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MARKOV DECISION-MAKING PROCESS FOR RISK REDUCTION STRATEGIES IN BREAST CANCER

A Thesis in

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Abstract

Breast cancer is a prevalent disease that undermines the quality of patients' lives and significantly impacts psychosocial wellness. Moreover, breast cancer has the highest occurrence and second-highest mortality probability among all types of cancer in American women. Different treatment methods, such as mastectomy, radiation, chemotherapy, and targeted therapy, vary in the perspective of cost, curability, and side effects. Advanced sensing provides unprecedented opportunities to develop smart cancer care. The available sensing data captured from individuals enable the extraction of information pertinent to the breast cancer conditions to construct efficient and personalized intervention and treatment strategies.

This research is aimed at improving the outcomes of treatments based on a data-driven Markov Chain model for breast cancer. We first used the conditional probability to estimate the transition dynamics, then deployed a novel Hierarchical Gaussian Distribution (HGP) to impute the missing elements in the estimated transition matrices. The patient's state space is defined by the patient's age, health status, and prior treatments. The data used in this research is derived from the Surveillance, Epidemiology, and End Results Program(SEER) dataset. The dataset contains the treatment record and diagnosis record of breast cancer patients from 1975 to 2016.

With the completed transition matrices, we designed a sequential decision-making framework to determine the optimal treatment strategy for breast cancer patients. We used a Markov decision process (MDP) model for both the objectives of cost and quality-

adjusted life-years (QALYs) with the data-driven and state-dependent treatment actions. The state space is defined as a vector of age, health status, prior treatments, as defined previously. Also, the action space includes wait, prophylactic surgery, radiation therapy, chemotherapy, and their combinations.

Experimental results demonstrate that prophylactic mastectomy or chemotherapy is more effective in minimizing the expected cancer cost of 25 to 65 years-old patients with in situ stage of cancer. However, the wait action is the optimal policy for a patient with the same condition when we change the objective function from cost to quality adjusted of lifetime. The proposed MDP framework can also be generally applicable to a variety of medical domains that entail evidence-based decision making.

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Chapter 1

Introduction

1.1 Breast Cancer Overview

Female breast cancer constitutes the highest proportion, 15.2%, of new cancer cases in the United States for 2019. Furthermore, 12.8% of women in the United States will be diagnosed with breast cancer in their whole lifetime. As shown in Fig. 1.1, female breast cancer also contributes to the second-highest estimated deaths in 2019 due to its high prevalence [1]. Moreover, based on the National Cancer Institute report, medical expenditures for breast cancer care in the United States surges from $21.6 billion to $25.1 billion between 2010 to 2017 [2]. Preventive surgeries and diagnosis techniques are effective in reducing the risk of cancer among patients. Also, treatment strategies (e.g., Chemotherapy and radiation therapy) can control the progression of breast cancer and return a patient to a healthy life.

However, most of intervention and treatment strategies are usually costly and cause severe side effects. For example, prophylactic mastectomy as an intervention strategy may

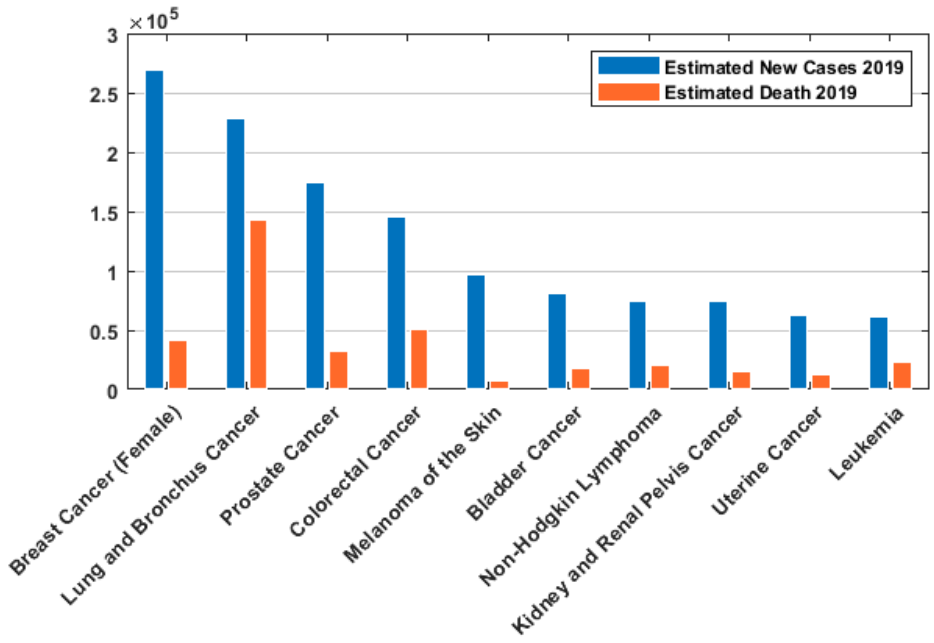

Figure 1.1. Estimated Cancer Cases and Deaths in 2019

be considered medically necessary in a patient at high risk of breast cancer. However, this strategy is in conflict with the desire of women for natural body image, and it surges the loss of sexuality and gender identity, and also enlarges the risk of osteoporosis. Furthermore, physical and psychological differences (e.g., age, stage of cancer, and personal treatment history) impacts breast cancer progression and thereby leads to significant uncertainty on patients' health status and treatment planning.

The current breast cancer study focuses on different perspectives. Besides biological perspectives such as research on the development of cancer cells [3], studies on breast cancer are mostly related to the effects of different factors. For example, there are studies about how cancer-related genes affect the occurrence and curability, like breast cancer (BRCA) gene [4], Human epidermal growth factor receptor 2 (HER2) gene [5]. There are also research efforts about the effects of the behavioral factors on breast cancer, such as

alcohol use, tobacco use [6].

Other than making treatment choices based on the specification of treatments, patients and doctors tend to rely upon patients' specific conditions, and medicines revolve around the standard of care to make decisions. The biology of the tumor, cancer stage, overall health, and age are all considered when making decisions. Also, advancements in medical sensing technology provide an unprecedented opportunity for smart health management in breast cancer [1], which enables a detailed treatment plan for breast cancer patients.

The data generated in breast cancer consists of various intervention and treatment decisions from a heterogeneous population (i.e., patients of different ages and stages of cancer and various treatment histories). Additionally, there is a vast amount of data in the healthcare system related to disease status and patients' decision-making on treatment selection. While datasets contain a significant amount of information and many features, those datasets may not be well-organized, and some features are trivial or not directly related to the purpose of breast cancer research. Consequently, how to take advantage of the available big data to improve the wellness of breast cancer patients is a challenge for many researchers.

1.2 Overview of Thesis

In this thesis, first, we applied a Markov Chain model on data from the Surveillance, Epidemiology, and End Results Program (SEER) dataset. Based on features in the

SEER dataset, we defined the state in the Markov Chain model by age, health status, and prior treatments. The stage of cancer in health status and the age of the patient are two vital factors impacting the transition dynamics of breast cancer. Considering the availability of data, we only consider the general type of Mastectomy, Radiation, and Chemotherapy in prior treatments. Treatments for breast cancer can affect patients' health status and then transition. However, on the other hand, treatments also increase the incidence of other diseases or even result in death from other causes.

With defined states and models, we estimated transition probabilities between different states with conditional probability. Although the SEER dataset contains over one billion data, some specific breast cancer cases are still inadequate for the estimation. In order to impute the missing elements in transition matrices, we deployed an HGP methodology. The HGP method can impute missing values based on adjacent values in the transition matrices layer by layer, which enables a higher accuracy.

Further, We developed a novel MDP framework to derive the optimal treatment strategies (i.e., wait, prophylactic surgery, radiation therapy, Chemotherapy, and their combinations) for any state defined previously. In the MDP model, we derived the optimal strategies by maximizing the total reward measured in terms of quality-adjusted life-years (QALYs) and the expected cost of treatment.

1.3 The SEER Data

In this thesis, we utilized the Surveillance, Epidemiology, and End Results (SEER) data from the year 1973 to 2016 to estimate the state-action transition dynamics in breast cancer.The SEER program, supported by the U.S. National Cancer Institute (NCI), collects data from tumor registries and covers 14% to 25% of the U.S. population. These registries' data are vital to analyze and report the evolving burden of breast cancer in the population.

In the dataset, we first extracted data from all regions in the United States and deleted the male cases. There are a total of 1,667,890 entries in the extracted data. Each entry has the same size with coded cancer-related variables such as year of diagnosis, the month of diagnosis, grade, and stage.

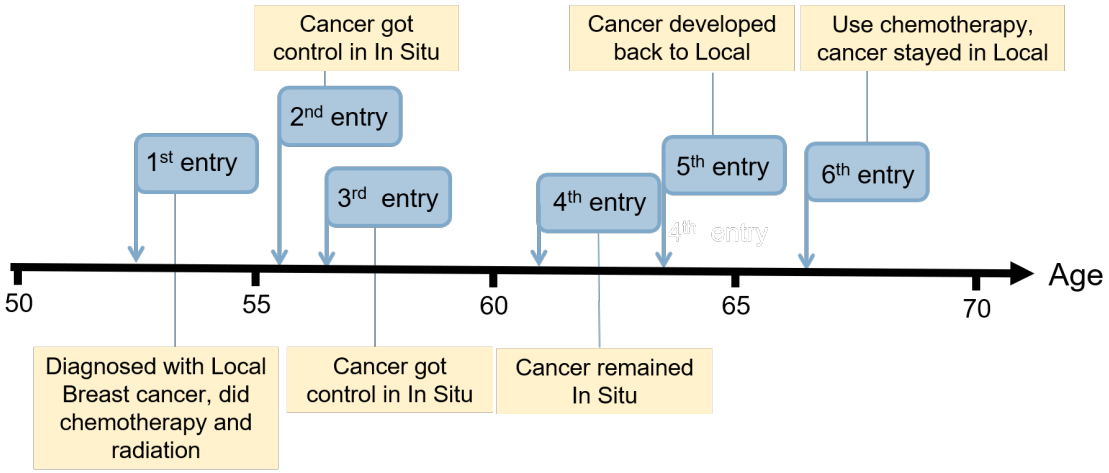

Figure 1.2. An example of state-action transition dynamics of breast cancer over lifespan of a patient in the database.

The total extracted data have 397 ASCII positions for each data entry. The 397 positions in the dataset contain information like Patient ID, Race, Sequence Number,

Table 1.1. Data Structure

Patient ID	**Registry ID**	**Marital Status**	**Race**	**...**	**M value**	**Total # of *in situ*/malignant**	**Total # of Benign/ Borderline**	**...**
07000002	0000001502	2	01	...	0	02	00	...
07000057	0000001502	5	01	...	0	02	00	...
07000067	0000001502	5	01	...	0	02	00	...
07000082	0000001502	2	02	...	N/A	02	00	...
07000100	0000001502	5	02	...	N/A	02	00	...
...	...	...	...	...	...	...	...	...

and et al. As shown in Table 1.1, positions 1-8 indicate Patient ID; positions 9-18 indicate registry ID, which contains information which hospital system the patient entered; position 19 indicates Marital Status. Note that the patient ID is utilized to identify a patient in the SEER database uniquely. Based on the patient ID, we created a tensor structure (i.e., 3-dimensional data structure of patient, variables, and breast cancer entries) for all patients with re-retry records. Note that in each layer, we store data of all records of the same patient. As shown in Fig. 1.2, there are six entries for this patient in the database, and the breast cancer state has evolved over her lifespan as a function of age, stage of cancer, and treatment history (i.e., she has multiple records).

We decoded each feature by the reference table. For the first and fourth patients in Table 1.2, the marital status is married, represented by 2, and other patients in Table 1.1 are widowed, represented by 5, as shown in Table 1.2. However, there are a large number of missing values in the dataset, like the M value in Table 1.1. In the next step, we selected features from the dataset based on the data availability and the model we defined.

This thesis is organized as follows. Chapter. 2 introduces the research background for

Table 1.2. Code Description

Code	Description
1	Single (never married)
2	Married (including common law)
3	Separated
4	Divorced
5	Widowed
6	Unmarried or domestic partner (same sex or opposite sex or unregistered)
9	Unknown

breast cancer progression and missing value imputation. Chapter. 3 presents the transition probability estimation and Hierarchical Gaussian Process for missing value imputation. Chapter. 4 shows experimental results and benchmarking study, and Chapter. 5 concludes this thesis.

Chapter 2

Literature Review

Due to the prevalence of breast cancer and the rich data environment, many studies have been done to research breast cancer and improve the survival chance of breast cancer patients. Some studies are from biology and medical perspective. Gupta *et al.* [3] researched the dynamics of phenotypic proportions in human breast cancer cell lines with a Markov model; they also showed how subpopulation of cells return to equilibrium phenotypic proportions over time and how non-stem-like cells transit to stem-like cells. On the other hand, some studies are focusing on the patients' perspective. Kurian and Das [4] built a Monte Carlo model for BRCA mutation carriers to simulate screening methodology, prophylactic mastectomy (PM) and/or prophylactic oophorectomy (PO) at various ages to guide patients with complex choices. In this chapter, we provide a view of previous works on how researchers estimate the transition probability and develop intervention and treatment strategies for breast cancer patients.

2.1 Estimation of Transition Dynamics

Transition dynamics estimate the progression of tumors based on patients' evolving data of health status. A deep understanding of transition dynamics can help patients with their decision making on treatments. With estimated transition dynamics, we can move forward to the next step to develop a treatment policy.

2.1.1 Calculation of Risk Reduction Strategy with Big Data

Generally, there are three ways to estimate the risk reduction of breast cancer. The first methodology is to do an estimation based on collected data from a designed experiment like a cohort study. Perez *et al.* [7] analyzed data collected from a cohort of 300 women with breast cancer with a non-homogeneous Markov process. The states are defined as no relapse, relapse, and death, and the survival probability functions for different treatments are estimated from the data. In order to analyze the effect of various factors, such as pregnancy history, alcohol use, tobacco intake, Barnett *et al.* [6] analyzed data from 4,560 women with invasive breast cancer. Early Breast Cancer Trialists' Collaborative Group [8] implemented meta-analysis on individual data from 10801 women patients. They applied the data on 17 randomized trials to estimate the factor that affects the effectiveness of radiation on preventing cancer recurrence. The advantage of designing an experiment is that the collected data can directly serve the research purpose. On the other hand, the weakness of this method is that the data collecting process may last for several years or even several decades, and the cost is high.

The second method is to use available data to do simulation. In the 1990s, There are researches about using computer simulation on breast cancer to find better intervention strategies for patients. On the one hand, Boer *et al.* [9] simulated based on a given strategy and modified strategies to study how different intervention strategies affect the number of deaths and the number of life-years saved. On the other hand, Michaelson *et al.* [10] research on the course of breast cancer growth and metastasis based on the rate of tumor growth and spread model. Subsequently, the Monte Carlo simulation is widely used. Plevritis *et al.* [11] used the Cancer Intervention and Surveillance Network base case inputs, which describe breast cancer risk, treatment and screening pattern, and non-cancer caused deaths. They used information generated from the Monte Carlo simulation to estimate the impact of mammography and adjuvant therapy. What is more, Monte Carlo simulation can also be used to estimate transition probability, which can further be used to estimate the risk reduction strategy. Kurian *et al.* [12] simulated a Monte Carlo model for BRCA1/2 gene carriers with screening options, prophylactic mastectomy(PM), and/or prophylactic oophorectomy. Based on the generated survival probability and causes of death, they provide a reference for BRCA1/2 mutation carriers on their choices between screening or PM. Le *et al.* [13] used a Monte Carlo simulation to apply lapatinib in the treatment for HER-2-positive patients. They estimated the incremental cost-effectiveness ratio based on the estimated transition probabilities.

Furthermore, the third method uses available data to defined models, then directly estimate transition probabilities; this method typically requires a large amount of data. Yen *et al.* [14] used data from the Swedish Two-County Trial and service screening

programs in several countries. They estimated the incidence of progressive and non-progressive ductal carcinoma *in situ* and the detection rates of screening based on the Markov process model.

However, due to the complexity of breast cancer-related problems, researchers use different parameters when estimating transition probabilities. Abdollahian *et al.* [15] focused on BRCA gene carriers' prevention problem based on screening and preventive actions. Le *et al.* [13] studied HER gene's effects to understand more about the effect on progression and new lapatinib use on the treatment of HER-2-positive breast cancer. Most researchers concentrate on a preventive strategy for breast cancer. However, very little has been done to estimate post-treatment state-action transition dynamics for breast cancer patients. With a vast amount of data about post-treatment states, we choose to build a Markov Chain model to estimate the post-treatment transition dynamics.

2.1.2 Modeling and Analysis of Incomplete Data

Even in transition matrices estimated from big data, there are some missing elements in our transition matrices because of unbalanced data. The missing element is a common problem that occurs in all kinds of data related research. In the literature, researchers generally deal with missing data in two ways. The first one is the case analysis, including complete-case analysis and available-case analysis, which is removing the cases or variables with missing elements, then analyzing the data with full information. The second method is missing data imputation, which estimates the missing elements with predicted values from single imputation or multiple imputation [16, 17]. Single imputation includes

mean imputation, regression imputation deck imputation, etc. On the other hand, multiple imputation is a more sophisticated and valid method in dealing with missing elements. Zhang [18] implemented regression imputation on 150 elements of data, which is generated from simulation. Shrive *et al.* [19] intentionally remove some values from 1580 questionnaires with 20 questions, then use multiple imputation methods, including multiple imputations, single regression, mean method to estimate the missing values. Myrtveit [20] implemented listwise deletion, mean imputation, similar response pattern imputation, and full information maximum likelihood to impute the missing values. Moreover, machine learning algorithms are used on missing value imputation. Pantanowitz and Marwala [21] used data from HIV seroprevalence data, then implemented random forest and neural network-related methodologies to impute the missing values. There are also complicated methodologies introduced to capture the missing values. Li *et al.* [22] applied the clustering method combined with soft computing together, and the fuzzy clustering algorithm to impute the missing values. In this chapter, we implemented a Hierarchical Gaussian Process to impute the missing elements.

2.2 Markov Decision Making Process

Markov decision process (MDP) modeling is an effective way to determine policies for sequential stochastic decision problems according to patients' specific conditions [23]. The multi-stage decision processes have been previously implemented in medical domains such as optimal timing of living-donor liver transplantation and treatment of ischemic

heart disease [24]. In the breast cancer domain, Anderson et al. [25] developed Markov modeling with Monte Carlo simulations to evaluate the cost-effectiveness of the preventive strategies that are available to unaffected women carrying a single BRCA1 or BRCA2 mutation with high breast cancer penetrance. Abdollahian and Tapas [26] studied an MDP model that incorporates yearly state transitions for the mutation carriers and state-dependent intervention actions. They considered to separate reward function and determine the best policies under each of them.

However, most of previous decision models focused on optimization of intervention strategies for patients with BRCA1 or BRCA2 mutation careers, which only limited just to the intervention strategy for the small portion of the population that has a higher risk of having breast cancer (i.e., 5% to 10%). Also, their calculations for the state-action dynamics were based on the simulation studies, which may not be accurate due to the high level of uncertainty in complex and human-based systems. There is an urgent need to utilize available big data and design inclusive decision-making frameworks for personalized and multi-stage intervention and treatment planning in breast cancer.

Chapter 3

Estimation of State-action Transition Dynamics

3.1 Introduction

In this chapter, we first research the data structure and look insight the data. Through data mining, we discovered a clear trend in treatment options, cancer stage, and the likelihood of mortality as age changes. For example, among treatment options, Chemotherapy is more likely to be utilized in the regional and the distant cancer stage compared with *in situ* and local stage. In contrast, less than 25% of patients at *in situ* stage choose to use Chemotherapy. Afterward, we defined a Markov Chain model to estimate the patients' multi-age transitions to predict breast cancer progression. The patient state is defined by the patient's age, health status, and prior treatments. However, due to the imbalance in the SEER dataset, we need to deal with missing elements in the transition matrices. We deployed a novel Hierarchical Gaussian Distribution (HGP) to

impute the missing elements in the transition matrices.

In order to show the effectiveness of the HGPs methodology, we implemented a benchmarking study to validate our methodology. In benchmarking study, The Root Mean Square Error (RMSE) of HGP imputation is 35% lower than Gaussian Process and 40% lower than Linear Regression. Moreover, the transition matrices reveal astoundingly elderly distant cancer patients have even higher survival chances than young age distant breast cancer patients.

3.2 Research Methodology

3.2.1 Data Processing

In the feature selection process, we retrieved Patient ID, patients' status including age, cancer stage, and available treatment records. The dataset we used only contains information for Mastectomy, Radiation, and Chemotherapy, which we further used to define our model. Since the standards for treatments and cancer stage definition varies over time, we processed data from different standards to keep the information. For missing values in raw data, we chose to eliminate them in order to avoid artificial bias. Moreover, more detailed treatment information is not considered due to multiple data standards and unbalanced problem; we treated the treatment values as binary variables.

For some patients, they entered the system more than once due to health examination or status deterioration. We added the previous record to new entries to keep track of their treatment history. However, we have no information about the health condition

between and after their entry, so that we can only approximate the cancer progression with those re-entry data. On the other hand, when estimating mortality probability, we can take advantage of all data due to the completed record of death time.

3.2.2 Model Definition and State Transition Dynamics

Based on the features retrieved from the previous step, we defined a Markov Chain model to formulate the transition dynamics [23]. The state of a patient is defined as follows:

$$S = \{a + c + t\} \tag{3.1}$$

where a denotes patients' age, where we only consider the age between 25 to 65 years; c denotes cancer stage of the patient, which includes *in situ*, Local, Regional and Distant; and t denotes the patients' treatment history, which contains information about mastectomy, radiation, and Chemotherapy.

Moreover, we assume that patients can only transit from "good" state to "worse" state because the data only contains information for one entry, which results in inadequate information about how patients progress after the entry. As in Fig. 3.1, we defined that patients in c_{i0} can transit to all other stages, but patients at stage c_{i3} can only stay in the current stage state or transit to death state. Note that the *de* in Fig. 3.1 represents the death state, which is an absorbing state in our model.

Further, we estimated the mortality probability for patients based on the "Survival

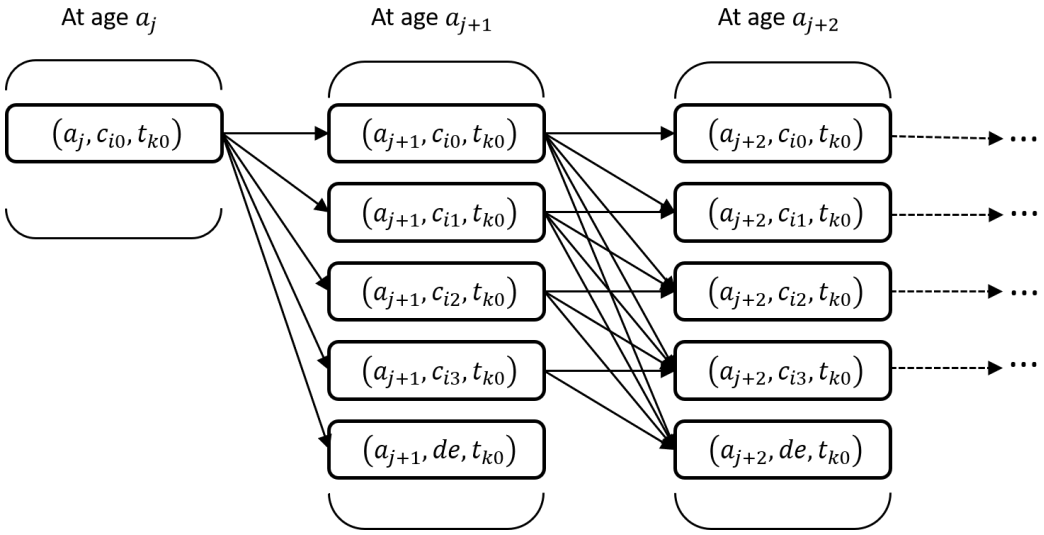

Figure 3.1. Markov Chain Model Transition at t_{k0}

Month" feature. With the massive amount of data, we can estimate mortality probability based on individual state and age. On the other hand, we need re-entry data to keep track of the cancer condition for patients, which is unavailable for most patients. Therefore, the transition probability we estimated is not a function of age.

In this Markov chain model, we use the following transition probability function to calculate the transition probabilities:

$$P_{mn}(a) = Pr\{X(a+1) = n \mid X(a) = m\}, m, n \in S, 25 \leqslant a \leqslant 65 \tag{3.2}$$

where m,n is the state at age a and $a+1$ respectively; $X(a)$ denotes the state at age a; $P_{mn}(a)$ means the transition probability at age a from state m to state n.

3.2.3 Hierarchical Gaussian Process

However, the transition probabilities estimated from conditional probability are incomplete; many stage-to-stage probabilities are missing because of the limited amount of re-entry data. Nevertheless, the transition probabilities in the transition matrix are correlated with each other due to cor relationship between different states. As a result, adjacent values inside a matrix and values at the same position across matrices can be utilized to impute the missing value. As shown in Fig. 3.2, the transition probability at position A can be estimated from three dimensions [27], age, cancer stage, and treatment history. First, the transition probabilities are correlated through cancer stage and age. On the other hand, the effect of treatment gives a correlation between different treatment histories. Based on the correlation, we can approximate the missing value in the transition matrix based on Gaussian Process on different dimensions.

Fig. 3.3 shows how we utilized the hierarchical structure of the HGP method to estimate the missing values in our transition matrices.

First, $X_c(t_k, a_j)$ denotes the value of transition probability at cancer stage c for patients with treatment history t_k at age a_j. We construct a level I Gaussian process(GP) model as:

$$X_c(t_k, a_j) \sim \mathcal{GP}(\mu_c, K_c) \tag{3.3}$$

where μ_c is the mean function, and K_c is the covariance function. The order of stage, treatment history, and age is derived from the correlation of transition probability with

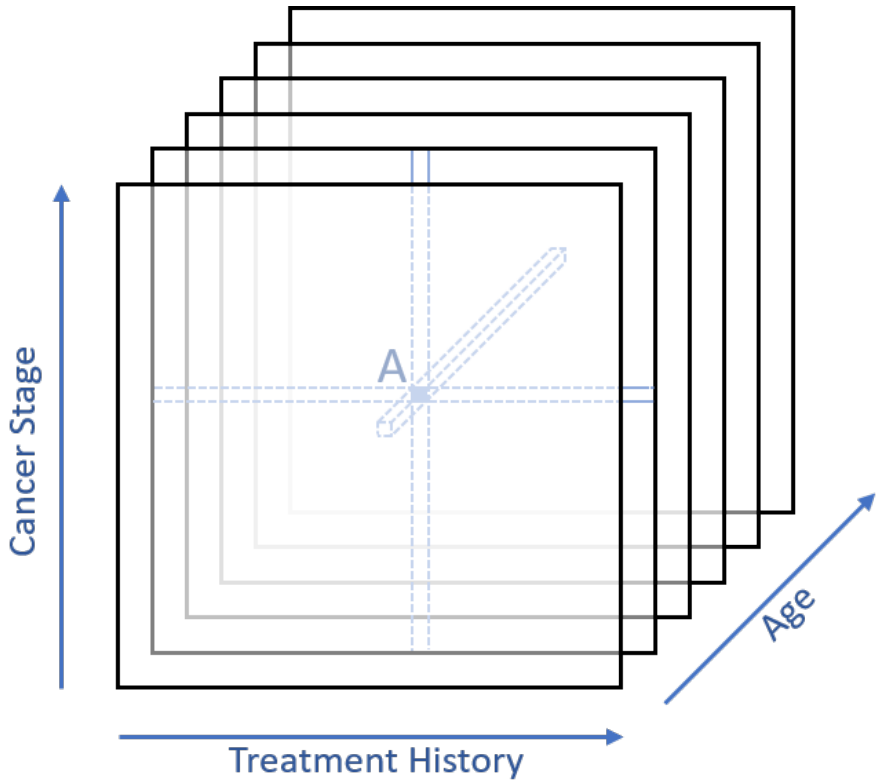

Figure 3.2. 3D Tensor Structure of BC patients data

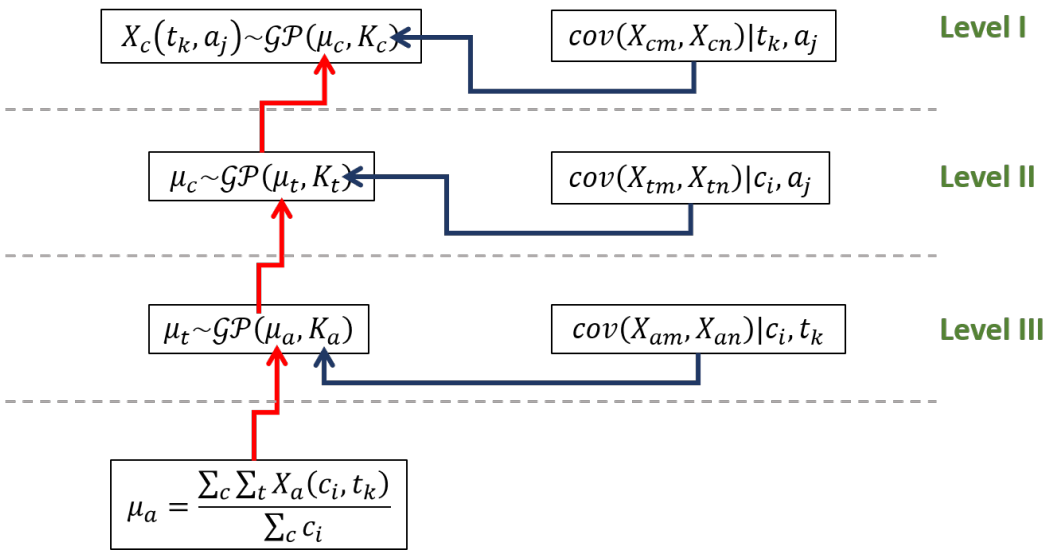

Figure 3.3. The Hierarchical structure of Gaussian Process

those factors. We use covariance function K_c as:

$$cov(X_{cm}, X_{cn})|t_k, a_j = \sigma_c^2 exp[-\frac{(c_m - c_n)^2}{l_c^2(t_k, a_j)}] \tag{3.4}$$

Eq. 3.4 is based on squared exponential covariance function. σ_c^2 is the signal variance in the dimension of stage, and $l_c(t_k, a_j)$ is the length scale of the exponential covariance function. Note that X_{cm} and X_{cn} should be similar if s_m and s_n are close to each other. Second, we model μ_c in Eq. 3.1 using a level II GP model as:

$$\mu_c \sim \mathcal{GP}(\mu_t, K_t) \tag{3.5}$$

where μ_t is the mean function for transition probability, and K_t is the covariance function between treatment histories. The hierarchical design is to incorporate nonstationary in the underlying stochastic process through the GP model of mean functions. We ordered treatment histories based on their impact on mortality probability. If two patients have similar treatment histories, their transition probability should be close to each other. The covariance function K_t is defined as:

$$cov(X_{tm}, X_{tn})|c_i, a_j = \sigma_t^2 exp[-\frac{(t_m - t_n)^2}{l_t^2(c_i, a_j)}] \tag{3.6}$$

Then we model the mean function μ_t in Eq. 3.5 as the level III GP:

$$\mu_t \sim \mathcal{GP}(\mu_a, K_a) \tag{3.7}$$

where the K_a is the covariance between different ages, as shown in Eq. 3.8.

$$cov(X_{am}, X_{an})|c_i, t_k = \sigma_a^2 exp[-\frac{(a_m - a_n)^2}{l_a^2(c_i, t_k)}] \tag{3.8}$$

Also, the mean function μ_a is the average of transition probability for specific age across the treatment history and stage:

$$\mu_a = \frac{\sum_c \sum_t X_a(c_i, t_k)}{\sum_c c_i} \tag{3.9}$$

With the HGP, we can estimate transition probability for the patient at age a^*, with stage c^* breast cancer and with t^* treatment history. The posterior mean of level I GP is given as:

$$\overline{X}_{c^*}(t^*, a^*) = \overline{X}_c(t^*, a^*) + K_{c^*c}[K_{cc} + \sigma_{nc}^2 I]^{-1}[X_c(t^*, a^*) - \mu_c(t, a^*)] \tag{3.10}$$

where K_{c^*c} is the temporal covariance, σ_{nc}^2 is the noise variance in temporal domain and $\overline{X}_c(t^*, a^*)$ can be calculated from:

$$\overline{X}_c(t^*, a^*) = \frac{\sum_c X_c(t^*, a^*)}{C_{t^*a^*}} \tag{3.11}$$

$C_{t^*a^*}$ is the number of stages at age a^* with treatment history t^*. Then the mean function, Eq. 3.10, can be estimated from level II GP:

$$\mu_c(t, a^*) = \overline{X}_{t^*}(c, a^*) + K_{t^*t}[K_{tt} + \sigma_{nt}^2 I]^{-1}[\overline{X}_t(c, a^*) - \mu_t(c, a^*)] \tag{3.12}$$

where K_{t^*t} is the covariance between treatment histories, σ_{nt}^2 is the noise variance in treatment history and $\overline{X}_t(c, a^*)$ is the mean function for transition probability across all treatment histories. Then we estimate $\mu_c(t, a^*)$ use level III GP:

$$\mu_t(c, a^*) = X_{a^*}(c, t) + K_{a^*a}[K_{aa} + \sigma_{na}^2 I]^{-1}[\overline{X}_a(c, t) - \mu_a] \tag{3.13}$$

where K_{a^*a} is the covariance between ages, σ_{na}^2 is the noise variance in the perspective of age and $\overline{X}_a(c, t)$ is the prior of age a for all stages and treatment histories.

3.3 Experimental Design And Results

3.3.1 Descriptive data analysis

Before estimating transition matrices, we investigated processed data to understand the relationship between patients' age and the cancer stage. In Fig. 3.4, the population of breast cancer patients for each stage is displayed in a different color, and the height of the bar represents the total population of breast cancer patients. From Fig. 3.4, the population of patients increase by age and start to decrease after around 70 years old. Moreover, patients at the local stage consist of the highest proportion almost all the time. Notably, there is an apparent difference between age 39 and age 40; the reason is that most researches and instructions indicate that the female population should apply

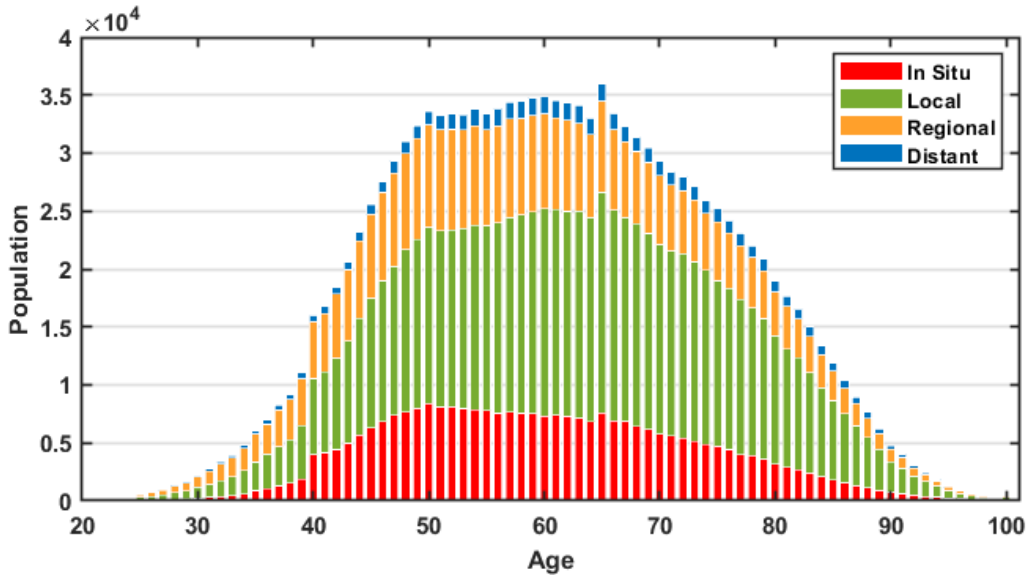

Figure 3.4. Population of breast cancer stage among different ages

screening every year after 40 years old [28].

Besides the stage proportion, the processed data also contains information about the treatment selection among different ages. Fig. 3.5(a) to Fig. 3.5(d) shows the treatment selection proportion at stage *in situ*, local, regional, distant respectively. In Fig. 3.5(a), due to the benign type of cancer, data shows more patients choose mastectomy at a younger age and radiation at a higher age. However, few patients use Chemotherapy at *in situ* stage. Fig. 3.5(b) shows that patients at local stage might use all those three methods depending on case to case situations; Nevertheless, for elderly patients, radiation is more likely to be used. Starting with Regional cancer in Fig. 3.5(c), most patients undergo Chemotherapy other than Mastectomy and Radiation. Distant cancer patients in Fig. 3.5(d) use less radiation and mastectomy compared to the Regional stage because those two treatments would introduce a high risk.

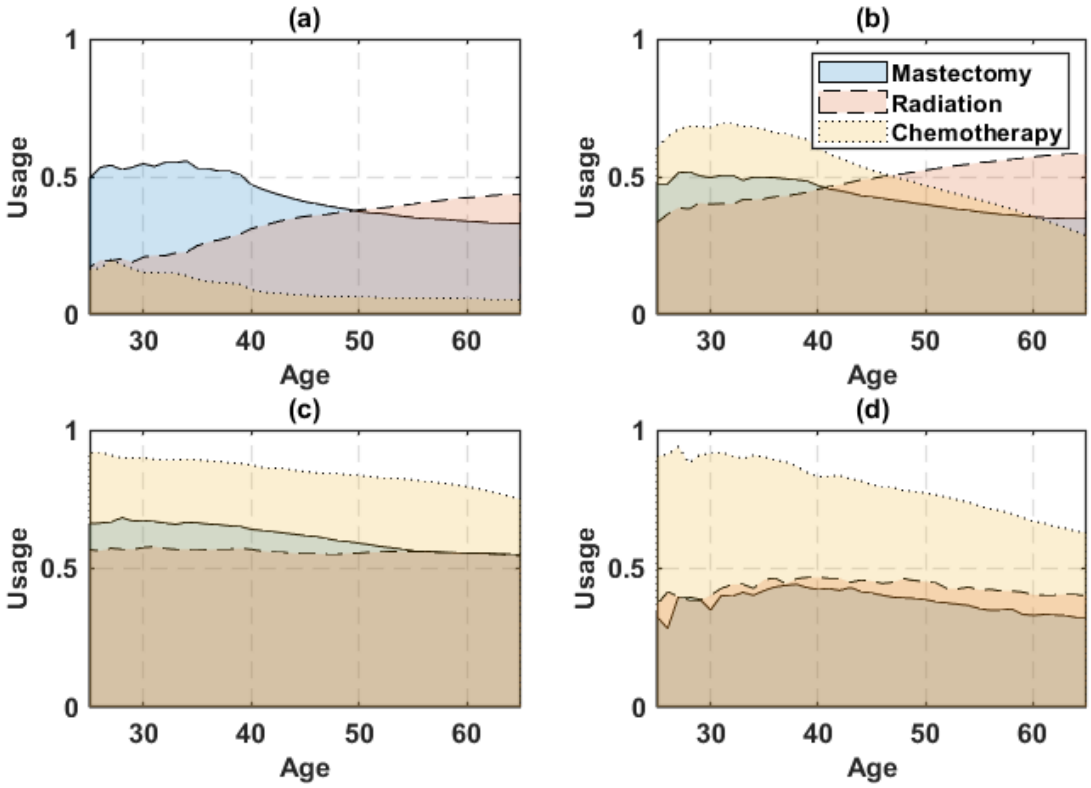

Figure 3.5. Distribution of treatment selections among patients at different ages and stages of cancer

3.3.2 Transition Probability Estimation

The estimated transition matrices consist of 33×33 matrices for each age, where 33 represents the number of the combination of treatment history and stage, with a death state. Table 3.1 is one part of the 39-year-old transition matrix; it shows how the cancer stage of a 39-year-old patient with no treatment history would progress. As shown in the table 3.1, *in situ* stage cancer has a 0.71% probability to transit to local stage at age 40. Also, patient with distant cancer has 7.21% death probability, which is the highest compared with other stages. Note death can only transit to death state, which we consider as an absorbing state.

Table 3.1. STATE-ACTION TRANSITION MATRIX FOR A PATIENT AT AGE 39 WITH NO TREATMENT HISTORY

	In Situ	Local	Regional	Distant	Death
In Situ	0.9818	0.0071	0.0023	0.0003	0.0086
Local	0	0.9746	0.0016	0.0003	0.0236
Regional	0	0	0.9859	0.0007	0.0134
Distant	0	0	0	0.9279	0.0721
Death	0	0	0	0	1

Fig. 3.5 presents the mortality probability at different stages among all defined ages. Generally, the mortality probability increases as age increases. Moreover, the dark blue represents the low mortality probability for breast cancer patients. However, the mortality probability around age 33 for Distant stage cancer is higher than in middle ages, as shown in red in the figure. We believe the reason is that patients would do more examinations like screening at an older age, which results in a late diagnosis. Besides, elderly patients have higher risk both from breast cancer and other causes. While the patients in middle ages are healthier than elderly patients, and they tend to do more health tests.

3.3.3 Hierarchical Gaussian Process

To evaluate the HGP and compare it with other methods, we simulate by removing some values from transition matrices, then utilized HGP, GP, and Linear Regression(LR) to estimate the removed values, respectively. We implemented three methods for 100 replications, each for three different percentages of removed values, 25%, 50%, and 75%, and then implemented HGP, GP, and LR to impute the missing values we removed.

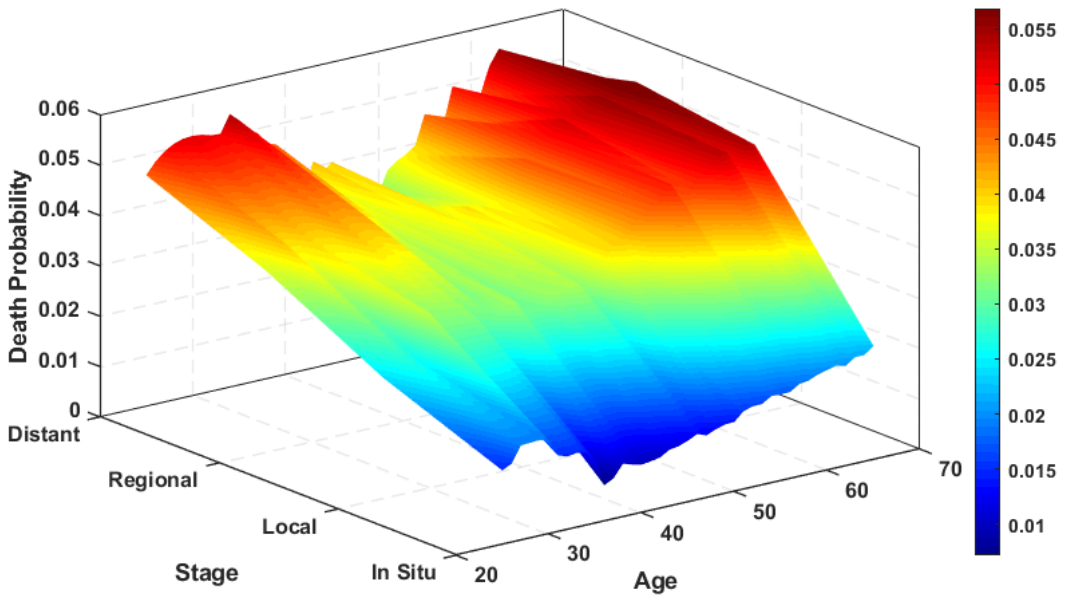

Figure 3.6. The Mortality Probability for different ages and stages

The Root Mean Square Error(RMSE) is used to compare the imputation errors, which can reflect the error between the predicted values and actual values. As shown in Fig. 3.7, the RMSE for HGP is 40% less than LR, 35% less than GP for all three percentages, which reflects the effectiveness of HGP compared with other two methods. Furthermore, the range of RMSE increases with the removed percentage, which indicates the uncertainty increases with the removed percentage increase. However, the range for HGP increases much less than the other two methods. Even with less training data, the HGP methodology has stable performance.

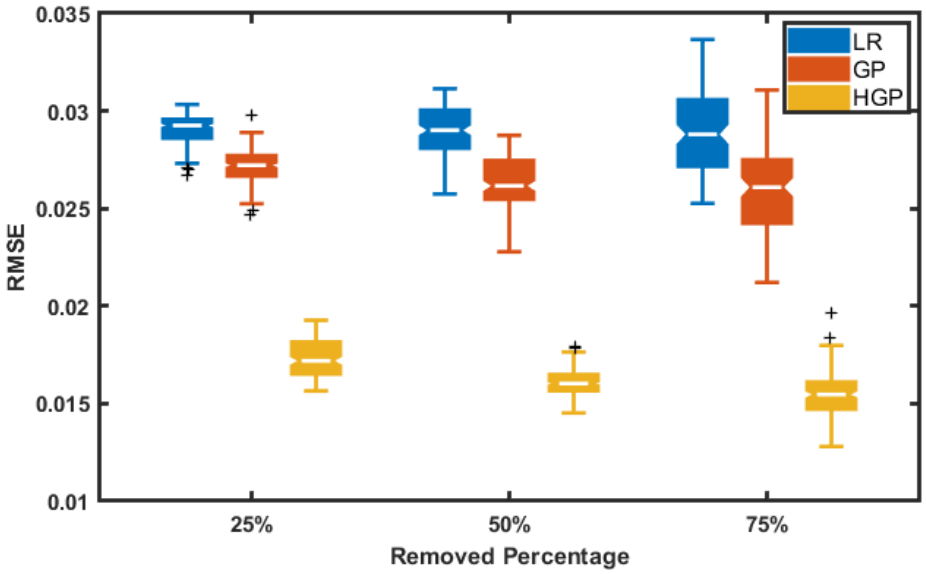

Figure 3.7. RMSE for different removed data percentages

3.4 Conclusions

In this chapter, we developed transition probability matrices for female breast cancer patients for different ages, treatment histories, and cancer stages. We defined a Markov Chain model based on available features on the retrieved SEER dataset. With information derived from the SEER dataset, we conduct data mining to get a closer look into the data structure and learn more insight about the data. Further, basic conditional probability is applied to the estimation of transition probabilities, and a novel Hierarchical Gaussian Process is utilized as a complement to missing parts in the matrices. In order to validate the methodology we utilized in missing value imputation, a benchmarking study is conducted, linear regression, simple Gaussian process, and proposed HGP model are compared. The result shows that HGP is more effective than the other two methods in imputing the missing values in our model.

The result of this chapter can provide insightful information on the progression of breast cancer associated with age, stage, and treatment history. In the next chapter, the estimated transition matrices will be implemented on Markov Decision Making process models.

Chapter 4

Markov Decision Making Process for Multi-stage Optimization

4.1 Introduction

In this chapter, we utilized transition matrices estimated from Chapter. 3 to design an MDP model. The MDP framework is designed to derive the optimal treatment strategies (i.e., wait, prophylactic surgery, radiation therapy, Chemotherapy, and their combinations) for any state that is composed of age, health, and prior treatments. The objective function is to maximize the total reward measured in terms of quality-adjusted life-years (QALYs) and to minimize expected cost of treatments.

The remainder of this chapter is organized as follows: Section. 4.2 introduces the research methodology of the proposed MDP. Section. 4.3 presents the experimental results for the real-world case study.

4.2 Research Methodology

In this chapter, a data-driven decision-making platform is developed. We focused on individuals who are already diagnosed with breast cancer, making this a retrospective study. As shown in Fig. 4.1, the proposed methodology consists of the following steps: 1)state-action transition dynamics and 2) MDP modeling of optimal and sequential decision making for breast cancer patients. We first integrated different SEER data files and then organized them based on patients' ID in the tensor structure. Next, we utilized the state-action transition dynamics that estimated from previous chapter for breast cancer patients between 25 to 65 years old. Finally, we deployed an MDP framework with cost and QALYs as reward functions, which yields the optimal treatment strategies over lifespan based on patients' specific states.

4.2.1 MDP Modeling of Breast Cancer

The proposed MDP framework is defined by age, health status, and prior treatments. Components of the finite MDP are decision epoch, state space, decision space, state transition, and reward function, additional reward function, and probability mass function are defined over state space.

- **Decision epoch:** The decision epoch is assumed to be initiated from age 25 to age 65.

- **State space:** The state space for a patient p is defined using a three-tuples as

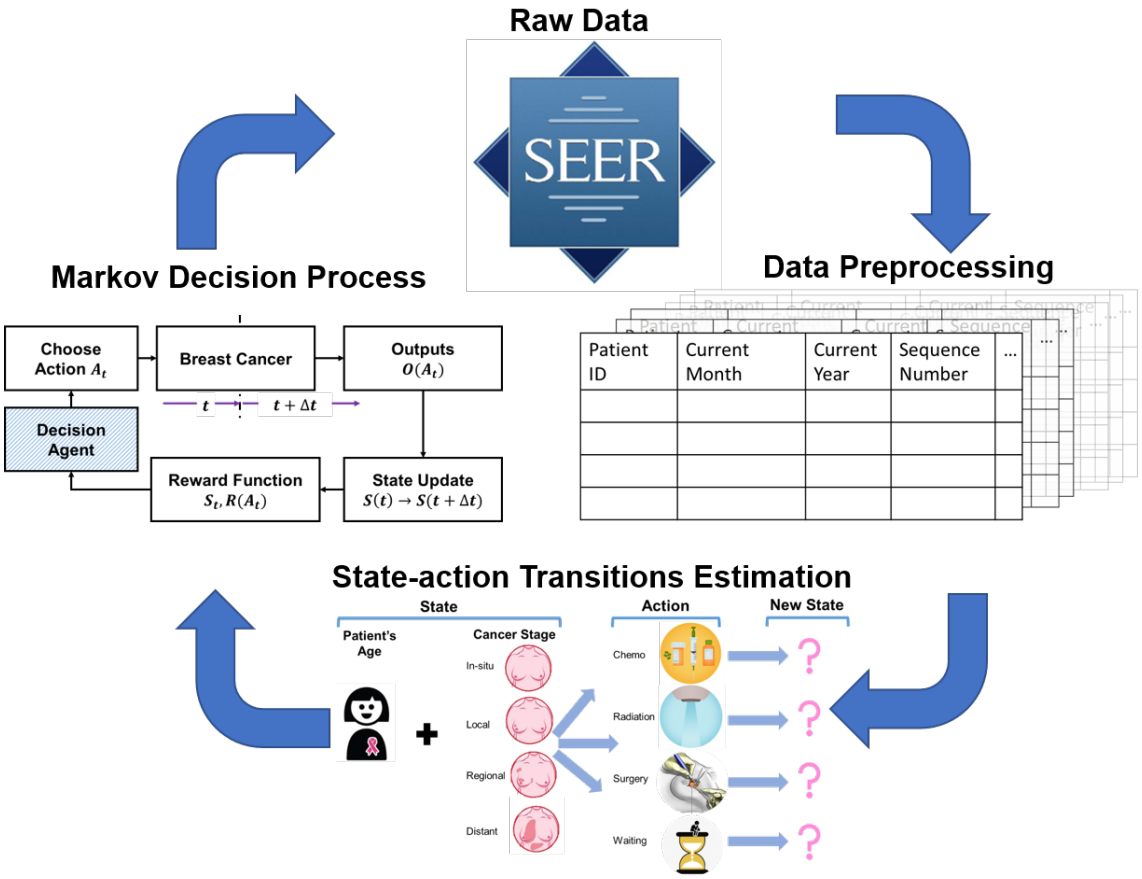

Figure 4.1. Flow diagram of the research methodology.

$s = (a, c, t)$, where a denotes age of patient, $a \in \{A_{min} = 25, 26, ..., A_{max} = 65\}$, c represents health status based on the stage of the cancer (i.e., *in situ*, local, regional, and distant). t is the treatment history of a patient, which is defined as three-tuple as prophylactic mastectomy, radiation therapy, Chemotherapy. We denote $X_a, a \in \{25, 26, ..., 65\}$ the state random variable at the age a. Also, the state process $X = \{X_a : a = 25, ..., 65\}$. The probability of being at a particular stage at the age $a + 1$ relies on the health status and treatment history. Therefore, $P(X_{a+u} = k|X_q, \forall q \leq a; a + u \leq 65) = P(X_{a+u} = k|X_q = v)$; as a result, X has a Markov chain property.

- **Action space:** The action space is defined as D, and d shows a possible decision from the action space. The decision are wait, prophylactic mastectomy, radiation therapy, Chemotherapy, and their combinations (i.e., prophylactic mastectomy, radiation therapy, and Chemotherapy) based on patient's age, health status and prior treatments.

- **Decision space:** The decision rule is denoted by $Q(s_a; d)$, which is the probability of selecting action $d \in D$ given the state s and at age index a.

- **State transition:** Let $P_a(s'|s)$ be the transition probability from state s in age a to state s' in age $a+1$ under the action $d \in D$. The transition probabilities are estimated from previous Chapter, based on the action space, we developed a state-action transition dynamics.

As shown in Fig 4.2, a 35 years old patient with *in situ* stages of cancer and no treatment history can transit to various states between ages 36–37 and 37–38 under the decisions of wait and Chemotherapy, respectively.

4.2.2 MDP Solution

We leveraged the finite-horizon dynamic programming algorithm for solving our MDP model. Let $V_k(s)$ represents the value of state s in the iteration k. Also, α is the discounting factor. In addition, $r(s, a)$ and $p(s'|s, a)$ are the immediate reward of selecting decision a at state s and the one-step transition probability from state s to s' under decision a, respectively. Note that the value of the state is updated in each

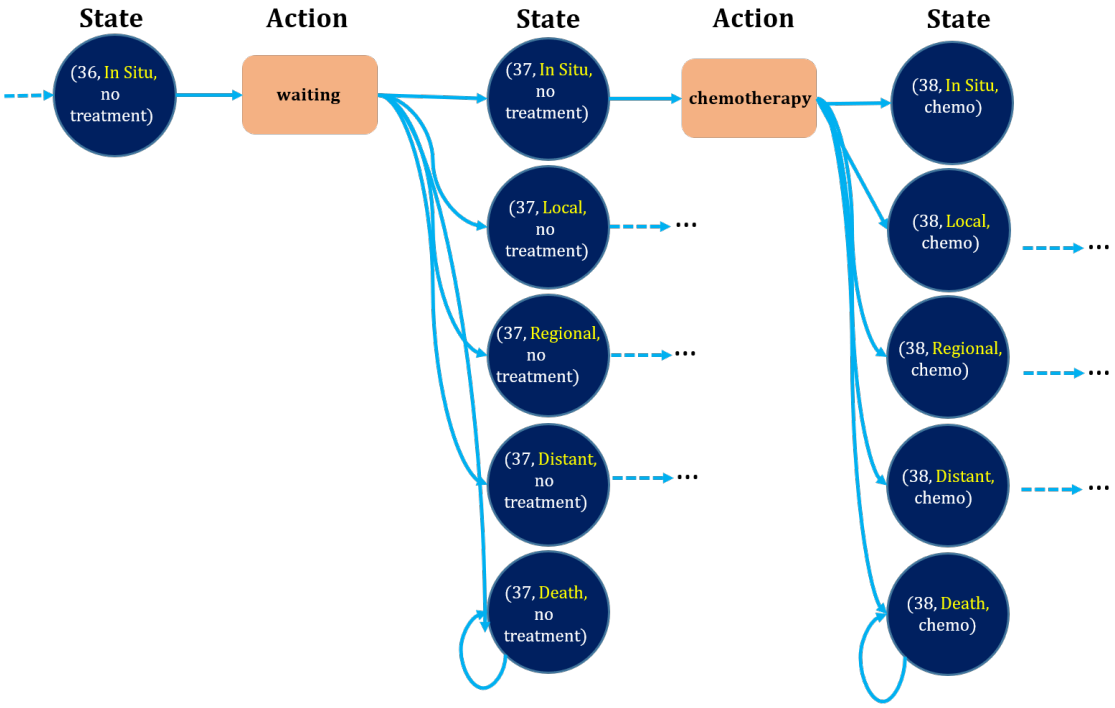

Figure 4.2. An example of two-step state-action transitions dynamics in the MDP framework.

iteration as follows:

1. Put $V^*_{A_{max}}(s) = r_{A_{max}}(s)$ if $a = A_{max} \forall s \in S$

2. Let $a = k$ for $k = A_{max} - 1, ..., A_{min}$, update the value for each state:

$$V^*_k(s) = \max_{d \in D_k} \{r_k(s,d) + \alpha \sum_{s' \in S_{k+1}} p_k(s'|s,d), V^*_{k+1}(s')\} \tag{4.1}$$

3. Choose optimal policy:

$$\pi^*_k(s) = \arg\max_{d \in D_k} \{r_k(s,d) + \alpha \sum_{s' \in S_{k+1}} p_k(s'|s,d)\, V^*_{k+1}(s')\} \tag{4.2}$$

In Eq. (4.2), $\pi^*_k(s)$ is the optimal policy in the state s at the age k. Note that the

Table 4.1. Cost values and utility for QALYs

	Health Condition and Treatment	Cost Within a Year	Mean Utility Weights
Health Conditions	BC *in situ*	60,637	0.965
	BC Local	82,121	0.86
	BC Regional	129,387	0.675
	BC Distant	134,682	0.38
	Healthy	0	1
	Death	1,000,000	0
Treatments	Prophylactic Mastectomy	686,980	0.76
	Radiation Therapy	91,335	0.76
	Chemotherapy	115,006	0.81

above solution assumes that the decision horizon is finite.

4.2.3 Reward functions

Cost and QALYs are two reward functions investigated in this chapter. The cost function includes expenses of health state and cancer treatment. Therefore, the total cost depends on the health state of patients. Table 4.1 shows the expected mean utility weights (also called preference rating), the cost of health state and treatments, which are adopted from [29] and [30], respectively.

4.3 Experimental Results

4.3.1 Optimal Treatment Strategies

As shown in Table 4.2, the optimal policies (i.e., wait (w), prophylactic mastectomy (p), radiation therapy (r), Chemotherapy (c), and/or their combinations (i.e., p+r, p+c, r+c, and p+r+c)) vary based on patient's age, health status, and prior treatments as well

Table 4.2. Cost-Optimal Treatment Strategies for Breast Cancer Patients of Ages 25 to 65

	Stage and History											
	In Situ			Local			Regional			Distant		
Age	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)
25	w	p	w	w	w	w	w	w	w	w	p	w
35	w	c	w	p	w	w	c	w	w	p	p	w
45	w	c	w	p	w	w	c	w	w	p+r	p	w
55	w	c	w	p	w	w	p	w	w	p+r	p	w
65	w	c	w	p	w	w	w	w	w	c	c	w

Table 4.3. QALYs-Optimal Treatment Strategies for Breast Cancer Patients of Ages 25 to 65

	Stage and History											
	In Situ			Local			Regional			Distant		
Age	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)	(0, 0, 0)	(0, 1, 0)	(1, 1, 1)
25	w	p	w	w	w	w	w	w	w	w	w	w
35	w	p+c	w	p+c	w	w	c	c	w	p+c	c	w
45	w	c	w	p	w	w	c	w	w	c	c	w
55	w	w	w	p	w	w	w	w	w	c	c	w
65	w	w	w	w	w	w	w	w	w	w	w	w

as the reward function. Note the optimal policy for a patient at the age of 25 and with no treatment history (i.e., (p, r, c) = (0, 0, 0)), and *in situ* stage is to wait. However, for the patient with the same stage of cancer with radiation therapy history, prophylactic mastectomy in this age is the optimal policy when the cost is our objective function.

It is worth mentioning that for a patient at the age of 65, and when the stage of the cancer is *in situ*, the proposed model recommends prophylactic mastectomy. However, as the cancer stage progresses, Chemotherapy is the optimal solution. Also, for middle-aged patients with the regional and distant stage of cancer, the combination of prophylactic mastectomy and radiations decreases the chance of death. The result also shows that as patients with *in situ* or distant types of cancer get aged, the optimal treatment strategies change from prophylactic mastectomy to Chemotherapy.

As shown in Table 4.3, the optimal treatment strategies when QALYs are the reward function are different from the results in Table 4.2. Note for patients with *in situ* stages of cancer with radiation history; the optimal action is prophylactic mastectomy. However,

as age increases, the Chemotherapy becomes more effective than prophylactic mastectomy to keep the QALYs high. Also, for a patient with a more invasive stage of cancer (i.e., distant), Chemotherapy is more effective than prophylactic for higher QALYs.

Chapter 5

Conclusions

Breast cancer is the most common type of cancer and leads to the death of a woman approximately every 13 minutes. Intervention and treatment strategies are the common actions that may reduce and prevent the risk of breast cancer occurrence and progression; the strategies also help patients to return to their healthy life. The important challenge for breast cancer individuals is to find the best timing and type of effective intervention and treatment actions. The available historical data provides an unprecedented opportunity to revolutionize cancer care delivery. In this study, we used the SEER dataset to define a Markov Decision Making Process model to derive the optimal breast cancer treatment strategy.

We first processed SEER data based on the availability and research purposes and conducted data mining on the processed data to learn more about the breast cancer data. Then we estimated the transition probability matrices based on conditional probability and defined the Markov Chain model. The Markov Chain is defined with patients' age, health status, prior treatments. In order to complete the matrices, the Hierarchical

Gaussian Process is developed to impute the missing parts in the matrices.

Further, we developed an multi-stage MDP model as a dynamical approach to address this problem and obtain a robust sequential decision making for QALY and cost as reward functions. The results show that as age increases from 25 to 65, chemotherapy becomes more effective than prophylactic mastectomy to keep the QALYs high. The proposed evidence-based decision support tool has the potential to improve treatment planning in different healthcare domains such as prostate cancer and cardiac diseases.

Bibliography

[1] Imani, F., R. Chen, C. Tucker, and H. Yang (2019) "Random Forest Modeling for Survival Analysis of Cancer Recurrences," in *2019 IEEE 15th International Conference on Automation Science and Engineering (CASE)*, IEEE, pp. 399–404.

[2] Cronin, K. A., A. J. Lake, S. Scott, R. L. Sherman, A.-M. Noone, N. Howlader, S. J. Henley, R. N. Anderson, A. U. Firth, J. Ma, et al. (2018) "Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics," *Cancer*, **124**(13), pp. 2785–2800.

[3] Gupta, P. B., C. M. Fillmore, G. Jiang, S. D. Shapira, K. Tao, C. Kuperwasser, and E. S. Lander (2011) "Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells," *Cell*, **146**(4), pp. 633–644.

[4] Kurian, A. W., D. F. Munoz, P. Rust, E. A. Schackmann, M. Smith, L. Clarke, M. A. Mills, and S. K. Plevritis (2012) "Online tool to guide decisions for BRCA1/2 mutation carriers," *Journal of Clinical Oncology*, **30**(5), p. 497.

[5] Nahta, R., L. X. Yuan, B. Zhang, R. Kobayashi, and F. J. Esteva (2005) "Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells," *Cancer research*, **65**(23), pp. 11118–11128.

[6] Barnett, G. C., M. Shah, K. Redman, D. F. Easton, B. A. Ponder, and P. D. Pharoah (2008) "Risk factors for the incidence of breast cancer: do they affect survival from the disease?" *Journal of Clinical Oncology*, **26**(20), pp. 3310–3316.

[7] Pérez-Ocón, R., J. E. Ruiz-Castro, and M. L. Gámiz-Pérez (2001) "Non-homogeneous Markov models in the analysis of survival after breast cancer," *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, **50**(1), pp. 111–124.

[8] Group, E. B. C. T. C. et al. (2011) "Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials," *The Lancet*, **378**(9804), pp. 1707–1716.

[9] Boer, R., H. de Koning, A. Threlfall, P. Warmerdam, A. Street, E. Friedman, and C. Woodman (1998) "Cost effectiveness of shortening screening interval or extending age range of NHS breast screening programme: computer simulation study," *Bmj*, **317**(7155), pp. 376–379.

[10] Michaelson, J. S., E. Halpern, and D. B. Kopans (1999) "Breast cancer: computer simulation method for estimating optimal intervals for screening," *Radiology*, **212**(2), pp. 551–560.

[11] Plevritis, S. K., B. M. Sigal, P. Salzman, J. Rosenberg, and P. Glynn (2006) "Chapter 12: a stochastic simulation model of US breast cancer mortality trends from 1975 to 2000," *JNCI Monographs*, **2006**(36), pp. 86–95.

[12] Kurian, A. W., B. M. Sigal, and S. K. Plevritis (2010) "Survival analysis of cancer risk reduction strategies for BRCA1/2 mutation carriers," *Journal of Clinical Oncology*, **28**(2), p. 222.

[13] Le, Q. A. and J. W. Hay (2009) "Cost-effectiveness analysis of lapatinib in HER-2–positive advanced breast cancer," *Cancer*, **115**(3), pp. 489–498.

[14] Yen, M.-F., L. Tabar, B. Vitak, R. Smith, H.-H. Chen, and S. Duffy (2003) "Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening," *European journal of cancer*, **39**(12), pp. 1746–1754.

[15] Abdollahian, M. and T. K. Das (2014) "A MDP model for breast and ovarian cancer intervention strategies for BRCA1/2 mutation carriers," *IEEE journal of biomedical and health informatics*, **19**(2), pp. 720–727.

[16] Haukoos, J. S. and C. D. Newgard (2007) "Advanced statistics: missing data in clinical research—part 1: an introduction and conceptual framework," *Academic Emergency Medicine*, **14**(7), pp. 662–668.

[17] Newgard, C. D. and J. S. Haukoos (2007) "Advanced statistics: missing data in clinical research—part 2: multiple imputation," *Academic Emergency Medicine*, **14**(7), pp. 669–678.

[18] Zhang, Z. (2016) "Missing data imputation: focusing on single imputation," *Annals of translational medicine*, **4**(1).

[19] Shrive, F. M., H. Stuart, H. Quan, and W. A. Ghali (2006) "Dealing with missing data in a multi-question depression scale: a comparison of imputation methods," *BMC medical research methodology*, **6**(1), p. 57.

[20] Myrtveit, I., E. Stensrud, and U. H. Olsson (2001) "Analyzing data sets with missing data: An empirical evaluation of imputation methods and likelihood-based methods," *IEEE Transactions on Software Engineering*, **27**(11), pp. 999–1013.

[21] Pantanowitz, A. and T. Marwala (2009) "Missing data imputation through the use of the Random Forest Algorithm," in *Advances in Computational Intelligence*, Springer, pp. 53–62.

[22] Li, D., J. Deogun, W. Spaulding, and B. Shuart (2004) "Towards missing data imputation: a study of fuzzy k-means clustering method," in *International conference on rough sets and current trends in computing*, Springer, pp. 573–579.

[23] Yao, B., F. Imani, and H. Yang (2018) "Markov decision process for image-guided additive manufacturing," *IEEE Robotics and Automation Letters*, **3**(4), pp. 2792–2798.

[24] Schaefer, A. J., M. D. Bailey, S. M. Shechter, and M. S. Roberts (2005) "Modeling medical treatment using Markov decision processes," in *Operations research and health care*, Springer, pp. 593–612.

[25] Anderson, K., J. S. Jacobson, D. F. Heitjan, J. G. Zivin, D. Hershman, A. I. Neugut, and V. R. Grann (2006) "Cost-effectiveness of preventive strategies for women with a BRCA1 or a BRCA2 mutation," *Annals of internal medicine*, **144**(6), pp. 397–406.

[26] Abdollahian, M. and T. K. Das (2015) "A MDP model for breast and ovarian cancer intervention strategies for BRCA1/2 mutation carriers," *IEEE journal of biomedical and health informatics*, **19**(2), pp. 720–727.

[27] Imani, F., C. Cheng, R. Chen, and H. Yang (2019) "Nested Gaussian process modeling and imputation of high-dimensional incomplete data under uncertainty," *IISE Transactions on Healthcare Systems Engineering*, **9**(4), pp. 315–326.

[28] Oeffinger, K. C., E. T. Fontham, R. Etzioni, A. Herzig, J. S. Michaelson, Y.-C. T. Shih, L. C. Walter, T. R. Church, C. R. Flowers, S. J. LaMonte, et al. (2015) "Breast cancer screening for women at average risk: 2015 guideline update from the American Cancer Society," *Jama*, **314**(15), pp. 1599–1614.

[29] Blumen, H., K. Fitch, and V. Polkus (2016) "Comparison of treatment costs for breast cancer, by tumor stage and type of service," *American health & drug benefits*, **9**(1), p. 23.

[30] Plevritis, S., A. Kurian, B. Sigal, B. Daniel, D. Ikeda, F. Stockdale, and A. Garber (2006) "Cost-effectiveness of screening for breast cancer with magnetic resonance imaging in BRCA1/2 mutation carriers," *JAMA*, **295**, pp. 2374–2384.