiments, an initial band of scalar concentration ($\phi = 1$) was placed at the upper boundary, with the lid held fixed at $\phi = 1$ for the duration of the
simulations (see Figure 3.11(a)). The moving (left to right) upper lid drives the flow in a circulatory motion such that the nutrients are advected downward over the villi on the lower surface of the cavity (also shown in Figure 3-11(a)). The 2D nature of the model restricts the flow relative to the 3D flow that occurs around real villi. The model therefore likely underestimates absorption over the sides of the villi enhanced by villi-induced advective motions. On the other hand, the infinite lateral extent of the 2D “villi” will likely create stronger 2D advective motions than would 3D finger-like villi moving in the longitudinal plane. This 2D cavity flow model provides the first basic insights into the physics by which villous motion could create a micro-scale mixing layer and thereby alter absorption at the epithelial surface in a controlled manner.

**Villous Height.** The effect of villous height on absorption rate was investigated by varying the height of the villi over a range of anatomically relevant values. Five simulations are performed: 200µm, 300µm, 400µm, 500µm, and a control case with no villi are present (0µm). The other simulation parameters are held constant to isolate the role of the villous height. The frequency ratio (the ratio of villous frequency to bulk lid-driven circulation frequency, \(f_v/f_L\)) is held constant at \(f_v/f_L = 10\). The villi are grouped in four groups, each containing five villi. The groups oscillate with identical frequency ratio, but neighboring groups counter-oscillate 180° out-of-phase.

**Oscillation Frequency.** The effect of villous oscillation frequency was investigated by varying frequency ratio, \(f_v/f_L\). The villous oscillation frequency was non-dimensionalized by the macro-scale eddy frequency as a measure of macro-micro time scale disparity. Very little information exists on the details of \textit{in vivo} villous motility. All \textit{ex vivo} observations have been made using highly invasive procedures mostly on dog models. Therefore, we are left to
speculate the range of physiological villous frequencies existent in the real gut. Eleven simulations were carried out, ranging from the control case lower limit of zero frequency ratio (stationary villi) to the highest frequency ratio of $f_v/f_L = 20$, in increments of two. The other simulation parameters were again held constant to isolate the effect of oscillation frequency. The villous height is $l_v = 300\mu m$. The grouping of the villi was identical to villous height experiment (four groupings of counter-oscillating villi).

**Villous Grouping.** We investigate the effect of grouping villi together in different numbers. That is, we investigate groups of 2, 5, 11, and 23 villi (23 being a single group) that oscillate 180° out-of-phase with neighboring groups. Figure 3-11 illustrates the manner in which the groups of villi counter-oscillate for four groups of five villi. The frequency ratio was held constant at $f_v/f_L = 20$, and the villous height was held constant at $l_v = 300\mu m$.

### 3.2.5 Results

**Villous Height.** Figure 3-12 shows the effect of villous height on the absorption rate. The time-averaged absorption rate is plotted versus villous height for each of the villous height simulations. The absorption rate increases with villous height, in an increasing manner. That is, each increase in villous height causes an increasingly higher enhancement of the absorption rate. Although the temporally averaged absorption rate is plotted in Figure 3-12, the absorption rate is oscillatory. This is likely associated with the sweeping of the highest concentration fluid over the villous tips.

**Oscillation Frequency.** Figure 3-13 shows the effect of oscillation frequency on the absorption rate. The time-averaged absorption rate is plotted versus frequency ratio for each oscillation frequency. Increasing the oscillation frequency monotonically increased the
absorption rate. Each increase in frequency ratio had an increasingly larger impact on the absorption rate.

**Villous Grouping.** Figures 3-14(a,b) show streamlines generated in two simulations: Figure 3-14(a) shows four groups of counter-oscillating 180° out-of-phase, and Figure 3-14(b) shows those generated by a single group of villi in which all villi oscillate in unison. When the villi are grouped into counter-oscillating groups, a net pumping effect is generated. This is evidenced by the nearly vertical streamlines that extend out into the macro-scale flow (see Figure 3-14(a)). This pumping effect is absent when the villi are arranging in a single group in which the villi oscillate in unison. Figure 3-14(c) shows the absorption rate versus time (normalized by the lid-driven eddy period) for each of the groupings, including the no-villi case. The absorption rate increases with the number of groups. Presumably, this is due to the pumping effect seen in Figure 3-14(a). With more groups of villi, there are more instances of this type of pumping.

**Other Results.** In Figure 3-15, we examine the effect of the surface area alone. There is very little increase in absorption rate with the addition of stationary villi ($l_v = 300\mu m$). This seems to contradict the standard explanation that the existence of villi is primarily to increase absorption by increasing the absorptive surface area. While it is true that the villi do increase the surface area of the gut substantially as compared to a case where no villi exist (by a factor of 10 in the human, 5 in the rat), our 2D results do not support this explanation. The reason for this contradiction is that absorption on the sides of the villi is a relatively small percentage of total absorption since advective effects are restricted there and the primary increases in absorption rate occur at the villous tips. Three dimensionality will
reduce the differentials in absorption over the villous surface while increased packing will enhance these differences.

Evidence of the potential role of villi as micro-mixers is illustrated in Figures 3-16(a,b). Figure 3-16(a) shows isocontours of the magnitude of the vertical component of velocity. The regions of high velocity are shown in red, the low regions in blue. The highest velocity magnitudes occur in the gaps between villous groups, due to the in-and-out pumping effect occurring between two oppositely moving villi. These ejections help transport the nutrients toward the surface, and their oscillatory nature agitates the local fluid, causing mixing. This can be measured quantitatively by measuring the magnitude of the oscillation velocity across the domain. Figure 3-16(b) shows this measurement as a function of vertical distance from the bottom surface. There is a substantial oscillation in the velocity generated just above the villi. We call this phenomenon a “micro-mixing layer (MML)”.

Further evidence of the MML is illustrated in Figures 3-17(a,b). Figure 3-17(a) shows streamlines based on a velocity field averaged over one period of micro-scale motion. In analyzing the averaged velocity field, one can appreciate the net effect of the villous oscillations. The eddies that exist just to the left of the gaps between the villous groups in Figure 3-17(a) rotate in a counter-clockwise direction. This indicates that, on average, there is a net movement of fluid upward out of the gaps. Figure 3-17(b) shows pathlines for three fluid particles over several micro-scale villous motility periods. The pathlines show the same net upward trajectory of the fluid. Fluid particles are advected upward by the ejection effect generated by the counter-oscillating groups of villi. The particles are carried from the low-concentration fluid in the gaps to the interface between the macro- and micro-scale flows,
where they pick up more scalar from the more highly-concentrated fluid outside the MML (by diffusion induced by high scalar concentration gradients) before being advected back downward toward the absorptive walls. This phenomenon turns out to be an important mechanism for enhancing absorption and is discussed in much more detail by Wang et al. [163].

3.2.6 Discussion

Using a simplified, 2D villous motility model of pendular movement, we developed preliminary insight useful for designing the more complex, physiologically relevant macro-micro models discussed in Chapters 4 and 5. With the 2D model, we confirm that the modeled villous motion increases the nutrient (scalar) absorption rate. The rate of absorption increased both with villous height and frequency of villous oscillation. Both factors were shown to have an increasingly larger effect as the parameters increased.

The grouping of the villi (the number of villous groups) has an important impact on the absorption rate. More counter-oscillating 180° out-of-phase groups produce more net ejections between neighboring groups, enhancing the strength of the MML and increasing the absorption rate. This result may be consistent with the observations of Womack et al. [93] in which villi are observed to move more individually rather than in large groups in unison.

Interestingly, in comparing the case of stationary villi to the case of no villi, the absorption rate did not vary significantly. This seems to contradict the standard explanation for the existence of the villi as a means of increasing absorptive surface area. While the villi
do increase the surface area substantially [e.g. 1,2], the simplified model shows that this increase has little affect on the absorption rate.

We showed that a micro-mixing layer was formed by the villous motion at the tips of the villi. These results seem to suggest that the villi may have a function role as local mixers that reduce the UL and increase the rate of absorption. We find that the micro-mixing layer is a complex, but important potential mechanism for enhancing absorption and reducing the UL thickness. A much more complete discussion of the formation and implications of the MML is presented in Wang et al. [163].

We stress the concession that the 2D model may be limited in its representation of true in vivo villous motility. The lack of in vivo motility data limits the study to speculative villous motions. The model, however, is the first such study of any such potential in vivo villous motility, and provides insight that cannot be currently attained using experimental methods. We have gained useful insight that we explore further with our more complex, 3D, multi-scale models discussed in Chapters 4 and 5.
Figures 3-1: The geometry used for the macro-scale intestinal motility model: (a) the sinusoidal peristalsis model, (b) the alternating segmentation model. The black, blue, and red geometries represent t=0, t=0.25 periods, and t=0.5 periods respectively. The geometry is periodic in both space (axial direction) and time.
Figure 3-2: Three initial condition/boundary conditions used on passive scalar (nutrient) concentration shown for the equally weighted 50% peristalsis-50% segmentation case: (a) “blob”, (b) “inlet”, and (c) “line”. The colored isocontour represents scalar concentration: red indicates high values; blue indicates low values.
Figure 3.3(a): Total absorbed scalar versus number of time for systematically varied $Sc$ for the “blob” case (pure peristalsis). Note: See the following page for Figure 3.3(b).
Figure 3.3(b): Total absorbed scalar (scaled by $N^*$) versus time (scaled by $\tau_{adv}$) for systematically varied $Sc$ for the “blob” case (pure peristalsis).
Figure 3-4(a): Total absorbed scalar (normalized by total initial amount of scalar) as a function of macro-scale period (time normalized by contraction period) for nine motility mode combinations for the “blob” case. Note: See the following page for Figure 3-4(b).
Figure 3.4(b): Zoomed in view of Periods 0-8 showing the transition between Phase I and Phase II of absorption for the 87.5% Segmentation, 12.5% Peristalsis motility mix for the “blob” case. The transition occurs at roughly four periods.
Figure 3-5: Maximum average absorption rate (normalized) versus percent peristaltic contribution for the “blob” (blue) and “line” (red) cases.
Figure 3-6: UL (diffusion barrier) thickness versus percent peristaltic contribution for the “blob” (blue), “line” (red), and “inlet” (green) cases.
Figure 3-7: Axial component center of mass versus time (number of macro-scale motility periods) for nine motility mode combinations for the “blob” case.
Figure 3-8(a): Transverse component of “scalar spread parameter” versus time (number of macro-scale motility periods) for pure segmentation (red), pure peristalsis (blue) and an equally weighted 50%/50% mix of both (black) for the “blob” case. Note: See the following page for Figure 3-8(b).
Figure 3.8(b): Axial component of “scalar spread parameter” versus time (number of macro-scale motility periods) for pure segmentation (red), pure peristalsis (blue) and an equally weighted 50%/50% mix of both (black) for the “blob” case.
Figure 3-9: A typical multiple-grid lattice with overlapping coarse (top) and fine grids (bottom). The white circles denote coincident nodes that lay both on the coarse and fine grids. The black circles are “hanging nodes” (fine grid nodes that lie in between coarse grid nodes). Source: [135].
Figure 3-10: Flow chart of multiple-grid scheme. Source: [123] (modified from the original)
Figure 3-11: Computational setup for the 2D villous motility model: lid-driven cavity flow with “villi” lining the lower surface. (a): The initial distribution of scalar concentration (red band at the top of cavity). The blue arrow indicates the direction of lid motion. The white curved arrow represents the macro-scale eddy generated by the lid-driven flow. (b): The multiple-grid setup as applied to 2D villous motility model. The red grid is the coarse grid; the green grid is the fine grid. Source: Dr. Yanxing Wang (modified from the originals).
Figures 3-12: Absorption rate versus villous length (height). Frequency ratio is held constant at $f_v/f_L = 10$ for all cases. Source: Dr. Yanxing Wang.
Figure 3-13: Absorption rate versus frequency ratio. The height of the villi was held at \( l_v = 300 \, \mu m \) for all cases. Source: Yanxing Wang.
Figure 3-14: The effect of villous grouping on absorption rate. (a): Streamlines generated by four groups of five villi oscillating 180° out-of-phase. (b): Streamlines generated by one group of 23 villi oscillating in unison. (c): Absorption rate versus time (number of lid-driven circulation periods) for five grouping cases. The villous height and frequency ratio were held constant at $l_v = 300\mu m$, and $f_v/f_L = 10$ respectively for all cases. Source: Dr. Yanxing Wang.
Figure 3.15: Absorption rate versus time (number of lid-driven circulation periods) is plotted for two cases: fixed villi with no oscillation (red) and pure cavity flow with no villi (blue).

Source: Dr. Yanxing Wang.
Figure 3-16: Evidence of a “micro-mixing layer” (MML). (a): Isocontours of the magnitude of the vertical component of the “oscillation velocity”. (b): The magnitude of the vertical component of the oscillation velocity along lines 1 (red) and 2 (blue) as marked in white in Figure 3-17(a). Source: Dr. Yanxing Wang.
Figure 3-17: Further evidence of the micro-mixing layer (MML). (a): Streamlines averaged over one period of micro-scale villous motion. (b): Pathlines of three fluid particles over several periods of micro-scale villous motion. The isocontours represent scalar concentration (red is high concentration; blue is low concentration). Source: [163]
Figure 3-18: Spatio-temporal maps of (a): peristalsis, and (b): segmentation. Analysis conducted on MRI acquired during our companion study of motility in the rat intestine.

Source: Dr. Amit Ailiani.
Table 3.1: Motility parameters for segmentation and peristalsis. The first column under each motility pattern contains the values obtained from analysis of the MRI images; the second column contains the values that were used as input into the computational model simulations. Source (for the values extracted from the MRI imaging): Dr. Amit Ailiani.

<table>
<thead>
<tr>
<th></th>
<th>Segmentation</th>
<th>Peristalsis</th>
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<tbody>
<tr>
<td></td>
<td>MRI</td>
<td>Mode</td>
</tr>
<tr>
<td>Wavelength (mm)</td>
<td>9.08 ± 2.74</td>
<td>10.0</td>
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<tr>
<td>Period of Contraction (s)</td>
<td>3.14 ± 0.14</td>
<td>2.50</td>
</tr>
<tr>
<td>Wave Propagation Speed (mm/s)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Nominal Diameter (mm)</td>
<td>4.60 ± 1.35</td>
<td>5.00</td>
</tr>
<tr>
<td>Occlusion Ratio (ε/a)</td>
<td>0.64 ± 0.16</td>
<td>0.50</td>
</tr>
</tbody>
</table>
CHAPTER 4: THREE-DIMENSIONAL INTESTINAL MODEL SIMULATIONS

In the process of combining the two simpler 2D models discussed in Chapter 3 into the more complex multi-scale model of the macroscopically deforming intestine with moving villi on the surface discussed in Chapter 5, it was necessary to extend the technology to three-dimensions. With this extension came the need to parallelize the computer codes such that they could be run on distributed computing systems as discussed in more detail in Section 4.1.1.

Upon completion of the 3D versions of the simpler 2D models discussed in Chapter 3, it was useful to conduct similar studies as were completed with the 2D results, both to validate the models, and compare with the 2D results. With the reduced computational expense inherent without the inclusion of both macro-scale and micro-scale motility in the same model, we are also able to use the 3D independent models to understand more about the fluid dynamics of the macro- and micro-scale flows separately. Our findings with the 3D models are discussed in the coming sections.

4.1 Macro-Scale Intestinal Motility Model

Chapter 1 provides a complete introduction to the physiology of the gut, but a brief review is presented here so that this chapter could be read independently. The primary functions of the small intestine (gut) are the absorption of nutrients from processed food material (chyme) passed from the stomach, and the transport of that chyme through the length of the gut where it is eventually passed to the large intestine. During the absorption process, chyme must be continually mixed and homogenized such that nutrient-depleted
regions formed near the inner surface as a result of uptake into the bloodstream are replenished by radial transport from the relatively nutrient-rich regions near the central lumenal axis. Radial transport must be coupled with axial transport to ensure exposure of the chyme to the entire length of absorptive epithelial surface of the lumen, and to achieve the necessary transition to the large intestine for eventual evacuation from the body. These radial and axial transport requirements are accomplished by contractile motility of the intestinal walls, peristalsis and segmentation, which generate fluid flow within the gut lumen.

Segmentation is characterized by rhythmic, repetitive radial contractions of short segments of the gut. Neighboring contractions encapsulate portions of chyme, creating a series of well formed segments. As these contractions relax, new contractions appear at the center of the previous segments, dividing them in two and creating new segments. This pattern continues in a periodic manner during the fed state. Historically, segmentation has been associated with mixing of the luminal content; that is, homogenization of the chyme by exchanging fluid between the relatively nutrient-rich centerline and the relatively nutrient-depleted region near the epithelial surface [e.g. 1,4,6]. This association appears to have formed through observations of gut movements, with few studies quantifying such associations [8].

While segmentation is generally identified as a relatively stationary motility pattern, peristalsis is characterized by propulsive, traveling wave-like propagations. Peristaltic contractions vary substantially in presentation in the gut. Some contractions propagate relatively rapidly (a few cm/s) [e.g. 7], while other contractions propagate much more slowly (a few cm/min) [e.g. 8]. A third type of highly occlusive peristaltic motion, referred to as Phase III MMC or “housekeeper” contractions, serve to clean the gut, sweeping over long
sections of the intestine to clear any remaining contents during the fasting state [e.g. 12]. In this study, we focus on the first type, which is the most frequently observed peristaltic motility during the fed state [7,55].

Analytical and computational models have been developed to study the fluid motions generated by the motility modes of the gut [e.g. 13-16]. Such models, although necessarily simplified, can provide valuable qualitative information pertaining to the transport and absorption in the gut. Peristalsis, especially as a general means of mechanically pumping fluid, has been particularly well-studied [e.g. 17,18]. Few similar quantitative studies, however, have been conducted segmentation. Macagno et al. [11] provide a brief qualitative description of flow phenomena resulting from a very simplified segmental-type motility pattern, and suggest that this mode of motility may generate advective fluid motions that promote mixing of the chyme.

To provide a more complete understanding of the fluid mechanics of the gut and further understand the influence of intestinal motility on absorption, we have developed a three-dimensional (3D), bimodal, lattice-Boltzmann-based computational model of fluid mechanics in the gut. We utilized our model to predict the fluid flow and consequent nutrient transport generated by the gut motility patterns. Both segmentation and peristalsis can be simulated individually or simultaneously in any desired weighted linear combination.

For anatomical and physiological relevance, we parameterized the model using data extracted from in vivo magnetic resonance imaging (MRI) of rats conducted in a companion study by our research group [55]. These parameters can be adjusted freely, however, to investigate isolated effects on the absorption process. Although necessarily simplified, the
model is, to our knowledge, the most complete computational model of fluid mechanical gut function to date.

In this study, we use our model to specifically understand and describe the fluid flow phenomena generated by motility patterns in the gut. Further, we evaluate the relative impacts of these mechanisms on the nutrient absorption process. In the coming sections, the details of the model, the numerical experiments and associated results are discussed. Section 4.1 concludes with a discussion of the physiological implications with respect to normal gut function.

4.1.1 The Numerical Method

As with the 2D models discussed in Chapter 3, the 3D models in this chapter rely on the lattice Boltzmann method (LBM) to predict the flow of chyme in the gut as generated by deformations of the intestinal walls. As has been discussed in previous sections, the LBM is an algorithmically straight-forward, yet powerful technique known for its ability to relatively easily handle low-Reynolds number flows, complex moving boundaries, and computational parallelization strategies [e.g. 100]. Previous studies have demonstrated its ability to accurately simulate fluid flow within other parts of the gastrointestinal (GI) tract [50,142].

We incorporate a passive scalar concentration field to model a nutrient concentration suspended within the flow. The model is geometrically parameterized by physiological information extracted from MRI imaging of the rat intestine acquired in a companion in vivo study of gut motility [55]. The interface between the physiological parameters and the numerical model is a simplified spatiotemporal geometry model incorporating both segmental and peristaltic motility operating alone, or in specified linear combinations.
**Fluid flow model: the lattice Boltzmann algorithm.** The differences between 2D and 3D LBM are subtle, and thus, the methods (see Section 3.1.1) used for the 2D simulations presented in Chapter 3 differ only modestly with those used for the 3D simulations discussed in this chapter. However, they are reviewed here so that this chapter can be read independently. If Chapter 3 has already been studied, the reader can skip to Section 4.1.5. The standard LBM utilizes a discretized form of the Boltzmann equation to calculate the distribution functions, \( f_i(x,t) \), of groups of microscopic particles as they evolve on a uniform, equally-spaced lattice. We apply the three-dimensional, fifteen-speed model (D3Q15) [e.g. 100], chosen for its inherent advantages in computational efficiency and memory requirements versus the nineteen-speed (D3Q19) model. The lattice Boltzmann equation with the Bhatnagar-Gross-Krook (BGK) collision operator is as follows:

\[
\begin{align*}
\tau \delta t \frac{\partial f_i}{\partial t} &= f_i(x+\delta x, t+\delta t) - f_i(x, t) - f_{i,eq}(x,t) \\
\end{align*}
\]

where \( f_i(x,t) \) is the particle distribution function at discretized location \( x \) at discretized time \( t \), with discretized velocity \( e_i \), and \( f_{i,eq}(x,t) \) is the equilibrium distribution, toward which the distribution functions relax with time scale \( \tau \). In the low Mach number limit, the equilibrium distribution function is given by:

\[
\begin{align*}
\rho \left[ 1 + 3 \frac{e_i \cdot u}{c^2} + \frac{9}{2} \left( \frac{e_i \cdot u}{c^2} \right)^2 - 3 \left( \frac{u}{c} \right)^2 \right],
\end{align*}
\]

where \( \rho \) and \( u \) are the continuum-level density and velocity, \( w_i = \frac{4}{9}, \frac{1}{9}, \frac{1}{36} \), are the direction-specific weighting coefficients for center, off-diagonal, and diagonal directions respectively, and \( c \) is the basic speed on the lattice. The relaxation parameter, \( \tau \), defines the kinematic lattice viscosity as follows:
\[ \nu = \frac{1}{2} c_s^2 \delta t (2 \tau - 1) , \quad (4.3) \]

where \( c_s \) and \( \delta t \) are the lattice sound speed and time step respectively.

The LBM is based on statistical mechanics, where continuum-level density and velocity fields, \( \rho(\mathbf{x}, t) \) and \( \mathbf{u}(\mathbf{x}, t) \), respectively, are obtained from moments of the distribution function as follows:

\[ \rho(\mathbf{x}, t) = \sum_i f_i(\mathbf{x}, t) , \quad \text{and} \tag{4.4} \]
\[ \mathbf{u}(\mathbf{x}, t) = \sum_i f_i(\mathbf{x}, t) \cdot \mathbf{e}_i / \rho(\mathbf{x}, t) , \quad (4.5) \]

Pressure is proportional to the local density using the following equation of state:

\[ P(\mathbf{x}, t) = \rho(\mathbf{x}, t) c_s^2 , \quad (4.6) \]

where the lattice sound speed is typically: \( c_s = \sqrt{RT} = \sqrt{1/3} \) in lattice units.

**Nutrient (passive scalar) concentration model.** To quantify the effectiveness of nutrient absorption, we incorporate a passive scalar concentration field, \( \phi(\mathbf{x}, t) \), into the LBM fluid flow model. Advection and diffusion of the concentration within the chyme are predicted as a result of fluid motions generated by the deforming walls. Nutrient concentration is evaluated with the “modified moment propagation method”, as described by Merks *et al.* [121]. Unlike other methods, where the LBM is used to concurrently calculate the evolution of a second distribution function for the scalar [e.g. 118], the moment propagation method evolves the continuum level scalar field directly with fluid flow LBM distribution functions, according to the following equation:

\[ \phi(\mathbf{x}, t + \delta t) = \sum_i \left( \frac{f_i}{\rho} - w_i \Delta^* \phi \right)_{\mathbf{x} - \mathbf{e}_i \delta t} + \Delta^* \phi(\mathbf{x}, t) , \quad (4.7) \]
where $\phi(x,t)$ is the continuum level concentration, in molecules per unit volume of scalar at location $x$ at time $t$. At each time step, $\phi(x,t)$ is recalculated as the sum of scalar advected from each $i$th neighboring node (first RHS term of Equation 4.7), and the portion remaining at the node according to the molecular diffusivity-dependent ($D_m$) parameter: $\Delta^* = 1 - 6D_m$ (second RHS term of Equation 4.7). By avoiding a second LBM distribution function for scalar concentration, the method has a lower computational expense and reduced memory demands, yet maintains accurate prediction of the evolution of scalar concentration within the domain.

4.1.2 Boundary Conditions

The boundary conditions used in the 3D simulations presented in this Chapter are identical to the corresponding 2D simulations from Chapter 3, differing only in the added complexity in extending the implementation to 3D. They are discussed here again for independent review of this chapter. In the small intestine, the fluid motions and resulting nutrient advection are induced by the deformation of the intestinal walls. Accurate simulation of these phenomena is therefore limited by the accuracy of the boundary conditions at the moving boundaries. In the current study, are careful to properly account for momentum transfer to the fluid from the deforming walls with second-order-accurate boundary conditions.

Nutrient concentration also requires a reasonable boundary condition at the moving surface to model absorption through the epithelium. We apply a zero-scalar concentration condition at inner luminal surface, implying effectively immediate nutrient absorption at the epithelium. This “immediate absorption” assumption is a reasonable model for most
nutrient molecules since resistance to absorption is typically small compared to the time scale associated with the transport of nutrients from the bulk flow to the surface [144]. The inlet and outlet of the intestine are modeled using periodic boundary conditions, taking advantage of the inherently periodic nature of the geometry and the numerical stability of this boundary condition [100].

**Boundary Conditions at the Moving Surfaces.** The momentum of the fluid in the near-wall region is affected by deformations of the surface. To properly capture the transfer of momentum from the surface to the fluid, we apply the second-order-accurate boundary condition of Lallemand et al. [114]. This method extends the moving boundary bounce-back formulation of Ladd [112] to include interpolation for more accurate location of complex boundaries. The method employs one of two expressions according to the relative distance from the nearest fluid node to the solid boundary, \( q \):

\[
f_i(x_i, t) = q(1 + 2q)[f_i^-(x_i, t)] + (1 - 4q^2)[f_i^-(x_2, t)] - q(1 - 2q)[f_i^-(x_1, t)] + 6w_i\rho(\mathbf{e}_i \cdot \mathbf{u}_b)
\]  

(4.8)

\[
f_i(x_i, t) = \frac{1}{q(2q + 1)}[f_i^-(x_i, t)] + \frac{(2q - 1)}{q^2}[f_i^-(x_2, t)] - \frac{(2q - 1)}{(2q + 1)}[f_i^-(x_1, t)] + \frac{6w_i\rho}{q(2q + 1)}(\mathbf{e}_i \cdot \mathbf{u}_b)
\]  

(4.9)

Equation (4.8) is used when \( q < \frac{1}{2} \), while Equation (4.9) is used when \( q \geq \frac{1}{2} \). Both equations collapse to the original formulation of Ladd when \( q = \frac{1}{2} \) [112,114].

**Zero-scalar-concentration Boundary Condition.** With the complex boundaries moving through the stationary lattice, the walls seldom coincide directly with a lattice node. Therefore, the specification of the conditions for the scalar concentration at the walls is a non-trivial task, as the zero-scalar concentration value can not be set directly. The scalar
concentration at the wall must be specified indirectly by setting the concentration at the each fluid node directly adjacent to the wall at each time-step. We employ an interpolation/extrapolation method developed by our research group (Dr. Yanxing Wang), as discussed in Section 3.1.2 [144].

4.1.3 Physiological Data

To ensure the use of anatomically and physiologically accurate geometric parameters in our computational model, we performed a companion study on the motility in the undisturbed *in vivo* rat intestine using dynamic MRI [55]. The details of these experiments are discussed in Section 3.1.3, and are briefly described here again to provide some limited background for independent reading of this chapter.

To extract the desired quantitative data from the dynamic image sequences, custom MATLAB™-based image analysis software was developed. Advanced edge detection techniques were used on each image to delineate the intestinal wall boundaries from the rest of the surroundings. Once the boundary information was extracted, quantitative values of the desired geometric parameters were calculated. The results of quantitative and statistical analysis of the acquired data are shown in Table 3-1 located in Chapter 3. These data establish a set of “base” parameters for the computational gut model presented in this chapter.

4.1.4 The Geometry Model

The geometry model used for the 3D simulations is nearly identical to the 2D geometry model (see Figure 3-1), with one notable exception: to reduce the computational
expense and lower the memory requirements, only one gut segment (rather than three as shown in Figure 3-1) was simulated. The use of more than one gut segment was useful for the 2D simulations, as we used the “inlet” initial/boundary condition (see Section 3.1.5) to obtain transport information in a larger computation domain. For the 3D simulations, we are less concerned with transport, and more with absorption. Thus, with the use of periodic boundary conditions creating an effectively infinite train of waves, simulating more than one segment serves no purpose. The geometry model is discussed again below to facilitate the ability to read this chapter independently.

The data extracted from the MRI experiments were used to parameterize a mathematical model of the wall geometry of the moving intestine. The model encompasses both modes of intestinal motility, peristalsis and segmentation, where the modes can be activated independently or in any desired weighted linear combination of the two. That is, the position of the intestinal wall, $h(x,t)$, at axial location, $x$, and time, $t$, is determined as follows:

$$h(x,t) = w_p h_p(x,t) + w_s h_s(x,t), \text{ subject to:}$$

$$w_s + w_p = 1$$

where $h_s(x,t)$ is the contribution from segmentation, and $h_p(x,t)$ is the contribution to the overall intestinal wall position from peristalsis. The weighting coefficients, $w_p$ and $w_s$, control the relative influence of peristalsis and segmentation respectively on the overall geometry. The geometry is symmetric about the centerline, and periodic in both space and time. A straight segment of the gut, rather than an intestinal segment, or loop, with more curvature, is used for simplicity.
Segmentation is modeled as a series of alternating 180° out-of-phase contractions. That is, as one particular segment contracts, the neighboring segments expand, and vice versa. This trend continues periodically in time. The time-changing geometry was constructed using straight piecewise sections for the contracting segments, and quarter sine waves connecting the straight sections for spatial continuity (see Figure 3-1(b)). As with peristalsis, the actual segmenting contractile patterns present in the intestine are more complex. In particular, a minor backwards-forwards axial motion at the contracting segments has been observed that is not included in the geometry model under the assumption that the dominant mixing motions within the chyme are generated by the radial displacement of the luminal surface. Our segmental model is otherwise qualitatively similar to the actual observed motions and to the simpler model presented by Macagno, et al., [11].

Peristalsis was modeled as continuous train of sinusoidal waves propagating along the upper and lower walls from left to right with constant velocity (see Figure 3-1(a)). The actual peristaltic motions in the gut are less ideal, both in shape and temporal continuity. However, the objective is to capture the average characteristics of propagating contraction waves. This simplistic representation is consistent with previously presented studies [e.g. 16,18].

Both motility modes are parameterized geometrically using the “base” set of quantitative values extracted from the MRI analysis given in Table 3-1. Important parameters include length scale (wavelength), time scale (period of contraction or wave propagation), and maximum and minimum radii from which an occlusion ratio can be defined:

\[ O.R. = \frac{R_{\text{min}}}{R_{\text{max}}} \]  

(4.12)
These parameters can then be altered systematically to provide more insight into possible optimizations and further functional/physiological significance.

4.1.5 Code Parallelization

The complexity of the geometry and motility patterns in the small intestine demand a sufficiently large computational domain with high enough resolution as to require distributed parallel computing. The fluid motions generated by the moving boundaries must be resolved, as must the gradients in the nutrient concentration fields, which tend to be higher than in the fluid due to the high Schmidt numbers (kinematic viscosity/nutrient diffusivity), characteristic of nutrients suspended in intestinal chyme. Thus, the 3D models incorporate parallel instructions using the message passing interface (MPI) framework to distribute the computational and memory load across multiple processing units and memory banks.

A domain decomposition technique is employed to allow each processing unit (processor or processor core) to perform the required algorithmic operations on its own subdomain of full computational domain. The full domain is divided in three directions, with the number of subdomains in each direction chosen to maximize the volume to surface area ratio as shown in Figure 4-1. The local nature of the LBM allows all of the operations to be completed wholly within each subdomain with the exception of the boundary nodes which must exchange only minimal information (distribution functions streaming in and out of the domain, density, and scalar concentration) with neighbouring subdomains. The result is a multiple instruction stream, multiple data stream (MIMD) architecture that is suitable for large-scale synchronous parallel computing systems such as the Lion-X clusters at Penn State.
and the TeraGrid supercomputer site, Kraken, at the University of Tennessee, where most of the computations described in this dissertation have been run.

The code has been developed to effectively utilize an arbitrary number of processing units (cores), with the load automatically distributed as evenly as possible given the number of computational nodes to be divided among the subdomains. Tests have shown reasonable scalability characteristics up to 10,000+ cores on Kraken.

4.1.6 Numerical Experiments

In this study we seek to understand the absorption process as influenced by the flow generated by patterns of macro-scale gut motility arising from contractions in the musculature of the intestinal walls. To couple this understanding of the mechanics with the physiology of normal gut function, we search for the existence of potential optimization to explain why the motility patterns exist in the manner in which they are observed. As such, we establish “base” parameters from data acquired through MRI imaging of the rat intestine, and then systematically vary these parameters to bolster a more complete understanding.

Using the 2D model discussed in Section 3.1, we conducted a preliminary sensitivity analysis to relevant geometric parameters: length scale, time scale, weighted mix of motility modes, and occlusion ratio. We found that length scale (wavelength) and time scale (period of contraction) within a reasonable extension of the physiological range played a negligible role in overall characteristics of absorption. The weighted mix of segmentation and peristalsis, as given by Equations 4.10 and 4.11, and the occlusion ratio, as given by Equation 4.12, however, have a much more significant and interesting impacts on the absorption and
thus we focus this paper on the results of our numerical experiments of varying these two parameters.

We use our numerical method to predict the fluid motions and associated nutrient (scalar) advection/diffusion in a series of experiments where the relative contributions of peristalsis and segmentation are systematically investigated. A series of nine numerical experiments were investigated, with the contribution ratio of percent segmental contribution to percent peristaltic contribution varied between the two single-mode cases. We, however, limit our discussion in this section to three cases: pure segmentation, pure peristalsis, and a 50:50 mix of the two modes.

To investigate the influence of occlusion ratio on the absorption process, we conducted a range of experiments for various motility patterns where the occlusion ratio was varied from 0.1 (highest occlusion) to 1.0 (no occlusion, no motility). Such a large range of occlusion ratios allows the examination of not only the quantified physiological range (~0.4 < O.R. < 0.7) [55], but can provide insight as to why this range is favored by the physiology of the gut.

We use two different initial conditions for the distribution of scalar concentration (nutrients) as shown in Figure 4.2: “uniform” and “blob”. For the uniform initial condition, the scalar concentration is set to $\phi=1.0$ at each computational node, and is thus uniformly distributed at the start of the scalar concentration calculation. For the blob initial condition (3D version of the blob initial condition used in the 2D simulations, see Section 3.1.5), the scalar concentration is set to an initially normalized 3D Gaussian distribution in the center of the computational domain. The true in vivo distributions of nutrient concentration are highly variant. Our initial conditions simulate the limiting cases of homogenized chyme (uniform
initial condition) and a localized concentration distribution far from the walls (blob initial condition). Once initially specified, the scalar concentration distributions evolve as a result of the fluid motions driven by the modeled motility patterns.

We quantify the effects motility on nutrient absorption using two methods: calculation of the normal flux of scalar through the absorptive walls to obtain local scalar flux versus axial position and tracking of the net exchange of scalar during the modified moment propagation method at the boundaries to calculate the rate of nutrient scalar absorption. The scalar flux, $J_\phi$, through the surface is calculated as follows:

$$J_\phi = D_m \frac{\partial \phi}{\partial n} |_s,$$

where $s$ indicates that the derivative is taken at the surface, and $n$ is the direction normal to the surface. The flux is calculated on a central axial cross-sectional plane to take advantage of the axisymmetry and to simplify interpolation of scalar concentration values necessary for calculation of the derivative.

To calculate the absorption rate, we track the net exchange of scalar at the boundaries that occurs with the modified moment propagation method. That is, we calculate the difference (first RHS term of Equation 4.7) between scalar exchanged between neighboring nodes that exist on either side of the intestinal surfaces. The total net difference of all the boundary exchanges at a given time step provides the total amount of scalar absorbed between the current and previous time step. The derivative of this running total with respect to time is the scalar absorption rate, $J_\phi$. 
The Schmidt number was \( Sc = 50 \). The \( Sc \) in the gut are orders of magnitude higher in the gut, however practical constraints restricted the use of such values. A discussion of the \( Sc \) and its influence on the simulations is presented in Section 3.1.5.

4.1.7 Results

Upon analysis of the flow patterns generated by segmentation and peristalsis of the two modes, it is apparent that very different fluid mechanical phenomena occur. Segmentation is characterized by the exchange of fluid between neighboring gut segments. That is, when one segment collapses from a contraction in the musculature of the gut walls, the fluid is forced axially, fore and aft, into neighboring segments. The fluid is subsequently forced back into the initially collapsed segment through simultaneous contraction of the neighboring segments. This pattern has been observed to continue for long periods of time [e.g. 8,55]. We model this behavior using periodic geometry and periodic boundary conditions at the inlet and outlet of the gut segment, creating an infinite train of alternating contractions.

Our results show that stagnation points form at the center of each segment when chyme from neighboring segments enters from either side. The flow, upon encountering the fluid from the opposing segment is diverted radially outward toward the absorptive walls. The chyme then follows the walls back in the direction from which it entered the segment, creating flow recirculation along the walls.

We find that while the segmental flow patterns look qualitatively similar over the range of occlusion ratios as shown in Figures 4-4(a,b), the strength of the recirculation patterns varies substantially, which has significant impact on the absorption characteristics.
At low occlusion ratios, where the contractile patterns are most fully occluded (0.1-0.3), the recirculatory eddies formed by the stagnation point in the center of each segment are sufficiently strong as to advect the scalar outward after encountering the wall, exposing the scalar concentration to a large percentage of the absorptive surface. Maximum gradients, leading to maximum uptake through the walls, are formed at axial locations corresponding closely with the axial locations of the eddy centers. This is reflected in the plots of local scalar flux versus axial location shown in Figure 4.4(f).

At large occlusion ratios, where the contractions are least occlusive (~0.7-0.9), the eddying motions are much weaker and can no longer advect the scalar outward as was the case at low occlusion ratios. In such large-\textit{O.R.} cases, the scalar is drawn toward the surface, but remains “focused” in a disk-shaped region at the center of the segment as a direct result of the stagnation point formed from the opposing flows from neighboring segments entering and colliding. This behavior is shown in Figures 4.4(d,e). As depicted in the corresponding local flux plots in Figure 4.4(f), a single peak in scalar flux occurs as a result of the local high scalar concentration gradients formed by this focusing effect.

At mid-occlusion ratios (~0.4-0.6), a transition occurs from the behaviors exhibited at the low occlusion ratios characterized by the outward advection by the formation of strong eddies and the behaviors of the high occlusion ratios characterized by the focusing of the scalar concentration into the central disk-shaped region. During this transition, which varies slightly depending on the initial condition of the scalar concentration and what the stage of absorption (early versus late stage, described in more detail later), three local maxima in scalar flux are formed as shown in Figure 4.4(f). Interestingly, during this trade-off between low- and high-\textit{O.R.} behaviors, the absorptive properties remain comparable
(roughly equal). This can be seen in Figure 4-5(a-f). Figures 4-5(a-d) show the percent of scalar absorbed relative the total amount initially in the domain plotted against occlusion ratio for the uniform and blob initial conditions, at 5 and 20 contractile time periods after the scalar concentration was introduced into the gut model. We note that during the late stages of absorption in Figures 4-5(c,d) (after 20 periods) a “plateau” is formed at the mid-occlusion ratios. This behavior is also exhibited in the early stages of absorption, as shown in Figures 4-5(a,b) (after five periods), but is less apparent.

The later stages of absorption in Figure 4-4 are likely more relevant to the *in vivo* intestinal function as the motility has had sufficient time to evolve the scalar concentration into distributions that result from the motility-driven fluid motions. The later stage is less sensitive to the initial condition of scalar concentration as evidenced in the notable similarities between Figures 4-5(c,d) after 20 periods of motility and more clearly evidenced in the consistency of Figures 4-5(e,f), where we plot the number of time periods necessary to achieve 90% absorption for the two initial conditions. The plots are strikingly similar, and clearly show the plateau effect in the segmental cases occurring between occlusion ratios of ~0.4-0.6.

At all occlusion ratios, stages of absorption, and for both initial conditions, it is interesting to note that the maximum absorption rates occur just before the segments reach their maximum diameter and begin their collapse. Figure 4-6 shows an example of this for the uniform and blob initial conditions at various occlusion ratios, where the absorption rates versus contractile period (time) are plotted the central and combined outer segments. One might have expected the absorption rate to peak when the segments are at their fully contracted position. Instead, because the scalar is actually advected out of the segment
during the collapse, the absorption rate is low. Because of this, the maximum absorption rate occurs during the expansion part of the cycle just before the maximum diameter occurs, when outward radial velocities advecting scalar toward the wall are strongest (as a result of fluid being pushed out of neighboring segments).

Peristalsis is distinctly different than segmentation, both in the flow patterns generated and in the corresponding absorptive characteristics. Figure 4-7 shows peristaltic flow patterns after 20 periods of motility at various occlusion ratios for the uniform initial condition case, with streamlines in the steady frame traveling with the wave (wave frame) depicted as black isocontour lines of the stream function, and nutrient concentration represented by colored isocontours.

Peristalsis is characterized by the presence (or absence) of the “trapping” phenomenon and its corresponding strength. Trapping was first mentioned by Shapiro [17] and is defined as the formation of a region in the peristaltic wave that is fully enclosed by a streamline in the wave frame, with stagnation points occurring along the centerline fore and aft of the trapped region. Fluid particles within the trapped region are carried along with the peristaltic wave, while fluid particles outside the trapped region “slip” from wave to neighboring wave against the direction of travel of the peristaltic waves. Within the trapped region, eddies are formed and the flow is recirculated. Outside the trapped region, the wave frame streamlines follow the contours of the walls. Scalar within the trapped region can only be removed from the trapped region through pure diffusion as there is no flow out of the region for advection to occur. As shown in Figures 4-7(a-c), the size of the trapped region is controlled by the occlusion ratio. At low occlusion ratios, the trapped region encompasses nearly the entire peristaltic wave. As occlusion ratio increases, the trapped region diminishes
until it eventually disappears entirely. The critical occlusion ratio is known as the “trapping limit”, and is $O.R. = 0.742$ for axisymmetric sinusoidal peristalsis [17]. Therefore, peristaltic flows with occlusion ratios less than the trapping limit contain a trapped region, while the rest do not.

One might hypothesize that the trapping phenomenon would hinder absorption, as advection is limited to within the trapped region. However, we find that the configuration of the flow during trapping is actually more advantageous for absorption than the configuration of the flow without trapping. At the lowest occlusion ratio ($O.R. = 0.1$), the streamline that encapsulates the trapped region is very close to the wall as shown in Figures 4-7(a-c). As scalar is advected by the eddies within the trapped region, it is carried along the central axis in the direction of wave propagation. Upon encountering the frontal stagnation point, it is redirected along the streamline that encapsulates the trapped region. Since the trapped region is very close to the wall when the lumen is highly occluded, high scalar concentration gradients are formed and, as shown in Figure 7(f), a local maximum in scalar flux is formed toward the front of the wave. As occlusion ratio increases, less of the scalar is absorbed at the front, leaving more of the scalar to be absorbed further back on the wave. A second local maximum forms toward the back of the wave, where scalar concentration gradients are also high as visually seen in Figures 4-7(b-d). As occlusion ratio increases further, the trapped region becomes smaller and the encapsulating streamline is moved farther away from the wall. As a result, the overall scalar flux decreases and becomes more spatially uniform in the axial direction. Above the trapping limit, scalar absorption is diffusion dominated, and motility has less of an impact on absorption. This is apparent in Figure 4-5, where a
noticeable change in the slope of the plots occurs between 0.7 and 0.8 for the peristaltic cases.

When observing actual intestinal motility patterns with non-invasive imaging modalities, patterns sometimes occur that are not clearly identifiable as segmental or peristaltic motility [48,55]. This leads to the question of whether these patterns are comprised of concurrent mixes of the two. Using our model, we investigated several systematically varied mixes of segmentation and peristalsis to determine if an optimal mix exists. We found, however, that the absorption characteristics were less optimal in such concurrent mixes than with “pure” motility patterns of segmentation and peristalsis. Therefore, we limit our discussion here only to the results of an equally weighted 50% segmentation, 50% peristalsis case.

Figure 4K8 shows the flow patterns produced for the 50/50 mix case, with black isocontour lines of the stream function depicting instantaneous wave frame streamlines and colored isocontours representing nutrient concentration. Interestingly, although the 50/50 mix case is equally weighted, the geometry and flow patterns are much more peristaltic than segmental. This observation is consistent with Figures 4-5, which show that in all cases, the shape of the 50/50 mix curves corresponds much more closely with the shapes of the peristaltic curves than with the segmental curves.

Mixed motility is inherently more complex than pure motility. As such, it is more difficult to describe the fluid mechanical mechanisms that govern nutrient absorption. However, there seems to be a trapping-like mechanism present which would support the notion that peristalsis is the dominant motility pattern in the mix even though it is comprised of equal segmental and peristaltic parts. This is shown in the flow patterns presented in
Figure 4-8. For occlusion ratios from 0.1-0.5, there are clear trapped regions that exist throughout the motility cycle. For occlusion ratios ranging from 0.6-0.7, we find that the trapped region exists at certain times in the motility cycle, but is interrupted and non-trapped during other times in the cycle. At occlusion ratios at or above 0.8, no trapping is observed.

Figure 4-5 shows that the change in slope that occurs between the trapped and non-trapped occlusion ratios for the peristaltic cases is present in the 50/50 mix as well. This change occurs earlier, however, between 0.6 and 0.7. This presumably reflects the finding that at $O.R. \approx 0.6$, there are already portions of the motility cycle at which trapping is not present and that by $O.R. \approx 0.7$ any present trapping is weak. Figure 4-5 also shows that for all occlusion ratios, stages of absorption, and scalar concentration initial conditions, at least one of the pure motility modes is more effective at absorption than is the 50/50 mix.

When comparing the absorptive properties of segmentation, peristalsis, and mixes of the two modes, interesting similarities and differences are apparent. In most cases, as shown in Figure 4-5, the more occluded the contractions (lower occlusion ratios), the better the effectiveness of absorption. The notable exception to this, however, is the plateau phenomenon discussed previously. In general, peristalsis is more effective for absorption than segmentation at low occlusion ratios, and segmentation is more effective at higher occlusion ratios for all cases. As noted in the previous paragraph, however, the 50/50 mix is never the most effective form of motility for absorption. The finding that peristalsis is more effective for absorption at any occlusion ratio is in contrast to our findings using our 2D model discussed in Section 3.1. In Appendix A, we discuss this discrepancy in further detail.
4.1.8 Discussion

The results highlighted in the previous section have significant implications for the physiological function of the gut. Analysis of MRI acquisitions on rats as presented by Ailiani, et al. [55], which corresponds to observations of video fluoroscopy of dogs in videos published by Ehrlein et al. [48], indicates that although gut motility can often be complex, segmentation is the overwhelmingly dominant motility pattern observed after digestion of a normal meal, present 93% and 97% of the total acquisition time for isoflurane and inactin datasets, respectively. However, Figures 4-5(a-c,e) show that peristalsis is the most effective motility pattern for absorption when occlusion ratio is small (O.R. < ~0.5).

Peristalsis is needed to axially transport intestinal chyme from location to location in the gut, since segmentation is an essentially stationary motility pattern with little or no axially movement of chyme [4,6]. One might question, therefore, the functional reason that segmentation is the most observed motility pattern after a meal. It would be, in some sense, simpler to have a single mode of intestinal motility.

We find that the reason could lie in the power, and therefore energy, required by the muscle layers within the intestinal walls to generate the contractions that produce these motility patterns. Figure 4-9 shows the average power required for segmentation, peristalsis, and the equally weighted mix of both motility modes versus occlusion ratio. We find that over the same range of occlusion ratios over which peristalsis is more effective for absorption, the power requirement is significantly higher. For instance, at an occlusion ratio of 0.4 (at the low end of the occlusion ratios typically observed in the gut) [55], we find that peristalsis is at most 28% more effective than segmentation in the later stages of absorption as seen in Figures 4-5(c-d). The power requirement at 0.4, however, is 181% higher. To
optimize the efficiency of the absorption process, the physiological system may seek to maximize the effectiveness of absorption while minimizing the energy expended to absorb the nutrients from a meal. Over the physiological *in vivo* occlusion ratios we have observed in the rat gut (see Table 3-1), we find that segmentation is 45-200% more efficient than peristalsis [55].

It is interesting to note that the situation can vary for earlier stages of absorption. Figure 4-5(a-b) shows that when using the blob scalar concentration initial condition, peristalsis is much more effective than segmentation after five periods (200% more effective for absorption for the same 181% increase in power requirement at an occlusion ratio of 0.4.) Although we note that the early stage results are sensitive to initial condition used, this suggests a possible explanation of why peristalsis is not often observed to occur for as long as segmentation. Typically, peristalsis will occur as a series of reoccurring waves that last for only a short time in the fed state. Segmentation, however, typically lasts for much longer durations of many periods of contractions. Therefore, it is possible that the gut has optimized the occlusion ratios such that peristalsis and segmentation are optimally effective in terms of absorption while they are active.

Figure 4-9 also shows that in addition to the 50/50 mix being always less optimal than either segmentation or peristalsis over the entire range of occlusion ratios, it is never the most efficient either. For all occlusion ratios, either pure segmentation or pure peristalsis requires less power then any a mix of the two modes, suggesting that independent application of peristaltic and segmental motility is physiologically and functionally preferred over mixes of mode types to maximize absorption while minimizing power. This would limit the negative effects of interference from each motility mode on the other.
Such active control by motility optimization is implicated when considering the times at which these two modes are generally active. Peristalsis is the dominant pattern observed after a meal of non-caloric content, while segmentation is the dominant contractile pattern observed after a caloric meal [e.g. 48]. This suggests that the enteric receptors in the gut sense the nutrient content of the chyme and control motility according to functional need. For a non-caloric meal, the absorption process is effectively bypassed, and peristalsis is employed to evacuate the content from the body. Similarly, when fed a caloric meal, segmentation is utilized to promote absorption of the present nutrients [e.g. 7].

It must be noted, however, that for any normal meal, both modes of motility are necessary. The lack of propagatory component in the pure segmentation case requires peristalsis to be present in some respect to transport the chyme axially for additional epithelial exposure and eventual evacuation. But we assert that to optimally utilize the two modes, interference should be minimized.

Observations of actual gut motility indicate that this optimal condition may indeed be realized. In the companion MRI study of the rat intestine, we describe segmentation as the primarily observed contractile pattern after the animals were allowed caloric meals [55]. Peristalsis, however, proved difficult to capture despite extensive searching. In over 50 collected datasets of eight separate animals, peristalsis was only captured twice. This phenomenon may be partially explained by a reduction in peristalsis from the administered anesthesia; however it is unlikely that this provides a full explanation, as peristalsis was present only minimally while rats were under both types of anesthesia, and inactin is known to impact motility patterns less than isofluorane [55,151,152].
Another, perhaps more plausible, explanation is that peristalsis is simply utilized less frequently, allowing optimal utilization of segmentation to maximize the effectiveness of absorption without interference from peristaltic patterns for most of the digestive process. Peristalsis would then be optimally employed, only intermittently, to transport the content axially to further locations, where segmentation is resumed, the process repeating until the available nutrients have been absorbed from a given meal.

### 4.2 Multi-Scale 3D Cavity Flow Villous Motility Model

In Section 3.2, we described a 2D multi-scale villous motility model of lid-driven cavity flow with 2D micro-scale “villi” lining the lower surface. This 2D model was extended to a 3D cavity flow model with 3D villi by Dr. Yanxing Wang, a postdoctoral researcher in our group and developer of the 2D cavity flow model. While the model results were analyzed as a team, Dr. Wang led the technological advances and numerical experiments. Like the 2D model (see Section 3.2), the results of the experiments are integral to this research as a whole and are important to the full combined computational model (see Chapter 5).

To develop the technology needed to incorporate 3D finger-like villi into the combined model discussed in Chapter 5, we found it useful to extend the 2D villous motility model to three dimensions. We then were able to use the model to examine the difference between the absorptive behavior predicted by the 2D model, which effectively modeled villi that were very long in the third dimension, and the more realistic 3D model that models the villi as cylindrical, finger-like projections more similar to those found in the human. Figure 4-10 illustrates the 3D cavity flow model. In the coming sections, an overview of the details of
the model, numerical experiments, and associated results are presented. The section is concluded with a discussion of the physiological conclusions we have drawn.

4.2.1 The Numerical Method

The numerical methods used in the villi model are largely identical those used in the macro-scale intestinal model (see Section 4.1.1) with the added complexity of using multiple computational grids in the same calculation, and with slight variations of the boundary conditions. The multiple-grid strategy (see Section 3.2) needed to be extended to three dimensions, and the code parallelized. Parallel communication is complex in itself, but adding the complexity of parallel communication across the coarse-fine grid interface proved a substantial challenge. Therefore, the parallel strategy discussed in Section 4.2.5 could not be applied in a similar arbitrary manner, and is geometry-specific and much less scalable.

**Multiple-grid Strategy.** We extend the multiple-grid strategy for LBM of Yu et al. [135] (see Section 3.2.1) to three-dimensions. A brief description is provided here also to facilitate the reading of this chapter independently. Here we describe the application of two grids, one coarse grid and one fine grid, as an example of the approach. Each sub-grid is uniform, the shape, location, and resolution of which is chosen according to the requirements of the local flow structure. At the interface of neighboring sub-grids, an overlap of one coarse-grid spacing, two rows of coarse grid nodes, is used.

To ensure consistent lattice viscosity and basic lattice speed across the entire domain (ensuring a consistent $Re$), the fine grid relaxation parameter must satisfy the following
relation (found by equating $\nu = c\delta x(2\tau - 1)/6$ for the two grids):

$$\tau_f = \frac{1}{2} + m\left(\tau_c - \frac{1}{2}\right),$$  \hspace{1cm} (4.14)

where $m = \delta x_c / \delta x_f$ is the ratio of the lattice spacings. To conserve mass and momentum, and maintain continuity in continuum level density, velocity, and deviatory stresses at the interface, the following equations are used to transfer information between grids [135]:

$$\hat{f}_i^c = f_i^{eq,f} + m \frac{\tau_c - 1}{\tau_f - 1} (\hat{f}_i^f - f_i^{eq,f}),$$  \hspace{1cm} (4.15)

$$\hat{f}_i^f = f_i^{eq,c} + \frac{\tau_f - 1}{m(\tau_c - 1)} (\hat{f}_i^c - f_i^{eq,c}),$$  \hspace{1cm} (4.16)

where $\hat{f}_i^f$ denotes the post-collision distribution function. As is apparent in Equations 4.15 and 4.16, care must be taken to avoid values close to one for the relaxation parameters, $\tau_c$ and $\tau_f$, as a singularity occurs, causing numerical instability. Further details of the algorithmic implementation are discussed in Section 3.2.1.

We developed a generalization of the multiple-grid algorithm for the passive scalar concentration field into the multiple-grid scheme required the development of such. The modified moment propagation method, as described in Section 4.1.1, is only valid for a single-grid system. Merks, et al. [121] show that the molecular diffusivity on a single grid is given by $D_m = (1 - \Delta^*)/6$, where $\Delta^*$ is the proportion of scalar concentration remaining on each lattice node after streaming. Warren [154] reported that $D_m = c_s^2 (1 - \Delta^*)/2$. Comparing the two equations, it is clear that they are equivalent since $c_s = 1/\sqrt{3}$. Both expressions
implicitly contain the choice that \( c = \delta x = \delta t = 1 \). Substituting this more general information, the first expression for diffusivity becomes:

\[
D_m = c\delta x(1-\Delta^s)/6,
\]

which is analogous to the expression for the lattice kinematic viscosity. Requiring continuity in diffusivity and basic lattice speed, the parameter, \( \Delta^s \), must be modified on the fine grid as follows:

\[
\Delta^*_f = 1 - m(1-\Delta^*_r),
\]

With this modification, the scalar concentration can be calculated during each streaming step on both the fine and coarse grids according to Equation 4.7. When the scalar concentration information is transferred from the coarse grid to the fine grid, spatial and temporal interpolations are needed at the fine grid boundary of both scalar concentration and the distribution function.

### 4.2.2 Boundary Conditions

**Fluid Boundary Conditions.** To specify the no-slip condition, we employ the standard bounce-back scheme to the stationary walls of the domain, the left and right sides, and in between the moving villi on the lower surface of the domain (see Figure 3-11). The walls are placed half-way in between rows of nodes to maintain second order accuracy [111]. Since the upper lid moves, driving the bulk flow, momentum must be transferred from the lid to the fluid. The lid is also placed half-way between two rows, and moves parallel to the rows, so we apply a simple extension given by Ladd [112] to the standard bounce-back scheme. The villi, however, move such that their surfaces can lie in arbitrary locations relative to the computational nodes that make up the lattice. Thus, on the villous surfaces,
we apply the same method as is used for the macro-scale intestinal model for the complex moving boundaries, the interpolated version of Ladd’s method, given by Lallemand and Luo [114] (see Section 3.1.2).

**Scalar Concentration Boundary Conditions.** As described in Section 4.1.2 for the macro-scale intestinal model, we specify a zero-scalar concentration condition along and in between the villi to model rapid nutrient absorption at the luminal surface. At all other surfaces we apply zero-flux boundary conditions. Merks *et al.* [121] indirectly points out that a bounce-back scheme analogous to the standard bounce-back of the distribution functions can be used to implement a zero-scalar-flux boundary condition. We apply this method where non-absorptive walls are present.

4.2.3 The Geometry Model: A 3D Lid-driven Cavity Flow with Finger-like Villi

The geometry model specified for the 3D multi-scale lid-driven cavity flow villous motility model is illustrated in Figure 4-10. The 3D model is an extension of the 2D model shown in Figures 3-11(a,b). The flow domain is a rectangular prism, with x and z dimensions consistent with the lower half of a single wavelength as observed in the rat gut. The domain is periodic in the y-direction. This allows a significant savings of computational expense, as only a single row of villi needs to be simulated to investigate an effectively infinite third dimension. The upper lid moves with constant velocity in the x-direction, driving the flow in a clockwise circulatory motion through the domain. This geometry is chosen to study the fundamental dynamics underlying the interaction between the macro-scale eddies (e.g. peristalsis) and potential micro-scale motions generated by actively moving intestinal villi.
The villi were modeled as cylindrical protrusions with hemispherical tips, distributed along the lower surface as shown in Figure 4.10, and have dimensions typical of what is reported in the literature for the rat (see Section 2.4). Womack et al. [3] states that while leaf-like villi are restricted in their motility, finger-like villi have been observed to exert contractile pumping motions, side-to-side whipping or pendular motions, and/or tonic contractions, in which several or all villi move together. In the 2D simulations, we limited our investigations to the latter two types of motility, modeling the villous motility as an oscillatory side-to-side motion. In some simulations, the villi are grouped, and oscillate such that the villi in each group oscillate in unison, but each neighboring group is 180° out-of-phase as an attempt to simulate the possibility of the tonic contractions mentioned above. We continue the analysis of these motions here and investigate the tonic contractions by arranging them in groups of synchronously moving villi.

4.2.4 Numerical Experiments

In the numerical experiments, a source of scalar was placed at the upper boundary such that the simulations evolved to a stationary state while simulating the highly concentrated core region of nutrients in the bulk flow. The stationary state provided by the source allows a straightforward analysis versus transient experiments. The moving upper lid drives the flow in a circulatory motion such that the nutrients are swept down and over the bottom of the domain where they encounter the moving villi. Most of the 2D model experiments discussed in Section 3.2.4 were repeated with the 3D model, and are discussed below. However, since the strongest effect from the 2D experiments was that of the pumping mechanism created by groups of villi oscillating 180° out-of-phase, all experiments
were conducted with groups of villi oscillating in such a manner. A systematic variation of
the number of groups was not conducted to save computational expense. The focus of the
3D experiments is further understanding of the formation and influence of the micro-
mixing-layer (MML), as described in the Section 4.2.5.

**Villous Height.** The effect of villous height on absorption rate was investigated by
varying the height of the over a range of physiologically relevant values. Three simulations
are performed: 100µm, 200µm, and 400µm. The other simulation parameters are held
constant to isolate the effect of the height. The frequency ratio (the ratio of villous frequency
to bulk lid-driven circulation frequency, $f_v/f_L$) is held constant at $f_v/f_L = 40$. The villi are
grouped in seven groups, each containing five villi in the x-direction. The groups oscillate
with identical frequency ratio, but neighboring groups oscillate 180° out-of-phase.

**Oscillation Frequency.** The effect of villous oscillation frequency is investigated by
varying frequency ratio. Three simulations: the control case lower limit of zero frequency
ratio (stationary villi), $f_v/f_L = 20$, and $f_v/f_L = 40$. The other simulation parameters are again
held constant to isolate the effect of oscillation frequency. The villous height is $l_v = 200µm$.
The grouping of the villi is identical to the villous height experiment, with seven groups of
five x-direction villi.

**Villous Spacing.** Villous grouping was not systematically varied using the 3D model
as it was using the 2D model. However, the spacing between the villi in the x-direction ($\Delta x_v$)
was systematically varied to investigate the effect of the number of villi in a given area. In
doing so, the grouping was held constant at seven groups, but the number of villi in each
group was varied. The distance between the villi in the y-direction ($\Delta y_v$) was also varied. As
illustrated in Figure 4-11(a-d), four cases were examined: (1) $\Delta x_v=\Delta y_v=2D_v$, (2)
\[ \Delta x_v = \Delta y_v = 4D_v, \quad \Delta x_v = 4D_v, \quad \Delta y_v = 2D_v, \quad \text{and} \quad \Delta x_v = 2D_v, \quad \Delta y_v = 4D_v, \] where \( D_v \) is the diameter of the villous cylinder.

### 4.2.5 Results

**Villous Height.** Figure 4-12 shows the effect of villous height on the absorption rate. The average absorption rate at stationary state is plotted versus villous height for each of the three villous height simulations. The absorption rate increases with villous height. However, the effect is not as strong in 3D as it is in 2D. Figure 3-12 shows the effect of villous height versus absorption rate for the 2D case. In 2D, absorption rate increases at an increasing rate with villous height. In 3D, the absorption rate increases at a slightly decreasing rate. This suggests that the extra degree of freedom present in 3D affects the flow significantly. In 2D, the flow was constrained in the \( y \)-direction, such that the mixing effects were concentrated in the vertical direction. Three-dimensionality allows some of the flow to be directed into the intravillous space between the villi where it has less of an impact on the macro-scale circulation. This phenomenon can be seen in Figure 4-13, where the streamlines developed in the average velocity field (over one micro-scale period) can be seen to go around the sides of the villous cylinders into the intravillous space. For the packing ratio studied, the increased absorption through the sides of the villi is apparently insufficient to compensate for an apparent reduction in strength of the MML.

**Oscillation Frequency.** Figure 4-14 shows the effect of oscillation frequency on the absorption rate. The average stationary-state absorption rate is plotted versus frequency ratio for each oscillation frequency. The effect of increasing the frequency in 3D is similar to the effect in 2D (see Figure 3-13). Increasing the oscillation frequency monotonically increases
the absorption rate, with each increase in frequency ratio having an increasingly larger impact. Although a diminished effect may exist because of the extra degree of freedom intrinsic in 3D (as is evidenced in Figure 4-12), villous motility apparently augments the absorption rate with higher frequency oscillations having more of an effect.

**Villous Spacing.** In experiments varying the spacing between the villi, the focus was placed on investigating the formation of the micro-mixing layer and the effect of the induced flow in the intravillous space. Four configurations were examined, as depicted in Figure 4-11. In Figure 4-15(a), the time-averaged scalar concentration over one micro-scale villous motility period, $\langle \phi \rangle$, is plotted versus distance in the $z$-direction (from the bottom of the cavity where the villi are located to the top where the moving lid is located) for four cases: $\Delta y_v=2D_v$ with a fixed lid ($U_0 = 0\text{mm/s}$) shown in red, $\Delta y_v=2D_v$ with a moving lid ($U_0 = 2\text{mm/s}$) shown in orange, $\Delta y_v=4D_v$ with a fixed lid ($U_0 = 0\text{mm/s}$) shown in green, and $\Delta y_v=4D_v$ with a moving lid ($U_0 = 2\text{mm/s}$) shown in blue.

Advective mixing of scalar concentration leads to vertically homogeneous concentration profiles. Thus, the effect of advective mixing by the macro-scale eddy motions is seen when comparing the moving lid cases (blue and orange curves) to the fixed-lid cases (red and green) from $\sim1\text{mm} < z < \sim2.5\text{mm}$. The concentration profiles shown blue and orange are more vertically uniform, indicating more homogenous scalar concentrations in this region due to the advective circulatory flow produced by the moving lid. Toward the bottom of the cavity, the influence of the micro-scale villous motility can be detected. Comparing the red and green curves in the region of $\sim0.3\text{mm} < z < \sim0.7\text{mm}$, the concentration profile shown in red (which has more closely spaced villi) undergoes a change in slope, indicating a stronger mixing effect from the villous motility as compared to the
more sparsely spaced villi of the green curve. The same phenomenon can be seen when comparing the blue and orange curves in the region of \(0.25 \text{mm} < z < 0.5 \text{mm}\), where the orange curve \((2D_v \text{ spacing})\) has a change in slope, indicating a stronger mixing effect as compared with the more sparsely spaced blue curve \((4D_v \text{ spacing})\). This additional mixing effect seems to only be present when the villi are sufficiently closely packed. There is an obvious limit to this physics when the villi are too closely packed to create vertical pumping from groups of counter-oscillating villi.

**The Micro Mixing Layer.** Figures 4-15(b,c) show the effects of increasing villous height and villous frequency respectively on nutrient mixing. The average scalar concentration (over one micro-scale villous motility period) is plotted versus vertical distance. In Figure 4-15(b), the effect of villous length is shown. The curves are plotted relative to the villous tips. In the region of \(0.1 \text{mm} < z < 0.3 \text{mm}\), the change in slope toward more constant scalar concentration indicates the influence of villous mixing for the red and blue curves. A mixed region is particularly apparent for \(l_v=400 \mu\text{m}\) (red curve). When \(l_v=200 \mu\text{m}\) (blue curve), mixing is significantly reduced and becomes negligible when the \(l_v=100 \mu\text{m}\) (green curve). In Figure 4-15(c), the effect of villous frequency is shown. Mixing is again apparent in the region of \(0.2 \text{mm} < z < 0.5 \text{mm}\), most clearly for \(f_v/f_L=40\) (red curve). Mixing is only slightly noticeable when \(f_v/f_L=20\) (green curve), and not at all when the villi are fixed (red curve).

**4.2.6 Discussion**

Consistent with the findings from the 2D villous motility experiments, we have shown that villous motility increases the nutrient (scalar) absorption rate in the 3D lid-driven cavity flow model with 3D finger-like villi. The rate of absorption increased both with villous
height and frequency of villous oscillation. However, the fluid dynamics of the 3D system are more complex, and the strength of the effect depends on the spatial configuration of the villi.

We focused our attention on the formation of the micro-mixing-layer (MML), since the results of the 2D model simulations indicate the importance of the MML in increasing the nutrient gradients near the villi, increasing the absorption rate. The vertical pumping motions between neighboring groups that exist in the 2D model are less effective in this 3D model, as fluid can “escape” around the sides of the villi into the intravillous space, as shown in Figure 4-13. The effect of reduction in vertical pumping due to 3D fluid motions around the villous bases is diminished when the villi are more closely packed. In closely packed configurations, the MML is stronger and the absorption rate is increased.

In the real intestine, the villi tend to are very closely packed, almost touching in most cases (see Figures 1-5 through 1-7). There is obviously a limit to how closely the villi can be packed for the type of motility mechanisms we have identified to be effective. However, the diminished effects we see when the villi are more sparsely configured are less likely in the real structure of the intestine. We also note that in the real intestine, the villi are not “fixed” and passively move when macro-scale contractions of the intestinal walls occur. The combined, 3D, multi-scale model of the small intestine with villi sheds additional light on the potential role of villi under active motion in the presence of macro-scale intestinal motility (see Chapter 5).
Figure 4-1: Two examples of the 3D domain decomposition technique: (a) 48 subdomains, (b): 96 subdomains.
Figure 4-2: The two initial conditions, “blob” and “uniform”, on passive scalar concentration for the peristalsis, segmentation, and equally weighted (50/50) mix cases. Colored isocontours represent initial distribution of scalar concentration as depicted by the legend. Black lines represent isocontours of the stream function. $O.R. = 0.5$ for all cases shown.
Figure 4.3: Flow patterns and nutrient (scalar) distribution for segmentation over one period (Periods 20-21) for the “uniform” initial condition case. Colored isocontours represent the nutrient concentration distribution: blue corresponds to low concentration; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines). O.R. = 0.5.
Figure 4.4: (a)-(e): Flow patterns and nutrient distribution for segmentation for various occlusion ratios for the “uniform” initial condition case after 20 periods of motility. (f): Local nutrient flux for each of the occlusion ratios in (a)-(e). Colored isocontours represent the nutrient (scalar) distribution: blue corresponds to low concentrations; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines).
Figure 4-5: (a-d): Percent of scalar absorbed after five (a-b) and 20 (c-d) periods of motility versus occlusion ratio. (e-f): Number of time periods for 90% absorption versus occlusion ratio. Left column is the “blob” initial condition case; right column is the “uniform” case.
Figure 4.6: Scalar (nutrient) absorption rate in the central straight portion of segmental motility over one contractile period (20-21) for the: (a) “uniform” and (b) “blob” initial conditions.
Figure 4.7: (a)-(e): Flow patterns and nutrient distribution for peristalsis for various occlusion ratios for the “uniform” initial condition case after 20 periods of motility. (f): Local nutrient flux for each of the occlusion ratios in (a)-(e). Colored isocontours represent the nutrient (scalar) distribution: blue corresponds to low concentrations; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines).
Figure 4.8: (a)-(e): Flow patterns and nutrient distribution for the 50/50 mix case for various occlusion ratios for the “uniform” initial condition case after 20 periods of motility. (f): O.R. = 1.0: control case, pure diffusion in a fixed tube. Colored isocontours represent the nutrient (scalar) distribution: blue corresponds to low concentrations; red corresponds to high concentration. Black lines represent isocontours of the stream function (streamlines).
Figure 4.9: Average power requirement versus occlusion ratio for peristalsis (blue), segmentation (red), and 50/50 mix (black).
Figure 4-10: Schematic of the 3D multi-scale cavity-flow/villous motility model. The arrow indicates the direction of the lid driving the flow (although the lid is stationary in this particular figure). The isocontours indicate scalar (nutrient) concentration on an arbitrarily selected x-z plane, blue indicates low concentrations; red indicates high concentrations.
Figure 4.11: Top view of 3D villous motility model for four different villous spacings: (a) \( \Delta x_v = \Delta x_v = 2D_v \), (b) \( \Delta x_v = \Delta x_v = 4D_v \), (c) \( \Delta x_v = 4D_v \), \( \Delta y_v = 2D_v \), and (d) \( \Delta x_v = 2D_v \), \( \Delta y_v = 4D_v \).

Source: Dr. Yanxing Wang.
Figure 4-12: Absorption rate versus villous height. The frequency ratio was held constant at \( f_v/f_L = 40 \) for all cases.
Figure 4-13: A zoomed-in view of streamlines formed by the interaction between the flows generated by villous motility and macro-scale circulation. Blue arrows point to sites where the streamlines wrap around the villi, indicating fluid movement into the intravillous space. \( \Delta x_v = \Delta x_e = 2D_v \). Source: Dr. Yanxing Wang.
Figure 4.14: Absorption rate versus frequency ratio. The height of the villi was held at $l_v = 200\mu$m for all cases.
Figure 4-15: Profiles of average scalar concentration (averaged over one micro-scale villous motility period) versus vertical distance (z-direction) showing the effects of: (a) villous spacing, (b) villous height (length), and (c) villous frequency.
CHAPTER 5: COUPLED MACRO-/MICRO-SCALE INTESTINAL MOTILITY MODEL SIMULATIONS

Although the results of the 2D and 3D lid-driven cavity flow models of macro-micro-scale interactions with villous motility discussed in Sections 3.2 and 4.2 show that villous motility can induce flow patterns that increase mixing in the near-wall region and enhance the effectiveness of absorption, true physiology and function are more complex. In particular, the contractions of the lumen both generate the macro-scale motions modeled by a single eddy in the lid-driven cavity models and also force patterned motions not included in the less complex models.

With the development of the models discussed in Chapters 3 and 4, however, we have established the necessary technology to more completely investigate the fluid mechanics and absorption in the small intestine with a combined multi-scale model that encompasses both macro-scale intestinal motility as well as micro-scale villous motility. This chapter contains a discussion of the details of the combined model (see Figure 5-1), the numerical experiments and associated results, and the conclusions we have drawn with respect to gut physiology and function.

5.1 The Numerical Method

As with the simpler models discussed in Chapters 3 and 4, we construct the multi-scale intestinal model within the lattice Boltzmann framework. We incorporate the modified moment propagation scheme for passive scalar concentration discussed in Sections 3.1.1 and 4.1.1 to model nutrient concentrations suspended within the intestinal fluid. The macro-scale
motility is geometrically parameterized by physiological information extracted from MRI imaging of the rat intestine [55], and is similar to that used for the 3D macro-scale model presented in Section 4.1. We use symmetry to simulate only one quarter of the gut to reduce computational expense. The model is parallelized in the same manner as discussed in Section 4.1.4 to allow for computation on an arbitrarily large distributed computing platform. Although the macro-scale geometry model contains the ability to simulate both segmental and peristaltic motility, as well as arbitrary linear combination, we focus our attention on the pure modes of segmentation and peristalsis alone.

Fluid flow model: the lattice Boltzmann algorithm. The lattice Boltzmann method (LBM) used for the model presented in this chapter is identical to that presented in Section 4.1, however, it is discussed here again briefly to facilitate reading of this chapter independently. Those who have read previous discussions of the lattice Boltzmann method may skip these sections without loss of continuity. The standard LBM utilizes a discretized form of the Boltzmann equation to calculate the distribution functions, \( f_i(x,t) \), of groups of microscopic particles as they evolve on a uniform, equally-spaced lattice. We apply the three-dimensional, fifteen-speed model (D3Q15) [e.g. 100], chosen for its inherent advantages in computational efficiency and memory requirements versus the nineteen-speed (D3Q19) model. The lattice Boltzmann equation with the Bhatnagar-Gross-Krook (BGK) collision operator is as follows:

\[
\begin{align*}
\frac{f_i(x + e_i \delta t, t + \delta t) - f_i(x, t)}{\delta t} &= \frac{1}{c^2} \left[ f_i(x, t) - f_i^{eq}(x, t) \right], \\
\end{align*}
\]

(5.1)

where \( f_i(x, t) \) is the particle distribution function at discretized location \( x \) at discretized time \( t \), with discretized velocity \( e_i \), and \( f_i^{eq}(x, t) \) is the equilibrium distribution, toward which the
distribution functions relax with time scale $\tau$. In the low Mach number limit, the equilibrium distribution function is given by:

$$ f_i^{eq}(x,t) = w_i \rho(x,t) \left[ 1 + 3 \frac{\mathbf{e}_i \cdot \mathbf{u}}{c^2} + \frac{9}{2} \left( \frac{\mathbf{e}_i \cdot \mathbf{u}}{c^2} \right)^2 - \frac{3}{2} \left( \frac{\mathbf{u}}{c} \right)^2 \right], \quad (5.2) $$

where $\rho$ and $\mathbf{u}$ are the continuum-level density and velocity, $w_i = \frac{4}{9}, \frac{1}{9}, \frac{1}{36}$, are the direction-specific weighting coefficients for center, off-diagonal, and diagonal directions respectively, and $c$ is the basic speed on the lattice. The relaxation parameter, $\tau$, defines the kinematic lattice viscosity as follows:

$$ \nu = \frac{1}{2} c_s^2 \delta t (2\tau - 1), \quad (5.3) $$

where $c_s$ and $\delta t$ are the lattice sound speed and time step respectively.

The LBM is based on statistical mechanics, where continuum-level density and velocity fields, $\rho(x,t)$ and $\mathbf{u}(x,t)$, respectively, are obtained from moments of the distribution function as follows:

$$ \rho(x,t) = \sum_i f_i(x,t), \quad (5.4) $$

$$ \mathbf{u}(x,t) = \sum_i f_i(x,t) \cdot \mathbf{e}_i / \rho(x,t), \quad (5.5) $$

Pressure is proportional to the local density using the following equation of state:

$$ P(x,t) = \rho(x,t) c_s^2, \quad (5.6) $$

where the lattice sound speed is typically: $c_s = \sqrt{RT} = \sqrt{1/3}$ in lattice units.

**Nutrient (passive scalar) concentration model.** To quantify the effectiveness of nutrient absorption, we incorporate a passive scalar concentration field, $\phi(x,t)$, into the LBM fluid flow model. Advection and diffusion of the concentration within the chyme are
predicted as a result of fluid motions generated by the deforming walls. Nutrient concentration is evaluated with the “modified moment propagation method”, as described by Merks et al. [121]. Unlike other methods, where the LBM is used to concurrently calculate the evolution of a second distribution function for the scalar [e.g. 118], the moment propagation method evolves the continuum level scalar field directly with fluid flow LBM distribution functions, according to the following equation:

\[
\phi(x,t + \delta t) = \sum_i \left( \frac{f_i}{\rho} - w_i \Delta^* \phi \right)_{x-e_i,t} + \Delta^* \phi(x,t),
\]

(5.7)

where \(\phi(x,t)\) is the continuum level concentration, in molecules per unit volume of scalar at location \(x\) at time \(t\). At each time step, \(\phi(x,t)\) is recalculated as the sum of scalar advected from each \(i\)th neighboring node (first RHS term of Equation 5.7), and the portion remaining at the node according to the molecular diffusivity-dependent \((D_m)\) parameter: \(\Delta^* = 1 - 6D_m\) (second RHS term of Equation 5.7). By avoiding a second LBM distribution function for scalar concentration, the method has a lower computational expense and reduced memory demands, yet maintains accurate prediction of the evolution of scalar concentration within the domain.

5.2 Boundary Conditions

The boundary conditions used in the combined model are taken from the respective 3D simulations presented in Chapter 4. That is, both the macro- and micro-scale movements of the walls influence the intestinal fluid via the momentum-exchange scheme discussed in Section 4.1.2. Passive scalar concentration is held fixed at the macro- and micro-scale surfaces with zero-concentration to model immediate uptake, thus the entire inner gut
surface (outer gut walls and villous surface area) is absorptive. The details of the implementation are discussed more thoroughly in Section 4.1.2, but are presented here again for independent review of this chapter.

**Boundary Conditions at the Moving Surfaces.** The momentum of the fluid in the near-wall region is affected by deformations of the surface. To properly capture the transfer of momentum from the surface to the fluid, we apply the second-order-accurate boundary condition of Lallemand et al. [114]. This method extends the moving boundary bounce-back formulation of Ladd [112] to include interpolation for more accurate location of complex boundaries. The method employs one of two expressions according to the relative distance from the nearest fluid node to the solid boundary, \( q \):

\[
f_i \left( x_i, t \right) = q \left( 1 + 2q \right) \left[ f_i^- \left( x_1, t \right) \right] + \left( 1 - 4q^2 \right) \left[ f_i^- \left( x_2, t \right) \right] - q \left( 1 - 2q \right) \left[ f_i^- \left( x_3, t \right) \right] + 6w_i \rho \left( e_i \cdot u_b \right)
\]

\[
f_i \left( x_i, t \right) = \frac{1}{q \left( 2q + 1 \right)} \left[ f_i^- \left( x_1, t \right) \right] + \frac{\left( 2q - 1 \right)}{q} \left[ f_i \left( x_2, t \right) \right] - \frac{\left( 2q - 1 \right)}{2q + 1} \left[ f_i \left( x_3, t \right) \right] + \frac{6w_i \rho}{q \left( 2q + 1 \right)} \left( e_i \cdot u_b \right)
\]

Equation (5.8) is used when \( q < \frac{1}{2} \), while Equation (5.9) is used when \( q \geq \frac{1}{2} \). Both equations collapse to the original formulation of Ladd [112] when \( q = \frac{1}{2} \) [114].

**Zero-scalar-concentration Boundary Condition.** With the complex boundaries moving through the stationary lattice, the walls seldom coincide directly with a lattice node. Therefore, the specification of the conditions for the scalar concentration at the walls is a non-trivial task, as the zero-scalar concentration value can not be set directly. The scalar concentration at the wall must be specified indirectly by setting the concentration at the each fluid node directly adjacent to the wall at each time-step. We employ an
interpolation/extrapolation method developed by Wang et al. [144]. The scheme is discussed in more detail in Sections 3.1.2.

**Symmetry Boundary Conditions.** To reduce the computational expense that is intrinsically included with the high-resolution needed to capture the complexity at both the macro- and micro- scales, symmetry boundary conditions were incorporated along x-z and y-z planes (see Figure 5-1). The symmetry boundary conditions take advantage of the axisymmetry specified in the macro-scale geometry model, and reduce the computational expense by a factor of four. This reduction is important, because it was determined that the geometric complexity did not allow for the effective use of a multiple-grid strategy of the type discussed in Section 4.2.1.

The implementation of such a boundary condition is straight-forward with the LBM. Similar to the “bounce-back” boundary condition for no-slip conditions at solid walls, the symmetry boundary condition involves re-directing of distribution function that stream out of the domain. Whereas the bounce-back condition sends the distribution functions back in the direction from which they came, the symmetry condition effectively “bounces” the distribution function to the next neighboring node. A schematic of these two boundary conditions is shown in Figure 5-2.

Figure 5-2(a) depicts the bounce-back boundary condition. The black arrow indicates a pre-streamed distribution function that would normally stream out of the computational domain, crossing the solid wall shown as a black line, and becoming the post-streamed distribution function indicated by the red arrow. However, the bounce-back boundary condition demands that the pre-streamed distribution function is streamed back in the direction from which it came, becoming the post-streamed distribution function represented
by the blue arrow. Effectively, this is equivalent to specifying a second pre-streamed distribution function at the phantom node (indicated by the green arrow) with the same momentum magnitude as the original distribution function, but in the opposite direction. This produces a net-zero momentum exchange, and effectively creates a no-slip boundary condition at the solid wall.

Figure 5-2(b) depicts the symmetry boundary condition. The black arrow again indicates a pre-streamed distribution function that would normally stream out of the computational domain, crossing the plane of symmetry represented by the dot-dash line, becoming the post-streamed distribution function indicated by the red arrow. The symmetry boundary condition demands that the pre-streamed distribution function is streamed forward as it were bounced off a solid surface, becoming the post-streamed distribution function represented by the blue arrow. Effectively, this is equivalent to specifying a second pre-streamed distribution function at the phantom node (indicated by the green arrow) with the same momentum magnitude, but with a symmetric direction. As seen when comparing the black and green, or red and blue arrows, this creates a line of symmetry. Both the bounce-back and symmetry boundary conditions are of the same second-order accuracy as the LBM scheme itself as long as the solid wall or line of symmetry is placed half-way in between neighboring nodes.

5.3 Physiological Data

One of our initial goals was to capture true \textit{in vivo} villous motility using high-resolution MRI. However, limitations imposed by an inescapable tradeoff between spatial and temporal resolution using this imaging modality have not allowed for time resolved
imaging of such small structures. Therefore, we are limited to the relatively minimal amount of quantitative information available in the literature.

It is known that humans have primarily finger-like villi and that rats have primarily leaf-like villi (although rats do have finger-like villi as well) [3]. It is also known that fewer motility patterns have been observed in leaf-like than in finger-like villi, however, very little information, with no quantitative data, given in the literature for either the human or the rat. The macro-scale motility data that we have gathered using MRI has been in the rat, so there is motivation to continue with this animal model; however, we know very little of the villous motility patterns in the rat. Ideally, we would model the human intestine for direct relevance to human implications; however, this would create a complete dependence on the literature for parameters, little of which exists for the villi. Therefore, for practicality purposes, we continue to use the physiological parameters extracted from the MRI analysis (see Section 3.1.3) for the macro-scale portion of the model.

5.4 The Geometry Model

The macro-scale motility is identical to that used for the 3D macro-scale model presented in Section 4.1, with the exception of the use of symmetry to simulate only one quarter of the gut to reduce computational expense. The geometry model is discussed again here to facilitate the ability to read this chapter independently.

The data extracted from the MRI experiments were used to parameterize a mathematical model of the wall geometry of the moving intestine. The model encompasses both modes of intestinal motility, peristalsis and segmentation, where the modes can be activated independently or in any desired weighted linear combination of the two. That is,
the position of the intestinal wall, $h(x,t)$, at axial location, $x$, and time, $t$, is determined as follows:

$$h(x,t) = w_s h_s(x,t) + w_p h_p(x,t), \quad \text{subject to: (5.10)}$$

$$w_s + w_p = 1 \quad \text{(5.11)}$$

where $h_s(x,t)$ is the contribution from segmentation, and $h_p(x,t)$ is the contribution to the overall intestinal wall position from peristalsis. The weighting coefficients, $w_p$ and $w_s$, control the relative influence of peristalsis and segmentation respectively on the overall geometry.

The geometry is symmetric about the centerline, and periodic in both space and time. A straight segment of the gut, rather than an intestinal segment, or loop, with more curvature, is used for simplicity.

Segmentation is modeled as a series of alternating 180° out-of-phase contractions. That is, as one particular segment contracts, the neighboring segments expand, and vice versa. This trend continues periodically in time. The time-changing geometry was constructed using straight piecewise sections for the contracting segments, and quarter sine waves connecting the straight sections for spatial continuity (see Figure 3-1(b)). As with peristalsis, the actual segmenting contractile patterns present in the intestine are more complex. In particular, a minor backwards-forwards axial motion at the contracting segments has been observed that is not included in the geometry model under the assumption that the dominant mixing motions within the chyme are generated by the radial displacement of the lumenal surface. Our segmental model is otherwise qualitatively similar to the actual observed motions and to the simpler model presented by Macagno, et al., [11].

Peristalsis was modeled as continuous train of sinusoidal waves propagating along the upper and lower walls from left to right with constant velocity (see Figure 3-1(a)). The
actual peristaltic motions in the gut are less ideal, both in shape and temporal continuity. However, the objective is to capture the average characteristics of propagating contraction waves. This simplistic representation is consistent with previously presented studies [e.g. 16,18].

Both motility modes are parameterized geometrically using the “base” set of quantitative values extracted from the MRI analysis given in Table 3-1. Important parameters include length scale (wavelength), time scale (period of contraction or wave propagation), and maximum and minimum radii from which an occlusion ratio can be defined:

$$O.R. = \frac{R_{\text{min}}}{R_{\text{max}}}$$  \hspace{1cm} (5.12)

These parameters can then be altered systematically to provide more insight into possible optimizations and further functional/physiological significance.

We extend the macro-scale geometry to include the finger-like villi developed for the 3D villous motility model discussed in Section 4.2.3. The villi are modeled as thin, cylindrical protrusions with hemispherical tips, located along the inner lumenal surface (see Figure 5-1). An arbitrary number of villi can be specified in the domain using two parameters: the number of villi in the axial direction and the number of villi in the azimuthal direction. Although any independent spacing could be specified in this manner, all of the experiments conducted with this model were done with uniformly spaced villi. That is, the center-to-center distances between neighboring villi in both the axial and azimuthal directions are equal.

The villi move passively with the movement of the outer gut walls. That is, at all times, they remain normal to the surface. In addition, active villous moments can be
specified. Womack et al. [3] state that finger-like villi have been observed to exert contractile pumping motions, side-to-side whipping or pendular motions, and/or tonic contractions, in which several or all villi move together. We continue the convention of our villous motility models for consistency and simplicity and limit our experiments to the case of oscillatory pendular motions, and investigate the tonic contractions by arranging them in groups of synchronously moving villi. However, we include oscillatory movements in both axial and azimuthal directions.

5.5 Numerical Experiments

We utilize the 3D combined model of macro- and micro-scopic motility to predict the fluid motions, and associated nutrient (scalar) advection/diffusion in a series of experiments designed to understand the influence of each type of motility, and the coupling between the disparate motility scales.

We use the “uniform” initial condition case, as described in Section 4.1.6, and shown in Figure 4-2 for the macro-scale 3D model without villi. The scalar concentration is set to $\phi \approx 1.0$ at each fluid node within the computational domain, and is thus uniformly distributed at the start of the scalar concentration calculation. The true physiological distributions of nutrient concentration are impossible to know, and could vary infinitely in presentation. However, the uniform initial condition allows a simple, standard means of comparison, in which we can compare the effectiveness of different experiments by how efficiently the nutrients are absorbed from the initial distribution. For each case, the quantity of fluid (volume) within the domain varies based on the macro-scale geometry as well the
number of villi in the domain. Therefore, the actual value of scalar concentration is varied such that the total amount of scalar in each experiment remains constant for consistency.

We quantify nutrient absorption using two methods: calculation of the normal flux of scalar through the absorptive walls to obtain local scalar flux versus axial position, and tracking of the net exchange of scalar during the modified moment propagation method at the boundaries to calculate the rate of scalar absorption. The flux, $J_\phi$, through the surface is given by:

$$J_\phi = D_s \frac{\partial \phi}{\partial n},$$  \hspace{1cm} (5.13)

where $s$ indicates that the derivative is taken at the surface and $n$ is the direction normal to the surface. The flux is calculated on a central axial cross-sectional plane to take advantage of the axisymmetry and to simplify interpolation of scalar concentration values necessary for calculation of the derivative.

To calculate the absorption rate, we track the net exchange of scalar at the boundaries that occurs with the modified moment propagation method. That is, we calculate the difference (first RHS term of Equation 5.7) between scalar exchanged between neighboring nodes that exist on either side of the intestinal walls. The total net difference of all the boundary exchanges at a given time step represents the total amount of scalar absorbed between the current and previous time step. The derivative of this running total with respect to time is the scalar absorption rate, $J_\phi$.

The Schmidt number was $Sc=50$. The $Sc$ in the gut are orders of magnitude higher in the gut, however practical constraints restricted the use of such values. A discussion of the $Sc$ and its influence on the simulations is presented in Section 3.1.6.
Villous Height. The effect of villous height on absorption rate was investigated by varying the height of the over a range of physiologically relevant values. Five heights were investigated for both axial and azimuthal pendular motility: 200µm, 300µm, 400µm, 500µm and 600µm. The other simulation parameters were held constant to isolate the effect of the height. The frequency ratio (the ratio of villous frequency to macro-scale motility frequency, $f_v/f_m$, was held constant at $f_v/f_m=50$. With the macro-scale period being $T_m=2.5s$, the macro-scale frequency ($f_m=1/T_m$) was 0.4Hz. Thus, the villous frequency is 20Hz. This frequency was chosen for consistency with the villous motility simulations carried out with the 3D lid-driven cavity model discussed in Section 4.2. The villi oscillate in unison, and are distributed uniformly over the inner lumenal surface (i.e. same spacing between villi in the axial and azimuthal directions) with 48 villi in the axial direction and 20 villi in the azimuthal direction (960 villi total in the quarter-domain). The effect of height was examined without the influence of macro-scale motility due to physical geometrical limits existing in the contracted regions of macro-scale motility. If the villi are too large, they touch in the contracted region, and cause numerical instability. A suitable structure-structure interaction scheme might allow such touching to occur without stability issues, however the complexity of modeling such schemes was prohibitively impractical for our needs.

Oscillation Frequency. The effect of villous oscillation frequency was investigated by varying frequency ratio. Six frequency ratios for both axially and azimuthally moving villi are investigated: $f_v/f_m=10$, 20, 30, 40, 50, and 60. This corresponds to villous frequencies of 4Hz, 8Hz, 12Hz, 16Hz, 20Hz, and 24Hz. A control case of zero frequency (stationary villi) was also included. The other simulation parameters were held constant to isolate the effect
of oscillation frequency. The villous height is $l_v = 300\mu m$. There were 960 uniformly distributed villi as in the villous height simulations.

**Villous Grouping.** The effect of villous grouping is investigated by dividing the villi into specified counter-oscillating groups in the axial direction, which move in opposite, $180^\circ$ out-of-phase directions with respect to neighboring groups. This means that at the dividing line, the villi are oscillating directly against each other, potentially creating the vertical pumping effect found to underlie the creation of a micro-mixing-layer in the lid-driven cavity flow models (see Sections 3.2.5 and 4.2.5). When the villi are divided into groups, a row of villi in the axial direction between the groups must be removed to ensure that the villi do not touch as they oscillate toward each other. Four groupings of axially moving villi are investigated: 2, 3, 4, and 8 groups. Only axially moving villi were used, as the symmetry boundary condition limits the groupings possible in the azimuthal direction. However, as a result of the symmetry boundary condition itself, there are always four groups of villi in the azimuthal direction; villi oscillate in opposite directions on each side of the plans of symmetry.

**Villous Spacing.** The effect of villous spacing is investigated by varying the total number of uniformly-spaced villi in the domain. In maintaining the uniform spacing, the distance between neighboring villi varies: the space between them is inversely proportional to the number of villi in the domain. Four cases were examined for both axially and azimuthally moving: 60 villi (12 axial rows by 5 azimuthal rows), 240 villi (24 axial rows by 10 azimuthal rows), 540 villi (36 axial rows by 15 azimuthal rows), and 960 villi (48 axial rows by 20 azimuthal rows).
Macro-/Micro-scale Motility Interaction. The numerical experiments outlined above were restricted to movements of the villi alone, in the absence of macro-scale motility. In such cases, the “gut” was a straight, fixed tube with no wall movements. The utility in the combined model presented in this section, however, lies in the analysis of the interactions between motility at the macro- and micro-scales. While it is difficult to conduct a systematic parameter variation as in the previous experiments, we can strategically investigate the impact of macro-scale intestinal motility, micro-scale villous motility, and the interaction between the two. First, we investigate the control cases: (1) no macro-scale intestinal motility (fixed tube) with no villi on the inner surface, (2) peristaltic motility with no villi, and (3) segmental motility with no villi. These cases establish a baseline to which to compare the cases that include the presence of villi. Then we investigate the cases where the villi are present, but are not actively moving: (4) no macro-scale intestinal motility (fixed tube) with fixed (non-moving) villi on the inner surface, (5) peristaltic motility with passively moving villi (villi that move along with the macro-scale motility, but do not have any active axial or azimuthal component of villous motility), and (6) segmental motility with passively moving villi. These cases allow the influence of active villous motility to be isolated from the simple presence of villi on the inner surface, which inherently have an influence on the available absorptive surface area. The final cases provide information on the actual effect of active villous motility, and are conducted for both axial and azimuthally moving villi: (7) no macro-scale intestinal motility (fixed tube) with actively moving villi on the inner surface, (8) peristaltic motility with actively moving villi (villi that move both with the macro-scale motility, as well as with an active axial or azimuthal component of villous motility), and (9) segmental motility with actively moving villi. These experiments will be the most useful in
investigating our hypothesis that active villous motility, coupled with macro-scale intestinal motility patterns, provides a critical interaction that allows for the efficient absorption observed in the gut.

5.6 Results

**Villous Height.** Figure 5K3 shows the effect of villous height on absorption, where the general term “absorption” refers to the percentage of nutrients absorbed after equivalent of three periods of macro-scale motility, or 7.5 total seconds (the walls are held fixed for the villous height calculations, but the time scale is still used as a reference). Seven and a half seconds corresponds to 150 periods of micro-scale motility, so the effects of the various lengths have had sufficient time to evolve. The percentage of nutrients (scalar) absorbed after three equivalent macro-scale periods is plotted versus villous height for each of the five villous height simulations, for both axially (shown in blue) and azimuthally moving villi (shown in red). Absorption rate increases rapidly with villous height. The effect is stronger for azimuthally moving villi, which is better for absorption than axially moving villi in all cases. It is interesting that there is such a difference between 500µm and 600µm for the axial villous motility case. It is not immediately clear why this is the case, as it is not consistent between the two different directions of villous motility.

**Oscillation Frequency.** Figure 5K4 shows the effect of oscillation frequency on absorption. The percentage of scalar absorbed after three equivalent macro-scale periods (7.5s, the walls again are fixed for these experiments) is plotted versus villous oscillation frequency for both axially (shown in blue) and azimuthally moving 300µm villi (shown in green). Two other cases are also presented in Figure 5K4 for comparison. In addition, a case
with four groupings of villi is shown (in orange). Increasing the oscillation frequency monotonically increases absorption for all cases tested, except the single group of axially moving villi. Each increase in frequency ratio has an increasingly larger impact in all cases.

Interestingly, the azimuthally moving case and the case in which the villi are grouped into four groups are very similar. Presumably, this is due to both cases being effectively grouped, generating wall-normal fluid motions and a stronger MML. In the axial case, the grouping is specified. In the azimuthal case, the grouping occurs as a result of the symmetry boundary conditions imposed at the x-z and y-z planes of symmetry. This result supports the observations of the pumping effect and MML formation made with the 2D and 3D cavity flow models. We also find that absorption is less sensitive to the specific direction of villous oscillation and more sensitive to the number of pumping regions created.

**Villous Grouping.** Figure 5-5 shows the effect of grouping the villi into 180° out-of-phase counter-oscillating groups. The percentage of scalar absorbed after three equivalent macro-scale periods (7.5s, the walls again are fixed for these experiments) is plotted versus the number of groups of axially moving villi. The absorption increased for each increase in the number of groups. The curve is not smooth, however. For instance, there is a slightly more than 2.5% increase between a single group of villi moving in unison, and two groups of villi counter-oscillating. The difference between two groups, and three groups, however, is much more modest. Increasing the grouping from three groups to four groups has a much more substantial impact, with four groups being more than 5% more effective than three groups. Doubling the number of groups from four groups to eight groups increases absorption effectiveness by less than 2%. It not apparent why the curve is not smooth. Perhaps due to a sensitivity to the specific configuration of the villi, which did not seem
present in the investigation of villous frequency where the curves for four axially moving
groups of villi and four azimuthally moving groups of villi were so similar (see Figure 5-4).

**Villous Spacing.** The effect of villous spacing on absorption is quantified in Figures
5-6 and 5-7. Figure 5-6 shows the instantaneous absorption rates at the equivalent of three
macro-scale periods (7.5s, the walls are again fixed for these experiments) versus the number
of villi in the axial direction for axially moving villi. With an increase in the number of villi in
the axial direction comes an increase in the number of villi in the azimuthal direction, as the
villi are uniformly spaced. The black curve shows the total absorption rate through all
absorptive surfaces in the model. The blue curve shows the absorption rate through the
villous surfaces, and the red curve shows the absorption rate through the intravillous space
on the inner surface of the gut. There is an obvious trade-off between the contributions to
the total absorption rate from the villous surfaces and the inner intravillous surface. When
the number of villi is low (sparsely packed), most of the absorption occurs through the inner
intestinal surface. As the number of villi increases, more of the absorption occurs through
the villous surfaces. When the number of villi in the axial direction is ~20, the contributions
are roughly equal. This is reasonably intuitive, and is most likely a surface area effect. More
of the absorption will occur simply where more of the available absorptive surface area is
available.

Figure 5-7 shows the instantaneous absorption rates at the equivalent of three
macro-scale periods (7.5s, the walls are again fixed for these experiments) versus the number
of villi in the axial direction for azimuthally moving villi. The black curve shows the total
absorption rate through all absorptive surfaces in the model. The blue curve shows the
absorption rate through the villous surfaces, and the red curve shows the absorption rate
through the intravillous space on the inner surface of the gut. The trade-off between the contributions to the total absorption rate from the villous surfaces and the inner intravillous surface still exists; however, the overall absorption rate now increases rapidly with number of villi in the gut segment. This increase is due to villous motility since the absorption rate through the intravillous space on the macroscopic gut surface is nearly identical for both axially moving and azimuthally moving villi.

The difference between axially and azimuthally moving villi highlights the potential importance of the villi working together in coordinated groups. As previously mentioned, azimuthally moving villi are inherently grouped by construction due to the symmetry boundary conditions. The pumping that results from neighboring groups oscillating toward each other plays an important role, perhaps a dominant role, in the mixing of the nutrients in the near wall region and enhancing absorption. In the absence of this mechanism, the overall absorption rate does not increase substantially, even when the villi are oscillating at 20Hz in the axial direction (see Figure 5-6).

**Macro-/Micro-scale Motility Interactions.** The effects of the interaction between the fluid motions driven by macro-scale intestinal motility and those driven by micro-scale villous motility is summarized in Figure 5-8, where the percent of the initial amount of scalar (nutrients) absorbed after three periods of macro-scale motility (7.5s) is shown for various cases. The bar chart is organized such that the black bars indicate cases with macro-scale motility turned off, leaving a fixed tube of nominal gut diameter (6mm) with no macro-scale flow. The blue bars indicate cases with peristaltic motility; red bars indicate segmental motility.
Each of the five groups of bars corresponds to a specific type of villous motility as indicated below each group. The left-most group in Figure 5-8 is the control case, with no villi present. For instance, the black bar in the leftmost group indicates the case with no macro-scale motility, and no micro-scale motility, or pure diffusion in a stagnant tube. The other four groups of bars, from left to right, correspond to: a single group of passively moving villi (villi that move only because they remain normal to the moving macroscopic surfaces, a single group of fixed villi in the case of no macro-scale motility), a single group of axially moving villi at 20Hz, azimuthally moving villi at 20Hz (inherently four groups), and four groups of axially moving villi.

The addition of villi increased absorption by 48%, 53%, and 52% for the cases of no macro-scale motility, peristalsis, and segmentation respectively relative to the no villi case. Presumably, the cases in which macro-scale motility was present created a larger increase in absorption due to the additional passive movement of the villi induced by the requirement that the villi remain normal to the deforming lumenal surface.

When an active component of villous motility was added to the passive component of villous motility, absorption increased further than with passive movements alone. A single group of axially moving villi on the inner surface cases with no macro-scale motility, peristaltic motility, and segmental motility increased absorption by only an additional 1-2% relative to the case with only passive villous motility. Azimuthally moving villi (inherently four groups, see Section 5.5) have a substantially stronger effect, increasing the absorption by an additional 25%, 18%, and 16% for cases with no macro-scale motility, peristaltic motility, and segmental motility, respectively, relative to the case with only passive motility. Four groupings of axially moving villi increase the absorption by an additional 25%, 11%,
and 6% for the cases with no macro-scale motility, peristaltic motility, and segmental motility case, respectively, relative to the passive villous motility case alone.

The increase in absorption with four active groups is nearly the same for azimuthally and axially moving villi when no macro-scale motility exists. When macro-scale motions interact with micro-scale motions, the influence of the villi on absorption is enhanced. In both cases, the wall-normal fluid motions generated by counter-oscillating groups of villi appear to be the primary effect on enhancement of absorption. This is an observation that extends back to our first macro-micro-scale experiments with the 2D lid-driven cavity flow model (see Section 3.2).

We learn from the current simulations that a second important effect is three-dimensionality. Axial villous movements largely maintain axisymmetry of the flow, interacting mostly in the r-z plane with the macro-scale fluid motions. Azimuthal villous motility increases mixing by introducing 3D fluid motions caused by the interaction with the macro-scale flow. The 3D effects that enhance mixing likely increase absorption along the sides of the villi. This is in addition to the enhancement at the MML by wall-normal ejections between groupings of counter-oscillating villi.

5.7 Discussion

The intestinal fluid mechanics model presented in this chapter (see Figure 5-1) represents the most complete model to date applied to the study of nutrient absorption in the gut. Previous models presented in the literature model only a single motility pattern, mostly peristalsis, and have not quantified absorption and its relationship to the fluid patterns generated by the gut deformations. Our model not only includes peristaltic and
segmental motility patterns, with the ability to combine the two patterns to analyze more complex forms of gut motility, but also macro-micro-scale interactions with a MML induced by villous motility. This presents the opportunity to analyze the multi-scale physics as a unified coupled system. The ability to study villous motility as a means of fluid mixing and absorption enhancement has not been previously attainable, and is currently only possible computationally with massive computational resources.

Using this multi-scale three-dimensional model of coupled macro-scale and micro-scale intestinal motility, we have gained a much more complete understanding of the absorption process as generated by the fluid patterns induced by both types of motility. In our initial series of experiments, we were able to confirm the findings from the 2D and 3D lid-driven cavity flow villous motility models. We have shown that villous motility increases nutrient (scalar) absorption. Nutrients were absorbed more efficiently when either villous height and/or villous oscillation frequency was increased. These trends were true in all types of motility tested, whether the villi moved axially, azimuthally, or in coordinated counter-oscillating groups (see Figures 5-3 and 5-4).

The wall-normal pumping effect between neighboring groups of villi was consistent with our previous findings using the cavity flow models and is an important element in the enhancement of absorption by villous motility. The effect seems to diminish with increasing number of groups, however, with eight groups of villi being only slightly more advantageous than four groups (see Figure 5-5). Four moving groups seems to be an optimal, advantageous configuration in our simulations, independent of whether the four groups are axially or azimuthally moving. This is evidenced in the cases when macro-scale motility was
not present, such as in Figure 5-4, when the curves of these two configurations of villous motility are very similar.

Azimuthally moving villi appear to enhance absorption more relative to axially moving villi. In Figures 5-6 and 5-7, azimuthally moving villi increased the absorption rate through the villi themselves more substantially than axially moving villi; the effect increased as the number of villi in the domain increased. Azimuthally moving villi are even more advantageous when combined with macro-scale motility.

The combined macro-/micro-scale motility experiments were the motivation for the development of the model presented in this chapter. Figure 5-8 summarizes the findings, as we systematically varied the types of macro- and micro-scale motility to seek an optimal configuration. An investigation for an optimal configuration was necessary, as there is currently no quantitative information on how villi actually move in the undisturbed \textit{in vivo} small intestine. The experiments we have conducted provide a guide to intestinal absorption if the villous motility were to be in the configurations we have tested. The actual motions of the villi \textit{in vivo} are currently unknown.

With our assumed villous motility pattern simulations, we were able to confirm that the best absorption characteristics occur when both macro- and micro- motility are active. We showed that adding villi to the simulation increased absorption by roughly 50% for all types of macro-scale motility (including no macro-scale motility). It has been our hypothesis, however, that it is active villous motility, not passive, that causes mixing in the near wall region, increasing absorption beyond that produced by macro-scale motility alone. When such active villous motility was added to the model, the absorption did indeed increase beyond that of the passive motility alone. Axially moving villi, however, only slightly
increased absorption, by 1 to 2% over the case of passively moving villi. Azimuthally moving villi, on the other hand, produced the optimal absorption characteristics.

Azimuthal villous motility enhanced absorption by an additional 16-25% relative to the passively moving villi case. There are two effects that contribute to the advantage of azimuthally moving villi over axially moving villi. The first is the inherent grouping configuration of the villi themselves as discussed in Section 5.5. We have shown that the pumping effects associated with villous grouping enhance the generation of micro-mixing-layer and have a major impact on absorption. The second effect is a stronger 3D interaction between the fluid patterns generated at macro- and micro-scales. With the axisymmetry of the intestine, the fluid patterns at the macro-scale level take place only in the r-z plane, when no villi are present to introduce 3D effects. Axial movements largely maintain this axisymmetry, while azimuthal movements introduce substantial 3D fluid velocities in the azimuthal direction, transverse to the macro-scale fluid movements. Such transversely interacting fluid motions generate 3D motions that enhance mixing and absorption.

In reflecting on our conclusion that active villous motility does indeed enhance absorption when compared to passive villous motility, we note that the villous oscillation frequencies used to generate these results are reasonably high. Twenty hertz (20Hz), which was used as the “base” case, means that the villi travel through one periodic side-to-side pendular motion 20 times each second. This was chosen be consistent with the 2D and 3D cavity flow villous motility models as the frequency at which the effects of villous motility were most apparent with the previous models.

If the villi do move in the azimuthal direction, as they would if the gut wanted to optimize the impact of villous motility on absorption, Figure 5.3 shows that the villi would
need to oscillate at more than 4Hz before an effect on the absorption is noticeable, and 8Hz before the effect becomes appreciable. Four or eight oscillations per second is still reasonably fast, when considering it takes 2.5 seconds (corresponding to a frequency of 0.4Hz) for one period of segmental or peristaltic intestinal motility.

This said, however, we do not know how the in vivo villi move in their undisturbed state. It is possible that the villi oscillate at high frequencies or that highly impulsive high-frequency oscillations exist in burst for shorter periods of time but over regular intervals. Womack, et al. [3] describes “whip-like” villous motility patterns in ex vivo intestinal segments. Although the authors do not describe the motions in further detail, these words suggest a sudden movement of the villi in one direction and snapping back into the opposite direction. Such whip-like movements could certainly take place at higher frequencies than the sustained oscillations that we use in our model. In the absence of in vivo data, we have presented a comprehensive study that describes the fluid and absorptive mechanics that could underlie the macro-micro-scale interactions in the intestine and enhance absorption.
Figure 5-1: The combined multi-scale model of both macro-scale intestinal motility and micro-scale oscillatory villous motility. The case of segmental intestinal motility with 960 villi is shown.
Figure 5.2: Schematic of pre- and post-streamed distribution functions according to the: (a) the “bounce-back” boundary condition for the no-slip condition at a solid wall (black line), and (b) the symmetry boundary condition at a plane of symmetry (dot-dash line). Black circles are nodes within the computational domain; white circles are “phantom” nodes outside the domain. Black arrows indicate pre-streamed distribution functions; red arrows indicate post-streamed distribution functions if the phantom nodes were “normal” (black) nodes within the fluid domain; blue arrow indicate post-streamed distribution functions at the nodes where they are actually streamed according to the respective boundary conditions; green arrows indicate the effective pre-streamed distribution functions that become the blue post-streamed distribution functions.
Figure 5.3: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus villous height. The frequency ratio was held constant at $f_v/f_m=50$ (20Hz) for all cases. No macroscopic motility. Villi are in a single group (960 villi).
Figure 5.4: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus villous oscillation frequency for various cases. The villous length was held constant at $l = 300\,\mu m$; the villous grouping was held constant at a single group of villi, with the exception of the orange curve, which had four groups of villi. No macroscopic motility. Villi are in a single group (960 villi). Note: To convert from “frequency” to “frequency ratio”, the frequencies can be divided by the macro-scale motility frequency (0.4 Hz).
Figure 5.5: Percentage of initial scalar remaining after three equivalent periods of macro-scale motility (7.5 total seconds) versus number of groups of villi. The villous length was held constant at \( l = 300 \mu m \); the villous frequency ratio was held constant at \( f_v / f_m = 50 \) (20Hz). No macroscopic motility. Villi move axially.
Figure 5-6: Instantaneous absorption rate at three equivalent periods of macro-scale motility (7.5 seconds) versus number of villi axial direction for axial villous motility. The villous length was held constant at $l_v=300 \mu m$; the villous frequency ratio was held constant at $f_v/f_m=50$ (20Hz). The black curve shows the total absorption rate; the red curve shows the absorption rate through the intravillous space on the macroscopic inner gut surface; the blue curve shows the absorption rate through the villous surfaces. No macroscopic motility. Villi are in a single group.
Figure 5.7: Instantaneous absorption rate at three equivalent periods of macro-scale motility (7.5 seconds) versus number of villi axial direction for azimuthal villous motility. The villous length was held constant at $l_v=300\mu m$; the villous frequency ratio was held constant at $f_v/f_m=50$ (20Hz). The black curve shows the total absorption rate; the red curve shows the absorption rate through the intravillous space on the macroscopic inner gut surface; the blue curve shows the absorption rate through the villous surfaces. No macroscopic motility. Villi are in a single group.
Figure 5.8: Percent of initial amount of scalar (nutrients) absorbed after three macro-scale motility periods (7.5s) for various cases. The black bars represent cases with no macro-scale motility; the blue bars represent cases with peristaltic macro-scale motility; the red bars represent cases with segmental motility. The bar groups represent different cases of villous motility, as indicated by the labels below the groups. For all cases with active villous motility, the villous length was held constant at $l_v=300\mu m$; the villous frequency ratio was held constant at $f_v/f_m=50$ (20Hz). The occlusion ratio for all cases with macro-scale motility is held constant at $O.R. = 0.65$. 

No Villi Passive Villous Motility (1 group of villi) Active, Axial Villous Motility (1 group of villi) Active, Azimuthal Villous Motility (4 groups of villi) Four Groups of Axial Villous Motility (4 groups of villi)
Table 5.1: Base motility parameters used as input for combined multi-scale model of intestinal/villous motility.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal Intestinal Diameter (mm)</td>
<td>6.00</td>
</tr>
<tr>
<td>Wavelength (mm)</td>
<td>12.00</td>
</tr>
<tr>
<td>Occlusion Ratio (mm)</td>
<td>0.65</td>
</tr>
<tr>
<td>Period of Contraction (s)</td>
<td>2.50</td>
</tr>
<tr>
<td>Wave Speed* (mm/s)</td>
<td>4.00</td>
</tr>
<tr>
<td>Villous Height (μm)</td>
<td>300.00</td>
</tr>
<tr>
<td>Villous Diameter (μm)</td>
<td>60.00</td>
</tr>
<tr>
<td>Villous Oscillation Frequency (Hz)</td>
<td>4.00</td>
</tr>
</tbody>
</table>

* Wave speed applicable to peristalsis only.
6.1 Review of Overall Study

Previous studies presented in the literature [e.g. 22,23] suggest the existence of some (as of yet) unknown \textit{in vivo} mechanism which provides highly effective mixing of the lumenal contents, reducing the thickness of the diffusion-dominated region near the inner surface of the intestinal walls, and promoting quicker and more effective nutrient absorption. It has been difficult to study this unknown mixing mechanism, largely due to the difficulty of observing micro-scale gut function without intrusive methods that disturb the natural state of the gut. Thus, essentially no details of the \textit{in vivo} mechanism are known. It has been suggested, however, that local mixing might be generated by active movement of the villi [e.g. 21]. The smooth muscle fibers that run along the central axis of each villus (see Figure 1-4) provide a possible means for movement.

While no \textit{in vivo} data exists to confirm or refute this hypothesis, \textit{ex vivo} experiments have been performed in which such active villous movements have been observed in animals [3]. Segments of the gut have been exteriorized, cut open, placed in holding devices, exposed to a variety of stimuli, and observed under a microscope. Villous movements are reported to be of three distinct types: (1) axial contractions in which individual villi shorten in height, (2) whip-like or pendular side-to-side motions of a one more villi, or (3) tonic contractions of groups of villi [3]. All three of these motions could, from a fluid mechanics perspective, generate fluid motions that could enhance transport in the diffusion-dominated region. However, there has been no data provided in the literature to support this claim.
To facilitate a more complete understanding of the influence of macro- and microscale intestinal motility, as well as the interplay between the two scales on the efficacy of gut function, we have developed a multi-scale, lattice-Boltzmann-based computational fluid dynamics model of a simplified, yet physiologically relevant intestinal segment (see Chapter 5). The model incorporates both macro-scale motility (contractile patterns of deformations in the gut walls) as well as micro-scale motility (coordinated pendular movements of the finger-like villi that line the lumenal walls). The motility patterns at both scales can arbitrarily controlled, and/or turned on/off such that a more complete understanding of the interaction between the scales can be understood more clearly.

Along the way to the complete, multi-scale model, we developed less complex computational models, which we utilized to gain preliminary, but important specific information pertaining to gut function. These models were an important means developing the technological advances in modeling needed for the multi-scale model discussed above. The first of such models is a two-dimensional (2D) model of a simplified small intestinal segment, including peristaltic and segmental motility, but without villi (Figure 3-2a,b,c). The second is a stationary lid-driven cavity flow with moving “villi” on the bottom surface (Figure 3-11a,b). Both models include a passive scalar as a model of nutrient concentration suspended within the bulk flow of chyme such as to simulate the gut in the fed state. For anatomical and physiological relevance, the models are parameterized using magnetic resonance imaging (MRI) data gathered in the rat by our research group in a companion study [55].

With the 2D macro-scale intestinal model (see Section 3.1), we were able to show that peristaltic motility is integral to gut function, as propulsion of the intestinal fluid is
purely reliant on such contractile movements. Segmentation itself cannot provide such propulsive movements, and was shown to be the primary motility pattern that promotes mixing and absorption in the gut. Although we suspected that combinations of peristalsis and segmentation into more complex motility could be more advantageous with respect to normal gut function (absorption and transport), we found that it was the pure, independent modes that provided optimal results. That is, for transport, pure peristalsis provides the most desirable characteristics; for absorption, segmentation provides the optimal characteristics. Combinations of the two actually significantly degraded the function of the pure modes, even with only 5% interference from either motility pattern on the other (see Sections 3.1.6 and 3.1.7).

The 2D villous motility model (see Section 3.2) provided preliminary insight into the interaction between villous motility and a macro-scale circulatory pattern invoked by the moving cavity lid. The model was designed to simulate the circulatory nature of highly-occlusive peristaltic motility in the wave-frame. We verified our hypothesis that the modeled villous motion had the effect of increasing the nutrient (scalar) absorption rate. The rate of absorption increased both with villous height and frequency of villous oscillation. Both factors were shown to have an increasingly larger effect as the parameters increase. The grouping of counter-oscillating villi has an important impact on absorption, producing jet-like pumping motions between neighboring groups that enhance absorption and promote the formation of a “micro-mixing layer” (see Sections 3.2.5 and 3.2.6), that could be the unknown mixing mechanism discussed in previous studies [e.g. 22,23].

These 2D models were then extended to three dimensions (3D) to obtain further relevance to the true physiological system (see Chapter 4). The extended models were nearly
identical representations of the 2D models, but with the added complexity and degree of freedom afforded by the third dimension. The 2D macro-scale gut motility model became a 3D axisymmetric motility model (still without villi), while the 2D villous motility model became a rectangular lid-driven prism with finger-like villi.

Using the 3D macro-scale intestinal model (see Section 4.1), we were able to investigate the fluid mechanical mechanisms present in the gut in much more detail. We showed that peristaltic motility is not only integral to gut function as propulsive mechanism, but that the flow patterns created by peristalsis actually create high nutrient gradients at the wall, promoting absorption as well. Previous literature only makes mention of peristalsis as a transport mechanism, not as an absorptive mechanism. We showed segmentation to again be the principal mechanism for absorption in the gut for physiological occlusion ratios (ratio of minimum radius to average radius), confirming our findings using the 2D macro-scale model.

The power requirement analysis conducted provides a potential explanation as to why segmentation is the most often observed motility pattern in the gut even though peristalsis could in theory provide both the transport and absorption functions required by the small intestine. That is, although peristalsis promotes absorption as well as transport, to obtain the same level of absorption with peristalsis as with segmentation, the gut requires substantially more power. For instance, at an occlusion ratio of 0.4, we find that peristalsis is actually 28% more effective that segmentation in the later stages of absorption as seen in Figures 4-5(c-d). The power requirement at 0.4, however, is 181% higher for peristalsis versus segmentation. If the gut were optimizing the employed motility patterns, it would
seem reasonable that it would seek to minimize the amount of energy expended to absorb the nutrients from a meal (see Section 4.1.8).

The extension of the 2D villous motility model to 3D was insightful, as the effects of 3D villi could be examined. It was apparent from the 2D model that the three-dimensionality could have a substantial impact on the mixing effects generated above the villi. Using the 3D villous motility model, however, we found significant consistency with the 2D model for reasonably closely spaced 3D villi, showing that the absorption rate increased both with villous height and frequency of villous oscillation. However, the physics of the 3D system are more complex, and the effects change when the spatial configuration of the villi is changed.

We focused our attention on the formation of the micro-mixing-layer (MML) in the 3D experiments, as we have showed with the 2D model that this is the mechanism that reduces the nutrient gradients near the lower surface, increasing the absorption rate. The pumping motions between neighboring groups that exist in the 2D case are less effective for 3D, as fluid can “escape” around the side of the villi into the intravillous space, as shown in Figure 4-13, when the extra degree of freedom is introduced. The ability for the fluid to escape in such a manner is reduced when the villi are more closely packed. In closely packed configurations, the MML is more readily identified, and the absorption rate is increased.

In the real intestine, the villi are very closely packed, almost touching in most cases (see Figures 1-5 through 1-7). There is obviously a limit to how closely the villi can be packed for the type of motility mechanisms we have identified to be effective. However, the diminished effects we see when the villi are more sparsely configured are less likely in the real structure of the intestine.
After establishing the necessary technology required to develop the much more complex multi-scale model of coupled macro- and micro-scale motility, we were able to construct the combined model and utilize it to examine the fluid mechanics of the small intestine in a much more detailed way than has been done in the past. Our model represents the most complete model to date applied to the study of nutrient absorption in the gut. Previous models presented in the literature model only a single motility pattern, mostly peristalsis, and generally do not include the technology to study absorption along with the fluid patterns generated by the gut deformations. The model we have developed not only includes both motility patterns, with the ability to combine the motility patterns to analyze more complex forms of gut motility, but includes micro-scale villous motility, something that only has only been studied from a fluid mechanics point of view with our previously discussed models.

We first used the multi-scale model to confirm the findings from the 2D and 3D lid-driven cavity flow villous motility models, by turning off the macro-scale motility patterns. We showed that nutrients were absorbed more efficiently when either villous height and/or villous oscillation frequency was increased. These trends were true in all types of motility tested, whether the villi moved axially, azimuthally, or in coordinated counter-oscillating groups (see Figures 5-3 and 5-4).

We found that pumping motions between neighboring groups continued to be an important factor (as is consistent with the cavity flow villous motility models presented in Sections 3.2 and 4.2), evidenced by an increase in absorption when grouping was present. The effect seems to diminish with increasing number of groups, however, with eight groups of villi being only slightly more advantageous than four groups (see Figure 5-5).
We introduced azimuthally moving villi into the model, whereas the cavity flow models only contained axially moving villi (villi moving along the same axis as the macro-scale motions). Azimuthally moving villi were found to be more optimal for absorption than axially moving villi, both in cases where macro-scale motility was turned off, and when it was present.

Although it was important to confirm our previous findings with the cavity flow villous motility models, the combined macro-/micro-scale motility experiments were the true motivation for the development of the model presented in this chapter. Figure 5-8 summarizes the findings, as we systematically varied the types of macro-scale and micro-scale motility to seek an optimal configuration. We were limited to such a systematic search, as there is currently no quantitative information on how villi actually move in the undisturbed *in vivo* small intestine.

With our assumed villous motility pattern simulations, we were able to confirm that the best absorption characteristics occur when both macro- and micro- motility are active. We showed that adding villi to the simulation increased absorption by roughly 50% for all types of macro-scale motility (including no macro-scale motility). It has been our hypothesis, however, that it is active villous motility, not passive, that causes mixing in the near wall region, increasing absorption beyond that produced by macro-scale motility alone. When such active villous motility was added to the model, the absorption did indeed increase beyond that of the passive motility alone. Axially moving villi, however, only slightly increased absorption, by 1 to 2% over the case of passively moving villi. Azimuthally moving villi, on the other hand, produced the optimal absorption characteristics.
Azimuthal villous motility enhanced absorption by an additional 16-25% relative to the passively moving villi case. There are two effects that contribute to the advantage of azimuthally moving villi over axially moving villi. The first is the inherent grouping configuration of the villi themselves as discussed in Section 5.5. We have shown that the pumping effects associated with villous grouping enhance the generation of micro-mixing-layer and have a major impact on absorption. The second effect is a stronger 3D interaction between the fluid patterns generated at macro- and micro-scales. With the axisymmetry of the intestine, the fluid patterns at the macro-scale level take place only in the r-z plane, when no villi are present to introduce 3D effects. Axial movements largely maintain this axisymmetry, while azimuthal movements introduce substantial 3D fluid velocities in the azimuthal direction, transverse to the macro-scale fluid movements. Such transversely interacting fluid motions generate 3D motions that enhance mixing and absorption.

In reflecting on our conclusion that active villous motility does indeed enhance absorption when compared to passive villous motility, we note that the villous oscillation frequencies used to generate these results are reasonably high. Twenty hertz (20Hz), which was used as the “base” case, means that the villi travel through one periodic side-to-side pendular motion 20 times each second. This was chosen be consistent with the 2D and 3D cavity flow villous motility models as the frequency at which the effects of villous motility were most apparent with the previous models.

If the villi do move in the azimuthal direction, as they would if the gut wanted to optimize the impact of villous motility on absorption, Figure 5-3 shows that the villi would need to oscillate at more than 4Hz before an effect on the absorption is noticeable, and 8Hz before the effect becomes appreciable. Four or eight oscillations per second is still
reasonably fast, when considering it takes 2.5 seconds (corresponding to a frequency of 0.4Hz) for one period of segmental or peristaltic intestinal motility.

This said, however, we do not know how the \textit{in vivo} villi move in their undisturbed state. It is possible that the villi oscillate at high frequencies or that highly impulsive high-frequency oscillations exist in burst for shorter periods of time but over regular intervals. Womack, \textit{et al.} [3] describes “whip-like” villous motility patterns in \textit{ex vivo} intestinal segments. Although the authors do not describe the motions in further detail, these words suggest a sudden movement of the villi in one direction and snapping back into the opposite direction. Such whip-like movements could certainly take place at higher frequencies than the sustained oscillations that we use in our model. In the absence of in vivo data, we have presented a comprehensive study that describes the fluid and absorptive mechanics that could underlie the macro-micro-scale interactions in the intestine and enhance absorption.

\section*{6.2 Opportunities for Future Investigations}

Although we have developed a significantly complex model of combined intestinal motility across two disparate scales, as with any model, there are opportunities for improvement. The most obvious opportunity would be to improve the macro-scale geometry model to reflect more realistic contractile motility patterns. The patterns we have specified, while parameterized by geometrical values extracted from the true physiological conditions, are admittedly simplified. When extending our 2D models to 3D, we had attempted to devise a model that would accept direct boundary information from segmented MRI images. Code instability problems developed at the inlet/outlet boundaries, however, with a loss of the spatial periodicity inherent in our geometry model. It was apparent that a
better treatment of the inlet/outlet boundaries was required such that instability issues do not occur. Fixed pressure or velocity boundary conditions are a natural option, but without real data to use as boundary conditions, we are left to assume a pressure and velocity profiles. In addition, fixed pressure boundary conditions can create spurious oscillations that carry through the domain, causing further instability. We abandoned this model to focus on developing the combined model, leaving it as an opportunity for future improvement.

The micro-scale villous motility geometry could also be improved in the model. For our purposes, we used only pendular motions. However, pumping up/down motions have also been observed. We did not implement such villous motility, as there is a lack of information as to how the villi actually contract during this up/down type of motility. Do they drop down completely below the macroscopic gut surface? Do they merely shorten, with a corresponding thickening in diameter to conserve mass? The first option would require that when one villus contracts below the surface, another would need to be appearing such that mass is conserved in the computational domain. The second option would require more information as to how the villi actually contract: how far do they go down? How much do they thicken? Is there some amount of pseudo-compressibility from fluid being ejected below the surface such that the villi do not thicken much? These uncertainties introduced a sufficiently large unknown parameter space that we made the practical decision to stick to the pendular type motility that we had used in the past for the lid-driven cavity flow models.

Further improvements to the micro-scale villous motility geometry model could be introduced if a suitable imaging modality was used to acquire actual data on \textit{in vivo} movements of the villi. At this point, we are limited to largely qualitative description of
villous motility from the available literature. One of our initial goals was to use micro-MRI imaging to obtain this data in our rat experiments. However, capturing such small structures with enough temporal resolution as to quantify the motion proved to be beyond the limits of the equipment we had available to us, likely beyond the limits of current MRI technology. Advancements in imaging technology in the future could significantly enhance the geometry model if real data could be acquired.

Once the model has been geometrically improved, advancements could be made with the inclusion of other effects into the code. For instance, we currently model the fluid as Newtonian. It is likely that the non-Newtonian effects are of higher-order, however extending the model to simulate non-Newtonian would eliminate any question of the use of a Newtonian fluid, and provide a more realistic view of the flow in the intestine. Another opportunity would to simulate absorption of various types of nutrients. Currently, we use a passive scalar concentration to model the nutrients in the flow domain. While this is satisfactory for small molecules, such as simple sugars, larger molecules such as proteins could be simulated by incorporating molecular dynamics into the code. The LBM, with is mesoscopic, Lagrangian framework is particularly well suited for such an inclusion. Simulating multiple phases (gas bubbles and/or solid particles) could also improve the accuracy of the simulations. Intestinal fluids are approximately homogeneous viscous liquids; however, the system is not perfect, and solid particles and/or gas bubbles could possibly have an impact on the flow, mixing, and absorption in the gut.

Our intestinal model has provided insight on the fluid dynamics and absorption in a normally functioning gut, but it could also be employed to provide information on abnormal absorption in individuals with digestive diseases such as celiac disease (CD), an autoimmune
disorder characterized by deterioration of the villi as a response to gluten (the protein in wheat, rye, and barley). Historically, the role of the villi has been accepted as a means of increasing absorptive surface area, with little attention given to the role of active villous movement. Thus, it has been assumed that the reduction in surface area resulting from villi deterioration in gluten-exposed celiac patients produces the malabsorption that typically occurs in such patients. If villous motility plays a more important role than does surface area, it is possible that the shape of damaged villi produces inferior mixing agents from a fluid mechanical point of view. Several studies in the literature have presented high resolution microscopy images of damaged villi biopsies, from which an adequately representative geometry model could be developed and used for boundary conditions to simulate absorption phenomena existing in celiac patients [e.g. 164]. Alternatively, the reduction of the villous motility may itself inhibit absorption. A sensitivity analysis of various pertinent parameters such as shape, length, and frequency of villous motility could quantitatively indicate the factors responsible for malabsorption in celiac patients.

Such analysis could indicate that as gluten-exposed villi deteriorate in affected celiac patients, the longitudinal muscle fibers become increasingly less effective in generating sufficient amounts of the motility we believe is critical for normal absorption. This implicates drug therapy as a possible means of alleviating malabsorption until the villi regenerate in response to the removal of gluten from the diet. Data has been compiled in the literature showing the influence of various stimuli on villous motility [3]. If this hypothesis is correct, a pharmaceutical stimulus could induce more vigorous motions in less damaged villi, in effect compensating for the reduced motions of the more deteriorated structures.
APPENDIX A: TWO-DIMENSIONAL VS. THREE-DIMENSIONAL MODELING: A CAUTIONARY TALE

It is often advantageous to study three-dimensional (3D) systems with two-dimensional (2D) models as this reduces complexity and computational/experimental effort. In such 2D models, an implicit assumption is generally made that the overall physics and basic conclusions drawn from the results and analysis of the 2D model will apply to the actual 3D system. Examples include the basic non-dimensional relationship between drag and flow velocity over long cylinders (2D) versus spheres (3D), and the basic flow-occlusion-pressure relationships and qualitative flow structure in planar (2D) versus axisymmetric (3D) peristaltic pumps. There is danger, however, in blithely replacing 3D physics with the 2D physics of the model. Incorrect conclusions may result when the differences between 2D and 3D are more than incremental. We present here a cautionary tale in which seemingly sensible and potentially important conclusions drawn from a 2D model were nearly submitted for publication before a fundamental and important difference between 2D and 3D physics was discovered.

Our aim was to explore the hypothesis that absorption rate is neurophysiologically controlled and that optimal combinations of segmental and peristaltic motility exist that maximize absorption rate in the small intestine. To test this hypothesis, we developed a lattice-Boltzmann-based model of fluid flow and nutrient (scalar) absorption in a 2D gut for specified motions of the lumenal surface, with the intent to follow with a 3D, axisymmetric model to quantify what were assumed to be higher order 3D effects. This assumption was supported by years of previous axisymmetric and 2D studies. From the 2D model we
concluded that segmental contractions were always superior for absorption, and peristalsis was needed only for axial transport. This relatively simple conclusion, which has been an accepted assumption the literature for generations, seemed functionally sensible. We convinced ourselves that intestinal magnetic pill trajectories displayed segmental or peristaltic motility in binary fashion, with more complex motility occurring less frequently.

While putting the finishing touches on a manuscript with this conclusion, we generalized our 2D model to 3D and repeated some key simulations from the 2D study and were perplexed to obtain completely different results. In the axisymmetric 3D flow, peristalsis produced greater absorption than segmental motility! Many months later, after an exhaustive series of new simulations and analysis from the 2D and 3D models, we discovered that the complete physics is a great deal more complex and interesting than previously concluded, and potentially more significant for gut physiology and function. Here we focus on the cautionary tale and show that the assumption that a 2D model provides the basic physics of 3D systems may not be correct, especially when additional complexities such as scalar transport and surface fluxes are involved. We argue that greater caution should be exercised when reduced-dimensional modeling strategies are applied.

A.1 Introduction

When choosing a strategy to investigate the physics of a system of interest, one must carefully weigh the trade-offs between the cost and complexity of replicating the exact physical system and the possible deviation from the true physics when utilizing a simpler model. Often times it is prohibitively expensive, time-consuming, space-consuming, or otherwise impractical to replicate the true physical system. In such cases, one is forced to
develop a simpler, more practical model that still adequately represents the original system within some desired level of accuracy.

One frequently used technique to obtain relevant results from a simpler model of a more complex system is to reduce the dimensionality of the model being used. That is, for example, to develop a two-dimensional (2D) model of a three-dimensional (3D) system. Such reduced-dimensionality models can provide results similar to the 3D system with dramatic savings over true 3D models. In theoretical models, the mathematical equations that define the system are inherently simplified and more manageable; in computational models, the domain size and, thus, the computational expense and memory requirements are decreased; in experimental models, the space requirements and construction time could be reduced significantly. These appealing advantages have driven the use of 2D models of 3D systems throughout history.

A classic example of when the use of 2D results are relevant to 3D physics is in the basic non-dimensional relationship between drag coefficient, $C_D$, and Reynolds number ($Re$) in cross-flow over smooth circular cylinders (2D for sufficiently long cylinders) versus the same relationship for flow over a smooth sphere. Figure A-1 shows the average $C_D$ versus $Re$ for cross-flow over a smooth circular cylinder and a smooth sphere. As shown, the trends are very similar for the two cases throughout a broad range (seven orders of magnitude) of $Re$. $C_D$ is highest at low $Re$, decreases with increasing $Re$ until roughly constant between $\sim 10^3 < Re < \sim 10^5$, and then has a characteristic dip when the flow in the boundary layer becomes turbulent between $\sim 10^5 < Re < \sim 10^6$. Furthermore, the flow fields for these flows are nearly identical when scaled to account for modest differences in
magnitudes. In this example, if one were investigating flow over a sphere, a 2D model could provide qualitatively similar results with significantly less model complexity.

Another classic example is the similarity between 2D versus 3D laminar pressure-drive Hagen-Poiseule flow [157]. The 2D case represents pressure-driven flow between two parallel plates that are infinite in one dimension; the 3D case represents pressure-driven flow in a circular pipe. The fully-developed velocity and pressure profiles for the 2D and 3D cases are, as in the previous example, nearly identical when scaled properly. It is clear why the similarity exists when considering the analytical solutions for the 2D and 3D versions are given respectively as follows by Equations A.1 and A.2:

\[
u = \frac{1}{2\mu} \frac{dP}{dx} (y^2 - hy); \quad v = 0
\]  

(A.1)

\[
u_x = \frac{1}{4\mu} \frac{dP}{dx} (r^2 - R^2); \quad u_r = 0; \quad u_\theta = 0
\]  

(A.2)

where \(u\) and \(v\) are the axial and transverse velocity components respectively in the \(x\) and \(y\) directions for the 2D case in Equation A.1, and \(u_r, u_r,\) and \(u_\theta\), are the axial, radial, and azimuthal velocity components in for the 3D case in Equation A.2. The axial pressure gradient, \(dP/dx\), is driving the flow, \(\mu\) is the dynamic viscosity, \(y\) and \(r\) are the transverse and radial coordinates, and \(h\) and \(R\) are the height and radius for the 2D and 3D cases respectively [157]. The similarities between Equations A.1 and A.2 are apparent. It follows that one could obtain a significant amount of relevant qualitative information modeling 3D pipe flow using a 2D model.

An extension of the Hagen-Poiseulle Law flow to more complex geometries has yielded another example of when 2D models can be useful in predicting 3D physics. Flows
generated in peristaltic pumping at low $Re$ can be predicted using lubrication theory under the right conditions [e.g. 17,158]. Figure A-2 shows streamlines produced in 2D and axisymmetric (3D) sinusoidal peristaltic pumping for $Re=1$ [158]. There are apparent similarities between the qualitative flow structure in the 2D and 3D cases. The flow-occlusion-pressure relationships generated by 2D models, are also similar to those of the 3D, axisymmetric system [17,18]. Such peristaltic pumping is directly relevant to the flow in the gut, our personal research interest as presented in this paper. Contractile patterns (motility) of the musculature in the walls of the gut generate flow and mixing of the viscous fluid (chyme) within the lumen.

In weighing our own modeling options when setting out to model the inherently complex flow within the gut, we chose to proceed with development of an initial 2D model to obtain preliminary insight with reduced computational expense, memory requirements, and algorithmic complexity versus a larger 3D model. Our implicit assumption that the 2D model would provide relevant information to the actual 3D gut was based largely on years of studies presented in the literature on 2D and axisymmetric (3D) peristaltic pumping [e.g. 17,158]. We planned to follow the 2D model with a subsequent 3D model to quantify what we assumed to be higher-order 3D effects not captured with the 2D model.

In the following sections, we describe our experience in drawing seemingly relevant and logical physiological conclusions from our 2D model that were nearly published before determining that the actual 3D flow and nutrient absorption phenomena within the gut were quite different than the 2D model led us to believe. Our intention is to provide this experience as a “cautionary tale” to remind our readers (and of course ourselves) to exercise
great caution when utilizing reduced-dimensional modeling strategies to predict inherently 3D physical phenomena.

A.2 Methods

The motility patterns in the gut can be complex and difficult to classify. Motility varies with axial location, digestion phase, and caloric content of the chyme. Despite the complexity, however, two general classes of motility patterns (modes) can be identified: peristalsis and segmentation [e.g. 4,6,8]. Peristalsis is characterized by propulsive, wave-like propagations, and has been long associated in the literature with axial transport of chyme along the length of the gut. Segmentation is distinctly different from peristalsis as it is an essentially stationary motility pattern, characterized by rhythmic, repetitive radial contractions of short segments of the gut. The literature generally associates segmental motility with mixing of the lumenal content during the fed state to promote the absorption of nutrients [e.g. 8].

Our approach in this study was to develop a computational fluid dynamics (CFD) model of the flow of chyme within the lumen of the gut as generated by the two aforementioned motility modes, peristalsis and segmentation. The model was designed to facilitate an understanding of the details of mixing, transport, and absorption of nutrient concentrations in the normally functioning gut. Similar, albeit less comprehensive, studies have been presented in the literature [e.g. 13-16]. Peristalsis has been particularly well studied as a means of mechanically pumping fluid [e.g. 17,18]. Few similar quantitative studies, however, have been conducted on segmentation. Macagno et al. [15] provided one simple, but interesting model of a segmental-type motility pattern. We are unaware of any other such
studies on segmentation, or of any models developed to study both modes (segmentation and peristalsis) simultaneously.

We began with a 2D CFD model to gain preliminary insight before moving on to the development of a more complex 3D model. Both models were in-house codes developed within the lattice-Boltzmann framework, with moving boundary conditions, and passive scalar concentration components to model nutrient concentrations within the fluid flow. Both segmentation and peristalsis were incorporated into the model, and can be simulated individually or simultaneously in any desired weighted linear combination. The geometry of the motility patterns was specified using parameters extracted from \textit{in vivo} magnetic resonance imaging (MRI) of rats conducted in a companion study [55].

Although necessarily simplified, our model is (to our knowledge) the most complete CFD model of the gut to date. In this section, we present the details of the model and numerical experiments before going to discuss the seemingly conflicting results of the 2D and 3D models and reflecting on the lessons learned in the process.

\subsection{A.2.1 The Computational Model}

We applied the lattice Boltzmann method (LBM) to investigate the flow and mixing of chyme in the gut as generated by the motility patterns of the intestinal walls. The LBM is a simple, yet powerful technique that can handle the low-$Re$ flow and complex moving boundaries found in the gut [e.g. 100]. We incorporate a passive scalar concentration, via the modified moment propagation method to model concentrations of nutrients suspended in the chyme [121]. The computational model is parameterized by using data acquired from
MRI imaging of the rat intestine via a simplified time-dependent geometry model of gut motility patterns.

**Fluid flow model: the lattice Boltzmann algorithm.** The standard LBM solves a discretized form of the Boltzmann equation on a uniform (square or cubic) lattice. The lattice Boltzmann equation, with the Bhatnagar-Gross-Krook (BGK) collision operator, is given by as follows:

\[
 f_i(x + e_i \delta t, t + \delta t) = f_i(x, t) - \frac{1}{\tau} \left[ f_i(x, t) - f_i^{eq}(x, t) \right],
\]

where \( f_i(x, t) \) is the particle distribution function at discretized location \( x \) at time \( t \), with discretized velocity \( e_i \). The equilibrium distribution function, \( f_i^{eq}(x, t) \), toward which the distribution functions relax with time scale, \( \tau \), is typically as follows:

\[
 f_i^{eq}(x, t) = w_i \rho(x, t) \left[ 1 + 3 \frac{e_i \cdot u}{c^2} + \frac{9}{2} \left( \frac{e_i \cdot u}{c^2} \right)^2 - \frac{3}{2} \left( \frac{u}{c} \right)^2 \right],
\]

where \( \rho \) and \( u \) are the continuum-level density and velocity, \( w_i = \frac{4}{9}, \frac{1}{3}, \frac{1}{36} \) are the direction-specific weighting coefficients for center, off-diagonal, and diagonal directions respectively, and \( c \) is the basic speed on the lattice. The relaxation parameter, \( \tau \), defines the kinematic lattice viscosity as follows:

\[
 \nu = \frac{1}{2} c_s^2 \delta t (2\tau - 1),
\]

where \( c_s \) and \( \delta t \) are the lattice sound speed and time step respectively. Using a statistical mechanics approach, the continuum-level density and velocity are obtained from the first and second moments of the distribution function respectively:

\[
 \rho(x, t) = \sum_i f_i(x, t), \quad \text{and}
\]

\[
 u(x, t) = \sum_i f_i(x, t) \cdot e_i.
\]
\[
\mathbf{u}(\mathbf{x},t) = \sum_i f_i(\mathbf{x},t) \cdot \mathbf{e}_i / \rho(\mathbf{x},t),
\]

Pressure proportional to the local density using the following equation of state:

\[
P(\mathbf{x},t) = \rho(\mathbf{x},t) c_s^2,
\]

where the sound speed is typically: \( c_s = \sqrt{RT} = \sqrt{\gamma / \rho} \). We apply the nine-speed (D2Q9) form for our 2D model, and the 15-speed form (D3Q15) for our 3D model [e.g. 100].

**Nutrient concentration model: passive scalar.** To quantify the effectiveness of nutrient absorption, we incorporate a passive scalar concentration field, \( \phi(\mathbf{x},t) \), into the LBM fluid flow model. Advection and diffusion of the concentration within the chyme are predicted as a result of fluid motions generated by the deforming walls. Nutrient concentration is evaluated with the “modified moment propagation method”, as described by Merks et al. [121]. Unlike other methods, where the LBM is used to concurrently calculate the evolution of a second distribution function for the scalar [e.g. 118], the moment propagation method evolves the continuum level scalar field directly with fluid flow LBM distribution functions, according to the following equation:

\[
\phi(\mathbf{x},t+\delta t) = \sum_i \left( \frac{f_i}{\rho} - w_i \Delta^* \phi \right)_{x-\mathbf{e}_i \delta t} + \Delta^* \phi(\mathbf{x},t),
\]

where \( \phi(\mathbf{x},t) \) is the continuum level concentration of scalar at location \( \mathbf{x} \) at time \( t \). The molecular diffusivity-dependent \( (D_m) \) parameter, \( \Delta^* \), is given as follows:

\[
\Delta^* = 1 - 6D_m
\]
A.2.2 Boundary Conditions

In the small intestine, the fluid motions and resulting nutrient advection are induced by the deformation of the intestinal walls. Accurate simulation of these phenomena is therefore limited by the accuracy of the boundary conditions at the moving boundaries. In the current study, are careful to properly account for momentum transfer to the fluid from the deforming walls with second-order-accurate boundary conditions. Nutrient concentration also requires a reasonable boundary condition at the moving surface to model absorption through the epithelium. We apply a zero-scalar concentration condition at inner lumenal surface, implying effectively immediate nutrient absorption at the epithelium. This “immediate absorption” assumption is a reasonable model for most nutrient molecules since resistance to absorption is typically small compared to the time scale associated with the transport of nutrients from the bulk flow to the surface [144]. The inlet and outlet of the intestine are modeled using periodic boundary conditions, taking advantage of the inherently periodic nature of the geometry and the numerical stability of this boundary condition [100].

**Boundary Conditions at the Moving Surfaces.** The momentum of the fluid in the near-wall region is affected by deformations of the surface. To properly capture the transfer of momentum from the surface to the fluid, we apply the second-order-accurate boundary condition of Lallemand *et al.* [114]. This method extends the moving boundary bounce-back formulation of Ladd [112] to include interpolation for more accurate location of complex boundaries. The method employs one of two expressions according to the relative distance
from the nearest fluid node to the solid boundary, $q$:

$$f_i(x_i, t) = q(1 + 2q)[f_i^- (x_i, t)] + (1 - 4q^2)[f_i^- (x_2, t)] - q(1 - 2q)[f_i^- (x_3, t)] + 6w_i \rho (e_i \cdot u_i)$$

(A.11)

$$f_i(x_i, t) = \frac{1}{q(2q + 1)}[f_i^- (x_i, t)] + \frac{2q - 1}{q}[f_i^- (x_2, t)] - \frac{2q - 1}{(2q + 1)}[f_i^- (x_3, t)] + \frac{6w_i \rho (e_i \cdot u_i)}{q(2q + 1)}$$

(A.12)

Equation A.11 is used when $q < \frac{1}{4}$, while Equation A.12 is used when $q \geq \frac{1}{2}$.

**Zero-scalar concentration Boundary Conditions.** As the complex moving boundaries rarely align directly with nodes on the stationary lattice, the application of the zero-scalar concentration boundary condition is non-trivial. We force the scalar concentration to be zero at the walls indirectly by specifying the scalar concentration values at neighboring fluid nodes as prescribed by Wang et al. [145]. The process is omitted here for brevity, but discussed in more detail in Section 3.1.2.

**A.2.3 Physiological Data**

To ensure anatomical and physiological relevance of the CFD model, we performed an investigative study on the motility in the undisturbed *in vivo* rat intestine using dynamic MRI [55]. Quantitative values for important parameters such as diameter of the gut, magnitude of contractions, wavelengths, wave speeds, etc. were extracted using image and statistical analysis. The relevant results of the analysis, which establish a set of “base” parameters for the CFD model, are provided in Table 3-1. The details of the techniques used and further results are omitted here for brevity, discussed in more detail in Section 3.1.3.
A.2.4 The Geometry Model

The data acquired through the MRI experiments were used to parameterize a geometry model that specifies the wall movements that drive the flow within the CFD model. Both modes of motility, peristalsis and segmentation, are modeled, and can be enacted independently or in weighted combinations of the two as specified by:

\[ h(x, t) = w_s h_s(x, t) + w_p h_p(x, t), \quad \text{subject to:} \]

\[ w_s + w_p = 1 \]

where \( h(x, t) \) is the height in 2D (or diameter in 3D) of the gut at axial position, \( h_s(x, t) \) is the contribution from segmentation, and \( h_p(x, t) \) is the contribution from peristalsis according to weighting coefficients, \( w_p \) and \( w_s \), for peristalsis and segmentation respectively. The peristaltic and segmental components of the overall wall height/diameter, \( h_s(x, t) \) and \( h_p(x, t) \), are specified analytically as a function of the key parameters, shown in Table 3-1, extracted from the MRI data. Important parameters include length scale (wavelength), time scale (period of contraction or wave propagation), and maximum and minimum radii from which an occlusion ratio can be defined:

\[ O.R. = R_{\text{min}}/R_{\text{max}} \]

These parameters can then be altered systematically to provide more insight into possible optimizations and further functional/physiological significance. A sample of the geometries produced by the model is shown in Figures A-3(a-c).

A.3 Numerical Experiments

In this study, we investigated the strategic employment of segmentation and peristalsis as a feasible means of controlling the absorption and transport processes. We
hypothesize that the intestine can potentially utilize the two motility modes, either independently or in some combination, to optimize gut function. We define this optimization as a minimization of the time scale of scalar absorption through the walls and/or the time scale of axial transport along the length of the computational domain.

We use our numerical method to predict the fluid motions and associated nutrient (scalar) advection/diffusion in a series of experiments where the relative contributions of peristalsis and segmentation are systematically investigated. A series of nine numerical experiments are presented, across which the contribution ratio of percent segmental contribution to percent peristaltic contribution is varied between the two single-mode cases.

Scalar concentration is given an initial Gaussian distribution about the central axis in both the 2D and 3D cases (see Figure A-3). The scalar concentration value at the centerline is held constant at $\phi = 1$ to provide a source of scalar for the duration of the simulation. This allows the simulation to evolve to a stationary state, in which the scalar concentration distribution is periodically homogeneous in the axial and transverse/radial directions. The scalar concentration in the rest of the domain, once initially specified, evolves temporally as a result of the movements the gut walls.

The Schmidt number was $Sc = 50$. The $Sc$ in the gut are orders of magnitude higher in the gut, however practical constraints restricted the use of such values. A discussion of the $Sc$ and its influence on the simulations is presented in Section 3.1.6.

A.4 Results

In systematically varying the relative contributions of segmentation and peristalsis in weighted linear combinations using the 2D model, several interesting phenomena emerge.
The average absorption rate (normalized) versus percent peristalsis is plotted in Figure A-4. The percentage of peristaltic contribution ranges from zero (pure segmentation) to one (pure peristalsis). It is apparent in Figure A-4 that the maximum absorption rate results from the pure segmentation case. The absorption rate quickly drops off with any addition of peristalsis. With only a 5% peristaltic contribution (95% segmental contribution), the absorption rate is decreased by almost 15%, and with a 12.5% peristaltic contribution, the absorption rate is reduced by nearly 30%. This suggests that pure segmentation is the most effective means of promoting the absorption of nutrients through the intestinal surface, and that any level of peristaltic contribution interferes with this maximum effectiveness.

In conducting the same set of experiments using the 3D model, however, we found completely different results. The normalized average absorption rate versus percent peristaltic contribution for the 3D case is plotted in Figure A-5. Surprisingly, the results for the 2D case, namely that pure segmentation provides the best absorption rate, do not hold at all in 3D. In fact, pure segmentation provides the worst absorption rate, and pure peristalsis provides the best. Using the 2D model, we found that any level of peristalsis degraded the absorptive characteristics; using the 3D model, we found that maximizing the level of peristalsis maximized the absorptive characteristics.

These contradictory results were baffling. Studies presented in the literature show that the velocity and pressure fields are qualitatively similar between 2D and 3D peristalsis (see Figure A-2) [17,158]. The results of our simulations are consistent with those studies. Figures A-6(a,b) show isocontours of pressure for 2D and 3D peristalsis. Figures A-6(c,d) show that the pressure in pure segmentation is also qualitatively similar. When investigating
and comparing the distribution of nutrients for the 2D and 3D cases, however, differences are clear.

Figures A-7(a-d) show isocontours of nutrient concentration (passive scalar concentration) for the 2D and 3D cases for peristalsis and segmentation. Although Figure A-6 shows that pressure is very similar for the 2D and 3D simulations, Figure A-7 shows that when extending the study to include the effects of mass advection/diffusion, the 2D and 3D results are quite different. The isocontours of nutrient concentration in Figure A-7 are shown after the simulations have reached a periodically-steady (stationary) state. For the 2D cases, the nutrient concentrations are significantly higher than they are in the 3D case.

The differences in scalar concentration distribution stem from the extra degree of freedom present in the 3D geometry that is absent from the 2D geometry. In 2D, the scalar is limited to transport primarily in the transverse direction, from the centerline toward the walls. The “area” through which the scalar can be absorbed at the wall is limited by the lack of a third dimension. As a result of this restriction, scalar accumulates much more in the domain. In 3D, this restriction is removed, and much more space is available for mass transport to occur. In addition, with the full three dimensions of the walls simulated, significantly more surface area through which the scalar can be absorbed is available. These inherent geometrical differences between the 2D and 3D simulations are the root of the aforementioned disparities in the absorptive characteristics in each case, but only upon further investigation, through which we varied the occlusion ratio for each case, was the situation clear.

Figures A-8(a-b) show the normalized average absorption rate versus occlusion ratio using the 2D and 3D models respectively for pure peristalsis (blue) and pure segmentation.
At first glance, the curves seem very different. When focus is placed on the point at which the peristaltic and segmental curves intersect, however, \( O.R. \approx 0.345 \) for 2D, and \( O.R. \approx 0.68 \) for 3D) some similarities are present. Extending by \( O.R. \pm 0.1 \) from the intersection point, both the 2D and 3D cases show similar behavior: peristalsis is best at occlusion ratios less than the intersection \( O.R. \), and segmentation is best at occlusion ratios greater than the intersection \( O.R. \), with the absorption rate changing relatively linearly in this range of occlusion ratios. The \( O.R. \) at which the trapping limit for peristalsis occurs (see [17]) also is in roughly the same position relative to the intersection point in both the 2D and 3D cases. With these similarities, it is still not immediately apparent why the results generated by the 2D and 3D models disagree so blatantly as shown in Figures A-4 and A-5.

The answer lies in the “base” \( O.R. \) used in the simulations (see Table 1). From the MRI data analysis, we determined that an \( O.R. \) of 0.5 was adequate to model both peristalsis and segmentation. Focusing on \( O.R. = 0.5 \) in Figure A-8(a-b), the reason for the discrepancy is clear. For the 2D case, the absorption rate is higher pure segmentation at \( O.R. = 0.5 \), while in the 3D case at the same \( O.R. \), peristalsis produces a higher absorption rate. The intersection point occurs at \( O.R. < 0.5 \) in 2D, and \( O.R. > 0.5 \) in 3D.

**A.5 Discussion**

The primary responsibilities of the small intestine are the absorption of nutrients from the bulk flow of ingested material, and the transport of the material axially along its length. These roles are accomplished by the two intestinal wall contractile motility patterns: segmentation and peristalsis. The results obtained from our 2D model showed that segmentation is very effective for absorption and mixing (see Figure A-4). The 2D model
furthermore showed that peristalsis, while an obviously effective means of transporting fluid along the length of the gut, degrades the effectiveness of absorption when any component of such motility is combined with segmentation. This suggests that if the gut actively controls and optimizes transport and absorption through the utilization of the two types of motility, it should employ each motility pattern as independently as possible. This would limit peristaltic interference on the absorption process, as well any segmental interference on the transport process.

Evidence of the ability for such active control of gut processes using motility patterns can be found through examining when the motility modes are generally active. Peristalsis is often the dominant motility pattern after a non-caloric meal. With little or no useful nutrients to be absorbed, the gut uses peristaltic motility to evacuate the non-caloric meal from the body. After a normal caloric meal, however, the dominant motility pattern is segmentation [7,55]. For the motility patterns to be employed in this manner, the gut must sense the content of the chyme, and react accordingly to carry out the necessary process [e.g. 7].

Although the motility patterns promote distinct processes (peristalsis for transport, segmentation for absorption), any normal meal requires both motility patterns to be present. Segmentation alone cannot propel the chyme along the length of the gut, and therefore peristalsis is necessary to move it toward the large intestine for further processing. The results of the 2D simulations show, however, that interference should be minimized.

The notion that optimal gut function is obtained with independently active motility is supported through observations of actual gut motility. In our own MRI studies of the rat intestine, segmentation was the dominant motility pattern after feeding the rats caloric meals,
occurring 97% of the time of acquisition. Peristalsis was much less frequent, occurring the remaining 3% of the time [55]. Interestingly, although complex motility patterns can be observed in videofluoroscopy studies done by [7], we observed such complex (perhaps mixes of peristalsis and segmentation) only briefly as one motility patterns transitioned to another. These observations, combined with the results from the 2D simulations indicating that segmentation is best for absorption, and that each mode is most efficient when operating independently, suggest that after a normal meal, peristalsis should be employed only intermittently, between longer periods of segmental motility to transport the chyme to farther regions of the gut. This segmentation-peristalsis-segmentation pattern process repeats until the available nutrients have been absorbed, and all the chyme has been passed to the large intestine.

This conclusion is supported by analysis of studies done by Weitschies, et al., in which the group tracked magnetically labeled extended release drug tablets in human subjects during the fasting state and after a normal meal [e.g. 159]. Examination of videos created from their tracking data shows that in the fasting state, the tablets are transported through the small intestine at a roughly constant rate. This presumably stems from peristalsis being utilized to pass the non-caloric tablets through the system for evacuation. In the fed state, however, the tablets can be seen to remain relatively stationary for periods of time, and then be transported to a farther portion of the gut where they remain relatively stationary for a subsequent period of time. This seemingly corresponds with the segmentation-peristalsis-segmentation pattern described in the previous paragraph through which nutrients are absorbed from chyme in one portion of the gut during long periods of segmentation before
being subsequently passed to a farther portion through peristalsis where segmentation resumes, continuing the absorption process.

The conclusions discussed in this section to this point have been drawn namely from the results of our 2D simulations. Although the conclusion that peristaltic and segmental motility patterns interfere with one another with respect to the absorption process was supported by the results of the 3D simulations, we noted in the previous section that the absorption rate results from the 3D model were completely contradictory to those of the 2D model as evident when comparing Figure A-4 to Figure A-5. We were convinced from the 2D results that segmentation, as is commonly noted in the literature, is not only associated with absorption, but is far better than peristalsis in promoting absorption in the gut. However, the 3D results showed just the opposite, that peristalsis was far better than segmentation with respect to absorption.

This contradiction was found just before we submitted a completed manuscript based on the results of the 2D model for publication. After putting the manuscript submission on hold, we spent significant amounts of time re-verifying and re-validating the 3D model. The years of studies completed on the fluid dynamics of peristalsis indicated that the results of the 2D and 3D cases should be similar, so we were baffled at why the results were not only dissimilar, but were completely contradictory. When we had proven that the 3D model was indeed producing valid results, but still in disagreement with the 2D results, we began to investigate our puzzling situation more deeply.

It was not until we varied the occlusion ratio over a significantly broad parameter space that the answer became clear. There was a transitional point in the occlusion ratio parameter space in which the respective efficacies of peristalsis and segmentation with
respect to the nutrient absorption rate switch their dominance as shown in Figure A-8(a,b).

For the 2D case, the critical point is $O.R. \approx 0.345$ (lower than $O.R. = 0.5$ used as our base simulation parameter). In this region, segmentation is more effective than peristalsis for absorption. For the 3D case, the critical point is higher, $O.R. \approx 0.68$ (higher than the $O.R. = 0.5$ used in the simulations). With our simulation $O.R.$ being lower than the critical $O.R.$ in the 3D case means that peristalsis is more effective than segmentation for absorption.

It is possible that true physiological occlusion ratios are indeed as high as $O.R. \geq 0.68$. The latest results of our own observations show that the segmental occlusion ratios are of this order [55]. If that is the case, then the conclusions drawn from the 2D simulations may still hold. However, a more thorough investigation of true physiological occlusion ratios is needed before any concrete conclusion is drawn.

The main purpose of this paper, however, is not to describe gut function in any great detail, but present our humbling experience as a reminder that adequate caution must be used when employing the simplifications, approximations, and assumptions that are often necessary when modeling complex behavior. We have discussed our example of a case when a 2D model, although seemingly applicable, was not sufficient to provide results pertinent to the true physics of the system we were studying. We believe, however, that similar issues occur more often than are reported.

Koseff and Street published a series of three papers in which they show, through both physical and numerical experiment, that velocity profiles obtained in 3D lid-driven cavity flow are “drastically different” from those obtained with 2D models, even when the third (span-wise) dimension omitted in the 2D model is reasonably large, with a ratio of span to width ratio of 3:1 [160,161]. Street notes that this type of flow had long been previously
studied using 2D models, under the assumption that the flows were similar. It was not until modeled in full 3D was it apparent that the physics was notably different and more interesting.

Another classic example involves instability of plane shear flows, such as plane Poiseulle flow and plane Couette flow. As Reynolds number increases in such flows, Squire’s theorem states that the first linear mode to go unstable during the transition to turbulence is 2D [157]. Therefore, for a long period of time, many researchers considered only the 2D case when determining stability thresholds. This practice led to critical Reynolds numbers that were far too high. It wasn’t until Orszag and Kells showed that the situation was more complex than consideration of only the 2D modes made it appear, and that only by considering the 3D mechanisms as well, that the critical Reynolds numbers produced by theoretical models agreed with those obtained by physical experiment [162].

Our colleagues were kind enough to provide us with many examples of when seemingly sufficient 2D models could not produce the correct physics pertinent to the true 3D systems under consideration. The fields ranged from hurricane modeling, to magneto-hydrodynamics, to microfluidics, to cloud formation among several others. It was our own frustration with the process we presented in this paper, as well as the positive response and numerous other examples provided by our colleagues that inspired us to present our cautionary tale. We hope that this reminds our readers, as it certainly did us, that due caution must be used when any type of simplification technique, especially the reduction of dimensionality, is employed as a means of making a problem more manageable. In some situations, as was our case, the time “saved” was most likely far surpassed by the time spent in determining the reason for disagreement with the true physics. We surmise that in other
situations, if proper caution is not taken when applying incorrect results from an oversimplified model, far worse consequences could occur.
Figure A-1: Log-log plot of drag coefficient (CD) versus Reynolds number (Re) for cross flow over smooth circular cylinders and spheres. Source: [156]
Figure A.2: Streamlines for 2D (top) and Axisymmetric/3D (bottom) right traveling peristalsis in the wave frame for $Re=1$. Source: [158]
Figure A-3: Example geometries for (a) segmentation, (b) 50%/50% mix of segmentation/peristalsis, and (c) peristalsis from the 2D model. (The 3D geometries are identical, but axisymmetric). The isocontours show the initial scalar (nutrient) concentrations for each simulation. Blue denotes low concentrations; red denotes high concentrations.
Figure A-4: Average absorption rate (normalized) versus percent peristaltic contribution (2D).
Figure A-5: Average absorption rate (normalized) versus percent peristaltic contribution (3D).
Figure A-6: Comparison of pressure fields (colored isocontours: blue indicates low pressure, red indicates high) for 2D (left) and 3D (right) flow fields for peristalsis (top) and segmentation (bottom): (a) 2D peristalsis, (b) 3D peristalsis, (c) 2D segmentation, (d) 3D segmentation. Black lines are streamlines for the 3D cases (b,d).
Figure A-7: Comparison of scalar concentration fields (colored isocontours: blue indicates low concentration, red indicates high concentration) for peristalsis (top) and segmentation (bottom): (a) 2D peristalsis, (b) 3D peristalsis, (c) 2D segmentation, (d) 3D segmentation. Black lines are streamlines for the 3D cases (b,d).
Figure A-8: Normalized absorption rate versus occlusion ratio for the (a) 2D model, and the (b) 3D model. Peristalsis is shown in blue; segmentation is shown in red.
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