STOCHASTIC AND DETERMINISTIC COAGULATION MODELS,
THEIR NUMERICAL APPROXIMATIONS AND APPLICATIONS TO
CELL AGGREGATION

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Abstract

The work in the present thesis is to study the stochastic and deterministic coagulation models, their numerical approximations, and applications to polymorphonuclear neutrophil (PMN) and tumor cell aggregation in the parallel plate flow chamber. The work is motivated by some experimental and theoretical studies on tumor cell metastasis, in particular, the earlier studies that have been done in Prof. Cheng Dong’s biomechanics lab. Some previous work demonstrated that PMNs can facilitate tumor cell adhesion to the endothelium. Parallel plate flow chamber experiments have shown that under different flow conditions, tumor cells and PMNs adhere to each other and to the endothelium with different efficiencies. The comprehensive study of the cell aggregation and adhesion is proceeded from three aspects: experimental studies on the kinetics of cell aggregation, adhesion and deformation; computational fluid dynamical (CFD) modeling of individual PMN and tumor cell interaction and adhesion; statistical study of large populations of cell aggregation. The experimental study and CFD modeling work conducted by Prof. Dong in his lab provided us the basis of the present thesis work focusing on the statistical study of cell aggregation.

The primary focus of this work is the development of mathematical models and numerical simulation methods for cell aggregation in populations and the exploration of how the flow condition changes the interactions of PMNs and tumor cells in the nonuniform shear flow. In this thesis, the coagulation equations (also called Smoluchowski or population balance equations) are used to model cell aggregation in the near wall region in nonuniform shear flow. These equations have been used widely to study the time evolution of the particle concentration in physics, biological and chemical engineering.

This thesis is organized as follows. First, we study the population balance equations with bounded kernels and their numerical approximations. A comprehensive review of the coagulation equations is given first, such as the well-posedness problem and some other basic properties. For the numerical approximation of the coagulation equation, a new formulation motivated by the Wild sum is utilized to offer a convenient framework for the analysis of the population balance equations. It also leads naturally to a time relaxed method for the numerical solution of the coagulation equations. This time re-
laxed method is shown to be a high order convergent numerical scheme that preserves the non-negativity of the solution and the total volume conservation. Furthermore, we study several deterministic algorithms for the numerical approximations of the discrete Smoluchowski coagulation equations, such as the time relaxed marching method and the stabilized Euler method. Their stability and convergence properties are examined, and error estimates are derived. Particular attention is given to issues such as the high order accuracy, the preservation of the total volume, and the non-negativity of the population density. The numerical examples and comparison tests are presented to demonstrate the performance of the algorithms. We also check the consistency of the computational complexity estimation and the real CPU running time. The application of these numerical methods to coagulation-fragmentation is also taken into account.

In order to bridge the deterministic coagulation equation and the stochastic coagulation dynamical system, we also develop a stochastic interpretation of the coagulation equation. We show that the density function of the stochastic coagulation process satisfies the coagulation equation. Based on this model, a backward Monte Carlo method is developed. We also present a formulation of the coagulation equation by using an energetic variation framework in which case the model can be described by the energy law. Overall, we provide both the stochastic and deterministic formulations for the coagulation equation. Furthermore, our studies on the relations of stochastic and deterministic formulations show the consistency of these two formulations. Several examples, for instance, the transport equation, the diffusion equation, and the coagulation equation, demonstrate that the deterministic model can be derived from the stochastic model and its consistency is verified.

The applications of the coagulation model to cell aggregation are done jointly with Prof. Dong and his research group. We develop a simple population balance model for cell aggregation and adhesion process in a nonuniform shear flow. Some Monte Carlo simulation results based on the model are presented for the heterotypic cell-cell collision and adhesion to a substrate under dynamic shear forces. In particular, we focus on leukocyte (PMN)-tumor cell emboli formation and subsequent tethering to the vascular endothelium (EC) as a result of cell-cell aggregation. The simulation results are compared with the results of experimental measurement. We also develop a modified population balance model to describe the cell aggregation in the near wall region. In this model, the tethering frequency, adhesion efficiency, and collision rate of deformable cells are also discussed.

For the spatially inhomogeneous coagulation equation, we first introduced the Lagrangian model. By the deterministic formulation in Section 3.4, we derive the equation by considering the conservation law of a coupled system which involves spatial variable and particle size variable. By the conservation law formulation, first, we develop a model in which the coagulation kernel and fluid dynamics are given, then we consider a self-consistent model where the particle motion and coagulation are induced by a given transition probability.

Finally, we present some issues for future studies.
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Chapter 1

Overview

1.1 Cell aggregation

Neutrophil and tumor cell adhesion in a nonuniform shear flow is a problem of great interest in the study of tumor extravasation during metastasis. There have been many computational and experimental studies of cell aggregation in the flow environment. Detailed investigations of the aggregation and adhesion process involving individual cells have been done for both uniform and nonuniform shear flows in [2, 3, 4, 5, 6, 7, 8, 9]. Statistical population studies have also been done for the constant shear flow case. For example, Laurenzi and Diamond (see [10]) used Monte Carlo method to simulate platelet and neutrophil heterotypic aggregation in a cone-plate linear-shear assay. Parallel plate flow chamber experiments have shown that under different flow conditions, tumor cells and polymorphonuclear neutrophil leukocytes (PMN) adhere to each other with different efficiencies. However, compared with the case of constant shear rate, the study of aggregation of cells in nonuniform shear flows poses an even greater challenge.

By collaborating with Dr. Dong and his lab members, we have undertaken both experimental and theoretical studies to explore how the interactions between PMNs and tumor cells are affected by the fluid dynamics in nonuniform shear flows. A special focus is on the PMN tumor cell emboli formation in a nonuniform shear flow and subsequent tethering to the vascular endothelium (EC) as a result of cell-cell aggregation. In our in-vitro experiment, the fluid flow in the parallel plate flow chamber assays can be described as Poiseuille's flow through a rectangular geometry, which characteristically has a parabolic velocity profile instead of a uniform shear rate. In the case of tumor cells and PMNs collision and aggregation, a vessel wall or experimental substrate is
always present, and, therefore changes the hydrodynamics of the system, and thus the collision probability (see Figure 1.1, courtesy of the Cellular Biomechanics Laboratory at PSU). At the microscopic level where the collision and adhesion of two cells takes place, the aggregation depends mainly on two parameters: namely, the collision rate and the adhesion efficiency. The collision rate describes the collision probability of two given particles, which may depend on the shear rate, the diffusion, the gravity force, and the particle size. Two cells stick to each other due to the receptor ligand bonds. The adhesion efficiency is the probability that two cells will adhere to one another when they collide, and it reveals how this probability may be affected by numerous factors, such as the shear rate, the particle size, and the particle surface properties, and etc.

The comprehensive study of the cell aggregation and adhesion proceeds from three aspects. One is the experimental studies on the kinetics of cell aggregation, adhesion and deformation; the second is computational fluid dynamical (CFD) modeling of individual PMN and tumor cell interaction and adhesion. The third point is the statistical study of large populations of cell aggregation. My thesis work focuses on the statistical study of cell aggregation. The experimental study and CFD modeling work conducted by Prof. Dong in his Lab provide us the basis of the present thesis work. For instance, some work has been done by Prof. Dong [4, 6, 11, 12, 13, 14, 15] and his lab members: Maggie Slattery, Meghan H. Hoskins, and Shile Liang, who are focusing on cellular mechanics and CFD modeling involved in tumor cell capture by endothelial and white blood cells.

In detail, Shile Liang and Maggie Slattery [11, 15] have conducted some experimental studies of cell aggregation and adhesion. In [11], the effect of shear stress and shear rate on PMN-facilitated melanoma extravasation was studied by increasing the medium viscosity with dextran to increase shear stress independently of shear rate. PMN-tumor aggregation and adhesion to the endothelium via \( \beta_2 \)-integrin/intracellular adhesion molecule-1 (ICAM-1) interactions were also studied. In [15], they investigated a two-step adhesion hypothesis that involves initial PMN tethering on the EC and subsequent tumor cells being captured by tethered PMNs. Different effects of hydrodynamic shear stress and shear rate were analyzed using a parallel-plate flow chamber.

In addition to the experimental studies, Meghan H. Hoskins is developing a CFD tool to simulate PMN-tumor-EC adhesion, that includes cell deformability, inter-cellular forces, and receptor-ligand bonds, and will output flow parameters for use in our statistical studies. In detail, she is modeling deformable cells as non-Newtonian fluid-filled bodies with a cortical shell under tension, and creating a contact model for interactions between PMN and tumor including inter-cellular forces and receptor-ligand bonding.
We also refer to [6, 16, 17, 18] for deformability studies. For example, in [16, 17], the authors investigated numerically how changes in the channel height affected leukocyte adhesion to the lower plate in a parallel-plate flow chamber provided that the leukocyte was deformable and viscoelastic. The three-dimensional (3D) numerical simulation of leukocyte adhesion in a parallel plate flow chamber has been carried out by their incompressible CFD code in which the volume-of-fluid (VOF) method was used for tracking leukocyte shapes over time.

On macroscopic level, the simulation of cell aggregation via population balance model [19, 20, 10], and modeling of cell tethering/adhesion in parallel plate flow chamber, are studied also [9, 21]. The parallel plate flow chamber is applied in immunological studies to quantify the adhesivity of cells (e.g. leukocytes) onto ligand-bearing substrates (e.g. endothelial cells) under fluid flow conditions that mimic the human vasculature. For instance, Neelamegham and Zhang [9, 21] developed a mathematical model to quantify the efficiency of cell-substrate attachment in the parallel plate flow chamber. The model decoupled the physical features of the system that affected cell-substrate collision rates from the biological features that influenced cellular adhesivity. They analyzed flow chamber data using a kinetic model in which the flux of cells to the substrate was determined by cell settling and convection velocities. A series of first order partial differential equations were set up to quantify the steady and unsteady state flux corresponding to the cells in the free stream, the rolling cells, and the firmly adherent cells.

Overall, the work introduced as above provided us a basis to study cell aggregation with large populations in nonuniform shear flow. So, our present focus is to set up the coagulation (population balance) models to investigate the roles played by the nonuniform shear field, the collision rate, and the adhesion efficiency in the aggregation process and to compare them with the in-vitro experiments. At the mean time, we would also like to get a better understanding on the mathematical and computational issues involved in the simulation of coagulation phenomena.
1.2 Coagulation Modeling

In this section, we will describe briefly the framework of the coagulation models, the coagulation equations with different forms and the corresponding formulations.

1.2.1 Modeling framework

Cell aggregation in the flow chamber can be modeled in both spatially homogeneous and inhomogeneous cases. It is assumed that the cells are distributed uniformly in the flow chamber for spatially homogeneous formulation, in which, we only need to take into account the distribution of particle size. For the inhomogeneous formulation, the particles are nonuniformly distributed in the chamber, and both the particle size and position need to be taken into account.

For both spatially homogeneous and inhomogeneous formulations, cell aggregation can be modeled in three scales: the microscopic, mesoscopic, and macroscopic levels. On the microscopic level, we consider a finite number of cells which move and coagulate randomly. On the macroscopic level, we consider the rheological properties affected due to the cell coagulation. In the stochastic coagulation system, the cell transportation and aggregation will be determined by the transition probability. For details, we refer to Section 4.1 for cell aggregation simulation in spatially homogeneous case. On the mesoscopic level, the interaction cells are modeled in continuous level, for both cell size and position. This naturally leads to the spatially inhomogeneous coagulation equation (will be spatially homogeneous coagulation equation if only the particle size is taken into account). If a non-trivial interaction of the cell with a fluid is to be taken into account, for example, the feedback of the coagulation to the fluid flow conditions cannot be ignored, it is necessary to look at the mesoscopic regime first before a macroscopic closure. This leads to an energetic variation formulation.

1.2.2 Coagulation equations

Stochastic coagulation equations [22] are also called as Smoluchowski equations [23] or population balance equations [10, 20]. They are often used to describe the rate of the concentration change in time in a dynamic coagulation process and have been applied to a wide range of applications such as aerosol growth, polymerization problems, and the kinetics of platelet aggregate formation and disaggregation. For example, many researchers used them to study the heterotypic aggregation kinetics of platelets and neutrophils, most notably in the uniform shear field (see for instance [10, 20]). In [24],
we used it to model the PMN and tumor cell adhesion in nonuniform shear flow, which will be discussed in detail in Section 4.1.

Our starting point is the spatially homogeneous coagulation equation. Let $N = N(u, t)$ represent the concentration of the particle at time $t$. Then, a continuous form of the coagulation equation is given by

$$\frac{\partial N(u, t)}{\partial t} = \frac{1}{2} \int_0^u \beta(v, u - v)N(v, t)N(u - v, t)dv - \int_0^\infty \beta(u, v)N(u, t)N(v, t)dv, \quad (1.1)$$

with an initial condition

$$N(u, 0) = N_0(u) \geq 0, \quad (1.2)$$

where $\beta(u, v)$ is the coagulation kernel which determines the aggregation probability of the particles with volumes $u$ and $v$. The first term on the right-hand side of equation (1.1) represents the generation of particle with volume $u$ by the aggregation of smaller particles and the second term describes the loss of the particle with volume $u$ by aggregation with other particles. More specifically, according to Smoluchowski’s original derivation [23] for rigid spherical particles, at time $t$, consider an arbitrary target particle of size $u$, per unit time per unit volume, the number of collisions between the target particle and the group of particles having size $v$ is just $\beta(u, v)N(v, t)$ so that the total collision numbers between the two groups of particles having sizes $u$ and $v$ is $\beta(u, v)N(u, t)N(v, t)$. Thus, the rate of change of the population for particles having size $u$:

- will be increased by $\frac{1}{2} \int_0^u \beta(u - v, v)N(u - v, t)N(v, t)dv$ due to the coagulations between two groups of particles having sizes $u - v$ and $v$,
- will be decreased by $\int_0^\infty \beta(u, v)N(u, t)N(v, t)dv$ due to the coagulations between two groups of particles of sizes $u$ and $v$.

This thus leads to equation (1.1).

A discrete form of the equation describing the rate of change of the concentration $N(i, t)$ of the particles with $i$ monomers is given by:

$$\frac{\partial N(i, t)}{\partial t} = \frac{1}{2} \sum_{j=1}^{i-1} \beta(j, i - j)N(j, t)N(i - j, t) - \sum_{j=1}^\infty \beta(i, j)N(i, t)N(j, t) \quad (1.3)$$

with an initial condition

$$N(i, 0) = N_0(i), \quad i = 1, 2, 3, ... \quad (1.4)$$
where $\beta(i, j)$ is the coagulation kernel.

The basic properties of equations (1.1) - (1.2) and (1.3) - (1.4) will be discussed further in later sections. Various numerical methods for their approximations are also presented.

There are many other forms of the coagulation equations available in the literature. For example, there are models that take into account the fragmentation effect. One particular form of the continuous coagulation-fragmentation equation is given by:

$$\frac{\partial N(u, t)}{\partial t} = \frac{1}{2} \int_0^u \beta(v, u - v)N(v, t)N(u - v, t)dv - \int_0^\infty \beta(u, v)N(u, t)N(v, t)dv$$

$$+ \int_0^\infty \gamma(u, v)N(u + v, t)dv - \frac{1}{2} \int_0^u \gamma(u - v, v)N(u, t)dv . \quad (1.5)$$

where $\gamma(u, v)$ denotes the fragmentation rate [25, 26, 27, 28, 29, 30].

In the spatially homogeneous coagulation equation, it is assumed that the particles are uniformly distributed. In other words, it does not explicitly relate to the particle distribution in space. For the leukocyte (PMN) and tumor cell aggregation and adhesion in the parallel plate flow chamber, due to the nonuniform flow profile, the cells are not uniformly distributed in the chamber; therefore, we would like to develop a spatially inhomogeneous coagulation equation to model this problem so that we can investigate the cell distribution in the whole chamber, instead of the spatially homogeneous modeling in the near wall region.

In [31] and [1], the authors derived the inhomogeneous coagulation equation and considered a numerical solution. The equation including the convection and the diffusion terms is given by:

$$\frac{\partial N(x, u, t)}{\partial t} + V(t, x) \cdot \nabla x N(x, u, t) = \frac{1}{2} \int_0^\infty \beta(u - v, v)N(x, u - v, t)N(x, v, t)dv$$

$$- \int_0^\infty \beta(u, v)N(x, u, t)N(x, v, t)dv + \sigma \Delta x N(x, u, t) \quad (1.6)$$

where $V(t, x)$ is the velocity field and $\sigma$ is the diffusion constant. However, there is an extra term in their derived equation when compared with equation (1.6) above. Although they argued that this extra term is small enough. Furthermore, it is assumed that the coagulation kernel has the form $\beta(u, v)$, which is only a function of two variables $u$ and $v$, and independent of the velocity field, and the spatial conditions.

In our ongoing work, we consider all these different approaches. Both spatially homo-
geneous and inhomogeneous coagulation equations are utilized to model cell aggregation in nonuniform shear flow, including both the modeling and the numerical approximation aspects.

1.2.3 **Stochastic and deterministic formulations**

The derivation and numerical solutions of coagulation equations are often vary, depending on the formulations of the equation. In the present thesis, we discuss two formulations: the stochastic formulation (microscopic), and the deterministic formulation via conservation law (mesoscopic and macroscopic), for both spatially homogeneous and inhomogeneous coagulation equations.

**Stochastic formulation** In general, the homogeneous coagulation equation is a consequence of the stochastic coagulation system. The relation between the equation and the dynamical system is an interesting problem worth investigating. Consider a particle size random growth in the coagulation dynamical system and denote the particle size change in time by a stochastic process \( \{X_t\} \). For a particle of size \( x \) at time \( t \), if we denote its status by \( X_t = x \), then the probability that it can coagulate with a particle of size \( y \) in the time interval \([t, t + \Delta t]\) is estimated by:

\[
p = \beta(x, y)N(y, t)\Delta t .
\]

By the Chapman-Kolmogorov formula of Markov process, we can show that the concentration \( N(x, t) = f(x, t)/x \) satisfies the coagulation equation, where \( f(x, t) \) is the density function of \( \{X_t\} \).

A classical stochastic model, the Marcus-Lushnikov process [32, 33, 22], is widely used to study the coagulation dynamical system. The comparison of these two different approaches and their relations to the coagulation equation will be revealed in detail.

The Marcus-Lushnikov process is described as a Markov process. Consider a discrete coagulation dynamical system with total volume \( V \), where the approach to the continuous case can be set up analogously. The particles coagulate with each other under some influence of random factors. Two random particles with \( i \)-monomer and \( j \)-monomer will coagulate with probability \( \beta(i, j)/V \). We describe the system state by

\[
X = \{n_1, n_2, ..., n_m, ...\} ,
\]

where \( n_m \) is the number of \( m \)-monomer containing particles. If we assume the monomer
volume is $v_0$, then we have
\[ \sum_m n_m v_0 = V. \]

In this system, the state is changed due to the coagulation event. If two particles with $i$ and $j$ monomers coagulate and grow into a big particle containing $i + j$ monomers, with probability $\beta(i,j)/V$, we say that the state of this dynamical system is changed from $X$ to state $X'$ where
\[ X' = \{n_1, n_2, ..., n_i - 1, ..., n_j - 1, ..., n_{i+j} + 1, ..., n_m, ...\}. \]

More details of the Marcus-Lushnikov process will be given in Section 3.1.

**Conservation law formulation** Define the volume density function $f(x,t) = xN(x,t)$, where $N(x,t)$ is the particle concentration. It has been pointed out in [34] that the coagulation equation can be written in terms of the conservation law:
\[ f_t + \partial_x (F(x,t)) = 0, \tag{1.7} \]
where the coagulation flux $F(t,x)$ is given by
\[ F(t,x) = \int_0^x \int_x^\infty \frac{\beta(u,v)}{v} f(u,t)f(v,t)dvdu. \tag{1.8} \]

Filbert and Laurencot [35] developed a numerical scheme which relies on this conservation law formulation and finite volume approach.

This conservation law formulation also can be applied to the derivation of spatially inhomogeneous coagulation equation. For details, we refer to Chapter 5, in which we apply the conservation law for a coupled system by taking into account both particle transportation and coagulation.

### 1.3 Spatially homogeneous and inhomogeneous models

In the present section, we give an overview of the thesis work and outline the different approaches used in the thesis such as the spatially homogeneous coagulation equation and the spatially inhomogeneous coagulation equation.

As we indicated, cell aggregation could be modeled by two different approaches: the spatially homogeneous model and the spatially inhomogeneous model. In Chapter 2 and 3, we discuss the numerical methods and the formulations of the spatially homogeneous
coagulation equation. We also apply the spatially homogeneous model to cell aggregation in Chapter 4. The spatially inhomogeneous coagulation equation is discussed in Chapter 5. We now describe the framework of these two approaches.

1.3.1 The spatially homogeneous model

In the present thesis, cell aggregation is modeled by spatially homogeneous coagulation model.

Model formulation In Chapter 3, we explore the various forms of stochastic and deterministic models and discuss their relations with the spatially homogeneous coagulation equation. In addition to the widely used Marcus-Lushnikov process, a stochastic interpretation and the simulation of the coagulation equation are introduced in Section 3.2. An energetic variation formulation is also developed in Section 3.3 based on the discussion with Prof. Liu. In Section 3.4, the relations between the stochastic and deterministic formulations are explored. Several examples show the consistency of these two different formulations. The work in this chapter provides a good theoretical basis not only for spatially homogeneous model, but also for the spatially inhomogeneous model.

Numerical methods In Chapter 2, we present preliminary studies of the coagulation equations, such as the well-posedness problem, volume conservation, bounded derivatives and so on. Then we focus our discussions on the numerical approximations of spatially homogeneous coagulation equation. Based on the Wild sum, we define a bilinear operator and represent the solution of the equation as a infinity series which is convergent uniformly. In Sections 2.4 and 2.5, we develop a time relaxed (marching) method by truncating the finite terms of the series expansion. In Section 2.6, we get a stabilized Euler method by modifying the first order time relaxed method. Their stability and convergence properties are examined, and error estimates are derived. Particular attention is given to issues such as the high order accuracy, the preservation of the total volume and the non-negativity of the population density. The numerical examples and comparison tests are presented to demonstrate the performance of the algorithms. The application of these numerical methods to coagulation-fragmentation is also discussed in Section 2.7.

Model implementations The applications of spatially homogeneous models are documented in Chapter 4 and they are based on the joint work with Prof. Dong and his
research group. We use two different spatially homogeneous coagulation models to simulate cell aggregation in the near wall region and compare the numerical results with the experimental data. Furthermore, we discuss the tethering frequency, adhesion efficiency, and collision of deformable cells in Section 4.2 in order to improve the accuracy of the model, where the local concentrations of PMNs and tumor cells in the near wall region are calculated by the computational fluid dynamics model. The CFD work has been done by Meghan M. Hoskins.

1.3.2 The spatially inhomogeneous model

Model formulation An alternative approach to cell aggregation is the spatially inhomogeneous coagulation equation since the cells are distributed nonuniformly in the plate flow chamber. Sabelfeld [1] developed a Lagrangian model to derive the equation, which is briefly introduced in Section 5.1. We develop another method to derive the equation by conservation law for a coupled system, which is discussed in Section 5.2 and Section 5.3. In this formulation, similar to the homogeneous stochastic coagulation model, we consider a coupled stochastic process \( \{X_t, S_t\} \) where \( X_t \) represents the position of the particle and \( S_t \) represents the particle size. This derived equation is better than Sabelfeld’s derivation since our equation has no extra term. A self-consistent model is also developed through the conservation law formulation and we get a more general form for the spatially inhomogeneous coagulation equation.

Numerical methods and model implementation The numerical methods and the application of the spatially inhomogeneous model to cell aggregation are briefly discussed in Chapter 6.
Chapter 2

Spatially homogeneous coagulation equation

2.1 Overview of basic properties

In this section, we study some basic mathematical properties of the spatially homogeneous coagulation equation:

\[
\frac{\partial N(u,t)}{\partial t} = \frac{1}{2} \int_0^u \beta(v, u-v)N(v,t)N(u-v,t)dv - \int_0^\infty \beta(u,v)N(u,t)N(v,t)dv . \quad (2.1)
\]

First, let us be more specific about the assumptions we make on the kernel function \(\beta\). It is assumed that for the continuous form,

A1. \(\beta(u,v) \geq 0\),

A2. \(\beta(u,v) = \beta(v,u)\),

A3. \(\beta_{\text{sup}} = \sup_{u,v} \beta(u,v) < \infty\);

and for the discrete form,

B1. \(\beta(i,j) \geq 0\),

B2. \(\beta(i,j) = \beta(j,i)\),

B3. \(\beta_{\text{sup}} = \sup_{i,j} \beta(i,j) < \infty\).

One important motivation for only caring about the bounded kernel case is due to an application problem on which we are currently working. We are studying the neutrophil
and tumor cell adhesion in a nonuniform shear flow. In the experimental setup, we in
general consider only a finite particle system, and the kernel remains bounded. Therefore
we start with these assumptions and work on the equations with bounded kernels.

There have been many mathematical studies of population balance equations, for
instance, on issues such as the uniqueness and existence of solutions and then volume
conservation properties. Ball and Carr [25] proved the existence and volume conservation
when $\beta(u,v) \leq u + v$. In [36], Dubovskii showed the existence for the kernels with com-
 pact support. Some other unbounded kernels were also discussed. This work was later
extended in [27] where the global existence and uniqueness and volume conservation were
shown for an unbounded kernel with possible linear growth at infinity. In [37], spatially
inhomogeneous coagulation equations were studied. In [38], the existence and unique-
ness of solutions were proved when $\beta(u,v) \leq \varphi(u)\varphi(v)$ for some continuous sublinear
function $\varphi$. Moreover, a counterexample was constructed to show the nonuniqueness of
the solution in more general cases, and the hydrodynamic limit theorems were proved for
the stochastic coalescence. Many of the above works also analyzed population balance
equations (PBEs) with fragmentation effects which add additional complications. For a
comprehensive survey of the coagulation equations, we refer to [22] and [39].

The nonlinear PBEs admit exact solutions in some special cases [22, 39], but in
general, they can only be solved numerically. To find accurate and efficient numerical
solutions of the PBEs, various computational algorithms have been developed. (see [40,
41, 42, 43, 44, 45, 46, 47] and the references cited therein.) Most of these papers are based
on stochastic simulations, such as using the classical Marcus-Lushnikov process. For
deterministic methods, a second order Runge-Kutta method was used in [44] to examine
the asymptotic solution, and a deterministic scheme based on binary grid refinement
was used in [47]. Another popular approach for the numerical solution is through series
expansions. For example, Melzak [48] used a power series in time to represent the solution
of equation (2.1). A review of different series approximations was given in [49], and we
note that most of these series approaches discussed here have finite convergent radii that
are local in time.

In the present work, we provide a different series approach for the case where the
PBEs have bounded kernels and have nonnegative and integrable (summable) initial
conditions. Our series is convergent globally for all time $t > 0$. The main idea is
to define a bilinear operator and represent the solution as a series (using the Wild
sum given in [50]) with the coefficients being determined iteratively through the defined
bilinear operator. From the Wild sum, many interesting properties of the PBEs may be
revealed, such as conservation and stability properties. A simple deterministic method, which is named as the time relaxed method following [51], can also be constructed for the numerical solution of the population balance equation which enjoys high order accuracy and preserves many properties of the PBEs including: the total volume conservation, the monotonicity of the total concentration, and non-negativity preservation. Detailed convergence analysis and the numerical implementation of this time relaxed method are both provided. Much of this discussion can be found in Sections 2.4 and 2.5. We also refer to [52, 53].

2.1.1 Moment behavior

In the aggregation process, the adhesion event changes the composition of particles but does not induce volume loss, hence, the total volume of the particles in the aggregation system is conserved, see [36] for a brief proof. For simplicity, we assume that $N_0 = N_0(u)$ is non-negative and is not identically zero to avoid the trivial case where the solution remains identically zero. Then, if $N = N(u,t)$ is the solution of the PBE (2.1), the following identity can be derived for any function $\phi = \phi(u)$,

$$
\frac{d}{dt} \int_{0}^{\infty} \phi(u) N(u,t) \, du = \frac{1}{2} \int_{R^2_+} (\phi(u+v) - \phi(u) - \phi(v)) \beta(u,v)N(u,t)N(v,t) \, dv \, du \quad (2.2)
$$

where $R^2_+ = (0, \infty)^2$.

Thus, by taking $\phi(u) = u^n$, we can define the moment $M_n(t)$ for each integer $n$ by

$$
M_n(t) = \int_{0}^{\infty} u^n N(u,t) \, du. \quad (2.3)
$$

Notice that the physical interpretation of the moments can be described as follows:

<table>
<thead>
<tr>
<th>Moment</th>
<th>Physical interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_0(t)$</td>
<td>the total concentration of the coagulation system</td>
</tr>
<tr>
<td>$M_1(t)$</td>
<td>the total volume of the coagulation system</td>
</tr>
<tr>
<td>$M_2(t)$</td>
<td>the average volume of the particle in the system</td>
</tr>
</tbody>
</table>

Table 2.1. The physical interpretation of moments
Non-increasing total concentration  Define the zeroth moment $M_0(t)$, i.e., the total concentration for a nonnegative solution $N = N(u, t)$, by

$$M_0(t) = \int_0^\infty N(u, t) du.$$  

Then we have,

**Lemma 1.** If $N = N(u, t)$ is the solution of equation (2.1) with an initial condition $N_0(u) \geq 0$, then $M_0(t)$ is a non-increasing function. Consequently,

$$\int_0^\infty N(u, t) du \leq \int_0^\infty N_0(u) du .$$  \hspace{1cm} (2.4)

**Proof.** Consider the population balance equation (2.1) and integrate both sides with respect to $u$. Then we have

$$\int_0^\infty \frac{\partial N(u, t)}{\partial t} du = \frac{1}{2} \int_0^\infty \int_0^u \beta(v, u - v)N(u - v, t)N(v, t) dvdu - \int_0^\infty \int_0^\infty \beta(v, u)N(u, t)N(v, t) dvdu = \frac{1}{2} \int_0^\infty \int_0^\infty \beta(v, u)N(u, t)N(v, t) dvdu \leq 0 .$$

So, we have

$$\frac{d}{dt}M_0(t) = \frac{d}{dt} \int_0^\infty N(u, t) du = \int_0^\infty \frac{\partial N(u, t)}{\partial t} du \leq 0 .$$  \hspace{1cm} (2.5)

Thus $M_0(t)$ is a non-increasing function and the lemma is proved. \hfill \square

Notice that, in the proof, we use the non-negativity property of $N(u, t)$. The non-negative solution of coagulation equation is referenced in [54]. We will also use this property to study the behavior of the moment $M_1(t)$ and $M_2(t)$. The above lemma provides a uniform bound for solution $N = N(\cdot, t)$ in $L^1(0, \infty)$ with respect to time. Such a bound assures the global Lipschitz continuity of the right-hand side of (2.1) , see Lemma 4. This essentially implies the global existence and uniqueness of the solution to (2.1).

**Volume conservation**  The volume conservation law then follows easily by taking $\phi(u) = u$.

**Lemma 2.** Assume $N(u, t)$ is the solution of equation (2.1) with an initial condition
$N_0(u)$ satisfying $uN_0(u) \in L^1(0, \infty)$. Then

$$\int_0^\infty uN(u, t)du = \int_0^\infty uN_0(u)du . \quad (2.6)$$

**Proof.** Multiplying $u$ on both sides of (2.1) and integrating, we have

$$\int_0^\infty u \frac{\partial N(u, t)}{\partial t} du = \frac{1}{2} \int_0^\infty \int_0^u u \beta(v, u-v)N(v, t)N(u-v, t)dvdu$$

$$- \int_0^\infty \int_0^\infty u \beta(u, v)N(u, t)N(v, t)dvdu .$$

By equation (2.2), note that we take $\phi(u) = u$, then

$$\phi(u+v) - \phi(u) - \phi(v) = 0 .$$

we have

$$\frac{\partial}{\partial t} \int_0^\infty uN(u, t)du = 0 . \quad (2.7)$$

Thus, the total volume $\int_0^\infty uN(u, t)du$ remains constant in time. □

The discrete analog can also be established similarly.

**Lemma 3.** Assume $N(i, t)$ is the solution of equation (1.3) with an initial condition $N_0$ as in (1.4), then

$$\sum_{i=1}^\infty iN(i, t) = \sum_{i=1}^\infty iN_0(i) . \quad (2.8)$$

**Non-decreasing average volume** Let $\phi(u) = u^2$. Then we have that the second moment $M_2(t)$ satisfies

$$\int_0^\infty u^2 \frac{\partial N(u, t)}{\partial t} du = \frac{1}{2} \int_0^\infty \int_0^u u^2 \beta(v, u-v)N(v, t)N(u-v, t)dvdu$$

$$- \int_0^\infty \int_0^\infty u^2 \beta(u, v)N(u, t)N(v, t)dvdu$$

$$= \int_{R^2_+} uv \beta(u, v)N(u, t)N(v, t)dvdu$$

$$\geq 0 .$$

So, $M_2(t)$, the average particle volume, is a non-decreasing function. If the second moment blows up in finite time, we claim that the gelation occurs.

For example, let us consider a special kernel $\beta(u, v) = uv$. For this kernel, the
equation of $M_2(t)$ is rewritten as

$$\frac{dM_2(t)}{dt} = M_2^2(t).$$

Upon solving this equation with initial condition $C_0$, we have

$$M_2(t) = \frac{C_0}{1 - C_0 t},$$

where $C_0 = \int_0^\infty u^2 N_0(u) du$.

It is easy to figure out that $M_2(t) \to \infty$ as $t \to T_{gel}$, where $T_{gel} = 1/C_0$ is the gelling time. This phenomenon is called gelation, and $T_{gel}$ is the gelling time. The physical interpretation of gelation is that, on average, the particle volume approaches infinity in finite time. Therefore, the kernel $\beta(u, v)$ is called gelling kernel if the second moment approaches infinity in finite time. For more detailed discussions on the determination of gelling time $T_{gel}$ and its relations to the gelling kernel, refer to [55, 56, 57, 58, 59].

### 2.1.2 Well-posedness

Some basic theories concerning the properties of the PBE model, such as the well-posedness problem and the volume conservation law, can be found in [25, 27, 28, 29, 30]. In our research, we are only interested in the case of a uniformly bounded kernel with a nonnegative initial condition $N_0(u)$ having finite total volume and finite total number. In such a case, the existence and uniqueness can be established in a straightforward manner using standard ODE theory [60]. We give a brief proof here.

Define a Banach space $B$ consisting of the functions $N = N(u, t)$ with

$$\|N\| = \sup_{t \in I} \int_0^\infty |N(u, t)| du < \infty,$$

where $I = [t_0, t_1]$.

We use $R = R(N)$ to denote the right-hand side of the equation (2.1). Then for any $N = N(u, t) \in B$,

$$R(N)(u, t) = \frac{1}{2} \int_0^u \beta(v, u - v)N(v, t)N(u - v, t) dv - \int_0^\infty \beta(u, v)N(u, t)N(v, t) dv.$$  (2.10)

Then, it is straightforward to check that the following lemma holds:
Lemma 4. For any pair of \( N = N(u, t) \) and \( N' = N'(u, t) \) in \( B \), we have

\[
\| R(N) \| \leq \frac{3}{2} \beta_{sup} \| N \|^2, \tag{2.11}
\]

\[
\| R(N) - R(N') \| \leq \frac{3}{2} \beta_{sup} (\| N \| + \| N' \|) \| N - N' \|. \tag{2.12}
\]

Proof. Let us prove equation (2.11) first. It is easy to check that

\[
\int_0^\infty |R(N)(u, t)| \, du \leq \frac{3}{2} \int_0^\infty \int_0^\infty \beta(u, v)N(u, t)N(v, t) \, dv \, du \tag{2.13}
\]

\[
\leq \frac{3}{2} \beta_{sup} \left( \int_0^\infty N(u, t) \, du \right)^2. \tag{2.14}
\]

Thus, we have equation (2.11) by the definition of the norm given in (2.9). We can also obtain (2.12) analogously.

Given a fixed constant \( c \in (1, 2) \), we let

\[
M = c \int_0^\infty N_0(u) \, du \tag{2.15}
\]

and we define the closed ball \( D \) with radius \( M \) in \( B \) by

\[
D = \{ N = N(u, t) \in B : \| N \| < M \}. \tag{2.16}
\]

In the time interval \( I = [t_0, t_1] \) with

\[
t_1 - t_0 = \frac{2(c - 1)}{3cm M \beta_{sup}} > 0, \tag{2.17}
\]

we define the operator

\[
T(N)(u, t) = N_0(u) + \int_{t_0}^t R(N)(u, s) \, ds = N_0(u) + \frac{1}{2} \int_{t_0}^t \int_0^s \beta(v, u - v)N(v, s)N(u - v, s) \, dv \, ds
\]

\[
- \int_{t_0}^t \int_0^\infty \beta(v, u)N(v, s)N(u, s) \, dv \, ds. \tag{2.18}
\]

Then,

**Theorem 1.** \( T \) is a contraction mapping from \( D \) to \( D \). Thus the equation (2.1) with initial data \( N_0 = N_0(u) \) has a unique solution in \( D \).
Proof. Using the results of the previous lemma, for any $N \in D$, we first have
\[
\|T(N)\| \leq \|N_0\| + \Delta t\|R(N)\| \leq \frac{1}{c}M + \frac{3}{2}\beta_{\text{sup}}M^2\Delta t = M.
\]
So, $T$ maps $D$ to $D$. Moreover, for any $N_1, N_2 \in D$, we have
\[
\langle T(N_1) - T(N_2) \rangle (u, t) = \int_{t_0}^{t} \langle R(N_1) - R(N_2) \rangle (u, s) \, ds,
\]
Therefore,
\[
\|T(N_1) - T(N_2)\| \leq \frac{3}{2}\beta_{\text{sup}}(\|N_1\| + \|N_2\|)\|N_1 - N_2\|\Delta t
\leq 3\beta_{\text{sup}}M\Delta t\|N_1 - N_2\| = 2\left(1 - \frac{1}{c}\right)\|N_1 - N_2\|.
\]
(2.19)

$T$ is thus a contraction mapping for $c \in (1, 2)$. So (2.1) has a unique solution in $D$. □

We can extend the local solution in the small interval to the whole interval using uniform bounds on the solutions. This extension is given later.

By the lemmas given earlier, the uniqueness and existence of the global solution of PBE (2.1) can be stated as follows.

**Theorem 2.** If initial condition $N_0 = N_0(u) \geq 0$ and $\int_0^{\infty} N_0(u)du < \infty$, then equation (2.1) has a unique global solution.

**Proof.** We consider the equation on the intervals
\[
\{I_n = [t_n, t_{n+1}]\}_{n=0}^{\infty},
\]
with $t_n$ to be specified later.

In the closed ball $D_n$ with radius $M_n$, consider using $N_n(u) = N(u, t_n)$, the solution at time $t_n$ solved on the interval $[t_{n-1}, t_n]$, as the initial solution on interval $[t_n, t_{n+1}]$.

Then, by the non-negativity of the solutions,
\[
\int_0^{\infty} |N_n(u)|du = \int_0^{\infty} N_n(u)du \leq \int_0^{\infty} N_0(u)du.
\]
(2.21)

That is, $\{N_n(u)\}_{n=0}^{\infty}$ is uniformly bounded in $L^1$. So, for some $c \in (1, 2)$, we take
\[
M_n = c \int_0^{\infty} N_n(u)du \leq c \int_0^{\infty} N_0(u)du.
\]
(2.22)
and specify the time step by

$$\Delta t_n = t_{n+1} - t_n = \frac{2(c - 1)}{3c^2 \beta_{\text{sup}} \|N_0\|_{L^1}} \leq \frac{2(c - 1)}{3cM \beta_{\text{sup}}}.$$  \hfill (2.23)

Then by the local existence result, we have a unique solution on each $I_n$. Since $\bigcup_n I_n = [0, \infty)$, we have the existence and the uniqueness of the global solution on $[0, \infty)$. \hfill \square

Similarly, for the discrete population balance equation with an initial condition $N(i, 0) = N_0(i), i = 1, 2, 3, \ldots$, we have the following result.

**Theorem 3.** Given $N_0 \in \ell^1$ with $N_0(i) \geq 0$ for $i = 1, 2, 3, \ldots$, the equation (1.3) has a unique global solution. Moreover, the solution satisfies $N(i, t) \geq 0$ for $i \geq 1$.

The proofs are analogous to the continuous case, and they are omitted here. We refer to [25, 27, 28, 29, 30] for the proofs of similar results.

### 2.1.3 Asymptotic behavior

In general, it is not easy to determine the asymptotic behavior of $N(i, t)$ due to the complexity of the aggregation kernels $\beta(i, j)$, the dependence of the behavior of other particles, and so on. In this subsection, we will discuss some special cases.

First of all, by Lemma 9, since the total concentration $C_N(t)$ is non-increasing and positive for all $t$, we easily obtain the following.

**Proposition 1.** There exists a constant $C_\infty \geq 0$ such that

$$\lim_{t \to \infty} \int_0^\infty N(u, t) \, du = C_\infty.$$ 

Furthermore, if the coagulation kernel $\beta(u, v) > 0$ almost everywhere, we claim that $C_\infty = 0$. Therefore, we have the following corollary.

**Corollary 1.** If the coagulation kernel $\beta(u, v) > 0$ a.e., then

$$\lim_{t \to \infty} \int_0^\infty N(u, t) \, du = 0.$$ 

For the discrete system (1.3), if we consider the single monomer in the aggregation system, the aggregation probability between two single monomers is represented by $\beta(1, 1)$. Without loss of generality, we assume $\beta(1, 1) > 0$. Intuitively, we can imagine that the single particles will collide and adhere with other big particles, at least with
the particle having the same size, until all the single monomers disappear in the system. This reminds us that the concentration of the monomers will go to zero as time goes to infinity. We provide the following two propositions. For more details, refer to [26].

**Proposition 2.** Assume $\beta(1, 1) > 0$, then $N(1, t)$ has the following properties:

$$ \frac{\partial N(1, t)}{\partial t} \leq 0 , \quad (2.24) $$

$$ N(1, t) \leq \frac{N(1, 0)}{N(1, 0) + \beta(1, 1) t} \quad (2.25) $$

and $N(1, t) \in L^2(0, \infty)$.

**Proof.** Taking $i = 1$ in equation (1.3), we get

$$ \frac{\partial N(1, t)}{\partial t} = - \sum_{j=1}^{\infty} \beta(1, j) N(1, t) N(j, t) \leq - \beta(1, 1) N(1, t)^2 \leq 0 . $$

Integrating the differential inequality, we further have

$$ N(1, t) \leq \frac{N(1, 0)}{N(1, 0) + \beta(1, 1) t} $$

which immediately implies $N(1, t) \in L^2(0, \infty)$. \hfill \square

The above proposition reveals the long-time behavior of $N(1, t)$. The result can be extended to more general cases. For example, the following proposition is given in [26].

**Proposition 3.** Assume $\beta(i, i) > 0$, for any $i \leq k$. Then $\{N(i, t)\}_{i=1}^{k}$ has the following properties:

a) $N(i, \cdot) \in L^2(0, \infty)$;

b) $\lim_{t \to \infty} N(i, t) = 0$, for any $i = 1, 2, \ldots, k$.

**Proof.** We prove by induction, the case $k = 1$ follows from the previous proposition. Assume that the conclusion holds for $k - 1$. We let

$$ g_k(t) = \sum_{j=1}^{k-1} \beta(j, k - j) N(j, t) N(k - j, t) $$

which implies that

$$ \frac{\partial N(k, t)}{\partial t} \leq g_k(t) - \beta(k, k) N(k, t)^2 $$
It is not difficult to show that function $g_k$ is bounded in $L^1(0, \infty)$ since $N(i, t) \in L^2(0, \infty)$ for $i = 1, 2, \ldots k - 1$, thus, integrating in time, we also have

$$\beta(k, k) \int_0^\infty N(k, t)^2 dt \leq N_0(k) + \int_0^\infty g_k(t) dt.$$ 

By induction, this proves the proposition. 

Notice that the above proposition implies that the smaller particles will eventually aggregate into bigger particles if there is a nontrivial probability of self coagulation, i.e., $\beta(i, i) > 0$. Moreover, by combining with earlier results, we see that if $\beta(i, i) > 0$ for all $i$, then, $\{N(i, t)\}_{i=1}^\infty$ approaches a delta mass situated at $i \to \infty$ when $t$ approaches to infinity. This property is consistent with our intuition.

### 2.1.4 Bounded derivatives

In many real applications, the discrete population balance equations are particularly useful because the particles in the coagulation systems tend to be finite, and the single (unit) particle has a fixed volume. In other words, $N(i, t)$ is often used to represent the distribution of the particle with $i$ monomers. For the discrete equations, we now derive some additional properties.

Based on earlier discussions, we know that the total volume, denoted by $V$, is preserved in the system. That is,

$$V = \sum_{i=1}^\infty iN(i, t) = \sum_{i=1}^\infty iN_0(i).$$

(2.26)

We now give some decay estimates on the time derivatives of $N(i, t)$.

**Lemma 5.** For any $i \geq 1, 2, \ldots$,

$$\left| \frac{\partial N(i, t)}{\partial t} \right| \leq \frac{\beta_{\text{sup}} V^2}{i}. \quad (2.27)$$

**Proof.** From equation (2.1), we have

$$\frac{\partial N(i, t)}{\partial t} \leq \frac{\beta_{\text{sup}}}{2} \left( \sum_{j=1}^{i/2} \frac{i - j}{i - j} N(i - j, t)N(j, t) + \sum_{j=i/2+1}^{i-1} \frac{j}{j} N(i - j, t)N(j, t) \right) \leq \frac{\beta_{\text{sup}} V^2}{i},$$

and

$$\frac{\partial N(i, t)}{\partial t} \geq -\frac{\beta_{\text{sup}}}{i} iN(i, t) \sum_{j=1}^\infty N(j, t) \geq -\frac{\beta_{\text{sup}} V^2}{i}.$$
Thus we get
\[ \left| \frac{\partial N(i, t)}{\partial t} \right| \leq \frac{\beta_{\text{sup}} V^2}{i}. \]

The above lemma can be extended to more general cases. It is easy to verify that the derivatives of \( N(i, t) \) of all orders remain bounded.

**Proposition 4.** For \( i = 1, 2, ..., \) there exists constant \( C = C(i, V, \beta_{\text{sup}}, n) \) such that
\[ \left| \frac{\partial^n N(i, t)}{\partial t^n} \right| \leq C, \quad \forall n \geq 1. \]  
(2.28)

### 2.2 Ideal kernels

It has been shown in [22] that the coagulation equations have analytical solutions for three ideal kernels: the constant kernel \( 1 \), the sum kernel \( u + v \), and the product kernel \( uv \). Their analytical solutions are listed in Table 2.2, in which the function \( B \) is given by,
\[ B(\lambda, i) = \left( \lambda i \right)^{-1} e^{-\lambda i / i!}. \]  
(2.29)

<table>
<thead>
<tr>
<th>kernel</th>
<th>constant kernel</th>
<th>sum kernel</th>
<th>product kernel</th>
</tr>
</thead>
<tbody>
<tr>
<td>continuous</td>
<td>( 4t^{-2}e^{-2u/t} ) ( t \in (0, \infty) )</td>
<td>( (2\pi)^{-1/2}e^{-t}u^{-3/2}e^{-2t}u^{-2/2} ) ( t \in (-\infty, \infty) )</td>
<td>( (2\pi)^{-1/2}u^{-5/2}e^{-t}u^{-2/2} ) ( t \in (-\infty, 0) )</td>
</tr>
<tr>
<td>discrete</td>
<td>( (1 + \frac{t}{2})^{-2} \left( \frac{t}{\pi t} \right)^{i-1} ) ( t \in [0, \infty) )</td>
<td>( e^{-1}B(1 - e^{-1}, i) ) ( t \in [0, \infty) )</td>
<td>( i^{-1}B(t, i) ) ( t \in [0, 1) )</td>
</tr>
</tbody>
</table>

**Table 2.2.** Analytical solutions of \( N(u, t) \) and \( N(i, t) \)

There are various methods to determine the analytical solutions for the ideal kernels [61, 62, 63, 64, 65]. In this section, we develop another method. Our method not only provides the analytical solution for the ideal kernels but also give us a reference to the numerical approach for some other general kernels. The basic idea is to divide the particles into groups and consider these groups individually. Therefore the infinite coagulation dynamical system will be transformed to a finite system if we have finite groups. An obvious way to achieve this is to group big particles together by introducing
a new function $N(t)$, which is defined by

$$N(t) = \sum_{i=K+1}^{\infty} N(i, t).$$ \hspace{1cm} (2.30)

We denote by $G$, the group in which each particle is composed of monomers greater than $K$. Thus, $N(t)$ is the concentration of group $G$.

We define the average size of group $G$ at time $t$ by

$$s(t) = \frac{\sum_{j=K+1}^{\infty} jN(j, t)}{N(t)}.$$ \hspace{1cm} (2.31)

Then similarly, we can write the new equations as follows:

$$\frac{\partial N(i, t)}{\partial t} = \frac{1}{2} \sum_{j=1}^{i-1} \beta(j, i - j)N(j, t)N(i - j, t)$$

$$- \sum_{j=1}^{K} \beta(i, j)N(i, t)N(j, t) - \alpha(i, t)N(i, t)N(t),$$ \hspace{1cm} (2.32)

$$\text{for } i = 1, 2, ..., K.$$

$$\frac{\partial N(t)}{\partial t} = \frac{1}{2} \sum_{i+j>K; i,j \leq K} \beta(i, j)N(i, t)N(j, t) - \gamma(t)N^2(t),$$ \hspace{1cm} (2.33)

where $\alpha(i, t)$ is the coagulation kernel between particle of size $i$ and group $G$, and represents the coagulation probability of particle of size $i$ with any particle in the group $G$; and $\gamma(t)$ is the coagulation kernel of group $G$, and represents the average coagulation probability between any two particles belonging to group $G$.

Note that the original Smoluchowski equation is an infinite ordinary differential system. By approximation, we get new equations (2.32) and (2.33) and they are reduced to a finite system with $K + 1$ equations. Hence, the finite system is much easier to be solved. The remaining question to us is to approximate the coagulation kernels $\alpha(i, t)$ and $\gamma(t)$.

Since $s(t)$ is the average size of group $G$, $\alpha(i, t)$ and $\gamma(t)$ can be approximated by

$$\alpha(i, t) \approx \beta(i, s(t))$$ \hspace{1cm} (2.34)

$$\gamma(t) \approx \frac{1}{2} \beta(s(t), s(t))$$ \hspace{1cm} (2.35)
Therefore, we get a complete ODE system as follows:

\[
\frac{\partial N(i, t)}{\partial t} = \frac{1}{2} \sum_{j=1}^{i-1} \beta(j, i-j)N(j, t)N(i-j, t) \quad (2.36)
\]

\[
- \sum_{j=1}^{K} \beta(i, j)N(i, t)N(j, t) - \beta(i, s(t))N(i, t)N(t) \,, \quad \text{for} \quad i = 1, 2, \ldots, K.
\]

\[
\frac{\partial N(t)}{\partial t} = \frac{1}{2} \sum_{i+j>K; \, i, j \leq K} \beta(i, j)N(i, t)N(j, t) - \frac{1}{2} \beta(s(t), s(t))N^2(t) \,, \quad (2.37)
\]

\[
s(t) = \frac{V - \sum_{j=1}^{K} jN(j, t)}{N(t)} \,, \quad (2.38)
\]

where \(V\) is the total volume of the coagulation system which is preserved by the system independent of time.

We now show that the total volume is preserved.

**Theorem 4.** The total volume is preserved for ODE system (2.36)-(2.38). i.e.

\[
\sum_{i=1}^{K} iN(i, t) + s(t)N(t) = V .
\]

As indicated above, we approximate \(\alpha(i, t)\) and \(\gamma(t)\) by equations (2.34) and (2.35) to solve equation (2.32). However, it is not known whether or not this is a good approximation. We want to show that this approximation will give us a solution which is identical to that of the original equation (2.1) for some ideal kernels. First, let us compare equations (2.36)-(2.38) with the original equation (1.3).

Subtracting equation (2.32) by (2.1), we have

\[
\alpha(i, t)N(i, t)N(t) = \sum_{j=K+1}^{\infty} N(i, t)N(j, t) .
\]

Thus, we get

\[
\alpha(i, t) = \frac{\sum_{j=K+1}^{\infty} \beta(i, j)N(j, t)}{N(t)} . \quad (2.39)
\]

Take the summation for (2.1) for \(i\) from \(K+1\) to infinity, we have the following equation:
\[
\frac{\partial N(t)}{\partial t} = \frac{1}{2} \sum_{i+j>K, i,j \leq K} \beta(i,j)N(i,t)N(j,t) - \frac{1}{2} \sum_{i,j=K+1} \beta(i,j)N(i,t)N(j,t) .
\]

Comparing with equation (2.33), we get

\[
\gamma(t) = \frac{\sum_{i,j=K+1}^{\infty} \beta(i,j)N(i,t)N(j,t)}{2N(t)^2} .
\]

Then, for any kernel, \( \beta(i,j) \), the problem we need to consider is to analyze how good the approximations to \( \alpha(i,t) \) and \( \gamma(t) \) are. The following theorem tells us that this approach is an exact approach for ideal kernels.

**Theorem 5.** For any \( i, j > K \), if the kernels have the form \( \beta(i,j) = c, \beta(i,j) = c(i+j) \) or \( \beta(i,j) = cij \), where \( c \) is a constant, then we have

\[
\alpha(i,t) = \beta(i,s(t)) ,
\]

\[
\gamma(t) = \beta(s(t),s(t)) .
\]

**Proof.**

Without loss of generality, we only consider the kernel \( \beta(i,j) = ij \). The proof is similar for other kernels. Observe that

\[
\alpha(i,t) = \frac{\sum_{j=K+1}^{\infty} \beta(i,j)N(j,t)}{N(t)} = \frac{i \sum_{j=K+1}^{\infty} jN(j,t)}{N(t)} = is(t) = \beta(i,s(t)) ,
\]

and

\[
\gamma(t) = \frac{\sum_{i,j=K+1}^{\infty} \beta(i,j)N(i,t)N(j,t)}{2N(t)^2} = \frac{\sum_{i,j=K+1}^{\infty} ijN(i,t)N(j,t)}{2N(t)^2} = \frac{(\sum_{i,j=K+1}^{\infty} iN(i,t))^2}{2N(t)^2} .
\]
Hence, by this approach, we have successfully reduced the original infinite ODE system (2.1) to a finite system (2.36)-(2.38). Based on these finite equations, we can solve the equation for the ideal kernels analytically. This method is also a good approximation for some other kernels.

2.3 Bilinear operator

Most of the existing series approximation methods for spatially homogeneous coagulation equation have finite convergent radius for time $t$. In this section, we set up a bilinear operator and give a series approach for the coagulation equation based on the reformulation of the equation by this bilinear operator. We show this series expansion is globally convergent in time. Time relaxed method is derived from this series expansion.

First, we consider the continuous form and construct a bilinear operator $P$ for two functions $f = f(v)$ and $g = g(v)$ as follows:

$$
P(f, g)(u) = \frac{1}{2} \int_0^u \beta(v, u - v)f(v)g(u - v)dv - f(u) \int_0^\infty \beta(u, v)g(v)dv
+ \tilde{\lambda}f(u) \int_0^\infty vg(v)dv
= \frac{1}{2} \int_0^u \beta(v, u - v)f(v)g(u - v)dv
+ \tilde{\lambda}f(u) \int_0^\infty (\tilde{\lambda}v - \beta(u, v))g(v)dv.
\tag{2.42}
$$

A similar bilinear operator can be found in [51] in the context of Boltzmann equations.

Since $\beta = \beta(u, v)$ is bounded by $\beta_{sup}$, we take a positive constant $\tilde{\lambda}$ satisfying

$$
\tilde{\lambda} \geq \frac{\beta_{sup} \int_0^\infty N_0(u) \ du}{\int_0^\infty uN_0(u) \ du}.
\tag{2.43}
$$

By the volume conservation property stated in Lemma 2, it is easy to verify that with the choice of $\tilde{\lambda}$ in equation (2.43), the bilinear operator $P$ preserves non-negativity in the following sense:
Lemma 6. Let $N = N(u, t)$ be a nonnegative function satisfying the total volume conservation (2.6) with the total concentration non-increasing; that is,

$$
\int_0^\infty N(u, t)du \leq \int_0^\infty N_0(u)du .
$$

Then for any $t > 0$,

$$
P(N(u, t), N(u, t)) \geq 0 .
$$

Corresponding to $\tilde{\lambda}$ and $N_0$, we introduce another positive constant

$$
\lambda = \tilde{\lambda} \int_0^\infty uN_0(u)du .
$$

Then, it is again straightforward to obtain the following result.

Lemma 7. For any two functions $f = f(u)$ and $g = g(u)$ such that $uf$ and $ug$ are integrable on $(0, \infty)$, we have

$$
\int_0^\infty uP(f, g)du = \tilde{\lambda} \left( \int_0^\infty uf(u)du \right) \left( \int_0^\infty ug(u)du \right) .
$$

Notice that if $N = N(u, t)$ is the solution of equation (2.1), then we have conservation of the total volume (2.6). This leads to another useful form of the conservation property.

Lemma 8. If $N = N(u, t)$ is the solution of equation (2.1) with initial data $N_0$, then

$$
\int_0^\infty uP(N, N)du = \lambda \int_0^\infty uN_0(u)du .
$$

2.3.1 A reformulation and properties of the equations

First, using the parameter $\lambda$ and the total volume conservation property, the equation (2.1) can be rewritten as:

$$
\frac{\partial N}{\partial t} = P(N, N) - \lambda N .
$$

By the change of variables

$$
\tau = 1 - e^{-\lambda t} , \quad F(u, \tau) = N(u, t)e^{\lambda t} ,
$$

$$
\tau = 1 - e^{-\lambda t} , \quad F(u, \tau) = N(u, t)e^{\lambda t} ,
$$
we get an initial value problem for $F = F(u, \tau)$ as follows:

$$
\left\{ \begin{array}{l}
\frac{\partial F(u, \tau)}{\partial \tau} = \frac{1}{\lambda} \mathcal{P}(F, F) \\
F(u, 0) = N_0(u).
\end{array} \right. \quad (2.48)
$$

We expand $F(u, \tau)$ as a power series for $\tau \in [0, 1)$:

$$
F(u, \tau) = \sum_{k=0}^{\infty} \tau^k f_k(u). \quad (2.49)
$$

So, $N = N(u, t)$ can be written as

$$
N(u, t) = e^{-\lambda t} \sum_{k=0}^{\infty} (1 - e^{-\lambda t})^k f_k(u). \quad (2.50)
$$

The above expansion is similar to the Wild sum formulation for the solution of Boltzmann equations [50]. One can check that the coefficients $\{f_k(u)\}$ are determined by the recursive relation:

$$
f_{k+1}(u) = \frac{1}{k+1} \sum_{i=0}^{k} \frac{1}{\lambda} \mathcal{P}(f_i, f_{k-i}) \quad (2.51)
$$

with the first term given by

$$
f_0(u) = N_0(u). \quad (2.52)
$$

Combining equations (2.50), (2.51), and (2.52), we have an explicit construction for the solution of equation (2.1). While it will not be used to explicitly compute the solutions, it is, however, very useful in deriving a number of important properties of the PBE system (2.1). First, we have,

**Lemma 9.** For the coefficients $\{f_k(u)\}$ defined by the equation (2.51)-(2.52), we have

a) $\int_0^{\infty} uf_k(u) du = \int_0^{\infty} uN_0(u) du$;

b) $\int_0^{\infty} f_k(u) du \leq \int_0^{\infty} N_0(u) du$;

c) $f_k(u) \geq 0$.

**Proof.** We prove this result by induction.

To prove a), we first consider $f_1(u)$. By equation (2.51), we have

$$
f_1(u) = \frac{1}{\lambda} \mathcal{P}(f_0, f_0) = \frac{1}{\lambda} \mathcal{P}(N_0, N_0). \quad (2.53)
$$
Hence by (2.45), we have
\[ \int_0^\infty u f_1(u) du = \frac{1}{\lambda} \int_0^\infty u P(N_0, N_0) du = \int_0^\infty u N_0(u) du. \]

Now we assume a) is true for \( i \leq k \). We can then use (2.51) and (2.44) to get
\[
\int_0^\infty u f_{k+1}(u) du = \frac{1}{(k+1)\lambda} \sum_{i=0}^{k} \int_0^\infty u P(f_k, f_{k-i}) du
\]
\[
= \frac{1}{(k+1)\lambda} \sum_{i=0}^{k} \tilde{\lambda} \left( \int_0^\infty u f_i(u) du \right) \left( \int_0^\infty u f_{k-i}(u) du \right)
\]
\[
= \frac{(k+1)\tilde{\lambda}}{(k+1)\lambda} \left( \int_0^\infty u N_0(u) du \right)^2
\]
\[
= \int_0^\infty u N_0(u) du,
\]
which proves a).

We now prove b) and c) together. First, when \( k = 1 \), we have
\[
\int_0^\infty f_1(u) du = \frac{1}{\lambda} \int_0^\infty P(N_0, N_0) du
\]
\[
= \frac{1}{2\lambda} \int_0^\infty \int_0^u \beta(u - v, v) N_0(v) N_0(u - v) dv du
\]
\[
- \frac{1}{\lambda} \int_0^\infty \int_0^\infty \beta(u, v) N_0(v) N_0(u) dv du + \frac{\tilde{\lambda}}{\lambda} \int_0^\infty \int_0^\infty v N_0(v) N_0(u) dv du
\]
\[
= \frac{\tilde{\lambda}}{\lambda} \int_0^\infty v N_0(v) N_0(u) dv du - \frac{1}{2\lambda} \int_0^\infty \int_0^\infty \beta(u, v) N_0(v) N_0(u) dv du
\]
\[
\leq \frac{\tilde{\lambda}}{\lambda} \int_0^\infty N_0(u) du \int_0^\infty v N_0(v) dv = \int_0^\infty N_0(u) du.
\]
So b) holds for \( k = 1 \). Now,
\[
f_1(u) = \frac{1}{\lambda} P(N_0, N_0)(u)
\]
\[
= \frac{1}{2\lambda} \int_0^u \beta(u - v, v) N_0(v) N_0(u - v) dv du - \frac{1}{\lambda} \int_0^\infty \beta(u, v) N_0(v) N_0(u) dv
\]
\[
+ \frac{\tilde{\lambda}}{\lambda} \int_0^\infty N_0(u) v N_0(v) dv
\]
\[
\geq N_0(u) \left( -\frac{\beta_{\text{sup}}}{\lambda} \int_0^\infty N_0(v) dv + \frac{\tilde{\lambda}}{\lambda} \int_0^\infty v N_0(v) dv \right) = 0.
\]
So, c) also holds for $k = 1$.

Assume b) and c) hold for $i = 1, 2, ..., k$. Similar to before, we get

$$
\int_0^\infty P(f_i, f_{k-i})(u)du = \frac{1}{2} \int_0^\infty \int_0^u \beta(u-v, v)f_i(v)f_{k-i}(u-v)dvdu
$$

$$
- \int_0^\infty \int_0^\infty \beta(u, v)f_i(v)f_{k-i}(u)dvdu + \tilde{\lambda} \int_0^\infty \int_0^\infty v f_i(v)f_{k-i}(u)dvdu
$$

$$
= -\frac{1}{2} \int_0^\infty \int_0^\infty \beta(u, v)f_i(v)f_{k-i}(u)dvdu + \tilde{\lambda} \int_0^\infty \int_0^\infty v f_i(v)f_{k-i}(u)dvdu
$$

$$
\leq \lambda \int_0^\infty f_{k-i}(u)du \int_0^\infty v f_i(v)dv
$$

$$
\leq \lambda \int_0^\infty N_0(u)du \int_0^\infty v N_0(v)dv = \lambda \int_0^\infty N_0(u)du .
$$

Then by (2.51), it is easy to verify that

$$
\int_0^\infty f_{k+1}(u) \leq \int_0^\infty N_0(u)du .
$$

Now to prove $f_{k+1}(u) \geq 0$, we first show $P(f_i, f_{k-i}) \geq 0$:

$$
P(f_i, f_{k-i}) = \frac{1}{2} \int_0^u \beta(u-v, v)f_i(v)f_{k-i}(u-v)dv
$$

$$
- \int_0^\infty \beta(u, v)f_i(v)f_{k-i}(v)dv + \tilde{\lambda} \int_0^\infty v f_i(v)f_{k-i}(v)dv
$$

$$
\geq f_i(u) \left(-\beta_{\sup} \int_0^\infty f_{k-i}(v)dv + \tilde{\lambda} \int_0^\infty v N_0(v)dv \right)
$$

$$
\geq f_i(u) \left(-\beta_{\sup} \int_0^\infty N_0(v)dv + \tilde{\lambda} \int_0^\infty v N_0(v)dv \right) \geq 0 .
$$

By (2.51), we have the non-negativity of $f_{k+1}$. This proves c). 

\[ \square \]

The above lemma implies the uniform boundedness of $\{f_k(u)\}$ in $L^1(0, \infty)$ which leads to the convergence of the power series expansions in (2.49) and (2.50), and it also implies that the solution of equation (2.1) is nonnegative if we have a nonnegative initial condition.

**Lemma 10.** Given $N_0 = N_0(u) \geq 0$, $N_0 \in L^1(0, \infty)$, we have

a) the coefficients $\{f_k(u)\}$ are uniformly bounded in $L^1(0, \infty)$ by $\int_0^\infty N_0(u)du$;

b) for any $\tau \in [0, 1)$, the series (2.49) converges uniformly in $L^1(0, \infty)$;
c) for any $t \in [0, \infty)$, the series (2.50) converges uniformly in $L^1(0, \infty)$;

d) the solution of (2.1) satisfies $N(u, t) \geq 0$ for any $t \in [0, \infty)$ and

\[
\int_0^\infty N(u, t)du
\]

is non-increasing in time.

With the non-negativity of the solution, the non-increasing property of the total concentration can also be readily obtained from (2.2) by taking a constant function $\phi(u) = 1$.

### 2.3.2 The reformulation of the discrete equation

The results stated as above are all related to the continuous form of the PBE. The same results are also applicable to the discrete form (1.3). We now give a brief account.

In fact, it is easy to figure out that for any function $\phi = \phi(i)$, we have

\[
\frac{d}{dt} \sum_{i=1}^\infty \phi(i) N(i, t) = \frac{1}{2} \sum_{i=1}^\infty \sum_{j=1}^\infty (\phi(i + j) - \phi(i) - \phi(j)) \beta(i, j) N(i, t)N(j, t).
\]  
(2.54)

The volume conservation law then follows by taking $\phi(i) = i$.

For nonnegative sequences $\{N(i)\}_{i=1}^\infty$ and $\{M(i)\}_{i=1}^\infty$, we can define a bilinear operator $P = \{P_i\}_{i=1}^\infty$ as follows:

\[
P_i(N, M) = \frac{1}{2} \sum_{j=1}^{i-1} \beta(i - j, j)N(i - j)M(j) + \sum_{j=1}^\infty (\tilde{\lambda}j - \beta(i, j))N(i)M(j)
\]  
(2.55)

where we assume $\beta(i, j)$ is bounded such that:

\[
\beta_{sup} = \sup_{i,j} \beta(i, j) \leq \tilde{\lambda} < \infty.
\]  
(2.56)

It follows that $P$ is a nonnegative bilinear operator as shown in the following lemma:

**Lemma 11.** If both $\{N(i)\}_{i=1}^\infty$ and $\{M(i)\}_{i=1}^\infty$ are non-negative, so is $P(N, M)$. 

Let $\lambda = \tilde{\lambda} \sum_{i=1}^{\infty} i N_0(i)$, we then have a discrete analog of (2.50):

$$N(i, t) = e^{-\lambda t} \sum_{k=0}^{\infty} (1 - e^{-\lambda t})^k f_k(i),$$  \hspace{1cm} (2.57)

and the coefficients $\{f_k(i)\}$ are determined by the recursive formula

$$f_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_i(f_j, f_{k-j})$$  \hspace{1cm} (2.58)

where $f_0(i) = N_0(i)$ for any $i$.

The following proposition can be easily derived using a change of summation indices, similar to that in the continuous case.

**Proposition 5.** For any sequences $\{N(i)\}_{i=1}^{\infty}$ and $\{M(i)\}_{i=1}^{\infty}$ with finite total volumes, we have

$$\sum_{i=1}^{\infty} i P_i(N, M) = \tilde{\lambda} \left( \sum_{i=1}^{\infty} i N(i) \right) \left( \sum_{i=1}^{\infty} i M(i) \right).$$  \hspace{1cm} (2.59)

The above proposition, together with Lemma 11, leads to a useful bound on the operator norm of $P$. We will discuss this in detail later.

Corresponding to the continuous case, we derive the following lemma for coefficients $f_k$.

**Lemma 12.** Given a non-negative $N_0$ with $\{N_0(i)\} \in \ell^1$ and $\{i N_0(i)\} \in \ell^1$, the coefficients $\{f_k(i)\}$ defined by (2.58) satisfy

a) $f_k(i) \geq 0$;

b) $\sum_{i=1}^{\infty} i P_i(f_k, f_k) = \lambda \sum_{i=1}^{\infty} i f_k(i)$;

c) $\sum_{i=1}^{\infty} i f_k(i) = \sum_{i=1}^{\infty} i N_0(i), \quad \forall k = 0, 1, 2, ...$;

d) $\sum_{i=1}^{\infty} f_k(i) \leq \sum_{i=1}^{\infty} N_0(i), \quad \forall k = 0, 1, 2, ...$.

Consequently, we also have the following result:

**Lemma 13.** Given a non-negative $N_0$ with $\{N_0(i)\} \in \ell^1$ and $\{i N_0(i)\} \in \ell^1$,

a) the coefficients $\{f_k(i)\}$ are uniformly bounded in $\ell^1$ by $\sum_{i=1}^{\infty} N_0(i)$;

b) for any $t \in [0, \infty)$, the series (2.57) converges uniformly in $\ell^1$;

c) the solution of (1.3) satisfies $N(i, t) \geq 0$ for any $i$ and $t \in [0, \infty)$. 
In light of the identity (2.54), we now consider a slightly more general version of the lemma 12. First, for any given \( \{ \phi(i) \} \) and \( \{ N(i) \} \), straightforward calculation leads to:

\[
\sum_{i=1}^{\infty} \phi(i) P_i(N, N) = \frac{1}{2} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} \beta(i, j)[\phi(i+j) - \phi(i) - \phi(j)] N(i) N(j) + \tilde{\lambda} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} j \phi(i) N(i) N(j) .
\]  

(2.60)

Then, using (2.58) and the bilinearity of \( P_i \):

\[
2P_i(N, M) + 2P_i(M, N) = P_i(N + M, N + M) - P_i(N - M, N - M) ,
\]

we can use the equation (2.60) to get

\[
\sum_{i=1}^{\infty} \phi(i) f_{k+1}(i) = \frac{1}{2(k+1)\lambda} \sum_{m=0}^{k} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} \beta(i, j)[\phi(i + j) - \phi(i) - \phi(j)] f_m(i) f_{k-m}(k)
\]

\[
+ \frac{\tilde{\lambda}}{(k+1)\lambda} \sum_{m=0}^{k} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} j \phi(i) f_m(i) f_{k-m}(j) .
\]

Thus, by taking \( \{ \phi(i) = i \} \), and using induction, we easily get the conclusion in lemma 12c). In turn, this helps to further reduce the above equation to

\[
\sum_{i=1}^{\infty} \phi(i) f_{k+1}(i) = \frac{1}{2(k+1)\lambda} \sum_{m=0}^{k} \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} \beta(i, j)[\phi(i + j) - \phi(i) - \phi(j)] f_m(i) f_{k-m}(k)
\]

\[
+ \frac{1}{k+1} \sum_{m=0}^{k} \sum_{i=1}^{\infty} \phi(i) f_m(i) .
\]

From this, we get

**Lemma 14.** Given a non-negative \( N_0 \) with \( \{ \phi(i) N_0(i) \} \in \ell^1 \), the coefficients \( \{ f_k(i) \} \) defined by (2.58) satisfy

a) for any sub-additive function \( \phi \), i.e., \( \phi(i + j) - \phi(i) - \phi(j) \leq 0 \) for any \( i, j \), we have

\[
\sum_{j=1}^{\infty} \phi(j) f_{k+1}(j) \leq \frac{1}{k+1} \sum_{m=0}^{k} \sum_{j=1}^{\infty} \phi(j) f_m(j) ;
\]

b) for any sup-additive function \( \phi \), i.e., \( \phi(i + j) - \phi(i) - \phi(j) \geq 0 \) for any \( i, j \), we have

\[
\sum_{j=1}^{\infty} \phi(j) f_{k+1}(j) \geq \frac{1}{k+1} \sum_{m=0}^{k} \sum_{j=1}^{\infty} \phi(j) f_m(j) ;
\]
c) in addition, \( \sum_{i=1}^{\infty} i^K f_{k+1}(i) \leq M_K(0) \) for \( 0 \leq K \leq 1 \) and \( \sum_{i=1}^{\infty} i^K f_{k+1}(i) \geq M_K(0) \) for \( K \geq 1 \).

Then, using either the above result or directly working with (2.54), we can get the following well-known properties for the moments

\[
M_K(t) = \sum_{i=1}^{\infty} i^K N(i, t) \quad \text{for } n \geq 0 \quad (2.61)
\]

of the solutions of the discrete PBE (1.3):

**Lemma 15.** Given two non-negative numbers \( N_0 \) and \( K \), with \( \{i^K N(i)\} \in \ell^1 \), then we have \( \frac{d}{dt} M_K(t) \leq 0 \) for \( K \leq 1 \), and \( \frac{d}{dt} M_K(t) \geq 0 \) for \( K \geq 1 \).

### 2.3.3 More on asymptotic behavior

In this section, we discuss more results for the asymptotic behavior of the solution. By the properties of the Cesaro sum, we can conclude the long-time asymptotic of \( N(u, t) \) is the limit of \( f_k(u) \) if the latter is convergent.

First, we quote the modified Toeplitz theorem in [51] as follows:

**Lemma 16.** Let \( \{c_{nk}\} \) be a double sequence of real, nonnegative numbers which satisfies the following conditions:

\[
\sum_{k=0}^{\infty} c_{nk} = 1 \quad \forall n; \quad \lim_{n \to \infty} c_{nk} = 0, \quad \forall k. \quad (2.62)
\]

If \( \{h_k\} \) is a convergent sequence of elements in a Banach space \( B \), then the sequence

\[
g_n = \sum_{k=0}^{\infty} c_{nk} h_k \quad (2.63)
\]

is well defined for any \( n \), and \( \{g_n\} \) is convergent to the limit of \( h_k \), i.e.,

\[
\lim_{n \to \infty} g_n = \lim_{k \to \infty} h_k. \quad (2.64)
\]

Then, set \( c_{nk} = (1 - e^{-\lambda t})^k \) and \( h_k = f_k(u) \), by Lemma 16, we obtain the following proposition:

**Proposition 6.** If \( \lim_{k \to \infty} f_k(u) \) exists, then

\[
\lim_{t \to \infty} N(u, t) = \lim_{k \to \infty} f_k(u). \]
Similarly, for the discrete system (1.3), we have

**Proposition 7.** If \( \lim_{k \to \infty} f_k(i) \) exists, then

\[
\lim_{t \to \infty} N(i, t) = \lim_{k \to \infty} f_k(i).
\]

### 2.4 Time relaxed method

A new scheme called the time relaxed method for solving the is given Boltzmann equation is given in [51]. The key point of this method is to start from the Wild sum and represent the solution as a power series in which the coefficients are determined recurrently by a bilinear operator. This scheme is a deterministic method which also preserves many physical properties of the system. In general, it can be applied to a much wider class of hyperbolic systems. Due to the similarity of the coagulation equation and the Boltzmann equation, we are inspired to derive a similar method to solve the coagulation equation by a time relaxed method.

Notice that \( N(i, t) \) can be represented as a convergent series in equation (2.57). Intuitively, we can start from equations (2.57) and (2.58) to approximate the solution by a series of finite terms. We use \( N_i(t) \) to represent the numerical solution for \( N(i, t) \). This method is given by

\[
N_i(t) = e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k f_k(i) + (1 - e^{-\lambda t})^{K_0+1} f_{K_0}(i). \tag{2.65}
\]

Let us discuss a special case of the time relaxed scheme for \( K_0 = 1 \). In this case, the scheme can be equivalently given by

\[
e^{\lambda t} N_i(t) - N_0(i) = \frac{e^{\lambda t} - 1}{\lambda} P_i(N_0, N_0), \quad \forall i \geq 1. \tag{2.66}
\]

This may be viewed as an explicit first-order modified Euler time marching scheme of the discrete coagulation equation. As we see later, this explicit marching scheme, and its high order variant (2.65), are all unconditionally stable, and they preserve a number of nice properties enjoyed by the discrete coagulation equation.

#### 2.4.1 Non-negativity, volume preservation, and stability

We can verify that this method preserves non-negativity and the total volume since \( f_k(i) \) is nonnegative and preserves the total volume by Lemma 12.
**Theorem 6.** The time relaxed scheme defined by (2.65) preserves the non-negativity and the total volume, i.e.,

a) \( N_i(t) \geq 0 \)

b) \( \sum_{i=1}^{\infty} iN_i(t) = \sum_{i=1}^{\infty} iN_0(i) \).

We can also establish a stability result for the expansion. To do so, let us define a norm for a series \( \{N_i\}_{i=1}^{\infty} \) by

\[
\|N\| = \sum_{i=1}^{\infty} i|N_i| < \infty .
\] (2.67)

Thus by Lemma 11 and Proposition 5, we obtain the following lemma

**Lemma 17.** For any sequences \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \),

a) if \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \) are both nonnegative, then

\[
\|P(N, M)\| = \tilde{\lambda}\|N\| \cdot \|M\|;
\]

b) in general, we have

\[
\|P(N, M)\| \leq \tilde{\lambda}\|N\| \cdot \|M\|.
\]

**Proof.** For a), note that for nonnegative \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \), \( P(N, M) \) is also nonnegative. Thus by (2.59),

\[
\|P(N, M)\| = \sum_{i=1}^{\infty} iP_i(N, M) = \tilde{\lambda} \left( \sum_{i=1}^{\infty} iN(i) \right) \left( \sum_{i=1}^{\infty} iM(i) \right) = \tilde{\lambda}\|N\| \cdot \|M\| .
\]

For b), we rewrite \( N = N^+ - N^- \) and \( M = M^+ - M^- \) with \( N_i^+ = \max\{N_i, 0\} \), \( N_i^- = \max\{-N_i, 0\} \), \( M_i^+ = \max\{M_i, 0\} \), and \( M_i^- = \max\{-M_i, 0\} \) for all \( i \). Notice first that

\[
\|N\| = \|N^+\| + \|N^-\| , \quad \|M\| = \|M^+\| + \|M^-\| .
\]

Thus,

\[
\|P(N, M)\| = \|P(N^+, M^+) - P(N^+, M^-) - P(N^-, M^+) + P(N^-, M^-)\|
\leq \|P(N^+, M^+)\| + \|P(N^+, M^-)\| + \|P(N^-, M^+)\| + \|P(N^-, M^-)\|
\leq \tilde{\lambda} (\|N^+\| + \|N^-\|) (\|M^+\| + \|M^-\|) ,
\]
\[ = \tilde{\lambda} ||N|| ||M|| , \]

where we have used \( a \), as \( N^+, N^-, M^+ \), and \( M^- \) are all non-negative. This yields \( b \).

\[ \square \]

Now, consider two different initial conditions \( N_0(i) \) and \( \tilde{N}_0(i) \) with the same total volume. In other words, suppose that \( ||N_0|| = ||\tilde{N}_0|| \). And let

\[ f_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_t(f_j, f_{k-j}) , \text{ and} \]

(2.68)

\[ \tilde{f}_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_t(\tilde{f}_j, \tilde{f}_{k-j}) , \]

(2.69)

with the initial term \( f_0(i) = N_0(i) \) and \( \tilde{f}_0(i) = \tilde{N}_0(i) \). Define respectively

\[ N_i(t) = e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k f_k(i) , \text{ and} \]

(2.70)

\[ \tilde{N}_i(t) = e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k \tilde{f}_k(i) . \]

(2.71)

Then we have the following stability theorem:

**Theorem 7.** For \( f_k, \tilde{f}_k, N, \) and \( \tilde{N} \) defined in the equations (2.68), (2.69), (2.70), and (2.71), we have

\[ ||f_k - \tilde{f}_k|| \leq (k + 1)||N_0 - \tilde{N}_0|| , \text{ and} \]

(2.72)

\[ ||N(t) - \tilde{N}(t)|| \leq e^{\lambda t}||N_0 - \tilde{N}_0|| . \]

(2.73)

**Proof.** We prove (2.72) by induction. For \( k = 1 \), we have

\[ f_1(i) = \frac{1}{\lambda} P_t(N_0, N_0) , \text{ and} \]

\[ \tilde{f}_1(i) = \frac{1}{\lambda} P_t(\tilde{N}_0, \tilde{N}_0) . \]

Thus, by Lemma 17, we get

\[ ||f_1 - \tilde{f}_1|| = \frac{1}{\lambda} ||P(N_0, N_0) - P(\tilde{N}_0, \tilde{N}_0)|| \]

\[ \leq \frac{1}{\lambda} \left( ||P(N_0, N_0 - \tilde{N}_0)|| + ||P(N_0 - \tilde{N}_0, \tilde{N}_0)|| \right) \]

\[ = \frac{\lambda}{\lambda} \left( ||N_0 - \tilde{N}_0|| \right) \left( ||N_0|| + ||\tilde{N}_0|| \right) \]

\[ = 2 ||N_0 - \tilde{N}_0|| . \]
Now we assume that the result holds for all \( f_j \) and \( \tilde{f}_j \), where \( j \leq k \). Then, for \( j = k + 1 \), we get

\[
\|f_{k+1} - \tilde{f}_{k+1}\| = \frac{1}{\lambda(k+1)} \sum_{j=0}^{k} \|P(f_j, f_{k-j}) - P(\tilde{f}_j, \tilde{f}_{k-j})\|
\]

\[
\leq \frac{1}{\lambda(k+1)} \sum_{j=0}^{k} \left( \|P(f_j, f_{k-j} - \tilde{f}_{k-j})\| + \|P(\tilde{f}_j - \tilde{f}_j, \tilde{f}_{k-j})\| \right)
\]

\[
\leq \frac{1}{\lambda(k+1)} \sum_{j=0}^{k} \tilde{\lambda} \left( \|f_j\| \cdot \|f_{k-j} - \tilde{f}_{k-j}\| + \|\tilde{f}_{k-j}\| \cdot \|f_j - \tilde{f}_j\| \right)
\]

\[
\leq \frac{2}{k+1} \sum_{j=0}^{k} \|f_j - \tilde{f}_j\|
\]

\[
\leq \frac{2}{k+1} \sum_{j=0}^{k} (j+1)\|N_0 - \tilde{N}_0\|
\]

\[
= (k+2)\|N_0 - \tilde{N}_0\|.
\]

Hence (2.72) is proved.

Now, to complete the theorem, we have

\[
\|N(t) - \tilde{N}(t)\| \leq e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k \|\tilde{f}_k - f_k\|
\]

\[
\leq e^{-\lambda t} \sum_{k=0}^{K_0} (k+1)(1 - e^{-\lambda t})^k \|N_0 - \tilde{N}_0\|
\]

\[
\leq e^{-\lambda t} e^{2\lambda t} \|N_0 - \tilde{N}_0\| = e^{\lambda t} \|N_0 - \tilde{N}_0\|
\]

which leads to (2.73).

Note that in (2.74), we have picked a slightly larger bound on the finite sum so that the constant \( e^{\lambda t} \) in (2.73) is uniform with respect to \( K_0 \). The above stability result indicates that for any given time, the amplification of the initial perturbation is under control; yet, asymptotically for large \( t \), the bound on the amplification factor may grow exponentially. The impact of this on the accuracy of long-time numerical integrations will be discussed later in the error estimation as well as the numerical simulations.
2.4.2 Error estimate

Let \( N(i, t) \) be the solution of the discrete PBE (1.3), i.e., let \( N(i, t) \) be as given in (2.57), and let \( \{N_i(t)\} \) be the approximation given by the time relaxed scheme (2.65). Define the error \( e(t) = \{e_i(t)\} \) with \( e_i(t) = N(i, t) - N_i(t) \) for all \( i \). Notice that

\[
\|f_k - f_{K_0}\| \leq 2V = 2 \sum_{i=0}^{\infty} iN_0(i)
\]

for any \( k \). By comparing (2.57) with (2.65), we easily obtain the following error estimate:

**Theorem 8.** The error of the time relaxed method (2.65) satisfies

\[
\|e(t)\| \leq 2V(1 - e^{-\lambda t})^{K_0+1}.
\]

We note, however, that this is a rare case where we can construct a high order approximation which at the same time is non-negativity and total volume preserving. This is clearly the outcome of the reformulation in terms of the bilinear operator \( P \) and the nonlinear recursive construction of \( \{f_k\} \). From the above error estimate given in Theorem 8, we see that for any given time \( t \) in a finite time interval \([0, T]\), the error is exponentially small with respect to \( K_0 \), and goes to 0 asymptotically as \( K_0 \) goes to infinity. However, for large enough \( t \), \( 1 - e^{-\lambda t} \) becomes very close to 1, which consequently leads to accuracy deterioration for long-time computation. We note that a similar observation is made for the stability result.

A possible remedy to improve the accuracy in the large time approximation is to utilize the asymptotic behavior of the solutions of the PBE; that is, to replace the series (2.65) by

\[
N_i(t) = e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k f_k(i) + (1 - e^{-\lambda t})^{K_0+1} f_*(i), \tag{2.75}
\]

where \( f_*(i) \) is the limit of \( N_i(t) \) as \( t \) goes to infinity, or the steady state solution. In fact, such an idea is used in [51] for the Boltzmann equation since the steady state solution is given by the Maxwellian. For PBEs in general, the steady state solutions are unknown a priori. In Section 2.1.3, we have given the asymptotic behavior in some special cases. For example, if \( \beta(1, 1) > 0 \), then \( N(1, t) \) converges to 0 as \( t \) approaches infinity. Then it is reasonable to speculate that a better alternative strategy is to take \( f_*(1) = 0 \) in (2.75). This is applicable if it is known that \( N(i, t) \) converges to 0 as \( t \) goes to infinity, especially under the assumptions given in Proposition 3. In this case, we may modify
the time relaxed scheme as follows,

\[ N_i(t) = e^{-\lambda t} \sum_{k=0}^{K_0} (1 - e^{-\lambda t})^k f_k(i). \]  

(2.76)

It is easy to verify that this modified scheme preserves the same asymptotic behavior if \( N(i, t) \) converges to 0 as \( t \) goes to infinity. Moreover, the error \( e_i(t) \) also satisfies

\[ \|e(t)\| \leq V(1 - e^{-\lambda t})^{K_0 + 1} \]

for all time \( t \), thus providing possibly good approximations for small \( t \), as well. While (2.76) is still non-negativity preserving, it no longer preserves the total volume due to the simple truncation. Comparisons of (2.65) and (2.76) are made later in the numerical tests.

### 2.4.3 Computational complexity

To get an idea of the computational efficiency, we give a crude estimation on the computational complexity. For illustration, let us consider the case of a special initial condition \( N_0(1) = N_0, N_0(i) = 0 \) for \( i > 1 \). Then functions \( f_k = f_k(i) \) defined by equation (2.58) have regions of compact support, that is, \( f_k(i) = 0 \) for \( i > k + 1 \), and the computational complexity involved in computing \( f_k(i) \) for \( i \leq k \) is roughly on the order of \( O(k^2 + 2ik) \) if \( P(f_j, f_{k-j}) \) is evaluated directly from a multiplication table. The numerical solution of the time relaxed method (2.65) also has compact support \( N_i = 0 \) for \( i > K_0 + 1 \), and the complexity of computing \( \{N_i\} \) for \( i \leq K_0 \) is on the order of \( O(K_0^3 + iK_0^2) \). These estimates are made independently from any special structures of the coagulation kernel.

For a kernel which has compact support, for example, suppose \( \beta(i, j) = 0 \) for \( i, j > m \), then the domains of compact support of \( N_i \) and \( f_k(i) = 0 \) are also limited for \([0, 2m]\]. Therefore, for large \( K_0 \) (in comparison with \( m \)), the computational cost can be reduced, since the computational complexity of computing \( f_k(i) \) for \( i \leq 2m \) is roughly \( O(mk^2 + ik) \). The cost for computing \( \{N_i\} \) for \( i \leq 2m \) is thus on the order of \( O(mK_0^2 + iK_0^2) \).

### 2.4.4 Numerical examples

In this section, we present some numerical tests to verify the various observations we stated in the previous section. The time relaxed method is applied to the discrete PBE models with some special kernels. One such example is the case where the coagulation kernel \( \beta(i, j) \) is a constant so that the analytical solution can be calculated explicitly. We
compare the numerical solutions with the exact solutions. The second example belongs to the class of problems where the coagulation kernel has a compact support. In addition, we also use the third example to compare various different schemes (2.65) and (2.76).

**Numerical example 1.** In this numerical experiment, we assume $\beta(i, j) = 1$ for all $i$ and $j$ and take the initial condition to be $N_0(1) = 1$ and $N_0(i) = 0$ for $i \geq 2$. We set $\lambda$ to be $\lambda = \beta_{sup} \sum_{i=1}^{\infty} N_0(i) = 1$. For comparison purposes, the analytic solution is given explicitly by

$$N(i, t) = \frac{4N_0(1)T^{i-1}}{(T + 2)^{i+1}} \quad \text{for} \quad T = N_0(1)t.$$  

(2.77)

In Figure 2.7, by comparing the numerical results with the analytic solutions for $N(i, t)$ for $i = 1$ and $t \in [0, 5]$, we plot the errors, measured by absolute values of the differences between the numerical and analytic solutions, against time. The error curves correspond to different values of $K_0$, namely, $K_0 = 100, 200$ and $400$. The plot shows that the numerical errors decade for large $K_0$, which is consistent with our error estimation.

![Figure 2.1.](image)

*Figure 2.1.* The numerical error of $N(1, t)$ for the time relaxed method (2.65) as a function of time with the same initial conditions $N_0(1) = 1$, constant kernel $\beta(i, j) = 1$. $K_0 = 100$ (green), $K_0 = 200$ (blue), and $K_0 = 300$ (red).

To get a more precise dependence of the error on the values of $K_0$, since the error estimation theorem implies the exponential dependence of the numerical errors on $K_0$, we take the natural log of the maximum errors on time interval $(0, 5]$ for each $K_0$ and plot them against $K_0$. We expect to get a line for the exponential dependence, which is verified in Figure 2.8. The results for $N(i, t)$ with $i > 1$ are similar.

We can also verify the conservation properties through the computation of the mo-
Figure 2.2. Errors in the numerical solution of $N(1,t)$ in log scale with respect to $K_0$ for $K_0 = 100, 200, 300$.

The moments $M_n(t)$ of the system defined by

$$M_n(t) = \sum_{i=1}^{\infty} i^n N(i, t).$$

(2.78)

For the constant kernel, the moments can also be solved analytically. For example, for the kernel $\beta(i,j) = \beta$ and initial condition $N_0$, the moments $M_0(t)$, $M_1(t)$ and $M_2(t)$ are given by:

$$
M_0(t) = 2N_0(1)/(\beta N_0(1)t + 2),
M_1(t) = N_0(1),
M_2(t) = N_0(1)(1 + \beta N_0(1)t)
$$

where $M_1(t)$ is the total system volume $V$ which has been shown to be preserved by the time relaxed method. The zeroth order moment, $M_0(t)$, is the total number of particles which has been shown to be non-increasing.

In our numerical test, we set $K_0 = 500$, $\beta = 1$ and compare the numerical results with the analytical solutions of the moments $M_0(t)$, $M_1(t)$, and $M_2(t)$. Figure 2.3 shows that the time relaxed scheme preserves the first moment $M_1(t)$. The numerical results of $M_0(t)$ and $M_2(t)$ also have good accuracy, but the errors start to increase dramatically for large time $t$.

The deterioration in accuracy for larger time displayed in both the solution values
Figure 2.3. The moments $M_0(t)$ (green), $M_1(t)$ (blue), and $M_2(t)$ (red). Left: the analytical solution (solid lines) and numerical solutions (diamond) for the time relaxed method ($K_0 = 500$); Right: numerical errors.

and the moments is expected from the error estimation. While it can be improved with larger values of $K_0$, such improvement comes at greater computational cost. We will further examine this issue in the next two examples.

**Numerical example 2.** As another example, we apply the method to a more practical case where the coagulation kernel is of the form

$$
\beta(i, j) = \begin{cases} 
  (i^{1/3} + j^{1/3})^{7/3} & i, j \leq m, \\
  0 & \max(i, j) > m.
\end{cases}
$$

where $m$ is a small integer. Such a kernel is motivated by the modeling research we are currently conducting with bioengineering collaborators on the cell aggregation and adhesion in nonuniform shear flow conditions [24]. Discussions on the particular use of fractional powers in the kernel, associated with a nonlinear shear flow, can also be found in [22]. In the numerical test here, we set $m = 20$ and choose the initial condition to be $N(1,0) = 0.01$ and $N(i,0) = 0$ for $i > 1$. Notice that the kernel has a compact support; the discussion on the computational cost given earlier indicates that a more efficient computation can be conducted in this case.

Since an explicit exact solution is not available in this case, we first compute a numerical solution to sufficient accuracy and use it as the benchmark exact solution. Then, to verify the error estimates, the errors of the numerical results are plotted in Figure 2.4a) corresponding to solutions obtained with $K_0 = 200$ (green), $K_0 = 400$
(blue), and $K_0 = 600$ (red) respectively. In Figure 2.4b), we take the natural log of the maximum errors in time and plot them against $K_0$. The solid line serves as a reference line. We easily see the exponential accuracy as predicted in the error analysis. The errors of $N(i,t)$ for $i > 1$ show similar behavior and such results are thus omitted.

![Figure 2.4](image)

**Figure 2.4.** Errors of numerical solution of $N(1,t)$ in time with $K_0 = 200, 400, 600$ and logarithm of errors in $K_0$.

**Numerical example 3.** In this numerical test, we again consider a kernel with compact support:

$$
\beta(i, j) = \begin{cases} 
  i + j, & i, j \leq 5, \\
  0, & \max(i, j) > 5 
\end{cases}
$$

and initial condition $N(1,0) = 0.1$, $N(i,0) = 0$ for $i > 1$.

We first use this example to compare the time relaxed schemes (2.65) and the modification (2.76) for large time $t$. By Proposition 3, we know that $N(i,t)$ converges to 0 for $i \leq 5$, but $N(6,t)$ converges to a positive constant since it is bounded and non-decreasing. Similar to the previous example, we first take a very accurately computed numerical solution as the exact solution of $N(5,t)$ and $N(6,t)$. Then, we use both schemes (2.65) and (2.76) with $K_0 = 1000$ to approximate $N(5,t)$ and $N(6,t)$, with their numerical errors plotted in Figure 2.5.

In Figure 2.5a), the scheme (2.65) gives a more accurate solution for small $t$, but fails to preserve the asymptotic behavior, while the scheme (2.76) preserves the asymptotic behavior albeit has a larger error for moderate $t$. However, if $N(i,t)$ does not converge to 0, for example $N(6,t)$, the modified scheme (2.76) leads to an even bigger error than
the scheme (2.65), see Figure 2.5b). This is not surprising as the sequence \( \{f_k(6)\} \) no longer approaches zero.

Finally, we present in Figure 2.6 errors computed using the first-order marching scheme (2.66) for \( N(5, t) \) and \( N(6, t) \) with \( \Delta t = 0.01 \). As time increases, the errors do not increase exponentially. In fact, they eventually start to decay for both solutions. Thus, this special case of the time relaxed scheme, when implemented as a time-marching scheme, may provide another alternative for accurate long-time integration. This observation naturally motivates us to study some hybrid methods which combine the high order time relaxation expansion with the time marching in some suitable ways, such a study will be reported elsewhere.

### 2.5 A hybrid time relaxed and marching scheme

#### 2.5.1 Volume conservation, computational cost, and stability

To provide a better solution for large values of time, we now construct a hybrid time relaxed marching scheme. We will take a small time step \( \Delta t \) and perform iteration at each step. Denote the numerical solution at the \( n \)th step, \( t_n \), by \( N^n_i \). We re-calculate the coefficients of the series \( \{f_k(i)\}_{k=1}^K \), denoted by \( \{f^n_k(i)\}_{k=1}^K \) with \( f^n_0(i) = N^n_i \), to construct
a) error of $N(5,t)$  

b) error of $N(6,t)$

Figure 2.6. The errors in the numerical solution of $N(i,t)$ for $i = 5$ and 6 with respect to first time marching scheme (2.66) with $\Delta t = 0.01$.

the solution at $t_{n+1} = t_n + \Delta t$ of the $K$th order time relaxed scheme:

$$N_{i}^{n+1} = e^{-\lambda \Delta t} \sum_{k=0}^{K} (1 - e^{-\lambda \Delta t})^k f_{k}^{n}(i) + (1 - e^{-\lambda \Delta t})^{K+1} f_{K}^{n}(i)$$

where $f_{0}^{n}(i) = N_{i}^{n}$ and $\{f_{k}^{n}(i)\}$ is defined recursively for $k$ as in the equation (2.58), by the following equation

$$f_{k+1}^{n}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_{i}(f_{j}^{n}, f_{k-j}^{n}).$$

Conservation properties  This time relaxed marching scheme also preserves the non-negativity and total system volume.

Theorem 9. The time relaxed marching scheme defined by (2.79) has the following properties:

a) $N_{i}^{n} \geq 0$ ,

b) $\sum_{i=1}^{\infty} iN_{i}^{n} = \sum_{i=1}^{\infty} iN_{0}(i)$ .

Proof.

a) This is trivial since $P_{i}$ is a nonnegative bilinear operator.
b) It is easy to verify this result. By Lemma 12, the following equation holds for any \( k \):

\[
\sum_{i=1}^{\infty} i f_k^n(i) = \sum_{i=1}^{\infty} i N_i^n.
\]  

(2.81)

\[\square\]

**Computational complexity**  
The computational cost is expensive for this time relaxed marching method (2.79). Note that the initial condition has compact support in \( i \) since \( N_0(i) = 0 \) for \( i > 1 \). At we march in time, the region of compact support of \( \{N_i^n\} \) will grow exponentially as \( n \) increases. For example, for the first order time relaxation method, \( N_i^n = 0 \) for \( i > 2^n \). More generally, the numerical solution \( N_i^n \) of the \( K \)th order time relaxed marching method also has a compact support, i.e.

\[ N_i^n = 0, \quad \text{for} \quad i > (K+1)^n, \]

and the coefficients \( f_k^n(i) \) defined by equation (2.80) also have compact support,

\[ f_k^n(i) = 0 \quad \text{for} \quad i > (K+1)^n(k+1). \]

Moreover, the computational complexity is \( O(k^2(K+1)^n + 2ik) \). Hence the computational cost of \( N_i^n \) of the time relaxed marching method (2.79) is \( O(\frac{1}{3}(K+1)^{n-1}K^3 + iK^2) \). Therefore, a large number of iterations also lead to prohibitively large computational cost. We note that there is a special case where the computational cost may be significantly reduced. That special case is the coagulation kernel having compact support. The computational costs of both these two methods (2.65) and (2.79) will be reduced dramatically.

In fact, given initial condition \( N_0(1) = N_0, N_0(i) = 0 \) for \( i > 1 \), and a kernel \( \beta(i, j) \) with compact support such that

\[
\beta(i, j) = \left\{ \begin{array}{ll}
> 0 & i, j \leq m, \\
0 & \max(i, j) > m,
\end{array} \right.
\]

both \( \{f_k(i)\} \) in equation (2.58) and \( \{f_k^n(i)\} \) in equation (2.80) have compact support, i.e.,

\[ f_k(i) = f_k^n(i) = 0 \quad \text{for} \quad i > 2m. \]

In addition, the numerical solution \( N_i^n \) of the two methods given by (2.66) and (2.65)
also has compact support, i.e.,

\[ N^n_i = 0 \quad \text{for} \quad i > 2m. \]

The computational complexities for \( f_k(i) \) and \( N^n_i \) (with a particular \( n \)) of the scheme (2.65) are \( O(2ik + 2mk) \) and \( O(iK^2 + mK^2) \) respectively. Naturally, this implies that for all \( N^\ell_i \) with \( \ell \leq n \), the complexity is \( O(iK^2 + mK^2n) \).

For the kernel with compact support, by comparing the time relaxed method (2.65) and (2.66) with the same computational complexity, the error estimation Theorem 12 reveals that the scheme (2.66) is much better than (2.65) since the former gives a better error estimation for large time \( t \).

**Unconditional stability** To analyze the scheme (2.79), we now study its unconditional stability property. Let us consider the two different initial conditions \( N_0^i(i) \) and \( \tilde{N}_0^i(i) \) with the same total volume, i.e., \( \|N_0\| = \|\tilde{N}_0\| \). Let

\[ f_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_i(f_j, f_{k-j}), \quad \text{and} \]

\[ \tilde{f}_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_i(\tilde{f}_j, \tilde{f}_{k-j}) \]

with the initial terms \( f_0(i) = N_0^i(i) \) and \( \tilde{f}_0(i) = \tilde{N}_0^i(i) \).

It has been shown in [52] that we have the following result:

**Theorem 10.** For \( f_k \) and \( \tilde{f}_k \) defined in equation (2.82) and (2.83), we have

\[ \|f_k - \tilde{f}_k\| \leq (k + 1)\|N_0 - \tilde{N}_0\| . \] (2.84)

### 2.5.2 Error estimates

We now consider the error due to the truncation of the series. Define such an error at \( n \)th step by

\[ T^n_i = N(i, t_{n+1}) - e^{-\lambda \Delta t} \sum_{k=0}^{K} (1 - e^{-\lambda \Delta t})^k \tilde{f}_k(i) - (1 - e^{-\lambda \Delta t})^{K+1} \tilde{f}_{K+1}(i) \] (2.85)
where the coefficient \( \tilde{f}_k^n(i) \) is determined by

\[
\tilde{f}_{k+1}^n(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} P_i(\tilde{f}_j^n; \tilde{f}_{k-j}^n)
\]  

(2.86)

and the first term is given by

\[
\tilde{f}_0^n(i) = N(i, t_n).
\]  

(2.87)

Since

\[
N(i, t_{n+1}) = e^{-\lambda \Delta t} \sum_{k=0}^{\infty} (1 - e^{-\lambda \Delta t})^k \tilde{f}_k^n(i),
\]  

(2.88)

the truncation error satisfies

\[
|T_i^n| = \left| e^{-\lambda \Delta t} \sum_{k=K+1}^{\infty} (1 - e^{-\lambda \Delta t})^k \left( \tilde{f}_k^n(i) - \tilde{f}_K^n(i) \right) \right| 
\]  

(2.89)

and its norm can be estimated as

\[
||T^n|| = \sum_{i=1}^{\infty} i |T_i^n| 
\]

\[
\leq e^{-\lambda \Delta t} \sum_{k=K+1}^{\infty} (1 - e^{-\lambda \Delta t})^k \left| \tilde{f}_k^n - \tilde{f}_K^n \right| 
\]

(2.90)

\[
\leq 2V \left( 1 - e^{-\lambda \Delta t} \right)^{K+1}.
\]

Thus we obtain the following theorem about the truncation error.

**Theorem 11.** The error of truncation at the \( n \)-th step of the \( K \)-th order time relaxed scheme satisfies

\[
||T^n|| \leq 2V \left( 1 - e^{-\lambda \Delta t} \right)^{K+1}.
\]

Using this theorem, we can give the error estimation of the relaxed scheme. First we have

\[
e_{i}^{n+1} = N(i, t_{n+1}) - N_i^{n+1}
\]

\[
= e^{-\lambda \Delta t} \sum_{k=0}^{K} (1 - e^{-\lambda \Delta t})^k \left( \tilde{f}_k^n(i) - f_k^n(i) \right)
\]
\[ + (1 - e^{-\lambda \Delta t})^{K+1} \left( \tilde{f}_K^n(i) - f_K^n(i) \right) + T_i^n. \] (2.91)

Thus, by Theorem 10, we have

\[
\|e^{n+1}\| \leq e^{-\lambda \Delta t} \sum_{k=0}^{K} (1 - e^{-\lambda \Delta t})^k \|\tilde{f}_k^n - f_k^n\| + (1 - e^{-\lambda \Delta t})^{K+1} \|\tilde{f}_K^n - f_K^n\| + \|T^n\|
\]

\[
\leq e^{-\lambda \Delta t} \sum_{k=0}^{K} (1 - e^{-\lambda \Delta t})^k (k+1) \|e^n\| + (1 - e^{-\lambda \Delta t})^{K+1} (K+1) \|e^n\| + \|T^n\|
\]

\[
= e^{\lambda \Delta t} \|e^n\| + \|T^n\|
\]

(2.92)

Using this recursively, we obtain the following error estimate:

**Theorem 12.** The error of the \(K^\text{th}\) order time relaxation scheme at the \(n^\text{th}\) step in the time interval \([0, T]\) is given by

\[
\|e^n\| \leq \frac{e^{\lambda T} - 1}{e^{\lambda \Delta t} - 1} \|T^n\| = O(\Delta t)^K.
\] (2.93)

### 2.5.3 The method with variable orders and step sizes

By analyzing the two time relaxed methods given in (2.65) and (2.79), we observe that the computational cost of scheme (2.65) is low, but it does not give a good error estimate for large time. For scheme (2.79), it provides a convergent error estimate for any time \(t\); however, its computational cost is high for small time steps (unless we have a compact kernel).

A possible remedy to overcome these problems for general kernels is to introduce a variable order and adaptive time step. While it is sensible to implement such a strategy based on good a posteriori error estimators, we hereby consider a very heuristic variant that tends to provide an accurate approximation for large time, while maintaining a relatively lower computational complexity. Consider a finite time interval \([0, T]\) on which we are interested in computing the solution. The basic idea is to dynamically choose time steps and possible different orders at different steps. That is, let the whole interval be divided into a few subintervals, \([t_n, t_{n+1}]\), choose a sequence of \(K_n\), and apply the time relaxed scheme (2.65) on the interval, \([t_n, t_{n+1}]\), with starting time \(t_n\) and initial condition \(N^n_i\), the numerical solution obtained in the previous step. So the algorithm is
given as follows: for a suitably defined subdivision of \([0, T] = \bigcup [t_n, t_{n+1}]\) with step sizes \(\Delta t_n = t_{n+1} - t_n\) and a sequence of positive integers \(\{K_n\}\), we have

\[
N_i^{n+1} = e^{-\lambda \Delta t_n} \sum_{k=0}^{K_n} (1 - e^{-\lambda \Delta t_n})^k f_k^n(i) + (1 - e^{-\lambda \Delta t_n}) K_n+1 f_{K_n}^n(i) ,
\]

(2.94)

where \(f_0^n(i) = N_i^n\), and \(\{f_k^n(i)\}\) is defined recursively for \(k\) as in the equation (2.80).

A good balance of \(\{K_n\}\) and \(\{\Delta t_n = t_{n+1} - t_n\}\) can be made to achieve both accuracy and computational efficiency. For example, with a constant kernel, one may try to choose a sequence of decreasing \(\Delta t_n\) with a decreasing \(K_n\). An example will be provided in the numerical tests to illustrate the effectiveness of this heuristic approach.

### 2.5.4 Numerical experiment

In this section, we will perform some numerical tests to verify the observations we stated in the previous section.

We now apply the time relaxed method to the coagulation equation with some special kernels. For example, if the coagulation kernel \(\beta(u, v)\) is a constant, the analytical solution can be calculated. We compare the numerical solutions with the exact solutions.

**Numerical example 1.** In our first numerical experiment, we assume \(\beta(i, j) = 1\) for all \(i\) and \(j\) and take the initial condition to be \(N_0(1) = 1\) and \(N_0(i) = 0\) for \(i \geq 2\). We set \(\lambda = \beta_{\text{sup}} \sum_{i=1}^{\infty} N_0(i) = 1\). First, we apply the time relaxed scheme (2.65) for \(K = 100\). Then we do the numerical test by applying the first order scheme (2.79) with time step \(\Delta t = 0.5\). The analytical solution is

\[
N(i, t) = \frac{4N_0(1)T^{i-1}}{(T + 2)^{i+1}} \quad \text{for} \quad T = N_0(1)t .
\]

(2.95)

In Figure 2.7, we represent the numerical errors by comparing the numerical results with the analytical solutions for \(N(i, t)\) for \(i = 1\) and \(t \in [0, 5]\). It is evident that the error is much larger when \(t > 3\) for scheme (2.65). The error is big for small \(t\) for the first-order time relaxed method (2.79), but it gives us an accurate numerical solution for large time \(t\). Therefore, neither of these two methods is very efficient. It motivates us to use the modified time relaxed method to approach the problem.

In the numerical test of the modified time relaxed scheme, we pick three subintervals: \([0, 3], (3, 4], (4, 5]\) and the sequence \(K_0 = 50, K_1 = 5, K_2 = 4\). The numerical error is plotted in Figure 2.8.
Figure 2.7. The numerical error of \( N(1, t) \) for time relaxed method (2.65) (red), and the first-order time relaxed method (2.79) (blue) with the same initial conditions \( N_0 = 1 \) for the constant kernel \( \beta(i, j) = 1 \).

Figure 2.8. The error in \( N(1, t) \) for the first-order TR method (2.79) with \( \Delta t = 0.5 \) (blue), TR scheme (2.65) with \( K = 100 \) (red), and modified TR method (green).

It is evident that the modified time relaxed method gives a much more accurate numerical solution than the two other methods given in equations (2.65) and (2.79).

The moment \( M_n(t) \) of the dynamical system is defined by

\[
M_n(t) = \sum_{i=1}^{\infty} i^n N(i, t). \tag{2.96}
\]

For the constant kernel, the moments can be solved analytically. For example, for
the constant kernel $\beta(i,j) = \beta$ and initial condition $N_0(1)$, the moments $M_0(t)$, $M_1(t)$ and $M_2(t)$ are given by

\[
\begin{align*}
M_0(t) &= \frac{2N_0(1)}{\beta N_0(1)t} + 2, \\
M_1(t) &= N_0(1), \\
M_2(t) &= N_0(1)(1 + \beta N_0(1)t).
\end{align*}
\]

where $M_1(t)$ is the total system volume, $V$, which has been shown to be preserved by the time relaxed methods and modified Euler method.

In the numerical tests of the moments, we only take into account $M_0(t)$ and $M_2(t)$ since we have shown that $M_1(t)$ was preserved by the schemes. We use the previous numerical results of the time relaxed (marching) method and modified time relaxed methods as in Figure 2.8 and plot the numerical errors of the moments $M_0(t)$ and $M_2(t)$ in Figure 2.9. The figure shows that the modified time relaxed method are much better than two other methods.

**Figure 2.9.** The numerical error in the moments $M_0(t)$ and $M_2(t)$ for the first order TR marching method (2.79) with $\Delta t = 0.5$ (blue), TR method (2.65) with $K = 100$ (red), and modified TR method (green).
Numerical example 2. As another example, we apply the method to a more realistic case where the coagulation kernel is of the form

\[ \beta(i, j) = \begin{cases} (i^{1/3} + j^{1/3})^{7/3} & i, j \leq m, \\ 0 & \max(i, j) > m. \end{cases} \]  

(2.100)

where \( m \) is an integer. Such a kernel is motivated from a form used in some modeling research we are conducting with bioengineering collaborators on the cell aggregation and adhesion in nonuniform shear flow conditions [24] in which case \( m = 5 \). In our numerical test, we set \( m = 20 \) and the initial condition \( N(1, 0) = 1 \) and \( N(i, 0) = 0 \) for \( i > 1 \).

We choose the time relaxed marching method (2.79) to do our numerical experiments. Notice that this equation has no analytical solution; thus, we use a numerical solution with a sufficiently small error as the substitution of the exact solution.

In Figure 2.10, we present the numerical error for \( N(1, t) \) in time solved with different step sizes and orders of the time relaxed method. It is clear that the error is reduced if the higher order time relaxed method is applied or the time step \( \Delta t \) is reduced.

![Figure 2.10](image.png)

**Figure 2.10.** The numerical error in \( N(1, t) \) for the first-order (green), the second-order (blue) and the third-order (red) time relaxed method (2.79) with different time steps \( \Delta t = 0.05, 0.01 \). The initial conditions \( N_0 = 1 \), and the kernel \( \beta(i, j) \) is given in (2.100).

To verify the error estimates provided earlier, in Figure 2.11, the errors of the numerical results, of the first-order and the second-order time relaxed methods, measured in the B norm on the time interval \([0, 10]\) are plotted against the values of the step size \( \Delta t \) on a log-log scale. The diamonds are the data points corresponding to \( \Delta t = 0.05, \Delta t = 0.01, \) and \( \Delta t = 0.002 \) respectively. The solid line is a straight line which serves to
provide a reference line. We easily see the first-order accuracy as predicted in the error analysis.

![Graph showing error analysis](image)

(a) The first order TR method  
(b) The second order TR method

**Figure 2.11.** The errors of numerical solution of $N(1, t)$ with respect to $\Delta t = 0.05$, $\Delta t = 0.01$ and $\Delta t = 0.002$ on a log–log scale.

### 2.6 Stabilized Euler method

Let us discuss a special case of the time relaxed marching scheme for $K = 0$. In this case, the scheme can be given by

$$N_{i}^{n+1} = e^{-\lambda \Delta t}N_{i}^{n} + \frac{1 - e^{-\lambda \Delta t}}{\lambda}P_{i}(N^{n}, N^{n}), \quad \forall i \geq 1,$$

(2.101)

which may be viewed as an explicit, first-order marching scheme of the discrete PBE.

By using the approximation $e^{\lambda \Delta t} = 1 + \lambda \Delta t$, we get the following variation of the Euler scheme which may be called a stabilized Euler scheme:

$$(1 + \lambda \Delta t)N_{i}^{n+1} = N_{i}^{n} + \Delta tP_{i}(N^{n}, N^{n}), \quad \forall i \geq 1.$$

That is, we may compute $N_{i}^{n+1}$ explicitly by:

$$N_{i}^{n+1} = \frac{N_{i}^{n} + \Delta tP_{i}(N^{n}, N^{n})}{1 + \lambda \Delta t}.$$

(2.102)
2.6.1 Basic properties

The stabilized Euler scheme satisfies many of the properties of the time relaxed marching schemes, in particular, we have

**Lemma 18.** The solution obtained by the stabilized Euler method \((2.102)\) satisfies

a) \(N^n_i \geq 0;\)

b) the total volume is preserved, that is, \(\sum_{i=1}^{\infty} i N^n_i = \sum_{i=1}^{\infty} i N_0(i);\)

c) the low order moments are non-increasing, that is, \(\sum_{i=1}^{\infty} i^K N^{n+1}_i \leq \sum_{i=1}^{\infty} i^K N^n_i\)

for \(0 \leq K \leq 1,\)

including the total concentration \((K = 0);\)

d) the high order moments are non-increasing, that is, \(\sum_{i=1}^{\infty} i^K N^{n+1}_i \geq \sum_{i=1}^{\infty} i^K N^n_i\)

for \(K \geq 1,\)

including the total average volume \((K = 2);\)

**Proof.** It is easy to verify a) since \(P\) is a nonnegative operator.

For b), by Lemma 5, the volume conservation follows by induction on \(n.\)

For c) and d), since

\[
(1 + \lambda \Delta t) \sum_{i=1}^{\infty} i^k N^{n+1}_i = \sum_{i=1}^{\infty} i^K N^n_i + \Delta t \sum_{i=1}^{\infty} i^K P_i(N^n, N^n)
\]

we may take \(\{\phi(i) = i^K\}\) in the equation \((2.60)\) and apply the results of a) and b) to get c) and d) respectively. \(\square\)

Based on the above result, we see that the stabilized Euler method \((2.102)\) is unconditionally stable in the sense that the solution remains nonnegative and uniformly bounded for any \(\Delta t\) and for any time \(t_n > 0.\)

The stabilized Euler method \((2.102)\) can also be written as

\[
N^{n+1}_i = N^n_i + \frac{\Delta t}{1 + \lambda \Delta t} Q_i(N^n, N^n)
\]

where \(Q_i\) is the aggregation operator defined by

\[
Q_i(N, M) = \frac{1}{2} \sum_{j=1}^{i-1} \beta(i - j, j) N_j M_{i-j} - \sum_{j=1}^{\infty} \beta(i, j) N_j M_i .
\]  

\((2.103)\)
Note that with the volume conservation of the solution, \( N^n \), or for any \( N = \{N_i\} \) with \( \sum_{j=1}^{\infty} jN_j = V \) and \( \lambda = \tilde{\lambda}V \), also for any \( M = \{M_j\} \) we have

\[
Q_i(N, M) = -\lambda M_i + P_i(N, M) .
\]

The stabilized Euler method also shares other properties previously shown for (1.1) such as the non-increasing property of \( N(1, t) \) (see [52]):

**Lemma 19.** The numerical solution \( N_1^n \) is non-increasing with respect to \( n \).

**Proof.** Since

\[
Q_1(N^n, N^n) = -\sum_{j=1}^{\infty} \beta(1, j)N_j^n N_1^n \leq 0 ,
\]

by (2.6.1) and (2.103), we have

\[
N_1^{n+1} = N_1^n + \frac{\Delta t}{1 + \lambda \Delta t} Q_1(N^n, N^n) \leq N_1^n
\]

for all \( n \). \( \Box \)

### 2.6.2 Error estimate

To obtain an error estimate of the stabilized Euler method, we now give some estimates on the time derivatives of \( N(i, t) \). Again, we have that \( V = \sum_{i=1}^{\infty} iN(i, 0) \), then

**Lemma 20.** For any \( t > 0 \), there exist some generic constants \( C = C(V, \beta_{sup}) \) such that

\[
\left\| \frac{\partial N}{\partial t} \right\| \leq C , \quad \text{and} \quad \left\| \frac{\partial^2 N}{\partial^2 t} \right\| \leq C .
\]

**Proof.** By equation (2.46) and the Lemma 17, we have

\[
\left\| \frac{\partial N}{\partial t} \right\| \leq \|P(N, N)\| + \lambda \|N\| \leq \tilde{\lambda} \|N\|^2 + \lambda \|N\| \leq C .
\]

Differentiating equation (2.46), we have

\[
\frac{\partial^2 N(i, t)}{\partial^2 t} = P_i(N_t, N) + P_t(N, N_t) - \lambda N_t(i, t) .
\]

Applying the same technique as above, we get the estimates on \( \frac{\partial^2 N(i, t)}{\partial^2 t} \). \( \Box \)
Now we prove an error estimate. To this end, let \( e^n_i = N(i, t_n) - N^n_i \). Then following standard procedure, we get
\[
e^{n+1}_i = e^n_i + (Q_i(N(\cdot, t_n), N(\cdot, t_n)) - Q_i(N^n, N^n)) \frac{\Delta t}{1 + \Delta t} + \lambda \frac{\Delta t^2}{1 + \Delta t} Q_i(N(\cdot, t_n), N(\cdot, t_n)) + \int_{t_n}^{t_n+\Delta t} \int_{t_n}^{s} \frac{\partial^2 N(i, \tau)}{\partial \tau^2} d\tau ds.
\]
This implies
\[
\|e^{n+1}_i\| - \|e^n_i\| \leq \Delta t \|Q(N(\cdot, t_n), N(\cdot, t_n)) - Q(N^n, N^n)\| + \int_{t_n}^{t_n+\Delta t} \int_{t_n}^{s} \left\| \frac{\partial^2 N(i, \tau)}{\partial \tau^2} \right\| d\tau ds + \lambda \Delta t^2 \left\| Q(N(\cdot, t_n), N(\cdot, t_n)) \right\|
\]
We need to estimate the terms on the right-hand side of the above inequality. Notice that if both \( \{N_i\} \) and \( \{\tilde{N}_i\} \) are non-negative with \( \sum_{i=1}^{\infty} iN_i = \sum_{i=1}^{\infty} i\tilde{N}_i = V \), then
\[
\|Q(N, N) - Q(\tilde{N}, \tilde{N})\| = \|P(N, N) - P(\tilde{N}, \tilde{N})\| \leq \tilde{\lambda} \left( \|N\| + \|\tilde{N}\| \right) \|N - \tilde{N}\|
\]
Thus, for \( \{N(i, t_n)\} \) and \( \{N^n_i\} \), since \( \|N(\cdot, t_n)\| = \sum_{i=1}^{\infty} iN(i, t_n) = V \) and \( \|N^n\| = \sum_{i=1}^{\infty} iN^n_i = V \), we have,
\[
\|Q(N(\cdot, t_n), N(\cdot, t_n)) - Q(N^n, N^n)\| = \|P(N(\cdot, t_n), N(\cdot, t_n)) - P(N^n, N^n)\| \\
\leq 2\tilde{\lambda}V \|N(\cdot, t_n) - N^n\| \\
= 2\tilde{\lambda}V\|e^n\|.
\]
In addition, it is easy verify that
\[
\|Q(N(\cdot, t_n), N(\cdot, t_n))\| \leq \lambda V + \|P(N(\cdot, t_n), N(\cdot, t_n))\| \leq 2\lambda V.
\]
By earlier estimates on the derivatives of the solution, we get
\[
\int_{t_n}^{t_n+\Delta t} \int_{t_n}^{s} \left\| \frac{\partial^2 N(i, \tau)}{\partial \tau^2} \right\| d\tau ds \leq c\Delta t^2
\]
So, combining the above estimates, we have
\[
\|e^{n+1}\| \leq (1 + c_1 \Delta t)\|e^n\| + c_2 \Delta t^2,
\]
for some constants \( c_1 \) and \( c_2 \) depending only on \( V \) and \( \beta_{sup} \). Thus, using the discrete
Gronwall inequality and the initial condition $e^0 = \{0\}$, we get the error estimates:

**Theorem 13.** The error of the stabilized Euler method satisfies: for any $t_n \in (0, T)$,

$$\|e^n\| \leq c\Delta t$$

for some constant $c = c(T, V, \beta_{sup}) > 0$.

### 2.6.3 Numerical experiment

**Numerical example: comparison with the forward Euler method.** Theoretically, the time relaxed method has the advantage of preserving non-negativity and unconditional stability for any time step size. Naturally, in practice, accuracy considerations may also limit the choice of time step size. Let us consider the equation with constant kernel and compact kernel. We take the constant kernel

$$\beta(i, j) = 1$$

and the compact kernel as follows:

$$\beta(i, j) = \begin{cases} 
i + j & i, j \leq 5, \\
0 & \max(i, j) > 5. \end{cases}$$

We perform a two numerical tests for each of these two kernels with different numerical schemes, such as the forward Euler method, the stabilized Euler method, and time relaxed marching methods. The numerical results show that, for constant kernel, the error of the first order time relaxed marching method is much smaller than the forward Euler method, and the stabilized Euler method is more accurate than forward Euler method for small time, but not for large time. We plot the numerical errors in Figure 2.12.

Comparing with the forward Euler method, the high order time relaxed marching methods give much more accurate solutions. For the compact kernel as above, we plot the numerical errors in Figure 2.13.

Note that the Euler method does not preserve the nonnegativity and total volume for large time step $\Delta t$, even though it is more accurate than the stabilized Euler method for large time as was shown above for the constant kernel. Figure 2.14 shows that if we take a large time step size, for example, $\Delta t = 1.5$, the forward Euler method gives a negative solution for the constant kernel.
2.7 Coagulation-fragmentation equation

The coagulation-fragmentation equation is given by

\[
\begin{align*}
\frac{\partial N(u, t)}{\partial t} &= \frac{1}{2} \int_0^u \beta(u - v, v)N(u - v, t)N(v, t)dv - \int_0^\infty \beta(u, v)N(u, t)N(v, t)dv \\
&+ \int_0^\infty \gamma(u, v)N(u, v + t)dv - \frac{1}{2} \int_0^\infty \gamma(u - v, v)N(u, t)dv
\end{align*}
\]

(2.104)
with initial condition \( N(u, 0) = N_0(u) \).

The concentration \( N(u, t) \) describes the distribution of the particles of size \( u \) when time is progressing. Here \( \beta(u, v) \) is the coagulation rate which denotes the coagulation probability of particles of size \( u \) and \( v \), and \( \gamma(u, v) \) is the fragmentation rate of particle with size \( u + v \).

By equation (2.104), the concentration \( N(u, t) \) which describes the evolution of particle of size \( u \), will increase

- by coagulation between particles of size \( u - v \) and \( v \) for \( v < u \),
- by fragmentation of the particle of size \( u + v \) into \( u \) and \( v \),

and will decrease

- by coagulating with any other particle of size \( v \),
- by fragmentation into two particles of sizes \( u - v \) and \( v \).

Overview  The pure coagulation equation was first introduced by Smoluchowski in [23]. The combination of coagulation and fragmentation was first proposed by Melzak [48]. Both of the equations are from physical intuition and have a wide range of applications in physics, chemistry, and biology, such as the droplet coalition, blood cell aggregation and etc.
Global existence and uniqueness of the solution for the coagulation fragmentation equation was proved by Aizenman and Bak [66] for the constant kernels $\beta(u, v)$ and $\gamma(u, v)$. This result was extended for some bounded kernels by Melzak [48]. In [67], Melzak also considered a more general case for some proper kernels involving time, in which $\beta(u, v)$ and $\gamma(u, v)$ were replaced by $\beta(u, v, t)$ and $\gamma(u, v, t)$ respectively. He showed that for this type of kernel, the equation had a continuous and nonnegative solution.

Stewart and Dubovski ([54],[68],[28],[29]) proved global existence and uniqueness for the equation with unbounded coagulation kernel $\beta(u, v)$ with possible linear growth at infinity and a fragmentation kernel $\gamma(u, v)$ from a very large class of unbounded functions.

The equilibrium is another important issue of the coagulation fragmentation equation. Stewart and P.B. Dubovski [69] showed that the equation with constant kernels had a unique equilibrium which was given explicitly in terms of the initial data and the kernels via a Lyapunov functional. In [54], they also proved that for a linear coagulation kernel and a constant fragmentation kernel, the equilibrium existed and was unique. Gueron and Levin [70] showed that for the kernels which satisfied

$$\beta(u, v) = b(u)b(v), \quad \gamma(u, v) = b(u + v),$$

the equilibrium solution, $N(u)$, had an explicit form

$$N(u) = \frac{e^{-\lambda u}}{b(u)}$$

where the constant $\lambda$ was set such that $N(u, t)$ satisfied

$$\int_0^\infty uN(u)du = \int_0^\infty uN_0(u)du.$$

**Series expansion** The reformulation of the coagulation equation (2.46) can also be applied to the coagulation-fragmentation equation if we define a proper nonnegative bilinear operator $P$ analogously. Hence, we can represent the solution of the equation as a series similar to (2.57) and the time relaxed method can be set-up based on this series expansion. First, let us consider the discrete coagulation-fragmentation:
\[ \frac{\partial N(i, t)}{\partial t} = \frac{1}{2} \sum_{j=1}^{i-1} \beta(j, i-j) N(j, t) N(i-j, t) - \sum_{j=1}^{\infty} \beta(i, j) N(i, t) N(j, t) \]
\[ + \sum_{j=1}^{\infty} \gamma(i, j) N(i+j, t) - \frac{1}{2} \sum_{j=1}^{i-1} \gamma(i-j, j) N(i, t). \] 

(2.105)

We assume the coagulation kernel \( \beta(i, j) \) and fragmentation kernel \( \gamma(i, j) \) satisfy the following conditions:

B1. \( \tilde{\lambda}_1 = \sup_{i,j} \beta(i, j) < \infty \),

B2. \( \tilde{\lambda}_2 = \sup_i \left( \frac{1}{2} \sum_{j=1}^{i-1} \gamma(i-j, j) \right) < \infty \).

Thus, for any two nonnegative sequences \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \), we can define a non-negative bilinear vector operator \( R = \{R_i\}_{i=1}^{\infty} \) by:

\[ R_i(N, M) = \frac{1}{2} \sum_{j=1}^{i-1} \beta(i-j, j) N_{i-j} M_j + \sum_{j=1}^{\infty} (\tilde{\lambda}_1 j - \beta(i, j)) N_i M_j \]
\[ + c \sum_{j=1}^{\infty} \sum_{k=1}^{\infty} k \gamma(i, j) N_{i+j} M_k + c \sum_{k=1}^{\infty} \left( \tilde{\lambda}_2 k - \frac{1}{2} \sum_{j=1}^{i-1} k \gamma(i-j, j) \right) N_i M_k. \]

(2.106)

where \( c > 0 \) is any given constant.

Analogously, some properties of \( R \) can be verified:

**Proposition 8.** For any sequences \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \), we have

\[ \sum_{i=1}^{\infty} i R_i(N, M) = (\tilde{\lambda}_1 + c \tilde{\lambda}_2) \left( \sum_{i=1}^{\infty} i N_i \right) \left( \sum_{i=1}^{\infty} i M_i \right). \]

Similar to Lemma 17, we have the following lemma:

**Lemma 21.** For any sequences \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \), we have

\[ \|R(N, M)\| \leq (\tilde{\lambda}_1 + c \tilde{\lambda}_2) \|N\| \cdot \|M\|. \]

The equation holds if \( \{N_i\}_{i=1}^{\infty} \) and \( \{M_i\}_{i=1}^{\infty} \) are nonnegative.
Since the total volume is also preserved for the coagulation-fragmentation equation, i.e.,

\[ \sum_{i=1}^{\infty} iN(i, t) = V, \]

where \( V \) is the total volume of the dynamical system, we can reformulate the equation as follows:

\[
\begin{align*}
\frac{\partial N(i, t)}{\partial t} &= R_i(N, N) - \lambda N(i, t), \\
n(i, 0) &= N_0(i).
\end{align*}
\] (2.107)

where \( \lambda = \tilde{\lambda}_1 V + \tilde{\lambda}_2 \) and \( c = 1/V. \)

Therefore, the series expansion (2.57) also holds for the coagulation-fragmentation equation. Similarly, we have \( N = N(i, t) \), which is written as

\[ N(i, t) = e^{-\lambda t} \sum_{k=0}^{\infty} (1 - e^{-\lambda t})^k h_k(i), \]

and the coefficients \( \{h_k(i)\} \) are determined by

\[ h_{k+1}(i) = \frac{1}{k+1} \sum_{j=0}^{k} \frac{1}{\lambda} R_i(h_j, h_{k-j}) \] (2.109)

with the first term

\[ h_0(i) = N_0(i). \] (2.110)

We also have the following result:

**Lemma 22.** Given a non-negative \( N_0 \) with \( \{N_0(1)\} \in \ell^1 \) and \( \{iN_0(i)\} \in \ell^1 \), the coefficients \( \{h_k(i)\} \) defined by (2.109) satisfy

1. \( h_k(i) \geq 0; \)
2. \( \sum_{i=1}^{\infty} iR_i(h_k, h_k) = \lambda \sum_{i=1}^{\infty} ih_k(i); \)
3. \( \sum_{i=1}^{\infty} ih_k(i) = \sum_{i=1}^{\infty} iN_0(i), \quad \forall k = 0, 1, 2, ... . \)

So, by the third result of Lemma 22, we can reduce the computational complexity when calculating \( h_k(i) \) by the recurrent formula (2.109) as follows:
\[ R_i(h_k, h_l) = \frac{1}{2} \sum_{j=1}^{i-1} \beta(i-j,j)h_k(i-j)h_l(j) - \sum_{j=1}^{\infty} \beta(i,j)h_k(i)h_l(j) \]

\[ + \sum_{j=1}^{\infty} \gamma(i,j)h_k(i+j) - \frac{1}{2} \sum_{j=1}^{i-1} \gamma(i-j,j)h_k(i) + \lambda h_k(i). \] (2.111)

By the series expansion of \( N(i,t) \) given in (2.108), the time relaxed method can also be applied to the coagulation-fragmentation equation. The same stability analysis and error estimation results can also be applied. Since the structure is the same as the coagulation equation, we ignore the statements here.

### 2.8 Discussion and conclusion

In this chapter, we develop some deterministic numerical methods to solve the population balance equation. The computational complexity is also discussed for each method. We now compare the CPU run times for the time relaxed method which we compare with the theoretical computational complexity calculations. All the algorithms in the present chapter are written in C++ and were run on Linux machines with a CPU processor speed of 2792.012 MHz.

For example, let us consider the time relaxed method (2.65) with order \( K_0 = 200, 400, 600 \) and 800. Here, we provide the CPU running time for each order \( K_0 \). The kernel and the initial condition are the same as Example 1 in Section 2.4.4.

<table>
<thead>
<tr>
<th>Scheme order ( K_0 )</th>
<th>CPU running time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_0 = 200 )</td>
<td>4.5</td>
</tr>
<tr>
<td>( K_0 = 400 )</td>
<td>71</td>
</tr>
<tr>
<td>( K_0 = 600 )</td>
<td>356</td>
</tr>
<tr>
<td>( K_0 = 800 )</td>
<td>1134</td>
</tr>
</tbody>
</table>

Table 2.3. CPU time of TR method (2.65).

By the result in Section 2.4.3, we know that the computational complexity of the time relaxed method (2.65) for computing \( N_i \ (i = 1, 2, ..., K_0) \) is on the order of \( K_0^4 \). The CPU run times which are given in Table 2.3 are consistent with this computational complexity calculation. Thus, in general, the computational cost becomes more expensive when we increase the order \( K_0 \). As we indicated, the computation can be reduced if the kernel
has compact support. We can also apply the hybrid time relaxed marching method with variable orders and time step to reduce the computational cost. For details, we refer to Section 2.5.3. Another way to improve the computational efficiency is to parallelize the code to compute $f_k(i)$ for different $i$, where $f_k(i)$ is determined by the recursive formula in equation (2.58). Notice that the calculations of $f_k(i)$ for each $i$ are independent. Thus, parallelizing the code is possible, although we consider only the serial implementation in this thesis.

In the heterotypic cell aggregation experiments, the coagulation kernel in our coagulation model always has compact support since the number of cells is finite. So, the computational cost is not expensive for the numerical calculation of our cell aggregation model. The numerical methods can be also used to solve other biological, physical, and chemical problems in which the coagulation model is applied to describe the phenomenon. For example, the droplet coalition, polymer coagulation, and etc.

Over all, the population balance equation with bounded kernels and their numerical approximations are useful to the study of the cell aggregation and adhesion process. The present research explores some interesting properties of the PBE model and a high order time relaxed numerical method. The analysis and numerical experiments also lead to interesting work to be considered in the future such as the hybrid time relaxed and time marching schemes. A challenging issue in our future work includes the extension to the spatially inhomogeneous models corresponding to the cell aggregation and adhesion process in a non-uniform shear flow [24]. Such studies are applicable to the understanding of problems such as the heterotypic cell cell collision and adhesion to a substrate under dynamic shear forces. For more discussions on the comparison of numerical simulation and in-vitro experimental studies, we refer to Chapter 4.
Spatially homogeneous coagulation model

3.1 Overview of coagulation theory

Before we study the coagulation model, let us give an overview of the coagulation theory and explain the physical meaning behind the coagulation system. We know that the coagulation kernel plays an important role in the coagulation model since it determines the coagulation probability of any pair of particles in the coagulation system. For review of the coagulation kernel, we refer to [71]. Collet [71] discussed three types of coagulation kernels: the flow driven collision kernel, the Brownian motion collision kernel and the sedimentation collision kernels.

We also discuss a wildly used stochastic formulation for the coagulation equation, called the Marcus-Lushnikov process, and its Monte Carlo simulation.

3.1.1 Coagulation kernel

For the discussions of the coagulation kernel, we refer to [72, 71, 73, 74]. Hidy and Brock [73] gave a review on two different approaches of the collision and coagulation theory. One of the approaches is the classical method from Smoluchowski [23], who worked on the behavior of the dispersed system, where the particles were assumed to move randomly in a stagnant or uniform continuum flowing medium. However, this kind of approach is inadequate since the change of the continuum result should be taken into account. Furthermore, Smoluchowski did not consider the effects of nonuniform particle distribution and the effects of external fields, for example, the electric field. This leads
to the second approach by using the developments of free molecule theory [75, 76].

There is no general formulation for the coagulation theory in different medium environments by taking into account all the factors we mentioned above. However, some studies have been done on specific problems such as: the shear flow, the sedimentation, the external electrical fields, and the ultrasonic fields [77, 23].

In this section, we restrict our discussion based on three assumptions. The first assumption is the spatially homogeneity, which means the particles are distributed uniformly in space, and we only consider the spatially homogeneous coagulation model in this part. The second one is the particles are assumed to be rigid particles that do not deform during the coagulation process. As a starting point, we can also assume that two particles will stick to each other once they collide. Therefore, the coagulation only depends on the collision mechanics, and the coagulation rate is just the collision rate; otherwise, we need to consider one more parameter: the adhesion efficiency, which measures the coagulation percentage of two colliding particles.

The particles in the fluid may undergo a random walk or are advected by the fluid flow. Due to the nonuniformity of the fluid velocity profile, the moving particles have a chance of colliding and coagulating with one another with a certain probability. For a fixed particle, the other particles will collide with it if this particle reaches the collision region Ω for the target particle. For example, if we consider the collision between two rigid spherical particles having radii $r_1$ and $r_2$, respectively, then the collision region will be a sphere of radius $r_1 + r_2$ with the same center as the target particle.

In general, we consider a Fokker-Planck type fluid dynamical system. If we fix the coordinate system on the target particle, then the total flux of the other particles reaching the collision region Ω will be:

$$J = \int_{\partial\Omega} \sigma \frac{\partial N}{\partial n} - v_r \cdot nN ds,$$

(3.1)

where $\sigma$ is the diffusion constant, $n$ is the outward normal of $\Omega$, $v_r$ is the relative velocity of two collision particles, and $N$ is the concentration of the other particles. We also restrict this integral to the condition

$$\sigma \frac{\partial N}{\partial n} - v_r \cdot nN \geq 0 ;$$

(3.2)

therefore, only the incoming flux is taken into account.

For some special cases, such as linear velocity flow and Brownian motion, we can derive the analytical expression of equation (3.1). However, in general, we do not have
a uniform formula for the coagulation kernel. In some cases, we use numerical methods to approximate it. For details, see Chapter 4.

**Flow driven collision** Smoluchowiski [23] gave the original derivation of the coagulation kernel for rigid spherical particles in linear velocity flow. Linear velocity flow is the flow in which the particle moves in the $x-y$ plane towards the $x$-axis with the velocity linearly dependent on the $y$-axis. The velocity can be written as $v = (v_x, v_y, v_z) = (\gamma y, 0, 0)$, where $\gamma$ is the shear rate.

Now, let us compute the coagulation rate $\beta(i,j)$ of two particles with radius $r_i$ and $r_j$. By changing the variables to spherical coordinates, the velocity is rewritten as

$$v_x = (r_i + r_j)\gamma \sin \phi \sin \theta, \quad v_y = 0, \quad v_z = 0; \quad \phi \in [0, \pi], \quad \theta \in [0, 2\pi).$$

Thus, for the particle fixed at the origin having radius $r_i$, following equation (3.1), the incoming flux $J$ per unit time for unit concentration is:

$$J = -\int_{\Omega, v \cdot n \leq 0} v \cdot n \, ds \quad \int_{0}^{\pi} \int_{0}^{2\pi} (r_i + r_j)^3 \gamma \sin^3 \phi \sin \theta \cos \theta |v \cdot n \leq 0 \, d\phi \, d\theta = \gamma (r_i + r_j)^3 \int_{0}^{\pi} \sin^3 \phi d\phi \int_{0}^{2\pi} \sin 2\theta \, d\theta = \frac{4}{3} \gamma (r_i + r_j)^3.$$

So, the coagulation kernel in linear velocity flow is

$$\beta(i,j) = \frac{4}{3} \gamma (r_i + r_j)^3. \quad (3.3)$$

This integral approach to the coagulation kernel can also be extended to other flow conditions. Aldous [22] gave a full list of the coagulation kernel in different cases. See Table 3.1 for reference. In this table, the kernel $\beta(u, v)$ is represented as a function of volumes $u$ and $v$ for the continuous case. The constant parameters are ignored in this table.

In general, the coagulation kernel in fluid flow can be estimated numerically from the equation:

$$\beta(u, v) = -\int_{\Omega, v \cdot n \leq 0} v_r \cdot n \, ds,$$

where $\Omega$ is still the collision region and $v_r$ is the relative velocity of two moving particles.
Kernel $\beta(u, v)$ | Flow conditions
---|---
$(u^{1/3} + v^{1/3})(u^{-1/3} + v^{-1/3})$ | Brownian motion (continuum regime)
$(u^{1/3} + v^{1/3})^2(u^{-1} + v^{-1})^{1/2}$ | Brownian motion (free molecular regime)
$(u^{1/3} + v^{1/3})^{7/3}$ | shear flow with nonlinear velocity profile
$(u^{1/3} + v^{1/3})^2|u^{1/3} - v^{1/3}|$ | gravitational settling
$(u^{1/3} + v^{1/3})^2|u^{2/3} - v^{2/3}|$ | inertia and gravitational settling
$(u - v)^2(u + v)^{-1}$ | analytical approximation of Berry’s kernel
$(u + c)(v + c)$ | condensation/branched-chain polymerization
$(u^{1/3} + v^{1/3})(uv)^{1/2}(u + v)^{-3/2}$ | based on kinetic theory

**Table 3.1.** Coagulation kernel for some special flow conditions

Notice that the collision region is not restricted to rigid particles. It also can be applied to deformable particles.

**Brownian motion**  
Particles may also collide and stick in the case of Brownian motion. The derivation of the coagulation kernel can be found in [23, 71, 74]. We give a brief introduction of it in order to have a deep understanding of the coagulation theory in Brownian motion case. In this case, we also assume that the particles are spherical and undeformable particles.

Consider a particle with radius $r_j$ moving along a random walk path to collide with a fixed particle of radius $r_i$. Assume the diffusion constants for these two particles are $\sigma_j$ and $\sigma_i$. Thus, $N$, the concentration of the particles with radius, $r_j$, satisfies the diffusion equation:

$$\frac{\partial N}{\partial t} = \sigma_j \Delta N.$$  

(3.5)

If we fix the coordinate system on the target particle, the concentration $N$ is symmetric about the origin. By changing it to the spherical coordinate system, $N$ is written as $N(r, t)$, where $r$ is the distance to the origin or to the center of the target particle. Furthermore, we can rewrite the diffusion equation as

$$\frac{\partial N}{\partial t} = \sigma_j \left( \frac{\partial^2 N}{\partial r^2} + \frac{2 \partial N}{r \partial r} \right),$$  

(3.6)

with boundary condition

$$N = 0, \quad \text{for} \quad r = r_i + r_j,$$  

(3.7)

$$N = N_\infty, \quad \text{for} \quad r = \infty.$$  

(3.8)
Notice that the particles in the medium are very dilute. Comparing with the particle diffusion speed, collisions are very rare. Hence we are able to take the steady state approximation for $N$. Solving the diffusion equation, we get the analytical steady state solution:

$$N = N_\infty \left(1 - \frac{r_i + r_j}{r}\right).$$

(3.9)

Thus, by equation (3.1), the incoming flux is approximated by

$$J = \int_{\Omega} \sigma_j \frac{\partial N}{\partial r} \, ds = 4\pi \sigma_j (r_i + r_j) N_\infty.$$  

(3.10)

Since the target particle of radius $r_i$ also undergoes Brownian motion with diffusion constant $\sigma_i$, the effect to the collision also need to be taken into account. We know that the relative diffusion of these two particles is just the sum of their diffusions since motions are independent. Hence, in general, the total incoming flux to the target particle, is $4\pi (\sigma_i + \sigma_j)(r_i + r_j)$. So, the coagulation kernel for Brownian motion, $\beta(i,j)$, will be the incoming flux with unit concentration $N_\infty$, which is given by

$$\beta(i,j) = 4\pi (\sigma_i + \sigma_j)(r_i + r_j).$$

(3.11)

Notice that the diffusion constant is given by Stokes-Einstein formula

$$\sigma_i = \frac{kT}{6\pi r_i \mu},$$

where $k$ is the Boltzmann’s constant, $T$ is the absolute temperature, and $\mu$ is the viscosity.

Hence, the coagulation kernel for Brownian motion can be also written as

$$\beta(i,j) = \frac{2kT}{3\mu} \frac{(r_i + r_j)^2}{r_i r_j}.$$  

(3.12)

For some other cases, like sedimentation, we refer to [71, 78] for derivations of the coagulation kernel.

### 3.1.2 Marcus-Lushnikov process

In this section, we give a brief introduction to the Marcus-Lushnikov process [79, 32, 33, 22].

Consider a coagulation dynamical system with total volume $V_t$ at instant $t$. The particles coagulate with each other under some influence of random factors. Two random particles with volumes $x$ and $y$ will coagulate with probability $\beta(x,y)/V_t$ per unit time.
Assume there are \( n_t \) particles in this system at time \( t \). Then, we describe the system state by

\[
X_t = \{x^1_t, x^2_t, ..., x^i_t, ..., x^{n_t}_t\},
\]

where \( x^i_t \) is the volume of the \( i \)th particle. Thus, the total volume is

\[
V_t = \sum_{i=1}^{n_t} x^i_t.
\]

In general, the total volume \( V_t \) is a constant independent of time. In this system, the state is changed due to the coagulation event. If two particles coagulate and grow into a big particle, we update the system to the new state.

This stochastic coagulation process is called the Marcus-Lushnikov process, which was studied by Marcus [32] and Lushnikov [33] independently. Define this stochastic process by \( \{X(t)\} \). It is a time continuous Markov process. Assume the probability of the state \( X \) is \( P(X, t) \), and the transition probability from state \( Y \) to \( X \) is \( T(Y, X, t) \). Then we can set up the differential equation for \( P(X, t) \):

\[
\frac{\partial P(X, t)}{\partial t} = \sum_Y T(Y, X, t)P(Y, t) - \sum_{X'} T(X, X', t)P(X, t),
\]

where the transition probability \( T(Y, X, t) \) is linked to the coagulation kernel \( \beta(i, j) \), which sums up all the possible coagulation events such that the state \( Y \) is changed to \( X \). In specific, \( T(Y, X, t) \) is written as:

\[
T(Y, X, t) = V_t^{-1} \sum_{i,j} \beta(y^i_t, y^j_t),
\]

in which all the possible coagulation event between \( y^i_t \) and \( y^j_t \) that may change state \( Y \) to \( X \) are sum up. The analog can be set up for \( T(X, X', t) \) also.

Empirically, denote \( N_{x,t} \) as the concentration of the particles of volume \( x \) of the system, then we have

\[
N_{x,t} = V_t^{-1} \sum_{i=1}^{n_t} \delta_{x^i_t}(x),
\]

where \( \delta_{x^i_t}(x) \) is a delta function.

We want to investigate the convergence of the Marcus-Lushnikov process. That is,
we want to check if the following statement is correct:

\[ N_{x,t} \rightarrow N(x,t) \quad \text{as} \quad n_0 \rightarrow \infty , \quad (3.15) \]

where \( N(x,t) \) is the solution of the coagulation equation.

We can check that if the initial condition \( N_{x,0} \) is discrete, then it leads to a discrete coagulation equation. Otherwise, it corresponds to a continuous coagulation equation if \( N_{x,0} \) is continuous.

Actually, the convergence of the Marcus-Lushnikov process was an open problem in [22] and then was solved by Fournier and Giet in [80]. For the Marcus-Lushnikov process, a finite dynamical system, as the initial number of particles in this system goes to infinity, Fournier and Giet showed that the process converged to the modified coagulation equation for the kernel \( \beta(x,y) \), if the quantity \( l(x) = \lim_{y \to \infty} \beta(x,y)/y \) exists and is finite. In general, for non-gelling kernels or gelling kernels such that \( l(x) = 0 \), the modified coagulation equation is the same as the original equation. But for gelling kernels, \( l(x) \neq 0 \), these two equations are only equivalent for \( t \in [0, T_g] \), where \( T_g \) is the gelling time. Therefore, for some special cases, like the bounded kernel or the kernel with compact support, the Marcus-Lushnikov process is also consistent with the coagulation equation. For example, the cell aggregation system can be viewed as this special case since the total number of cells is finite.

**Monte Carlo simulation of M-L process** In this section, we start from the Marcus-Lushnikov process and introduce a Monte Carlo method for solving the discrete coagulation equation. This method was originally studied by Gillespie [81, 82]. We have used this method to simulate the PMN tumor cell aggregation in nonuniform shear flow [24]. Laurenzi [10] also used this method to simulate the aggregation of platelets and neutrophils. We go over this method briefly for discrete coagulation equation.

This method is set up based on a function called the coagulation probability function \( P(i,j;\tau) \). As before, consider a finite coagulation system with total volume \( V \):

\[ X = \{ n_1, n_2, \ldots, n_m, \ldots \}, \]

and define the set of coagulation events by \( R \):

\[ R = \{ r_{ij} \}_{i,j}, \]
where \( r_{ij} \) is the coagulation event between the \( i \)-monomer and \( j \)-monomer particles.

The coagulation probability function \( P(i, j; \tau) \) is defined as follows:

\[
P(i, j; \tau) d\tau = \text{the probability at time} \ t \ \text{that the next coagulation event} \ \ r_{ij} \ \text{will take place in the interval} \ (t + \tau, t + \tau + d\tau).
\]

We also define the probability \( P_0(\tau) \) as

\[
P_0(\tau) = \text{the probability at time} \ t \ \text{that there is no coagulation event taking place in the interval} \ (t, t + \tau).
\]

By the probabilistic representation of the coagulation kernel \( \beta(i, j) \), we know that for small time \( \delta t \),

\[
n_{ij} \beta(i, j) \delta t / V = \text{the probability that the coagulation event} \ r_{ij} \ \text{will take place in the next time interval} \ \delta t.
\]

The quantity \( n_{ij} \) is the number of coagulation combinations for coagulation event \( r_{ij} \). It is easy to see that

\[
n_{ij} = \begin{cases} 
n_i n_j, & \text{if} \ i \neq j, \\
(n_i - 1)/2, & \text{if} \ i = j.
\end{cases}
\]

Thus we have

\[
P(i, j; \tau) d\tau = P_0(\tau) n_{ij} \beta(i, j) d\tau / V. \tag{3.16}
\]

In order to derive the equation of \( P(i, j; \tau) \), we need to calculate \( P_0(\tau) \). We divide the interval \( (t, t + \tau) \) into \( M \) subintervals of equal length \( dt = \tau / M \). Thus the probability that there is no coagulation event taking place in the subintervals are all

\[
\prod_{i'j'} (1 - n_{i'j'} \beta(i', j') dt / V).
\]

Combining all the probabilities on these subintervals and taking the limit as \( M \) goes to infinity, we get the formula for \( P_0(\tau) \) as follows:

\[
P_0(\tau) = \exp \left( -\sum_{i'j'} n_{i'j'} \beta(i', j') \tau / V \right). \tag{3.17}
\]

Denote the quantity \( a_{ij} = n_{ij} \beta(i, j) \tau / V \), where \( a_{ij} dt \) represents the probability that the coagulation event \( r_{ij} \) will occur in the next time interval \( dt \). Thus, we get the probability function \( P(i, j; \tau) \) as follows:
\[ P(i,j; \tau) = a_{ij} \exp \left( - \sum_{i',j'} a_{i'j'} \tau \right). \] (3.18)

The basic idea of the Monte Carlo method is to simulate the stochastic coagulation process described by \( P(i,j; \tau) \). Two different procedures were presented by Gillespie in [83]. They are called the direct method and the first reaction method respectively.

For the direct method [83], the idea is to rewrite \( P(i,j; \tau) \) in terms of two functions:

\[ P(i,j; \tau) = P_1(\tau)P_2(i,j|\tau), \] (3.19)

Where, \( P_1(\tau)d\tau \) is the probability that the next coagulation event will occur in time interval \( (t + \tau, t + \tau + d\tau) \) and \( P_2(i,j|\tau) \) is the probability that this coagulation event will be \( r_{ij} \).

Hence, by simple calculation, we get

\[ P_1(\tau) = a (\exp a\tau), \] (3.20)
\[ P_2(i,j|\tau) = a_{ij}/a. \] (3.21)

where

\[ a = \sum_{i'j'} a_{i'j'}. \]

Since \( P_1(\tau) \) and \( P_2(i,j|\tau) \) both have simple expressions, it is very easy to sample these two functions. Next, we generate two random numbers \( r_1 \) and \( r_2 \) from a uniform distribution in \([0,1]\) and sample the coagulation time \( \tau \) and coagulation event \( r_{ij} \) such that they satisfy

\[ \tau = \frac{1}{a} \ln \left( \frac{1}{r_1} \right), \] (3.22)
\[ (i,j)^{-1} \sum_{i'j'} a_{i'j'} < r_2 a \leq \sum_{i'j'} a_{i'j'} \] (3.23)

An alternative method is called the first reaction method; for more details, we refer to [83].
3.1.3 A conservation law formulation

Consider a deterministic dynamical system

\[ \frac{dx}{dt} = V(t, x) , \tag{3.24} \]

where \( x \) is the state variable depending on time and \( V \) is a deterministic function. In kinetics, \( x(t) \) always represents the particle position and \( V \) is the velocity field. Equation (3.24) determines the trajectory of the particle. By solving this equation, we can track the particle at any time. Starting from the conservation law, we are also able to derive a PDE of the density function for any conserved quantity.

Let \( f(x, t) \) be the density of any quantity such as the mass, heat, momentum etc. The amount of \( f \) in any domain \( \Omega \) can be written as

\[ \int_{\Omega} f(x, t) dx . \tag{3.25} \]

The quantity \( f \) is conserved in the system if it is only gained or lost through the domain boundaries. Mathematically, we have

\[ \frac{d}{dt} \int_{\Omega} f(x, t) dx = - \int_{\partial \Omega} fV(x) \cdot n \, ds . \tag{3.26} \]

Thus we have

\[ \int_{\Omega} f_t + \nabla \cdot (V f) dx = 0 . \tag{3.27} \]

Since this equation holds for any domain \( \Omega \), we get the conservation law

\[ f_t + \nabla \cdot (V f) = 0 . \tag{3.28} \]

Equation (3.28) is the conservation law formulation for a deterministic dynamical system (3.24). We can also derive the PDE for the density function of a stochastic system which satisfies a SDE as follows:

\[ dX_t = V(t, X_t) dt + \sqrt{2}\sigma dW_t , \tag{3.29} \]

where \( W_t \) is a Wiener process.

We know that the probability density function of this stochastic process \( X_t \) is called the Fokker-Planck equation which is given as follows:
\[ f_t + \nabla \cdot (V f) = \sigma \Delta f . \]  

(3.30)

We can also extend the conservation law formulation to coagulation equation. Define the density function of the coagulation system by \( f(x, t) = xN(x, t) \), where \( N(x, t) \) is the concentration function. It has been pointed out in [34] that the coagulation equation can be written in terms of the conservation law:

\[ f_t + \partial_x(F(x, t)) = 0 , \]  

(3.31)

where the flux \( F(t, x) \) is given by

\[ F(t, x) = \int_0^x \int_{x-u}^{\infty} \frac{\beta(u, v)}{v} f(u, t) f(v, t) \, dv \, du . \]  

(3.32)

Thus, the stochastic coagulation system can be approximated by a deterministic dynamical system

\[ \frac{dx}{dt} = \int_0^x \int_{x-u}^{\infty} \frac{\beta(u, v)f(u, t)f(v, t)}{vf(x, t)} \, dv \, du , \]  

(3.33)

where we let the particle growth rate \( V(x, t, f) \) satisfy

\[ V(x, t, f) = \int_0^x \int_{x-u}^{\infty} \frac{\beta(u, v)f(u, t)f(v, t)}{vf(x, t)} \, dv \, du . \]  

(3.34)

3.2 Stochastic interpretation and simulation methods

3.2.1 Stochastic interpretation

In Section 3.1, we presented an overview of the coagulation theory, especially on the physical explanation of the coagulation kernel. We know that the coagulation kernel \( \beta(u, v) \) is just the incoming flux of the other particles per unit time for unit concentration. For the spatially homogeneous case, we assume the particles are distributed uniformly, therefore, \( \beta(u, v)N(v, t) \) is just the coagulation number per unit time between the target particle of volume \( u \) and other particles of volume \( v \). This leads to the probabilistic interpretation of the coagulation kernel \( \beta(u, v) \). In [81, 79, 82], Gillespie pointed out that for small time \( dt \),

\[ \beta(u, v)dt = \text{the probability that a given pair of particles with volume } u \text{ and } v \text{ will coagulate in the next time interval } dt \text{ per unit volume.} \]
Thus, for a target particle, its coagulation probability with other particles in the whole coagulation system can be represented by the coagulation kernel as follows:

\[ \beta(u, v)N(v, t)\, dt = \text{the probability that a target particle of volume } u \text{ will coagulate with other particles of volume } v \text{ in the next time interval } (t, t + dt) \text{ in the coagulation system.} \]

The probability representation of the coagulation kernel reveals the particle interaction theory in the stochastic coagulation system. It helps us to set up the stochastic coagulation model. Furthermore, it helps us to develop the Monte Carlo methods to simulate the stochastic system.

**Model development** In this section, we will set up a stochastic coagulation model and show the consistency with the coagulation equation.

In a stochastic coagulation system, we focus on one particular particle and track its increase in size. We define a stochastic process \( X_t \), which represents the volume of this particular particle at time \( t \). This stochastic process is a Markov process since the increase of the particle volume at time \( t + \Delta t \) only depends on the volume at time \( t \).

Let the density function of this stochastic process be \( f(x, t) \). Hence the concentration function \( N(x, t) \) is:

\[ N(x, t) = f(x, t)/x. \]

Let us assume the particle volume at time \( t \) is \( x \). By the probability representation of the kernel \( \beta(x, y) \), the probability that this particle will adhere to any particle of volume \( y \) is \( \beta(x, y)\Delta tN(y, t) \). Hence, the probability that it will not adhere to any particle is \( 1 - \int_0^\infty \beta(x, y)\Delta tN(y, t)\, dy \). If it sticks to a particle of volume \( y \), then its particle volume will increase to \( x + y \) at time \( t + \Delta t \), that is, \( X_{t+\Delta t} = x + y \). Otherwise, if there is no coagulation event taking place, \( X_{t+\Delta t} \) will keep the value \( x \).

In general, we assume that the particle size at time \( t \) is \( x \), i.e., \( X_t = x \). Then the stochastic coagulation system can be governed by the transition function as follows:

\[
X_{t+\Delta t} = \begin{cases} 
  x, & \text{Prob}(X_{t+\Delta t} = x) = 1 - \int_0^\infty \beta(x, y)\Delta tN(y, t)\, dy, \\
  x + y, & \text{Prob}(X_{t+\Delta t} = x + y) = \beta(x, y)\Delta tN(y, t).
\end{cases}
\] (3.35)

Therefore, the density function \( f(x, t + \Delta t) \) satisfies the Chapman-Kolmogorov equa-
\[ f(x, t + \Delta t) = \left(1 - \int_0^\infty \beta(x, y) \Delta t N(y, t) dy\right) f(x, t) + \int_0^x \beta(x - y, y) \Delta t N(y, t) f(x - y, t) dy. \] (3.36)

Thus, we have

\[ \frac{f(x, t + \Delta t) - f(x, t)}{\Delta t} = \int_0^x \beta(x - y, y) N(y, t) f(x - y, t) dy - \int_0^\infty \beta(x, y) f(x, t) N(y, t) dy. \] (3.37)

Taking the limit on the left-hand side as \( \Delta t \) approaches 0, we get an equation of \( f(x, t) \) as follows:

\[ \frac{\partial f(x, t)}{\partial t} = \int_0^x \frac{\beta(x - y, y)}{y} f(y, t) f(x - y, t) dy - \int_0^\infty \frac{\beta(x, y)}{y} f(x, t) f(y, t) dy. \] (3.38)

If we divide both sides of equation (3.37) by \( x \) and take the limit of the left-hand side as \( \Delta t \) approaches 0, then we have

\[ \frac{\partial N(x, t)}{\partial t} = \int_0^x \frac{x - y}{x} \beta(x - y, y) N(y, t) N(x - y, t) dy - \int_0^\infty \beta(x, y) N(x, t) N(y, t) dy. \] (3.39)

Notice that

\[ \int_0^x \frac{x - y}{x} \beta(x - y, y) N(y, t) N(x - y, t) dy = \int_0^x \frac{y}{x} \beta(x - y, y) N(y, t) N(x - y, t) dy. \] (3.40)
Thus,

\[
\int_0^x \frac{x - y}{x} \beta(x - y, y)N(y, t)N(x - y, t) dy = \frac{1}{2} \int_0^x \frac{x - y}{x} \beta(x - y, y)N(y, t)N(x - y, t) dy + \frac{1}{2} \int_0^x \frac{y}{x} \beta(x - y, y)N(y, t)N(x - y, t) dy.
\]

Substituting equation (3.41) into (3.39), we get the following coagulation equation:

\[
\frac{\partial N(x, t)}{\partial t} = \frac{1}{2} \int_0^x \beta(x - y, y)N(y, t)N(x - y, t) dy - \int_0^\infty \beta(x, y)N(x, t)N(y, t) dy.
\]

Hence we have shown that the stochastic coagulation model is consistent with stochastic coagulation equation.

### 3.2.2 Backward Monte Carlo method

**Fokker-Planck equation**  
Carlsson [84, 85] introduced a backward Monte Carlo method to solve the Fokker-Planck equation. The convergence and accuracy were also validated. This method provides great flexibility in choosing a critical point in phase space thus minimizing the statistical noise. In this section, we use this method to solve the coagulation equation.

Before we discuss the Monte Carlo method for solving the coagulation equation, we review how to solve the Fokker-Planck equation as follows:

\[
\begin{cases}
\frac{\partial f(x, t)}{\partial t} + v(t, x) \cdot \nabla_x f(x, t) = \sigma \Delta_x f(x, t), & t \in [0, T] \\
f(x, t = 0) = f_0(x).
\end{cases}
\]

(3.43)

For any given \( x \) and \( \tau \), let us see how to represent \( f(x, \tau) \) as the expectation of a random variable. First, we define a stochastic process \( \tilde{X}_t \) which is governed by the
stochastic differential equation:

\[ d\tilde{X}_t = -v(t, \tilde{X}_t)dt + \sqrt{2}\sigma dB_t \]  (3.44)

with initial position \( \tilde{X}_0 = x \).

Define a new stochastic process \( Y_t = f(\tilde{X}_t, \tau - t) \). By Itô’s formula, we have

\[
dY_t = (-f_t(\tilde{X}_t, \tau - t) - v \cdot \nabla_x f(\tilde{X}_t, \tau - t) + \sigma \Delta_x f(\tilde{X}_t, \tau - t)) dt
\]

\[
+ \sqrt{2}\sigma \nabla_x f(\tilde{X}_t, \tau - t) \cdot dB_t
\]  (3.45)

Notice that \( f(x, t) \) satisfies equation (3.43), thus, we get

\[ dY_t = \sqrt{2}\sigma \nabla_x f(\tilde{X}_t, \tau - t) \cdot dB_t \]

Therefore,

\[ Y_\tau = Y_0 + \int_0^\tau \sqrt{2}\sigma \nabla_x f(\tilde{X}_t, \tau - t) dB_t . \]

Since \( Y_\tau = f(\tilde{X}_\tau, 0) \) and \( Y_0 = f(\tilde{X}_0, \tau) = f(x, \tau) \), we have

\[ f(x, \tau) = f_0(\tilde{X}_\tau) - \int_0^\tau \sqrt{2}\sigma \nabla_x f(\tilde{X}_t, \tau - t) dB_t . \]  (3.46)

Taking the expectation of both sides, we obtain the Feynman-Kac formula

\[ f(x, \tau) = E(f_0(\tilde{X}_\tau)|\tilde{X}_0 = x) . \]  (3.47)

Equation (3.47) will be evaluated numerically. Here we start from equation (3.44).

We can write this equation as

\[ \tilde{X}_{t+\Delta t} - \tilde{X}_t = -v\Delta t + \zeta \sqrt{2\sigma\Delta t} \]

where \( \zeta \) is a Gaussian distributed random number \( \zeta \in N(0, 1) \).

Thus for a small interval \([0, \tau]\), we can simulate \( \tilde{X}_\tau \) by

\[ \tilde{X}_\tau = x - v\tau + \zeta \sqrt{2\sigma\tau} . \]  (3.48)

So for large number \( n \), the numerical approximation of equation (3.47) can be obtained by
\[ f(x, \tau) = n^{-1} \sum_{i=1}^{n} f_0(\tilde{X}_\tau^i). \] (3.49)

where \( \tilde{X}_\tau^i \) is simulated from equation (3.48).

Therefore we gave a Monte Carlo simulation for the Fokker-Planck equation based on the Feynman-Kac formula.

**Coagulation equation** Similar to the Feynman-Kac formula, we can derive a Monte Carlo scheme for the spatially homogeneous stochastic coagulation equation with initial condition \( N(x,0) = N_0(x) \). Without loss of generality, we also assume that \( N(0,t) = 0, \forall t \). The reason why we use the backward simulation method for the coagulation process is that the particles in the coagulation process interact. We cannot simulate each particle independently like the Fokker-Planck equation by the forward simulation method. Therefore, the backward Monte Carlo method has more advantages for the stochastic coagulation process.

First, let us consider a stochastic process \( \{S_t\} \). Assume \( S_t = x \) at time \( t \) and on the small time interval \([t, t + \Delta t]\). This process at time \( t + \Delta t \) is governed by the following distribution:

\[
S_{t+\Delta t} = \begin{cases} 
  x & P = 1 - \int_{0}^{\infty} \beta(x, y)N(y, t)\Delta tdy , \\
  x - y & P = \frac{1}{2} \beta(x - y, y)N(y, t)\Delta t, \quad 0 < y < x , \\
  0 & P = \int_{0}^{\infty} \beta(x, y)N(y, t)\Delta tdy - \frac{1}{2} \int_{0}^{x} \beta(x - y, y)N(y, t)\Delta tdy .
\end{cases}
\] (3.50)

Thus for a stochastic process \( \{S_t\} \) on small interval \([0, \tau]\) with initial status \( S_0 = x \), we define a new stochastic process by

\[ Y_t = N(S_t, \tau - t) . \]

Therefore, we have

\[ Y_0 = N(S_0, \tau) = N(x, \tau), \quad Y_\tau = N(S_\tau, 0) = N_0(S_\tau) . \]

Since the distribution of \( S_\tau \) follows equation (3.50), we get the following distribution for \( Y_\tau \):
\[ Y_\tau = \begin{cases} 
N_0(x) & P = 1 - \int_0^\infty \beta(x,y)N_0(y)\tau dy, \\
N_0(x-y) & P = \frac{1}{2}\beta(x-y,y)N_0(y)\tau, 0<y<x, \\
0 & P = \int_0^\infty \beta(x,y)N_0(y)\tau dy - \frac{1}{2} \int_0^x \beta(x-y,y)N_0(y)\tau dy.
\end{cases} \tag{3.51} \]

So we have the conditional expectation of \( Y_\tau \):

\[
E(Y_\tau|S_0 = x) = N_0(x) + \frac{\tau}{2} \int_0^x \beta(y,x-y)N_0(y)N_0(x-y)dy \\
- \tau \int_0^\infty \beta(x,y)N_0(y)dy. \tag{3.52}
\]

Notice that by Taylor’s expansion, we also have

\[
N(x,\tau) = N_0(x) + \frac{\partial N(x,0)}{\partial t}\tau + o(\tau^2) \\
= N_0(x) + \frac{\tau}{2} \int_0^x \beta(y,x-y)N_0(y)N_0(x-y)dy \\
- \tau \int_0^\infty \beta(x,y)N_0(y)dy + o(\tau^2). \tag{3.53}
\]

It’s easy to verify that the probability representation of \( N(x,\tau) \) is given by

\[
N(x,\tau) = E(Y_\tau|S_0 = x) + o(\tau^2). \tag{3.54}
\]

This gives us a Monte Carlo Scheme to approximate the spatially homogeneous equation. For any large number \( n \), we have

\[
N(x,\tau) = n^{-1} \sum_{i=1}^n Y^{i}_\tau, \tag{3.55}
\]

where \( Y^{i}_\tau \) is sampled from equation (3.51).

### 3.3 An energetic variation formulation

The content of this section is based on joint work with Prof. Chun Liu.

**Deterministic approximation** The coagulation dynamical system is a stochastic system and no energy is involved in the coagulation equation. A possible approach is to
reformulate it by a deterministic dynamical system with the form \( \frac{dx}{dt} = v \) and derive the conservation law consequently. Thus, we will have the nonlocal interaction energy of the coagulation system by this formulation.

Now let us recall the stochastic coagulation process \( \{X_t\} \). Assume the particle size at time \( t \) is \( x \), thus the conditional expectation of the particle size at time \( t + \Delta t \) is given by

\[
E(X_{t+\Delta t}|X_t = x) = \left(1 - \int_0^\infty \beta(x,y)\Delta t N(y,t)dy\right)x + \int_0^\infty \beta(x,y)\Delta t N(y,t)(x+y)dy .
\]

(3.56)

After simplifying, we obtain

\[
E(X_{t+\Delta t}|X_t = x) = x + \int_0^\infty \beta(x,y)\Delta t y N(y,t)dy .
\]

(3.57)

Therefore, we get the conditional expectation

\[
E(X_{t+\Delta t}|X_t) = X_t + \int_0^\infty \beta(X_t,y)\Delta t y N(y,t)dy .
\]

(3.58)

Rewrite it as

\[
\frac{E(X_{t+\Delta t}|X_t) - X_t}{\Delta t} = \int_0^\infty \beta(X_t,y)f(y,t)dy .
\]

(3.59)

If we replace the random variable \( E(X_{t+\Delta t}|X_t) \) by \( X_{t+\Delta t} \), equation (3.59) is written as

\[
\frac{X_{t+\Delta t} - X_t}{\Delta t} = \int_0^\infty \beta(X_t,y)f(y,t)dy .
\]

(3.60)

As the time step \( \Delta t \) approaches 0, we get a dynamical system to approximate the stochastic coagulation process:

\[
\frac{dx}{dt} = \int_0^\infty \beta(x,y)f(y,t)dy .
\]

(3.61)

By the conservation law (3.28), we get the PDE of the function \( f(x,t) \):

\[
\frac{\partial f(x,t)}{\partial t} = -\int_0^\infty \beta_x(x,y)f(x,t)f(y,t)dy - \int_0^\infty \beta(x,y)f_x(x,t)f(y,t)dy .
\]

(3.62)

Notice that in the derivation of equation (3.61), we made an approximation. We replaced \( E(X_{t+\Delta t}|X_t) \) by \( X_{t+\Delta t} \). So, we need to estimate the error of these two terms.
such that we are able to obtain the accuracy of this approximation. We will discuss the accuracy later.

Since the stochastic coagulation model can be approximated in the way indicated by equation (3.61), we are able to define the interaction energy. First we assume that there exits a function $K(x, y)$ such that

$$\beta(x, y) = -K_x(x, y),$$  \hspace{1cm} (3.63)

Then equation (3.61) can be rewritten as

$$\frac{dx}{dt} = -\nabla_x \int_0^\infty K(x, y)f(y, t)dy,$$  \hspace{1cm} (3.64)

and equation (3.62) becomes:

$$\frac{\partial f(x, t)}{\partial t} = \int_0^\infty K_{xx}(x, y)f(x, t)f(y, t)dy + \int_0^\infty K_x(x, y)f_x(x, t)f(y, t)dy.$$  \hspace{1cm} (3.65)

Define the local interaction energy by:

**Definition 1.** $\phi(x) = \int_0^\infty K(x, y)f(y, t)dy$,

and the nonlocal interaction energy of the coagulation system by:

**Definition 2.** $A = \int_0^\infty K(x, y)f(x, t)f(y, t)dx dy$.

Therefore, the coagulation system can be modeled by the following energy law.

$$\frac{dx}{dt} = -\nabla \phi(x).$$  \hspace{1cm} (3.66)

As we discussed above, we can use equation (3.61) to approach the stochastic coagulation process. However, due to the replacement of $E(X_{t+\Delta t}|X_t)$ by $X_{t+\Delta t}$ in the derivation of equation (3.61), it is not yet clear whether or not this is a good approximation. Here, we give an estimate of this error.

For fixed $t$ and $\Delta t$, define the random variable $Y_{t,\Delta t}$ by

$$Y_{t,\Delta t} = X_{t+\Delta t} - E(X_{t+\Delta t}|X_t).$$  \hspace{1cm} (3.67)

Obviously we have that $E(Y_{t,\Delta t}) = 0$. This means that the approach by equation (3.61) is consistent with the coagulation model in the mean value level. Thus we obtain the following theorem.
Theorem 14. Given the stochastic coagulation process \( \{X_t\} \), define
\[
Y_t = \frac{dX_t}{dt} - \int_0^\infty \beta(X_t, y)f(y, t)dy ,
\]
(3.68)

Then, it follows that
\[
E(Y_t) = 0.
\]

Proof. By the definition of \( Y_{t,\Delta t} \), it is easy to show that
\[
\frac{Y_{t,\Delta t}}{\Delta t} = \frac{X_{t+\Delta t} - X_t}{\Delta t} - \int_0^\infty \beta(X_t, y)f(y, t)dy ,
\]
Therefore, we get
\[
Y_t = \lim_{\Delta t \to 0} \frac{Y_{t,\Delta t}}{\Delta t} = \frac{dX_t}{dt} - \int_0^\infty \beta(X_t, y)f(y, t)dy .
\]
Since \( E(Y_{t,\Delta t}) = 0 \), we have that
\[
E(Y_t) = 0.
\]

Next, we estimate the variance \( V(Y_{t,\Delta t}) \). Notice that
\[
V(Y_{t,\Delta t}) = E(|Y_{t,\Delta t}|^2) - |E(Y_{t,\Delta t})|^2
= E(|Y_{t,\Delta t}|^2)
= E(|X_{t+\Delta t} - X_t - \int_0^\infty \beta(X_t, y)\Delta tf(y, t)dy|^2)
= E(|X_{t+\Delta t} - X_t|^2) + E \left( \int_0^\infty \beta(X_t, y)\Delta f(y, t)dy \right)^2
- 2E \left( X_{t+\Delta t} - X_t \right) \int_0^\infty \beta(X_t, y)\Delta f(y, t)dy .
\]
(3.69)
From the stochastic coagulation model, assume \( X_t = x \). Then, we also have
\[
X_{t+\Delta t} - X_t = \begin{cases} 
0 & P = 1 - \int_0^\infty \beta(x, y)\Delta t C(y, t)dy , \\
y & P = \beta(x, y)\Delta t C(y, t) .
\end{cases}
\]
(3.70)
Therefore, we get
\[
E(|X_{t+\Delta t} - X_t|) = \int_0^\infty \int_0^\infty y^2 \beta(x,y) \Delta t C(y,t) f(x,t) dx dy \\
= \int_0^\infty \int_0^\infty y \beta(x,y) \Delta t f(y,t) f(x,t) dx dy ,
\] (3.71)

and
\[
E \left( (X_{t+\Delta t} - X_t) \int_0^\infty \beta(X_t,y) \Delta t f(y,t) dy \right) \\
= \int_0^\infty \int_0^\infty y \left( \int_0^\infty \beta(x,y) \Delta t f(y,t) dy \right) \beta(x,y) C(y,t) \Delta t f(x,t) dx dy \\
= \int_0^\infty \left( \int_0^\infty \beta(x,y) \Delta t f(y,t) dy \right)^2 f(x,t) dx .
\] (3.72)

Substituting these two equations into equation (3.69), yields the following theorem whose proof is omitted.

**Theorem 15.** For the stochastic coagulation process \( \{X_t\} \), the variance, \( V(E(X_{t+\Delta t} | X_t) - X_{t+\Delta t}) \), is estimated by
\[
V(E(X_{t+\Delta t} | X_t) - X_{t+\Delta t}) = \Delta t \int_0^\infty \int_0^\infty y \beta(x,y) f(y,t) f(x,t) dx dy \\
- (\Delta t)^2 \int_0^\infty \left( \int_0^\infty \beta(x,y) f(y,t) dy \right)^2 f(x,t) dx \\
\rightarrow 0 \quad \text{as} \quad \Delta t \rightarrow 0.
\] (3.73)

Comparing the stochastic coagulation equations and equation (3.62), we find that although both are modeling the coagulation process, we get different equations. The reason is because we made a deterministic formulation for the stochastic coagulation system when equation (3.61) was derived. Next we will show that these two are quite similar although are not exactly the same.

As we know, if we substitute \( f(x,t) \) into the Smoluchowski coagulation equation, we have
\[
\frac{\partial f(x,t)}{\partial t} = \int_0^x \frac{1}{y} \beta(x-y,y)f(x-y,t)f(y,t) dy - \int_0^\infty \frac{1}{y} \beta(x,y)f(x,t)f(y,t) dy .
\] (3.74)
Let
\[ H(x, y) = \begin{cases} \frac{\beta(x,y)}{y} & x > y, \\ 0 & x \leq y. \end{cases} \] (3.75)

Then equation (3.74) is written as
\[
\frac{\partial f(x, t)}{\partial t} = \int_0^\infty H(x, y) f(x - y, t) f(y, t) \, dy - \int_0^\infty H(x + y, y) f(x, t) f(y, t) \, dy \\
+ \int_0^\infty H(x, y) f(x, t) f(y, t) \, dy - \int_0^\infty H(x + y, y) f(x, t) f(y, t) \, dy \\
= \int_0^\infty H(x, y) (f(x - y, t) - f(x, t)) f(y, t) \, dy \\
+ \int_0^\infty (H(x, y) - H(x + y, y)) f(x, t) f(y, t) \, dy \\
= - \int_0^\infty \int_0^y H(x, y) f_x(x - s, t) f(y, t) \, ds \, dy \\
- \int_0^\infty \int_0^y H_x(x + s, y) f(x, t) f(y, t) \, ds \, dy. \] (3.76)

Therefore, we obtain a new form of the Smoluchowski equation as below:
\[
\frac{\partial f(x, t)}{\partial t} = - \int_0^\infty \int_0^y H(x, y) f_x(x - s, t) f(y, t) \, ds \, dy \\
- \int_0^\infty \int_0^y H_x(x + s, y) f(x, t) f(y, t) \, ds \, dy. \] (3.77)

Returning to equation (3.62), let
\[ \alpha(x, y) = \beta(x, y) - \int_0^y H(x + s, y) ds. \] (3.78)

Substituting \( \alpha(x, y) \) into equation (3.62), we have
\[
\frac{\partial f(x, t)}{\partial t} = - \int_0^\infty \int_0^y H(x + s, y) f_x(x, t) f(y, t) \, ds \, dy \\
- \int_0^\infty \int_0^y H_x(x + s, y) f(x, t) f(y, t) \, ds \, dy \\
- \nabla_x \int_0^\infty \alpha(x, y) f(x, t) f(y, t) \, dy. \] (3.79)

Comparing equation (3.79) with equation (3.77), we find the second terms are inden-
tical, and the first terms are very similar. However, equation (3.79) contains a residue
\[ \nabla_x \int_0^\infty \alpha(x, y) f(x, t) f(y, t) dy. \]

### 3.4 Bridging stochastic and deterministic formulations

For any given stochastic process \( \{X_t\} \), if its probability density function \( f(x, t) \) represents a preserved physical quantity, such as the volume, mass, momentum, then the conservation law holds. In general, for any given domain \( \Omega \), the quantity change in this domain will be the flux. The conservation law is written as

\[ \frac{d}{dt} \int_{\Omega} f(x, t) dx = F^+(\Omega, t) - F^-(\Omega, t) = F(\Omega, t), \quad (3.80) \]

where \( F^+ \) and \( F^- \) represent the incoming flux rate and outgoing flux rate in the region \( \Omega \), respectively.

Furthermore, if the quantity can be only exchanged through the boundary \( \partial\Omega \), then we have:

\[
\frac{d}{dt} \int_{\Omega} f(x, t) dx = F(\Omega, t) \\
= - \int_{\partial\Omega} F(x, t) \cdot n ds \\
= - \int_{\Omega} \nabla_x \cdot F(x, t) dx,
\]

where \( F(x, t) \) is the flux rate at point \( x \). Then the probability distribution function (PDF) satisfies

\[ f_t + \nabla_x \cdot F(x, t) = 0. \quad (3.81) \]

However, for a stochastic process \( \{X_t\} \), the explicit form of the flux is not always given. Instead, the transition probability \( p(x', t'; x, t) \) is easy to determine, where \( p(x', t'; x, t) \) represents the probability that the particle is transferred from \( x' \) at time \( t' \) to \( x \) at time \( t \). So, we always derive the PDF thorough the Chapman-Kolmogorov equation:

\[ f(x, t) = \int p(x', t'; x, t) f(x', t') dx'. \quad (3.82) \]

For reference, see the derivation of the coagulation model in Section 3.2.

In this section, we discuss the relation of the stochastic model and the deterministic model. That is, for any given stochastic process \( \{X_t\} \) and its transition probability function \( p(x', t'; x, t) \), we want to write the flux in terms of the transition probability
function and derive the PDF through the conservation law.

First, let us give the definitions of the region flux \( F(\Omega, t) \) and point flux \( F(x, t) \), respectively.

We define the incoming flux rate \( F^+(\Omega, t) \) of the domain \( \Omega \) by

\[
F^+(\Omega, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} p(x', t'; x, t) f(x', t') dx' dx
\]

and the outgoing flux rate \( F^-(\Omega, t) \) by

\[
F^-(\Omega, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} p(x, t'; x', t) f(x, t') dx' dx .
\]

Combining these two terms, we have the following explicit form of the flux \( F(\Omega, t) \):

\[
F(\Omega, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} (p(x', t'; x, t) f(x', t') - p(x, t'; x', t) f(x, t')) dx' dx .
\]

As was discussed earlier, if the quantity can be only exchanged through the boundary \( \partial \Omega \), we define the point flux \( F(x, t) \) by

\[
F(x, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\mathbb{R}^n} p(x', t'; x, t) \frac{x - x'}{\Delta t} f(x', t') dx'
\]

where \( \Delta t = t - t' \).

**Transport equation** First, let us apply the definitions of the flux (3.85) and (3.86) to the transport equation to determine if they are consistent.

For a deterministic dynamical system

\[
\frac{dx}{dt} = v(x, t) ,
\]

the transition of the particle is determined by the velocity \( v(x, t) \). Thus the transition probability is a delta function which can written as:

\[
p(x', t'; x, t) = \delta(x - x' - v(x, t) \Delta t) .
\]

Then, by definition (3.85), the region flux \( F(\Omega, t) \) is

\[
F(\Omega, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n} (\delta(x - x' - v(x, t) \Delta t) f(x', t')
\]
$$-\delta(x' - x - v(x', t)\Delta t)f(x', t')dx'dx$$

$$= \lim_{\Delta t \to 0} \int_{\Omega} \left( \frac{f(x - v\Delta t, t') - f(x, t')}{\Delta t} - f(x, t')\nabla_x \cdot v(x, t) + O(\Delta t^2) \right) dx$$

$$= -\int_{\Omega} \nabla_x \cdot (v(x, t)f(x, t)) \, dx .$$

By definition (3.86), the point flux $F(x, t)$ is given by

$$F(x, t) = \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} p(x', t'; x, t) \frac{x - x'}{\Delta t} f(x', t')dx'$$

$$= \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} \delta_{x - v(x, t)\Delta t}(x') \frac{x - x'}{\Delta t} f(x', t')dx'$$

$$= \lim_{\Delta t \to 0} v(x, t)f(x, t')$$

$$= v(x, t)f(x, t) .$$

So, it is verified that for the dynamical system $dx/dt = v$ that

$$\frac{d}{dt} \int_{\Omega} f(x, t)dx = F(\Omega, t) = -\int_{\partial\Omega} F(x, t) \cdot nds = -\int_{\Omega} \nabla_x \cdot F(x, t)dx .$$

It is obvious that we obtain the transport equation by the conservation law:

$$f_t + \nabla_x \cdot (vf) = 0 .$$

**Diffusion equation**

Consider a Brownian motion:

$$dX_t = \sqrt{2}dW_t .$$

The transition probability function $p(x', t'; x, t)$ is a Gaussian distribution

$$p(x', t'; x, t) = \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} .$$

(3.90)

First, we consider the region flux $F(\Omega, t)$:

$$F(\Omega, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n} \left( \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} (f(x', t') - f(x, t')) \right) dx'dx .$$

(3.91)

Notice that

$$\int_{\mathbb{R}^n} \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} f(x', t')dx' = f(x, t') + \nabla_x f(x, t')\Delta t + O(\Delta t^2)$$

$$f_t + \nabla_x \cdot (vf) = 0 .$$

(3.89)
and
\[ \int_{\mathbb{R}^n} \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} \, dx' = 1. \]

Substituting these two results into equation (3.91), we obtain
\[ F(\Omega, t) = \int_{\Omega} \nabla_x f(x,t) \, dx . \] (3.92)

We can also calculate the point flux \( F(x,t) \) by using integration by parts
\[
F(x,t) = \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} p(x',t';x,t) \frac{x-x'}{\Delta t} f(x',t') \, dx' \\
= \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} \frac{x-x'}{\Delta t} f(x',t') \, dx' \\
= \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} \frac{1}{\sqrt{2\pi\Delta t}} f(x',t') \, dx e^{-\frac{|x-x'|^2}{2\Delta t}} \\
= - \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} \frac{1}{\sqrt{2\pi\Delta t}} e^{-\frac{|x-x'|^2}{2\Delta t}} \nabla_x f(x',t') \, dx' \\
= - \nabla_x f(x,t) .
\]

Hence, we have also verified that the following conservation law holds for Brownian motion:
\[
\frac{d}{dt} \int_{\Omega} f(x,t) \, dx = F(\Omega, t) = - \int_{\partial\Omega} F(x,t) \cdot ns = - \int_{\Omega} \nabla_x \cdot F(x,t) \, dx .
\]

So, we obtain the diffusion equation by the conservation law:
\[ f_t = \Delta_x f . \] (3.93)

These two examples verify that our flux definitions (3.85) and (3.86) are consistent with the classical flux definition. One can check that it is also consistent with the Fokker-Planck equation by defining the flux of the stochastic differential equation:
\[ dX_t = v(x,t) \, dt + \sqrt{2\sigma} dW_t . \]

Next, we will discuss the coagulation equation.

**Coagulation equation**  As was shown in the previous two examples, for any closed domain, if the physical quantity can be only exchanged through the boundary, then we
have
\[ F(\Omega, t) = - \int_{\partial \Omega} F(x, t) \cdot nds . \] (3.94)

However, in general, the physical quantity is not necessarily exchanged through the boundary; hence, equation (3.94) no longer holds. For example, let us consider the stochastic coagulation process.

The transition probability \( p(x', t'; x, t) \) of the coagulation process is given by
\[ p(x', t'; x, t) = \begin{cases} 
1 - \int_0^\infty \beta(x, y) \Delta t N(y, t') dy , & x' = x , \\
\Delta t \beta(x', x - x') N(x - x', t') , & x' < x , \\
0 , & x' > x , 
\end{cases} \] (3.95)

where we have set \( \Delta t = t - t' \).

For any interval \( \Omega = (a, b) \), one can verify that the region flux \( F(\Omega, t) \) is
\[ F(\Omega, t) = \int_a^b \int_0^x \frac{\beta(x', x - x')}{x - x'} f(x - x', t) f(x', t) dx' dx \\
- \int_a^b \int_x^\infty \frac{\beta(x, x' - x)}{x' - x} f(x' - x, t) f(x, t) dx' dx . \]

We can also check that the point flux \( F(x, t) \) is given by
\[ F(x, t) = \int_0^x \beta(x', x - x') f(x - x', t) f(x', t) dx' . \]

However, one can verify that
\[ F(\Omega, t) \neq F(a, t) - F(b, t) . \]

That is, equation (3.94) does not hold for the coagulation process. So, we need to derive the coagulation equation an alternative way.

Select the region \( \Omega_x = [x, \infty) \) and set \( F(\Omega_x, t) \) to be the flux to this region \( \Omega_x \). Notice that for the coagulation process,
\[ F^-(\Omega_x, t) = 0 . \]

Therefore, we have that
\[ F(\Omega_x, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega_x} \int_{\Omega} p(x', t'; \tilde{x}, t) f(x', t') d\tilde{x} dx' . \]
\[ \begin{align*}
= & \int_0^x \int_0^\infty \beta(x', \tilde{x} - x') N(\tilde{x} - x', t) f(x', t) d\tilde{x} dx' \\
= & \int_0^x \int_{x-x'}^\infty \frac{\beta(x', y')}{y'} f(x', t) f(y', t) dy' dx'.
\end{align*}\] (3.96)

The flux \( F(\Omega_x, t) \) we obtained in equation (3.96) is consistent with the flux definition in [34].

It is not hard to check that for an arbitrary interval \((a, b)\), we have

\[ \frac{d}{dt} \int_a^b f(x, t) dx = F(\Omega_a, t) - F(\Omega_b, t). \] (3.97)

in which we set \( \Omega_a = [a, \infty) \) and \( \Omega_b = [b, \infty) \).

Since \( a, b \) are arbitrary, we get the conservation law for the stochastic coagulation process as follows:

\[ f_t + \partial_x F(\Omega_x, t) = 0. \] (3.98)

Then we have

\[ f_t + \partial_x \int_0^x \int_{x-x'}^\infty \frac{\beta(x', y')}{y'} f(x', t) f(y', t) dy' dx' = 0. \] (3.99)

Replacing \( f(x, t) \) by \( xN(x, t) \), we get an exact spatially homogeneous coagulation equation:

\[ \frac{\partial N(x, t)}{\partial t} = \frac{1}{2} \int_0^x \beta(x - y, y) N(y, t) N(x - y, t) dy - \int_0^\infty \beta(x, y) N(x, t) N(y, t) dy. \]

Hence, we show the consistency of the probability model and the conservation law for the coagulation equation.

Overall, we bridged the probability model and the conservation law for the coagulation equation. The result also shows that our formulations are consistent for the transport equation, the diffusion equation, and the coagulation equation.

**3.5 Discussion and conclusion**

After giving an overview of the coagulation equation, especially the introduction of Marcus-Lushnikov process, a stochastic formulation of the coagulation equation is introduced. We also develop another stochastic interpretation and an energetic variation formulation.
Existing theory shows that the Marcus-Lushnikov process converges to a modified coagulation equation, which is not the standard equation unless the coagulation kernel $\beta(x, y)$ satisfies $\lim_{y \to \infty} \frac{\beta(x, y)}{y} = 0$.

The energetic variation formulation approximates the coagulation equation by a dynamical system $\frac{dx}{dt} = \int \beta(x, y)f(y)dy$ in which case the model can be described by an energy law.

Our studies on the relations of stochastic and deterministic formulations show the consistency of these two formulations. Several examples, such as the transport equation, the diffusion equation, and the coagulation equation, convince us that the deterministic model can be derived from the stochastic model.
Chapter 4

Modeling cell aggregation in nonuniform shear flow

This chapter is joint work with Prof. Cheng Dong and his research group.

4.1 Spatially homogeneous stochastic coagulation model

Shear induced aggregation is a phenomenon that, in the case of platelets or PMNs, has been analytically and numerically modelled [86, 19, 87, 88, 89, 90]. Of particular interest to us is the use of statistical type models for predicting and simulating cell aggregations, namely, the population balance or coagulation models. In such models, the aggregation of two individual cells mainly depends on two parameters: the collision rate and the adhesion efficiency. The collision rate characterizes the probability of two given particles colliding, which is a function of shear rate, particle size and convection. The adhesion efficiency is a measure of the probability of two cells adhering as a response to the collision, which is a function of shear rate, receptor/ligand density, and receptor/ligand avidity. The population balance equations, as introduced by Smoluchowski [23], are also referred to as the coagulation, or Smoluchowski, equations and have been applied to a wide range of applications such as aerosol growth, polymerization problems, and the kinetics of platelet aggregate formation and disaggregation.

In mathematical terms, the population balance model (coagulation model) describes a rate of change of the density of a particle of a particular size as a function of time.
Again, it is given by

\[ \frac{\partial N(u, t)}{\partial t} = \frac{1}{2} \int_{0}^{u} \beta(v, u - v)N(v, t)N(u - v, t)dv - \int_{0}^{\infty} \beta(u, v)N(u, t)N(v, t)dv, \] (4.1)

where \( N(u, t) \) is the concentration of the particles of size \( u \) at time \( t \), and \( \beta(u, v) \) is the coagulation kernel which describes the coagulation probability between two particles with size \( u \) and \( v \). The first term of the right-hand side describes the generation of the particle of size \( u \) by the aggregations of smaller particles. For example, the particle of size \( u - v \) adhere to the particle of size \( v \) will grow into a particle of size \( u \). The second term describes the loss by aggregation with other particles.

The coagulation kernel, originally derived for modeling collisions in laminar shear, contains a constant shear rate \( \gamma \) [23]. The basic idea is to consider a moving rigid spherical particle of volume \( u \) sticking to the one of volume \( v \) in the uniform shear flow. Then we compute the number of point masses which hit the sphere of the collision region per unit time. In Section 3.1, it was shown that the collision kernel has the following form:

\[ \beta(u, v) = \frac{\gamma}{\pi}(u^{1/3} + v^{1/3})^3. \] (4.2)

Such a kernel was designed to model systems that did not contain cells; thus, modifications of the original coalescence kernel have been proposed in the literature to accommodate kinetics properties of receptor ligand type binding in cellular systems. Generally, a term referred to as the adhesion efficiency, \( \varepsilon \), has been introduced, resulting in a new kernel of the following form (see [86, 19, 87, 88, 89, 90]):

\[ \beta(u, v) = \varepsilon \frac{\gamma}{\pi}(u^{1/3} + v^{1/3})^3, \] (4.3)

where \( \varepsilon \) is the adhesion efficiency and \( \gamma \) is the shear rate of the uniform shear flow. The adhesion efficiency term was first estimated by Belvel and Hellums [86] and later studied extensively by Huang and Hellums [19, 87, 88]. In their model, key intrinsic biological parameters were estimated by matching the theoretical results with an experimental volume distribution curve of shear induced platelet aggregates. The experimental data was obtained by shearing platelet suspensions in a cone plate viscometer and analyzing the size distribution of the aggregates by Coulter counter. In later [89, 90, 91], similar methods were also used to estimate adhesion efficiency by fitting experimental data to
equations based on the Smoluchowski coagulation theory. In such analysis, the estimated adhesion efficiency term was theoretically deconvoluted into a receptor component and a hydrodynamic component. Yet, the existing analyzes have focused on the cell collision/aggregation in a uniform shear flow far away from a boundary by using cone plate viscometer assays. However, in our experiments, due to the nonuniform shear flow condition, the aggregation kernel that they used for uniform shear flow is not appropriate anymore. The adhesion efficiency will be different under different flow conditions. Thus, these approaches, especially the coagulation kernels, are not appropriate to model the experimental setups that we are doing. Our task is to look for a more suitable aggregation kernel, measure the adhesion efficacy in the near wall region, and etc.

Other researchers have derived alternative coalescence kernels to accommodate different hydrodynamic conditions, for example, in the turbulence and gravitational settling. One particularly applicable form of the kernel was developed to model particle collisions in a nonlinear velocity profile [22]. It was derived by considering the collision frequency of droplets in a turbulent flow field [92] to have the following form:

\[
\beta(u, v) = c(u^{1/3} + v^{1/3})^{7/3},
\]

where the shear rate and the adhesion efficiency are not included in this equation. However, these and some other constant parameters have been lumped into a single term, \(c\).

Some existing studies have suggested PMN mediated melanoma cell extravasation is influenced by cell populations in a shear flow. In order to understand how heterotypic cell ratios affect melanoma PMN collisions and subsequent aggregation in the near wall region (hence affecting PMN facilitated melanoma extravasation) under flow conditions, we have begun to work with a special variation of the population balance (PB) model as introduced by Smoluchowski.

By comparing the simulations to experimental results, the model can be validated. Through both ad hoc and systematic modifications to existing models, the PB equation can accommodate changes in collision rate and adhesion efficiency due to changes in hydrodynamic parameters. The variation of the PB model studied here allows the simulation of the heterotypic cell-cell aggregation in a nonuniform shear field, especially the aggregation in the near wall region. This provides a potentially useful method to model the PMN melanoma collision and aggregation under a wider range of more physical conditions than those that can be reasonably tested experimentally. A more physiologically relevant case will be when the number of PMNs is significantly greater than melanoma.
cells (normal physiological levels are $2 \times 10^9 - 7.5 \times 10^9$ PMNs per liter of human blood). We will revisit this issue later in the discussion.

### 4.1.1 Simulations of the coagulation model, methods, and parameters

As discussed previously, most existing experimental and mathematical applications of PB models for analyzing cell-cell collision/aggregation have been based on spatially homogeneous coagulation in a linear velocity flow. Other researchers have derived alternate forms of the coagulation kernel to accommodate particle collisions in a nonuniform shear field [22], as shown in equation (4.4). An earlier study published by Laurenzi and Diamond [10] provided an example of modeling heterotypic cell-cell collisions. In this model, shear induced PMN platelet aggregation was predicted by the PB equation, which was solved by a Monte Carlo (MC) driven algorithm. Similar to the Laurenzi and Diamond study, the input parameters for the melanoma PMN collision model were chosen to be cell density, cell size, wall shear rate and approximate adhesion efficiency. The output was the percentage of aggregate formation at a given time.

There are two main problems that need to be solved in developing our PB model in order to make the simulations match our experiments. First, due to the nonuniform shear flow, the concentration in the near wall region will be different from the inlet cell concentration in the chamber. However, we can only use the inlet cell concentration as our model initial data since it is very difficult to measure the concentration in the near wall region experimentally. Fortunately, we can solve this problem through scaling invariance.

The second problem is to modify the existing coagulation kernels such that it can describe the collision in a nonuniform shear field, especially in the near wall region. These two problems will be discussed in the following.

**Scaling invariance** As we indicated, we will use the cell concentration in the inlet of the chamber as our initial concentration in our numerical simulation algorithm, since it is very difficult to measure the concentration in the near wall region in the experiments. It is evident that the local concentration in the near wall region will not be the same as the inlet concentration due to the flow action; thus, we need to scale it such that these two are consistent. Here we make a simple assumption, that is, that the ratio of the concentration in the near wall region to the concentration in the inlet of the chamber is a constant. Then, by taking this into account, we may normalize our initial data mathematically by using the scaling invariance of the population equations.
The scaling invariance refers to the following mathematical properties. Let \( N(u, t) \) be the solution corresponding to the initial concentration, \( C_0(u) \), and \( \lambda \) be any positive parameter; then, we define a new function:

\[
\tilde{N}(u, t) = \lambda N(u, \lambda t). \tag{4.5}
\]

One can easily see that \( \tilde{N}(u, 0) = \lambda N_0(u) \). Moreover, direct calculation gives

\[
\frac{\partial \tilde{N}(u, t)}{\partial t} = \frac{\lambda^2}{2} \int_0^u \beta(u - v, v) N(u - v, \lambda t) N(v, \lambda t) dv - \lambda^2 \int_0^\infty \beta(u, v) N(u, \lambda t) \tilde{N}(v, \lambda t) dv - \frac{1}{2} \int_0^u \beta(u - v, v) \tilde{N}(u - v, t) \tilde{N}(v, t) dv - \int_0^\infty \beta(u, v) \tilde{N}(u, t) \tilde{N}(v, t) dv.
\]

This shows that \( \tilde{N}(u, t) = \lambda N(u, \lambda t) \) is a solution of the same population balance equation with a scaled initial condition. This is an interesting scaling invariance property of the population balance model.

An alternative way to represent the scaling invariance without rescaling time is to explore the normalization of the coagulation kernel. We can also verify that if the coagulation kernel \( \beta(u, v) \) is multiplied by a positive constant \( \lambda \), denoted by \( \hat{\beta}(u, v) \), then the function

\[
\hat{N}(u, t) = \lambda^{-1} N(u, t) \tag{4.6}
\]

gives a solution of the population balance model corresponding to the kernel \( \hat{\beta}(u, v) \) with a scaled initial condition \( \lambda^{-1} N_0(u) \).

Of course, based on the above discussion, one can also obtain the scaling invariance by rescaling both the kernel \( \beta \) and the time while keeping the same initial condition.

An important conclusion based on the above observation is that we can modify the kernel function by a constant factor in order to renormalize the total initial concentration. It should be pointed out that the non-uniform flow conditions not only alter the total concentration of the cells near the wall, but also have different effects on different types of cells. The simple renormalization of the coagulation kernel cannot account for this further complication which leads to another issue discussed later.

Coagulation kernel  The coagulation kernel presented in equation (4.3) takes the presence of cells into account through the introduction of the adhesion efficiency \( \varepsilon \). Still, this formulation assumes a uniform shear field and a spatially homogeneous distribution
of cells considered to be rigid particles. Here we use the kernel which has the form similar to the one given by equation (4.4). We combine the shear rate and adhesion efficiency into this kernel. To estimate the shear rate that melanoma cells and PMNs likely experience in a near wall region, an average shear rate was calculated. This average shear rate was determined to be the average shear rate from one cell radius (the closest a cell can be to the wall without penetrating the wall) to four cell radii from the wall (two cell diameters) (Fig. 4.1).

![Figure 4.1. The average shear rate in the near wall region](image)

Note that nonuniform shear flow has a quadratic velocity distribution in the flow chamber [9]:

\[ v = \frac{3Q}{4b^2w}(2by - y^2), \]

where \( y \) is the \( y \)-axis coordinate, \( Q \) is volumetric flow rate, \( b \) is half the chamber height, and \( w \) is the flow chamber width. Thus, the shear rate along the \( y \)-axis is a linear distribution:

\[ \gamma = \frac{3Q}{2b^3w}(b - y). \]

Therefore, we get the average shear rate in the near wall region:

\[ \bar{\gamma} = \frac{3Q}{2b^2w}(1 - 5a/2b), \quad (4.7) \]

where \( a \) is the cell radius. Then, with this local shear utilized in the coagulation kernel we have:

\[ \beta(u, v) = \phi(C_M : C_{PMN}, R_e, C_a, \delta/D_{cell})\frac{\bar{\gamma}}{\pi}(u^{1/3} + v^{1/3})^{7/3}, \quad (4.8) \]

where we have introduced a renormalization function, \( \phi \), which is a function of the local melanoma and PMN concentrations \( C_M \) and \( C_{PMN} \), local cell Reynolds number \( R_e \) and Capillary numbers (deformation)\( C_a \), and wall proximity, \( \delta \). The renormalization
Adhesion efficiency  An important parameter used in equation (4.8) is the adhesion efficiency, \( \varepsilon \). Heterotypic collision models require three separate values. In the case of melanoma cells and PMN collisions, the relevant \( \varepsilon \) are \( \varepsilon_{T+P} \), \( \varepsilon_{P+P} \) and \( \varepsilon_{T+T} \). The most general definition for adhesion efficiency is the number of formed aggregates divided by the number of collisions that occur. In the model developed here, the values for PMN-PMN (\( P + P \)) homotypic adhesion efficiency, \( \varepsilon_{P+P} \), were taken from the same published source as Laurenzi and Diamond [10] (Table 4.6), and the value for \( \varepsilon_{T+T} \) was approximated to be zero based on our own experimental observation [93].

To determine melanoma PMN (\( T + P \)) adhesion efficiency, \( \varepsilon_{T+P} \), aggregation data from a parallel plate flow assay was used (see Table 4.1). Adhesion efficiency was calculated by dividing the number of melanoma PMN aggregates formed by the number of melanoma PMN collisions that were counted within the same field of view. The adhesion efficiencies were determined for three cases: untreated, anti-CD11a and anti-CD11b. CD11a and CD11b are two different \( \alpha \) chains involved in \( \beta_2 \) integrin expressed on PMNs. CD11b/CD18 is called LFA-1, and CD11b/CD18 is called MAC-1. Table (4.1) shows the \( \varepsilon_{P+P} \) and \( \varepsilon_{T+P} \) derived from experiments.

<table>
<thead>
<tr>
<th>shear rate</th>
<th>( \varepsilon_{P+P} )</th>
<th>( \varepsilon_{T+P} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated</td>
<td>Anti-CD11b</td>
</tr>
<tr>
<td>62.5/s</td>
<td>0.10</td>
<td>0.19</td>
</tr>
<tr>
<td>100/s</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>200/s</td>
<td>0.05</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 4.1. Adhesion efficiency values for \( P + P \) and \( T + P \) collisions for three shear rates. \( T + T \) was approximately zero.

The normalization factor  The normalization factor was determined by first solving the population balance equation (4.1), assuming a spatially homogenous 1 : 1 ratio of \( C_T : C_{PMN} \), using the new kernel (4.8), and running the simulation without normalizing the initial population. The predicted percentage of melanoma PMN aggregation near the substrate was then compared to the experimental percentage of aggregation determined from the parallel plate assays. The normalization factor \( \phi \), necessary to correct the initial concentration in the near wall region to match the experimental results, was then calculated. Its value was derived using the untreated melanoma and PMN cases...
as a control data set. The parallel plate experimental percentage of aggregation was determined by the number of melanoma cells that adhered to the substrate due to a melanoma PMN collision divided by the flux of melanoma cells near the surface [93]. This normalization by the flux of melanoma cells near the surface was necessary to account for the differences in cell flux with varied shear rate ([94]).

### 4.1.2 The numerical algorithm: A Monte Carlo method

Some numerical methods have been developed to solve the population balance equation. Here we use the Monte Carlo method introduced by Gillespie [81, 79, 82]. Although the original method is for homotypic aggregation, it is also efficient for the heterotypic case.

Since we consider the heterotypic cell aggregation, the kinetics of the multi-component aggregation process will be described by the discrete population balance equation as follows:

\[
\frac{\partial N(i, j; t)}{\partial t} = \frac{1}{2} \sum_{i' = 0}^{i} \sum_{j' = 0}^{j} \beta(i - i', j - j'; i', j') N(i - i', j - j'; t) N(i', j'; t) - \sum_{i' = 0}^{\infty} \sum_{j' = 0}^{\infty} \beta(i, j; i', j') N(i, j; t) N(i', j'; t). \tag{4.9}
\]

In this case, \(N(i, j; t)\) denotes the concentration of particles with \(i\) melanoma cells and \(j\) PMNs. \(\beta(i, j; i', j')\) is the coagulation kernel corresponding to the adhesion event \(A_i B_j + A_i' B_j' \rightarrow A_{i+i'} B_{j+j'}\), where \(A\) and \(B\) represent the melanoma cell and PMN, respectively. We denote the composition of particle \(A_i B_j\) by \([i, j]\) from now on.

We discuss Gillespie’s algorithm (see [81]) in Section 3.1.2. This algorithm also holds here. We have known that the coagulation frequency \(\gamma(i, j; i', j')\) in the population balance equation has the property that

\[
\gamma(i, j; i', j') \delta t = \text{the probability that a given pair of particles with compositions } [i, j] \text{ and } [i', j'] \text{ will aggregate in the next time interval } \delta t.
\]

The relationship between the coagulation frequency and the coagulation kernel is established in [81]:

\[
\gamma(i, j; i', j') = \frac{\beta(i, j; i', j')}{V}, \tag{4.10}
\]

where \(V\) is the total volume of the aggregation system.

Consider the aggregation between two particles with compositions \([i, j]\) and \([i', j']\) in an aggregation system. If the aggregation event is the the interaction between two dif-
ferent species, the aggregation probability in the next time interval $\delta t$ is $a([i, j]; [i', j'])\delta t$, where

$$a([i, j]; [i', j']) = \beta(i, j; i', j')X_{[i, j]}X_{[i', j']}/V.$$  \hspace{1cm} (4.11)

If the aggregation is the interaction between two particles of one species $[i, j]$, then

$$a([i, j]; [i, j]) = \beta(i, j; i, j)X_{[i, j]}(X_{[i, j]} - 1)/2V,$$  \hspace{1cm} (4.12)

where $X_{[i, j]}$ and $X_{[i', j']}$ are the populations of species $[i, j]$ and $[i', j']$, respectively.

For the Monte Carlo stochastic approach, the key point is the transition from one state of the aggregation system to the next one. The aggregation probability density function, $P([i, j]; [i', j']; t)$, is defined as the probability that two particles of species $[i, j]$ and $[i', j']$ will aggregate in the next time interval $\delta t$ after an interval of quiescence $(0, t)$.

Let $P_0(t)$ be the density function for imminent quiescence time $t$. By definition, $P([i, j]; [i', j']; t)\delta t$ is the probability density function that there is no aggregation in interval $[0, t]$, but the aggregation event only takes place in $[t, t+\delta t]$. Since $a([i, j]; [i, j])\delta t$ is the aggregation probability in $[t, t+\delta t]$, we have

$$P([i, j]; [i', j']; t)\delta t = P_0(t)a([i, j]; [i, j])\delta t ,$$

that is,

$$P([i, j]; [i', j']; t) = P_0(t)a([i, j]; [i, j]) .$$

Also note that for a small time interval $[t, t+\delta t]$, the probability $P_0(t+\delta t)$ that the aggregation system remains in the state will be

$$P_0(t+\delta t) = P_0(t)\left(1 - \sum_{i,j,i',j'} a([i, j]; [i', j'])\delta t\right),$$

where $(1 - \sum_{i,j,i',j'} a([i, j]; [i', j'])\delta t)$ is the probability that there is no aggregation event in $[t, t+\delta t]$.

Therefore we obtain the following equation for $P_0(t)$:

$$\frac{d}{dt}P_0(t) = -\alpha P_0(t),$$  \hspace{1cm} (4.13)

where

$$\alpha = \sum_{i,j,i',j'} a([i, j]; [i', j']) .$$  \hspace{1cm} (4.14)
Solving this equation, we have $P_0(t) = e^{-\alpha t}$. Then we get the following probability density function, as derived in [20, 81, 79, 82]:

$$P([i, j]; [i', j']; t) = a([i, j]; [i', j']) e^{-\alpha t}. \tag{4.15}$$

We may rewrite the aggregation probability density function as:

$$P([i, j]; [i', j']; t) = \alpha e^{-\alpha t} P_2([i, j]; [i', j']), \tag{4.16}$$

where $\alpha$ is the total aggregation probability frequency defined by equation (4.14). Thus, we obtain the probability of a particular type of aggregation in the time interval $t$.

$$P_2([i, j]; [i', j']; t) = a([i, j]; [i', j'])/\alpha. \tag{4.17}$$

By the Monte Carlo method, we generate two random numbers, $r_1$ and $r_2$ uniformly in the interval $[0, 1]$, to calculate $t$, the aggregation period, and the aggregation event between species $\mu$ and $\nu$. Here $t$ is generated by equation (4.18),

$$t = \frac{1}{\alpha} \ln \left(\frac{1}{r_1}\right). \tag{4.18}$$

The aggregation event between species $[i, j]$ and $[i', j']$ is generated in the following way. Assume the aggregation system has $m$ species at a certain time. Let us label the species by the integers from 1 to $m$. Thus any two species $[i, j]$ and $[i', j']$ correspond to a pair of numbers, $(p', q')$, respectively. Here the aggregation event between two species, $(p, q)$, is determined by inequality (4.19):

$$\sum_{p'=1}^{p-1} \sum_{q'=1}^{q-1} a(p', q') < r_2 \alpha \leq \sum_{p'=1}^{p} \sum_{q'=1}^{q} a(p', q'). \tag{4.19}$$

Therefore, the aggregation event can be determined. These calculations lead to the following simulation steps.

**Algorithm:**

1. Given $N$ initial species and their populations, $P_i$, calculate their aggregation probabilities by the aggregation kernel $\beta(i, j)$. Compute the total aggregation probability, $\alpha$.

2. Generate two random numbers, $r_1$ and $r_2$. Determine the aggregation time step,
t, by equation (4.18), and calculate the aggregation event by (4.19).

3. After the aggregation takes place, update the number of species and the populations.

4. Go back to step 1 until the aggregation stops.

**Consistency**  The consistency of the Monte Carlo algorithm with the PBE models can be easily established. In the population balance equation, the term $\beta(i, j; i', j')\delta t/V$ represents the coagulation probability between two given particles with components of $[i, j]$ and $[i', j']$, respectively, in the next time interval $(t, t + \delta t)$. This is consistent with equations (4.11) and (4.12) which represent the coagulation probability between two species. We will show that the population balance equation can be derived from the stochastic aggregation model contained in this Monte Carlo method.

For an arbitrary given particle, we assume its composition at time $t$ is $[i, j]$. Thus according to equation (4.10), the probability that this particle will adhere to any particle with component $[i', j']$ in the next time interval $(t, t + \delta t)$ should be

$$\beta(i, j; i', j')X(i', j'; t)\delta t/V ,$$

where $X(i', j'; t)$ is the population of the particles with component $[i', j']$ at time $t$. The probability that it will not adhere to any particle is thus

$$1 - \sum_{i'=0}^{\infty} \sum_{j'=0}^{\infty} \beta(i, j; i', j')X(i', j'; t)\delta t/V .$$

Assume the density distribution function of the particle with component $[i, j]$ at time $t$ is $f(i, j; t)$ which is defined as:

$$f(i, j; t) = \frac{(iv_1 + jv_2)X(i, j; t)}{V} ,$$

where $v_1$ and $v_2$ are the volumes of the tumor and PMN. Thus, it satisfies

$$f(i, j; t + \delta t) = \left(1 - \frac{1}{V} \sum_{i'=0}^{\infty} \sum_{j'=0}^{\infty} \beta(i, j; i', j')X(i', j'; t)\delta t \right) f(i, j; t)$$

$$+ \frac{1}{V} \sum_{i'=0}^{i} \sum_{j'=0}^{j} \beta(i - i', j - j'; i', j')\delta t \ X(i', j'; t) f(i - i', j - j'; t) .$$
Thus, we have

\[
\frac{f(i, j; t + \delta t) - f(i, j; t)}{\delta t} = -\frac{1}{V} \sum_{i'=0}^{\infty} \sum_{j'=0}^{\infty} \beta(i, j; i', j') X(i', j'; t) f(i, j; t) \\
+ \frac{1}{V} \sum_{i'=0}^{i} \sum_{j'=0}^{j} \beta(i - i', j - j'; i', j') X(i', j'; t) f(i - i', j - j'; t) .
\] (4.21)

Take the limit of the left hand side as \( \delta t \) goes to 0. We obtain

\[
\frac{\partial f(i, j; t)}{\partial t} = -\frac{1}{V} \sum_{i'=0}^{\infty} \sum_{j'=0}^{\infty} \beta(i, j; i', j') X(i', j'; t) f(i, j; t) \\
+ \frac{1}{V} \sum_{i'=0}^{i} \sum_{j'=0}^{j} \beta(i - i', j - j'; i', j') X(i', j'; t) f(i - i', j - j'; t) .
\] (4.22)

Note that for any two constants \( v_1 \) and \( v_2 \), we change the index \( i - i' = \tilde{i} \) and \( j - j' = \tilde{j} \); then, we have

\[
\sum_{i'=0}^{i} \sum_{j'=0}^{j} \frac{(i - i')v_1 + (j - j')v_2}{iv_1 + jv_2} \beta(i - i', j - j'; i', j') X(i', j'; t) X(i - i', j - j'; t)
\]
\[
= \sum_{i'=0}^{i} \sum_{j'=0}^{j} \frac{i'v_1 + j'v_2}{iv_1 + jv_2} \beta(i - i', j - j'; i', j') X(i', j'; t) X(i - i', j - j'; t).
\]

Thus, we get

\[
\sum_{i'=0}^{i} \sum_{j'=0}^{j} \frac{(i - i')v_1 + (j - j')v_2}{iv_1 + jv_2} \beta(i - i', j - j'; i', j') X(i', j'; t) X(i - i', j - j'; t)
\]
\[
= \frac{1}{2} \sum_{i'=0}^{i} \sum_{j'=0}^{j} \beta(i - i', j - j'; i', j') X(i', j'; t) X(i - i', j - j'; t).
\]

Note that the concentration \( N(i, j; t) \) is defined as

\[
N(i, j; t) = \frac{X(i, j; t)}{V}.
\] (4.23)

Then, dividing equation (4.22) by \( iv_1 + jv_2 \) on both sides and replacing \( f(i, j; t) \) by \( (iv_1 + jv_2)N(i, j; t) \), we get the discrete population balance equation (4.9) after simplification. This shows that our Monte Carlo method is consistent with the population
balance equation.

4.1.3 Model validation
To validate the preliminary model, with both $\varepsilon$ and $\phi$ values derived from untreated melanoma and PMN cases, we analyzed both the PMN melanoma aggregation results from parallel plate experiments and results from the model simulations in which the PMNs were treated with blocking antibodies. The average of the $\phi$ values calculated from the controlled (untreated cell cases) experiments was used in the coagulation kernel equation (4.8), and the percentage of aggregates was recalculated for antibody blocked cases (Table 4.2). The results (Table 4.2) show that the simulations predict the percent aggregation within the experimental range in nearly all the cases. The experimental range was calculated as the mean minus standard deviation (SD) to the mean plus SD from three separate experiments. In one case (Anti-CD11a with shear rate 200/s), the range is not reported because the experimental data was the same for the three different experiments; therefore, no standard deviation could be calculated. If we take a range using comparable standard deviation as in the other cases, the simulation result in this case would be consistent to such a range. Thus, the overall consistency of the simulation results with experimental data shows the feasibility of using population balance models to simulate PMN melanoma aggregation in the near wall region of the parallel plate and migration chambers.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Shear Rate</th>
<th>Percentage Aggregation</th>
<th>Simulation</th>
<th>Experimental Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD11a</td>
<td>62.5/s</td>
<td>2.26</td>
<td></td>
<td>1.50-3.79</td>
</tr>
<tr>
<td></td>
<td>100/s</td>
<td>2.51</td>
<td></td>
<td>0.50-2.40</td>
</tr>
<tr>
<td></td>
<td>200/s</td>
<td>2.15</td>
<td></td>
<td>1.26-1.26</td>
</tr>
<tr>
<td>Anti-CD11b</td>
<td>62.5/s</td>
<td>3.78</td>
<td></td>
<td>2.17-6.83</td>
</tr>
<tr>
<td></td>
<td>100/s</td>
<td>5.26</td>
<td></td>
<td>2.76-5.70</td>
</tr>
<tr>
<td></td>
<td>200/s</td>
<td>8.02</td>
<td></td>
<td>6.04-9.90</td>
</tr>
</tbody>
</table>

Table 4.2. Comparison of simulated tumor PMN aggregation results to experimental results that used PMNs treated with anti-CD11a or anti-CD11b.

While the numerical results are encouraging, it also demonstrates that to improve the accuracy of the model, a simple normalization of the initial population is not enough. For example, for the case of Anti-CD11a with shear rate 100/s, the simulation result is slightly outside of the experimental range. One possibility is that more realistic PMN
melanoma ratios near the EC substrate are needed, in addition to taking into account the change of total population near the substrate.

In the current population balance model, we used the scaling invariance to introduce a normalization factor to suitably adjust the local concentration in the near wall region since it can not be measured accurately experimentally. However, the limitation of this technique is that we are not able to change the ratio of PMN to tumor cell concentrations. For example, suppose the ratio of PMN to melanoma cell concentration is 1 : 1 in the inlet; it may be changed to a totally different ratio in the near wall region.

In order to estimate the cell concentrations in the near wall region directly, careful CFD simulations of cell transport within the chamber are under development. Such simulations can provide more precise quantification of the local cell number densities. Therefore our approach will be to perform direct numerical simulation of a statistically significant number of cells transported from a uniform reservoir concentration. Preliminary study provides feasibility of employing CFD to perform a detailed parametric study across a range of melanoma and PMN reservoir concentrations, Reynolds numbers and Capillary numbers to obtain statistically relevant local concentration predictions for integrating with PB modeling. In our future work, such CFD simulations will be combined with the population balance modeling to provide more accurate determination of the local cell concentration. Such studies will also help our understanding of the more physiologically relevant case where the number of PMNs is significantly greater than the number of melanoma cells (normal physiological levels are $2 \times 10^9 - 7.5 \times 10^9$ PMNs per liter of human blood). In particular, it would be important to develop a PB model in the case where the ratio of PMNs to melanoma cells is high in the free stream. It is then necessary to take into account changes in spatial ratios of PMNs and melanoma cell populations from the free stream ratios to final surface ratios near the EC substrate by using computational fluid dynamics simulations.

### 4.2 Modified spatially homogeneous coagulation model

In Section 4.1, we used a spatially homogeneous coagulation equation to model cell aggregation. However, the homogeneous equation assumes the particles are uniformly distributed in the flow chamber. Due to the nonuniform fluid velocity distribution, the cell concentration in the near wall region is different from the concentration in the inlet of the chamber. In order to correct this problem, we introduced a normalization factor $\phi$ in our previous work to correct the local concentration of PMNs and tumor cells in the
near wall region. In this section, we will use an alternative method, i.e., computational fluid dynamics, to compute the local concentrations. Hence, the model will be set up and will focus on the near wall region. We refer to [95].

The following symbols are used in this section.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N(i,j,t) )</td>
<td>population of the particles composed of ( i ) tumors and ( j ) PMNs adhered on the substrate at time ( t )</td>
</tr>
<tr>
<td>( \beta(i,j;i',j') )</td>
<td>aggregation kernel between the particles one is composed of ( i ) tumors ( j ) PMNs and the other one is composed of ( i' ) tumors ( j' ) PMNs</td>
</tr>
<tr>
<td>( C_p )</td>
<td>concentration of PMNs in the near wall region</td>
</tr>
<tr>
<td>( C_T )</td>
<td>concentration of tumor cells in the near wall region</td>
</tr>
<tr>
<td>( T_f )</td>
<td>tethering frequency of PMNs to the substrate</td>
</tr>
<tr>
<td>( N_{PT} )</td>
<td>number of PMN-tumor doublets adhered on the substrate</td>
</tr>
<tr>
<td>( N_P )</td>
<td>number of PMNs adhered on the substrate</td>
</tr>
<tr>
<td>( \beta_{PT} )</td>
<td>coagulation rate of tumor cells in the near wall region with the adhered PMNs on the substrate</td>
</tr>
<tr>
<td>( \tilde{\beta}_{PT} )</td>
<td>collision rate of tumor cells in the near wall region with the adhered PMNs on the substrate</td>
</tr>
<tr>
<td>( \varepsilon_{PT} )</td>
<td>adhesion efficiency of tumor cells in the near wall region with the adhered PMNs on the substrate</td>
</tr>
<tr>
<td>( \varepsilon_P )</td>
<td>adhesion efficiency of PMNs to the substrate</td>
</tr>
<tr>
<td>( \gamma_w )</td>
<td>wall shear rate</td>
</tr>
<tr>
<td>( \mu )</td>
<td>viscosity</td>
</tr>
<tr>
<td>( v_s^0 )</td>
<td>free settling velocity</td>
</tr>
<tr>
<td>( v_s, v_c )</td>
<td>settling and convection velocity</td>
</tr>
<tr>
<td>( r_p )</td>
<td>PMN cell radius</td>
</tr>
<tr>
<td>( r_t )</td>
<td>tumor cell radius</td>
</tr>
<tr>
<td>( \rho_m )</td>
<td>fluid density</td>
</tr>
<tr>
<td>( \rho_t )</td>
<td>tumor cell density</td>
</tr>
<tr>
<td>( H )</td>
<td>height of the deformed PMN</td>
</tr>
<tr>
<td>( J )</td>
<td>incoming flux to the collision region</td>
</tr>
</tbody>
</table>

**Table 4.3. Parameters glossary**

4.2.1 Cell aggregation in the near wall region

As was indicated, recently, we conducted some experimental and theoretical studies to explore how the interactions between PMNs and tumor cells are affected by the fluid dynamics in nonuniform shear flows. A special focus is on the PMN melanoma cell emboli formation in a nonuniform shear flow and subsequent tethering to the vascular
endothelium (EC) as a result of cell aggregation. In our in-vitro experiment, the fluid flow in the parallel plate flow chamber assays can be described as Poiseuille’s flow through a rectangular geometry, which characteristically has a parabolic velocity profile. In the case of PMN and tumor cell aggregation, a vessel wall or experimental substrate is always present and therefore changes the hydrodynamics of the system. The experimental setup and the aggregation process can be viewed in Figure 4.2. Our goal is to reveal the number of particles adhered on the substrate and how it is affected by the fluid flow conditions.

![Figure 4.2. Schematic of PMN-facilitated TC adhesion to the EC monolayer in a shear flow. Top left: a tumor cell in close proximity to the EC via a tethered PMN. Tumor cells are captured by tethered PMNs on the EC via 2 integrins/ICAM-1 interactions. Top right: cross-sectional view of the flow-migration chamber. Bottom: representative aggregation of melanoma cells (TC) to tethered PMN on an endothelial monolayer. Flow direction is from left to right: (A) at 0 second; (B) after 20 seconds; and (C) after 30 seconds.](image)

Adhesion experiments were performed to examine how PMN cell aggregates adhere to the EC monolayer. The experimentally determined tethering frequency, $T_f$, was the number of PMNs that adhered to the EC monolayer per unit time. At higher shear rates, a higher concentration of cells pass the endothelium and have the opportunity to adhere.

**The tethering frequency** We also check the effect of cell deformability on cell tethering. Parallel plate flow chamber experiments were performed in order to determine if a correlation exists between PMN tethering efficiency and the Capillary number, $C_a$. The Capillary number is a non-dimensional parameter which characterizes the relative importance of viscous forces and the cell deformability in the system. In this case, the deformability of the cell is represented by the membrane tension of the PMN. The Capillary number is equal to the Weber number, $W_e$, divided by the Reynolds number, $R_e$. 
defined by equation (4.24):

\[
C_a = \frac{W_e}{R_e} = \frac{\rho_m v^2 d}{\sigma} \frac{\mu}{\rho_m v d} = \frac{\mu \gamma_w d}{2 \sigma} = \frac{\mu \gamma_w r_p}{\sigma},
\]

(4.24)

where \( \rho_m \) is the fluid density, \( d \) is the PMN cell diameter (\( \sim 8 \mu m \)), and \( r_p \) is the radius. \( \sigma \) is the membrane tension (\( 3.1 \times 10^{-5} N/m \)), \( v \) is the average velocity of the cell approximated by \( \frac{1}{2} \gamma_w d \), and \( \gamma_w \) is the wall shear rate. The Reynolds number is defined by:

\[
R_e = \frac{\rho_m v d}{\mu} = \frac{2 \rho_m \gamma_w r_p^2}{\mu}. \quad (4.25)
\]

Using a standard application of non-dimensional numbers in fluid dynamics dimensional analysis, a correlation was found between experimental data and the Reynolds and Capillary numbers. Figure 4.3 shows PMN tethering frequency data regressed on \( R_e^{0.01} C_a^{-2.0} \) which gives the best fit to the data. The R-squared value of approximately 0.8122 indicates that this relation, and thus both the Reynolds and Capillary numbers, are good predictors of tethering frequency. This suggests that in addition to viscosity and inertia, PMN deformability is an important parameter and will be included in the model.

Figure 4.3. Fitting tethering frequency \( T_f \) as function of \( R_e^{0.01} C_a^{-2.0} \) on a log-log scale.

Hence, in general, we fit the tethering frequency \( T_f \) as a function of the wall shear rate, \( \gamma_w \), and viscosity, \( \mu \), as follows:

\[
T_f = 0.0083(R_e^{0.01} C_a^{-2.0})^{0.3382},
\]

(4.26)
where $R_e$ and $C_a$ are given by equations (4.25) and (4.24) respectively.

The parameters and data that we use to fit the tethering frequency $T_f$ are in Tables 4.4 and 4.5. The plotted result is shown in Figure 4.3.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_m$</td>
<td>fluid density</td>
<td>$1000kg/m^3$</td>
</tr>
<tr>
<td>$r_p$</td>
<td>PMN radius</td>
<td>$4.0 \times 10^{-6}m$</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>membrane tension</td>
<td>$3.1 \times 10^{-5}N/m$</td>
</tr>
</tbody>
</table>

Table 4.4. Parameters for computing $R_e$ and $C_a$.

<table>
<thead>
<tr>
<th>$\mu$ (Pa)</th>
<th>$\gamma_w$ (s$^{-1}$)</th>
<th>$R_e$</th>
<th>$C_a$</th>
<th>$T_f$ (s$^{-1}$)</th>
</tr>
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<tr>
<td>0.0032</td>
<td>62.5</td>
<td>6.25E-04</td>
<td>2.58E-02</td>
<td>0.1200</td>
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<td>5.16E-02</td>
<td>0.0533</td>
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<tr>
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<td>3.20E-03</td>
<td>1.29E-02</td>
<td>0.1100</td>
</tr>
<tr>
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<td>200</td>
<td>6.40E-03</td>
<td>2.58E-02</td>
<td>0.1278</td>
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</tbody>
</table>

Table 4.5. Data for fitting the tethering frequency

Now, we use equation (4.26) to determine how the tethering frequency $T_f$ depends on the change of the shear rate and viscosity. In order to verify the dependence of $T_f$ to the shear rate, we fix the viscosity $\mu = 1.0cp$ and let the shear rate vary from 50$/s$ to 1000$/s$. We also fix the shear rate $\gamma_w = 100$/s$ to see the change on $T_f$ with respect to the viscosity in the range from 1.0$cp$ to 4.0$cp$. We can see that $T_f$ is a decreasing function of both the shear rate and viscosity. The results are plotted in Figure 4.4.

**The adhesion efficiency** The tumor cell in the near wall region will collide with the adhered PMN on the substrate and will then stick to each other with a certain probability. The interaction between these two cells is of great interest to us. First, we need to figure out $\hat{\beta}_{PT}$, the collision rate of the tumor cell to PMN, second, we also need to determine the adhesion efficiency $\varepsilon_{PT}$. Due to the deformability of PMN, the collision rate and the adhesion efficiency not only depend on the flow conditions but also on the shape of PMN. The deformation of PMN also gives a feedback to the flow such
that the flow condition is also changed. The whole interaction of PMN and TC is very complicated.

In general, $\beta_{PT}$, the aggregation rate of PMN and TC is just the product of the adhesion efficiency and the collision rate and is written as:

$$\beta_{PT} = \varepsilon_{PT} \hat{\beta}_{PT},$$

(4.27)

where $\hat{\beta}_{PT}$ is the collision rate and $\varepsilon_{PT}$ is the adhesion efficiency.

The adhesion efficiency is obtained by fitting the experimental data. It is calculated by dividing the number of PMN and tumor aggregates formed by the number of PMN tumor collisions that were counted within the same field of view. We performed experiments with different flow conditions and list all the adhesion efficiencies with respect to shear rate, $\gamma_w$, and viscosity, $\mu$, in Table 4.6.

<table>
<thead>
<tr>
<th>$\mu$</th>
<th>$\gamma_w = 62.5/s$</th>
<th>$\gamma_w = 100/s$</th>
<th>$\gamma_w = 200/s$</th>
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<td>1.0cp</td>
<td>0.1563</td>
<td>0.1075</td>
<td>0.0738</td>
</tr>
<tr>
<td>2.0cp</td>
<td>0.1668</td>
<td>0.1179</td>
<td>0.0743</td>
</tr>
<tr>
<td>3.2cp</td>
<td>0.1530</td>
<td>0.1164</td>
<td>0.0734</td>
</tr>
</tbody>
</table>

Table 4.6. Adhesion efficiency values, $\varepsilon_{PT}$.

By observing trends in the experimental data, we find that the adhesion efficiency does not change much for different viscosities but is significantly affected by the shear
rate. It decreases as the shear rate increases. Hence, we can fit the adhesion efficiency as a decreasing function of the shear rate, $\gamma_w$, with the form

$$\varepsilon_{PT} = Ae^{-\lambda\gamma_w}.$$  \hspace{1cm} (4.28)

By nonlinear least squares fitting, we obtain the values of the coefficients as follows:

$$A = 0.2090, \lambda = 0.0053.$$

Figure 4.5. Fitting the adhesion efficiency as a function of $\gamma_w$ in linear-log scale.

Thus, substituting these coefficients into equation (4.28), we estimate the adhesion efficiency, $\varepsilon_{PT}$, for any given shear rate, $\gamma_w$. Notice that adhesion efficiency is a decreasing function of shear rate.

The collision model  Now, we discuss the modeling of the collision rate $\tilde{\beta}_{PT}$ so that we can have a complete form of the aggregation rate $\beta_{PT}$. First, we review the literature on collision theory. Smoluchowski [23] revealed that for two spherical rigid particles in linear velocity flow, the collision rate, which is defined as the collision numbers of two species per unit time per unit volume, could be derived rigorously. If we assume their radii are $r_1$ and $r_2$, and the shear rate is $\gamma$, then the collision rate is given by:

$$\tilde{\beta}(r_1,r_2) = \frac{4}{3}\gamma(r_1 + r_2)^3.$$ \hspace{1cm} (4.29)

Many researchers used this collision rate to study cell collision and coagulation problems. For example, I. J. Laurenzi and Scott L. Diamond [10] investigated the heterotypic
aggregation kinetics of platelets and neutrophils in linear velocity flow. They used equation (4.29) as the collision rate in their population balance equation to model the aggregation problem. However, this collision kernel is not applicable for our case. First, we study cell collision in a parallel plate flow chamber in which the shear rate is not constant across the height. Second, we deal with the deformable cells which cannot be assumed as the rigid particles. Therefore, our experimental condition does not match Smoluchowski’s assumptions. In addition, according to our experimental observation, we also find that the collision rate decreases quickly if we increase the shear rate from 100s$^{-1}$ to 200s$^{-1}$ which is not consistent with Smoluchowski’s theory since he showed that the collision rate was proportional to the shear rate by equation (4.29).

Recall the general form of the coagulation kernel in equation (3.4) in Section 3.1:

\[
\tilde{\beta} = -\int_{\partial \Omega, v \cdot n \leq 0} v \cdot nds \tag{4.30}
\]

where $\Omega$ is the collision region of tethered PMN and tumor cells. Notice that in this kernel formula, the particles are not necessary to be the rigid spherical particles. In this integral, we take into account the deformability of PMN.

We need to approximate the integral (4.30) numerically. First, let us consider the cell trajectory in the parallel plate flow chamber. The cell enters the flow chamber. Its trajectory depends on two forces: the gravity and the fluid flow convective force. The gravity causes them to settle and the fluid drives the cells horizontally. Let $r_t$ be the tumor cell radius, $\mu$ be the fluid viscosity, $\rho_t$ be the cell density, and $\rho_m$ be the media density. Let $h$ be the distance from the substrate to the cell’s center which represent the position of the cell. Davis and Giddings [96] showed that the settling velocity can be approximated by

\[
v_s = \frac{v_s^0}{1 + r_t/(h - r_t)} , \tag{4.31}
\]

where $v_s^0$ is the free settling velocity given by the Stokes’ equation as follows

\[
v_s^0 = \frac{2}{9} (\rho_t - \rho_m) g \frac{r_t^2}{\mu} . \tag{4.32}
\]

The convection velocity in the free stream varies quadratically with respect to the height from the substrate. Let $v_{max}$ be the maximum convection velocity at the center of the chamber; then the convection velocity, $v_c$, can be written as:

\[
v_c = \frac{v_{max}(2bh - h^2)}{b^2} , \tag{4.33}
\]
where \( b \) is the half height of the chamber and \( h \) is distance of the cell center to the substrate. If the cells are very close to the chamber substrate, the convection velocity is reduced by hydrodynamic wall effects. For example, if \( y < 4a \), the convection velocity can be approximated by the following far-field asymptotic formula:

\[
v_c = \gamma \omega h \left( 1 - \frac{5}{16} \left( \frac{r}{h} \right)^3 \right),
\]

where \( \gamma \omega \) is the wall shear rate (see [97, 9, 21]).

These two velocity formulas provide us the velocity profile of the cells in the near wall region. They help us to estimate the collision rate by setting up the proper mathematical models.

In our parallel plate flow chamber, the tumor cells in the near wall region collide with the adhered PMN on the substrate with convection velocity, \( v_c \), and settling velocity, \( v_s \). We assume the tumor cell is a rigid spherical particle which does not deform in the fluid flow. However, for the adhered PMN, its shape will be changed for different shear rate and viscosity. We also assume the flow condition does not change due to the deformability of PMN. Dong [6] developed a theoretical model to describe the deformation and adhesion of white blood cell to endothelial cell in shear flow. By using a two-dimensional approximation to the actual three dimensional cell body, a cross sectional slice of an adherent white blood cell was formulated. The cell was represented by a two-dimensional extensible elastic ring adhered to a plane surface with steady state fluid stress and adhesive contact stress as they were acting to deform the cell. In this model, only the dependence of the deformability on shear rate is taken into account. How the deformability depends on viscosity is not investigated.

In present section, in order to simplify the deformability problem and reveal how the collision rate depends on the shear rate and viscosity, we assume that PMN always has an arc shape, and maintains the volume but its height changes with respect to the change of the shear rate and viscosity, as shown in Figure 4.6. We will fit experimental data to figure out how the height of deformable PMN depends on shear rate and viscosity.

Let the radius of the deformed PMN be \( r \) and the height be \( H \). The height is determined by the shear rate and viscosity as follows:

\[
H = f(\gamma \omega, \mu),
\]

where \( f \) is a function of both shear rate \( \gamma \omega \) and viscosity \( \mu \).

Determining the function \( f \) will be a challenge. Next, we show that we can use
the population balance model to calculate this function. In general, if we determine function \( f \), for given shear rate and viscosity, we will have the shape of the deformed PMN. Furthermore, since we have the velocity profile around PMN, we can compute the collision rate, \( \hat{\beta}_{PT} \), by estimating the integral in equation (4.30). The details of the computation are described below:

We explain how to evaluate the integral in equation (4.30) for given velocity profile. We use spherical coordinates to determine all the related parameters. In our \( x, y, z \) coordinate system, we suppose the chamber cross section (Figure 4.6) is in the \( yz \)-plane and the \( x \)-axis points towards the reader. Define \( \theta \) to be the azimuthal angle in the \( xy \)-plane from the \( x \)-axis with \( 0 \leq \theta < 2\pi \), \( \phi \) to be the polar angle from the \( z \)-axis with \( 0 \leq \phi \leq \pi \), and \( r \) to be distance (radius) from a point to the origin.

In this spherical coordinate system, we assume the origin is the center of the sphere where the arc-shaped PMN lies. By a change of variables, we have

\[
x = r \sin \phi \cos \theta, \quad y = r \sin \phi \sin \theta, \quad z = r \cos \phi, \quad r \in [0, \infty), \quad \phi \in [0, \pi], \quad \theta \in [0, 2\pi).
\]

(4.36)

Therefore, we get

\[
v = (v_x, v_y, v_z), \quad v_x = 0, \quad v_y = v_c, \quad v_z = -v_s. \quad (4.37)
\]

We also assume the two bottom points of the PMN have spherical coordinates \((r, \phi_0, \frac{\pi}{2})\) and \((r, \phi_0, \frac{3\pi}{2})\). Since the deformable PMN preserves its volume \( V = \frac{4}{3} \pi r_p^3 \), where \( r_p = d/2 \) is the radius of the PMN, we have that

\[
V = \frac{2}{3} \pi(1 - \cos \phi_0)r^3. \quad (4.38)
\]
Therefore, we have a closed form for $H$, $r$, and $\phi_0$, which are given by the following explicit formulas:

\begin{align*}
H &= f(\tau_w) = 8.0 \times 10^{-6} \exp(-0.521 \gamma_w \mu), \quad (4.39) \\
r &= \sqrt{3V/2\pi H}, \quad (4.40) \\
\phi_0 &= \arccos\left(1 - \frac{H}{r}\right). \quad (4.41)
\end{align*}

Now, consider a tumor cell which is colliding with the PMN. Assume the point where they touch has coordinate $(r + r_t, \theta, \phi)$, where $r_t$ is the radius of tumor cell. Thus, $h$, the distance between the center of tumor cell and the substrate is given by

\begin{equation}
\begin{aligned}
h &= (r + r_t) \cos \phi - r \cos \phi_0. \\
&(4.43)
\end{aligned}
\end{equation}

Our task is to compute the coagulation kernel $\hat{\beta}_{PT}$ under different flow conditions. Then, for any given two parameters $\gamma_w$ and $\mu$, we can compute $H$ by the fitted function $f$ in equation (4.35) and then compute $\phi_0$ and $r$. Hence, $h$ is obtained from equation (4.43). Thus all the parameters and the flow velocity profile are both obtained. Substituting all these parameters into the integral (4.30) to compute the kernel, $\hat{\beta}_{PT}$, by estimating the integral on the collision region $\Omega$. By simplification, we have

\begin{equation}
\begin{aligned}
\hat{\beta}_{PT} &= -\int_0^\pi \int_0^{2\pi} F(\phi, \theta)|_{F \leq 0, h \geq r_t} d\phi d\theta \\
&(4.44)
\end{aligned}
\end{equation}

where the integrand, $F$, is given by

\begin{equation}
F(\phi, \theta) = \sin \phi (r + r_t)^2 (\sin \phi \sin \theta v_y + \cos \phi v_z).
\end{equation}

This integral is approximated by the composite trapezoidal rule. The parameters that are needed in the calculation are listed in the following table.

### 4.2.2 Coagulation modeling of PMN TC aggregation

In this section, our population balance model is applied to investigate the heterotypic cell aggregation in the near wall region of the parallel plate flow chamber.

We propose a specialized population balance model to describe the number of particles adhered to the chamber substrate. In order to simplify the problem, we make some assumptions. First, we assume that there is no aggregation event in the free stream near
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho_m$</td>
<td>fluid density</td>
<td>$1000 \text{ kg/m}^3$</td>
</tr>
<tr>
<td>$\rho_t$</td>
<td>tumor cell density</td>
<td>$1087 \text{ kg/m}^3$</td>
</tr>
<tr>
<td>$r_p$</td>
<td>PMN cell radius</td>
<td>$4.0 \times 10^{-6} \text{ m}$</td>
</tr>
<tr>
<td>$r_t$</td>
<td>tumor cell radius</td>
<td>$8.0 \times 10^{-6} \text{ m}$</td>
</tr>
<tr>
<td>$g$</td>
<td>gravity</td>
<td>$9.8 \text{ m/s}^2$</td>
</tr>
</tbody>
</table>

**Table 4.7.** Parameter values for computing the collision rate

the wall. Thus, there are only two types of cells in the near wall region, that is, PMN and tumor monomers. Hence, the aggregation only takes place between the cells in the near wall region and the tethered particles on the substrate. Second, we assume that the concentrations of PMNs and tumor cells are constants independent of time in the near wall region and will be calculated by CFD simulation.

Let $N(i,j,t)$ be the population of the particles composed of $i$ tumors and $j$ PMNs adhered on the substrate. According to the derivation of the spatially homogenous population balance equation, $N(i,j,t)$, the population of the particles on the substrate, can increase

- by aggregation of the tethered particle composed of $i - 1$ tumors, $j$ PMNs, and tumor monomer in the near wall region.
- by aggregation of the tethered particle composed of $i$ tumors, $j - 1$ PMNs, and PMN monomer in the near wall region.

It can decrease

- by aggregation with a PMN monomer in the near wall region.
- by aggregation with a tumor monomer in the near wall region.

Let us define $\beta(i,j;i',j')$ as the aggregation kernel between the particles. One is composed of $i$ tumors, $j$ PMNs, and the other one is composed of $i'$ tumors, $j'$ PMNs. Thus, the population balance model for simulating the aggregation in the near wall region is given by

$$
\frac{\partial N(i,j,t)}{\partial t} = \beta(i - 1,j;1,0)N(i - 1,j,t)C_T + \beta(i,j - 1;0,1)N(i,j - 1,t)C_P - \beta(i,j;1,0)N(i,j,t)C_T - \beta(i,j;0,1)C_P,
$$
\[
\frac{\partial N(i, j, t)}{\partial t} = -\beta(0, 1; 1, 0)N(0, 1, t)C_T - \beta(0, 1; 0, 1)N(0, 1, t)C_P + T_f,
\]

where \( T_f \) is the PMN tethering frequency, which measures the number of tethered PMNs per unit time. \( C_T \) and \( C_P \) are the concentrations of tumor and PMN in the near wall region respectively, which is calculated by CFD. We now discuss the computation of these parameters.

By investigating the experimental results, we find that there are only PMN-tumor doublets and PMN monomers tethered on the substrate. Some big particles which are composed of more than one PMN and tumor cells, such as the triplets, are very rare. Thus, there are only four types of particles that we need to take into account. They are the concentrations of PMN \( (C_P) \) and tumor cells \( (C_T) \) in the near wall region, and the populations of PMN-Tumor doublets \( (N_{PT}) \) and PMN monomers \( N_p \) tethered on the substrate. This motivates us to simplify the PB model further. We only need to consider the time change rate of \( N_{PT} \) and \( N_p \). In order to simplify the notation, we change some parameter labels. To be consistent with equations (4.45) and (4.46), for example, \( N_{PT} \) and \( N_p \) are just \( N(1, 1, t) \) and \( N(0, 1, t) \), respectively. The simplified model is as follows:

\[
\frac{\partial N_{PT}}{\partial t} = \beta_{PT} N_P C_T,
\]
\[
\frac{\partial N_p}{\partial t} = -\beta_{PT} N_P C_T + T_f,
\]

where \( \beta_{PT} \) is the aggregation kernel between the tethered PMNs on the substrate and tumor cells in the near wall region which is just \( \beta(0, 1; 1, 0) \) in equation (4.46). Notice that these two equations can be solved analytically as follows:

\[
N_{PT} = -\frac{\beta_{PT} C_T N_P^0 - T_f}{\beta_{PT} C_T} e^{-\beta_{PT} C_T t} + T_f t + N_{PT}^0 + \frac{\beta_{PT} C_T N_P^0 - T_f}{\beta_{PT} C_T},
\]
\[
N_p = \frac{T_f}{\beta_{PT} C_T} + \left( N_P^0 - \frac{T_f}{\beta_{PT} C_T} \right) e^{-\beta_{PT} C_T t},
\]

where \( N_P^0 \) and \( N_{PT}^0 \) are the initial populations of tethered PMNs and PMN-tumor doublets on the substrate, respectively, which will be given as the initial conditions of the model.

Therefore, in this simplified model, we only need to compute the parameters \( C_p, C_T, \beta_{PT}, \) and \( T_f \). Notice that \( C_p \) and \( C_T \) can be computed through CFD simulation, we only dis-
cuss how to estimate the two parameters $T_f$ and $\beta_{TP}$ in the present section.

As was indicated, the determination of the PMN deformation is complicated. However, we can use the population balance model to solve this problem. We ran $3 \times 3$ experiments for shear rate $\gamma = 62.5, 100, 200$ and viscosity $\mu = 1.0cp, 2.0cp, 3.2cp$. In these experiments, we recorded all the data such as: the tethering frequency, the adhesion efficiency, the initial population of PMNs, and the number of aggregates at five minutes, and etc. Hence, we are able to substituting these experimental data in the PB model and solve an inverse problem to determine the function $f$.

For example, in order to determine the height of deformed PMN for a given viscosity and shear rate, we can vary height from 0 to $2r_p$ with a small step size and compute the corresponding collision rate. Then we can use the initial data, the tethering frequency, the adhesion efficiency, into the PB model, to compute the number of aggregates, $N_{PT}$. Then, we can determine which height gives us the correct $N_{PT}$ by comparing with the experimental data.

Figure 4.7 and Table 4.8 give us the basic information of how the height depends on the shear rate and viscosity.

![Graph](image1)

**Figure 4.7.** The height of the deformed PMN for varying shear rate and viscosity. For a) $\mu = 1.0cp$ (blue), $\mu = 2.0cp$ (red), $\mu = 3.2cp$ (green) and b) $\gamma = 62.5/s$ (blue), $\gamma = 100/s$ (red), $\gamma = 200/s$ (green).

By observing the shape of the height curves in Figure 4.7, we want to fit the height function $f(\gamma_w, \mu)$ as a decreasing function of $\gamma_w$ with the form

$$H = f(\gamma_w, \mu) = g_1(\mu)e^{-\gamma_w g_2(\mu)},$$

(4.51)
where $g_1(\mu)$ and $g_2(\mu)$ will be fitted using the data in Table 4.8.

Upon fitting the data, we have

$$g_1(\mu) = e^{a\mu^2 + b\mu + c}, \quad g_2(\mu) = d\mu + e,$$

(4.52)

where

$$a = -1.8514e + 005, \quad b = 591.9292, \quad c = -11.8626, \quad d = -0.3039, \quad e = 0.0064.$$  

(4.53)

Thus, we get the function $H = f(\gamma_w, \mu)$ that we proposed in equation (4.35).

### 4.2.3 Aggregation prediction and model validation

By the discussion as above, the parameters we obtain from CFD simulations are $C_T, C_P$.

The tethering frequency, $T_f$, is computed from equation (4.26) and the collision rate $\hat{\beta}_{PT}$ is computed by equation (4.27). The flow chart of the PB model is as follows:

- compute $\epsilon_{PT}$ by equation (4.28)
- compute $\beta_{PT}$ by equation (4.27)
- compute $\hat{\beta}_{PT}$ by equation (4.44)
- CFD
- compute $C_T, C_P$
- compute $T_f$ by equation (4.26)
- compute $N_{PT}$ and $N_P$ by equation (4.49) and (4.50).

Since we can use the PB model to predict the number of the tethered PMN tumor

<table>
<thead>
<tr>
<th>H</th>
<th>$\mu = 1\text{cp}$</th>
<th>$\mu = 2\text{cp}$</th>
<th>$\mu = 3.2\text{cp}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>62.5/s</td>
<td>$7.6 \times 10^{-6}m$</td>
<td>$7.9 \times 10^{-6}m$</td>
<td>$6.3 \times 10^{-6}m$</td>
</tr>
<tr>
<td>100/s</td>
<td>$5.4 \times 10^{-6}m$</td>
<td>$5.9 \times 10^{-6}m$</td>
<td>$3.0 \times 10^{-6}m$</td>
</tr>
<tr>
<td>200/s</td>
<td>$3.2 \times 10^{-6}m$</td>
<td>$3.5 \times 10^{-6}m$</td>
<td>$2.6 \times 10^{-6}m$</td>
</tr>
</tbody>
</table>

Table 4.8. The height of deformed PMN for varying shear rate and viscosity by PB model
doublets, \( N_{PT} \), on the substrate, for a fixed viscosity, we will see how the shear rate changes the number of aggregate.

Here we define the aggregation percentage as the aggregation number (i.e., the number of PMN tumor doublets) divided by the total adhered PMNs during the experiments. From Figure 4.8, we can see that the aggregation percentage goes up when we increase the shear rate, but falls down when the shear rate is large enough. This phenomenon is consistent with our observation from the experiments.

![Figure 4.8](image)

**Figure 4.8.** The aggregation percentage as a function of \( \gamma_w \) for fixed viscosity \( \mu = 1cp \)

### 4.3 Model improvement

Notice that in our current model, the adhesion efficiency and the tethering frequency are both fitted from the experimental data. We can improve the model accuracy further if these two parameters can be estimated by a mathematical model.

**Adhesion efficiency** The adhesion efficiency is the probability that two colliding cells will stick to each other by forming the receptor-ligand bonds which can overcome the hydrodynamic force acting to separate this doublet.

Thus, a possible way to improve the accuracy is to develop a model to estimate the total number of bonds formed by the receptors and ligands of PMN and tumor cells. A model was constructed in [98, 99]. The master equation is given by:

\[
\frac{dp_n}{dt} = A_c m_r m_l k_f^p p_{n-1} - (A_c m_r m_l k_f^{n+1} + n k_r^n) p_n + (n + 1) k_r^{n+1} p_{n+1},
\] (4.54)
where, \( p_n \) is the probability of having \( n \) bonds at time \( t \), and \( m_r \) and \( m_l \) are the respective number densities of receptors and ligands, respectively. \( A_c \) is the contact area, and the forward rate coefficient per unit density is \( k_f \).

Thus, by solving the steady state of this ordinary differential equation, we can calculate how many bonds are formed after the collision occurs, and determine if the number of bonds are enough to keep the doublet, hence to estimate the adhesion efficiency.

For example, we assume the steady state solution of equation (4.54) is \( p_n^* \). The critical bound number is \( n^* \), which means the doublet can be kept if the bound number \( n \geq n^* \). Therefore, the adhesion efficiency, \( \varepsilon_{PT} \), can be estimated by

\[
\varepsilon_{PT} = \sum_{n \geq n^*} p_n^* .
\]

(4.55)

**Tethering frequency**  The tethering frequency, \( T_f \), can be modeled analogously as the adhesion efficiency since it is just the aggregation of PMN and endothelium. It can be also divided into two parts: the collision of PMN to the substrate, and the adhesion of PMN and endothelium. The adhesion can be determined by equation (4.54) also. We only focus on the collision of PMN and the substrate.

As was mentioned in the previous section, the cell trajectory in the parallel plate flow chamber is determined by the settling velocity, \( v_s \), and convection velocity, \( v_c \), where \( v_s \) is given by

\[
v_s = \frac{v_s^0}{1 + r_t/(h - r_t)} ,
\]

(4.56)

and \( v_s^0 \) is the free settling velocity given by the Stokes’ equation as follows:

\[
v_s^0 = \frac{2}{9} (\rho_t - \rho_m) g r_t^2 \mu .
\]

(4.57)

Only the settling velocity will contribute to the collision of the PMNs and the substrate. Hence, the collision rate, \( \xi_p \), is approximated by

\[
\xi_p = v_s S ,
\]

(4.58)

where \( S \) is the total area of the view field.

Overall, the tethering frequency, \( T_f \), will be the product of the adhesion efficiency, \( \varepsilon_p \), and the collision rate, \( \xi_p \):

\[
T_f = \varepsilon_p v_s S .
\]

(4.59)
Collision rate  For the calculation of the collision rate, $\hat{\beta}_{PT}$, we make two simple assumptions. The first assumption is that we assume the deformed PMN has an arc-shape, and the other assumption is that the fluid condition is not changed. For the shape of the deformed cell, previous numerical studies of cell deformation in shear flow have been conducted in [6, 16, 17, 18]. For example, in [16, 17], the three-dimensional (3D) numerical simulation of leukocyte adhesion in a parallel-plate flow chamber was carried out by their incompressible CFD code in which the volume-of-fluid (VOF) method was used for tracking leukocyte shapes over time. We will couple results from such studies with our numerical computation of the collision rate. We also need to take into account the change of fluid velocity profiles around the deformed PMNs in our PB model.

4.4 Discussion and conclusion

By using a spatially homogeneous population balance model, we can simulate the cell aggregation in the near wall region and predict the adhered PMN-TC doublets on the substrate. In order to determine the parameters of the PB model such as: the adhesion efficiency, the tethering frequency, and the local cell concentration in the near wall region. We analyzed the interaction of PMN with the substrate, PMN-TC collision/adhesion and we proposed appropriate models. Our model is more detailed than those found in the literature since both the local cell-cell interactions and the cell behavior with large populations are both taken into account.
Spatially inhomogeneous coagulation equation

The spatially homogeneous Smoluchowski equation describes the change of the rate of the particle concentration in time. However, the homogeneous equation assumes that the particles are uniformly distributed in space, so the concentration function $N(s, t)$ is only a function of size $s$ and time $t$. Actually, the modeling of the particle distribution in space is an important issue, for example, the modeling of particle coagulation in nonuniform shear flow, where the particles are not uniformly distributed. Our spatially homogeneous models in Chapter 4 are limited since we assume the cells are uniformly distributed in the flow chamber. Due to the nonlinear flow profile, actually the cells are not uniformly distributed, therefore we will get more accurate model by developing spatially inhomogeneous coagulation equation to model this problem.

In [31] and [1], the authors derived the inhomogeneous Smoluchowski equation and developed a numerical solution. However, the derivation shows that there is still an extra term comparing with the desired inhomogeneous equation, although they argued this extra term is small enough. Furthermore, they assumed that the coagulation kernel has the form $\beta(u, v)$, which is only a function of two variables $u$ and $v$, the sizes of those two collision particles. However, for a coagulation event in the velocity field $V$, we will show that the coagulation kernel not only depends on the particle size, but also depends on the position and time.

In this chapter, we will derive the spatially inhomogeneous coagulation equation by the conservation law formulation for coupled system.
5.1 Overview of Lagrangian model

As was mentioned above, Sabelfeld [31] derived the spatially inhomogeneous coagulation equation by Lagrange model. We give a brief description of their model in this section.

First, let us recall the stochastic differential equation:

\[ dX_t = V(t, X_t)dt + \sqrt{2\sigma}dW_t, \quad (5.1) \]

with initial condition

\[ X_0 = x_0, \]

which governs the particle random motion in the fluid. We denote \( P(x, t, x_0) \) as the transition function of the process \( X_t \), which is the probability that the particle is transported from initial position \( x_0 \) to \( x \) at time \( t \).

In this inhomogeneous coagulation system, we assume the initial particle concentration is \( N_0(x, s) \) which represents the distribution of particles with size \( s \) at position \( x \). Consider a sufficiently small region located at \( x \). We assume the particle distribution is homogeneous in this small region and the coagulation is independent in this region such that the particles located outside of this region will not affect the coagulation. Hence, the coagulation in this region can be described by the homogenous coagulation equation as follows:

\[
\frac{\partial N(s, t; x)}{\partial t} = \frac{1}{2} \left[ \int_0^s \beta(s - s', s') N(s', t; x) N(s', t; x) ds' - \int_0^\infty \beta(s, s') N(s, t; x) N(s', t; x) ds' \right],
\]

(5.2)

with initial condition

\[ N_0(s) = N_0(x, s). \]

Thus, the inhomogeneous function \( N(x, s, t) \) can be evaluated as

\[ N(x, s, t) = \int_{R^3} P(x, t, x') N(s, t; x') dx'. \quad (5.3) \]

Sabelfeld showed that the function \( N(x, s, t) \) satisfies
\[ \frac{\partial N(x, s, t)}{\partial t} + V(t, x) \cdot \nabla x N(x, s, t) - \sigma \Delta x N(x, s, t) = \frac{1}{2} \int_0^s \beta(s - s', s') N(x, s - s', t) N(x, s', t) ds' - \int_0^\infty \beta(s, s') N(x, s, t) N(x, s', t) ds' + \alpha(t, x), \]  

(5.4)

where the extra term \( \alpha(t, x) \) is

\[ \alpha(t, x) = K(N(x, s, t)) - \int_{R^3} K(N(s, t; x')) P(x, t; x') dx', \]  

(5.5)

where \( K \) is the coagulation operator, the right-hand side of the homogeneous coagulation equation.

However, in the development of Lagrangian model, it is assumed that the coagulation kernel \( \beta(s, s') \) is given in advance and is independent of the space. The coagulation is self-consistent and is independent of the particle motion and fluid condition. In the next section, we use a deterministic formulation by conservation law for a coupled system which involves both particle motion and coagulation.

### 5.2 Deterministic model by conservation law

In Section 3.4, we introduced a method to transform the stochastic model to a deterministic model and derived the PDF by the conservation law. Actually, this method also holds for a coupled system in which two stochastic processes are coupled together. For example, consider a coupled system:

\[ X_t = \left( \begin{array}{c} X^1_t \\ X^2_t \end{array} \right), \]  

(5.6)

where both \( X^1_t \) and \( X^2_t \) are stochastic processes. Assume the transition probability is given by \( p(x'_1, x'_2, t'; x_1, x_2, t) \) and the density function is \( f(x_1, x_2, t) \).

In general, the conservation law is written as:

\[ \frac{d}{dt} \int_{\Omega_1 \times \Omega_2} f(x_1, x_2, t) dx_1 dx_2 = F(\Omega_1 \times \Omega_2, t), \]  

(5.7)
where the flux $F(\Omega \times \Omega, t)$ is defined as:

$$F(\Omega \times \Omega, t) = \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega \times \Omega} \int_{\mathbb{R}^n \times \mathbb{R}^n} p(x'_1, x'_2, t'; x_1, x_2, t)f(x'_1, x'_2, t') dx'_1 dx'_2 dx_1 dx_2 \right) - p(x_1, x_2, t'; x'_1, x'_2, t)f(x_1, x_2, t) dx_1 dx_2 \right) \) . (5.8)

Modifying the flux $F(\Omega \times \Omega, t)$ further, we have the following theorem.

**Theorem 16.** The net flux $F(\Omega \times \Omega, t)$ can be modified by

$$F(\Omega \times \Omega, t) = \int_{\Omega_2} F_1(\Omega_1, x_2, t) dx_2 + \int_{\Omega_1} F_2(\Omega_2, x_1, t) dx_1 \) , (5.9)

where the flux $F_1(\Omega_1, x_2, t)$ and $F_2(\Omega_2, x_1, t)$ are constructed by the marginal distribution density functions $p_{x_1}$ and $p_{x_2}$ respectively:

$$F_1(\Omega_1, x_2, t) = \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega_1 \times \mathbb{R}^n} (p_{x_2}(x'_1, t'; x_1, t)f(x'_1, x_2, t) dx'_1 dx_2 \right) - p_{x_2}(x_1, t'; x'_1, t)f(x_1, x_2, t) dx_1 dx_2 \right) , (5.10)

$$F_2(\Omega_2, x_1, t) = \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega_2 \times \mathbb{R}^n} (p_{x_1}(x'_2, t'; x_2, t)f(x'_2, x_1, t) dx'_2 dx_1 \right) - p_{x_1}(x_2, t'; x'_2, t)f(x_2, x_1, t) dx_2 dx_1 \right) , (5.11)

The marginal distribution density functions $p_{x_1}$ and $p_{x_2}$ are given by

$$p_{x_1}(x'_2, t'; x_2, t) = \int_{\mathbb{R}^n} p(x_1, x'_2, t'; x'_1, x_2, t) dx'_1 \) , (5.12)

$$p_{x_1}(x'_2, t'; x_2, t) = \int_{\mathbb{R}^n} p(x_1, x'_2, t'; x'_1, x_2, t) dx'_1 \) , (5.13)

$$p_{x_2}(x'_1, t'; x_1, t) = \int_{\mathbb{R}^n} p(x'_1, x_2, t'; x'_1, x_2, t) dx'_2 \) , (5.14)

$$p_{x_2}(x_1, t'; x'_2, t) = \int_{\mathbb{R}^n} p(x_1, x_2, t'; x'_1, x_2, t) dx'_2 \) . (5.15)

**Proof.** By adding and subtracting one term to equation (5.8), we have

$$F(\Omega \times \Omega, t) = \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega \times \Omega} \int_{\mathbb{R}^n \times \mathbb{R}^n} p(x'_1, x'_2, t'; x_1, x_2, t)f(x'_1, x'_2, t') dx'_1 dx'_2 dx_1 dx_2 \right) - p(x'_1, x_2, t'; x_1, x_2, t)f(x'_1, x_2, t') dx_1 dx_2 \right) + p(x'_1, x_2, t'; x_1, x_2, t)f(x'_1, x_2, t') dx_1 dx_2 \right) - p(x_1, x_2, t'; x'_1, x_2, t)f(x_1, x_2, t') dx_1 dx_2 \right) . (5.8)$$
\[
\begin{align*}
&= \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega_1} \int_{\Omega_2 \times R^n \times R^n} p(x_1', x_2', t'; x_1, x_2, t) f(x_1', x_2', t') dx_1 dx_2 dx_1' \right. \\
&\quad \left. - p(x_1', x_2, t'; x_1, x_2', t) f(x_1', x_2, t') dx_1 dx_2 dx_2' \right) \\
&+ \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega_2} \int_{\Omega_1 \times R^n \times R^n} p(x_1', x_2, t'; x_1, x_2', t) f(x_1', x_2, t') dx_1 dx_2 dx_1' \right. \\
&\quad \left. - p(x_1, x_2, t'; x_1', x_2', t) f(x_1, x_2, t') dx_1 dx_2 dx_2' \right) \\
&+ \lim_{\Delta t \to 0} \left( \frac{1}{\Delta t} \int_{\Omega_1} \int_{\Omega_2 \times R^n \times R^n} p(x_1', x_2, t') f(x_1', x_2, t') dx_1 dx_2 dx_1' \right. \\
&\quad \left. - p(x_1, x_2, t') f(x_1, x_2, t') dx_1 dx_2 dx_2' \right) \\
&\quad \text{By changing the the order of integration and the variables } x_1 \text{ and } x_1', \text{ one can check easily that} \\
&F(\Omega_1 \times \Omega_2, t) = \int_{\Omega_2} F_1(\Omega_1, x_2, t) dx_2 + \int_{\Omega_1} F_2(\Omega_2, x_1, t) dx_1.
\end{align*}
\]

If the physical quantity in an arbitrary region can be only changed through the boundary, then the following conservation law holds:

\[
f_t + \nabla_x \cdot F(x_1, x_2, t) = 0,
\]

where the flux vector \( F(x_1, x_2, t) \) is given by

\[
F(x_1, x_2, t) = \begin{pmatrix} F_1(x_1, t) \\ F_2(x_2, t) \end{pmatrix}, \quad (5.16)
\]

and the fluxes \( F_1(x_1, t) \) and \( F_2(x_2, t) \) are given by:

\[
F_1(x_1, x_2, t) = \lim_{\Delta t \to 0} \int_{R^n \times R^n} \frac{(x_1 - x_1')}{\Delta t} p(x_1', x_2', t'; x_1, x_2, t) f(x_1', x_2', t') dx_1' dx_2', \quad (5.17)
\]

\[
F_2(x_1, x_2, t) = \lim_{\Delta t \to 0} \int_{R^n \times R^n} \frac{(x_2 - x_2')}{\Delta t} p(x_1', x_2', t'; x_1, x_2, t) f(x_1', x_2', t') dx_1' dx_2'. \quad (5.18)
\]

Now, we discuss how to use these results to derive the spatially inhomogeneous coagulation equation.

**Inhomogeneous coagulation equation** Consider the coupled system for the inhomogeneous coagulation process:

\[
Y = \begin{pmatrix} X_t \\ S_t \end{pmatrix}, \quad (5.19)
\]
where $S_t$ represents a stochastic coagulation process, and $X_t$ satisfies a Fokker-Planck dynamical system:

$$dX_t = V(t, X)dt + \sqrt{2}\sigma dW_t.$$ 

In this coupled system, we assume the particle motion is independent of the coagulation process. The coagulation kernel is $\beta(s, s'; x, t)$, which may depend on the space and time. The joint transition probability is given by:

$$p(x', s', t'; x, s, t) = p_1(x', t'; x, t)p_2(s', t'; s, t|x'),$$

where $p_1(x', t'; x, t)$ represents the particle transition probability in space, which satisfies the Fokker-Planck equation, and $p_2(s', t'; s, t|x')$ represents the coagulation probability from $s'$ to $s$ at position $x'$, and is given by

$$p_2(s', t'; s, t|x') = \begin{cases} \frac{1}{s-s'}\beta(s-s', s'; x', t')f(x', s-s', t')\Delta t, & s' < s, \\ 1 - \Delta t \int_0^\infty \frac{1}{s'}\beta(s', \hat{s}; x', t')f(x', \hat{s}, t')d\hat{s}, & s' = s, \\ 0, & s' > s. \end{cases}$$

Notice that $\int_{R^n} p_1(x', t'; x, t)dx = 1$, and $\int_0^\infty p_2(s', t'; s, t|x')ds = 1$. Thus, the marginal distribution density functions are as follows:

$$p_s(x', t'; x, t) = p_1(x', t'; x, t),$$

$$p_s(x, t'; x', t) = p_1(x, t'; x', t),$$

$$p_x(s', t'; s, t) = p_2(s', t'; s, t|x),$$

$$p_x(s, t'; s', t) = p_2(s, t'; s', t|x).$$

Therefore, we can write the flux for space transform $x$ and coagulation $s$ independently since the marginal distributions are just their own transition probabilities. For arbitrary $\Omega_1 \in R^n$ and any numbers $a, b$, let $\Omega_2 = (a, b)$. Then, the fluxes $F_1(\Omega_1, s, t)$ and $F_2(\Omega_2, x, t)$ can be written as the fluxes for the homogeneous case for fixed $s$ and $x$ respectively (refer to Section 3.4):

$$F_1(\Omega_1, s, t) = -\int_{\Omega_1} \nabla \cdot (V f(x, s, t) - \sigma \nabla_x f(x, s, t)) dx,$$

$$F_2(\Omega_2, x, t) = \int_a^b \partial_s \int_0^{s'} \beta(s', \hat{s}; x, t) \frac{f(x, s', t)f(x, \hat{s}, t)}{s'} d\hat{s}ds'.$$
Substitute these two equations into (5.7) and (5.9), and replace \( f(x, s, t) \) by \( sN(x, s, t) \). Then, we get the spatially inhomogeneous coagulation equation:

\[
\frac{\partial N(x, s, t)}{\partial t} = \frac{1}{2} \int_{0}^{s} \beta(s - s', s'; x, t)N(x, s - s', t)N(x, s', t)ds' \\
- \int_{0}^{\infty} \beta(s, s'; x, t)N(x, s', t)N(x, s, t)ds' \\
- \nabla \cdot (VN) + \sigma \triangle x N .
\] (5.28)

### 5.3 A self-consistent formulation by conservation law

For spatially homogeneous coagulation equation, the coagulation kernel can be derived for some special cases, for example, the uniform shear flow and Brownian motion. In the derivations of spatially inhomogeneous coagulation equations in Section 5.1 and 5.2, it is assumed that the kernel is given in advance, which means the coagulation is a self-consistent process and may be independent of the fluid flow. Physically speaking, the coagulation is induced by the particle random motion and collision due to the nonuniform distributions of the fluid velocities. Thus, the coagulation should depend on the background fluid flow. In this section, we will derive a self-consistent spatially inhomogeneous coagulation equation, in which case, the motion transition probability function \( p(x', t'; x, t) \) is given and it determines both the particle motion and coagulation of the system.

First, we make some simple assumptions. We assume the coagulation has no feedback to the background fluid. We also assume the particle motion is independent of the coagulation events. Without lose of generality, we also assume that the adhesion efficiency is 1, which means the particles will stick to each other when the collision occurs. Thus, the collision kernel is just the coagulation kernel.

**Joint transition probability** Let us still consider the coupled dynamical systems:

\[
Y = \begin{pmatrix} X_t \\ S_t \end{pmatrix} , \tag{5.29}
\]

where \( X_t \) represents the particle motion dynamical system, which is determined by the motion transition probability \( p(x', t'; x, t) \), and \( S_t \) represents a coagulation dynamical system. Because the particle motion is governed by \( p(x', t'; x, t) \), the nonuniform distribution and motion of the particles will lead to the collision, hence coagulation. So the
transition probability $p(x', t'; x, t)$ is the starting point of our coupled system.

Let $p(x', s', t'; x, s, t)$ represent the joint transition probability function, where we consider $s > s'$. It is the probability that a particle of size $s'$ located at $x'$ at instant time $t'$ will grow into a new particle of size $s$ and move to $x$ at time $t$. We will use $p(x', t'; x, t)$ to derive a complete form for this joint transition probability function. When the particle state is changed to $(x, s, t)$ from old state $(x', s', t')$, two events take place here. The first thing is the particle of size $s'$ is transported to $x$ from $x'$ with probability $p(x', t'; x, t)$, the second event is some other particle of size $s - s'$ is transported to $\hat{x}$ from $\tilde{x}$ with probability $p(\tilde{x}, t'; \hat{x}, t)$ to collide with the target particle. Where we set $\hat{x} \in \Omega$, and $\Omega$ is the collision region. We claim that the collision/coagulation occurs if $\hat{x} \in \Omega$. For example, if these two particles are rigid spherical particles with radius $r_1$ and $r_2$, then $\Omega$ is just the ball $B(x, r_1 + r_2)$, with center $x$ and radius $r_1 + r_2$.

Therefore, the joint transition probability function is written as

$$p(x', s', t'; x, s, t) = p(x', t'; x, t) \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} p(\tilde{x}, t'; \hat{x}, t) N(\tilde{x}, s - s', t') d\tilde{x} d\hat{x} ,$$

where $N(\tilde{x}, s - s', t')$ is the particle concentration, which satisfies the self-consistent spatially inhomogeneous coagulation equation that we will derive later on.

Denote $p_x = p(x', t'; x, t)$ and

$$p_s = \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} p(\tilde{x}, t'; \hat{x}, t) N(\tilde{x}, s - s', t') d\tilde{x} d\hat{x} .$$

Notice that in equation (5.31), we can also add an extra term $\epsilon$ in this double integral to represent the adhesion probability. In the present section, we just assume $\epsilon = 1$.

One can check the definition of the incoming flux in equation (3.83), we have the particle incoming flux and it is related to $p_s$ by the following equation:

$$p_s = F^+_{\Omega}(s', s - s'; x, t) \Delta t + O(\Delta t^2) .$$

If we get rid of the high order term of $\Delta t$, we can rewrite the joint transition probability distribution function for $s' < s$ as

$$p(x', s', t'; x, s, t) = p(x', t'; x, t) F^+_{\Omega}(s', s - s'; x, t) \Delta t ,$$
where

\[ F_\Omega^+(s', s - s'; x, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\Omega} \int_{\mathbb{R}^n \setminus \Omega} p(\tilde{x}, t'; \hat{x}, t) N(\tilde{x}, s - s', t') d\tilde{x} d\hat{x}. \]

If the transition function \( p(\tilde{x}, t'; \hat{x}, t) \) satisfies the Fokker-Planck equation, which means the particle flux is exchanged through the boundary of \( \Omega \), thus the incoming flux can be written as

\[ F_\Omega^+(s', s - s'; x, t) = \int_{\partial\Omega^+} (\sigma \nabla_x N - V \cdot nN) d\omega, \tag{5.34} \]

where \( \partial\Omega^+ \) is the collision region boundary restricted to \( \sigma \nabla_x N - V \cdot nN \geq 0 \), where we set \( N = N(y, s - s', t) \) for \( y \in \partial\Omega \), and \( \sigma \) is the diffusion constant, \( V \) is the velocity field, and \( n \) is the outward normal.

Therefore, if we ignore the high order term of \( \Delta t \), the coagulation transition probability function \( p_s \) for \( s' < s \) is given by

\[ p_s = \Delta t \int_{\partial\Omega^+} (\sigma \nabla_x N - V \cdot nN) d\omega. \tag{5.35} \]

Notice that, in general, we can not write an explicit formula for the coagulation kernel. In Section 5.2, we are given the kernel in advance. In that case, it is assumed that there exists a kernel \( \beta \) such that the particle incoming flux can be written as

\[ F_\Omega^+(s', s - s'; x, t) = \int_{\partial\Omega^+} (\sigma \nabla_x N - V \cdot nN) d\omega = \beta(s, s - s'; x, t) N(x, s - s', t), \tag{5.36} \]

but it is not obvious for general case.

**Framework of inhomogeneous coagulation equation**  Given a motion transition probability function \( p(x', t'; x, t) \), we have already got the joint transition probability function \( p(x', s', t'; x, s, t) \) in equation (5.33). Without loss of generality, we assume \( p(x', t'; x, t) \) is a transition function such that it carries the particles continuously and exchange the particle flux through the boundary. Hence we can define the boundary flux

\[ F_1(x, s, t) = \lim_{\Delta t \to 0} \int_{\mathbb{R}^n} p(x', t'; x, t) \frac{x - x'}{\Delta t} f(x', s, t') dx', \tag{5.37} \]

where \( f(x, s, t) = s N(x, s, t) \).

Similar to the derivation in Section 5.2, one can check the marginal distribution of the joint transition probability \( p(x', s', t'; x, s, t) \). Then, by Theorem 5.9, one can write
the coagulation flux as follows:

$$F_2(x, s, t) = \int_0^s \int_{\tilde{s}}^\infty F^+(\tilde{s}', \tilde{s} - \tilde{s}'; x, t) f(x, s', t) d\tilde{s} ds' ,$$

where the incoming flux $F^+_\Omega (s', \tilde{s} - s'; x, t)$ is given by

$$F^+_\Omega (s', \tilde{s} - s'; x, t) = \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int_{\tilde{s}}^\infty \int_{x \setminus \Omega} p(\tilde{x}, t'; \hat{x}, t) N(\tilde{x}, \tilde{s} - s', t') d\tilde{x} d\hat{x} ,$$

and $\Omega$ is the collision region at $x$ for particles of size $s'$ and $\tilde{s} - s'$.

Thus, by the conservation law, we have the self-consistent spatially inhomogeneous coagulation:

$$f_t + \nabla_x \cdot F_1(x, s, t) + \partial_s F_2(x, s, t) = 0 .$$

One can check this formulation is consistent with the special cases if the transition probability function $p(x', t'; x, t)$ satisfies the transport equation and Fokker-Planck equation respectively. In the following, the equations are derived by Chapman-Kolmogorov equation. The reader can check we will get the same results by the conservation law formulations. Before we derive the equations for these two special cases, let us check the consistency of the spatially inhomogeneous coagulation equation with the homogeneous equation.

### Coagulation convection model without diffusion

Consider the particle coagulation process where the particle is only transported by velocity field $V(x, t)$. We know that the motion transition probability $p_x$ is a $\delta$ function:

$$p_x = \delta(x - x' - V(x, t) \Delta t) ,$$

and we get the coagulation transition probability function by equation (5.35):

$$p_s = \begin{cases} J_1(s', s - s'; x, t) \Delta t & \text{if } s' < s \\ 1 - \Delta t \int_0^\infty J_2(s, \tilde{s}; x, t)(\tilde{s}) d\tilde{s} , & \text{if } s' = s \\ 0 & \text{if } s' > s . \end{cases}$$

We set

$$J_1(s', s - s'; x, t) = - \int_{\partial \Omega^+_t} V \cdot n N(y, s - s', t) d\omega ,$$

and
\[ J_2(s, \hat{s}; x, t) = - \int_{\partial \Omega_2^+} V \cdot n N(y, \hat{s}, t) d\omega. \]

Where \( \partial \Omega_1^+ \) is the incoming flux boundary of the collision region for the collision of particles with size \( s' \) and \( s - s' \) at \( x \), and \( \partial \Omega_2^+ \) is the incoming flux boundary of the collision region for the collision of particles with size \( s \) and \( \hat{s} \) at \( x \).

We have the transition probability function by equation:

\[ p(x', s', t'; x, s, t) = p_x p_s. \quad (5.43) \]

Let the density function of this coupled system be \( f(x, s, t) \), where \( f(x, s, t) = s N(x, s, t) \). By the Chapman-Kolmogorov equation, we have

\[ f(x, s, t) = \int \int p(x', s', t'; x, s, t) f(x', s', t') dx' ds'. \quad (5.44) \]

Plug the joint transition probability function in equation (5.44), so we can get

\[ f(x, s, t) = \Delta t \int_0^s \int_{R^3} p_x J_1(s', s - s'; x, t) f(x', s', t') dx' ds' \]
\[ + \int_{R^3} p_x \left( 1 - \Delta t \int_0^\infty J_2(s, \hat{s}; x, t) d\hat{s} \right) f(x', s, t') dx' \]
\[ = \Delta t \int_0^s J_1(s', s - s'; x, t) f(x - V \Delta t, s', t') ds' \]
\[ + \left( 1 - \Delta t \int_0^\infty J_2(s, \hat{s}; x, t) d\hat{s} \right) f(x - V \Delta t, s, t'). \quad (5.45) \]

By Taylor’s expansion, we have

\[ f(x - V \Delta t, s', t') = f(x, s', t') - V \Delta t \cdot \nabla_x f(x, s', t') + O(\Delta t^2) \quad (5.46) \]
\[ f(x - V \Delta t, s, t') = f(x, s, t') - V \Delta t \cdot \nabla_x f(x, s, t') + O(\Delta t^2) \quad (5.47) \]

Plug these two equations in equation (5.45), thus we get

\[ f(x, s, t) = \Delta t \int_0^s J_1(s', s - s'; x, t) f(x, s', t') ds' \]
\[ - \Delta t \int_0^\infty J_2(s, s'; x, t) f(x, s', t') ds' \]
\[ + f(x, s, t') - V \Delta t \cdot \nabla_x f(x, s, t') + O(\Delta t^2). \quad (5.48) \]
Divided by \( \Delta t \) both sides and take the limit when \( \Delta t \) approaches 0, we have

\[
\frac{f_t + V(t, x) \cdot \nabla_x f(x, s, t)}{\Delta t} = \int_0^s J_1(s', s - s'; x, t) f(x, s', t) ds' \\
- \int_0^\infty J_2(s, s'; x, t) f(x, s, t) ds'.
\]

(5.49)

Replace \( f(x, s, t) \) by \( sN(x, s, t) \), and \( f(x, s', t) \) by \( s'N(x, s', t) \), we get the flow driven spatially inhomogeneous coagulation equation:

\[
N_t + V(t, x) \cdot \nabla_x N(x, s, t) = \int_0^s \frac{s'}{s} J_1(s', s - s'; x, t) N(x, s', t) ds' \\
- \int_0^\infty J_2(s, s'; x, t) N(x, s, t) ds'.
\]

(5.50)

Coagulation convection model with diffusion

Let us consider the coagulation of the particles in the fluid transported by the velocity \( V(t, x) \) and diffuse with diffusion coefficient \( \sigma \). Thus the particle motion is described by the following stochastic differential equation:

\[
dX_t = V(t, X_t) \, dt + \sqrt{2\sigma} \, dB_t .
\]

(5.51)

Then motion the transition probability function \( p_x = p(x', t', x, t) \) satisfies the Fokker-Planck equation, and the coagulation transition probability function is given by equation (5.35):

\[
p_x = \begin{cases} 
J_1(s', s - s'; x, t) \Delta t, & \text{if } s' < s \\
1 - \Delta t \int_0^\infty J_2(s, \hat{s}; x, t) \, d\hat{s}, & \text{if } s' = s \\
0, & \text{if } s' > s .
\end{cases}
\]

(5.52)

We set

\[
J_1(s', s - s'; x, t) = \int_{\partial \Omega_1^+} \left( \sigma \nabla_x N(y, s - s', t) - V \cdot nN(y, s - s', t) \right) d\omega ,
\]

\[
J_2(s, s'; x, t) = \int_{\partial \Omega_2^+} \left( \sigma \nabla_x N(y, s', t) - V \cdot nN(y, s', t) \right) d\omega ,
\]

Where \( \partial \Omega_1^+ \) is the incoming flux boundary of the collision region for the collision of particles with size \( s' \) and \( s - s' \) at \( x \), and \( \partial \Omega_2^+ \) is the incoming flux boundary of the collision region for the collision of particles with size \( s \) and \( \hat{s} \) at \( x \).

Again, by Chapman-Kolmogorov equation, we have
\[
f(x, s, t) = \Delta t \int_0^s \int_{R^3} p_x J_1(s' - s; x, t) f(x', s', t') dx' ds' + \int_{R^3} p_x \left(1 - \Delta t \int_0^\infty J_2(\hat{s}; x, t) d\hat{s}\right) f(x', s, t') dx'.
\]

(5.53)

Also note that \(p_x = p(x', t'; x, t)\) satisfies the Fokker-Planck equation, then
\[
\int_{R^3} p(x', t'; x, t) f(x', s, t') dx' = f(x, s, t') - V \cdot \nabla_x f \Delta t + \sigma \Delta_x f \Delta t.
\]

(5.54)

Thus equation (5.53) can be simplified further:
\[
f(x, s, t) = \Delta t \int_0^s J_1(s' - s; x, t) f(x, s', t') ds' - \Delta t \int_0^\infty J_2(s, s'; x, t) f(x, s, t') ds' + f(x, s, t') - V \cdot \nabla_x f(x, s, t') \Delta t + \sigma \Delta_x f(x, s, t') \Delta t + O(\Delta t^2).
\]

Similarly to the inhomogeneous model without diffusion, after simplified, we get the inhomogeneous coagulation equation with diffusion:
\[
\frac{\partial N(x, s, t)}{\partial t} + V(t, x) \cdot \nabla_x N(x, s, t) - \sigma \Delta_x N(x, s, t) = \int_0^s J_1(s' - s; x, t) N(x, s', t') ds' - \int_0^\infty J_2(s, s'; x, t) N(x, s, t') ds'.
\]

(5.55)

Overall, we give the derivation of a self-consistent spatially inhomogeneous coagulation equation in which the coagulation kernel is not necessary to be given in advance. Instead of the coagulation kernel, the coagulation probability is described by the incoming flux \(J_1, J_2\).

### 5.4 Discussion and conclusion

For cell aggregation in the parallel plate flow chamber, comparing with the spatially homogeneous model, an alternative way is the spatially inhomogeneous coagulation equation if the nonuniform distribution of the cells is taken into account. Thus, we use three different models to derive the inhomogeneous equation. For example, Sabelfeld [1] used Lagrangian model, and we use both deterministic and probability models to derive the equation.
Future work

6.1 Comparison of different models

In Chapter 3, different models are introduced to study the coagulation equation, including both deterministic and stochastic models. For example, we set up a probability model and developed a Monte Carlo method in Section 3.2. The convergence of this method has not been verified. A deterministic dynamical system approximation is introduced in Section 3.3. By bridging the stochastic model and the conservation law in Section 3.4, we studied the coagulation equation by a deterministic formulation. The comparison of these different methods will be very significant.

We also introduced three different models to derive the spatially inhomogeneous coagulation equation in Chapter 5. The comparison of these three models is also of interest to us. We also need to develop the numerical methods and perform some numerical experiments for each model.

6.2 Energetic variation formulation

For the models discussed in Chapters 2, 3, and 5, we assume that the fluid flow is independent of the coagulations. The feedback of the coagulation to the flow velocity field is ignored if the particles are very dilute. However, this is not always obvious in some case. In order to take into account the change of the flow condition due to the coagulation, we want to use the energetic variation formulation to study this problem. In this formulation, a coupled system is considered.

An example of such a coupled system with the non-local interactions is given by the
electro-kinetic model [100]. In this model, the electro and kinetic energy are both taken into account. Hence, we want to borrow this idea in our coagulation system. First, let us take an overview of the Electro-kinetic model.

**Electro-kinetic model** The electro-kinetic model can be modeled by hydrodynamic systems describing the coupling between fluids and electric charges. Electro-kinetic describes the dynamic coupling between incompressible flows and diffuse charge systems. Under the no flux boundary conditions, the conservation of the total charge densities gives a nonlocal integral term.

In this model, we assume $u$ is the velocity field of the incompressible flow. $E = -\nabla \phi$ is the electric field and $\epsilon \Delta \phi = n - p$ is the net charge density, where $n$ and $p$ are the charge densities of a negatively and positively charged species respectively. $\epsilon$ is the Debye length which is related to vacuum permittivity and characteristic charge density.

First, we consider the electric charge system by taking into account the diffusion. The equation is as follows:

$$dX_t = -\nabla \phi(X_t)dt + \sqrt{2}dW_t$$  \hspace{1cm} (6.1)$$

where the electrostatic potential $\phi(x)$ satisfies the Poisson equation, which is defined by

$$\phi(x) = \int_0^\infty G(x, y)(n - p)(y)dy$$  \hspace{1cm} (6.2)$$

and $G(x, y)$ is the Green function.

The action functional is given by

$$A(x) = \int_0^T \int_\Omega \left( \frac{\rho}{2} |\dot{x}(x, t)|^2 - \frac{\epsilon}{2} |\nabla \phi(x, t)|^2 \right) dX dt$$  \hspace{1cm} (6.3)$$

By the least action principle, we get a coupled electro-kinetic model governing the hydrodynamic transport of binary diffuse charge densities([100]):

$$\begin{cases}
\rho(u_t + u \cdot \nabla u) + \nabla \pi = \lambda \Delta u + \epsilon^2 \Delta \phi \nabla \phi \\
\nabla \cdot u = 0 \\
n_t + u \cdot \nabla n = \nabla \cdot (n \nabla \phi - n \nabla \phi) \\
p_t + u \cdot \nabla p = \nabla \cdot (p \nabla + p \nabla \phi) \\
\epsilon^2 \Delta \phi = n - p
\end{cases}$$  \hspace{1cm} (6.4)$$
with boundary conditions

\[ u|_{\partial \Omega} = 0, \quad (6.5a) \]
\[ \phi|_{\partial \Omega} = \phi_0, \quad (6.5b) \]
\[ (\nabla n - n \nabla \phi) \cdot n|_{\partial \Omega} = 0, \quad (6.5c) \]
\[ (\nabla p + p \nabla \phi) \cdot n|_{\partial \Omega} = 0. \quad (6.5d) \]

where \( \rho \) is the fluid density and \( \pi \) is the pressure.

The first two equations are the linear momentum equations of incompressible flow. The third and the fourth equations model the balance between diffusion and convective transport of charge densities by flow and electric fields, which are derived from the conservation law. The fifth equation is the Poisson equation for the electrostatic potential \( \phi \), where the right-hand side is the net charge density.

**Coagulation-kinetic system**  In Section 3.3, we used an energy formulation to approximate the spatially homogeneous coagulation equation. We can also expand it to the inhomogeneous case involving space variable. Hence, the stochastic coagulation system is approximated by a deterministic dynamical system

\[ \frac{ds}{dt} = v(f, x, s, t) = \int_0^\infty \beta(s, s'; x, t)f(x, s', t)ds'. \quad (6.6) \]

We can also approximate it through the conservation law [34]:

\[ \frac{ds}{dt} = v(f, x, s, t) = \frac{F(x, s, t)}{f(x, s, t)}. \quad (6.7) \]

where \( F(x, s, t) \) is the flux defined by

\[ F(x, s, t) = \int_0^s \int_{s-s'}^\infty \beta(s, \hat{s}; x, t) f(x, \hat{s}', t) f(x, \hat{s}, t) d\hat{s} ds'. \quad (6.8) \]

For both of these two deterministic formulations, we can define the potential energy \( \phi(x, f, s, t) \) so that

\[ \nabla_s \phi(f, x, s, t) = v(f, x, s, t), \quad (6.9) \]

and the total potential of the whole system by

\[ E(f, t) = \int_{R^n} \int_0^\infty \phi f(x, s, t) dsdx. \quad (6.10) \]
This formulation is based on the approximation of the stochastic coagulation system through a deterministic dynamical system. We want to start from the stochastic system directly and use a proper energy formulation defined on the stochastic system. We will continue working on this problem in the future.

6.3 Improvement of spatially homogeneous model

Deformability and tethering of PMN The deformability of PMN tethered on the substrate plays an important role for the cell aggregation in the near wall region, including not only the tethering of PMN to the substrate, but also the collision and coagulation of tumor cell to the adhered PMN.

For example, the deformability of PMN leads to the change of the contact area of PMN and the substrate, such that the bound number that formed with the substrate is also changed. Thus, this may affect the tethering of the PMN since the bound will determine if the cell will stay there. The deformability of PMN not only changes the contact area of the PMN and the tumor cell in the near wall region, but it also has feedback to change the flow condition surrounding it, thus changing the collision and coagulation of PMN-TC.

In order to determine how the flow condition changes the shape and tethering of PMN, we can study some previous numerical studies of cell deformation in shear flow that have been conducted [6, 16, 17, 18]. There are different approaches to this problem. For example, in [16, 17], the authors investigated numerically how changes in the channel height affect leukocyte adhesion to the lower plate in a parallel-plate flow chamber provided that the leukocyte is deformable and viscoelastic. The leukocyte was modeled as a compound viscoelastic drop (a viscoelastic nucleus covered by a thick layer of a viscoelastic cytoplasm) with a thin ruffled membrane that possesses a cortical tension. The three-dimensional (3D) numerical simulation of leukocyte adhesion in a parallel-plate flow chamber has been carried out by their incompressible CFD code in which the volume-of-fluid (VOF) method is used for tracking leukocyte shapes over time. The Navier-Stokes equations are solved by Chorins projection method on a staggered marker-and-cell (MAC) grid. Liu [18] studied the deformation of an adherent leukocyte and calculated the forces exerted on it. Three model cells were proposed, considering the leukocyte as a single drop, a compound drop, and a nucleus drop, representing a cell without nucleus, a cell with a nucleus, and a nucleus only, respectively. These model cells were supposedly adherent to a smooth substrate under steady shear flow. In [6], a
two-dimensional model was developed consisting of an elastic ring adhered to a surface under fluid stresses to investigate the mechanics of leukocyte deformation and adhesion to endothelial cells in shear flow.

**Collision and coagulation of TC to PMN** Based on the work on the deformability of PMN, we can investigate the collision and coagulation rate of the tethered PMN and tumor cells in the near wall region. In general, we calculate the deformation of PMN by the 3D model that we proposed above. Then, the collision rate can be evaluated through the collision model as follows:

$$\hat{\beta} = - \int_{\partial \Omega | v \cdot n < 0} v \cdot nds,$$

where $\Omega$ is the collision region of PMN and TC, $n$ is the outward normal, and $v$ is the velocity profile surrounding PMN.

The PMN deformation also has a feedback to the flow and leads to a change in the flow condition, $v$. This effect of the cell shape change on the hydrodynamic flow field was estimated by a computational fluid dynamic model of flow over a deformed cell body, for example, by solving the Navier-Stokes equation with a proper boundary condition.

The adhesion efficiency is the probability that two colliding cells can stick with each other by forming the receptor-ligand bonds which can overcome the hydrodynamic force acting to separate this doublet.

A model was constructed to describe the shear induced formation and breakage of doublets of cells linked by receptor-ligand bonds in [98, 99]. The master equation is given by:

$$\frac{dp_n}{dt} = A_cm_r m_l k_f^n p_{n-1} - (A_c m_r m_l k_f^{n+1} + nk_r^n) p_n + (n + 1) k_r^{n+1} p_{n+1}.$$  \hspace{1cm} (6.11)

where, $p_n$ is the probability of having $n$ bonds at time $t$, and $m_r$ and $m_l$ are the respective number densities of receptor and ligand, $A_c$ is the contact area, and the forward rate coefficient per unit density is $k_f^n$.

Thus, by this model, we can calculate how many bonds are formed and determine if the number of bonds are enough to keep the doublet. Hence, the adhesion efficiency can be estimated. For details, we refer to Section 4.3.
6.4 Spatially inhomogeneous model

Model formulation We derived a spatially inhomogeneous coagulation equation in Section 5.3. In this model, we assumed the adhesion efficiency was 1. By coupling the coagulation flux given by equation (5.31) and the adhesion efficiency given by equation (6.11), we can apply the inhomogeneous equation to model cell aggregation in the flow chamber. To be more specific, we use the spatially inhomogeneous coagulation equation (5.55).

Numerical methods A possible method for the numerical approximation of the spatially inhomogeneous equation is splitting time. This method was used to solve the Boltzmann equation [101].

First, we rewrite the inhomogeneous equation in the form

\[
\frac{\partial N}{\partial t} = \mathcal{F}N + SN,
\]

(6.12)

where

\[
\mathcal{F} = -v \cdot \nabla_x + \sigma \Delta_x
\]

and \(S\) is the coagulation operator which is given by the right-hand side of the equation.

Therefore we can approach the inhomogeneous equation by solving the coupled equations

\[
\frac{\partial N}{\partial t} = \mathcal{F}N, \quad \frac{\partial N}{\partial t} = SN.
\]

(6.13)

So this problem is simplified since we only need to solve the Fokker-Planck equation \(\frac{\partial N}{\partial t} = \mathcal{F}N\) and the spatially homogeneous coagulation equation \(\frac{\partial N}{\partial t} = SN\). The homogeneous equation can be solved by the time relaxed method which was discussed in Chapter 2. To be more specific, for given time interval \([0, T]\) and integer \(N\), we divide this interval into \(N\) small intervals. Let

\[
\Delta t = t_n - t_{n-1} = \frac{T}{N} \quad \text{for} \quad n = 1, 2, \ldots, N.
\]

Thus on the small interval \([t_n, t_{n+1}]\), two sequences \(N^{n+1/2}\) and \(N^{n+1}\) are obtained by solving the following two equations.
First we solve the Fokker-Planck equation

\[
\begin{align*}
\frac{\partial N^{n+1/2}}{\partial t} &= \mathcal{F} N^{n+1/2} \\
N^{n+1/2}(x, s, t = t_n) &= N^n_0(x, s).
\end{align*}
\] (6.14)

Then we solve the spatially homogeneous coagulation equation:

\[
\begin{align*}
\frac{\partial N^{n+1}}{\partial t} &= S N^n \\
N^{n+1}(x, s, t = t_n) &= N^{n+1/2}_0(x, s),
\end{align*}
\] (6.15)

where

\[N^n_0(x, s) = N^n(x, s, t = t_n),\]

and

\[N^{n+1/2}_0(x, s) = N^{n+1/2}(x, s, t = t_{n+1}).\]

Overall, this thesis work has demonstrated the efficiency of the coagulation models applied to cell aggregation. Our work raises many interesting and important new questions. We are collaborating with biologists and trying to expand the techniques above broadly in biological engineering.


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Vita

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In 2002, he enrolled in the PhD program in Mathematics at Texas A&M University. In 2003, he transferred to The Pennsylvania State University to study Applied and Computational Mathematics under the guidance of Prof. Qiang Du.