Modeling of Cancer Tumour Growth and Optimum Control of Chemotherapy Drug Doses

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Originality Statement

I hereby declare that this submission is the own work of Rahat Hossain Faisal and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the University of Dhaka or any educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by others, with whom Mr. Rahat has worked at University of Dhaka or elsewhere, is explicitly acknowledged in the thesis. I also declare that intellectual content of this thesis is the product of Mr. Rahat's research work, except to the extent that assistance from others is acknowledged.

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Abstract

Cancer is a leading cause of death in Bangladesh as elsewhere in the world. Huge effort and measures have been taken to control cancer even though an alarming increase in new cases is predicted by doctors and health organizations. Successful treatment requires clear understanding of disease and its progression, early detection, optimum drug scheduling and expert oncologists/clinicians having experience and knowledge in cancer domain. Moreover, optimum control of chemotherapy drug dose scheduling is a very challenging task where many treatment constrains and objectives are to be meet which are often found inherently in conflict. This thesis presents an investigation into modeling of cancer tumour growth and optimum control of chemotherapy drug doses. A novel optimum chemotherapy drug scheduling is designed based on clinical practice and expert knowledge. Cancer tumour growth models are extensively investigated and one of the growth models is incorporated as an integral part of the chemotherapy drug dose scheduler to observe the response of a dose administered which, in turn, is used to calculate next schedule. In order to capture knowledge of a number of expert clinicians and oncologists, fuzzy systems are designed and used as the core components of the optimum control of chemotherapy drug doses.

The proposed optimum chemotherapy drug scheduler will act as a decision support system for the clinicians/oncologist. Objective of this decision support system is to generate optimum chemotherapy drug dose scheduling considering the constraints, mainly keeping the toxicity under control and the system has to be clinically relevant. Many researchers gave their efforts to develop chemotherapy drug dose model, but most of these are often criticized due to lack of clinical relevance or hardly understandable to the clinicians/oncologists, as a result those are not useful to the oncologist. With this view in mind present decision support system has been developed in two phases. In the first phase a clinically relevant fuzzy expert system (FES) for tumour growth modelling and optimum chemotherapy drug dose scheduler is developed and in the second phase a fuzzy expert system with Physiologically Based Pharmacokinetic (PBPK) model based feedback controlled Decision Support System (DSS) for the oncologists is developed.

Clinically relevant fuzzy expert system for tumour growth modelling and optimum chemotherapy drug dose scheduler, a computational model, considers the patient's Body Surface Area (BSA) and experts' opinions to calculate chemo doses following the clinical practice. A proper balance between reducing cancerous cells and toxic side effects is required for effective drug scheduling. Still, in many cases, traditional clinical approaches fail to determine appropriate therapeutic doses that balance all restrictions. In the proposed system, Fuzzy Expert System-1 (FES-1) is developed to determine primary drug doses based on experts' opinions and competing treatment objectives. To adjust the dose, Fuzzy Expert System-2 (FES-2) is developed based on clinical practices, the patient's BSA, and experts' opinions. The final chemotherapy drug dose schedule is generated by combining the outputs of FES-1 and FES-2, which is the proposed modular FES. A growth model is used in this work to observe response due to administration of chemotherapy drug doses and to determine the following doses by considering cancer patients' three weight patterns (increasing, decreasing, and random order). Extensive simulation results and comparative assessment with other current computational chemotherapy drug scheduling models validate the effectiveness and the superiority of the model proposed in this study over the other methods reported in relevant studies.

In the second phase, a fuzzy expert system with PBPK model based Feedback Controlled Decision Support System for the oncologists is developed. The system is developed to generate optimal chemotherapy drug doses with a view to reduce the cancerous tumour cells to zero, if possible, keeping the toxicity within the limit. Apart from these, the DDS model will also give the oncologists the opportunity to observe the drug concentration in different organs of the patient body. This will help/support the experts to justify the drug doses to be applied physically. The DSS model consists of three modules, which are a) Fuzzy Expert System for Chemotherapy Drug Dose Scheduler, b) Physiologically Based Pharmacokinetic (PBPK) Module for Drug Concentration Projection and c) Feedback Controller. The drug dose generated by the Fuzzy Expert System module will be inputted to the PBPK module to observe the drug concentration in different organs of the patient body, at the same time the feedback controller will help the fuzzy expert system to adjust the patient specific drug dose considering the output of the PBPK module and oncologist's suggested/expected drug concentration in different organs of the patient body. The first module, clinically

relevant fuzzy expert system, generates optimum drug doses, moreover in the present DSS model there is a provision to input threshold value of drug concentration for one or more organs considering the patient's physical condition (kidney function, liver function, etc.) and the type of cancer, as a result more patient specific and cancer specific optimum chemotherapy drug dose projection is possible. All the doses generated by the proposed drug scheduling schemes could reduce the cancerous cells to almost zero while keeping the toxic side effects within the safe limit.

This thesis is dedicated to my parents,

wife and children.

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It is a great pleasure that Allah, the almighty, who is the merciful and the most gracious, gave me the patience to travel a long journey of Ph.D. research and allowed me to complete my Doctoral Thesis.

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Rahat Hossain Faisal

Table of Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Motivation of the research

Cancer is a major health concern worldwide and despite advances in treatment, the disease remains a significant health challenge. Cancer can affect people of all ages, genders, and races, and can occur in any part of the body. Some of the most common types of cancer worldwide include lung cancer, breast cancer, colorectal cancer, and prostate cancer. According to the World Health Organization (WHO), cancer is the second leading cause of death globally, responsible for an estimated 9.6 million deaths in 2018. In addition, the number of new cases of cancer is expected to rise by about 70% over the next two decades. Like other countries in the world, cancer is the biggest threat to humanity in Bangladesh as well. In 2020, more than 1.5 lac new cancer patient were detected whereas in that year more than 1 lac cancer patient died in Bangladesh, which is really very alarming. The overall cancer scenario in Bangladesh in 2020 can be seen in the following fig. 1.2 (Global Cancer Observatory).

Every country in the world has been burdened with the incidence of one or more types of cancer. Globally, an estimated 19.3 million incidences and 10 million deaths due to cancer were reported in 2020 (Ferlay et al., 2021; Chhikara & Parang, 2023), where different types of cancer is shown in fig 1.1. The impact of cancer is not only felt by those who are diagnosed with the disease, but also by their loved ones and caregivers. The physical, emotional, and financial toll of cancer can be significant, and can have far-reaching effects on individuals, families, and communities. Family members of someone with cancer may experience a range of emotions, including fear, anxiety, sadness, anger, and guilt. Cancer treatment can be expensive, and family members may have to bear the huge cost. This can cause financial strain. Thus cancer affects not only the patient but also the whole family.

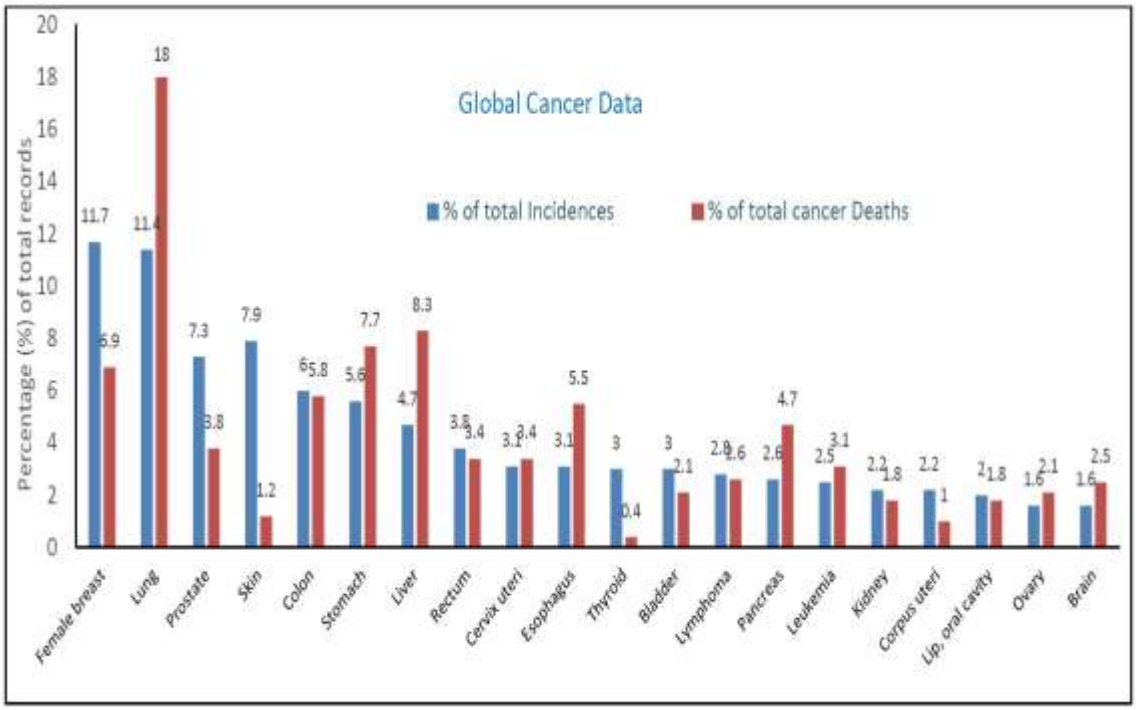


Fig. 1.1. Representation in % of total incidences (1.93 crores) and total deaths (1 crore) due to cancer (Ferlay et al., 2021; Chhikara & Parang, 2023)

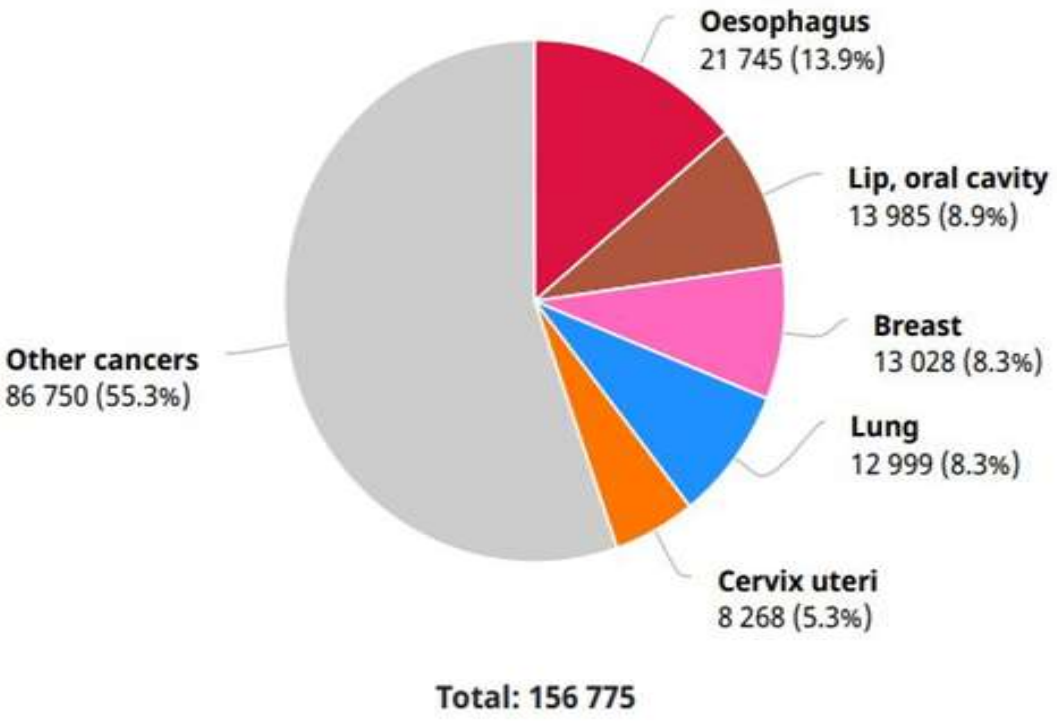


Fig. 1.2 Cancer statistics for Bangladesh (Global Cancer Observatory)

Due to this devastating situation of cancer worldwide, cancer research became a key concern of research in the western countries. Clinical research is very costly and time consuming. Moreover, every life is precious, ethically in most of the cases it become impossible to do trial directly on a patient's body, because it can be life threatening for him/her. In these circumstances, many researchers are trying to resolve this issue through mathematical and intelligent or artificial intelligence-based computational models, such as neural networks, fuzzy expert control, machine learning algorithms, evolutionary optimization-based hybrid systems to name a few as a complement to clinical research (Muthukaruppan and Er, 2012; Shahid and Singh, 2020). Although computational models have revealed valuable information regarding cancer dynamics, progression, diagnosis, drug discovery, scheduling and new range of treatment plans, but most of these techniques are often criticized due to the lack of clinical relevance and hardly understood by the clinicians/oncologists and they cannot use them in the cancer treatment. This is one reason of motivation to do research related to cancer treatment.

Again, from the above statistics, it is clear that cancer situation in Bangladesh is also too vulnerable. Due to overwhelming treatment costs, scarcity of trained professionals and unavailability of equipment, cancer care is still inaccessible to hundreds of thousands of cancer patients in Bangladesh. As a result, many cancer patients are dying without treatment and/or leading a measurable life with cancer. As a Bangladeshi researcher, it is one of the main reasons why one should be motivated to do research in the field of cancer.

It is clear that fight against cancer is still a serious issue for healthcare practitioners and researchers all over the world, despite the substantial breakthroughs that have been made in cancer treatment over the past few decades (Abdel-Wahab, et. al., 2017). But due to many variety of cancer and considering individual patient's physic, different oncologists may suggest different treatment plan. Like the chemotherapy drug dose and number of cycle for the same patient may very oncologist to oncologist. As a result in many occasions treatment may fail. In these circumstances, a cancer treatment effect prediction system may help to improve the cancer treatment plan and patient survival rate and quality of life may improve. For example, for chemotherapy treatment, before

applying the drug dose in a patient body, if the oncologist can have an idea of the best appropriate dose, number of cycles required, through a simulation system, and what would be the effect of the treatment in terms of tumour size, toxicity, drug concentrations in different organs of the patient then the oncologist would be able to take proper decision of treatment procedure; and this is the primary motivation of the present research.

Cancer is a disease of malignant cells that interact with and cooperate with their surroundings in complex ways, stimulating tumour (i.e. cancerous area) growth, while preventing the development of new blood vessels (Wu and Waxman, 2018). Some types of cancer do not form a tumour such as leukemias, myeloma and most types of lymphoma, which are not the focus of this research. There are four major approaches to cancer treatment: surgery, radiotherapy, bio-therapy with agents and chemotherapy (Ghasemabad et al., 2022). Surgery and radiotherapy are local treatments. Bio-therapy with agents uses biological agents (such as hormones, antibodies and growth factors) to treat cancer regardless of the location (Alam et al., 2013a; Alam et al., 2013b). Chemotherapy is an effective cancer treatment by applying drugs into human body that destroys cancer cells (Ghasemabad et al., 2022 & Behranvand et al., 2022). The key characteristics of cancer is the cell division that happens quickly. Chemotherapeutic drugs are applied at the time of cell division. Chemotherapy affects other living cells fast under usual conditions, such as those in the bone marrow, digestive system, and hair follicles, because it is unable to discriminate normal cells from cancerous ones (Alam et al., 2013a; Alam et al., 2013b; MacDonald, 2009). As a result, common adverse effects of chemotherapy include extreme tiredness, pain in muscles, myelosuppression (lower blood cell formation, resulting in immunosuppression), mucostisitis (inflammation of the digestion lining), and hair loss (baldness) (Alam et al., 2013a; Alam et al., 2013b; MacDonald, 2009; Johnsson et al., 2019). There are different classes of drugs such as alkylating agents, antimetabolites, anthracyclines and topoisomerase inhibitors. The dose of drug in chemotherapy is correlated with toxicity, side effects and many other factors. There is a direct correlation between dose of drug and the percentage of cells killed in chemotherapy [Beumer et al., 2012]. Therefore, the toxicity and side effects are considered in this study for drug dose scheduling in chemotherapy (Johnsson et al., 2019), which is the main interest of this research.

In chemotherapy treatment, the quantity of dose depends on the type of drugs. For determining the appropriate dose of chemotherapeutic, some oncologists use body weight, and others use body surface area. Besides some use the actual weight of patients, and others use the ideal body weight for the patient's height and frame. These dissimilarities affect considerable differences in calculated dose or dose intensity (Bastarrachea et al., 1994). In the last 50 years, with the relation to the patient's body surface area (BSA), most cytotoxics have been suggested, and this surface area is calculated by their height and weight. But this is not used for all types of cancer (Felici et al., 2002*).*

Maximum tolerated doses of chemotherapy are being used to the patients by the doctors at the outset to kill the most tumour cells and hope to eliminate the tumour before resistance appeared. According to the theory of cancer evolution, high doses of drug therapy not only cause significant side effects, but also remove the proliferation resistance of competitive drug-resistant tumour populations. High doses also accelerate the proliferation rate. This phenomenon is called competitive release (West et al., 2018; Enriquez-Navas et al., 2015). In many cases, the inaccurate body surface area-dosing found inconvenient and became important to find methods for more accurate dose calculation, which should be based on the known drug elimination processes for cytotoxic chemotherapy (Gurney, 2002). It is observed by the early study of the National Cancer Institute in Milan-patients who have lymph–node-negative early-stage breast cancer and were being randomized to undergo systemic adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) received more than 85% of the normal dose had better cancer reduction and recurrence rate than patients who received normal dose (Bonadonna et al., 1995). By changing some factors: administered dose, time interval of administration, or both, dose intensity can be increased or decreased (Lyman et al., 2009). According to Skipper (1971), it is observed that 20% of dose reduction can reduce the cure rates by 50% or more (Lyman et al., 2009).

For minimizing the toxicity of the drug and predicting the growth of the tumour, many mathematical models have been reported in recent years focusing on cancer chemotherapy (El-Garawany et al., 2017; Karar et al., 2020). The main suboptimal

problems in cancer chemotherapy are doses, drugs, and schedules (Salas-Benito et al., 2021). Some attractive efforts for optimizing scheduling problems are discussed in the literature review section which focused on maximum tolerated dosing. But none of them considered present clinical practice, which is weight-based dose calculation along with experts' opinion. In many cases, clinical people do not understand these computational models for drug dose calculation, as a result none of them are useful for them.

1.2 Aims and Objectives of this research

The aim of this research is to design and development of a novel chemotherapy decision support system for the oncologist which will generate an optimum chemotherapy drug dose schedule for a cancer patient. The research also aims to design the system as clinically relevant which will be understandable and usable to the clinicians. To incorporate expert knowledge, determine primary drug doses, competing treatment objectives and to adjust chemo doses, fuzzy expert drug scheduling scheme will be used. The objectives of this research are as follows:

1. To identify the challenges and drawbacks of previous research attempts on chemotherapy drug doses scheduling.
2. To develop of a novel clinically relevant fuzzy expert system for tumour growth modelling and optimal chemotherapy drug dose scheduling.
3. To incorporate a full body physiologically based pharmacokinetic (PBPK) model in the design procedure in order to show drug concentrations in different organs of patient body to support oncologist to treat a cancer patient more precisely.
4. To implement a feedback controller with the system to generate optimal drug doses considering the drug concentration in different organ of the patient's body; which will shape it as a complete decision support system (DSS) for optima chemotherapy drug doses scheduling.

1.3 Research Methodology

To design and develop the above mentioned systems, research methodology will be as follows:

- Study and analysis previous research related to tumour growth modelling.
- Analysis previous attempts of chemotherapy drug scheduling.
- Thorough investigation on chemotherapy drug dose scheduling in clinical context.
- Implementation of a growth model which will be used in the proposed system to observe the number of cancer cells and toxicity of patient body.
- Incorporate the basic growth model with our proposed clinically relevant model.
- Optimize the performance of the system with various alternative implementation of membership functions in the proposed fuzzy modules.
- Enhancing the system efficacy and to reduce system run time through alternative implementation of different fuzzy system like different decomposed fuzzy system approaches.
- Implementing Physiologically Based Pharmacokinetic (PBPK) model to observe the effect of optimal drug doses generated by the proposed fuzzy expert system in different organs' drug concentration.
- Design and implement a feedback controller to generate optimal drug dose considering the physic of the patient to support the oncologist for proper chemotherapy drug dose scheduling.

1.4 Proposed drug scheduling schemes

This section presents schematic diagrams and flow charts of proposed drug scheduling schemes. The detail design procedures and implementations of these schemes are explained in chapter 5 and 6.

1.4.1 Clinically relevant fuzzy expert system for tumour growth modelling and optimum chemotherapy drug dose scheduling

In this present research, a clinically relevant fuzzy system model for chemotherapy drug dose scheduling is proposed. In real-world situations, fuzzy logic allows decision makers to analyze the system from approximate information and convert linguistic variables into mathematical variables, even in ambiguous situations (Boadh et al., 2022 & Ozsahin and Ozsahin, 2018). The fuzzy expert system uses linguistic variable management system whose primary purpose is to provide expert advice in specific situations, and may improve the accuracy and efficiency of medical practice (Arab et al., 2021; Rogulj et al., 2021). In the fig 1.3 the block diagram of the proposed clinically relevant fuzzy expert system for tumour growth modeling and chemotherapy drug dose scheduler is shown. A flowchart for the working procedure of the proposed system is given in fig 1.4.

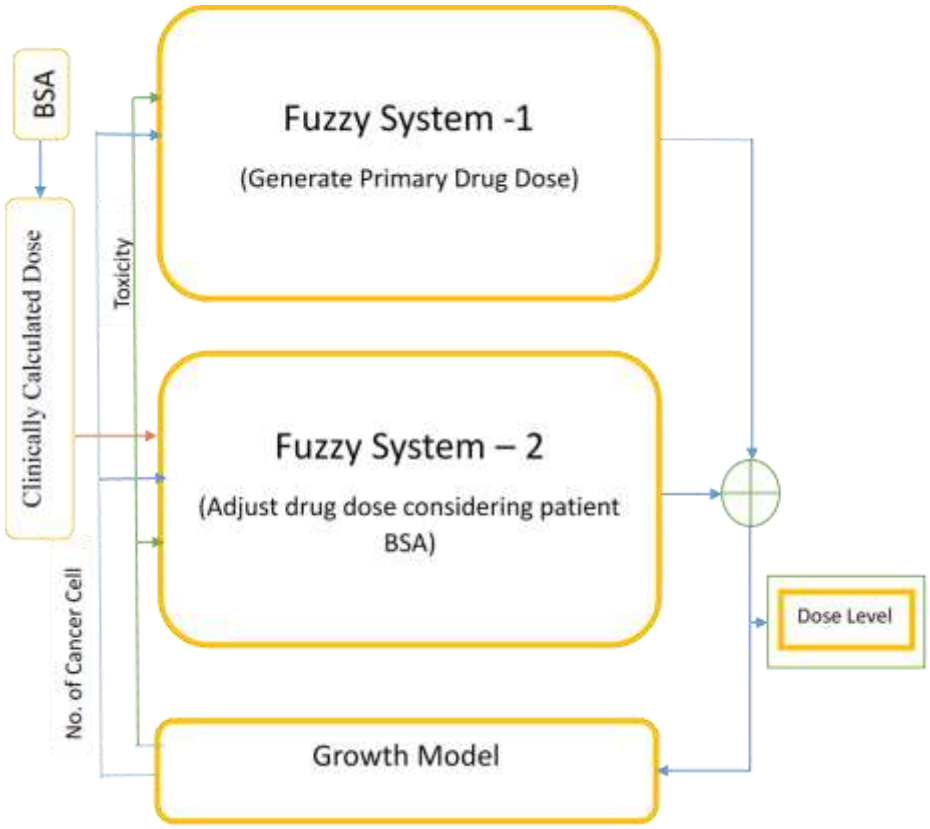


Fig. 1.3 Block diagram of the proposed clinically relevant fuzzy expert system for chemotherapy drug dose scheduler

In the first part of the proposed system, Fuzzy Expert System -1 is developed based on the Fuzzy System where experts' opinions are incorporated to determine primary drug doses, where competing objectives are considered. To determine the dose adjustment percentage, another Fuzzy Expert System, FES-2, is developed considering calculated dose, which is clinically calculated using patient's weight, and experts' opinion. Combining the outputs of these two Fuzzy Expert Systems, final chemotherapy drug dose schedule is generated. To determine and observe chemotherapy drug dose related parameters, a growth model, Martin's model, is used. The amount of drug calculated using BSA is an approximation based on the body height and weight. Though deterministic, fuzzy system is capable of reasoning better with such approximated or estimated information where direct measurement is not possible.

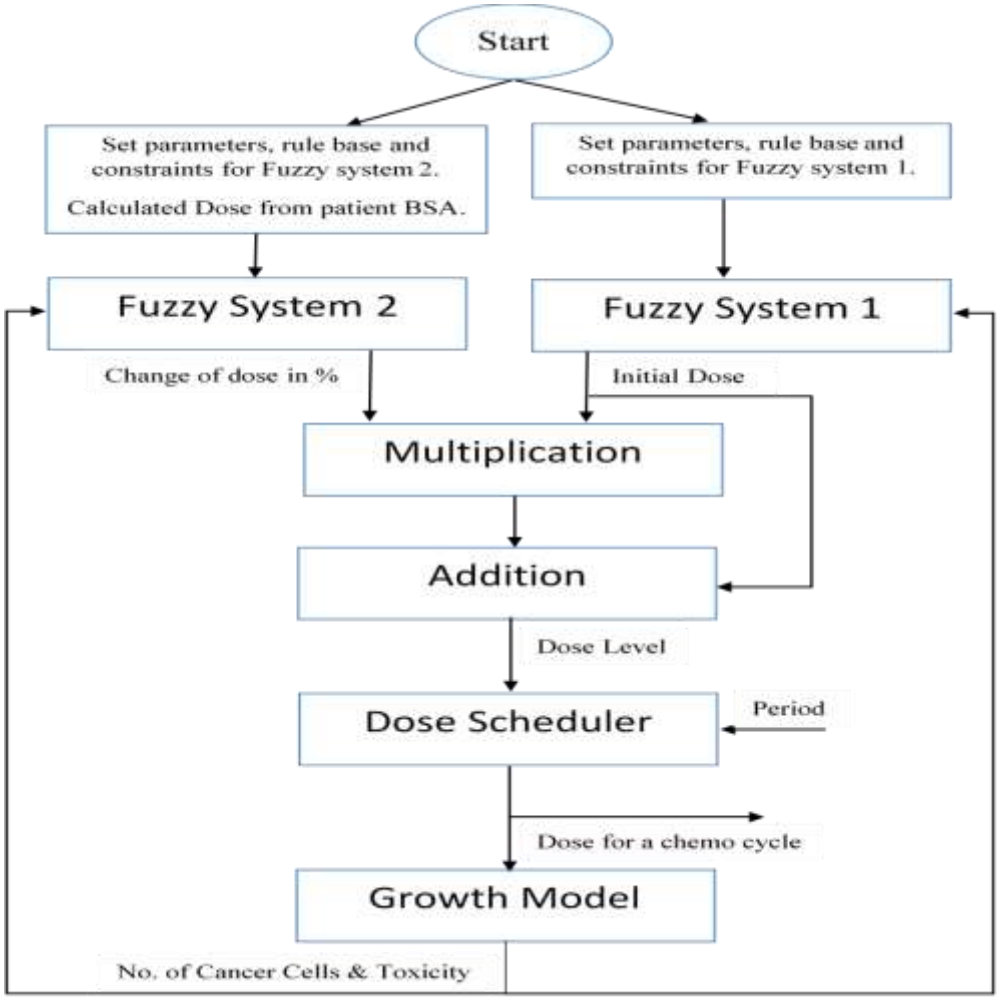


Fig 1.4 Flowchart for the working procedure of the proposed clinically relevant fuzzy expert system for chemotherapy drug dose scheduler.

1.4.2 FES based feedback controlled Decision Support System (DSS) for optimum chemotherapy drug dose scheduling

The fuzzy expert system-based DSS chemotherapy model is developed to track the chemotherapy dosage in the targeted organ and using the information on the concentration of drug in the target area, oncologists can decide the needed amount of drug to push on the patient's body. The inputs of the dose scheduler model are taken from the patient's information, and it recommends doses. This dose is applied to the PBPK model as input, and the concentration of the drug in all the organs is determined. Considering the kidney, liver function and overall physic of the patient the oncologist can set the threshold value of drug concentration of particular organs to generate safe and optimal drug dose for the patient. The block diagram of the architecture of the proposed model is depicted in Figure 1.5. The working procedure is explain through a flow chart in the fig. 1.6.

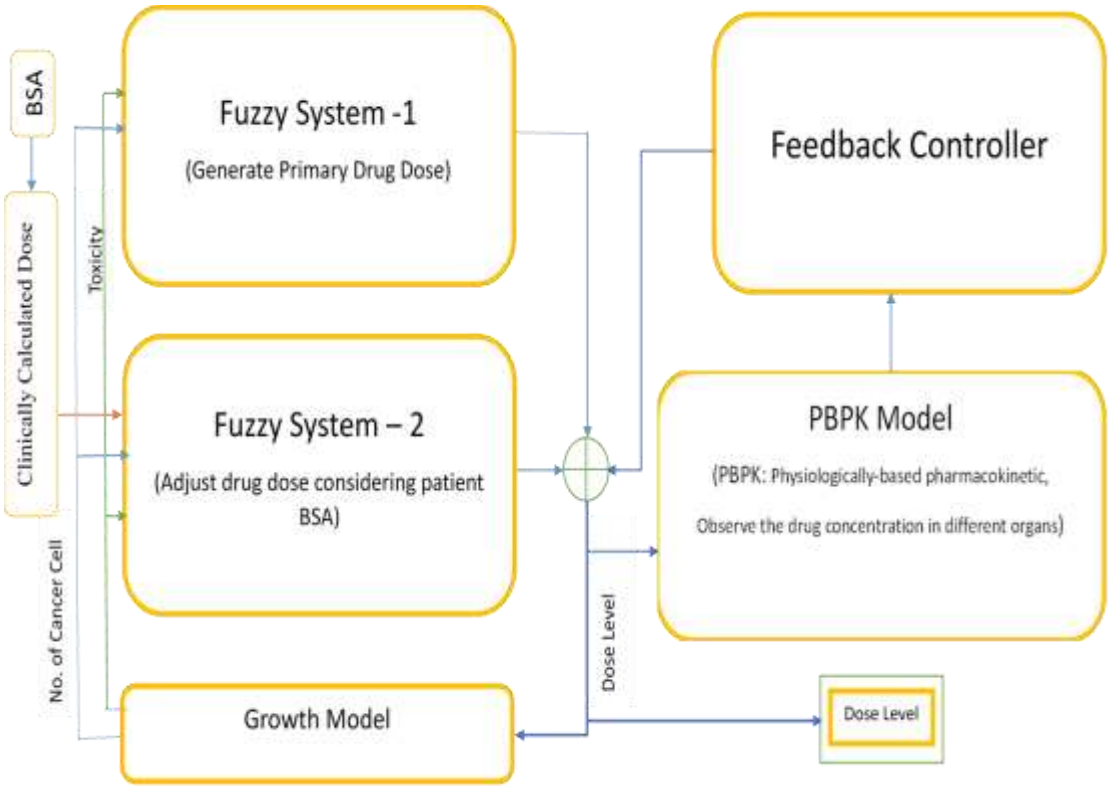


Fig. 1.5 Block diagram of the proposed FES based feedback controlled DSS for optimum chemotherapy drug dose scheduling

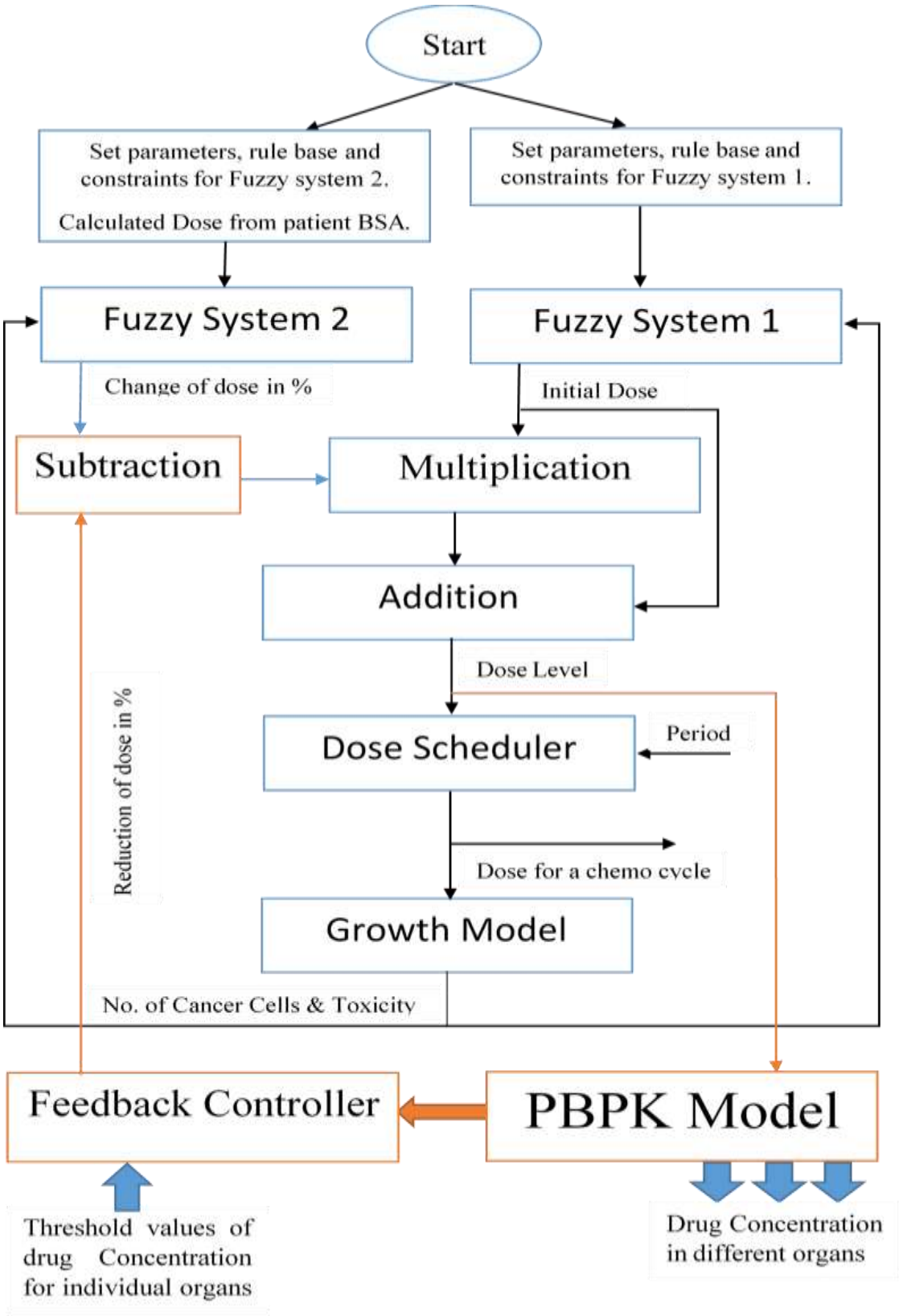


Fig 1.6 Flowchart for the working procedure of the proposed FES based feedback controlled DSS for optimum chemotherapy drug dose scheduler.

1.5 Outline of the Dissertation

This thesis proposes a clinically relevant fuzzy expert system based optimum chemotherapy drug dose scheduling model along with the provision to observe the tumour growth through the model. Furthermore, this dissertation report proposes a fuzzy expert system based oncologist support system for optimum chemotherapy drug dose considering the drug concentration of different organs of patient's body through incorporating the PBPK model. This model has the provision to observe the drug concentration in different organs of the patient's body which will also help the oncologist to treat the cancer. To explain the contributions and proposed system this dissertation report is organized in 7 chapters.

In the **2nd Chapter** relevant previous researches on chemotherapy drug dose scheduling and tumour growth modelling is discussed in details. None of the previous approaches were clinically relevant. Moreover most of the approaches were not good enough to reduce the cancer cells to ~0. In this chapter, research gap, research questions and contributions of this research are also discussed.

Since the aim of this research was to propose a clinically relevant optimum control chemotherapy drug dose scheduling, in the **3rd Chapter** cancer treatment in clinical context is discussed. Since chemotherapy drug dose scheduling is our research concern, mainly chemotherapy treatment procedure is discussed in details in the chapter three.

The proposed system/research is based on fuzzy expert system. Design, development and basic concept on fuzzy expert system is discussed in the **Chapter 4**. Fuzzy expert system is a huge domain, in this chapter mainly the components which are finally implemented in the present research are discussed.

Chapter 5 is the first working chapter of the present research. In this chapter the step by step development procedure of clinically relevant fuzzy expert system for optimum chemotherapy drug dose scheduler is discussed. Different tables, graphs and figures are used to explain the output of the proposed system. At the end of the chapter the proposed system is compared with the previous prospective research on the relevant field and showed that our proposed novel system outperforms other methods in prior

relevant studies, yielding the best performance in terms of performance index and the number of cancer cell remain at the end of the treatment, at a common day.

A new decision support system, to generate optimum chemotherapy drug dose scheduling considering drug concentrations in different organs of the patient body, for the oncologist based on fuzzy expert system and PBPK model is developed and presented in **Chapter 6**. In this chapter the PBPK model is explained, implemented and incorporated with the proposed system. The development procedure of the new proposed system is explained chronologically. System generated drug dose scheduling, tumour growth, toxicity profile and drug concentration in different organs of patient's body is shown through graphs. At the end of the chapter a hypothetical case study using the newly developed system is discussed to justify the effectiveness of the newly proposed system.

Finally in the last chapter, Chapter 7, summary of the findings, concluding remarks, limitations and possible extinction of this work is discussed.

Chapter 2

Literature Review

2.1 Previous researches on Tumor growth modelling and Chemotherapy drug Dose Scheduling

Many of the current chemotherapy drug dose scheduling models hold high potential and some important methods can be divided into three categories, which are described below.

One of the most important works is (Martin et al., 1990) that used differential equations to describe the drug scheduling models in the chemotherapy for treatment of cancer. In this research optimal parameter selection model of cancer chemotherapy was presented, describing the treatment of a tumor over a predetermined period of time via the repeated administration of a single medication. Throughout the treatment period, the substance was administered at evenly spaced intervals in doses determined by the model. The model generates a regimen that simultaneously minimizes the tumor population at the end of treatment and satisfies drug toxicity. But this model could not reduce the number of cancerous cell at a satisfactory level at the end of the treatment.

The works by (Skipper, 1978), (Crowther, 1974), and (Goldie & Coldman, 1979) proposed three-point constraints by the fact that the majority of the chemotherapy fails because of the drug resistance as the drug-resistant cells increase as the duration of tumor burden increases. The "three-point constraint" in chemotherapy refers to the balance between the maximum dose of chemotherapy that can be given, the frequency of administration, and the duration of treatment. The cancer chemotherapy three-point constraint is focused to achieve a 50% reduction of the tumor size in every three weeks and minimize the drug-resistant cell's potential emergence (Tan et al., 2002; Floares et al., 2003; Bojkov et al., 1993; Luus et al., 1995). Considering these three-point

constraints, (Martin and Teo's, 1994) performance index was not satisfactory and the final tumor size was too big.

(Bojkov, et. al., 1993) used the direct search optimization. Direct search optimization techniques are appealing due to their simplicity of application. When discontinuous functions or a large number of constraints make the calculation and application of gradients in the search for the global optimum extremely challenging, it is desirable to employ optimization techniques that do not calculate auxiliary functions such as gradients. (Luus, et. al., 1995) also used direct search optimization and the out number of tumour size was more than the desired level at the end of treatment. (Tan, et. al., 2002) also used evolutionary computation and (Floares, et. al., 2003) used adaptive neural networks to maintain the drug dose regimen but none of the models' performance was attractive.

In contrast, some researchers think that the overall efficiency and effectiveness of cancer chemotherapy cannot be improved by the three-point constraints (Tan et al., 2002; Floares et al., 2003; Bojkov et al., 1993; Luus et al., 1995; Liang et al., 2008). They only consider the drug toxicity. It simplifies the rules by excluding the constraints. (Carrasco & Banga, 1997) used this line of research and obtained a very few improvement.

In recent years Taguchi immune algorithm (TIA) helps the physicians selecting an efficient period for the drugs administration. It treated the drug schedule as a high dimensional and multimodal optimization problem (Tsai et al., 2013) which improved the overall effect on the simulation but the toxicity was 100 (Tsai et al., 2013) on most of the dosing dates which is the maximum limit. Thus, a patient with high toxicity tolerance uniquely can have a better schedule with this algorithm whereas others may suffer (Tsai et al., 2013). Another approach by Wang (Wang et al., 2018) was to use the memetic algorithm and general cell cycle algorithm with taking drug resistance, drug combination, and cell cycle into account. In this study, they formulated an algorithm that treats this problem as a nonlinear optimization problem and proposed a feasibility-based local search with a memetic algorithm. This approach does not have a regular cycle as the clinic has. This means the drug regiment set by them has no cycle like three

weeks or four weeks. El-Garawany (El-Garawany et al., 2017) used an embedded fuzzy controller to balance the trade-off between the cancer cell, toxicity, and drug, using Mamdani inference and hardware in the loop simulation study. The performance this system improved significantly.

Among recent studies, reinforcement learning (Shiranthika et al., 2022 & Eastman et al., 2021), evolutionary genetic algorithm (GA) (Panjwani et al., 2021), metronomic chemotherapy (Bodzioch et al., 2021), and other mathematical models in (Pachauri et al., 2022 & Nazari et al., 2021) were implemented to deal with cancer and chemotherapy.

2.2 Fuzzy Systems in contemporary researches

A similar but updated work using fuzzy, discussed in section 2.1, was proposed by Karar (Karar et al., 2020). It was specific for intravenous anti-cancer drug delivery that used invasive weed optimization (IWO) along with intuitionistic fuzzy sets. A mathematical patient model was used to evaluate this model and its performance improved than the previous attempts.

Different fuzzy deep models that take into account various neural architectures have been described in different research. The deep Takagi-Sugeno-Kang fuzzy classifier (Zhang et al., 2017) is a layered hierarchy with excellent reliability of fuzzy rules and fine results in terms of accuracy (Magdalena, 2019). It is established in (Sarabakha and Kayacan, 2019) to use deep fuzzy neural networks (DFNN) and expert knowledge to control nonlinear systems. The trajectory tracking capability of the unmanned aerial vehicle is outperformed by this adaptive offline and online based approach. Moreover, Human interpretability, efficient learning and optimized memory is triggered in a memristive modeling with fuzzy Deep Learning method (Zhang et al., 2020).

Recently, several fuzzy modular systems that take into account various adaptive architectures, which is also a research interest in the present research. The modular fuzzy system was applied in (Sharma & Sangal, 2020) to predict defects in the agile manifesto, where the explosion of fuzzy rules was controlled using modular fuzzy concepts adopted from (Mendel, 2017). (Oriani et al., 2020), predicted the rainfall by

implying the modular concept for creating twelve monthly FIS sub-models. The historical data has been examined at both seasonal and non-seasonal levels at the same time which has produced better prediction accuracy was the advantage of the modular concept. Further, wheelchair was stabilized in (Ahmad et al., 2011) by using modular fuzzy controlling system, where two different fuzzy system controller controls the torques, lifting, and stabilization of the chair to provide optimized fuzzy rule bases.

2.3 Physiologically Based Pharmacokinetic (PBPK) Model

PBPK model is a computational and simulation model that provides mechanistic representations of the drug in biological systems. This model combines information about drugs and prior knowledge of organs and tissues. Using this model, it is possible to know the drug concentration of the organ or compartments and gives concentration-time profiles to represent the drug concentration of the compartments and organs changes over time which may be difficult or impossible to measure experimentally (Kuepfer et al., 2016). On the basis of an interaction of physiological, physicochemical and biochemical properties and determinants, it allows to simulate the pharmacokinetics of drugs. For specific drug and having wider knowledge of physiology and biology, it may facilitate the drug discovery and development (Frechen & Rostami-Hodjegan, 2022).The vast majority of the references retrieved deal with three types of PBPK models (Nestorov, 2003):

1. Whole body PBPK models, describes the closed circulation loop with model structures.
2. Partial PBPK models of models of isolated body systems
3. Liver (metabolism) models, describing the hepatic elimination of drugs using physiological and biochemical parameters (i.e., liver blood flow, in-studied, the whole body PBPK model is a connectrinsic clearance, protein binding, etc.).

Pharmacokinetics is the kinetic process of examining the journey of drugs into the body and it is the summarization of the acronym of ADME where ADME describes the process of drug absorption into the body, distribution throughout the body, metabolizing enzymes in the body, and finally elimination from the body (Campbell,

2009). PBPK model is one of the PK models that linked to the advanced compartmental absorption and transit model (Miller et al., 2019). Nowadays, the application of PBPK model is increased as the different problems, diseases as well as thinking of optimization of previous solution are increased. To observe drug behavior, to translate the understanding to novel settings (e.g., to a different population), to identify an ideal therapeutic regimen, and to optimize risk–benefit ratios PBPK model is used. Basically, it is the main goal of PBPK model to generate, test and understand the mechanistic of physiological processes. Testing different drug schedules in a population is another important application of PBPK model. Besides, evaluating drug-drug interactions, assessing the impact of different drug formulations, extrapolations to diseased populations, etc. are the use of PBPK model (Kuepfer et al., 2016; Frechen & Rostami-Hodjegan, 2022). Basically, PBPK model is a successful model that is demanding than conventional empirical pharmacokinetic modeling. To implement it, the details of drug such as permeability, partition coefficient, transporters, metabolism, binding process and the details of organs such as organ volumes, surface areas, tissue composition, blood flow rate, protein abundance is required to know. Significant effort, resources, knowledge, time is needed to gain success in development and implementation of this model (Nestorov, 2003).

Recently, PBPK model usage has increased and complex full-blown PBPK models have been developed by several commercial platforms. Those platforms use the model by integrating physiological databases. GastroPlus (Simulations Plus, Lancaster, PA); SimCyp (SimCyp, Sheffield, UK), and PK-Sim and MoBi (Bayer Technology Services, Leverkusen, Germany) are those platforms that provide a generic model structure for the physiology of predefined species and populations(Kuepfer et al., 2016; Frechen & Rostami-Hodjegan, 2022).

Many types of researches have been conducted using the PBPK model resulting in original/novel outcomes. Some existing research that has used the PBPK model to develop systems in the last five years is described here. Using known anatomy and physiology of the brain, including the presence of distinct blood–brain barrier and blood–cerebrospinal fluid (CSF) barrier, a novel platform of PBPK model was developed to characterize the brain disposition of rat, monkey and human (Chang et al.,

2019). PBPK model was developed using a middle-out modeling approach to predict the magnitude and direction of food effects by combining bottom-up in vitro-based prediction with limited top-down fitting of key model parameters for clinical data (Pepin et al., 2021). A minimal PBPK (mPBPK) model of the brain was developed for antibodies to target CNS in (Bloomingdale et al., 2021). In this research, the author minimized the existing multi-species platform brain PBPK model to develop mPBPK model. A multi-pathway PBPK model was developed to predict the concentrations of trihalomethanes (THMs) in human body and the health risk of (THMs) in human tissues was analyzed in (Zhang et al., 2018). Zhangs' also analyzed the concentrations of trihalomethanes (THMs) in tap water and direct drinking water.

2.4 Research gap and research questions

In the previous sections different attempts in doing research in chemotherapy drug dose scheduling are discussed. To the best of our knowledge, none of the approaches were clinically relevant, as a result those were not understandable to the clinicians to be used for their purposes. Hardly, there is any approaches confirmed the reduction of number of cancer cell to ~0 at the end of the chemo cycles. Moreover, after applying the drug dose, the chemo drug concentration in different part of the patient's body were not studied, which could be helpful for the oncologist for safe treatment suggestion. As a result, the previous research approaches were not good enough to suggest an optimal chemotherapy drug dose schedule for cancer treatment.

Considering above issues research questions are as follows:

1. How to design a clinical relevant chemotherapy drug scheduling?
2. How to ensure optimum doses?
3. Which method/approach should be considered to incorporate the expert knowledge within the system?
4. How to achieve treatment goal and objectives?
5. How to observe the responses of doses?
6. How to observe toxic side effect and how to control it?

7. How to observe the drug concentration in different parts of the patient body after chemo dose is applied?
8. How to generate optimal chemo drug doses in different chemo cycle considering the drug concentration in different parts of the patient body?

2.5 Contributions of the research

Investigating different research attempts as discussed in the earlier sections and considering the above mentioned research gaps, following contributions have been achieved through my present research to design a complete decision support system for the oncologist for chemotherapy drug dose scheduling.

1. Previous attempts were not fully clinically relevant as a result they were not useful to the clinicians. In the present research, a novel clinically relevant fuzzy expert system for optimum chemotherapy drug dose scheduling with tumour growth projection system have already been developed. Clinicians will be able to use it as a decision support system for cancer treatment.

2. In general clinical practice, patient's Body Surface Area (BSA) is used to define the quantity of chemo dose, which is considered in the proposed system. Apart from general cases, for effective and quick recovery of cancer patient, dose can be enhanced to a certain percentage considering patient physical condition, which is dealt with expert opinion of the oncologist. This opinion may very oncologist to oncologist. 2^{nd} fuzzy expert system is used to incorporate the experts' opinions to generate more optimal drug dose.

3. Most of the previous relevant researches' performance index were not impressive and none of them could confirm number of cancer cell to 0 at the end of the chemo cycle. The developed fuzzy expert system proved to have best performance index, 29.242, and prescribe best drug dose to reduce cancerous cell ~0 keeping toxicity in control. The efficiency comparison of present research with previous attempts is shown in table 5.10 in chapter 5.

4. Chemotherapy drug scheduling is designed incorporating full body physiologically based pharmacokinetic (PBPK) model, which is a first-hand work, to observe the drug concentration in different organs of the patient body. This new feature will definitely help the oncologist to prescribe safe chemo drug and dose for a cancer patient.

5. In the present research, a feedback controller is introduced. The proposed FES based feedback controlled DSS for cancer/organ specific optimal chemotherapy drug dose scheduler for the oncologist is completely new, where the Oncologist will have their opportunity to find the optimum chemo drug dose and at the same time he/she will be able to observe the drug concentration of different targeted organs of the patient body, which will reduce the treatment risk.

6. Developed system's performance is optimized, veering decision weight pattern through alternative implementation of fuzzy membership functions in the proposed fuzzy modules.

7. System efficacy has been enhanced and system run time has been reduced through alternative implementation of different fuzzy system like different decomposed fuzzy system approaches.

1.5.1 Publications

Part of the research has been published in an Elsevier journal and another two papers have been prepared from the present research for submission. The published paper is mentioned bellow:

Faisal, R.H., Debnath, S., Islam, M.M.U., Sifath, S., Kakon, S.A., Alam, M.S., & Siddique, N. (2023). A modular fuzzy expert system for chemotherapy drug dose scheduling. Healthcare Analytics, 3, 100139. https://doi.org/10.1016/j.health.2023.100139

Accepted conference paper:

Debnath, S., Faisal, R.H., Islam, M.M.U., Sifath, S., Kakon, S.A., & Alam, M.S. (2023). Multi-objective Optimization and Feedback-based Chemotherapy Drug Scheduling. ICECCE 2023.

Chapter 3

Chemotherapy in Clinical Context

3.1. Cancer Basics

Cancer is a disease that causes certain cells in the body to grow in an uncontrolled manner and to spread to other parts of the body. Nearly any part of the human body, which is composed of trillions of cells, is a potential starting point for cancer (Weinberg, 1996; NCI, 2021).

Cancer can cause a number of severe side effects on the body, including fatigue, changes in weight (including unintended loss or gain), changes in skin, persistent coughing or breathing difficulties, and unexplained bleeding or bruising, among other symptoms. The aim of treatment for cancer is to eliminate the disease completely, thereby restoring the ability to lead a normal life span. Depending on the specific circumstances surrounding the patient, this may or may not be feasible. In the event that a cure cannot be achieved, one may undergo treatment in the hopes that their cancer will be shrunk or that the progression of their cancer will be slowed down, allowing them to live symptom-free for as long as possible. It is possible for the process of treating cancer to change in accordance with the mental and physical state of the patient.

Neoadjuvant treatment is the first line of defense when it comes to combating cancer. Treatment may consist of surgery, chemotherapy, or radiation therapy, all of which are required in order to eradicate all cancer cells and remove the cancer entirely from the body. In order to lessen the likelihood that the cancer will come back after primary treatment, adjuvant therapy's primary objective is to eradicate all cancer cells that are still in the patient's body. Palliative treatments, on the other hand, aim to alleviate the uncomfortable side effects of cancer treatment as well as the signs and symptoms caused by the cancer itself (Mayo Clinic, 2023).

According to the findings of the research, prehabilitation plays an important role in the implementation of appropriate interventions that aim to optimize the patient's health prior to the beginning of acute treatments. This is true for any stage of treatment for cancer (Silver & Baima, 2013; Chen & Kuo, 2017).

3.2. Types of Cancer Treatments

There are several different types of cancer treatment, including:

A. Surgery: In surgery cancerous tumor and surrounding tissues are removed. In many occasion, surgery is done at the beginning of treatment for solid tumors.

B. Radiation therapy: In radiation therapy high-energy radiation is used to destroy cancer cells. It can be delivered externally (external beam radiation) or internally (brachytherapy).

C. Chemotherapy: In chemotherapy different types of chemo drugs are used to kill cancerous cells. Chemotherapy can be given orally or intravenously.

D. Immunotherapy: This treatment works by stimulating the immune system to attack cancer cells.

E. Targeted therapy: In targeted therapy different types of drugs and/or other substances are used to target specific proteins or other molecules which involves to grow and spread of cancer cells.

F. Hormone therapy: This treatment is used for cancers that depend on hormones for their growth, such as breast and prostate cancer. It works by blocking the production or action of hormones.

G. Stem cell transplant: This treatment involves replacing damaged bone marrow with healthy stem cells.

H. Precision medicine: This treatment uses genetic information to personalize treatment for each patient. It may involve targeted therapy or immunotherapy.

The choice of treatment depends on the type and stage of cancer, the patient's overall health, their preferences and some other factors. Often, a combination of treatments may be used to provide the best chance of success. Among the above treatment options of cancer, surgery, radiation therapy and/or chemotherapy are most widely used treatment procedures. These treatment plans are applied individually or in a combinations of them.

Since chemotherapy drug dose scheduling is the present research interest, in this chapter chemotherapy in clinical context will be discussed in details.

3.3 Chemotherapy

Chemotherapy is a modality of treating cancer with anti-cancer drugs. These medicines accomplish their goal by destroying cancer cells. They are known as systemic treatments because they affect the patient's body as a whole (Davies & Epstein, 2010).

The type of cancer a patient has, cancer cells pattern under a microscope, whether the cancer is malignant, and the patient's overall health all play a role in determining whether or not chemotherapy is an appropriate treatment for that patient, as well as which drugs that patient might have (CRU, 2022).

While attempting to explain how chemotherapy works, some medical professionals use the word "cytotoxic." Cytotoxic is short for "cell killing." The patient may receive chemotherapy in the form of a single medicine or in the form of a combination of treatments. The chemotherapy medications a patient is given are determined by the location of the cancer in the patient's body (type of cancer). This is due to the fact that various medications have varying degrees of effectiveness against various cancers. So the drugs need for a cancer that started in the breast and has spread to the lung might be different to the drugs, which would have for a cancer that started in the lung (Skeel & Khleif, 2011).

The patient might just receive chemotherapy by itself. Alternately, the patient could have it in conjunction with other treatments, such as radiotherapy, surgery, hormone therapy, targeted cancer medications, immunotherapy, or any combination of any of these treatments. Patients might also have high dose chemotherapy as part of a bone marrow or stem cell transplant.

3.3.1 Working Procedure of Chemotherapy

The chemotherapy is delivered to all parts of the patient's body through the bloodstream. Because of this, it is able to kill cancer cells virtually everywhere in the body. Systemic treatment is another name for this approach. Cancer cells that are in the process of dividing into two new cells are killed by chemotherapy.

The individual cells that make up the body's tissues number in the billions. When we are adults, the majority of the cells in our bodies do not divide and multiply as frequently as they did when we were younger. They only do so when there is a need to remediate the damage. As cells divide, they give rise to two copies of themselves that are genetically identical. So, where there was once only one cell, there are now two. Then, when these are divided, we get 4, then 8, and so on (Davies & Epstein, 2010).

In cancer, the cells continue to divide indefinitely until they form a clump of cells. The lump that results from the accumulation of these cells is referred to as a tumor. Chemotherapy has a substantially better chance of killing cancer cells than it does most other types of cells due to the cancer cells' much accelerated rate of cell division. Certain pharmaceuticals are able to terminate dividing cells by inflicting damage on the portion of the cell's control center that is responsible for the process of cell division. The chemical pathways that are necessary for cell division are disrupted by other medications (Davies & Epstein, 2010).

The chemotherapy process causes harm to the cells as they divide. The nucleus is a black glob that can be found in the middle of each and every live cell. The nucleus serves as the cell's command and control hub. It is composed of chromosomes, each of which is composed of genes. In order to produce new cells, each instance of a cell dividing into two must involve the precise duplication of these genes.

The chemotherapy treatment causes harm to the genes that are housed within the nucleus of the cells. Several medications cause damage to cells just as they are about to divide. There are those that cause damage to the cells while they are in the process of producing copies of all of their genes prior to splitting. Chemotherapy is significantly less likely to cause damage to cells that are dormant, like the majority of normal cells.

It's possible that multiple types of chemotherapy medicines were combined in this treatment. This will include pharmaceuticals that cause damage to cells during various stages of the process of cell division. This indicates that there is a greater possibility of destroying more cells (Davies & Epstein, 2010).

3.3.2 Appropriate situations for chemotherapy

Chemotherapy is utilized by medical professionals due to the fact that it is transported throughout the body via the circulatory system. This means that it can effectively cure cancer in virtually any part of the body. Chemotherapy is a treatment that works on a systemic level. Surgery is only able to eliminate the cancer from the region of the body in which it is located. Radiotherapy, on the other hand, is only effective in treating the part of the body where it is directed.

Therefore, a patient may undergo chemotherapy in order to reduce the size of a cancer prior to undergoing surgery or radiotherapy, in order to try to prevent the cancer from returning after surgery or radiotherapy, as a treatment on its own if the type of cancer is very sensitive to it, and in order to treat cancer that has spread from the location where it first began. The following is a list of medical circumstances under which chemotherapy may be administered to the patient (DeVita et al., 2012):

A. **Prior to radiotherapy or surgery:** The purpose of chemotherapy administered prior to surgery is to reduce the size of a patient's tumor in order to reduce the amount of surgery required or to make it simpler to remove all of the cancerous tissue. If the chemotherapy is successful in shrinking the cancer, then the patient may just require radiation treatment to a more localized portion of their body. Neo-adjuvant treatment refers to the process of receiving chemotherapy prior to

other treatments in this manner. Primary treatment is a term that certain clinicians use from time to time.

B. **After surgical treatment or radiotherapy:** The purpose of chemotherapy following surgical treatment or radiotherapy is to reduce the likelihood of the cancer returning in the future. This type of treatment is known as adjuvant therapy.

C. **Blood Cancer:** If the patient has blood cancer, chemotherapy may be used as the only treatment, bypassing the need for surgery. Blood cancer is very sensitive to chemotherapy.

D. **For cancer that has spread:** Chemotherapy is a treatment option that may be suggested by a physician if there is a possibility that the cancer may spread at some point in the future. Or if it has already spread throughout the area.

E. **In conjunction with radiotherapy**: It is not uncommon for medical professionals to recommend chemotherapy at the same time as radiotherapy. This form of treatment is called chemo-radiotherapy or sometime chemo-radiation. It is possible that this will make the radiotherapy more successful, but it also has the potential to enhance the negative effects.

3.3.3 Methods of administering chemotherapy

The administration of chemotherapy through a drip can take anywhere from a few minutes to a few hours. The patient may receive his/her treatment via:

- Cannula, which is a tiny tube that is inserted into a vein in the patient's arm and is utilized for administering chemotherapy medications in a relatively expedient manner.
- Central line, which is a tube that is inserted into a vein in either the patient's neck (for a short period of time) or chest (long term).

- Portacath or port, which is a small chamber that rests under patient's skin at the end of the central line in the chest of the patient.
- PICC line is a form of central line that is inserted into a vein in the arm of the patient.

The amount of chemotherapy that is administered through the drip is tailored according to the patient's needs after your weight, height, and overall health are taken into consideration.

3.3.3.1 Administration of chemotherapy through a drip

It may be necessary to put some of the chemotherapy drugs to a drip bag in order to dilute them before they can be injected into a vein in the arm of the patient. An intravenous infusion is the proper term for this procedure. The patient's cannula will next have a set of plastic tubing connected to it by the nurse. This plastic tube has a hole in the top that allows for the attachment of the plastic bag that contains the therapy. Patient's vein is slowly injected with the medicine solution over the course of a predetermined amount of time. In today's world, administering chemotherapy through a drip nearly often requires the use of a pump. The rate at which the chemotherapy is infused into the patient's vein is precisely managed by the pump, which applies gentle pressure. The nurse administering the treatment will be able to adjust the timer to the appropriate duration. This ensures that the patient receives the necessary amount of chemotherapy at the appropriate pace. It is possible to undergo chemotherapy without the use of a pump. But, in that case the nurse will have to keep a much closer eye on the drip rate in order to ensure that the medication is being administered at the appropriate pace. Merely shifting the patient's arm can change the rate at which a drip is administered. Thus, the use of pumps is an essential component of a safety measure (CRU, 2022).

Chemotherapy using drip may cause couple of problems (DeVita et al., 2012):

- The drips that are going into the arm can be finicky; they can stop and start whenever the patient move his/her arm.
- The speed of drips is difficult to control as it is with a central line connected to a pump

- Cannula insertion can be challenging for some patients because of the fragility of the veins in their arms
- Cannulas have the potential to present a significant and potentially life-threatening risk because fluid may escape into the tissues that surround the vein rather than being absorbed into it. This phenomenon is known as extravasation.

Any fluid that escapes from the cannula has the potential to cause the region around it to become rigid, slightly bloated, and sometimes red. It may be possible for the nurse or doctor to remove the cannula and replace it with a fresh one in certain circumstances. And within about a day, the affected region will often have totally healed from the swelling. On the other hand, the leakage of certain chemotherapy medications can be harmful to the tissues and cause damage. These medications are referred to as vesicants. A vesicant medicine that is allowed to leak into the body might cause the tissues there to become inflamed and painful. It's not always the case that this takes place right away. Nonetheless, it is possible that the region will get more inflamed and uncomfortable during the next few days. Within the first two weeks, the patient may develop ulcers, which are sore and broken regions of skin. Healing from this kind of damage can take quite some time and, in most cases, does not necessitate the intervention of a plastic surgeon. Both the doctor and nurse are aware of whether or not the medication the patient is taking is a vesicant. They will keep a tight check on the chemotherapy drug to ensure that it does not enter into the patient's tissues by accident instead of his/her veins during the procedure. (DeVita et al., 2012; Davies & Epstein, 2010).

3.3.3.2 Treatment with chemotherapy administered via central lines

A long, flexible plastic tube that is termed a central line can be used to administer chemotherapy directly into a patient's bloodstream. Because they are inserted into a blood vessel that is central to the chest and close to the heart, these lines are referred to as central lines. There are several varieties of central lines to choose from. The first kind enters the body through a vein in the neck. This type of central line is referred to as an acute central line, and it is utilized for therapies that are only needed temporarily. Another type of line goes in through the chest of the patient. It then goes under the patient's skin to a large vein by his/her collarbone. The only bit that can be seen is the length of line that hangs out of the small entry hole in the chest. This is called a skin

tunneled central line. The connection ports are kept closed with caps. This is a picture of a skin tunneled central line in place (CRU, 2022).

3.3.3.3 Administration of chemotherapy by portacaths

A portacath allows for the delivery of chemotherapy as well as other medications and fluids. A portacath is a small chamber or reservoir that is placed beneath the skin at the end of patient's central line. It is also known as a subcutaneous catheter. The opposite end of the line is situated in a huge vein that is in close proximity to the heart of the patient. Patient should be able to feel the chamber of the portacath, but in most cases, patient won't be able to see it unless he/she is really thin. When it is the time for chemotherapy treatment, the nurse will insert a needle into the chamber and either give the patient injections or attach a drip to the IV line. Following their passage via the tubing, the medications will eventually reach the bloodstream of the patient. The portacath will remain in the patient's body for the duration of any necessary medical therapy. The fact that a portacath is not visible from the outside of the body is arguably the most significant benefit of having one. In contrast to having a central line, the patient will not have a tube protruding from his/her chest in this situation. On the other hand, some individuals like a central line because they dislike having a needle inserted into their skin each time they require therapy. It is possible that the patient may feel more comfortable if the nurse applied a topical anesthetic lotion to the skin above the portacath before inserting the needle (CRU, 2022).

3.3.3.4 Administration of Chemotherapy Through PICC Lines

PICC lines make it possible to receive chemotherapy as well as other medications and fluids. The elaboration of "PICC" is Peripherally Inserted Central Catheter. It is a variation on the concept of a center line. Under the influence of the local anesthetic, the catheter will be inserted into a vein in the patient's arm. During an outpatient visit, a physician or nurse might provide it to the patient. The line travels up the vein in the patient's arm until it reaches a major vein in the chest, where it terminates. PICC lines, like other types of central lines, can be left in place for a number of months at a time and utilized in the same way (CRU, 2022).

3.3.3.5 Chemotherapy Using Pumps

One way to get chemotherapy is with a chemotherapy pump. They give the patient control over the chemotherapy. Infusion pumps are another name for chemo pumps. A pump can be put on a central line, like a PICC line, that is used for chemotherapy. This will put a controlled amount of drugs into the patient's bloodstream in a very slow way. Different pumps do different things. If chemotherapy is given in the hospital, it will be given to the patient through a pump that is attached to a drip stand. The patient can move around with the drip stand and pump because it is on wheels and runs on a battery. The patient can also take pumps home with him/her. Most of these pumps have a constant pressure, so they don't need a battery. This kind of pump is not very big. The patient can carry it in a bag or holster that the hospital will provide. (CRU, 2022).

3.3.4 Tests before beginning chemotherapy

Tests will be performed prior to the start of any treatment in order to assist the physician in determining the appropriate course of treatment for the patient. They will also be able to evaluate the efficacy of the treatment by comparing the results to those of subsequent tests (CRU, 2022).

Among the possible tests are:

- blood testing
- x-rays
- scans
- patient's height and weight to calculate Body Surface Area (BSA)
- physical checkup

The doctor will take note of the patient's height and weight in order to determine the appropriate chemotherapy dosage for the patient. Chemotherapy medications have the potential to inhibit the production of sufficient numbers of red blood cells, white blood cells, and platelets by the bone marrow. Hence, before therapy begins, the patient will need to have a blood test done to determine the amounts of these in his/her body. Depending on the type of cancer, the patient might also have to undergo additional blood tests.

Depending on the treatment that a patient receives, he/she can also have some of the following tests done:

- **Lungs:** The operation of the lungs may be altered by the chemotherapy medications a patient take. Before a patient begins taking any of these medications, the primary care physician will make arrangements for the patient to have a test of his/her lung function. This determines how well the lungs are taking in oxygen as well as how much air they can contain at one time.

- **Heart Checkup:** Checking the heart is important because certain chemotherapy medicines can have an effect on the muscles of the heart. It's possible that this will alter the rhythm of heartbeat of the patient. After the chemotherapy is finished, in the vast majority of cases, everything will return to normal. Before beginning therapy with any of these medications, the patient is required to undergo a check-up on his/her heart regardless of which medication is intended to take. There is also a possibility that the patient may have to record the electrical activity of his/her heart, which is called electrocardiogram (ECG). The doctor can get information about how well the heart of the patient is operating via an electrocardiogram.
- **Liver Function**: Since certain chemotherapy medications can be harmful to the liver, the doctor may order blood tests to see how well the liver of the patient is functioning. A lot of medications are broken down by the liver. In order to eliminate the chemotherapy, it is necessary for it to function effectively.

- **Tests to examine the Kidneys:** There are certain chemotherapy medicines that can have an effect on the kidneys. A patient may have to undergo blood tests and/or urine test. The chemotherapy medications are eliminated from the body via the kidneys once they have been broken down in the body, thus the kidneys need to be in good operating order. The amount of creatinine that is present in the blood is one of the substances that are analyzed by the blood tests. Creatinine is a type of protein that is produced as a byproduct of muscle contraction. The creatinine that is found in the circulation comes from the muscle cells. It travels

to the kidneys via the circulatory system via blood. Creatinine is eliminated from the body through urine after being filtered out by the kidneys.

- **HIV and hepatitis:** There is a possibility that HIV and hepatitis will be found in the blood sample that is taken from the patient. The patient will be required to sign a consent form in order to indicate that he/she is okay with having his/her blood tested.

3.3.5 Adverse effects that can be caused by chemotherapy

There are more than one hundred distinct medications used in chemotherapy. These medication may have potential adverse effects. However different medications cause different negative effects.

Chemotherapy causes damage to cells that are dividing. Cancer cells undergo division at a rate that is significantly higher than that of most normal cells. Hence, chemotherapy is harmful to cancer cells and has the potential to kill them. Nonetheless, some kinds of normal cells divide quite often as well. This takes place in tissues that require a continuous supply of new cells, such as the skin, hair, and nails. Tissues like these are affected. Damage to these cells can also be caused by chemotherapy, which might result in negative effects. Nonetheless, the damaged normal tissues have the ability to recover and mend themselves.

Most common adverse effects are as follows (CRU, 2022):

- **Weakness and tiredness:** Exhaustion and a general feeling of weakness are common side effects of chemotherapy. It is possible that the sleepiness will get worse as the patient progress through therapy and that it will continue for a significant number of months after treatment is finished. This condition is known as tiredness. The patient may also have feelings of weakness and a lack of energy during this time. This state is known as lethargy, and it is often a symptom of weariness.

- **A decrease in the number of platelets:** This occurs because there is a decrease in the amount of platelets in the patient's blood, which are responsible for helping to clot the blood. If the platelet count drops dangerously low, the patient can develop a condition known as petechiae, which is characterized by a proliferation of extremely small, bright red patches or bruises on arms and legs of the patient.

- **Risk of infection:** Chemotherapy medications frequently inhibit the bone marrow from producing an adequate number of white blood cells, which might result in an increased risk of contracting an infection. White blood cells are an important component of the patient's body's immune response to illness.

- **Hearing Loss:** Hearing loss is a possible side effect of taking certain chemotherapy medicines. In most cases, this will get better once therapy is completed; nevertheless, the physician may reduce the dose of the medicine or change the treatment altogether.

- **Breathless and pale looking:** Chemotherapy reduces the number of red blood cells, which can leave patients feeling short of breath and looking pale (anaemia). Haemoglobin, which is found in red blood cells, is responsible for transporting oxygen throughout the body. When the red blood cell count is low, the amount of oxygen that is delivered to the patient's cells is reduced. This can leave patient feeling short of breath and making him/her seem pale. If the patient are feeling short of breath, the patient should let the doctor or nurse know. Regular blood tests, to determine the number of red blood cells in the blood, is very important. In the event that the level is really low, the patient may require a blood transfusion. After receiving a transfusion, the patient will feel less out of breath and the skin will not look as pale. When the blood count is low, the patient may also have feelings of fatigue and depression, but the patient should start to feel better once it returns to normal. The levels may go up and down while the patient is receiving treatment. As a result, it is possible that the patient will have feelings of being on an emotional and physical roller coaster.

- **Nerves:** Some chemotherapy medications have the potential to cause damage to nerves, particularly those in the hands and feet. They may experience numbness or a sensation similar to that of pins and needles as a result of it. It is typical for this to become better once treatment is over; however, it may take many months, and in a tiny percentage of patients, it may be a side effect that lasts permanently.

- **Kidneys, hearts, lungs, and livers:** There are certain chemotherapy medications that have the potential to induce alterations in the way that the patient's kidneys, liver, heart, or lungs work. The alterations are often only transitory and will revert back to normal once therapy has been completed. Nonetheless, the effects of the modifications may be long-lasting for certain individuals. The physician will be able to inform the patient whether or not the medications taken are likely to create any changes.

- **Hair, skin, and nails:** Some chemotherapy medications can cause to lose some of hair of the patient, which results in hair becoming thinner overall. The hair on the patient's head and body, including eyebrows and eyelashes, will fall out as a side effect of other chemotherapy medications. It can be upsetting to notice that the hair is falling out. However, this effect is only temporary, and new hair will begin to grow a few weeks after the therapy is finished.

3.3.6 Chemo dose calculation

The dose of chemotherapy drugs is calculated based on a number of factors, including the type of cancer being treated, the patient's body weight and height, overall health, kidney and liver function, and previous exposure to chemotherapy or radiation therapy.

There are several methods for calculating chemotherapy doses, but one commonly used method is based on body surface area (BSA). BSA is calculated using a formula that takes into account the patient's height and weight. The most commonly used formula is the Mosteller formula, which is (Mosteller, 1987):

$$BSA(m^2) = \frac{\sqrt{height(cm) \times weight(kg)}}{60}$$

Once the BSA is calculated, then the BSA is multiplied with the suggested amount of dose for a particular chemo medicine to calculate the appropriate dose for a particular cancer patient (Clinical Pharmacy Guide, 2020).

Calculated Dose = BSA X Suggested Drug Dose by the pharmaceuticals

The chemotherapy dose is typically expressed in milligrams per square meter (mg/m2). The dose may be adjusted based on the patient's individual factors, such as kidney function, liver function, and overall health. So, in many occasions the oncologist used to suggest some modification on the amount of "Calculated Dose" considering the patient physic. Which may vary expert to expert, oncologist to oncologist.

It's important to note that chemotherapy dosing is a complex process that requires careful consideration and monitoring by trained healthcare professionals. Different chemotherapy drugs have different dosing protocols, and the dose and frequency of administration may vary depending on the specific treatment regimen.

Chapter 4

Fuzzy Expert System

4.1 Fuzzy System

Fuzzy systems, also known as fuzzy logic systems, are a type of artificial intelligence that uses fuzzy set theory to model and reason with uncertainty and imprecision. Unlike classical logic systems, which rely on binary true/false values, fuzzy systems use degrees of truth, or fuzzy logic, to handle incomplete or ambiguous information (Zadeh, 1988).

In standard Boolean logic, a proposition can either be true or false. But, in fuzzy logic, a proposition can have a degree of truth between 0 and 1, signifying the degree of membership of an element in a given set. This method permits a more sophisticated approach to decision-making, as it can account for data uncertainty and imprecision. Fuzzy logic has applications in numerous industries, including engineering, medicine, finance, and robotics (Hájek, 2013).

Fuzzy systems consist of three main components as shown in figure 4.1:

- **Fuzzifier**: This component converts numerical or linguistic input data into fuzzy sets. For example, the temperature can be described as "hot", "warm", "cool", or "cold" using fuzzy linguistic variables.

- **Inference engine:** The inference engine uses fuzzy rules to reason with the fuzzy sets and make decisions. The rules are typically written in an "if-then" format, such as "If the temperature is hot, then turn on the air conditioning." The inference engine combines the input fuzzy sets and applies the fuzzy rules to produce an output fuzzy set.

- **Defuzzifier:** This component converts the output fuzzy set back into a numerical or linguistic value that can be used for control or decision-making.

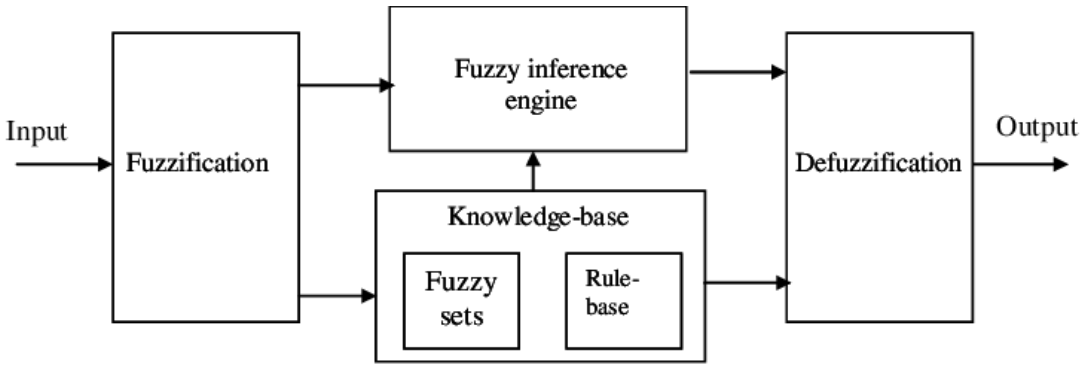


Fig. 4.1: Basic fuzzy system structure (El-kholy, 2006)

Fuzzy systems can be used in a variety of applications, including control systems, pattern recognition, data classification, and decision-making (Nguyen et. al., 2019). They are particularly useful in situations where the available data is imprecise, uncertain, or difficult to measure accurately. For example, a fuzzy system could be used to control the temperature in a building based on vague input such as "too hot" or "too cold," rather than precise numerical values (Kafuko & Wanyama, 2019).

One of the advantages of fuzzy systems is that they can handle complex relationships between variables that may be difficult to capture with traditional mathematical models. Fuzzy systems can also be combined with other artificial intelligence techniques such as neural networks and genetic algorithms to create more powerful hybrid systems.

However, one of the challenges of using fuzzy systems is that they can be difficult to design and tune. The fuzzy rules and membership functions used in the system must be carefully chosen and calibrated to ensure optimal performance. Additionally, the use of fuzzy logic can sometimes lead to results that are difficult to interpret or explain.

4.2 Fuzzy Expert System Components

4.2.1 Fuzzy Sets

Fuzzy sets are a type of mathematical set that allow the representation of uncertainty and vagueness in a formal mathematical framework, which makes them useful for a wide range of applications such as control systems, decision-making, and pattern recognition (Hájek, 2013). Unlike traditional sets, which are defined by binary membership functions (i.e., an element either belongs to the set or does not), fuzzy sets use membership functions that assign a degree of membership to each element of the set.

A fuzzy set "A" over a universe of discourse X is defined by a membership function $\mu_A(x)$, which assigns a degree of membership in the interval [0, 1] to each element $x \in X$. The membership function $\mu_A(x)$ can be defined in various ways, depending on the problem domain. One common way to define it is by using a linguistic variable and a set of linguistic terms. For instance, let X be the universe of discourse of temperature, and A be a fuzzy set representing the term "warm". The membership function for A can be defined using fuzzy linguistic terms such as "cold", "warm", and "hot" (Siddique, 2014).

There are different fuzzy set operations, such as union, intersection, and complementation, to form more complex fuzzy sets that represent more complex concepts. If A and B are two fuzzy sets then:

- Union of A and B,

$$(A \cup B)(x) = max(\mu A(x), \mu B(x))$$

- Intersection of A and B,

$$(A \cap B)(x) = \min(\mu A(x), \mu B(x))$$

- Complement of A,

$$\bar{A}(x) = 1 - \mu A(x)$$

4.2.2 Membership Functions

The degree to which an element belongs to the membership of a fuzzy set can be defined with the help of a mathematical function known as a membership function. It assigns each element in the universe of discourse a membership grade ranging from 0 to 1, where 0 indicates that the element does not belong to the fuzzy set and 1 indicates that the element fully belongs to the fuzzy set. In other words, it maps each element in the universe of discourse to a grade of membership. As an element comes closer to the middle of the fuzzy set, the membership grade will transition from 0 to 1 more quickly depending on the form of the membership function. There are a variety of membership functions available, and their use is contingent on the nature of the issue being addressed as well as the qualities of the elements. (Thiem, 2014; Ali et. al., 2015; Özsandıkçıoğlu, et. el., 2015).

Here's a list of some commonly used membership functions for defining fuzzy sets (Bouhentala, 2019; Narayanan & Sreekumar, 2021):

- Triangular membership function
- Trapezoidal membership function
- Gaussian membership function
- Bell-shaped membership function
- Sigmoidal membership function
- Singleton membership function
- Piecewise Linear Membership Function
- Generalized bell-shaped membership function
- Z-shaped Membership Function
- S-shaped Membership Function
- Pi-shaped membership function
- Gaussian sum membership function
- Product-sum membership function
- Difference-sum membership function
- Elliptic membership function
- Takagi-Sugeno membership function

In the following sections, membership functions which are used in the development of our proposed systems, are discussed.

4.2.2.1 Triangular membership function

In a fuzzy logic system, the triangle membership function is a type of fuzzy set that models the degree of membership of an element to a set. It is referred to as a "triangle" membership function because it has a triangular shape with two sides that slope linearly and a flat top. The triangular membership function is defined by three parameters: a, b, and c, where “a” represents the minimum value of the range of the fuzzy set, “b” represents the point at which the membership value is 1 (the peak of the triangle) and “c” represents the maximum value of the range (Pedrycz, 1994; Kreinovich, et. al., 2020). The mathematical equation for a triangular membership function is:

$$\mu(x) = \begin{cases} 0 & if\ x \leq a, \\ \dfrac{x-a}{b-a} & if\ a < x \leq b, \\ \dfrac{c-x}{c-b} & if\ b < x < c, \\ 0 & if\ x \geq c \end{cases}$$

μ(x) is the membership value of the input x in the fuzzy set. If x is less than or equal to a or greater than or equal to c, the membership value is 0. If x is between a and b, the membership value increases linearly from 0 to 1 as x moves from a to b. If x is between b and c, the membership value decreases linearly from 1 to 0 as x moves from b to c.

The common form of a triangular membership function is shown in the figure below:

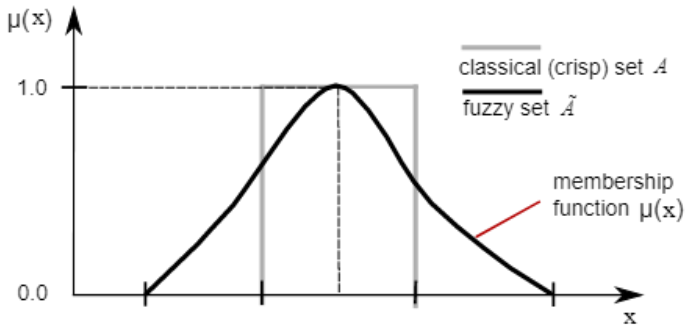


Fig. 4.2: Triangular Membership Function

4.2.2.2 Trapezoidal membership function

This type of function is called a "trapezoidal" membership function because it has a trapezoidal shape with two linearly sloping sides and two flat tops. The trapezoidal membership function is defined by four parameters: a, b, c, and d. The value of a represents the minimum value of the range of the fuzzy set, b represents the point where the membership value starts to increase from 0, c represents the point where the membership value reaches 1, and d represents the maximum value of the range (Khayatzadeh & Yelten, 2018; Kreinovich, et.al., 2020).

The mathematical expression for a trapezoidal membership function is:

$$\mu(x) = \begin{cases} 0 & if\ x \leq a, \\ \dfrac{x-a}{b-a} & if\ a < x \leq b, \\ 1 & if\ b < x < c, \\ \dfrac{d-x}{d-c} & if\ c \leq x < d, \\ 0 & if\ x \geq d \end{cases}$$

In this equation, μ(x) is the membership value of the input x in the fuzzy set. If x is less than or equal to a or greater than or equal to d, the membership value is 0. If x is between a and b, the membership value increases linearly from 0 to 1 as x moves from a to b. If x is between b and c, the membership value is 1. If x is between c and d, the membership value decreases linearly from 1 to 0 as x moves from c to d.

The common form of a triangular membership function is shown in the figure below:

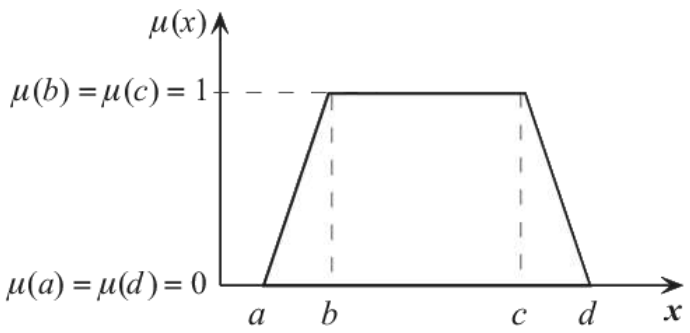


Fig. 4.3 Trapezoidal Membership Function

4.2.2.3 Gaussian membership function

It is a bell-shaped curve that is symmetric around its mean value. The Gaussian membership function is defined by two parameters: c and sigma. The value of c represents the center of the curve, and sigma represents the standard deviation of the curve (Ali et. al., 2015; Ajofoyinbo, et. al., 2011).

The mathematical expression for a Gaussian membership function is:

$$\mu(x) = \exp\left(-\frac{(x-c)^2}{2 * sigma^2}\right)$$

In this equation, μ(x) is the membership value of the input x in the fuzzy set. The function exp is the exponential function, which raises the constant e to the power of the argument. The expression $(x\text{-}c)^2$ is the squared distance between the input x and the center c of the curve. The value $2*sigma^2$ is a scaling factor that determines the width of the curve, and the negative sign in front of the fraction causes the curve to be inverted, so that the membership value decreases as the distance from the center increases. The figure below indicates the property,

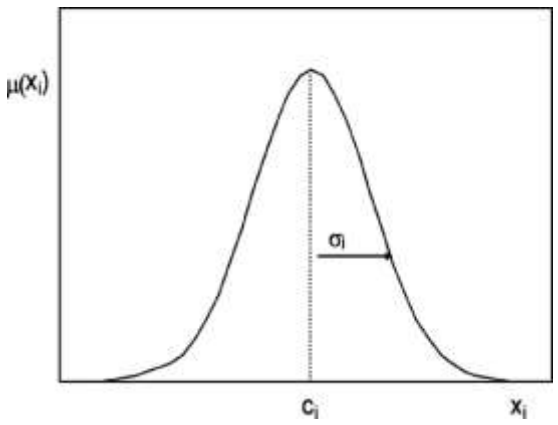


Fig. 4.4: Gaussian Membership Function

As we can see, the Gaussian membership function has a bell-shaped curve, with its peak at x = c and decreasing symmetrically on both sides of the peak. The width of the curve is controlled by the parameter sigma, where larger values of sigma result in wider and

flatter curves. The Gaussian membership function is often used in fuzzy control systems to model uncertain or imprecise information (Siddique, 2014).

4.2.2.4 Bell-shaped membership function

It is called a "bell-shaped" membership function because it has a shape similar to a bell curve (Siddique, 2014; Dutta & Limboo, 2017]. The bell-shaped membership function is defined by three parameters: **a**, **b**, and **c**. The value of **a** controls the shape of the curve, **b** represents the width of the curve, and **c** represents the center of the curve. The mathematical expression for a bell-shaped membership function is:

$$\mu(x) = \frac{1}{\left(1 + abs\left(\frac{x-c}{b}\right)^{2*a}\right)}$$

In this equation, **μ(x)** is the membership value of the input **x** in the fuzzy set. The function **abs** is the absolute value function, which returns the magnitude of the argument. The expression **(x-c)/b** is the normalized distance between the input **x** and the center **c** of the curve, and **^(2*a)** is an exponent that controls the shape of the curve. The value of **a** determines the steepness of the curve near its peak, and larger values of **a** result in steeper curves. The value of **b** determines the width of the curve, and larger values of **b** result in wider curves.

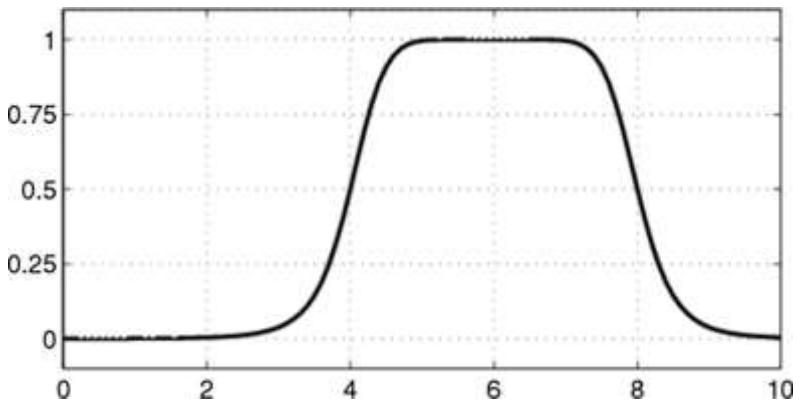


Fig. 4.5: Bell Shaped Membership Function

The bell-shaped membership function has a symmetric, bell-shaped curve that starts at zero and approaches 1 as **x** approaches **c**. The shape of the curve is controlled by the

parameters **a**, **b**, and **c**. It is often used in fuzzy control systems to model uncertain or imprecise information. The bell-shaped membership function can be used to model a variety of different fuzzy sets, depending on the choice of parameters.

4.2.3 Fuzzy Rules

The use of fuzzy rules is essential to the implementation of fuzzy logic, which is a mathematical framework for addressing issues of imprecision and uncertainty. In a fuzzy system, fuzzy rules are used to describe the relationship between the input variables and the output variables. Also, fuzzy rules provide a means by which judgments can be made based on data that is either imprecise or uncertain.

An antecedent and a consequent make up the two components that make up a fuzzy rule. The antecedent lays out the parameters within which the rule can be applied, and the consequent outlines the steps that must be followed in the event that the antecedent is verified to be accurate. In most cases, the antecedent and the consequent are articulated through the utilization of linguistic variables and fuzzy sets. These tools offer a method to both describe and handle data that is imprecise or ambiguous. (Siddique, 2014). If for an event “x” is defined as antecedent and “y” is consequent, then one of the fuzzy rule can be defined as,

IF x is A THEN y is B

Using fuzzy logic operations such as "AND" and "OR", fuzzy rules can be combined to create more complicated decision-making systems. If for an event “x” and “y” are defined as antecedent and “z” is consequent, then one of the fuzzy rule can be defined as,

IF x is A and y is B THEN z is C

The fuzzy logic operations give a method for combining the output of numerous fuzzy rules into a single, precise output value that can be utilized to make choices or manage a system. In general, fuzzy rules offer a robust and adaptable method for modeling complex systems and making judgments based on uncertain or imprecise input (Nguyen et. al., 2019).

4.2.4 Fuzzification

The act of transforming crisp, or precise, input data into fuzzy sets that may be processed by a fuzzy system is referred to as "fuzzification." In other words, fuzzification is the act of mapping precise data values onto membership functions that indicate the degree to which those values belong to a fuzzy set. These membership functions can be thought of as a representation of the degree to which values belong to a fuzzy set. Fuzzification is an important step in the fuzzy logic process, as it enables the use of linguistic variables to represent input data. Linguistic variables are variables that use natural language terms, such as "low," "medium," and "high," to describe a range of values. By using linguistic variables, fuzzy logic can deal with imprecise and uncertain data in a more human-like way (Siddique, 2014).

The fuzzification process involves three steps:

1. *Defining linguistic variables:* The first step in fuzzification is to define the linguistic variables that will be used to represent the input data. For example, if the input data is temperature, the linguistic variables might be "cold," "warm," and "hot."

2. *Creating membership functions*: The next step is to create membership functions for each linguistic variable. Membership functions map input data onto a fuzzy set, indicating the degree to which the input value belongs to the set. For e

3. xample, the membership function for "warm" might have a triangular shape, with the peak at the temperature that is considered "warm."

4. *Mapping input data onto membership functions*: The final step is to map the crisp input data onto the appropriate membership functions. This is done by evaluating the degree of membership of the input value in each fuzzy set. For example, if the input temperature is 25°C, the degree of membership in the "warm" set might be 0.8, while the degree of membership in the "cold" and "hot" sets might be 0.2 and 0.0, respectively.

After the input data has been fuzzyfied, a fuzzy logic system can use it to make decisions based on imprecise or uncertain data. By employing language variables and membership functions to express imprecise and uncertain facts, fuzzification enables fuzzy logic to model complicated systems and make judgments in a more human-like fashion.

4.2.5 Fuzzy Inference

Fuzzy inference is the process of mapping fuzzy input variables to fuzzy output variables using fuzzy logic rules. There are several types of fuzzy inference models, which are (Fantuzzi & Rovatti, 1996; Trillas & Guadarrama, 2010; Pitchipoo, et al., 2013; Shoureshi & Hu, 2000):

- Mamdani Model
- Takagi-Sugeno Model
- Tsukamoto Model
- Larsen Model
- Hybrid Models

In the present research Mamdani-type fuzzy inference system is used.

4.2.5.1 Mamdani Model

In practical applications, the Mamdani model is one of the most often employed fuzzy inference models. It is a powerful and flexible tool for solving problems in a wide range of applications, including control systems, decision-making, and pattern recognition. The model bears the name of its creator inventor, Ebrahim Mamdani. It is a rule-based system that uses fuzzy logic to map inputs to outputs (Iancu, 2012).

The four basic components of the Mamdani model are the fuzzifier, the rule base, the inference engine, and the defuzzifier. The fuzzifier transforms discrete inputs into fuzzy sets by assigning membership values based on previously determined membership functions. The rule base includes a collection of rules that relate inputs to outputs. Each rule has an antecedent (if-portion) and a consequent (then-portion), with the antecedent being a fuzzy set defined over the input variables and the consequent being a fuzzy set

defined over the output variable. The inference engine applies the rules to the fuzzy inputs and produces a collection of fuzzy outputs. Using methods such as centroid, bisector, or mean of maximum, the defuzzifier then transforms the fuzzy output set into a crisp output. (Iancu, 2012; Siddique, 2014).

Mathematically, the Mamdani model can be expressed as follows:

1. Fuzzification: For each input variable x_i, the corresponding membership function μ_i(x_i) is applied to map the crisp input value x_i to a fuzzy set A_i.

2. Rule evaluation: Each rule in the rule base is evaluated by computing the degree of match between the antecedent fuzzy set and the corresponding input fuzzy set. This is done by applying a t-norm operator, such as minimum or product, to the membership values of the fuzzy sets.

3. Aggregation: The degree of match for each rule is then combined into a single fuzzy output set using a t-conorm operator, such as maximum or probabilistic sum.

4. Defuzzification: The final output is obtained by applying a defuzzification method, such as centroid or mean of maximum, to the aggregated fuzzy output set.

Though, Mamdani model is a powerful and flexible tool, and widely used, its complexity and computational requirements can be a limitation in some cases, especially for large-scale problems.

4.2.6 Defuzzification

Defuzzification is a method in fuzzy logic that transforms the output of fuzzy inference into a crisp output that may be easily comprehended by humans or utilized by control systems. The output of the fuzzy inference system in fuzzy logic is a fuzzy set that represents the degree of membership of an output variable to each linguistic phrase. Defuzzification is used to extract a single, distinct output value from this fuzzy set.

The most prevalent defuzzification technique is the center of gravity method (COG), often known as the centroid method. This method determines the crisp output value by locating the center of gravity of the fuzzy set that represents the output variable. The center of gravity is calculated as the weighted average of the degrees of membership of the output variable to each linguistic term. The weight of each term is the degree of membership of the output variable to that term (Nguyen et. al., 2019; Chakraverty, et. al., 2019).

The mathematical equations for defuzzification using the center of gravity method are discussed below:

- In case of discrete membership function, if the defuzzified value is defined as X^* then,

$$x^* = \frac{\sum_{i=1}^{n} x_i \,.\mu(x_i)}{\sum_{i=1}^{n} \mu(x_i)}$$

  Here X_i defines the sample element, $\mu(X_i)$ is the membership function and n is the number of elements in the sample.

- In case of continuous membership function,

$$x^* = \frac{\int x\, \mu_A(x)\, dx}{\int \mu_A(x)\, dx}$$

This equation represents the weighted average of the centers of gravity of the linguistic terms, where the weights are the degrees of membership of the output variable to each term. The result is a crisp output value that represents the overall degree of satisfaction of the fuzzy rules.

Chapter 5

Clinically relevant Fuzzy Expert System for Tumor Growth Modelling and Optimum Chemotherapy Drug Dose Scheduling

In this chapter a clinically relevant modular Fuzzy Expert System (FES) for chemotherapy drug dose scheduling is developed and discussed in details. The computational model considers the patient's Body Surface Area (BSA) and experts' opinions to calculate chemo doses following the clinical practice. A proper balance between reducing cancerous cells and toxic side effects is required for effective drug scheduling. Still, in many cases, traditional clinical approaches fail to determine appropriate therapeutic doses that balance all restrictions. In the proposed system, FES-1 is developed to determine primary drug doses based on experts' opinions and competing treatment objectives. To adjust the dose, FES-2 is developed based on clinical practices, the patient's BSA, and experts' opinions. The final chemotherapy drug dose schedule is generated by combining the outputs of FES-1 and FES-2, which is the proposed modular FES. A growth model, Martins Model, is used in this work to observe response due to administration of chemotherapy drug doses and to determine the following doses by considering cancer patients' three weight patterns (increasing, decreasing, and random order). Extensive simulation results and comparative assessment with other current computational chemotherapy drug scheduling models

validate the effectiveness and the superiority of the model proposed in this study over the other methods reported in relevant studies.

5.1 Cancer Cell Growth Analysis

A growth model is used for detection of cancer cells and its constraints formula is used for helping dose scheduling. Mainly the amount of dose is controlled by the fuzzy system. The output of growth model is input into both the FES, where FES-1 receives only the number of cancerous cells and toxicity of patient's body and FES-2 receives input as number of cancerous cells, toxicity of patient's body and calculated dose using weight of the patient.

5.1.1 Martins model for determination of cancer cell and toxicity

Martin's model is used as a growth model in our research to observe different parameter of a cancer patient. This model defines the effect of toxicity and doses concentration on the cancer cells and establishes a relationship among them using equations also calculates the number of tumor cell at a certain time. The equations are (Martin and Teo, 1994; Martin et al., 1990):

$$\dot{C}(t) = D(t) - \lambda C(t) \tag{5.1}$$

$$\dot{N} = \frac{1}{\tau g}\left[\frac{\ln\frac{\rho g}{N_0}}{n\frac{\rho g}{2N_0}}\right] N(t)\ln\left[\frac{\rho g}{N(t)}\right] - K_{eff}\, C_{eff}\,(t) N(t) \tag{5.2}$$

$$C_{eff}\,(t) = \left[C(t) - C_{th}\right] H\left[C(t) - C_{th}\right] \tag{5.3}$$

$$H\left[C(t) - Ctxh\right] = \begin{cases} 1 & if\ C(t) \geq C_{th} \\ 0 & if\ C(t) < C_{th} \end{cases} \tag{5.4}$$

$$\begin{cases} C(0) = C_0 = 0 \\ N(0) = N_0 \\ \dot{T}(t) = C(t) - \eta T(t) \end{cases} \tag{5.5}$$

Where, $C(t)$ is plasma drug concentration, $D(t)$ is the amount of intravenous infusions of the drug, λ is the elimination kinetics rate, ρg and τg, describe the cancerous cells proliferate in a Gompertzian fashion, N_0 is the initial number of cancer cells, $N(t)$ is the number of cancer cells after every treatment cycle, $C_{eff}(t)$ is the effective drug plasma concentration, Cth is the minimum therapeutic concentration.

According to this equation, the initial drug concentration C_0 is considered as 0 and Cth controls the lower amount of drug concentration. $H[C(t)-C_{th}]$ is the Heaviside step function helps to calculate effective drug concentration (Martin et al., 1990; Martin, 1992). K_{eff} is the constant that helps to evaluate the drug effect by multiplicity with number of cancer cells and effective drug concentration. The toxicity level is defined after infusion of drugs. For measuring toxicity η is a constant.

5.1.2 Constraints for dose schedule

A. As drug dose contains relationship with other factors, a limitation procedure needs to apply over a particular range of dose level, as follows (Harrold, 2005):

$$D_{th} \le D(t_i) \le D_{\max}$$

$$\text{or } D(t_i) = 0, \ \forall \boldsymbol{i} \in \{1,2,\cdots,m\} \tag{5.6}$$

Here, t_i is the i_{th} dosing time and m is the final dosing point and D_{th}, $D_{\max}$ are the lower and upper bounds of the therapeutic dosing range. Since, in the present research Fixed Interval Variable Dosing (FIVD) scheme is used, $D(t_i)$ will be zero in those days when chemo dose is not applied and during scheduled dates, dose ($D(t_i)$) will be within the range of D_{th} and D_{max}.

B. There is an upper limit of toxicity for human that can be tolerated. During the whole period of chemotherapy treatment, the maximum toxicity needs to be remained under the $T_{\max}$. Researcher suggest that the toxicity should not exceed $T_{\max}$ during the treatment (Algoul et al., 2011). If the last cycle is given with a final time t_f then T(t) should be

$$T(t) \le T_{\max} \text{ and } \forall t \le t_f \tag{5.7}$$

C. Researchers suggested that total drug concentration must be remained below the cumulative drug concentration and total drug concentration, C_{Tot} is calculated by integrating drug plasma concentration over the treatment interval (Harrold, 2005).

$$C_{Tot} = \int_{1}^{t_f} C(t)dt \leq C_{cum} \tag{5.8}$$

D. It is the obvious demand to reduce the number of tumor cells of a patient. So, it is an efficacy constraint that the number of tumor cells need to be remained less than the initial condition during the treatment (Harrold, 2005).

$$N(t) \leq N_0 \text{ and } \forall t \leq t_f \tag{5.9}$$

5.1.3 Constraints for dose schedule

Table 5.1 shows the values of constants used in this research, which are taken from the case study by Martin (Martin and Teo, 1994, Martin et al., 1990; Martin, 1992).

Table 5.1: Description and values of parameters used in Martins model.

Parameter	Description	Value	Units
τ_g	First doubling time of the cancer tumor during exponential growth	150	Days
ρ_g	Plateau population of cancer cells without treatment	10^{12}	Cells
N_0	Initial cancer cell population	10^{10}	Cells
K_{eff}	Fractional cell kill term for a highly effective drug	2.7×10^{-2}	$\frac{1}{days.[D]}$
λ	Decrease in concentration of drag per unit time	.27	$\frac{1}{days}$
η	Toxicity rate constant	.4	$\frac{1}{days}$
D_{th}	Threshold drag level	10	[D]
D_{max}	Maximum tolerable drug level	50	[D]
C_{cum}	Maximum tolerable drug exposure in plasma	4.1×10^3	[D].days
T_{max}	Maximum tolerable toxicity	100	[D]

5.2 BSA Calculation

Estimation of BSA can be done applying a number of different methods such as formulas, slide rulers, or nomograms among which two equations are most commonly used equations (Bois & Bois, 1989). Mosteller (Mosteller, 1987) used body height and weight for BSA.

$$BSA(m^2) = \frac{\sqrt{height(cm) \times weight(kg)}}{60} \tag{5.10}$$

Also weight base formula is used in calculation of BSA as

$$BSA(m^2) = \frac{weight(kg) \times 4 + 7}{90 + weight(kg)} \tag{5.11}$$

The most recent measurement of height and weight are used in Eq. (5.10)-(5.11). The dose is calculated by multiplying the amount of dose administered per cycle by BSA (Felici et al., 2002; Kaestner and Sewell, 2007).

5.3 Performance Index Calculation

x_1, a transformed variable which is inversely related to the tumor mass N, defined as

$$x_1 = \ln(N * 10^{12}) \tag{5.12}$$

To determine the maximum effectiveness of chemotherapy drug dose scheduling performance index I can be calculated as follows (Karar et al., 2020; Martin, 1992; Khadraoui et al., 2016):

$$I = x_1(t_f) \tag{5.13}$$

Where, $x_1(t_f)$ means value of x_1, calculated from Eq.5.12, at treatment time t_f when tumor mass is N. In the present study the final treatment time t_f is considered as 84 days.

5.4 Modular Fuzzy System for Dose Scheduling

The architecture of the proposed modular fuzzy system is shown in fig. 5.1. The modular fuzzy system comprises two fuzzy systems with different inputs-output and rule-bases placed in a hierarchy. FS-1 calculates an initial dose and FS-2 determines the percentage of required change in initial dose considering experts' opinion and present clinical dose calculation practice. After combining these two outputs from FS-1 and FS-2, Dose Level is feed in to dose schedule generator, developed as per clinical practice, which gives the final dose schedule. This dose is applied into the growth model (Martin's model), to observe the effect of applied dose in to a cancer patient's body. The response of the body (number of cancer cells and toxicity) is continuously feedback into the developed fuzzy systems to generate the next best dose for the patient.

In this research, the fuzzy system is integrated with a growth model to observe the numerous cancer cells, toxicity and changed doses. Fuzzy system maintains the uncertainty of the inputs and growth model helps to calculate the numerous tumor cell and toxicity. A dose scheduler is also helps to reduce the complexity. Considering patient's weight along with tumor size and toxicity while calculating and further calibrating the dose for chemotherapy will result in destroying more cancerous cell, in other words, better outcome.

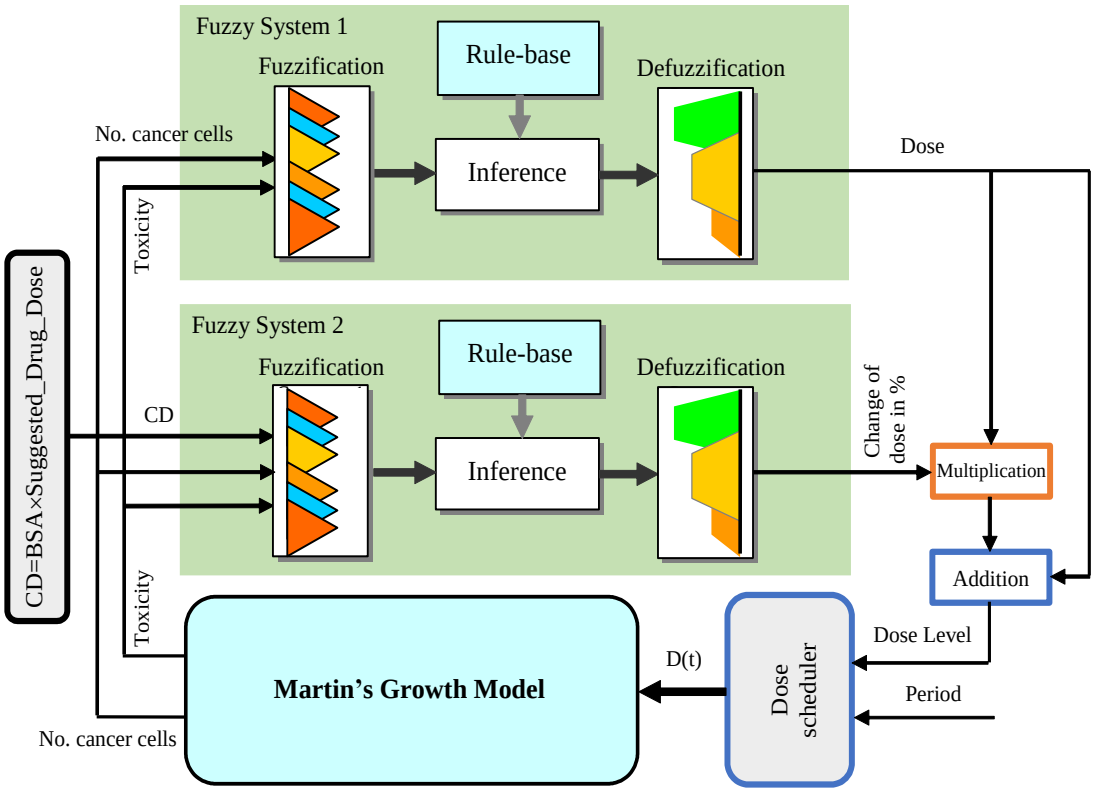


Fig. 5.1: Architecture of proposed Modular FES-based Model

5.4.1 Fuzzy Modelling

Fuzzy modelling is a great solution where the system is complex and partially known and the inputs and output cannot be measured directly. Also, the inputs contain some level of uncertainty. In this research, Mamdani-type fuzzy inference system (Siddique, 2014) is used in both fuzzy systems. Tumor size and toxicity are used as the inputs to the first fuzzy system and tumor size, toxicity and calculated dose are used as inputs to the second fuzzy system. Two fuzzy systems are used to calculate the final dose to be applied to the patient. The inputs and outputs of the two fuzzy systems are described next.

- **Tumor size:** It describes the number of tumor cells. Tumor size distribution is very effective in cancer systematic therapy (Welch et al., 2016). Which is a better predictor for calculated doses (Yu et al., 2007). The overall tumor size of a cancer patient also affects the survival rate. We have considered the initial number of tumor cells (10^{10}) and then we take the input of tumor cells from the output of the growth model.

- **Toxicity:** Toxicity has some characteristics that are trade off among other variables. It correlates with chemotherapy doses. Different doses build different type and amount of toxicity (Plenderleith, 1990). Human body can tolerate a certain amount of toxicity. Doses of chemotherapy decrease the number of tumor cells along with that the normal cells are also destroyed (Laviano and Rossi, 2012). When the doses are increased, the numbers of tumor cells are decreased but toxicity increases. This is the limiting factor for infusion of drug doses.

- **Estimated dose with weight:** It describes the dose which is calculated according to the body surface area (BSA) of the person for a certain time which is calculated using Eq. 5.11. Different medicines need different amounts of dose for every cycle. By multiplication of BSA with the amount of dose that is given for one cycle, is the result of calculated dose (Kaestner and Sewell, 2007; Beumer et al., 2012).

- **Dose:** It is the output of the first fuzzy system. Tumor size and toxicity are used as input in this expert system. Trapezoidal and triangle membership function and optimized fuzzy rules are used to calculate dose in this fuzzy system.

- **Changed Dose:** This is the output of the second fuzzy system. ChangedDose is calculated considering the input values of tumor size, toxicity and calculated dose. It describes the percent of increase in dose calculated from FS-1, while considering the patient's weight.

Both the fuzzy systems are designed employing Mamdani-type inferencing, general fuzzification (Qu and Nussbaum, 2008; Yahia et al., 2012), appropriate choice for defuzzification method (Ross, 2010), fuzzy rule-base developed using experts' opinion from the domain and through calibration of parameters in several runs and patterns.

5.4.2 Fuzzy System 1

Fuzzy system 1 has two inputs: tumor size (i.e. the number of cancerous cells) denoted as TS and toxicity of patient's body, denoted as TX, and one output as chemotherapy dose (primary dose) denoted as D. To determine the best and suitable combination of membership function, (in terms of performance of the system, tumor size at the end of the treatment and the performance index), different types and combination of Membership function is experimented. According to our experiment the best suited Membership functions (MFs) which are used in our proposed method for TS, TX and D are described in the following sections.

5.4.2.1 Tumor size (TS) for FES1

Taking into account a slight chance of increase in tumor population, its practical range for tumor cell number can be considered 0 to 10^{11} (Martin and Teo, 1994, Martin et al., 1990; Martin, 1992). However, in this study, the number of tumor cell is calculated from model. So, fractional values like 0.24 or 1.3×10^{-4} can be possible. We set the range for tumor cell number 10^{-3} to 10^{11}. For convenience in representation, original TS is transformed in logarithmic form. Taking the logarithm of 10^{-3} gives -3 and logarithm of 10^{11} gives 11. Now the transformed range for TS becomes [-3, 11]. Five bell-shaped MFs for tumor size are used for TS={VS, S, M, B, VB}. Bell-shaped membership function is defined by three parameters [*p*, *q*, *r*], the parameters are defined bellow:

p is the half width,

q (along with *p*) controls the slopes,

r is the center of the associated MF,

The parameters of the MFs for TS are given in Table 5.2(a).

Table 5.2(a): Parameters of Bell-shaped MFs for tumor size TS.

MFs	MF Parameters
Very Small (VS)	[0.8242 3.278 -2.5]
Small (S)	[0.8242 3.278 5.551e-17]
Medium (M)	[0.8242 3.278 3]
Big (B)	[1 2.5 6.5]
Very Big (VB)	[1 2.5 10]

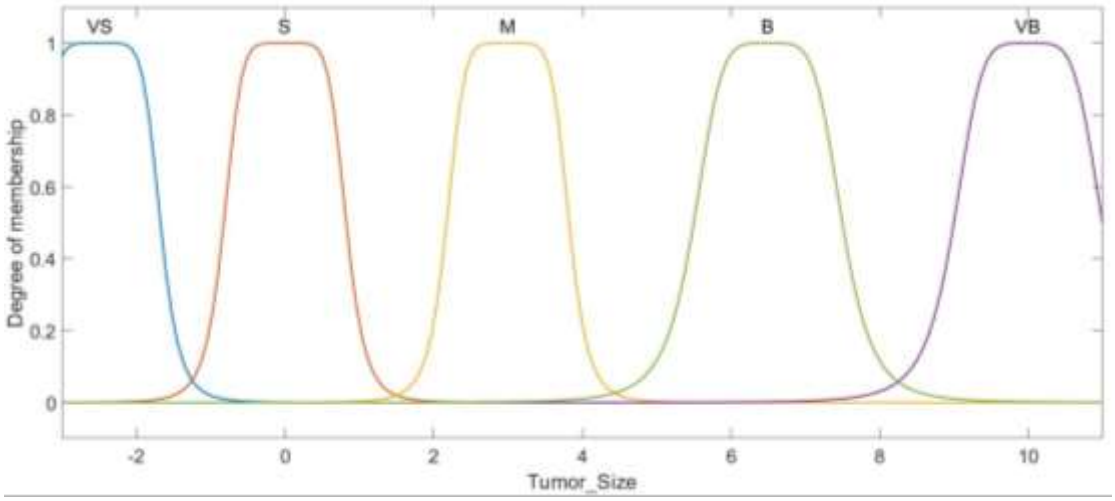


Fig. 5.2(a): Five MFs for tumor size

5.4.2.2 Toxicity (TX) for FES1

Toxicity level per day is expressed as linguistic variable "Toxicity". The considered range is from 0 to 105. Though the maximum allowable toxicity is 100 per day (Martin and Teo, 1994, Martin et al., 1990; Martin, 1992), to identify the unacceptable drug dose values maximum range is slightly elevated to 105. Five MFs are used for toxicity TX = {VL, L, M, H, VH}. Gaussian MFs are chosen for VL and VH and triangular MFs are chosen for L, M, and H. The parameters of the MFs for TX are given in Table 5.3.

Table 5.3: Parameters of Gaussian and triangular MFs for TX

MFs	Parameters
Very Low (VL)	[13.89 0.15]
Low (L)	[0 30 60]
Medium (M)	[30 60 90]
High (H)	[60 90 120]
Very High (VH)	[2.421 117.2]

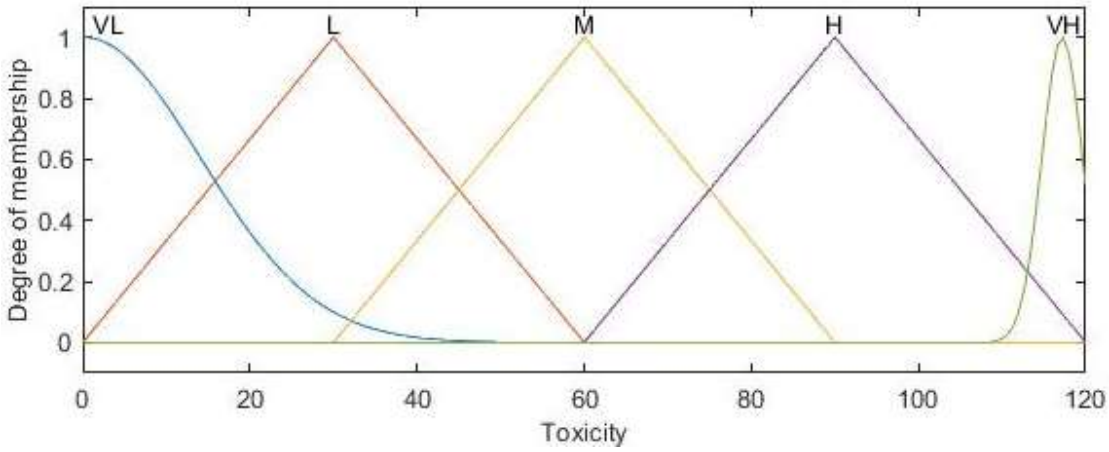


Fig. 5.3: Five MFs for toxicity.

5.4.2.3 Dose (D) for FES1:

Output variable is expressed as linguistic variable “Dose”. It characterizes dose level per day. The considered range is 10 to 50, where 10 being the threshold drug concentration (Martin and Teo, 1994, Martin et al., 1990; Martin, 1992). Seven MFs are used for D={VVL, VL, L, M, H, VH, VVH}. Triangular MFs are chosen for all MFs. The parameters of the MFs for D are given in Table 5.4.

Table 5.4: Parameters of triangular MFs for D.

MFs	Parameters
Very very Low (VVL)	[10 10 16.67]
Very Low (VL)	[10 16.67 23.33]
Low (L)	[16.67 23.33 30]
Medium (M)	[23.33 30 36.67]
High (H)	[30 36.67 43.33]
Very High (VH)	[36.67 43.33 50]
Very very High (VVH)	[43.3 50 50]

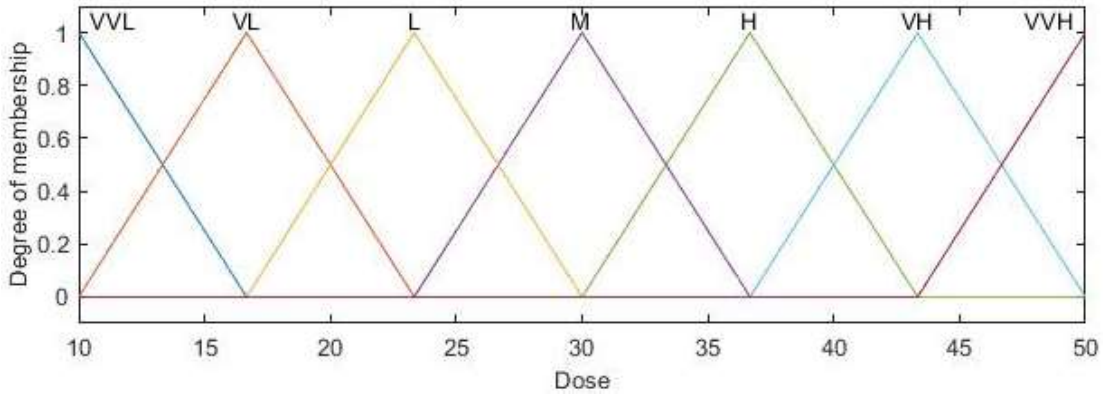


Fig. 5.4: Seven MFs for Dose.

5.4.2.4 Rule-base for FES1:

The fuzzy rule-base is constructed using expert knowledge. For the five MFs for both TS and TX, the rule-base should contain 25 rules for all possible combinations of inputs and output variables. Due to insufficient work-space coverage, some rules will never fire. Considering the model constrains (eq. 5.6-5.9) and through trial and error, the number of rules is minimized to 21. The fuzzy system 1 with the two inputs (TS and

TX) and one output (D) has 21 rules, which are presented in table format in Fig. 5.5. It shows the impact of Dose on the primary concern which is tumor size and how it gets reduced while keeping the toxicity below the maximum threshold.

TS	TX				
	VH	H	M	L	VL
VS	VVL	∅	∅	∅	∅
S	VVL	VVL	VL	L	M
M	VVL	VL	L	L	H
B	VL	L	M	H	VH
VB	L	M	H	VH	VH

Fig. 5.5: Rule base for FES-1 in table format.

5.4.3 Fuzzy System 2

Fuzzy System 2 has three inputs: tumor size TS, toxicity of patient's body TX, and calculated dose CD. The fuzzy system provides increase/adjustment of chemotherapy dose in percent as output denoted as I. The MFs for TS, TX, CD and I are described below:

5.4.3.1 Tumor size (TS) for FES2:

In fuzzy system 2 the TS is divided into four MFs within the range [-3, 11]. The four MFs are TS = {VS, S, B, VB}. The parameters of the MFs for TS are given in Table 5.2(b).

Table 5.2(b): Parameters of MFs for tumor size TS.

MFs	Type	MF Parameters
VS	Gaussian	[2.2 -1.6]
S	Triangular	[-0.5 2.25 5]
B	Triangular	[3 5.75 8.5]
VB	Gaussian	[1.2 9.85]

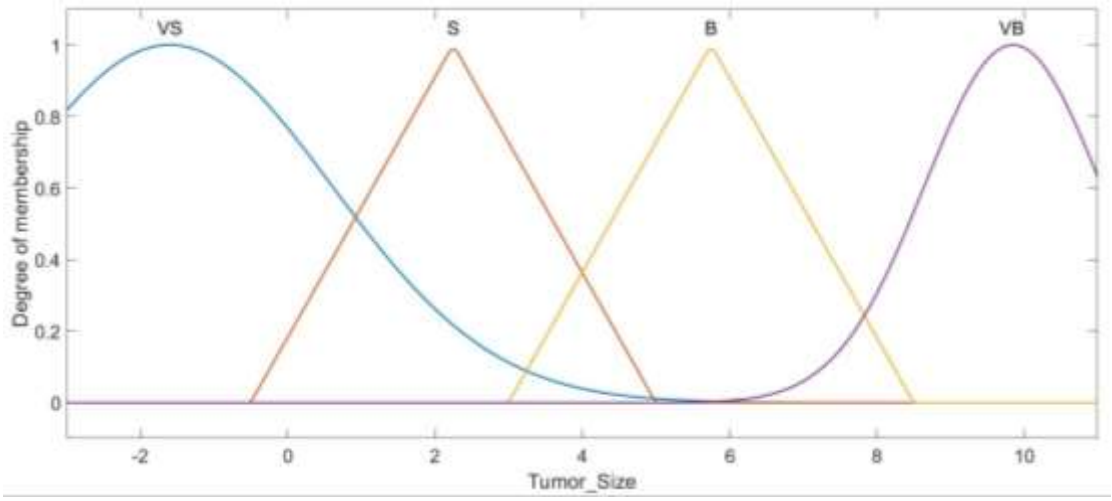


Fig. 5.2(b): Four MFs for tumor size

5.4.3.2 Toxicity (TX) for FES2:

The input TX is the same as in fuzzy system 1. Five MFs are used for TX = {VL, L, M, H, VH}.

5.4.3.3 Calculated Dose (CD) for FES2:

In Clinics, dose is generally calculated as product of BSA with the suggested amount of drag (Clinical Pharmacy Guide, 2020).

$$CD = BSA \times Suggested\_Drug\_Dose \tag{5.14}$$

Suggested drug dose varies from drug to drug, as per the drug guideline. Here, drag amount is considered 100 mg/m^2 for drag like Docetaxel. Considering Mosteller rules obese adults' BSA is 2.25 ± 0.21 m^2 (Verbraecken et al., 2006). In the present study, fixed interval variable dose (FIVD) scheme is used. So, at a certain interval drug dose will be applied to the patient and in other days no drug will be applied, that is the amount of drug dose will be zero. So, the range of the third input, calculated dose CD, is considered as 0 to 300. This interval will be changed if a different drug is used drug amount is changed as per the drug guideline. Four MFs are used for CD= {LD, ND, OD, VOD}. The parameters of the MFs for CD are given in Table 5.5.

Table 5.5: Parameters of triangular MFs for CD.

MFs	Type	Parameters
LowDose (LD)	Trapezoidal	[0 0 165 180]
NormalDose (ND)	Triangular	[165 180 202]
OverDose (OD)	Triangular	[184 202 216]
VeryOverDose (VOD)	Trapezoidal	[200 245 300 300]

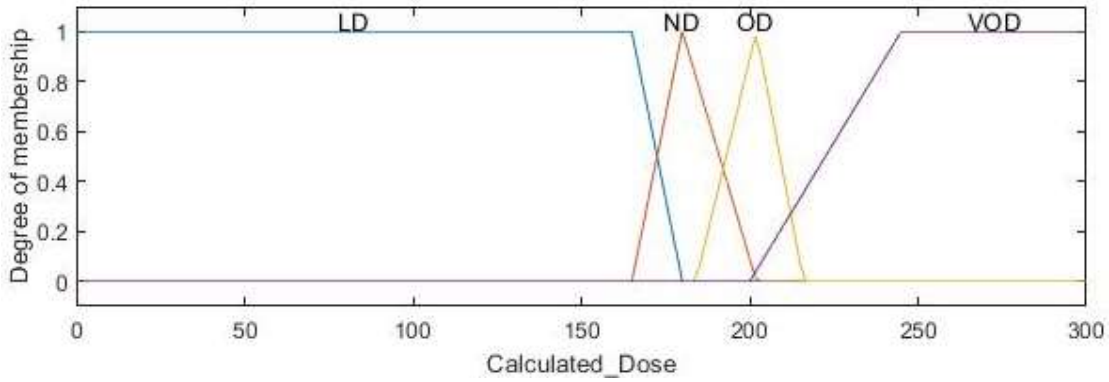


Fig. 5.6: Membership functions for Calculated_Dose.

5.4.3.4 Percent dose I for FES2:

Output variable for percent of increase in dose is expressed as linguistic variable "Percent dose I". Here, we calculated the changed dose according to the input value Tumor size, Toxicity and Calculated dose using patient's weight. It describes the percent of increase in dose calculated from fuzzy system 1, while considering the patient's weight, measured in every chemo cycle. According to Skipper (Skipper, 1971), it is observed that 20% of dose reduction can reduce the cure rates by 50% or more [15]. Considering Bonadonnas' (Bonadonna et al., 1995) observation, in our experiment we considered the range for "Percent dose I" 0% to 80%. Four MFs are used for "Percent dose I", I = {N, LI, IN, VI}. Trapezoidal MFs are chosen for N and VI and triangular MFs are chosen for LI and IN. The parameters of the MFs for I are given in Table 5.6.

Table 5.6: Parameters of MFs for percent_dose_I.

MFs	Type	Parameters
Normal (N)	Trapezoidal	[0 0 0 0.1]
Low Increase (LI)	Triangular	[0.05 0.15 0.25]
Increase (IN)	Triangular	[0.2 0.3 0.4]
Very_Increase (VI)	Trapezoidal	[0.35 0.45 0.8 0.8]

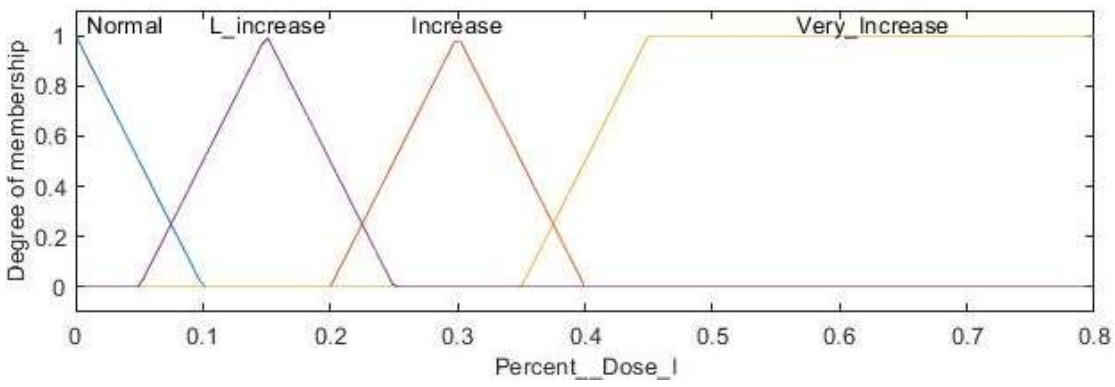
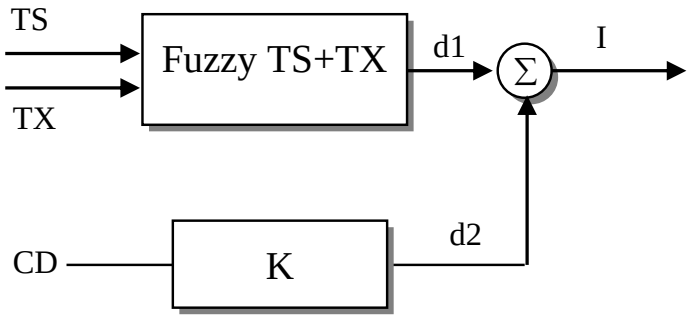


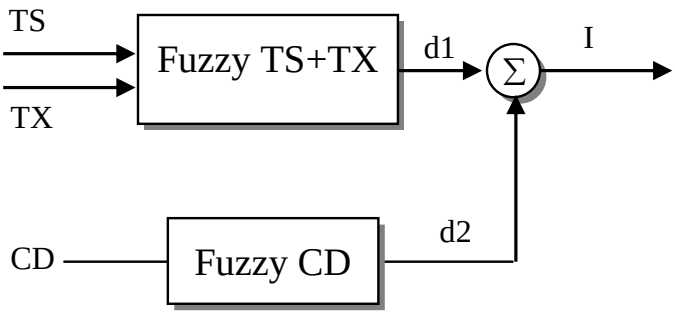
Fig. 5.7: Membership functions for Percent_Dose_Increase.

5.4.3.5 Rule-base for FES2:

Rule-base: The number of rules of a fuzzy system increases with number of inputs and their MFs. Processing huge number of rules of fuzzy systems is time consuming, which is detrimental to performance. Therefore, the reduction of rules for fuzzy systems is seen as an objective. For three inputs TS, TX and CD with 4, 5 and 4 MFs respectively, the number of rules becomes 80 ($4\times5\times4=80$) for the fuzzy system 2 in Figure 5.1. A variety of approaches are available to reduce the number of rules for a three-inputs and single output fuzzy system (Siddique, 2014). The three-inputs single-output fuzzy system can be decomposed into a two-inputs fuzzy system in parallel with a fuzzy gain or a single-input fuzzy system as shown in Figure 5.8 (a)-(b). The outputs are summed to produce the final output percent dose I. In 8(a), a fuzzy system with two inputs {TS, TX} is implemented in parallel with a fuzzy gain for $CD\in\{0,300\}$ where K is a gain factor to be tuned. For 5.8(a), K= .035 is considered, after tuning it to find the optimal performance of the system. This implementation requires 20 rules. In 5.8(b), a fuzzy system with two inputs {TS, TX} is implemented in parallel with a single input {CD} fuzzy system. This implementation of decomposed fuzzy system requires 24 rules ($4\times5+4=24$). These two decomposed versions of fuzzy systems are implemented, evaluated and compared with the optimized three-inputs fuzzy system.



8(a): Fuzzy TS+TX with scaled CD



8(b): Fuzzy TS+TX with Fuzzy CD

Fig. 5.8: Two different implementations of three-inputs and single output fuzzy systems

In case of three-inputs fuzzy system, the initial 80 rules, we get, in general, are generated from all combinations of fuzzy sets of all inputs and output of the fuzzy system. But expert knowledge following the clinical practice, as followed, suggests that some cases (some rules in fuzzy systems, generated initially) hardly/never appear as far as the disease, treatment, drugs used and physiological conditions of patients are concerned. To devise/develop a generalized procedure to optimize rule base, model constraints, as used in this work and listed in Eqs. 5.6-5.9 are used. It is to be noted that the constraints, as listed in Eqs. 5.6-5.9 and imposed on the model are consistent with clinical practice, such as, maximum allowable drug dose, maximum toxicity, tumor size, drug concentration at plasma etc.

After optimization the rules are stated as follows:

1. If TS=VS & CD=LD then I=N

2. If TS=VS & CD=ND then I=LI

3. IF TS=VS & CD=OD then I=IN

4. IF TS=VS & CD=VOD then I= IN

5. IF TS=S & TX=VL & CD=LD then I=N

6. IF TS=S & TX=VL & CD=ND then I=LI

7. IF TS=S & TX=VL & CD=OD then I= IN

8. IF TS=S & TX=L & CD=LD then I=N

9. IF TS=S & TX=L & CD=ND then I=LI

10. IF TS=S & TX=L & CD=OD then I= IN

11. IF TS=S & TX=M & CD=LD then I=N

12. IF TS=S & TX=M & CD=ND then I=N

13. IF TS=S & TX=M & CD=OD then I= IN

14. IF TS=S & TX=H then I=N

15. IF TS=S & TX=VH then I=N

16. IF TS=B & TX=VL then I=N

17. IF TS=B & TX=L then I=N

18. IF TS=B & TX=M then I=N

19. IF TS=B & TX=H then I=N

20. IF TS=B & TX=VH then I=N

21. IF TS=VB & TX=VL then I=N

22. IF TS=VB & TX=L then I=N

23. IF TS=VB & TX=M & CD=LD then I=N

24. IF TS=VB & TX=M & CD=ND then I=N

25. IF TS=VB & TX=M & CD=OD then I= IN

26. IF TS=VB & TX=H then I=N

27. IF TS=VB & TX=VH then I=N

28. IF TS=S & TX=VL & CD=VOD then I=N

29. IF TS=S & TX=L & CD=VOD then I=N

30. IF TS=S & TX=M & CD=VOD then I=N

The optimality criteria, J is defined using the performance index I (Eq. 5.13), tumor size (TS) and Toxicity (TX)

$$J = f(I, TS, TX) \tag{5.15}$$

Subject to

$$\begin{cases} I > 0 \\ TS \approx 0 \\ TX < 100 \end{cases} \tag{5.16}$$

The first approach, shown in Fig. 5.8(a), satisfies all the constraints but has a lower value of I. But the second approach, shown in Fig. 5.8(b), does not satisfy the third constraint TX, where TX >100 (5.8(b) in Figure-5.10,) even though it has the highest value of 35.64 for I (Table 5.7). The "Third Approach" satisfies all three constraints, where I=29.57, TS ~0 (0.1438) and TX <100 ("Third Approach" in Table 5.7 & Figure-5.10). Therefore, among the three approaches, the "Third Approach" is optimal.

Table 5.7: Comparison among different optimization approach (Increasing weight pattern data on 84th day is considered)

Optimization Approach	Number of rules	No. of Tumor Cell	Performance Index
5.8(a)	20	~0 (1.6698)	27.12
5.8(b)	24	~0 (3.3186×10^{-4})	35.64
"Third Approach"	30	~0 (0.1438)	29.57

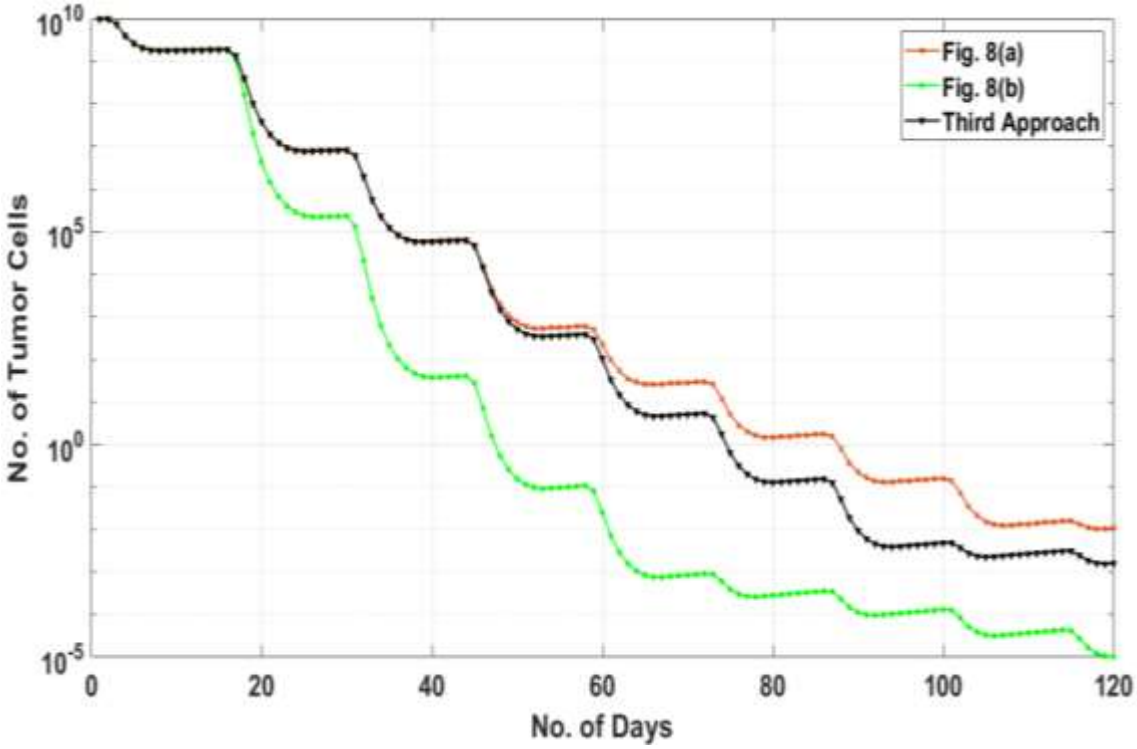


Fig. 5.9: Combined plot of the number of cancerous tumor cells, considering decomposed fuzzy systems in Fig. 5.8 (a), Fig. 5.8(b) and "Third Approach".

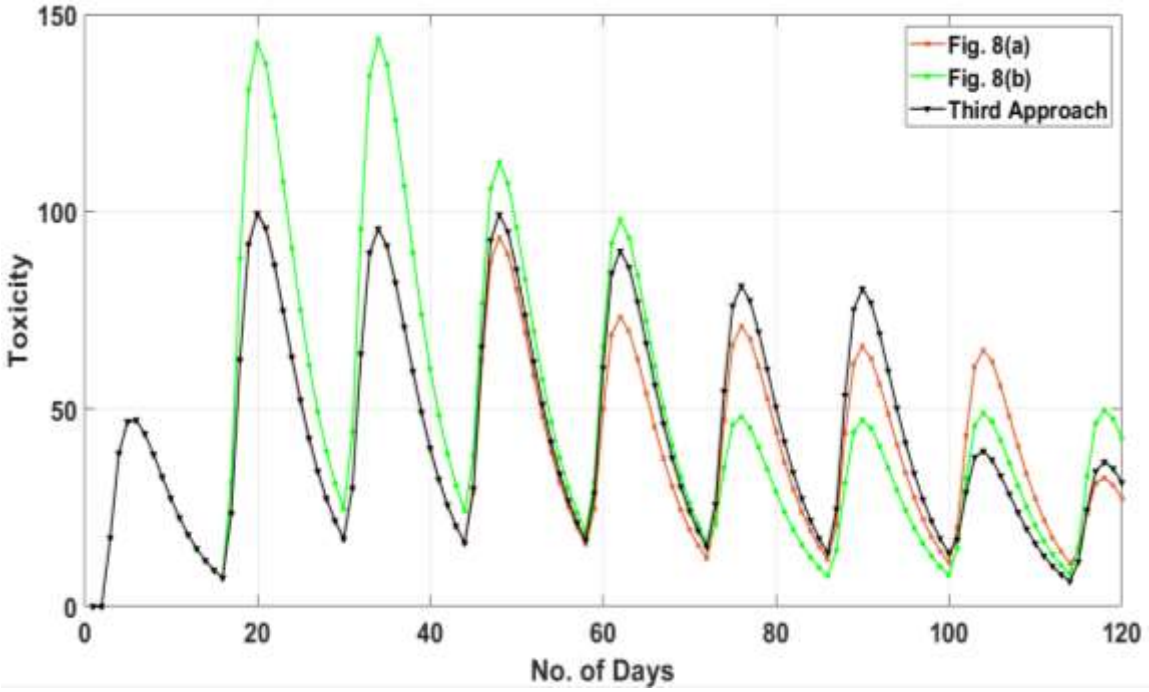


Fig. 5.10: Combined plot of Toxicity, considering decomposed fuzzy systems in Fig. 5.8 (a), Fig. 5.8(b) and "Third Approach".

5.5 Simulation and Results

The MATLAB/Simulink software and Fuzzy Logic Toolbox have been used to implement and perform simulation tests of our FES-based dose scheduler. In this study, the simulation time, 120 days is considered but to compare with other computational chemotherapy drug dose scheduling models up to 84th day's simulation output is considered. Table 1 describes all the parameters considered in our present research.

The main target of chemotherapy planning is to eliminating tumors as early as possible at the same time maintaining minimum toxicity. To provide efficient treatment while keeping the toxicity in limit, proper schemes of dose schedule should be chosen. To evaluate our proposed system for optimal dose generation, a clinically relevant dose scheme called fixed interval variable dose (FIVD) is used for interval between scheduled sessions and it is 14 days. The initial dose for the first day of treatment is considered as 40[D], which can be varied based on patient's weight and for the next cycle our proposed system will provide optimal dose considering weight, number of cancerous cells and toxicity of the patient's body.

We have used three streams of patient's weight considering increasing order of weight, decreasing order of weight and a mixed order where during treatment both increase and decrease of weight may occur. Table 8 describes three patterns of cancer patient's weight considered in this research, based on which the following arresting results (Table 10) are achieved. Only the first dose applied on the first day and next to all doses will be applied on two consecutive days as the 15th and 16th days. The increasing weight order for the patient starts from 90 and ends with 146 kgs. The decreasing weight order for the patient starts from 110 and ends with 64 kgs. And the mixed order contains both increasing, decreasing and unchanged weight order which start with 65 and ends with 80 kgs.

Table 5.8: Patterns of weight in kg (increasing, decreasing and mixed order)

Days	1	15-16	29-30	43-44	57-58	71-72	85-86	99-100	113-114
Increasing order	90	97	104	111	118	125	132	139	146
Decreasing order	110	104	98	92	86	80	74	68	64
Mixed order	65	70	75	80	86	80	74	80	80

The time amongst two consecutive chemotherapy treatments is constant for the whole treatment phase in this fixed interval variable dose. Chemotherapy is given to patients on the first two days of every third week, with a 13-day break between treatments. Chemotherapy is only given nine times over the course of four months, with the first time being on a single day and the remainder of the time being on two consecutive days as shown in Fig. 5.11.

Different Membership functions have been experimented in both FES-1 and FES-2 along with various weight patterns. Table 5.9 shows that among various membership function combinations, the Bell-shaped-Gaussian-Trapezoidal-Triangular combination performed better than the others and this combination is implemented in our system.

Table 5.9: Results of different MFs combination for both FES-1 & FES-2.

Membership Functions	Increasing	Decreasing	Random	Average	Performance Index
Gaussian-trapezoidal	0.2542	0.4262	0.4308	0.3704	28.624
Gaussian	0.1952	0.3058	0.2977	0.2662	28.955
Gaussian-triangular	0.1468	0.2489	0.2407	0.2121	29.182
Gaussian-trapezoidal-triangular	0.1485	0.2427	0.2345	0.2086	29.198
Bell-shaped-Gaussian-Trapezoidal-Triangular	0.1438	0.2323	0.2229	0.1997	29.242

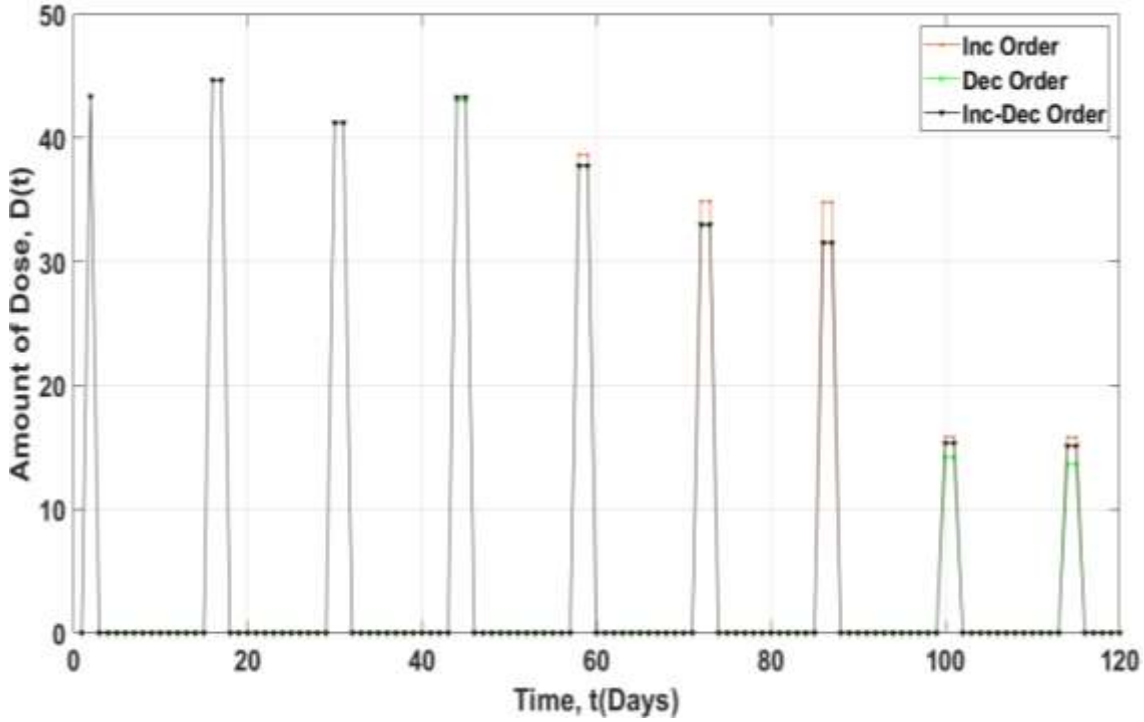


Fig. 5.11: Dose schedule for 120 days, considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

One of the main goals of chemotherapy treatment is to reduce malignant cells, as these cells might spread cancer to other major organs. The number of malignant cells is considered as 10^{10} before treatment begins, which is supported by other studies (Martin and Teo, 1994). Fig. 5.12 depicts the reduction of cancerous cells during the whole treatment period, where one can easily identify the number of cells is almost zero within 84 days of treatment period. If we analyze Figure 13, we can observe in the present context our proposed FES-2 suggests maximum 30% increase of drag dose over the dose provided by FES-1 during the treatment period. It may vary in other context.

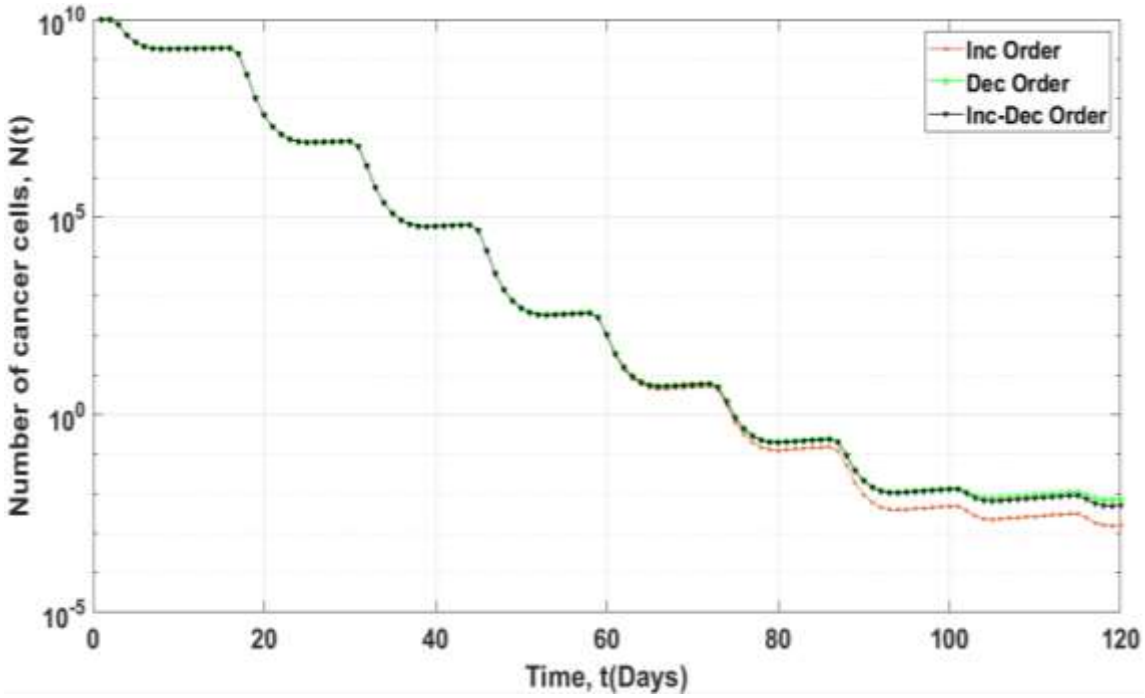


Fig. 5.12: Combined plot of the number of cancerous tumor cells for 120 days (interval 14 days), considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

In Fig. 5.13, the increase of dose in percent over the dose provided by FES-1 is depicted for three patterns of patient's weight.

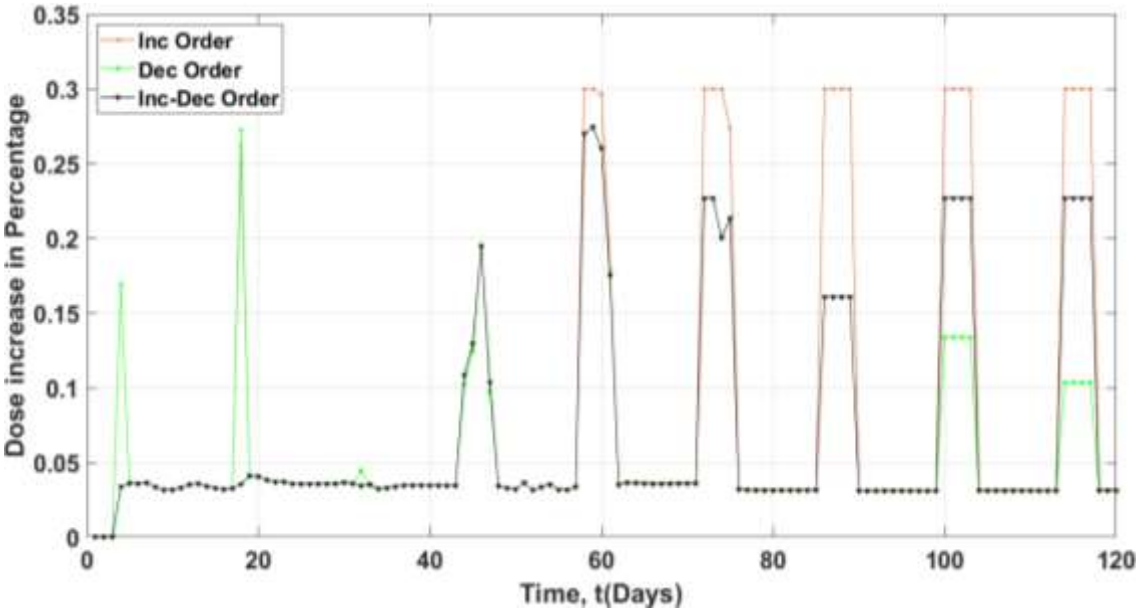


Fig. 5.13: Increase/Decrease of Dose in percent (%) over the dose calculated using No. of cell and toxicity.

This output is observed from FES-2, where input constraints is used as No. of cancerous cells, toxicities of patient's body and the calculated dose using weight, which is always followed in clinical practice. FES-2 provides a percent value, which indicates how much drag dose can be added over the calculated dose from FES-1. It suggests a high increase of dose on an average can be applied for increasing order of weight flow. In decreasing weight flow, FES-2 suggests a high increase of dose in the second day for a large weight of patient. For increase-decrease flow of weight, FES-2 suggests a low increase of dose by considering both number of cancerous cells and toxicity in patients' bodies. For a patient, staying with high toxicities, the proposed system does not suggest a high increase of drag dose, which can be life threatening for a patient.

The toxicities for the three weight patterns corresponding drag dose scheduling are depicted in Fig. 5.14. For each three cases toxicity highly increased after the second dose was applied, but never crossed the maximum level of toxicity (100). The maximum level of toxicity (TX) is observed for the mentioned three cases, which is less than 100. It is worth to be noted that in all cases, toxicities remain under control and lower than the maximum limiting value.

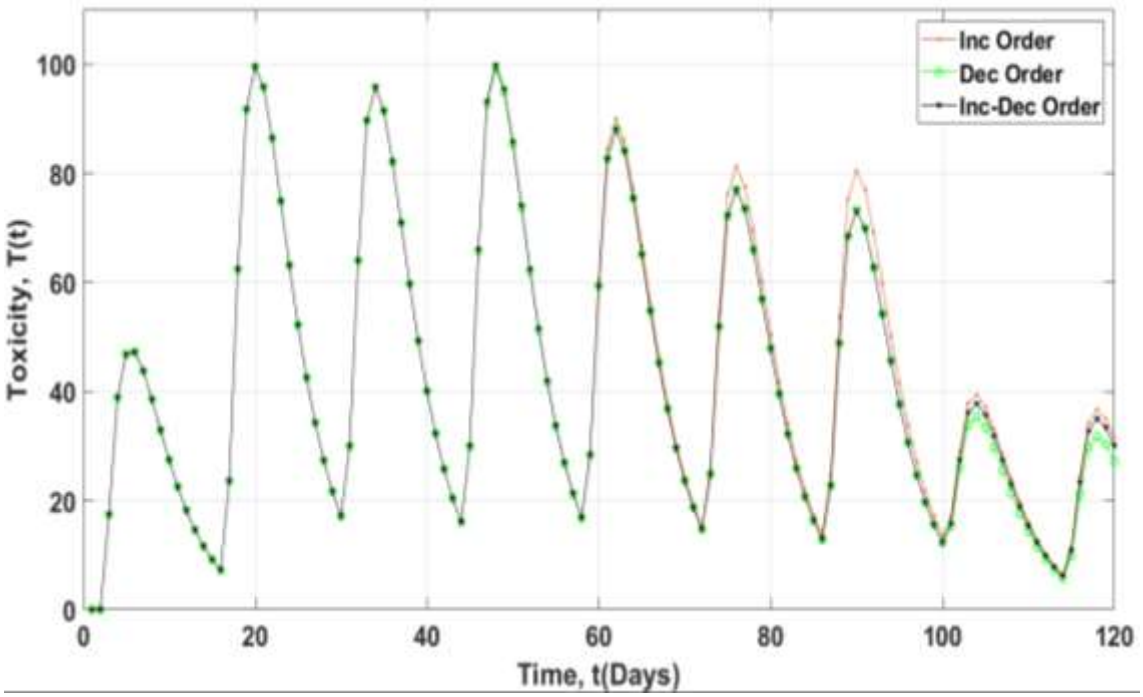


Fig. 5.14: Toxicity for 120 days (14 days of interval), considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

A summary of the performance measure in response to three cases of weight pattern for proposed chemotherapy dose scheduling is shown in Table 5.10. The code schemes generated by the mentioned three cases successfully maintained the constraints described in the methodology section. Toxicity levels are kept below 100 and drag dose for a particular day never exceeds 50[D].

Table 5.10: Performance measure in response to three weight cases.

Case	Weight type	Drag Dose	Toxicity	Dose increase (%)	Cum. drag. Concentration	Initial Tumor cell No.	Final Tumor cell No.	Cell Reduction
		Avg	Avg	Avg				
1	Increasing order	40.7430	48.4685	14.2059	448.1732	10^{10}	~0.1438	~100%
2	Decreasing Order	40.2296	47.8966	12.361	442.5253	10^{10}	~0.2323	~100%
3	Increasing-decreasing order	40.2730	47.9483	12.4614	443.0028	10^{10}	~0.2229	~100%

The cumulative drag concentration is lower than the maximum allowable level which is 4.1×10^3. The efficacy constraint is also maintained as the number of cells has never risen to a value above the initial number 10^{10}. The final tumor cell counts for case 1, 2 and 3 are respectively 0.1438, 0.2323 and 0.2229, which is the result till 84 days. In addition, after 120 days the number of tumor cells for the mentioned three cases is respectively 0.0017, 0.0075, 0.0052. The cell reduction is close to ~100% as compared to initial tumor cell number. By observing all three cases, it can be noted that the proposed methodology is effective in terms of cancer treatment. Further, the Maximum

drug dose, Toxicity, and Dose increase for all 3 cases were 44.6474, 99.505, and 30% respectively. Cell reduction was close to ~100% for all cases and the initial number of cells was 10^{10}.

5.6 Efficacy comparison

Table 5.11 compares the performance of the proposed approach with other optimal control methods in previous comparable studies, based on the performance index (Eq. 5.13) and the ultimate number of malignant cells left after 84 days assuming normal toxicity sensitivity. Clearly, the proposed approach was successful in achieving the cancer treatment goal, as evidenced by the highest performance index of 29.242 and a tiny tumor size.

Table 5.11: Efficacy comparison with proposed method and existing methods of chemotherapy drag scheduling.

Drag Schedule Method	Performance Index	Final Number of cancerous cells
Tan et al., 2002 [27]	17.99	1.53×10^4
Tsai et al., 2013 [34]	24.74	18.0
Algoul et al., 2011 [48]	24.92	15.0
El-Garawany et al., 2017 [16]	25.51	~8 (8.34)
Khadraoui et al., 2016 [52]	27.56	~1 (1.078)
Karar et al., 2020 [17]	27.63	~1 (0.806)
Proposed method	29.242	~0 (0.1997)

Chapter 6

Fuzzy Expert System and PBPK based Feedback Controlled Decision Support System for Oncologists

6.1 FES Based Feedback Controlled DSS Model Architecture

The proposed Fuzzy Expert System (FES) based feedback controlled Decision Support System (DSS) chemotherapy model is designed to support the oncologists to treat cancer through chemotherapy. The system is developed to generate optimal chemotherapy drug doses with a view to reduce the cancerous tumor cells ~0, keeping the toxicity within the limit. Apart from these, the DDS model will also give the oncologists the opportunity to observe the drug concentration in different organs of the patient body. Which will help/support the experts to justify the drug doses to be applied physically. The DSS model consists of three modules, which are as follows (Fig. 6.1):

1. Modular Fuzzy Expert System for Chemotherapy Drug Dose Scheduling
2. Physiologically Based Pharmacokinetic (PBPK) Module for Drug Concentration Projection
3. Feedback Controller

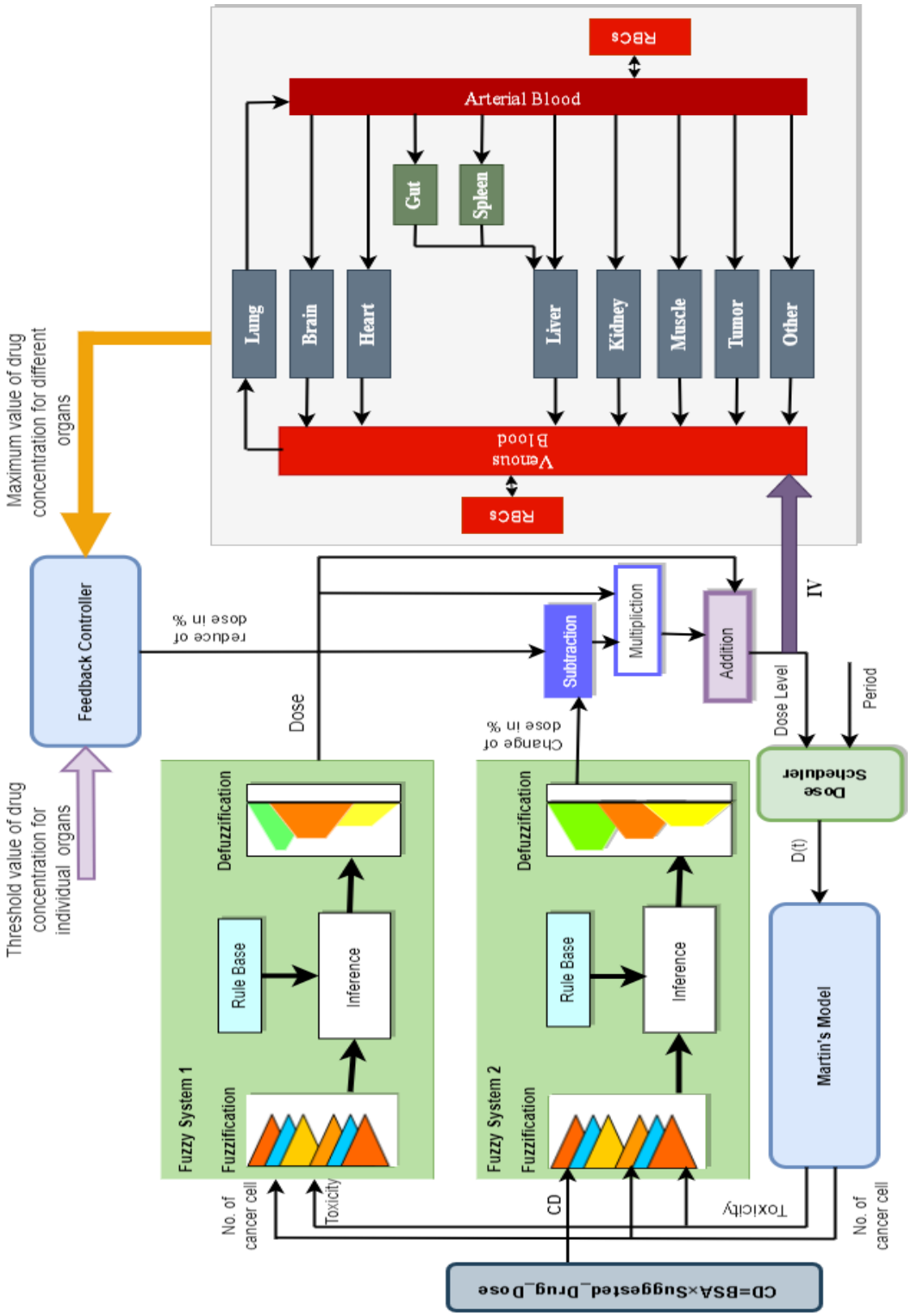


Fig. 6.1: Architecture of proposed DSS model

The drug dose generated by the Modular Fuzzy Expert System module will be inputted to the PBPK module to observe the drug concentration in different organs of the patient body, at the same time the feedback controller will help the modular fuzzy expert system to adjust the patient specific drug dose considering the output of the PBPK module and oncologist suggested/expected drug concentration in different organs of the patient body.

Most of the inputs and output used in the present DSS model are same as we described in the previous chapter which are tumor size, toxicity, calculated dose as input and drug dose as output. Apart from these inputs and output, threshold values of drug concentration for individual organs are used as input and maximum values of drug concentration of different organs are used as output generated by PBPK module. The inputs and outputs are described as follows:

6.1.1 Model Inputs

- **Tumor size:** The tumor cell is a crucial factor for cancer chemotherapy analysis (Welch et al., 2016). Tumor sizes represent the number of tumor cells and are used to calculate doses. Based on tumor size and toxicity, the situation and survival rate of the patients can be predicted. Initially, the number of tumor cells is considered 10^{10}, and then the number of tumor cell is found through the growth model (used in fig. 6.1) after each cycle of drug dose (Faisal et al., 2023).

- **Toxicity:** Toxicity is the essential input in this research. It has a positive correlation with chemotherapy doses, and for this purpose, we can't increase drug doses without consideration of toxicity, as the human body can only tolerate a certain amount of toxicity (Faisal et al., 2023). In this research, the trade-off characteristics of toxicity with other factors of chemotherapy are considered.

- **Calculated Dose:** As it is discussed in the previous chapter, it is the amount of dose for every cycle, which is measured based on the body surface area (BSA) of the person and the suggested amount of dose of a particular drug. The value

of the calculated dose is evaluated by multiplying the value of BSA by the suggested dose (Coletti et al., 2021; Beumer et al., 2012; Kaestner & Sewell, 2007).

- **Threshold values of drug concentration:** Kidney and liver functions are responsible for drug metabolism and excretion. These organs are main determining factors for plasma concentrations of drugs in general and anticancer agents in particular (Hendrayana et al., 2017). Precision medicine in oncology entails tailored drug treatment for individual patients. Since during cancer treatment each patient's physical condition differ from each other, personalized dosing regimens based on tumor drug penetration play a critical role (Bartelink et al., 2019). Tolerable drug concentration in different organs of a patient body may vary depending on the patient physic and/or type of cancer occurred. To generate more patient specific optimum drug dose, during chemotherapy the oncologist can determine the threshold values of drug concentration in the targeted organs.

6.1.2 Model Outputs

- **Drug Dose:** It is the output of the first module, modular fuzzy expert system for chemotherapy drug dose scheduling, of the DSS model, which has already been discusses in the previous chapter. After combine processing/run of all the module in the present DSS model, patient specific optimum drug dose will be generated.

- **Maximum values of drug concentration:** It means how much drug exists in a compartment or organ after administering drug dose in a chemo cycle. When the drug enters into the blood circulation system, drug distribution occurs. The distribution of drugs mostly depends on membrane permeability and perfusion rate. The differential equations cover all of the issues, and by using the equation, drug concentration can be determined for individual organs (Nestorov, 2003).

6.2 Modular Fuzzy Expert System for Chemotherapy Drug Dose Scheduling

The chemo drug dose scheduling module is a modular Fuzzy Expert System (FES) for chemotherapy drug dose scheduling, which is discussed in the previous chapter in details (fig. 5.1) (Faisal et al., 2023). The computational model considered the patient's Body Surface Area (BSA) and experts' opinions to calculate chemo doses following the clinical practice (Faisal et al., 2023). In this module two fuzzy systems are used, fuzzy system 1 takes two inputs (toxicity and number of cancer cells) and produces an output (the dose). Fuzzy system 2 is developed considering toxicity, the number of cancer cells, and the calculated dose using patient BSA. The output (% of changed dose) from fuzzy system 2 plays a vital role in improving the precision of the dose scheduler. Moreover, two strong and optimized fuzzy rule base is developed to make the dose scheduler more effective and efficient (Faisal et al., 2023). A growth model (Martin's model) is used in this model to observe the number of tumor cells, toxicity, and changed doses. It helps to calculate tumor size and toxicity in the patient's body. Fuzzy System 1 and Fuzzy System 2 both use the output of the growth model as their input. The growth model's equations and implementation are discussed in the previous chapter.

6.3 Physiologically Based Pharmacokinetic (PBPK) Model for Drug Concentration Projection

To describe a patient's organ's toxicity, the Physiologically-based pharmacokinetic (PBPK) model plays the most essential role (Miller et al., 2019). In the disciplines of predictive toxicology and pharmacology, PBPK modeling is significant (Hsieh, 2018). PBPK models provide a concise evaluation of pharmacokinetic processes such as absorption, distribution, metabolism, and excretion by using the physiological structures of organisms and the physiochemical properties of chemicals. They can be used to investigate mechanistic processes, evaluate hypotheses, and guide experiment design. This model is very effective for designing better therapies and/or estimating risks for vulnerable communities, whether it's with medications or environmental chemicals (Hsieh, 2018). The PBPK models outperform to other empirical models for

forecasting pharmacokinetics (Jones et al., 2006; Zhang et al., 2015), and as is shown from a recent cross-industry viewpoint (Miller et al., 2019), many large and medium pharmaceutical industries are now consistently employing the approach. The PBPK model has been effectively used for risk assessment in nanotoxicology (Cheng et al., 2018), dose modification recommendations for pregnant women (Abduljalil et al., 2020), and threat assessment for drugs in human and animal bodies (Li et al., 2018; Yamamoto et al., 2018).

Physiologically-based Pharmacokinetic Model (PBPK), a system which can be used to anticipate drug distribution, determine target tissue drug concentrations, and provide simultaneous tissue concentration versus time profiles for the various compartments in the model, has applied in this study to simulate a clinically relevant chemotherapy drug dose. Relating the possible correlation between dose, exposure, and reaction would be a crucial step towards precisely estimating the potential adverse risk to human health because some medications (such as epirubicin, fluorouracil, and cyclophosphamide) can induce toxicity at extremely low concentrations in experimental patients (Campbell, 2009). The clinically relevant chemotherapy drug doses are obtained from the fuzzy expert system-based model which considers patients weight and experts opinion to calculate chemotherapy drug dose (Faisal et al., 2023). After applying chemo drug dose, generated from FES system, into the PBPK model the impact of chemotherapy drug dose and the concentration of drug dose on different organs will be generated.

6.3.1 PBPK Model for Docetaxel

This research is developed considering Docetaxel as the applied drug. Docetaxel is one of the active agents for cancer chemotherapy and the pharmacokinetics of Docetaxel is largely linear (Ebrahimi et al., 2017). Docetaxel (Doc) based PBPK model, as shown in fig 6.2, is developed to represent different tissues or organs in the body (Florian et al., 2007). The model contains 35 linear differential equations to capture the Docetaxel drug concentration on plasma, tissues and intracellular tissues in each tissue compartment.

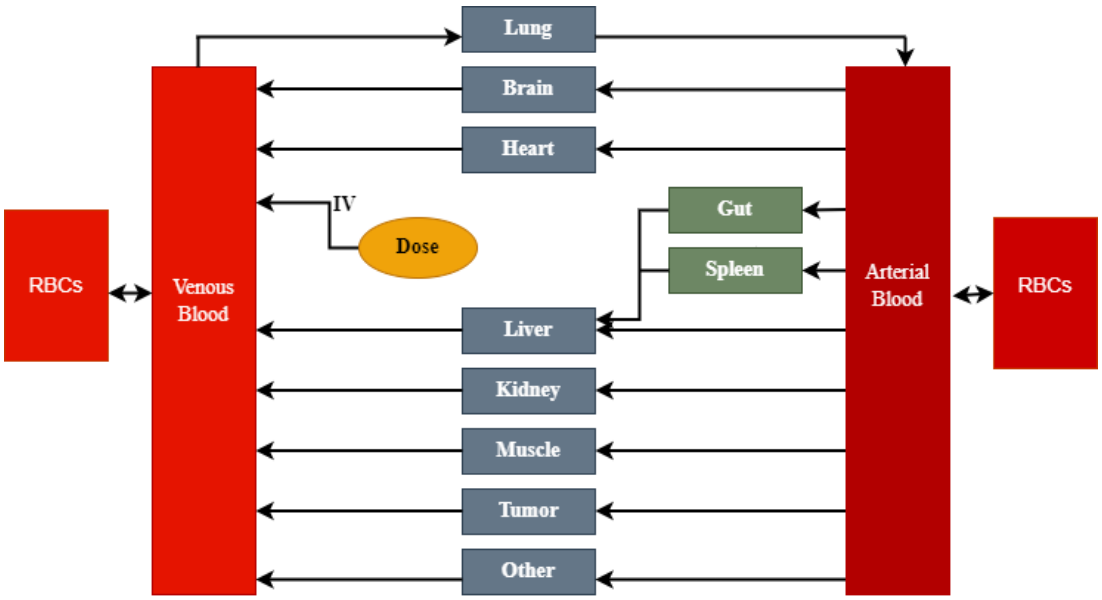


Fig. 6.2: Docetaxel PBPK model (Florian et al., 2007)

6.3.2 PBPK Model Equations

PBPK model equations were developed with the concept of distribution of drugs in the whole body (Florian et al., 2007). The whole body was divided into some compartments or different organs of the human body. Compartment and organ division of PBPK model and the distribution of drug (DOC) are depicted in Figure 6.2. Some differential equations were used to represent these organs of the human body. The equations were developed depending on response, characteristics, behavior, and examined data (Florian et al., 2007). Dose is infused into venous blood in this model that is known as IV administration. After infusing the drug, it subsequently distributes throughout the rest of the body. The drug dose schedule is represented by U(t) in the equation 6.1.

The complete set of equations for the Docetaxel human PBPK model are shown in the below (equation 6.1-6.35):

Venous Blood:

$$\frac{dC_v}{dt} = \frac{\sum F_j C_{j_e} - F_{tot} C_{ven}}{V_{ven}\,(1 - f_{hem})} + \frac{f_{hem}}{(1 - f_{hem})} K_{rbcplas} C_{rbcv} - K_{plasrbc} f_{unb} C_{ven} + \frac{U(t)}{V_{ven}\,(1 - f_{hem})} \quad 6.1$$

$$\frac{dC_{rbcv}}{dt} = -K_{rbcplas} C_{rbcv} + \frac{(1 - f_{hem})}{f_{hem}} K_{plasrbc} f_{unb} C_{ven} \quad 6.2$$

Lung:

$$\frac{dC_{l_v}}{dt} = \frac{F_l}{V_{l_v}} \left(C_{ven} - C_{l_v}\right) - K_{l_{ve}} f_{unb} C_{l_v} + \frac{V_{l_e}}{V_{l_v}} K_{l_{ev}} C_{l_e} \quad 6.3$$

$$\frac{dC_{l_e}}{dt} = \frac{V_{l_v}}{V_{l_e}} K_{l_{ve}} f_{unb} C_{l_v} - K_{l_{ev}} C_{l_e} + K_{bind_{out}} C_{l_b} - K_{bind_{in}} C_{l_e} \quad 6.4$$

$$\frac{dC_{l_b}}{dt} = -K_{bind_{out}} C_{l_b} + K_{bind_{in}} C_{l_e} \quad 6.5$$

Arterial Blood:

$$\frac{dC_{art}}{dt} = \frac{(F_l\, C_{lv} - F_l C_{art})}{V_{art}(1 - f_{hem})} + \frac{f_{hem}}{(1 - f_{hem})} K_{rbcplas} C_{rbca} - K_{plasrbc} f_{unb} C_{art} \quad 6.6$$

$$\frac{dC_{rbca}}{dt} = -K_{rbcplas} C_{rbca} + \frac{(1 - f_{hem})}{f_{hem}} K_{plasrbc} f_{unb} C_{art} \quad 6.7$$

Gut:

$$\frac{dC_{g_v}}{dt} = \frac{F_g}{V_{g_v}} \left(C_{art} - C_{g_v}\right) \quad 6.8$$

Brain:

$$\frac{dC_{b_v}}{dt} = \frac{F_b}{V_{b_v}} \left(C_{art} - C_{b_v}\right) - K_{b_{ve}} f_{unb} C_{b_v} + \frac{V_{b_e}}{V_{b_v}} K_{b_{ev}} C_{b_e} \quad 6.9$$

$$\frac{dC_{b_e}}{dt} = \frac{V_{b_v}}{V_{b_e}} K_{b_{ve}} f_{unb} C_{b_v} - K_{b_{ev}} C_{b_e} + K_{bind_{out}} C_{b_b} - K_{bind_{in}} C_{b_e} \quad 6.10$$

$$\frac{dC_{b_b}}{dt} = -K_{bind_{out}} C_{b_b} + K_{bind_{in}} C_{b_e} \quad 6.11$$

Spleen:

$$\frac{dC_{s_v}}{dt} = \frac{F_s}{V_{s_v}} \left(C_{art} - C_{s_v}\right) - K_{s_{ve}} f_{unb} C_{s_v} + \frac{V_{s_e}}{V_{s_v}} K_{s_{ev}} C_{s_e} \quad 6.12$$

$$\frac{dC_{s_e}}{dt} = \frac{V_{s_v}}{V_{s_e}} K_{s_{ve}} f_{unb} C_{s_v} - K_{s_{ev}} C_{s_e} + K_{bind_{out}} C_{s_b} - K_{bind_{in}} C_{s_e} \quad 6.13$$

$$\frac{dC_{s_b}}{dt} = -K_{bind_{out}} C_{s_b} + K_{bind_{in}} C_{s_e} \quad 6.14$$

Liver:

$$\frac{dC_{li_v}}{dt} = \frac{1}{V_{li_v}} \left(F_{li} C_{art} + F_g C_{g_v} + F_s C_{s_v} - (F_g + F_s + F_{li}) C_{li_v}\right) - K_{li_{ve}} f_{unb} C_{li_v} + \frac{V_{li_e}}{V_{li_v}} K_{li_{ev}} C_{li_e} \quad 6.15$$

$$\frac{dC_{li_e}}{dt} = \frac{V_{li_v}}{V_{li_e}} K_{li_{ve}} f_{unb} C_{li_v} - K_{li_{ev}} C_{li_e} + K_{bind_{out}} C_{li_b} - K_{bind_{in}} C_{li_e} - K_{cl_{li}} C_{li_e} \quad 6.16$$

$$\frac{dC_{li_b}}{dt} = -K_{bind_{out}} C_{li_b} + K_{bind_{in}} C_{li_e} - K_{cl_{li}} C_{li_b} \quad 6.17$$

Kidney:

$$\frac{dC_{k_v}}{dt} = \frac{F_k}{V_{k_v}} \left(C_{art} - C_{k_v}\right) - K_{k_{ve}} f_{unb} C_{k_v} + \frac{V_{k_e}}{V_{k_v}} K_{k_{ev}} C_{k_e} \quad 6.18$$

$$\frac{dC_{k_e}}{dt} = \frac{V_{k_v}}{V_{k_e}} K_{k_{ve}} f_{unb} C_{k_v} - K_{k_{ev}} C_{k_e} + K_{bind_{out}} C_{k_b} - K_{bind_{in}} C_{k_e} \quad 6.19$$

$$\frac{dC_{k_b}}{dt} = -K_{bind_{out}} C_{k_b} + K_{bind_{in}} C_{k_e} \quad 6.20$$

Muscle:

$$\frac{dC_{m_v}}{dt} = \frac{F_m}{V_{m_v}}\left(C_{art} - C_{m_v}\right) - K_{m_{ve}} f_{unb} C_{m_v} + \frac{V_{m_e}}{V_{m_v}} K_{m_{ev}} C_{m_e} \quad 6.21$$

$$\frac{dC_{m_e}}{dt} = \frac{V_{m_v}}{V_{m_e}} K_{m_{ve}} f_{unb} C_{m_v} - K_{m_{ev}} C_{m_e} + K_{bind_{out}} C_{m_b} - K_{bind_{in}} C_{m_e} \quad 6.22$$

$$\frac{dC_{m_b}}{dt} = -K_{bind_{out}} C_{m_b} + K_{bind_{in}} C_{m_e} \quad 6.23$$

Fat:

$$\frac{dC_{f_v}}{dt} = \frac{F_f}{V_{f_v}}\left(C_{art} - C_{f_v}\right) - K_{f_{ve}} f_{unb} C_{f_v} + \frac{V_{f_e}}{V_{f_v}} K_{f_{ev}} C_{f_e} \quad 6.24$$

$$\frac{dC_{f_e}}{dt} = \frac{V_{f_v}}{V_{f_e}} K_{f_{ve}} f_{unb} C_{f_v} - K_{f_{ev}} C_{f_e} + K_{bind_{out}} C_{f_b} - K_{bind_{in}} C_{f_e} \quad 6.25$$

$$\frac{dC_{f_b}}{dt} = -K_{bind_{out}} C_{f_b} + K_{bind_{in}} C_{f_e} \quad 6.26$$

Tumor:

$$\frac{dC_{t_v}}{dt} = \frac{F_t}{V_{t_v}}\left(C_{art} - C_{t_v}\right) - K_{t_{ve}} f_{unb} C_{t_v} + \frac{V_{t_e}}{V_{t_v}} K_{t_{ev}} C_{t_e} \quad 6.27$$

$$\frac{dC_{t_e}}{dt} = \frac{V_{t_v}}{V_{t_e}} K_{t_{ve}} f_{unb} C_{t_v} - K_{t_{ev}} C_t + K_{bind_{out}} C_{t_b} - K_{bind_{in}} C_{t_e} \quad 6.28$$

$$\frac{dC_{t_b}}{dt} = -K_{bind_{out}} C_{t_b} + K_{bind_{in}} C_{t_e} \quad 6.29$$

Heart:

$$\frac{dC_{h_v}}{dt} = \frac{F_h}{V_{h_v}}\left(C_{art} - C_{h_v}\right) - K_{h_{ve}} f_{unb} C_{h_v} + \frac{V_{h_e}}{V_{h_v}} K_{h_{ev}} C_{h_e} \quad 6.30$$

$$\frac{dC_{h_e}}{dt} = \frac{V_{h_v}}{V_{h_e}} K_{h_{ve}} f_{unb} C_{h_v} - K_{h_{ev}} C_{h_e} + K_{bind_{out}} C_{h_b} - K_{bind_{in}} C_{h_e} \quad 6.31$$

$$\frac{dC_{h_b}}{dt} = -K_{bind_{out}} C_{h_b} + K_{bind_{in}} C_{h_e} \quad 6.32$$

Other:

$$\frac{dC_{o_v}}{dt} = \frac{F_o}{V_{o_v}}\left(C_{art} - C_{o_v}\right) - K_{o_{ve}} f_{unb} C_{o_v} + \frac{V_{o_e}}{V_{o_v}} K_{o_{ev}} C_{o_e} \quad 6.33$$

$$\frac{dC_{o_e}}{dt} = \frac{V_{o_v}}{V_{o_e}} K_{o_{ve}} f_{unb} C_{o_v} - K_{o_{ev}} C_{o_e} + K_{bind_{out}} C_{o_b} - K_{bind_{in}} C_{o_e} \quad 6.34$$

$$\frac{dC_{o_b}}{dt} = -K_{bind_{out}} C_{o_b} + K_{bind_{in}} C_{o_e} \quad 6.35$$

6.3.3 PBPK Model Parameter

Equations mentioned in the above section are for Docetaxel PBPK model to observe the distribution of doc in human body where F_i is the blood flow rate into tissue i, V_i is the volume of tissue i and C_i is the drug concentration in tissue i. (Florian et al., 2007).

Diffusion-limited tissues have both a vascular (v) and extra-vascular tissue (e) space (for tissue i, volumes of vascular (v) and extra-vascular tissue (e) space have been defined as V_{iv} , and V_{ie}, respectively), with separate concentrations, C_{iv} and C_{ie} , intra-tissue transfer rates, K_{iev} and K_{ive}, vascular tissue fraction, f_i and an unbound drug fraction, $f_{unb.}$ C_{ib} is the drug concentrations in the additional "bound" subcompartment, K_{bindin} and $K_{bindout}$ are retention rates within the tissue, f_{hem} is the hematocrit fraction, k_{clli} is the drug clearance rate from the liver, Fj and C_{je} are the flow rates and extra-vascular concentrations, respectively, from tissue j (Florian et al., 2007).

C_{ven} and C_{rbc} are the concentrations in venous plasma and circulating red blood cells respectively, U represents IV administration of Doc. $k_{plasrbc}$ and $k_{rbcplas}$ represents transition rates between plasma and RBCs. Now, vascular and extra-vascular tissue volume of tissue i are calculated as

$$V_{iv} = V_i f_i \quad 6.36$$

$$V_{ie} = V_i - V_{iv} \quad 6.37$$

Similarly, the tissue volume and blood flow rate for the other compartment is calculated as (Florian et al., 2007)

$$V_o = V_{tot} - \sum_{i \neq o} Vi \quad 6.38$$

$$F_o = F_{tot} - \sum_{i \neq o,l} F_i \quad 6.39$$

For parameters F_i, V_i and f_i, parameters values for human (70 kg) PBPK model is used. (Florian et al., 2007; Brown et al., 1997). By minimizing the weighted sum squared error between model predictions and mouse PK data, the remaining parameters (tissue-specific exchange rates, plasma-RBC exchange rates, tissue binding rates, and liver clearance rate) were estimated (Florian et al., 2007).

Finally parameters values used to implement the model are given in the following tables.

Table 6.1: Parameters (F_i, V_i, f_i, V_{iv} & V_{ie}) values for the human (70 kg) PBPK model (Florian et al., 2007)

Tissue (i)	Tissue blood flow rate (F_i) (L/min)	Tissue Volume (V_i) (L)	Tissue vascular fraction (f_i)	Vascular tissue volume (V_{iv}) (L)	Extra-vascular tissue volume (V_{ie}) (L)
Liver (li)	$F_{li} = 0.45$	$V_{li} = 1.80$	$f_{li} = 0.16$	$V_{liv} = 0.288$	$V_{lie} = 1.512$
Lung (l)	$F_l = 5.60$	$V_l = 0.53$	$f_l = 0.30$	$V_{lv} = 0.159$	$V_{le} = 0.371$
Tumor (t)	$F_t = 0.03$	$V_t = 0.2$	$f_t = 0.05$	$V_{tv} = 0.01$	$V_{te} = 0.19$
Gut (g)	$F_g = 1.13$	$V_g = 1.19$		$V_{gv} = 1.2769$	
Muscle (m)	$F_m = 0.59$	$V_m = 28.0$	$f_m = 0.03$	$V_{mv} = 0.84$	$V_{me} = 27.16$
Spleen (s)	$F_s = 0.02$	$V_s = 0.18$	$f_s = 0.20$	$V_{sv} = 0.036$	$V_{se} = 0.144$
Heart (h)	$F_h = 0.26$	$V_h = 0.33$	$f_h = 0.02$	$V_{hv} = 0.0066$	$V_{he} = 0.3234$
Fat (f)	$F_f = 0.74$	$V_f = 15.0$	$f_f = 0.03$	$V_{fv} = 0.45$	$V_{fe} = 14.55$
Kidney (k)	$F_k = 1.24$	$V_k = 0.31$	$f_k = 0.24$	$V_{kv} = 0.0744$	$V_{ke} = 0.2356$

Brain (b)	$F_b = 0.78$	$V_b = 1.40$	$f_b = 0.04$	$V_{bv} = 0.056$	$V_{be} = 1.344$
Other (o)	$F_o = 0.36$	$V_o = 15.8$	$f_o = 0.05$	$V_{ov} = 0.79$	$V_{oe} = 15.01$
Venous Blood (ven)	$F_{tot} = 5.60$	$V_{ven} = 3.318$	$f_{unb} = 0.05$ $f_{hem} = 0.45$		
Arterial Blood (art)		$V_{art} = 2.212$			

Table 6.2: Intra-tissue transfer rates, plasma-RBC exchange rates, tissue binding rates, and liver clearance rate (Florian et al., 2007)

Tissue (i)	Vascular to extra-vascular (ve) (1/min)	Extra-vascular to Vascular(ev) (1/min)	Others Parameters (1/min)
Liver (li)	$k_{live} = 10.253$	$k_{liev} = 0.0965$	$k_{clli} = 0.1023$
Lung (l)	$k_{lve} = 0.2662$	$k_{lev} = 0.0365$	
Tumor (t)	$k_{tve} = 0.110$	$k_{tev} = 0.0006$	
Muscle (m)	$k_{mve} = 0.5952$	$k_{mev} = 0.0158$	
Spleen (s)	$k_{sve} = 1.8667$	$k_{sev} = 0.0445$	
Heart (h)	$k_{hve} = 2.246$	$k_{hev} = 0.0495$	
Fat (f)	$k_{fve} = 0.2161$	$k_{fev} = 0.0079$	
Kidney (k)	$k_{kve} = 2.924$	$k_{kev} = 0.1859$	
Brain (b)	$k_{bve} = 0.0547$	$k_{bev} = 0.0573$	
Other (o)	$k_{ove} = 0.7451$	$k_{oev} = 0.0099$	
Blood			$k_{rbcplas} = 0.00128$ $k_{plasrbc} = 0.000348$
Bind			$k_{bind\text{-}in} = 0.001015$ $k_{bind\text{-}out} = 0.000895$

6.4 Feedback Controller

Feedback controller is designed to support the modular fuzzy expert system to adjust the patient specific optimal drug dose considering the output of the PBPK module and oncologist suggested/expected drug concentration in different organs of the patient

body. It is the controlling system that controls the output of the dose scheduler through comparing the patient specific threshold value of drug concentration in individual organs, inputted by the oncologist and the maximum drug concentration in different organs generated by the PBPK module. Here, threshold value of drug concentration in individual organs means maximum drug concentration that can an organ tolerate and it varies according to patient's physic, which can be decided by the oncologist during treatment. In this study, the maximum drug concentration in different organs represents the remaining drug concentration in individual organs after injecting a drug dose into the patient's body. The feedback controller works with a condition: if the threshold values of drug concentration in individual organs is less than the maximum drug concentration in different organs, then the changed drug dose is subtracted by 0.05; otherwise, there is no change. Which means 5% drug dose enhancement will be reduced from the prescribed drug dose enhancement by the "fuzzy system 2" and the 5% dose enhancement reduction will continue until the maximum drug concentration in each and every organs of the body, derived from PBPK module, is less than or equal to the threshold values inputted by the oncologist. The value of subtraction (0.05) is determined by running the main program a number of times. And using 0.05 as a subtractor value reduces the number of tumor cells to zero, where toxicity remains under control. The Feedback controller is implemented in Python, which is given in Appendix C.

6.5 Experimental Analysis

6.5.1 Model development

Implementation of the 1st module, modular fuzzy expert system for chemotherapy drug dose scheduling, has already been discussed and shown in the previous chapter. PBPK model has been implemented using MATLAB Simulink and the feedback controller using Python. Along with the 1st and 3rd (Feedback Controller) modules, the 2nd module, Physiologically Based Pharmacokinetic (PBPK) Module for Drug Concentration Projection, has been implemented using MATLAB Simulink, which is the present FES based Decision Support System for chemotherapy drug dose scheduling. In the 3rd module, Feedback Controller, threshold values of drug concentration in individual

organs of the patient, which will be inputted by the oncologist considering the physic of the concerning patient are set to 50 for the present simulation, which is the maximum tolerable drug level for our present model, as discussed in the previous chapter.

The MATLAB/Simulink software and Fuzzy Logic Toolbox have been used to implement and perform simulation tests of the FES based Decision Support System for chemotherapy drug dose scheduler. In this study, the simulation time, 120 days is considered but to compare with other computational chemotherapy drug dose scheduling models, as I discussed in the previous chapters, up to 84th day's simulation output is considered. Within the period, considering 14 days (FIVD: fixed interval variable dose) interval chemotherapy model, 6 cycle chemo dose is applied. For the present DSS model this duration is also justified because if we observe the following simulation fig. 6.4, it is found that on the 84^{th} day tumor size become ~0, maintaining toxicity within the safe limit.

The optimum drug dose generated by the model will also predict the drug concentration, of docetaxel for every single dose, in targeted organs of the patient during the treatment. Figures in the following sections will show how different organs in the human body respond differently in different chemo doses in different cycles.

6.5.2 Model Generated Drug Dose, Cancerous Cell Population & Toxicity

In the DSS model one day single dose is applied in the 1^{st} cycle, and from the 2^{nd} and onward cycle after each 14 days interval same drug dose is administrated in consecutive two days. In the figure 6.3 projected drug dose, for a patient with increasing weight pattern during treatment, is shown. If we analyze following figures, fig. 6.4 and 6.5, it is found that number of tumor successfully reduced to ~0 while the toxicity was within the threshold level. It is also to be noted that the drug dose is very justified because if we compare two fig 6.3 and fig. 6.5, it is found that immediately before each and every cycle the toxicity became nearly 0. That is with in the 14 days interval the patient is fit to take drug dose in the next cycle.

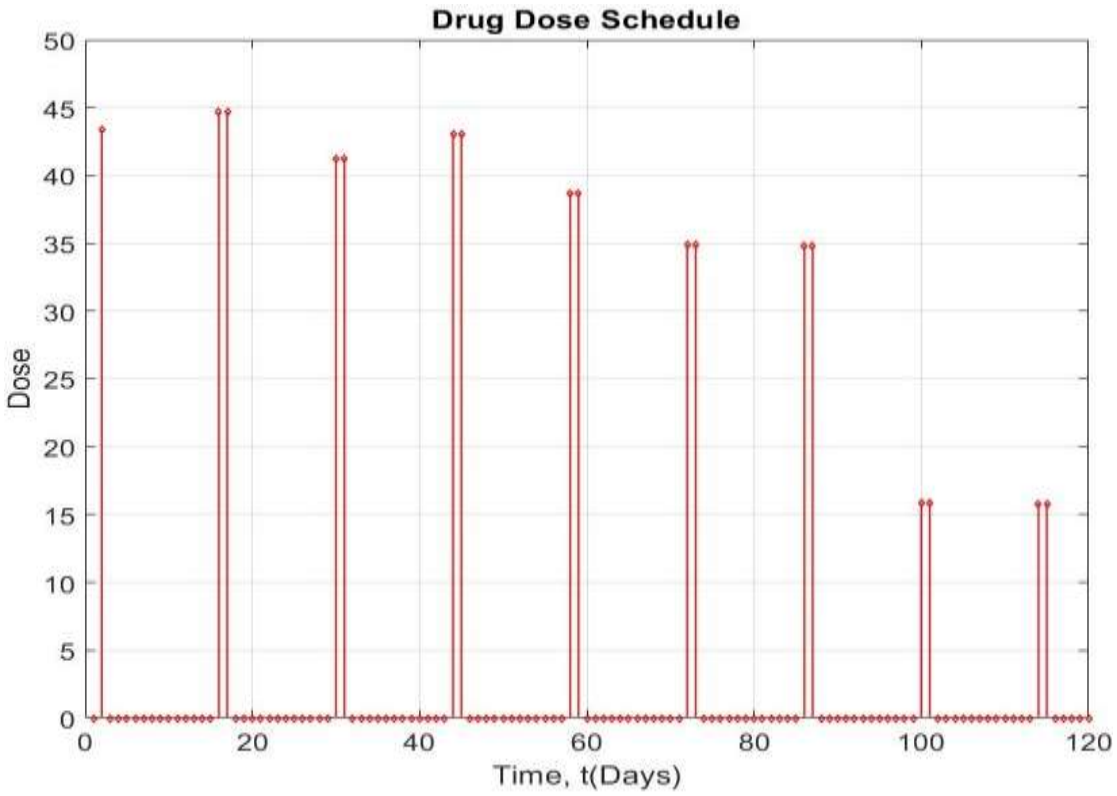


Fig. 6.3: Chemo Drug Dose generated by the FES based DSS for 120 days

6 unique doses (in mg) within 84 days of treatment for increasing weight pattern are as follows:

Table 6.3: Dose generated by the FES based DSS model

Drug Dose Cycle No.	Drug Dose Amount (mg)
1	43
2	45
3	41
4	43
5	39
6	35

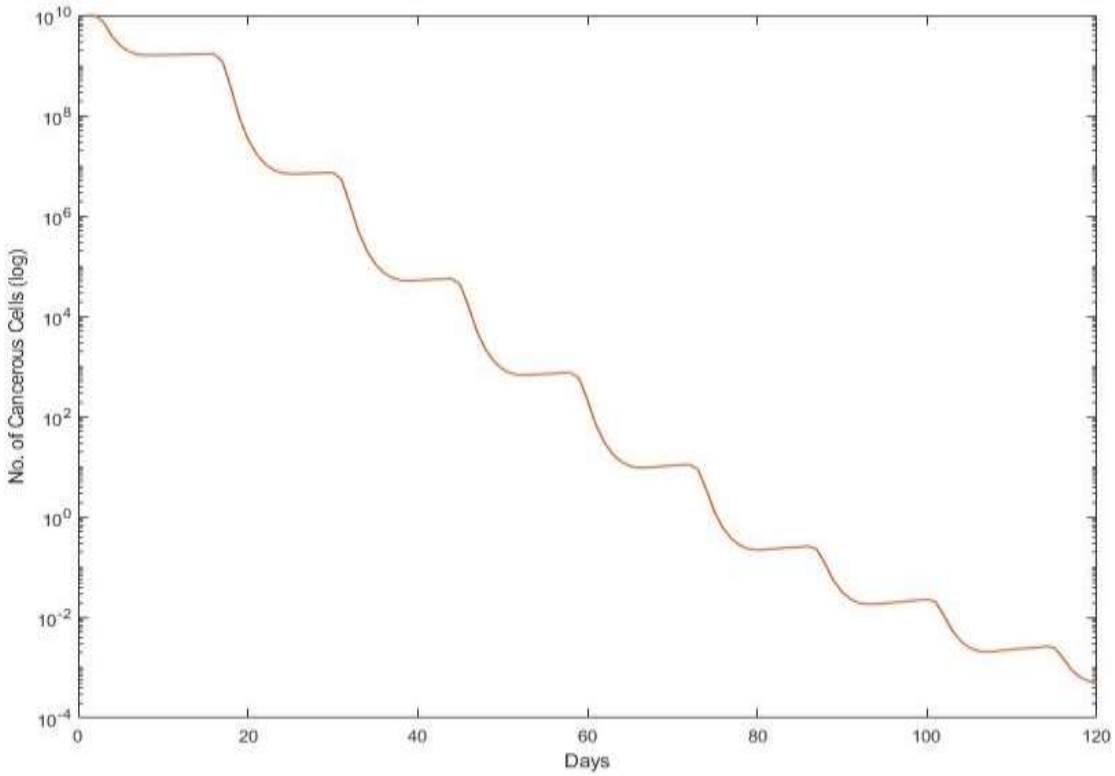


Fig. 6.4: Number of Cancerous cells during the treatment period

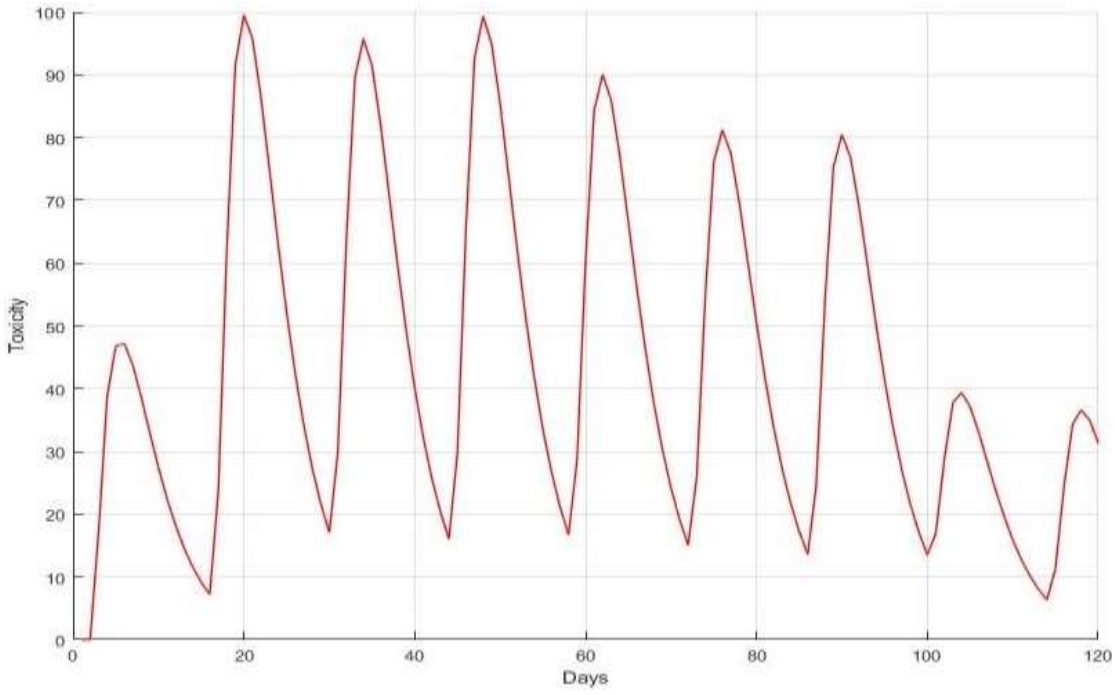


Fig. 6.5: Toxicity for 120 days (14 days of interval)

6.5.3 Model Generated Drug Concentration in Different organs

6.5.3.1 Drug Concentration in VENOUS BLOOD

In the model, venous blood consists of two sub-compartment, plasma, the main compartment, and red blood cells (RBC). Since the drug is administrated in the vein, the venous will have the first drug appearance and highest concentration. Then it will spread throughout the whole body. The fig. 6.6 has justified this property. Since in the 1st cycle single day single dose was applied, at the end of the 2nd day (48 hour after IV-dose is pushed) the drug concentration declined to ~0. From 2nd cycle and onward, same dose was applied in consecutive two days, as a result in the fig. 6.6 we see drug concentration in the second day became more than the starting of the first day and started declining, since the drug distributes in other organs from venous.

Observing the fig. 6.7, it is found that the RBC started absorbing the drug slowly in the beginning and it is constantly rising. Although the amount of drug it has is not as high as venous plasma instead plasma and RBC has totally opposite slope of the curve. Thus, one is declining and another is inclining as time goes by. These represents the ADME (Absorption, distribution, metabolism, and excretion,) properties of the compartments.

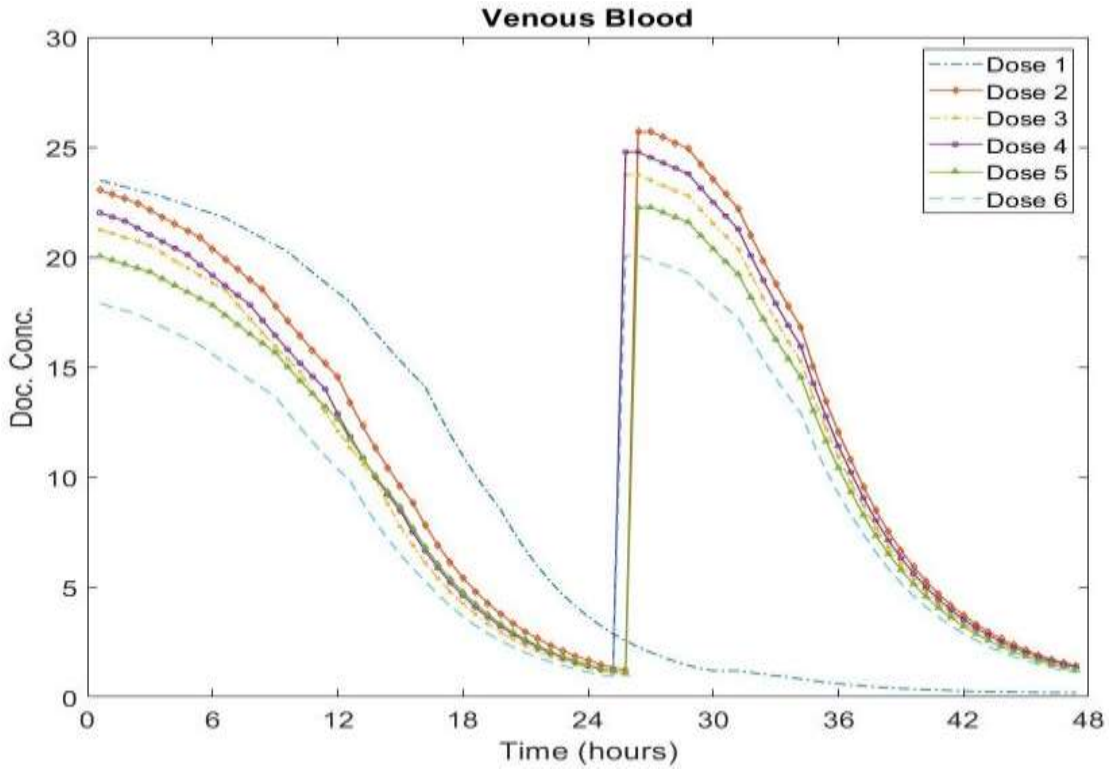


Fig. 6.6: Drug concentration in Venous Blood (plasma)

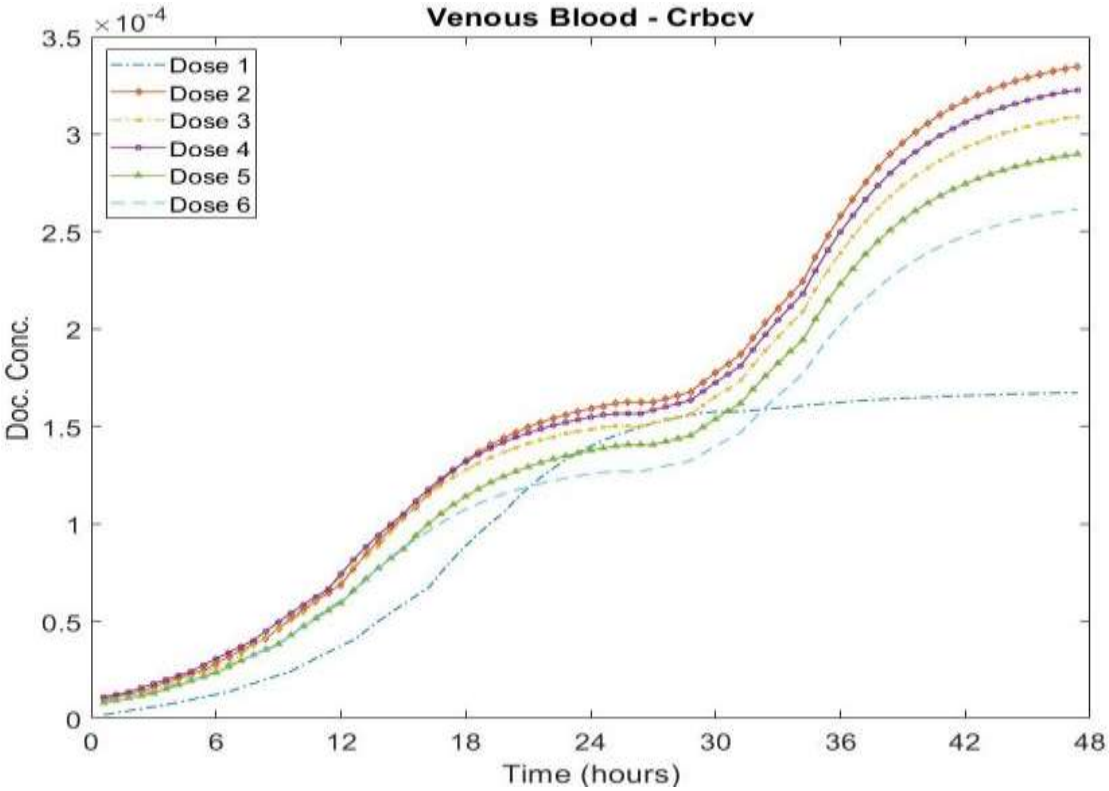


Fig. 6.7: Drug concentration in Venous Blood (RBC)

6.5.3.2 Drug Concentration in Lung

Lung gets its drug from venous blood. For lung three sub compartments are considered, which are vascular tissue, extra-vascular tissue and bound tissue. Drug concentration in 6 different chemo cycle in the vascular tissue sub compartment can be observed in figure 6.8. It resembles the venous plasma plot as they both has the same pattern. All the vascular tissue should have the same pattern as they are directly connected to the body's blood flow. Then some of this drug will be absorbed, distributed, metabolized and excreted. The distribution portion will get to the extravascular tissue, bound tissue and to other compartments.

The drug concentration in the extra-vascular tissue is shown in figure 6.9. The concentration in extra-vascular tissue is constantly increasing and at the end of 24 hours, it became stable, but from the second cycle the concentration starts rising again since from the 2^{nd} cycle 2^{nd} dose has been applied in the 2^{nd} day.

In the bound sub-compartment the drug is reversibly bound to plasma proteins or tissues. In other words, when a drug is administered, a portion of the drug molecules bind to proteins in the blood or tissues, forming a drug-protein complex. This complex is too large to pass through cell membranes, which affects the drug's distribution and elimination from the body. The more drug flows to the lung and its vascular tissue, the more is the concentration in the bound sub-compartment (fig. 6.10). It can be seen that the concentration of drug here is not very high but the binding of a drug to plasma proteins can also affect its pharmacodynamics altering the drug's affinity for its target site, which can affect its efficacy. Therefore, it is important part of the model to include the bound sub-compartment for a better prediction.

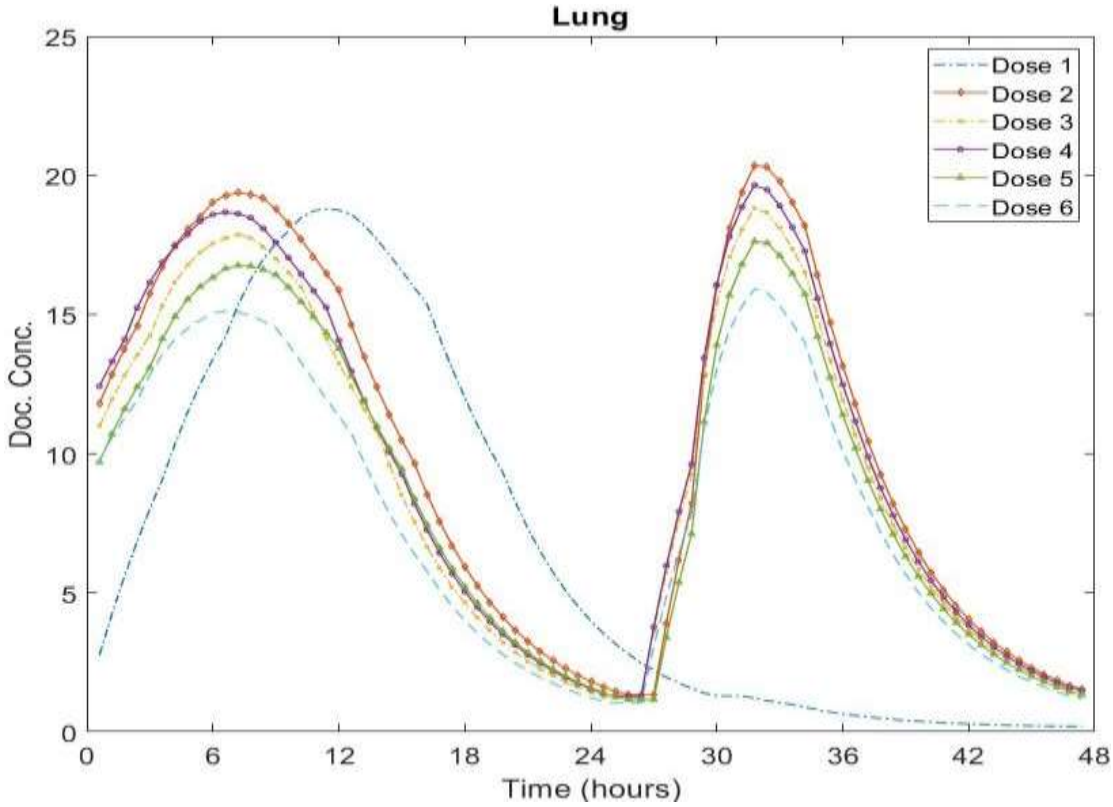


Fig. 6.8: Drug concentration in Lung (vascular tissue)

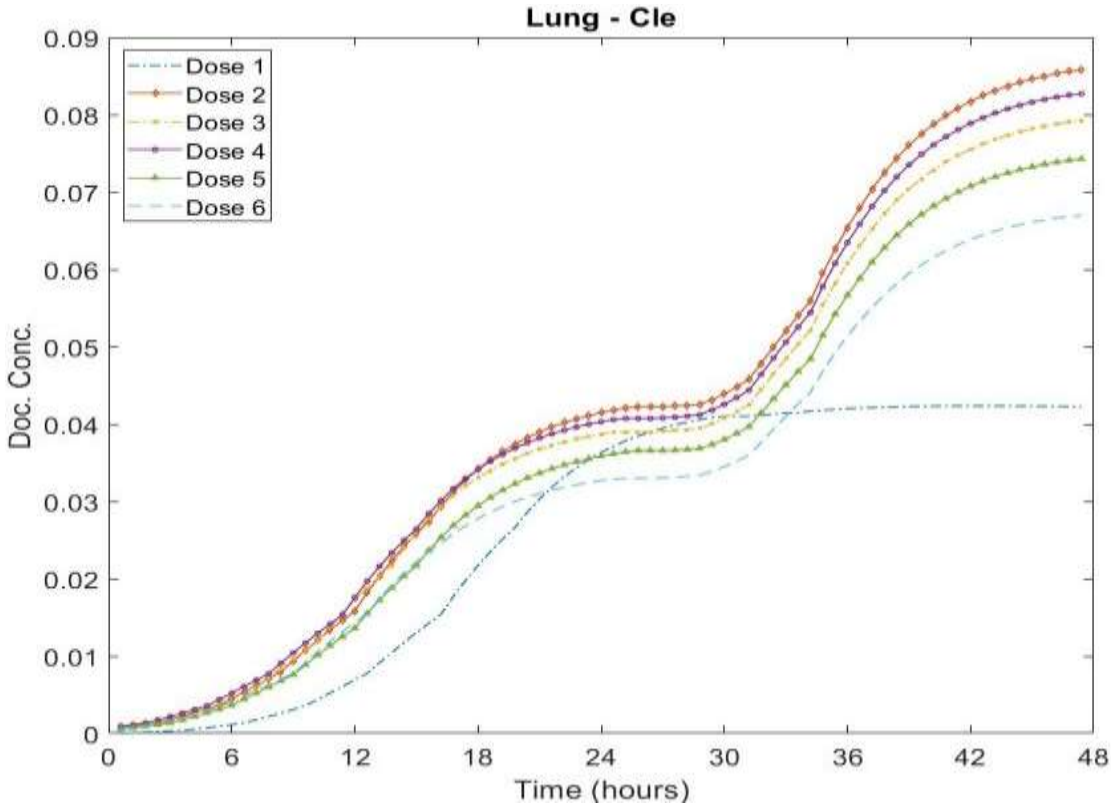


Fig. 6.9: Drug concentration in Lung (extra-vascular tissue)

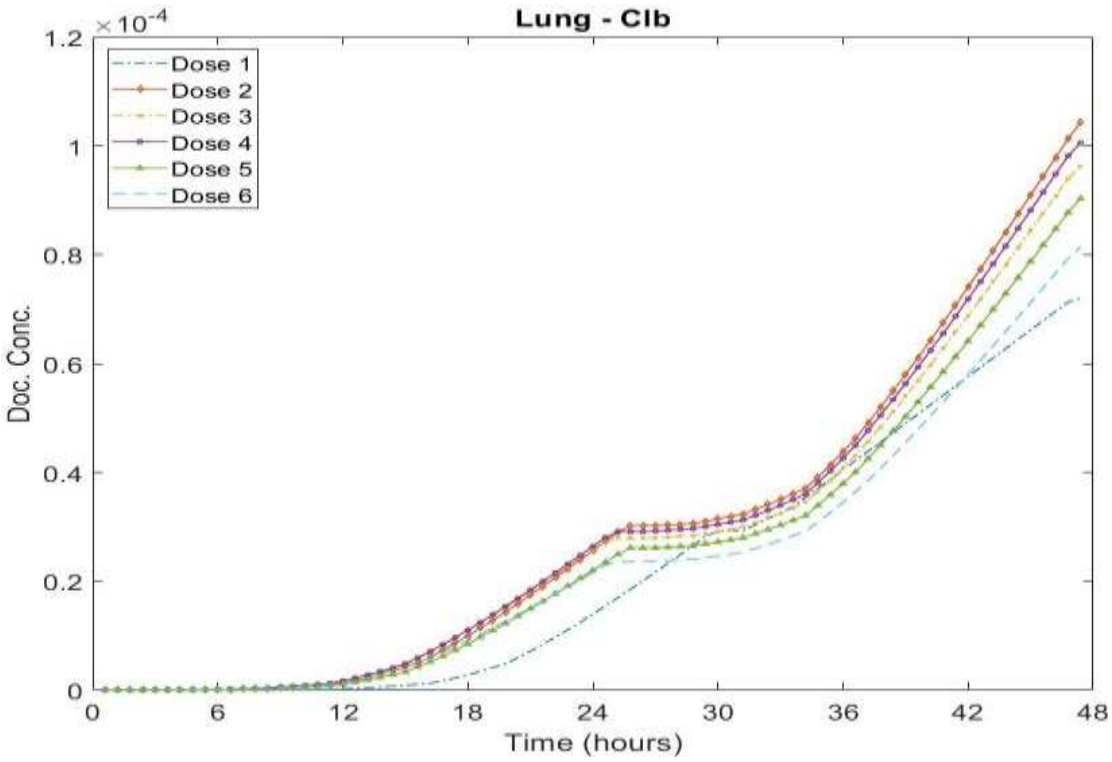


Fig. 6.10: Drug concentration in Lung (bound sub-compartment)

6.5.3.3 Drug Concentration in ARTERIAL BLOOD

The next drug flow is done via arterial blood, as the artery carries blood from lung to others compartments of the body. Now, being blood, it has two components same as venous blood. These are arterial blood plasma and arterial blood RBC. The plasma absorbs the most of the drugs as shown in fig. 6.11. Similar pattern of graph is observed as in venous blood. The main difference is the concentration in venous blood raised immediately the IV-dose is administrated whereas the rise of drug concentration in arterial blood started after around 1 hour. The drugs in the arterial blood plasma are the major portion that came from the lung. The minor portion is in the RBC (fig. 6.12).

The drug concentration in RBC is naturally low than the plasma as RBC is denser than plasma and the volume of plasma far surpasses the volume of RBC. Though the numbers are not great but it has significant value in the PBPK model as well as in the treatment. Through the arterial blood, the drug is continuously spreading to other compartments of the body.

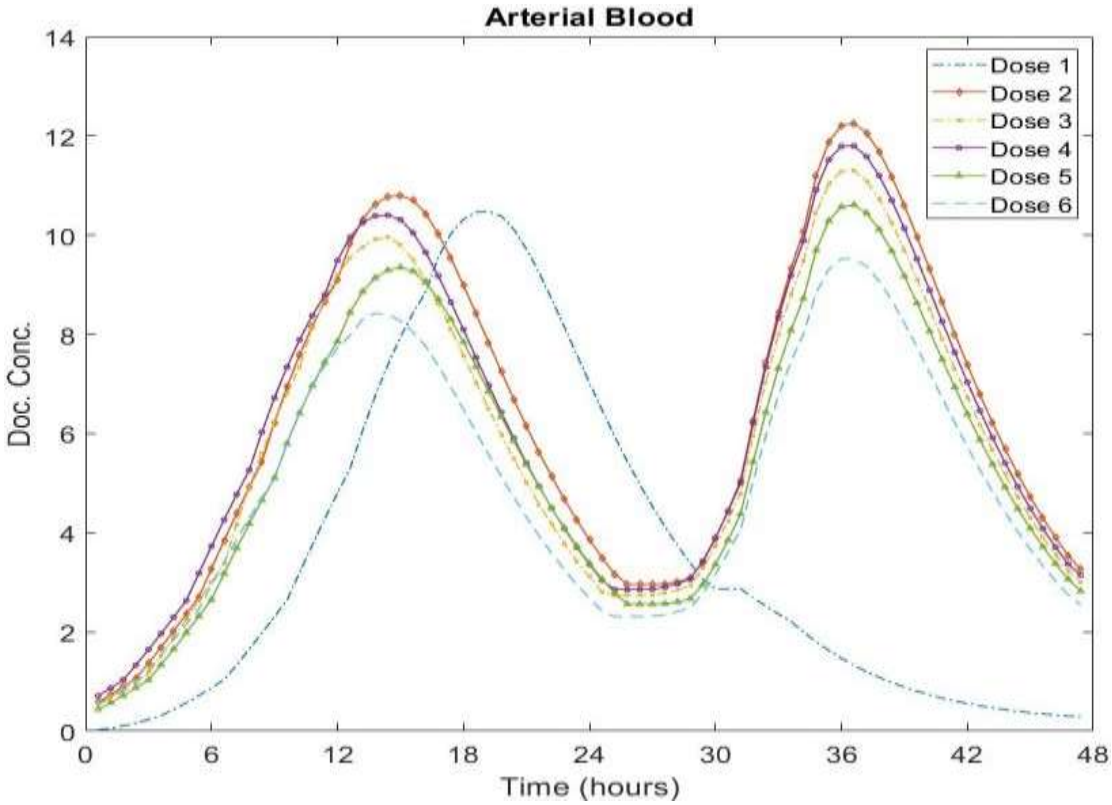


Fig. 6.11: Drug concentration in Arterial blood plasma

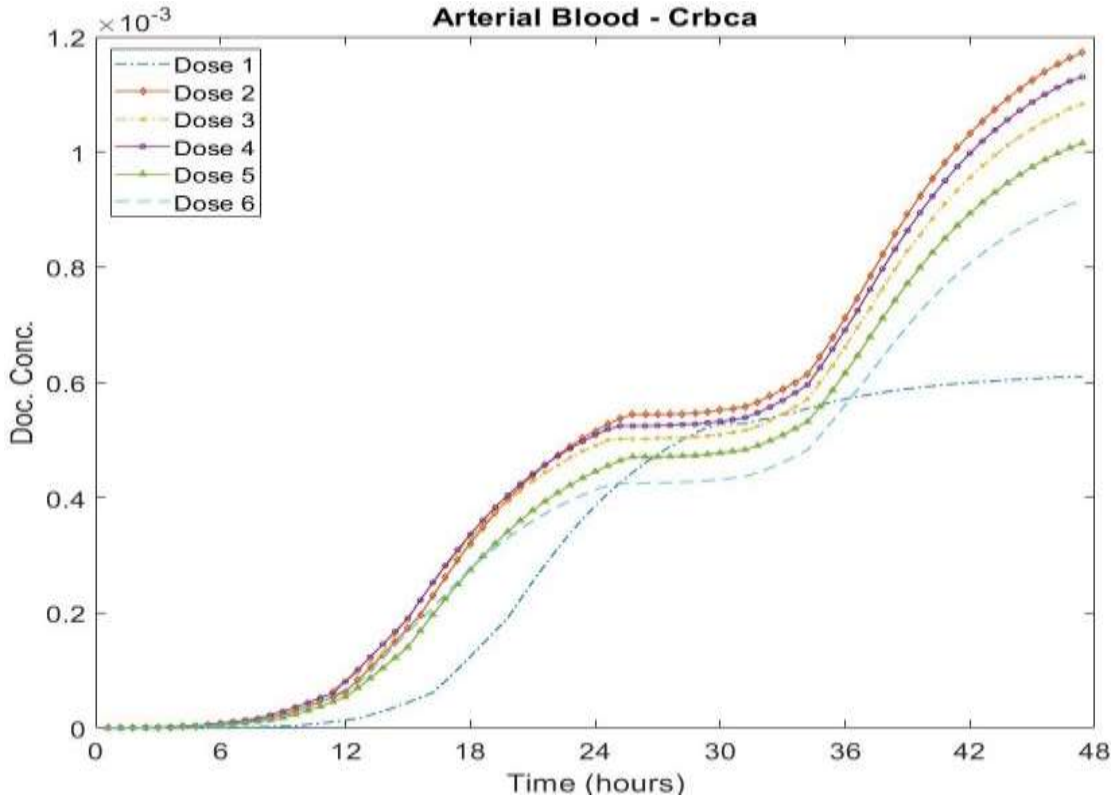


Fig. 6.12: Drug concentration in Arterial blood RBC

6.5.3.4 Drug Concentration in GUT

The gastrointestinal tract (GUT) is responsible for influencing the rate and degree of medication absorption, and so effects the drug's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug affects the body) (the way the drug affects the body). The gastrointestinal tract is also responsible for drug-drug interactions, in which the presence of one medicine affects the absorption of another. Consequently, this compartment is a crucial intermediate step in the diffusion of drugs to other compartments. It is the most compact compartment. It has no sub-compartments, hence there is no extravascular or bound tissue. Only the vascular sub compartment is present. Figure 6.13 depicts the rate of drug diffusion.

The drug concentration in gut is constantly increasing but after around 24 hours this drug diffusion property starts to decrease the drug concentration in GUT.

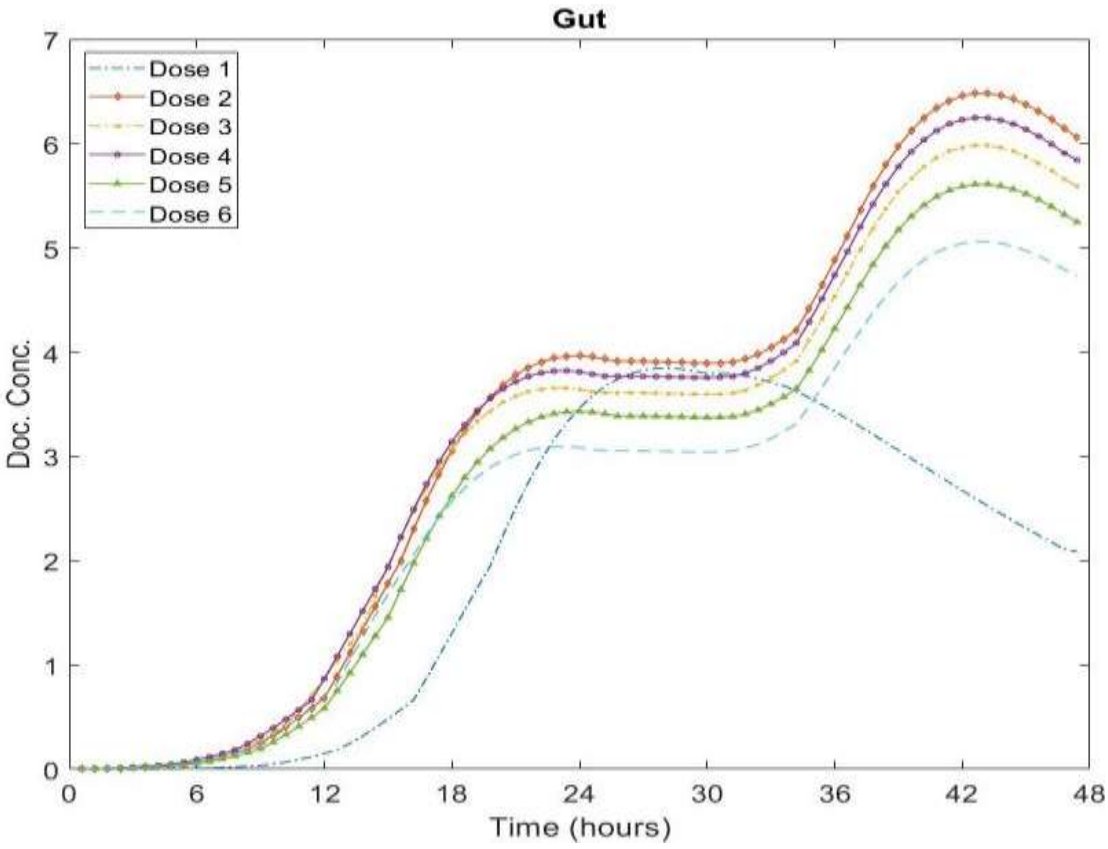


Fig 6.13: Drug concentration in GUT

6.5.3.5 Drug Concentration in BRAIN

The human brain is widely regarded as one of the most significant parts of the body. The catastrophic condition of the brain is something that specialists have to deal with frequently. Knowing the amount of medicine that is present in the brain can therefore make a significant difference. The vascular compartment, the extra-vascular compartment, and the bound compartment make up the three sub-compartments that make up the brain. Figure 6.14 depicts the pace at which drug molecules diffuse through the vascular sub-compartment.

It is clear from looking at the figure that the drug concentration in the brain is comparable to the drug concentration in the venous plasma, arterial plasma, and the lungs. That is an indication that the medicine is passing with flying colors. The brain is the organ that is responsible for forecasting how medications will be distributed and eliminated inside the brain. The blood-brain barrier is formed by the capillary-rich vasculature that surrounds the brain and keeps it isolated from the rest of the body. This tissue in the brain is known as the brain vascular tissue (BBB). This BBB allows just certain types of molecules through. Hence, medications that specifically target the brain will need to be developed to circumvent this issue. This can have an effect on the outcome of the PBPK in the brain compartment because it has an effect on the ability of the medication to cross into the brain and have its effect.

The next sub-compartment of the brain to be discussed is the extra-vascular tissue. Figure 6.15 depicts the drug concentration that is found in the extravascular tissue of the brain. When compared to the concentration in the extra-vascular tissue of the lung, the concentration in the brain's extra-vascular tissue is lower. This is due to the fact that the volume of tissue in the brain is significantly lower.

An essential sub-compartment for the brain is called the bound compartment, and it is responsible for protein binding. Figure 6.16 provides an illustration of the diffusion rate. Within the bound compartment, the medication that has dispersed has no substantial effect. Every single confined sub-compartment that is a component of another main compartment behaves in the same way.

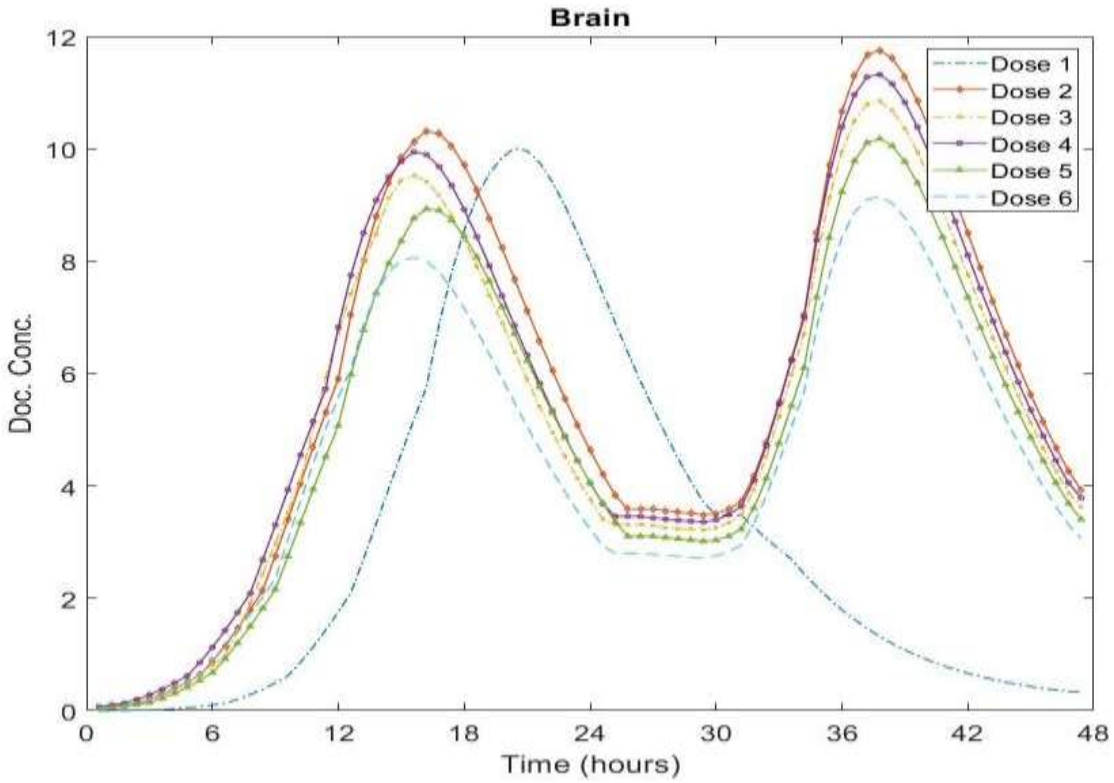


Fig. 6.14: Drug concentration in Brain (vascular tissue)

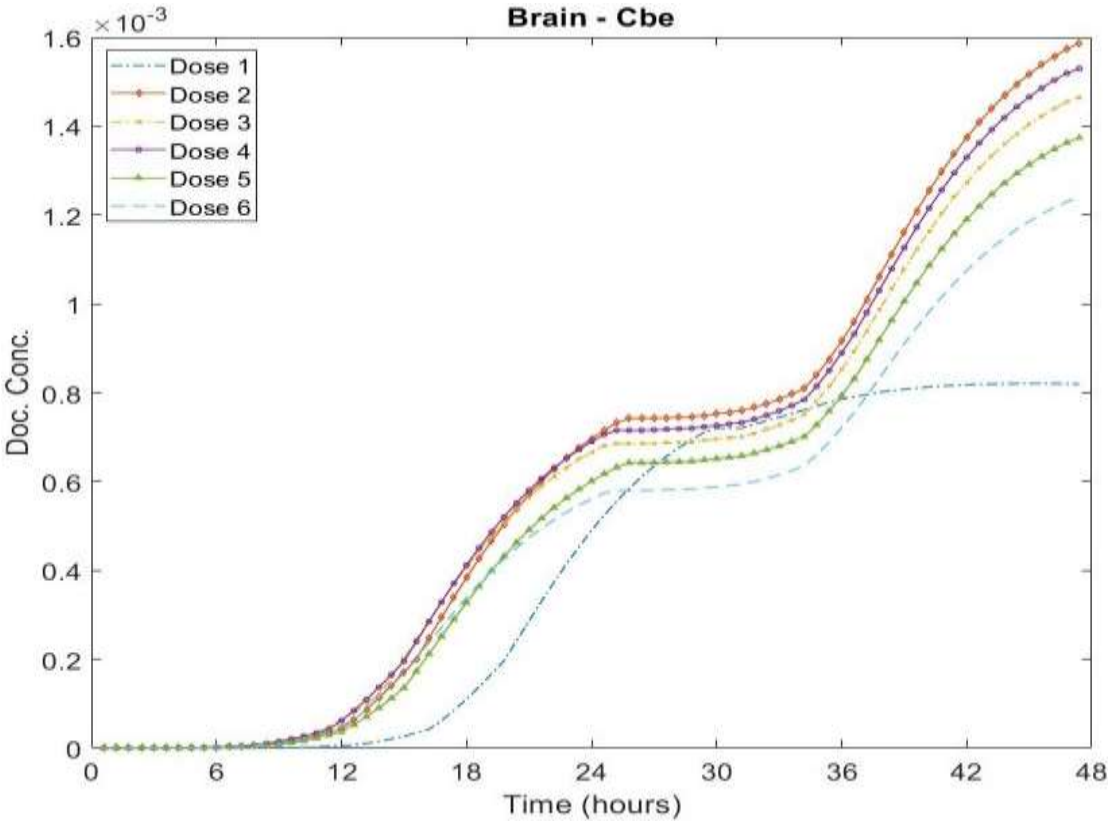


Fig. 6.15: Drug concentration in Brain (extra-vascular tissue)

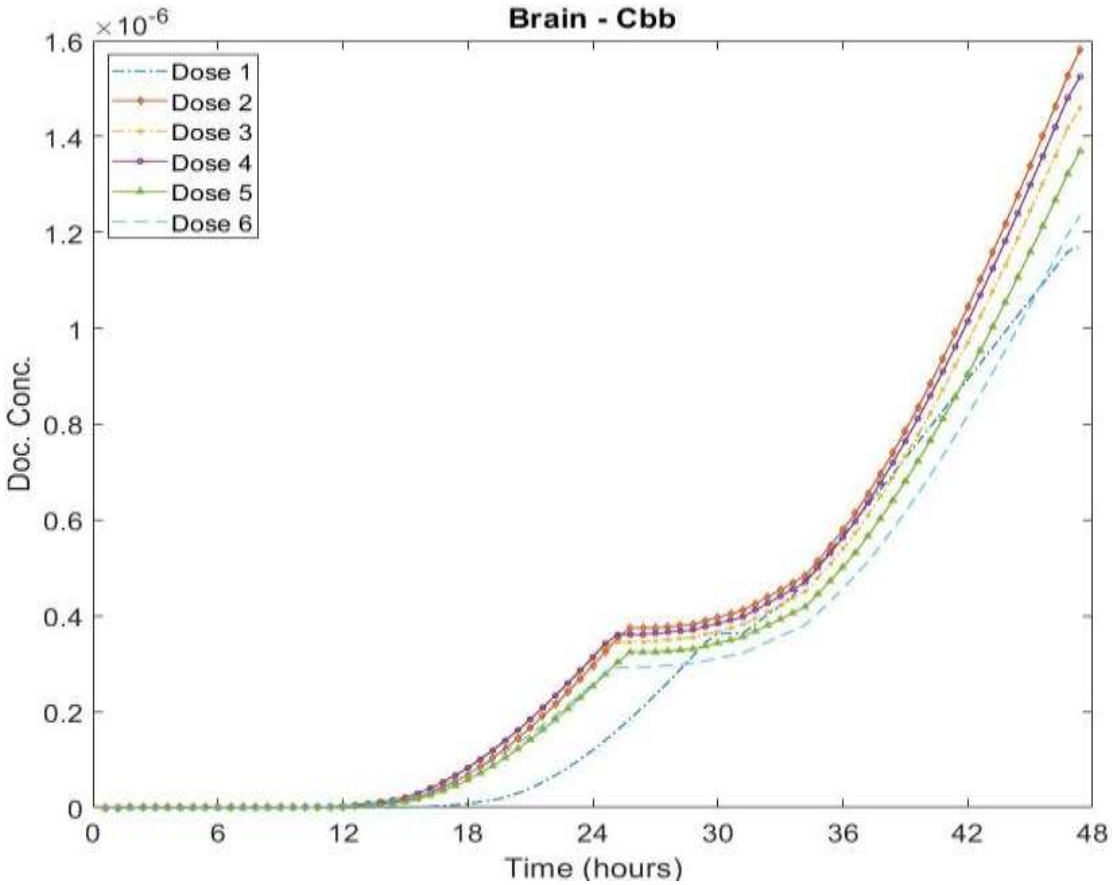


Fig. 6.16: Drug concentration in Brain (bound sub-compartment)

6.5.3.6 Drug Concentration in SPLEEN

The spleen is a large lymphatic organ that is positioned on the upper left side of the abdomen. Its primary function is to filter blood and remove from circulation any blood cells that are damaged or have become damaged over time. In addition, the spleen is capable of acting as a reservoir for medications, particularly those that are able to bind to red blood cells or proteins found in plasma. These medications have the potential to be released and digested as blood passes through the spleen, which has the potential to alter the pharmacokinetics and pharmacodynamics of the pharmaceuticals.

The drug diffusion rate of vascular tissue, extra-vascular tissue and bound sub-compartment of the spleen is shown in fig. 6.17, fig. 6.18 and fig. 6.19 respectively.

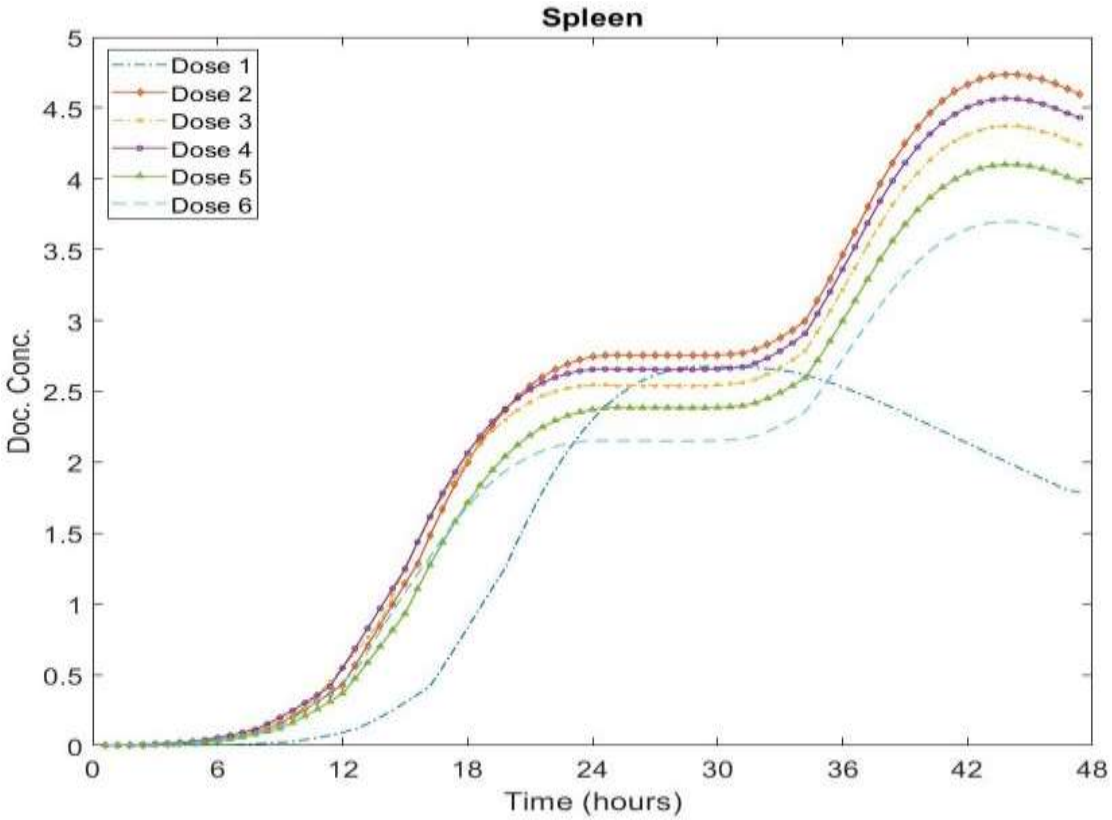


Fig. 6.17: Drug concentration in Spleen (vascular tissue)

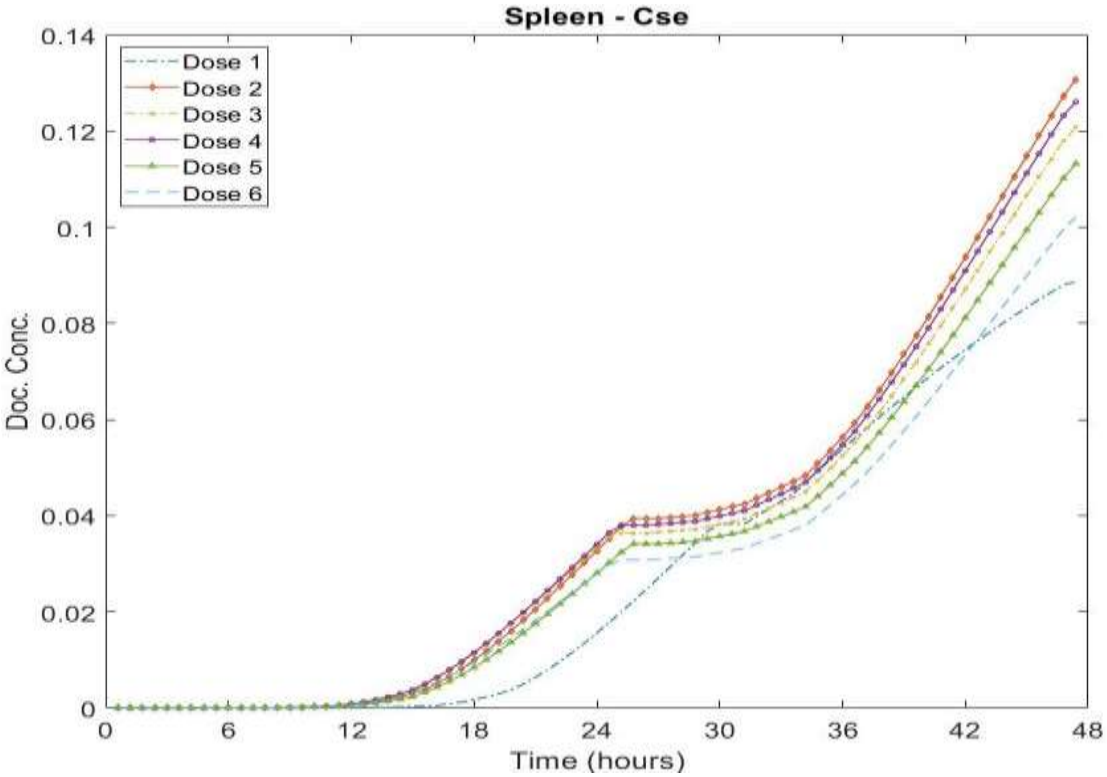


Fig. 6.18: Drug concentration in Spleen (extra-vascular tissue)

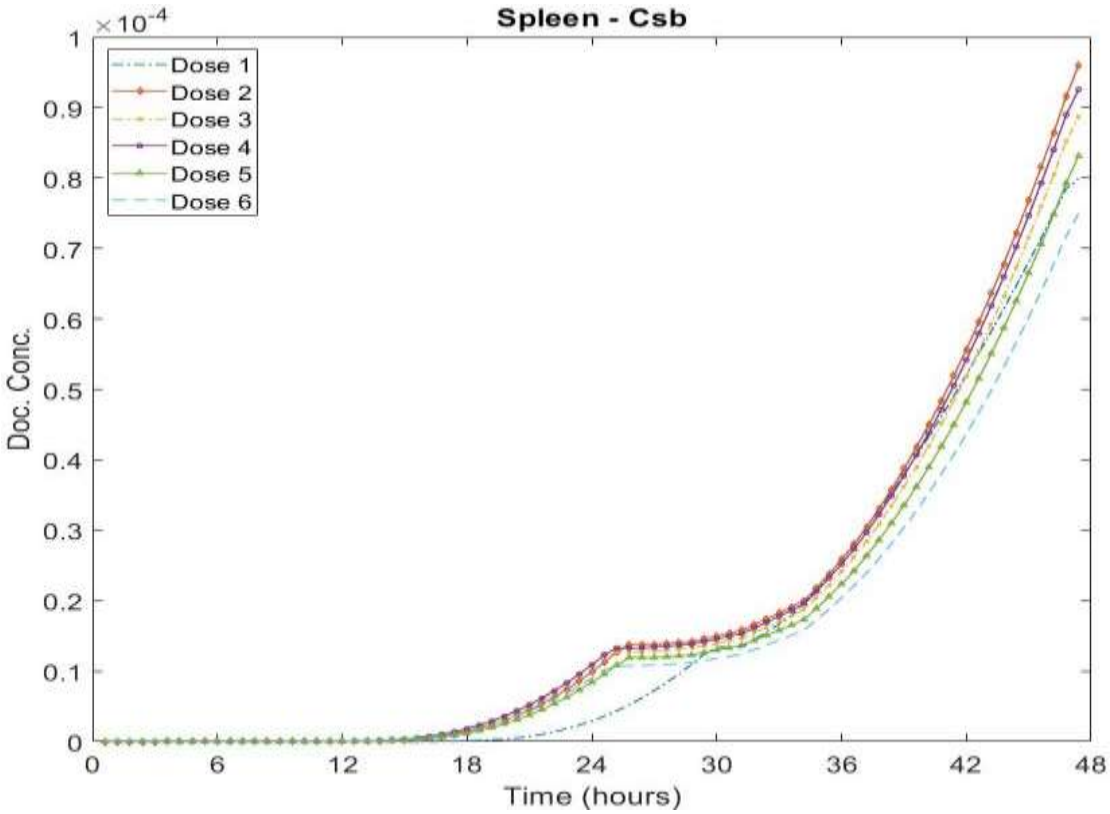


Fig. 6.19: Drug concentration in Spleen (bound sub-compartment)

6.5.3.7 Drug Concentration in LIVER

The liver is responsible for the processing of drugs and other xenobiotics through a variety of metabolic pathways, such as oxidation, reduction, and conjugation, in order to convert them into more water-soluble compounds that can be excreted from the body. These compounds are then able to be eliminated. The liver is capable of storing medicines in a variety of cell types, including hepatocytes and Kupffer cells, which has the potential to influence both the pharmacokinetics and pharmacodynamics of the medication. As a result, it is essential to have knowledge about the substances that are concentrated in the liver.

Fig. 6.20 depicts the drug concentration found in vascular tissue for each of the medications cycle. Drug concentration in the extra-vascular tissue can be found in fig. 6.21. The bound sub-compartment is the last and final sub-compartment in the liver, which drug's diffusion rate can be seen in Fig. 6.22.

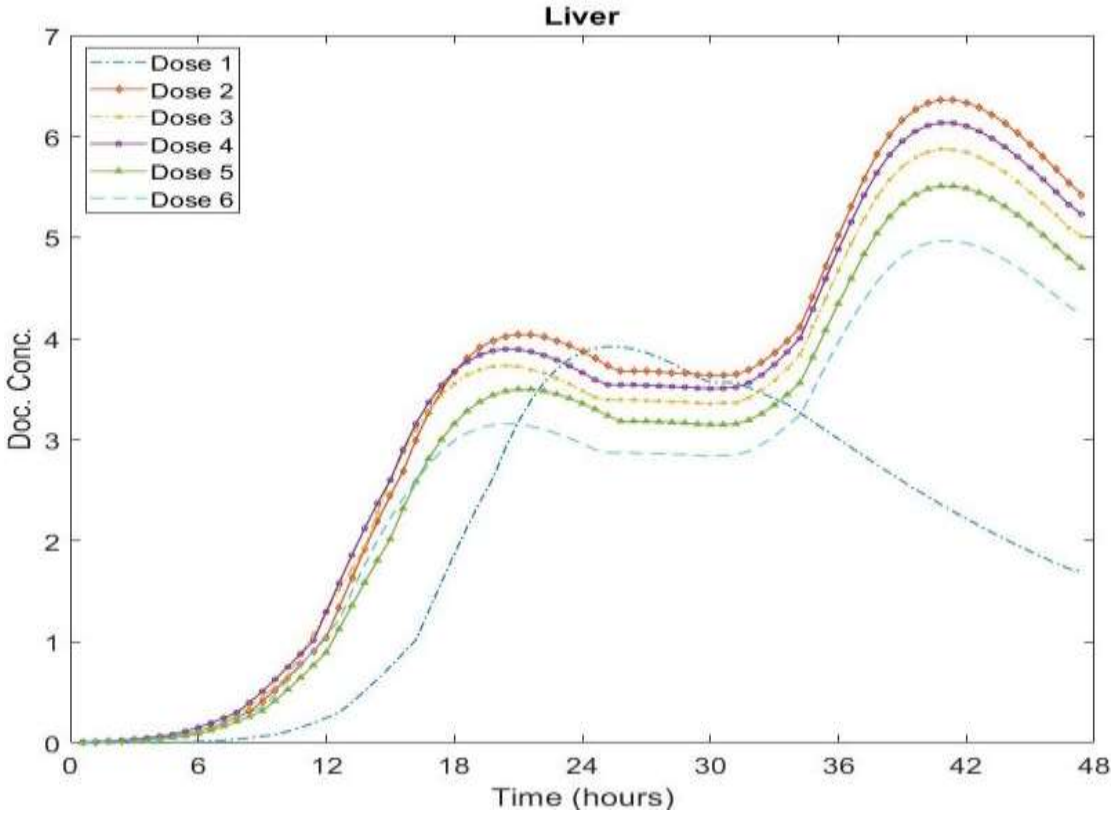


Fig. 6.20: Drug concentration in Liver (vascular tissue)

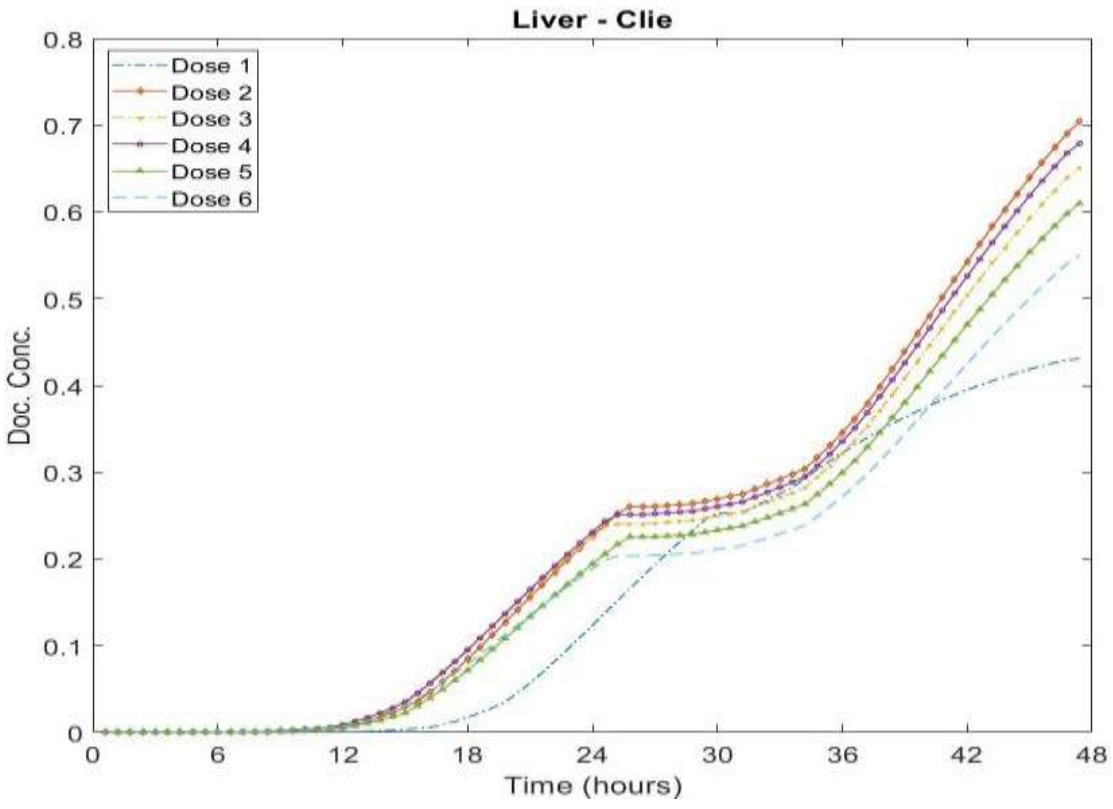


Fig. 6.21: Drug concentration in Liver (extra-vascular tissue)

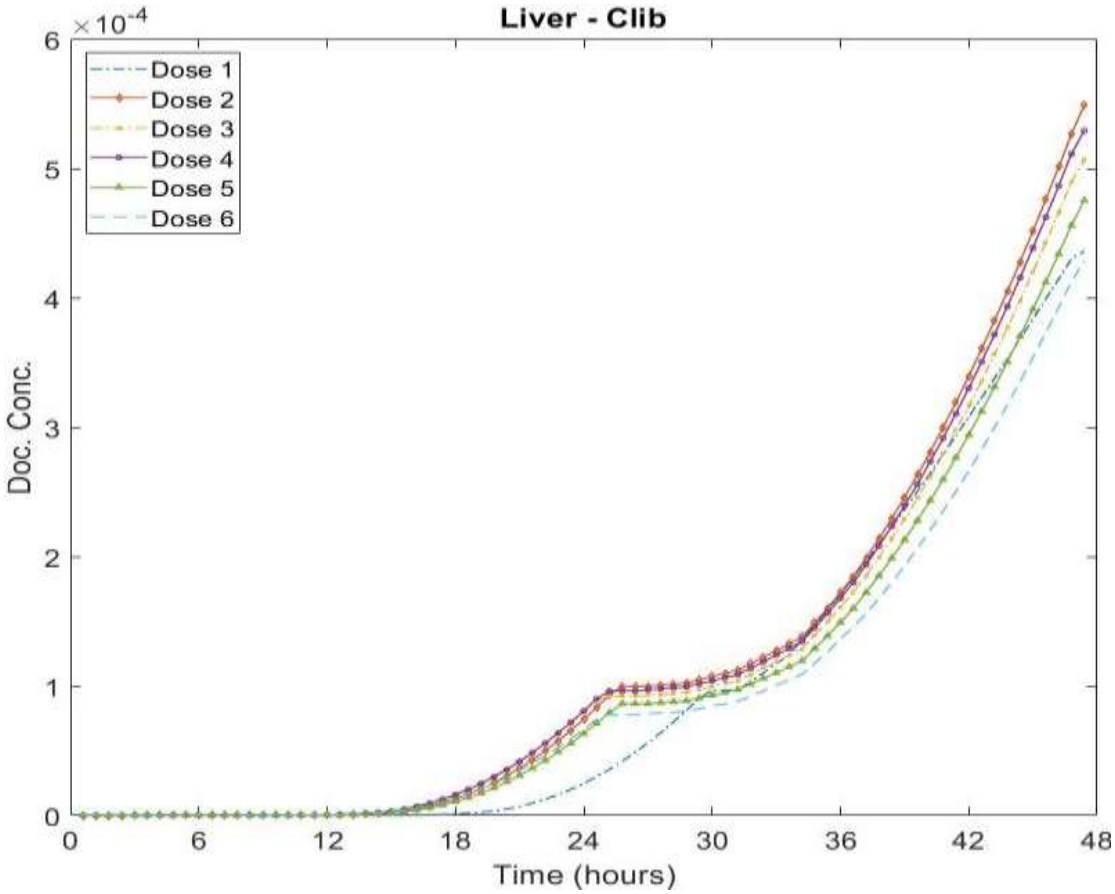


Fig. 6.22: Drug concentration in Liver (bound sub-compartment)

6.5.3.8 Drug Concentration in KIDNEY

It is the job of the kidney to clean the blood and get rid of waste items, including metabolites of pharmaceuticals and other substances, through the urine.

The vascular sub-compartment drug diffusion rate is shown in fig. 6.23. It can be noticed from the figure that the drug concentration in kidney is staying till around 48 hours while other compartment has a tendency to decline too early. Most of the drugs are excreted through the kidney.

The diffusion rate of the extra-vascular tissue is illustrated in the fig 6.24 and the bound sub-compartment's drug concentration is presented in the figure 6.25.

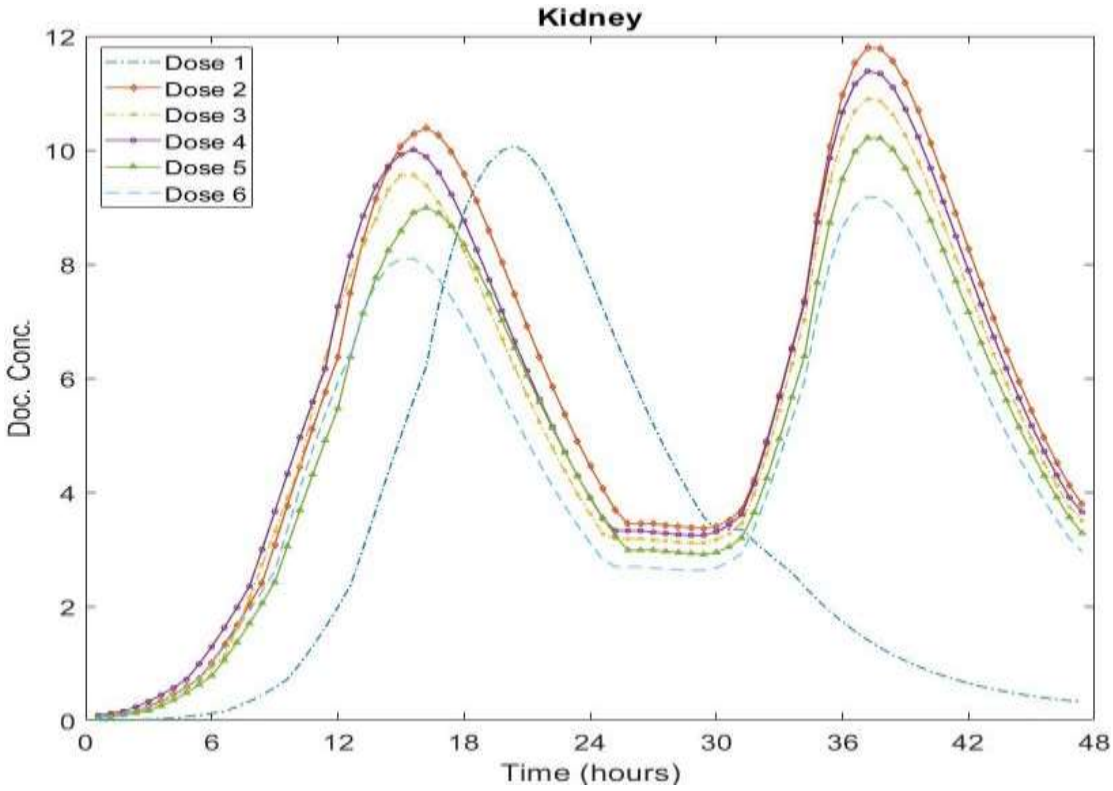


Fig. 6.23: Drug concentration in Kidney (vascular tissue)

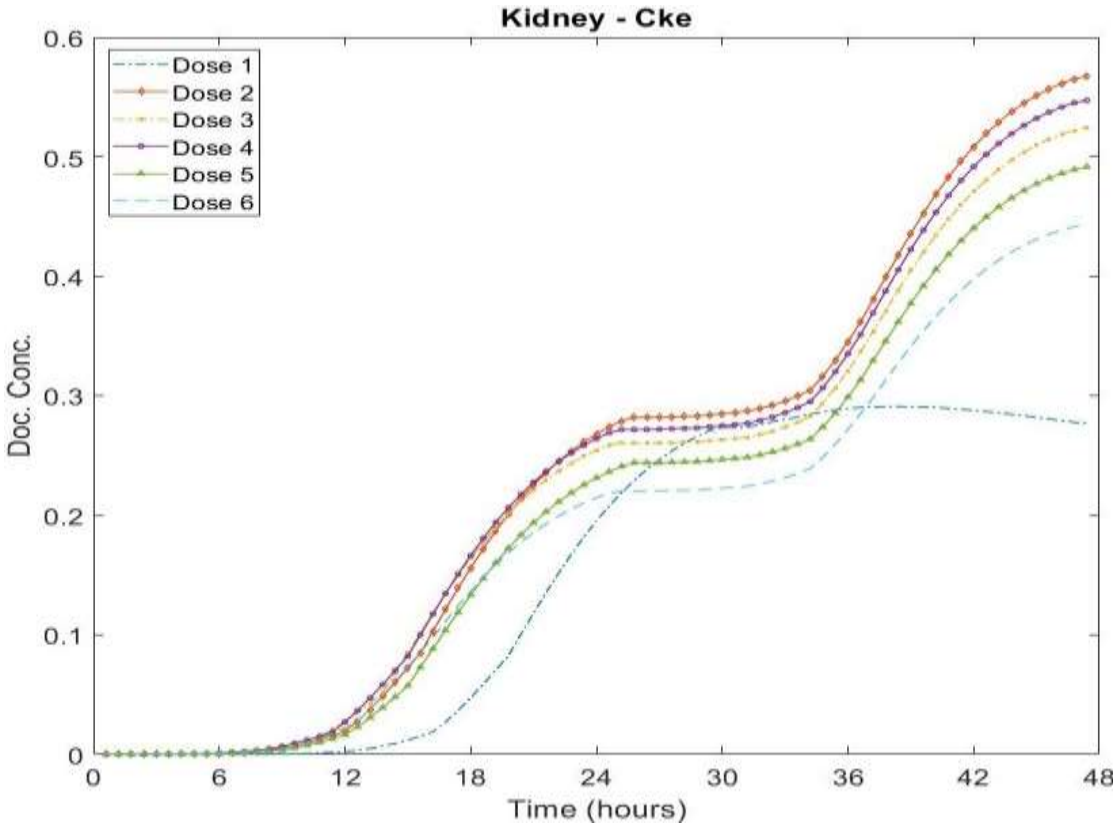


Fig. 6.24: Drug concentration in Kidney (extra-vascular tissue)

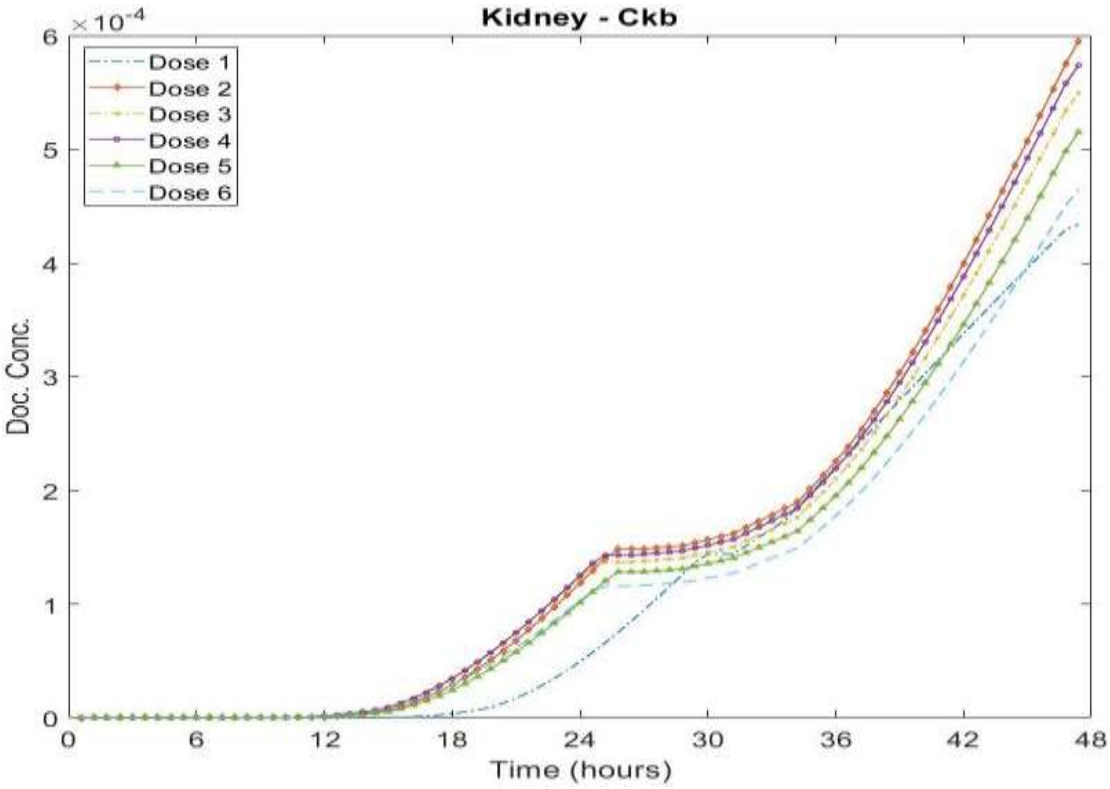


Fig. 6.25: Drug concentration in Kidney (bound sub-compartment)

6.5.3.9 Drug Concentration in MUSCLE

Because it contributes a sizeable portion to the total body mass and plays a role in drug distribution, metabolism, and elimination, muscle is an essential compartment in PBPK (Physiologically Based Pharmacokinetic) modeling. Muscle is a highly vascularized tissue, meaning that it receives a large amount of blood flow, which allows for rapid drug distribution. The binding of medications to muscle tissue, on the other hand, can impede their transport to other tissues, which can result in longer exposure and possibly higher toxicity. Muscle, in addition to its role in the distribution of drugs, also plays a role in the metabolism and removal of drugs. Muscle not only includes enzymes that are able to metabolize some medications but also plays a role in the removal of drugs through biliary and renal excretion. Muscle also has enzymes that can digest certain foods. The drug concentration in the primary sub-compartment of a muscle is depicted in fig. 6.26. Fig 6.27 illustrates the second sub-compartment, which is comprised of extravascular tissue. Similarly, Fig. 6.28 depicts the drug flow rate that occurs within the bound sub-compartment.

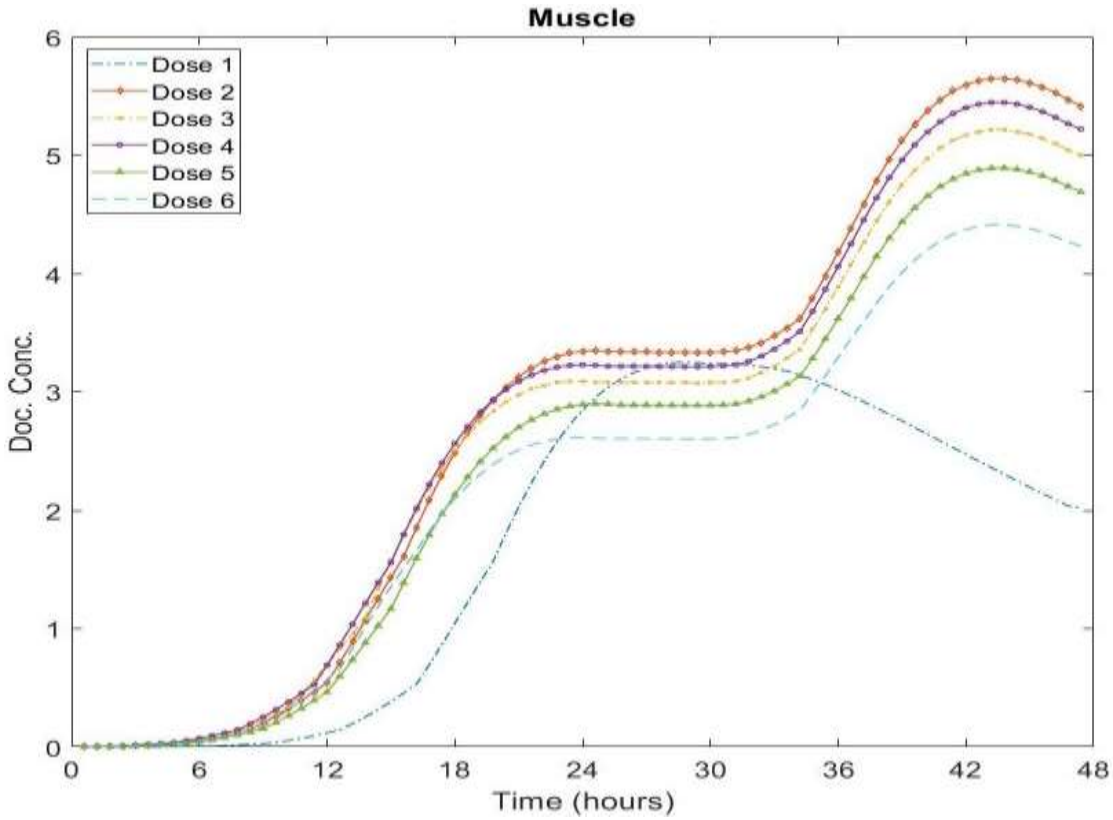


Fig. 6.26: Drug concentration in MUSCLE (vascular tissue)

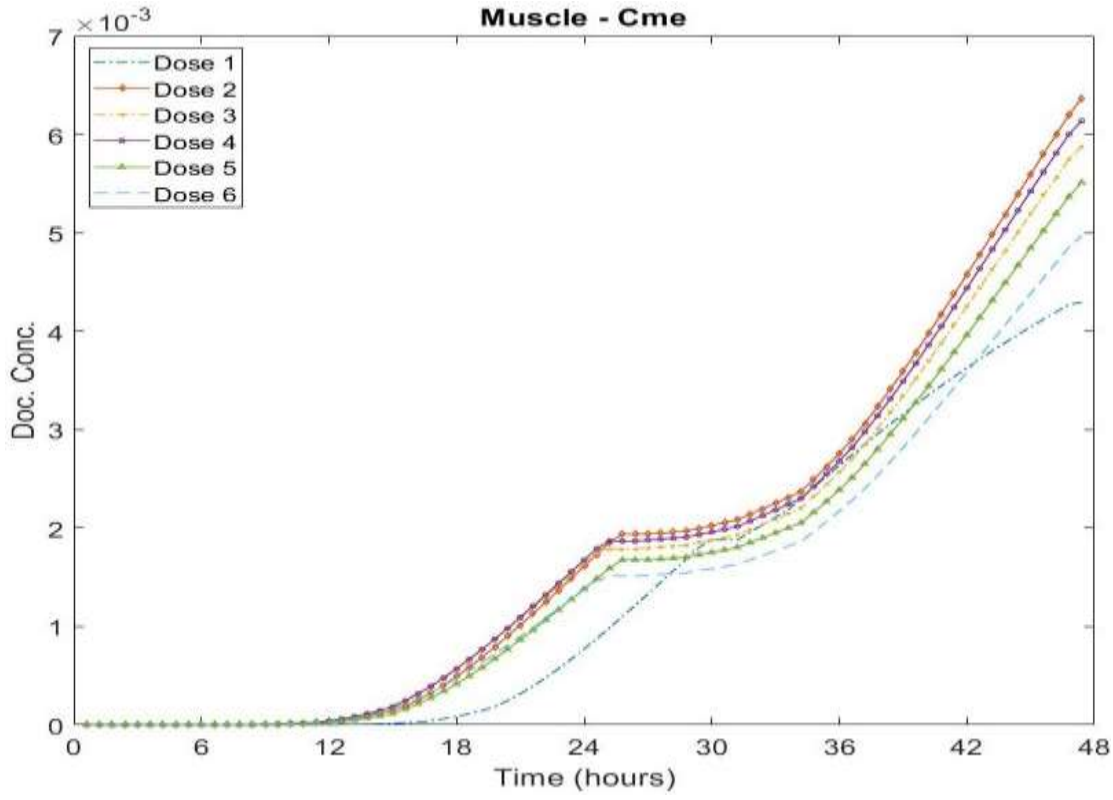


Fig. 6.27: Drug concentration in MUSCLE (extra-vascular tissue)

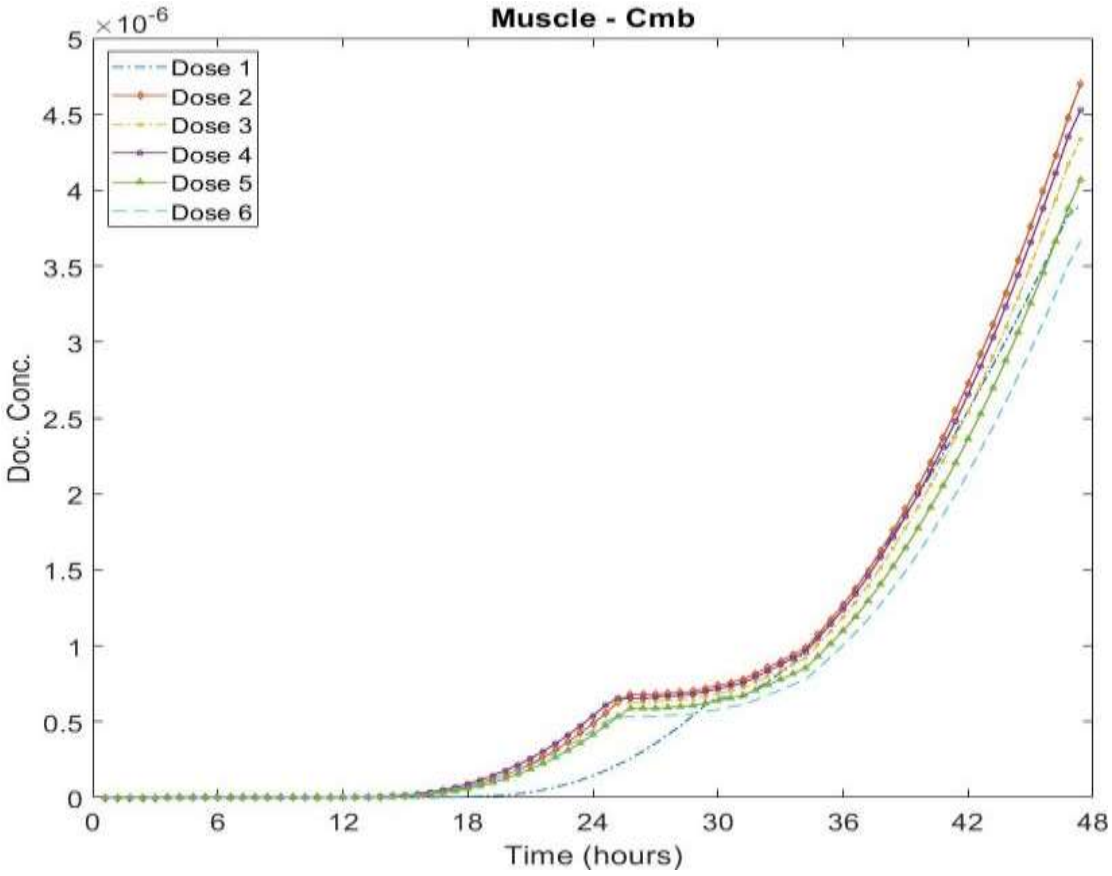


Fig. 6.28: Drug concentration in MUSCLE (bound sub-compartment)

6.5.3.10 Drug Concentration in FAT

The quick delivery of medications is made possible by the fact that fat is a highly vascularized tissue that receives a significant quantity of blood flow. The high lipid content of fat is an essential property of fat because it can have an effect on the distribution and metabolism of drugs. The drug concentration for the vascular tissue for all cycle in fat is illustrated in figure 6.29. The extra-vascular tissue's drug flow rate is shown in figure 6.30. Finally, the drug diffusion rate for the bound sub-compartment is shown in fig. 6.31.

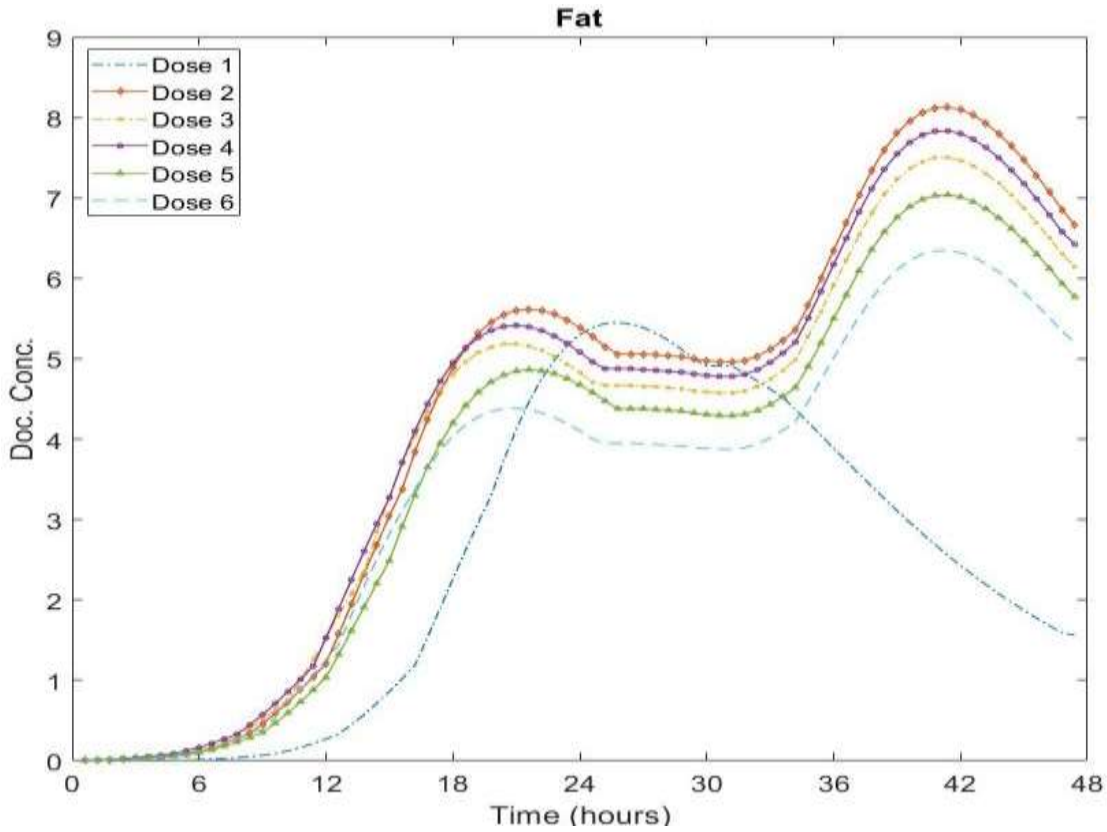


Fig. 6.29: Drug concentration in FAT (vascular tissue)

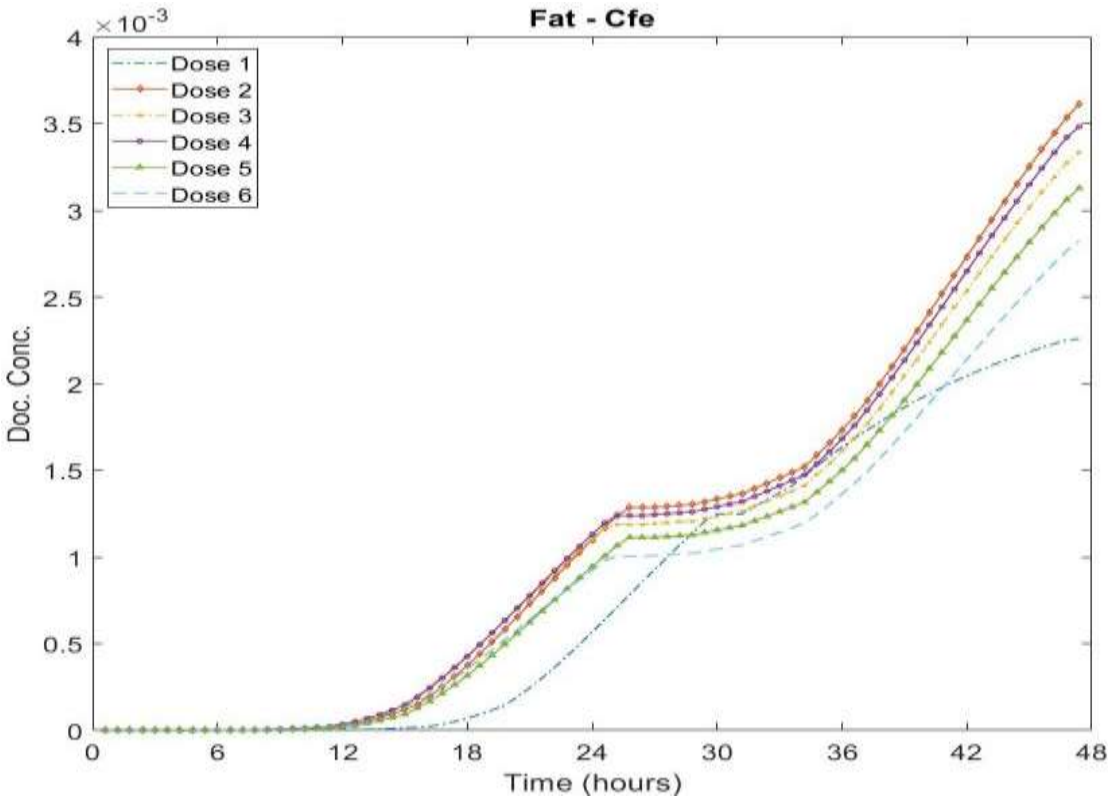


Fig. 6.30: Drug concentration in FAT (extra-vascular tissue)

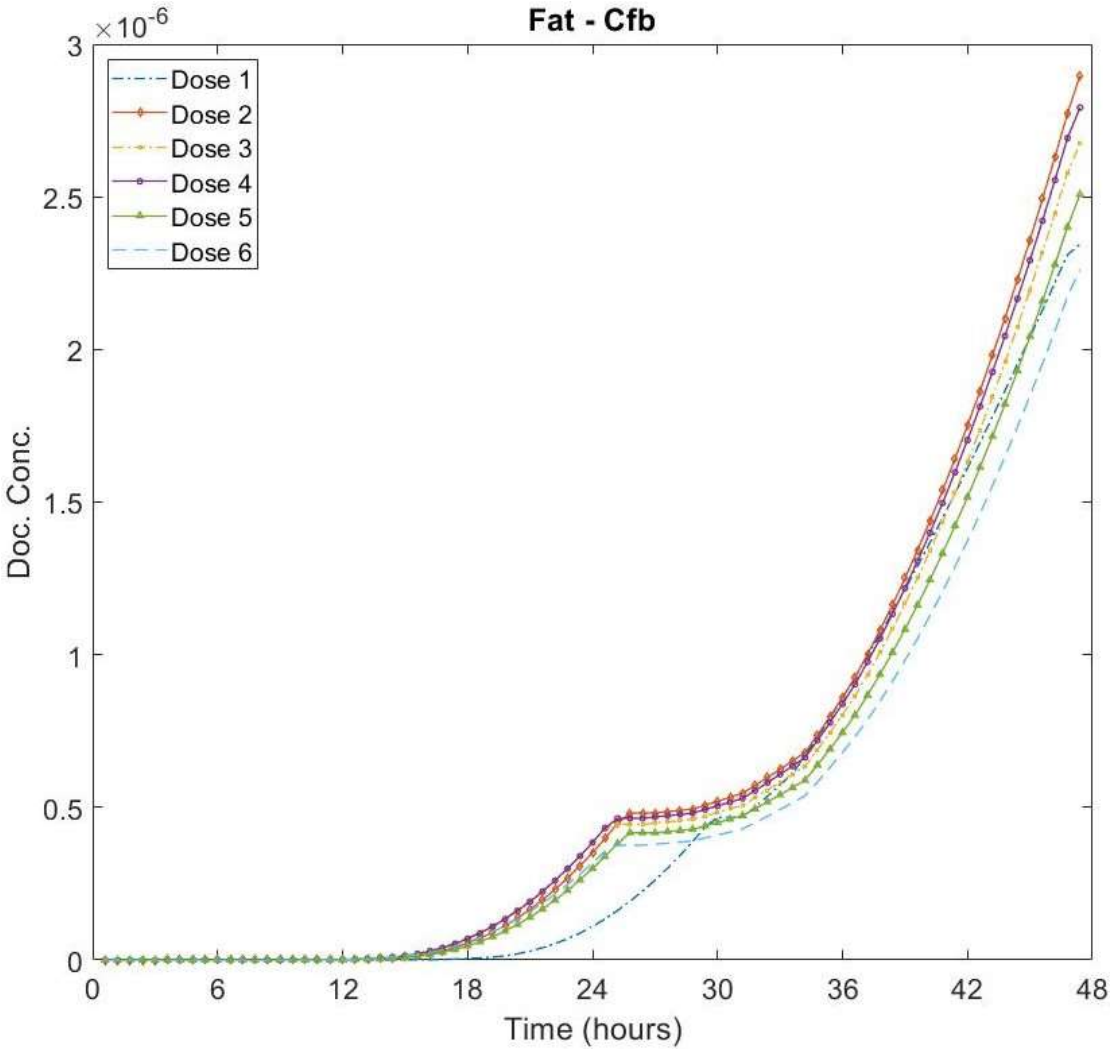


Fig. 6.31: Drug concentration in FAT (bound sub-compartment)

6.5.3.11 Drug Concentration in TUMOR

Both the distribution and metabolism of drugs can be drastically altered by tumors. When compared to healthy tissues, tumor tissues exhibit distinct differences, such as increased interstitial pressure, decreased blood flow, and altered microvasculature. These differences can have an effect on the distribution and metabolism of drugs in the body. The model generated drug diffusion rate for each sub-compartment of tumor is shown in fig. 32, fig. 33 and in fig. 34.

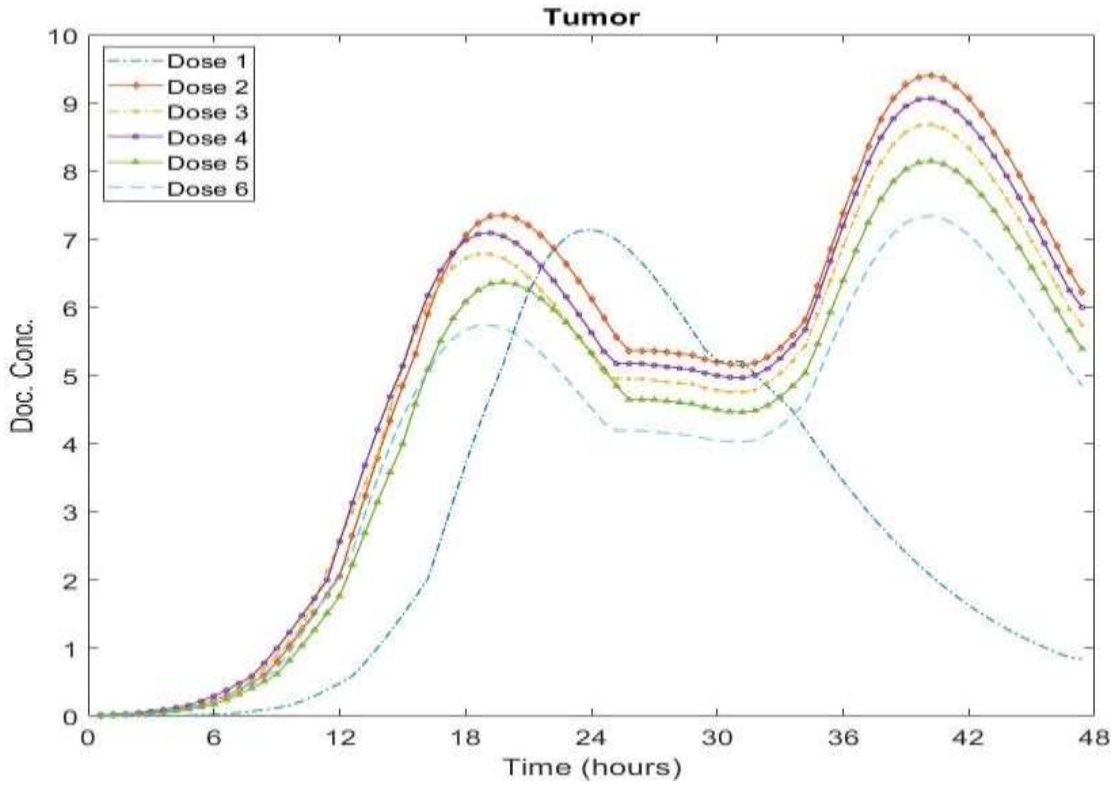


Fig. 6.32: Drug concentration in TUMOR (vascular tissue)

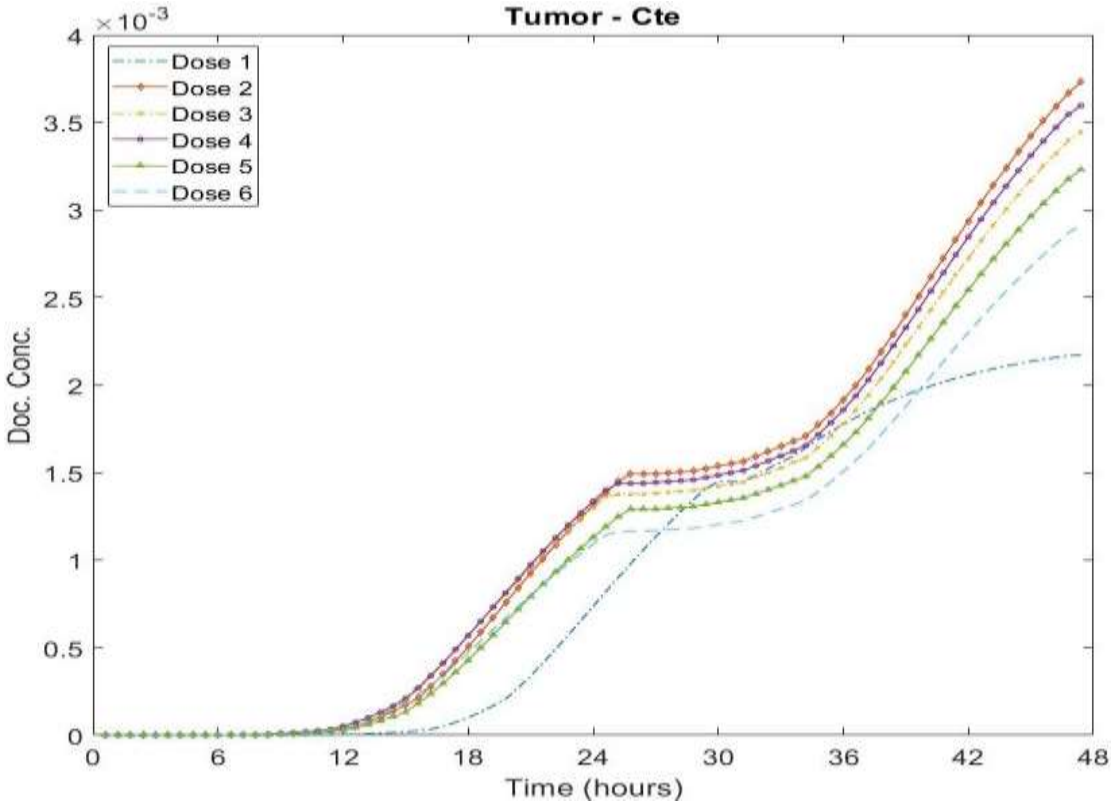


Fig. 6.33: Drug concentration in TUMOR (extra-vascular tissue)

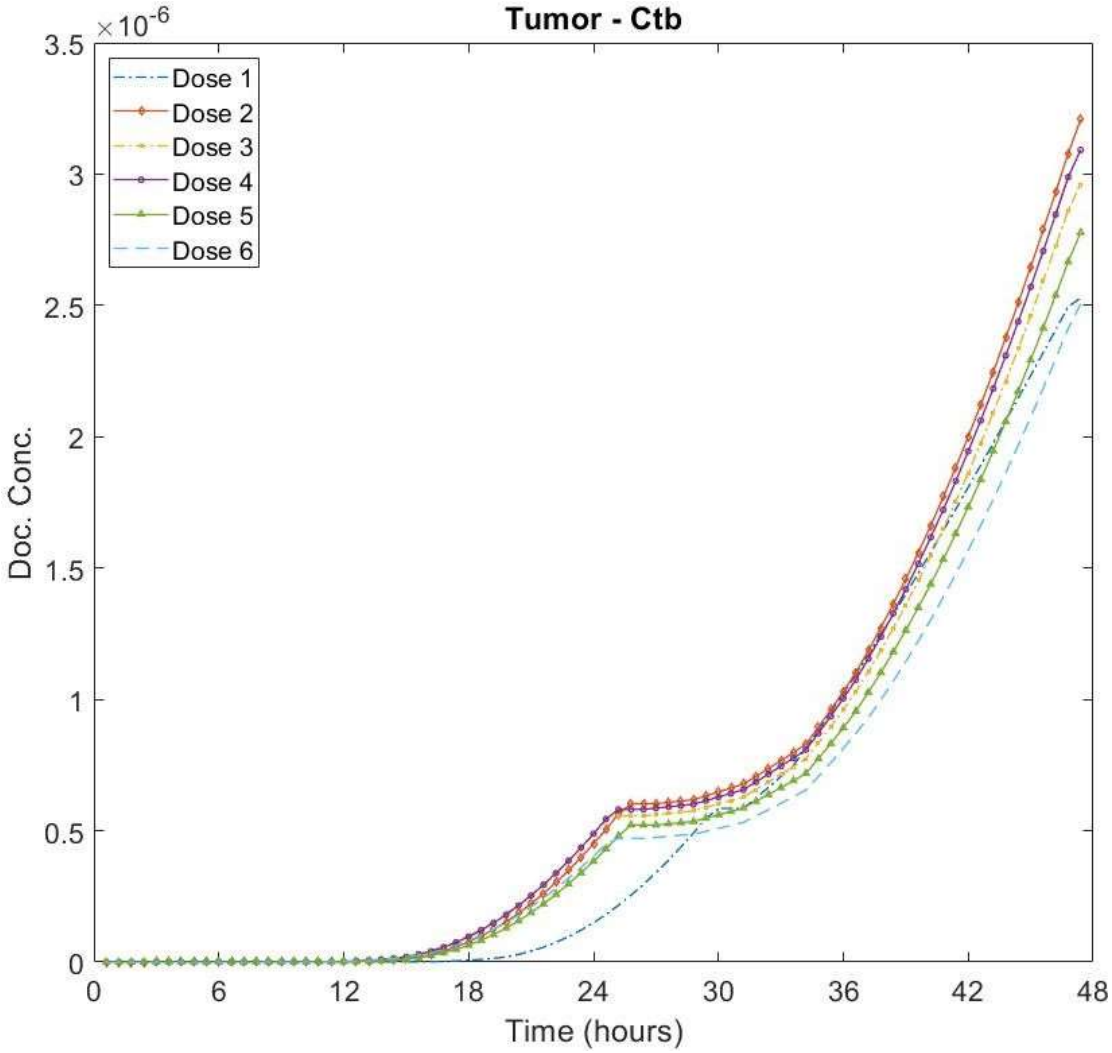


Fig. 6.34: Drug concentration in TUMOR (bound sub-compartment)

6.5.3.12 Drug Concentration in HEART

It is the job of the heart to pump blood, which delivers medications and other chemicals to the various parts of the body, including organs and tissues. Because of this, all of the medications that were carried initially by venous blood are now transported by arterial blood, so completing the cycle and re-incorporating themselves into venous blood. The drug concentration for the vascular tissue for all cycle in heart is illustrated in figure 6.35. The extra-vascular tissue's drug flow rate is shown in figure 6.36. Finally, the drug diffusion rate for the bound sub-compartment is shown in fig. 6.37.

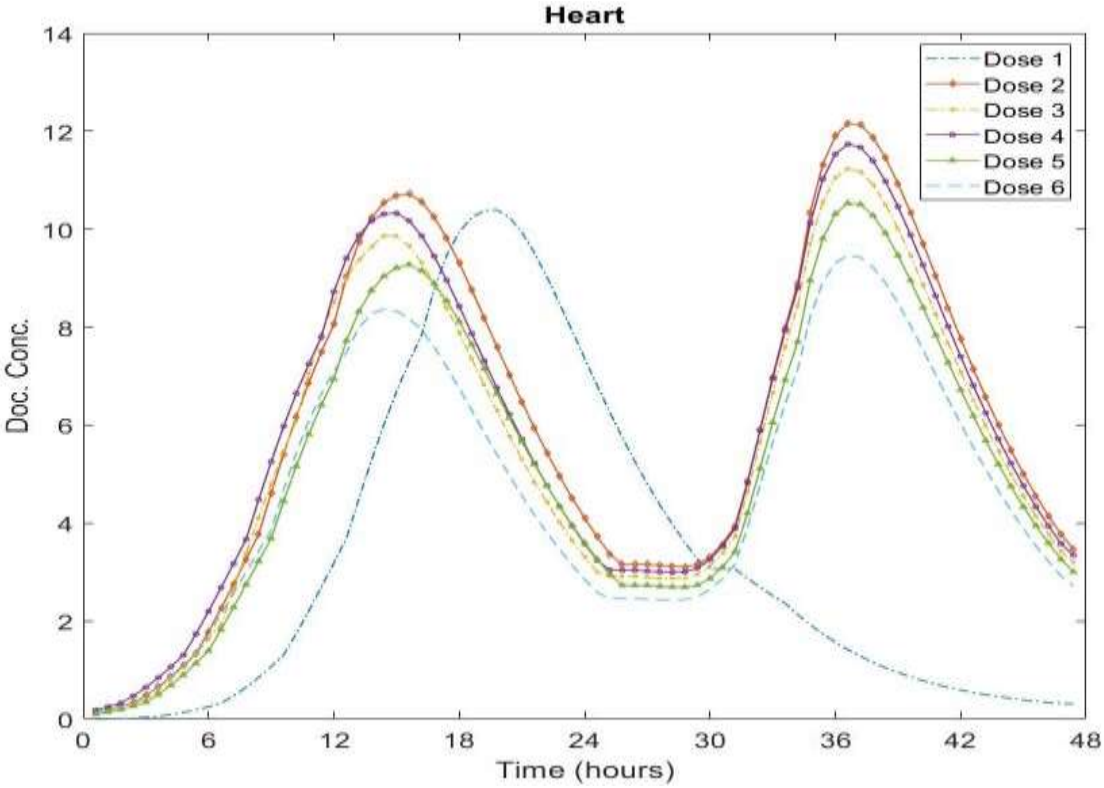


Fig. 6.35: Drug concentration in HEART (vascular tissue)

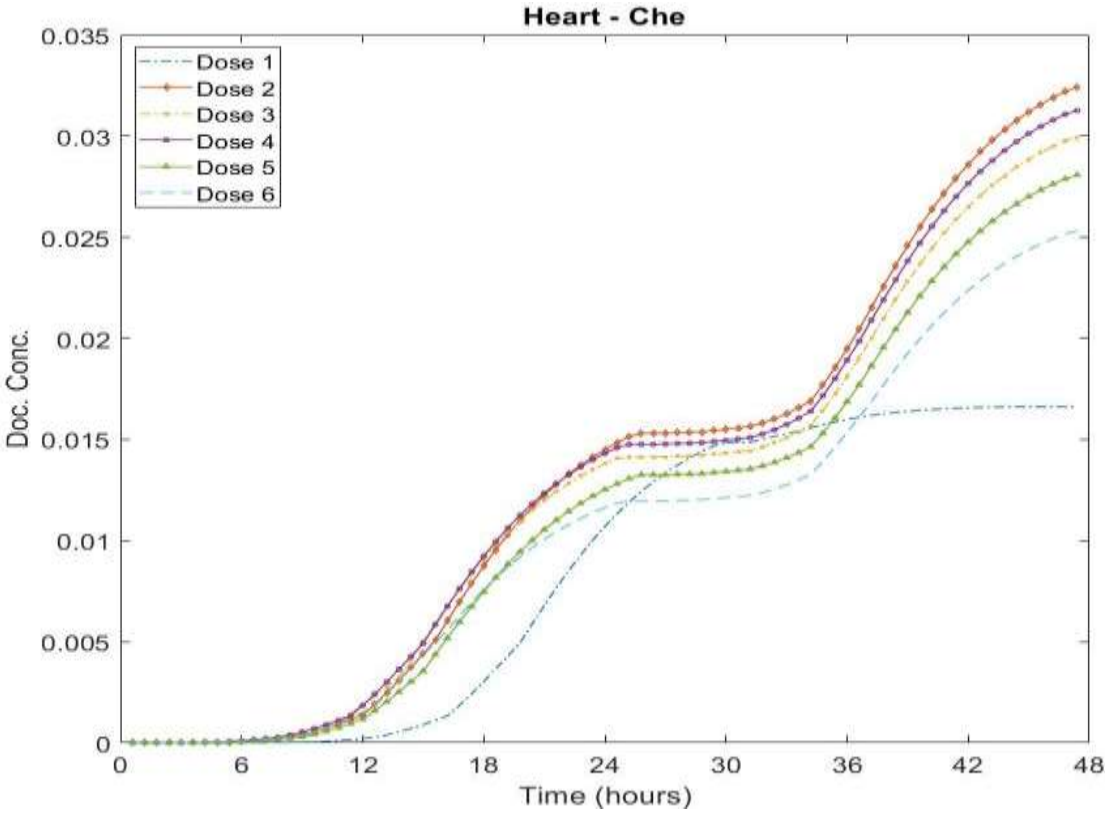


Fig. 6.36: Drug concentration in HEART (extra-vascular tissue)

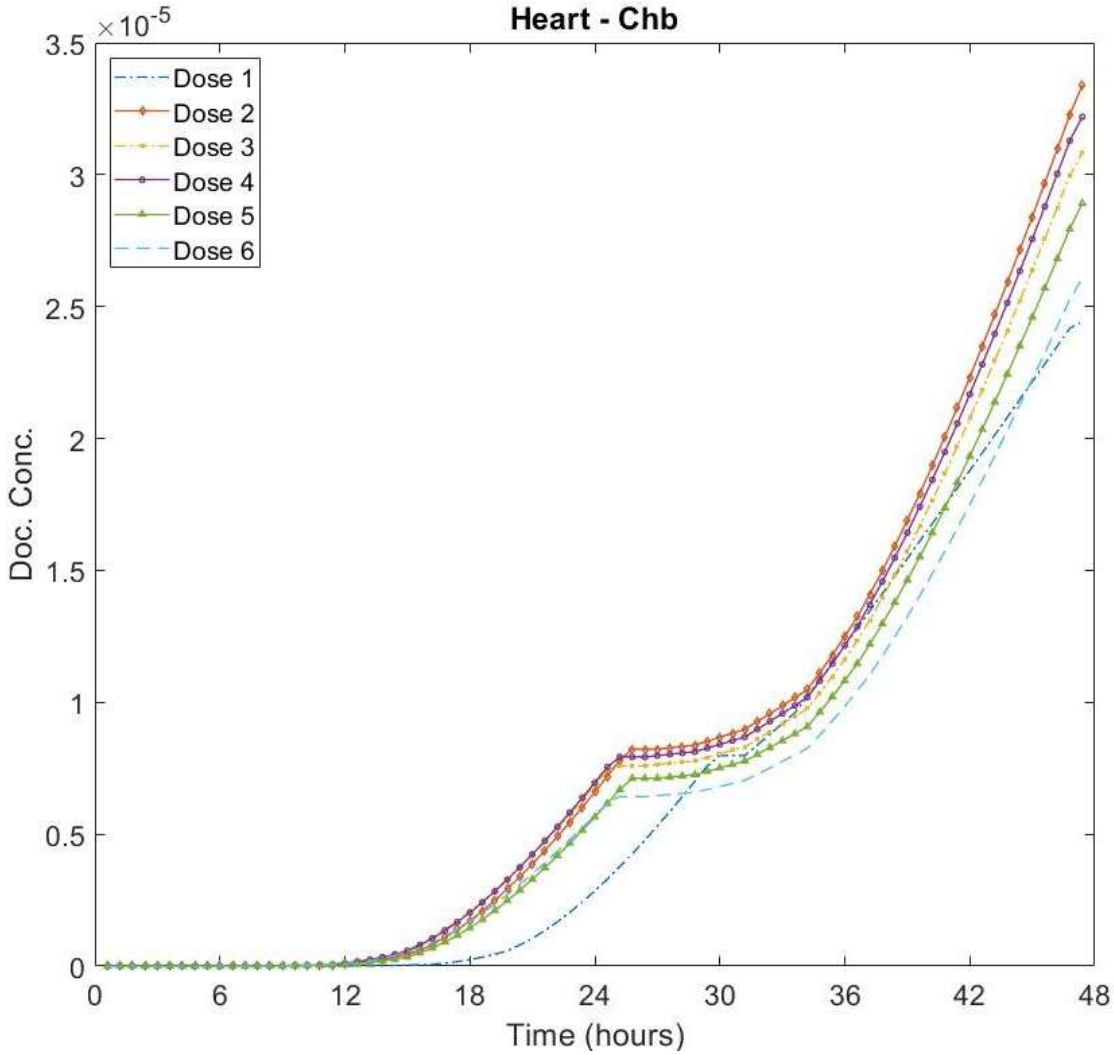


Fig. 6.37: Drug concentration in HEART (bound sub-compartment)

6.5.3.13 Drug Concentration in OTHERS

Apart from the organs discussed above, in PBPK model all other organs and sub organs are treated as one compartment, named as "others". It also has three sub-compartments, vascular tissue, extra-vascular tissue and bound sub-compartment. The drug concentration of these sub compartments are illustrated in fig. 6.38, fig. 6.39 and in fig. 6.40 respectively.

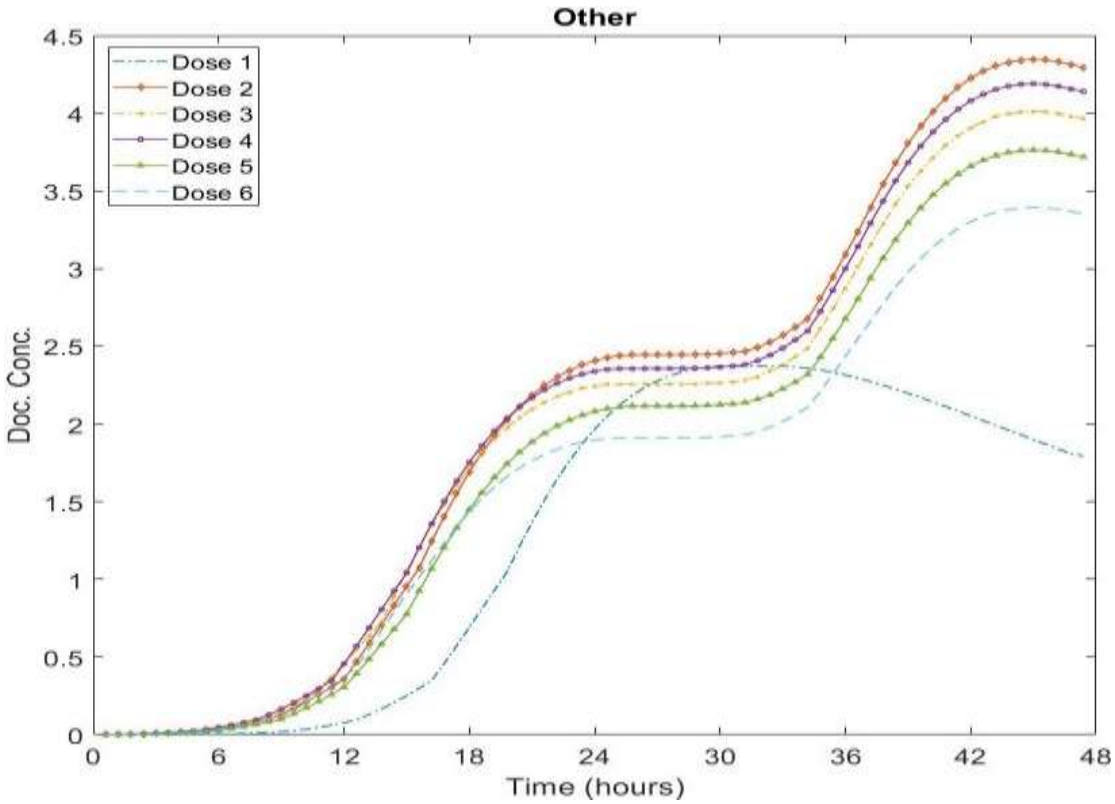


Fig. 6.38: Drug concentration in OTHERS (vascular tissue)

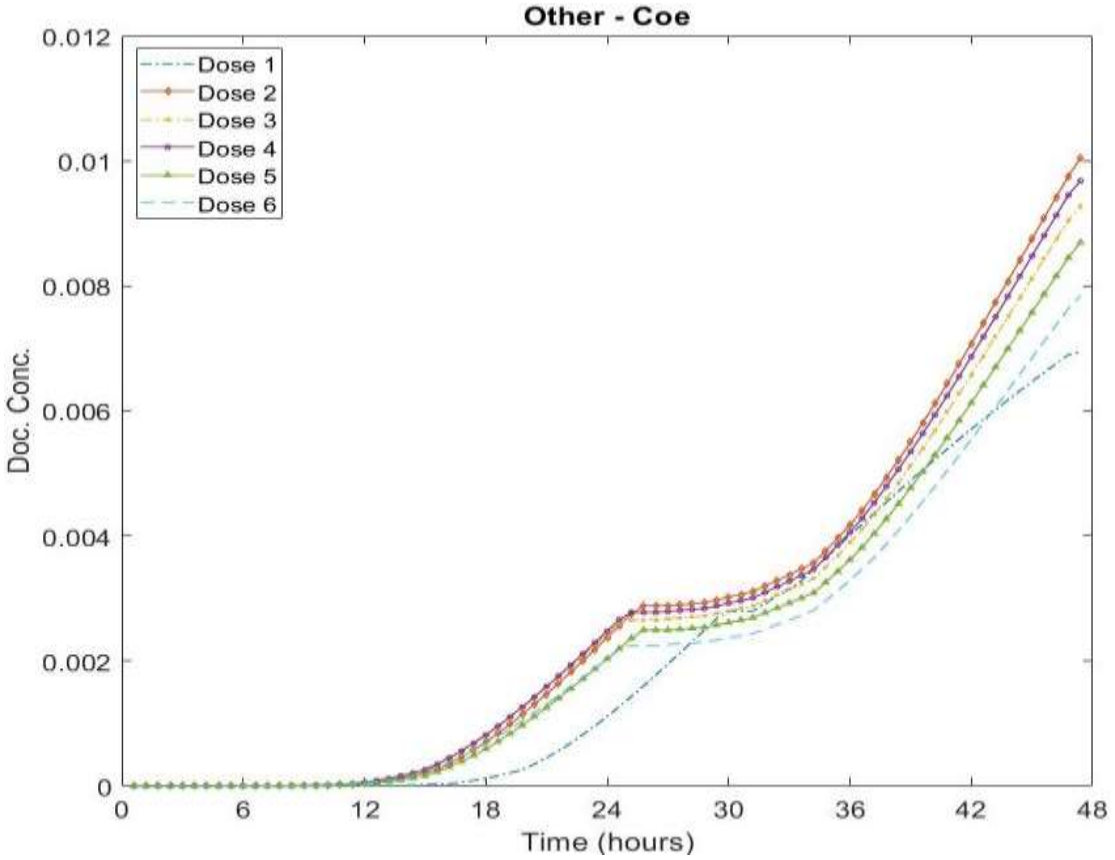


Fig. 6.39: Drug concentration in OTHERS (extra-vascular tissue)

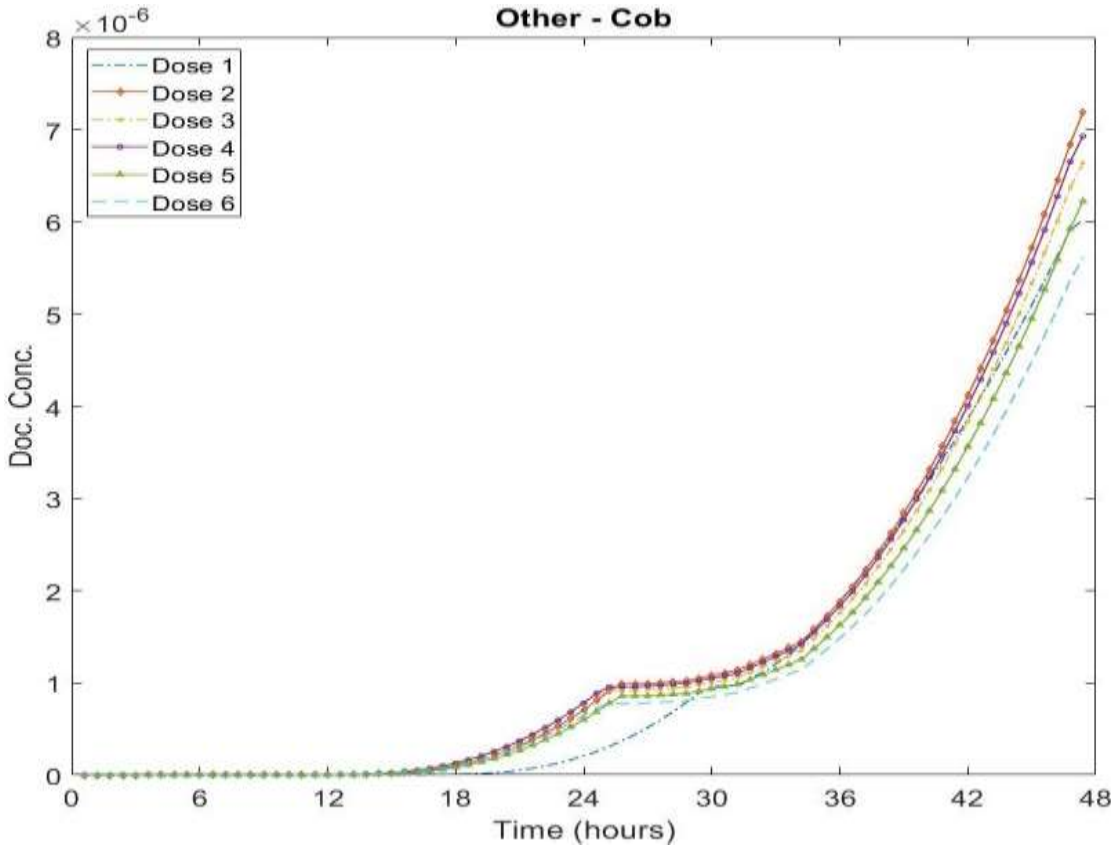


Fig. 6.40: Drug concentration in OTHERS (bound sub-compartment)

Through the chemotherapy drug (Docetaxel) dose generated by the proposed system, drug concentration in different organs of a patient body which are also generated by the proposed system is discussed above. It can be seen that the output doc concentration in different organs in the human body is different for the same input dose. By these system generated drug dose and related data an oncologist can decide treatment plan for a particular patient. The first module, clinically relevant fuzzy expert system, generates optimum drug doses, moreover in the present DSS model there is a provision to input threshold value of drug concentration for one or more organs considering the patient's physical condition (kidney function, liver function, etc.) and the type of cancer, as a result more patient specific optimum chemotherapy drug dose projection is possible.

6.5.4 Maximum drug concentration in different organs through the present run

Table 6.4 describes the maximum drug concentrations in individual organs in human body which are determined by the model in the present run, where threshold values of drug concentration are considered 50mg for all above mentioned organs. From the table 6.4 it is clear that none of the organs' drug concentration crossed their threshold values.

Table 6.4 Maximum drug concentration in different organs through present run

Organs Name	**Maximum drug concentration(c_{max}) (for dose = 50)**
Venous blood	25.7
Arterial blood	12.26
Kidney	11.79
Lung	21.69
Liver	6.36
Fat	8.13
Muscle	5.65
Spleen	4.74
Tumor	9.41
Brain	11.76
Gut	6.478
Heart	12.16
Others	4.35

6.6 Case study

Considering a cancer patient's physical condition and the type of cancer if an oncologist decide to set threshold value of the patient's muscle drug concentration to 6.5mg while the patient body weight is 70 kg the system generated drug doses will be as in the table 6.5. Drug dose generated by the 1st module is given in "Initial Dose" column and considering constrains (threshold value of drug concentration for muscle is 6.5mg), in feedback controller, final drug dose is shown in "Adjusted Dose" column. From fig. 6.42 and fig. 6.43 it is clear that on 84th day the tumor size became ~0 and toxicity throughout the treatment tenure was under control.

Table 6.5 Case Study: System generated Drug Dose (6 cycles, upto 84th day)

Cycle Number	Initial Dose	Adjusted Dose
1	40	40
2	42.63	40.50
3	42.7	40.55
4	42.7	40.57
5	42.6	40.52
6	36.45	26.8

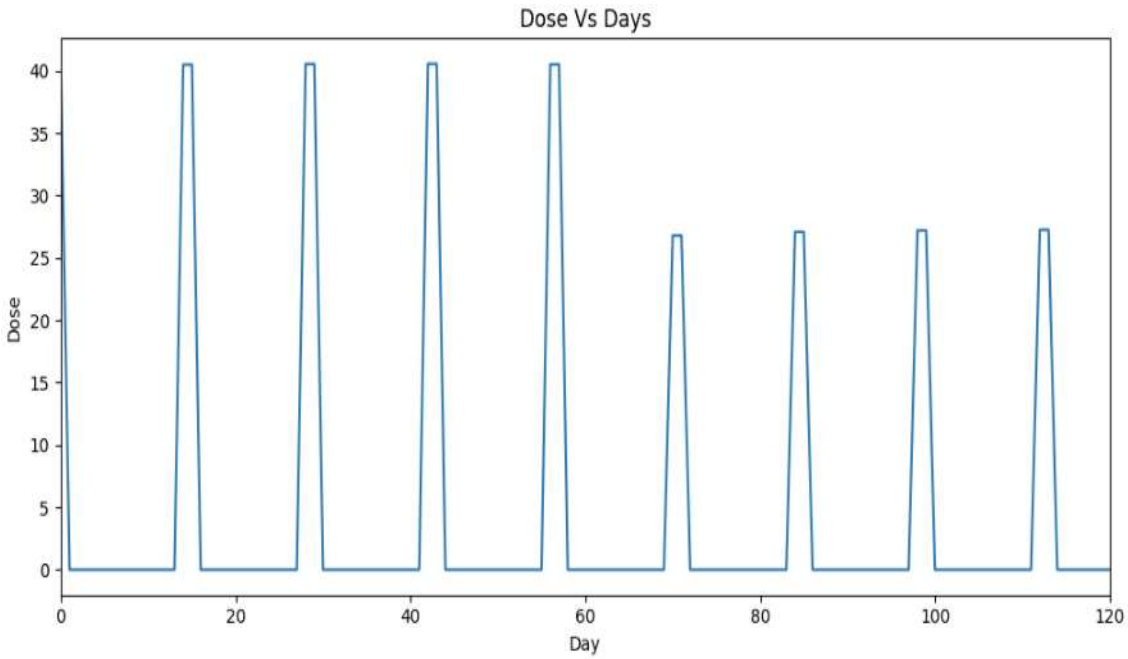


Fig. 6.41: Case Study: Chemo Drug Dose generated by the FES based DSS

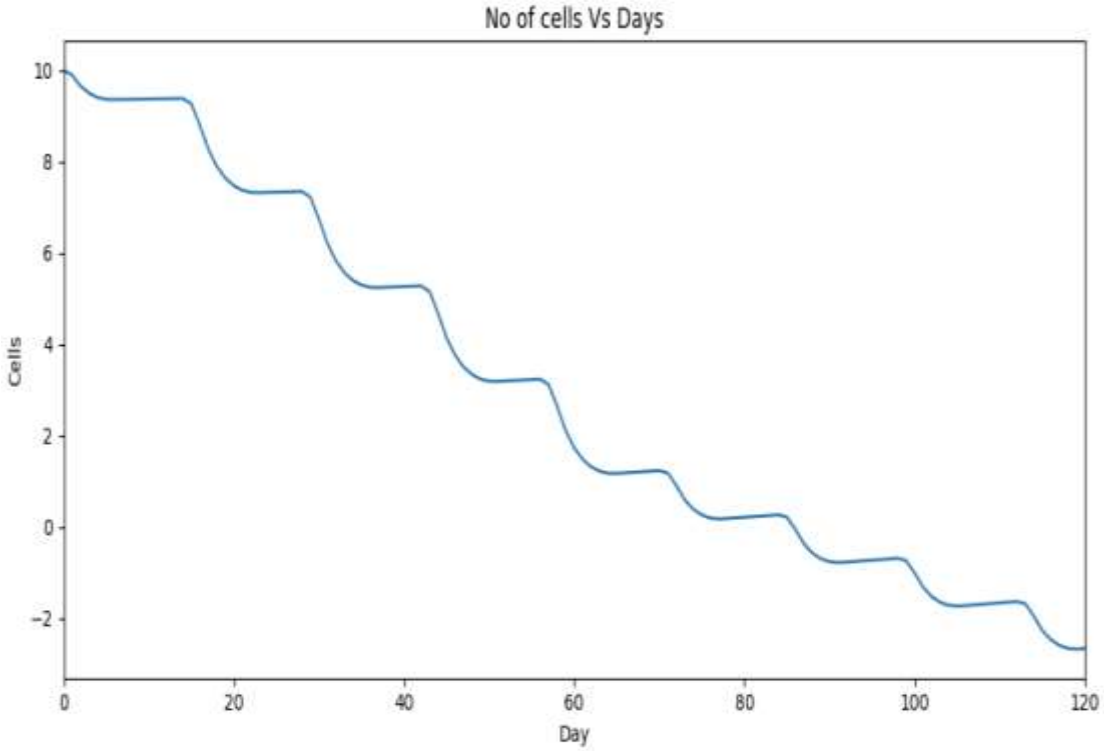


Fig. 6.42: Case Study: Number of Cancerous cells during the treatment period

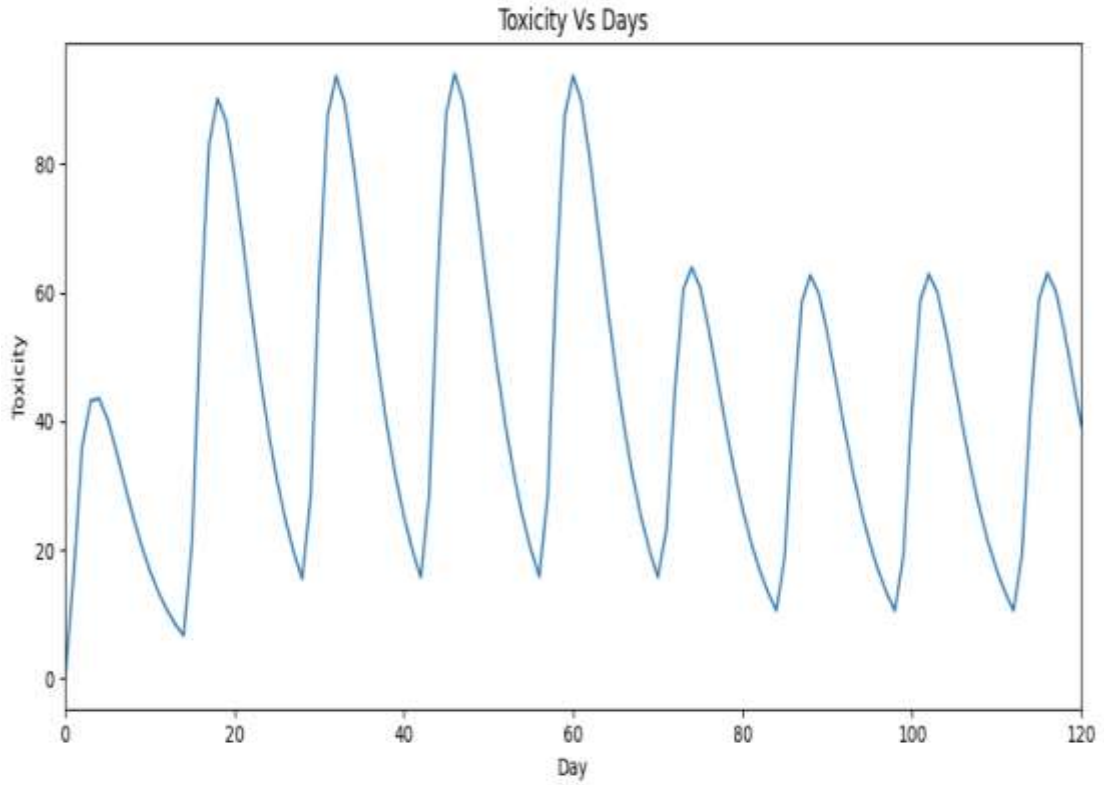


Fig. 6.43: Case Study: Toxicity for 120 days (14 days of interval)

Chapter 7

Conclusion and Future Works

This thesis has presented an investigation into different tumour growth models and design of optimum chemotherapy drug doses using fuzzy expert systems. Initially, different tumour growth models are studied extensively and at the same time thorough investigation is done on chemotherapy drug dose scheduling in clinical context with a view to select appropriate growth models to be incorporated with the optimum controlled chemotherapy drug dose scheduler. Models and chemotherapy procedures are investigated through studying many contemporary research, many literature and taking opinions from experts'/oncologists' in different cancer institutes. Martin's model is chosen to observe the number of cancer cell and toxicity in a patient's body after each chemo cycle. Incorporating the growth model a clinically relevant fuzzy expert system for optimum chemotherapy drug dose scheduler is developed. Fuzzy expert system is used to easily incorporate the experts' opinion and to confirm the optimality criterion of the system. The system outperformed all other relevant studies in terms of number of tumour cell reduction, which is ~0 at the end of chemo cycles, and having best performance index, 29.242, at the same time toxicity was within the limit. After confirming the optimality criterion, to project drug dose concentration in different organs of a patient's body, after each treatment cycle, Physiologically Based Pharmacokinetic (PBPK) model has been incorporated with a chemotherapy drug dose scheduler, which is a first-hand work, to facilitate the oncologist to take proper decision. At the same time a feedback controller is introduced to support the fuzzy expert system to generate optimal chemo drug dose for specific type of cancer and considering patient physical condition.

Chemotherapy is a procedure that is used most frequently for treating systemic cancer, including solid tumors and the metastases that might arise from them. When it comes to administering chemotherapy treatments, finding the optimal balance between the elimination of cancer cells and the reduction of host toxicity continues to be a difficulty

for clinicians. The proposed system presents an optimal chemotherapy dose scheduling system using the Fuzzy expert system. All monitoring doses were effectively applied throughout the treatment period, and the convergent result was a 100% reduction of cancer cells without violating treatment restrictions. More notably, the highest toxicity level during the treatment period remained below the maximum allowable value as previously reported and suggested by other researchers (Martin and Teo, 1994, Martin et al., 1990; Martin, 1992). The proposed dose regimen may be preferred by the clinical people to adjust the chemo drug doses, if they feel. The proposed strategy clearly illustrates that, in addition to traditional methods, the proposed FES-based model for chemotherapy dose scheduling can assist oncologists/clinicians in planning optimal chemotherapy treatment scheduling. When compared to existing state-of-the-art models, our optimization technique with well-defined limits produces highly satisfying results. Furthermore, personalized treatment plans can be created by adjusting model parameters based on the patient's physiological condition and tumor stage. The same design process can also be used to construct multi-drug or combination chemotherapy regimens although cell-compartment models of cancer growth may be required in such case.

This research has presented the significance of the modular fuzzy expert system-based Physiologically Based Pharmacokinetic (PBPK) model for making an efficient decision support system (DSS) for optimal chemotherapy dose scheduling. Most chemotherapy dose scheduling approaches have typically focused on finding mathematically optimal solutions but they are not generally relevant to the clinical procedure. In addition, different oncologists suggest chemotherapy drug doses based on their expertise but they don't have a supportive projection to provide them with a visualized result about the impact on a particular patient before applying the drug dose. Moreover, the suggested dose from the oncologists may not be appropriate for a particular patient. In this work, a modular fuzzy rule-based system and clinically relevant concepts are incorporated to provide better chemo dose by considering the patient's weight and the expert’s opinion. Based on the different constraints and objectives the proposed system suggests an optimal amount of dose considering tumor cells while not exceeding the toxicity threshold. Furthermore, for each cycle of input dose, output drug concentration at different organs of a patient's body have measured and observed by the PBPK model.

Point to be noted that, the drug concentration has remained approximately similar for all kinds of the input drug dose schedule and the drug concentration has decreased within a few days. Apart from that, cancerous cells can grow in different parts of a patient's body (e.g. lung, liver, kidney, or brain, etc.). By applying the proposed system an oncologist can differentiate how much drug concentration the cancerous organ needs and how much it is receiving considering the patient's toxicity. Before applying the chemotherapy drug dose to the patient's body, the proposed decision support system (DSS) can verify the effect and impact of the drug concentration in a particular organ of the patient's body. Moreover, the proposed system also provides better outcomes for eliminating tumor cells by keeping the toxicity at an acceptable level.

In many cases, MTD (maximum tolerated dose) approach used in oncology drug scheduling may not be ideal, and improving dose selection is needed. Traditionally, the MTD approach has dominated the oncology dose-finding paradigm. Its origin lies in developing cytotoxic agents based on the assumption that the higher the dose, the greater the likelihood of efficacy and toxicity. Dose-limiting toxicities (DLTs) are predefined in phase I dose escalation trials, and, based on DLT criteria, dose is escalated until MTD is reached. Due to the life-threatening nature of the disease, oncology clinical trials are often complex and data interpretation is challenging. Moreover, cancer may occur in different parts of the patient’s body, like the Lung, Liver, Kidney, and others. Capturing patient’s disease dynamics and predict future dynamics is very important for the oncologist to settle the drug doses for a specific organ. Also it is imperative to identify the pharmacokinetics (PK) and pharmacodynamics (PD) of the intended drug before applying it to the patient. The proposed DSS intends to mitigate these issues to support the oncologist for appropriate drug dose selection. The DSS model consists of three parts; a) the clinically relevant fuzzy expert system for tumor growth modelling and optimum chemotherapy drug dose scheduling is responsible to generate the optimum drug dose, b) Physiologically Based Pharmacokinetic (PBPK) module for drug concentration projection is responsible to show the drug concentration in different organs of the patient’s body, and c) feedback controller is responsible to generate optimum drug dose considering cancer type and the physical condition of the parient. The first module is designed to generate an optimum drug dose that will give projections of reducing cancerous cells to ~0, keeping the toxicity in control. The

second part is effective for estimating internal drug dosage to targeted organs in a patient's body. It gives a quantitative description of pharmacokinetic processes including absorption, distribution, metabolism, and excretion. The model will generate a details analysis of the variation of drug concentration in different organs of the patient's body, which will guide optimal drug dosing schemes and predict drug interactions with the patient's body organs. And the third module is very important for cancer specific treatment. Considering the liver function, kidney function and other physical phenomenon of the patient's body the oncologist will set threshold drug concentration values for different organs and accordingly the feedback controller will help the first module to generate cancer specific optimum drug doses restricting the drug concentration in the targeted organs according to the threshold valued provided by the oncologist. The proposed DSS model will mitigate the challenges of "human dose projection", "exposure and target engagement at site of action", "Dose Optimization", "Regimen and dosing schedule optimization", "Effects of intrinsic and extrinsic factors", etc.

Although the proposed system is smart enough to project optimal drug dose keeping toxicity in control, even it can provide optimal drug dose considering patients' physical condition and location of cancer, still it has some limitations. We know the human body is a very complex system, in terms of that complexity, used growth model, martin's model, which is used to observe the tumor size and toxicity in the proposed system, is a simplified model. So, system performance may be affected for that.

Threshold values of drug concentration for different organs are to be inputted by the oncologist in the proposed system. Oncologist have to set the threshold value considering the type/location of the cancer and patient's different physical parameters, like liver function, kidney function, etc. Separate module could be added to automate this issue.

It is a simulation model, the aim of this work is to support the oncologists to finalize the best cancer treatment plan before applying the chemo drug to the patient body. To justify the realistic performance of the system, it should be given to the oncologists to use for couple of years. During this trial, the system performance could be taken with

confidence, at the same time as per the feedback of the oncologist, the system could be fine-tuned.

Drug resistance and disease recurrence are major challenges in cancer treatment. Cancer cells can develop resistance to chemotherapy drugs, which can result in the recurrence of the disease. Cancer cells can become resistant to chemotherapy drugs due to genetic mutations, tumor heterogeneity, micro-environmental factors and epigenetic changes. In the present model, these phenomenon has not been considered.

7.1 Future works

Cancer is a very complex disease with a high probability of recurrence in course of time due to its nature, cell to cell interactions, metastasis property etc. Research can be extended further by incorporating different factors like complex bio-chemical process, drug resistance, cell-to-cell interaction, etc., which are responsible for cancer tumour growth and may affect cancer treatment. These researches will create new avenue and dimension in cancer treatment. Not only in cancer treatment but also considering the research idea of this thesis, some other disease, like diabetics, Alzheimer etc. can be treated. Some of the potential research scopes are discussed in the following sections.

7.1.1 Other growth models can be implemented

In the present research Martin's model is used as growth model to observe the toxicity and tumor size during the treatment period. Different growth models have different aspects of potentiality and limitations, so other mathematical models (dePillis, et. al., 2009) can be implemented.

7.1.2 Automation in threshold value of drug concentration generation

In the present system threshold values of drug concentration for different organs of a patient will have to set manually considering liver function, kidney function and other physical condition of the patient. The value may differ oncologist to oncologist. Another fuzzy expert system or other engineering method can be generated, which will

generate optimum threshold values of drug concentration for different organs of the patient.

7.1.3 Multi drug chemotherapy

Now-a-days, in many cases multiple drug is used simultaneously to treat cancer. In terms of efficacy, there are three possible outcomes when medications are combined. The combination can generate a synergistic effect and improve the treatment's overall efficacy. It is possible that mixing medications reduces the efficacy of treatment and has an adverse effect. Lastly, the effects of the different substances may be additive. In the present implementation single drug is considered to generate drug doses. Same development procedure can be used to develop the system for multiple drug, but above mentioned effects have to be addressed.

7.1.4 Hybrid-fuzzy expert system

A hybrid-fuzzy expert system is a type of expert system that combines the knowledge representation and reasoning techniques of fuzzy logic with other AI techniques such as neural networks, deep neural network, genetic algorithms, and others. Using AI techniques with fuzzy expert system can complement and enhance the reasoning capabilities of the system. For example, neural networks can be used to learn from FES data and improve the accuracy of the system's predictions. Genetic algorithms can be used to optimize the system's performance by finding the best set of parameters for the fuzzy rules. So, combining the above mentioned techniques with the proposed fuzzy expert system, prediction of disease progression and disease dynamic may be possible.

7.1.5 Multi-objective optimization

Multi-objective optimization, also known as multi-criteria decision-making, is a field of research that deals with finding the best possible solutions to problems that have multiple conflicting objectives. Research on multi-objective optimization has been ongoing for many years, and there are many different approaches and algorithms that have been developed, among them some popular methods are: genetic algorithms,

particle swarm optimization, evolutionary algorithms etc. Present work can be extended using different multi-objective optimization techniques to fine tune the performance of the system.

7.1.6 Drug dose scheduling for other diseases

There are different life threatening diseases, where the physicians have to be very careful to decide different drug dose and treatment plan for individual patient, like diabetics, heart disease, parkinson's and some other chronic diseases. Before applying final drug dose in patient's body, if the physician could poses similar type of drug dose projection system then the treatment could be more lifesaving. In these cases, extensive research can be done and following similar development plan and techniques optimum drug dose projection system can be generated for life threatening diseases.

Appendix A

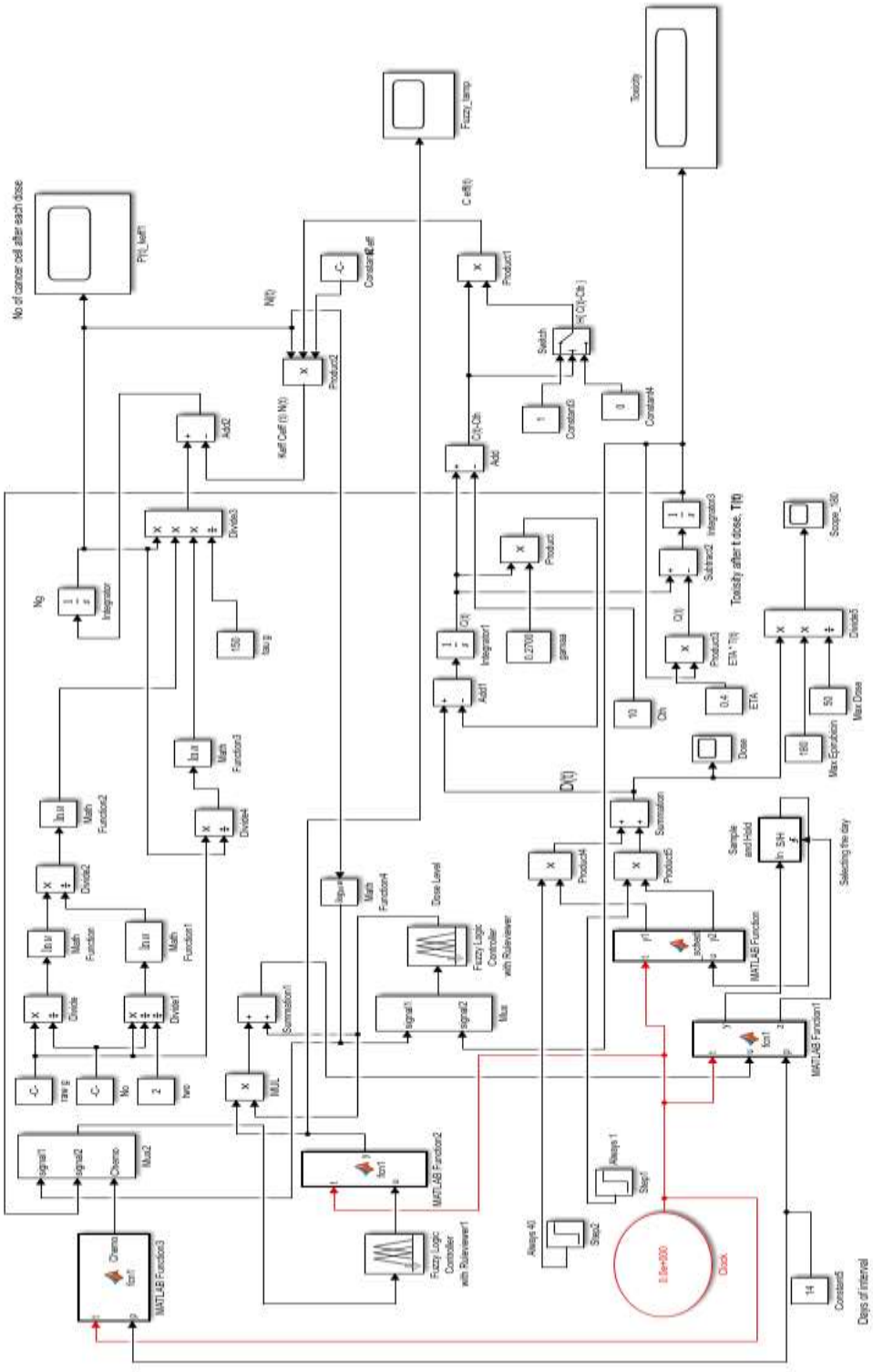


Fig. A.1 Simulink implementation of clinically relevant Fuzzy Expert System for Tumor Growth Modelling and Chemotherapy Drug Dose Scheduling

Appendix B

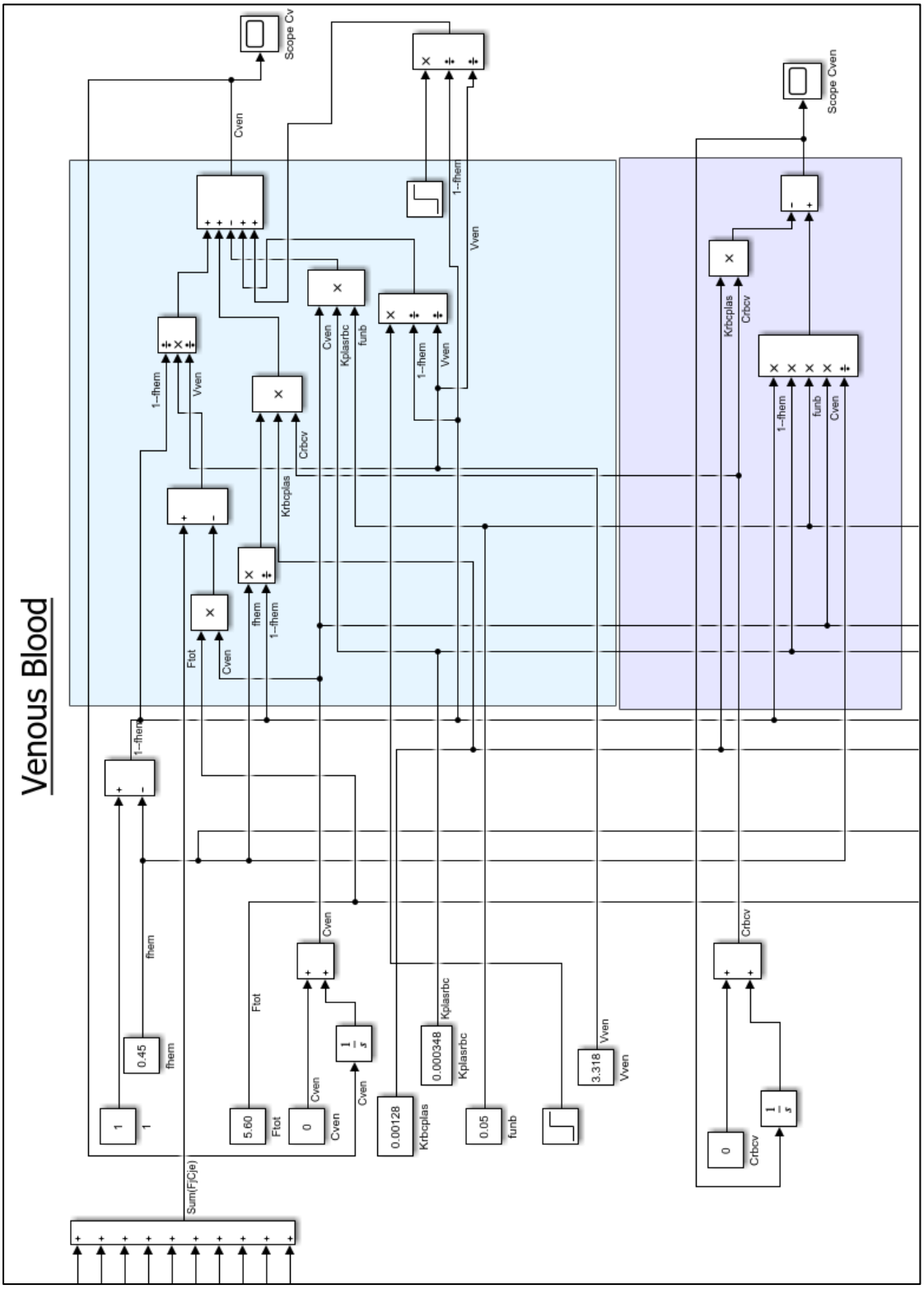


Fig. B.1 Simulink implementation of Venous Blood Compartment of PBPK Model

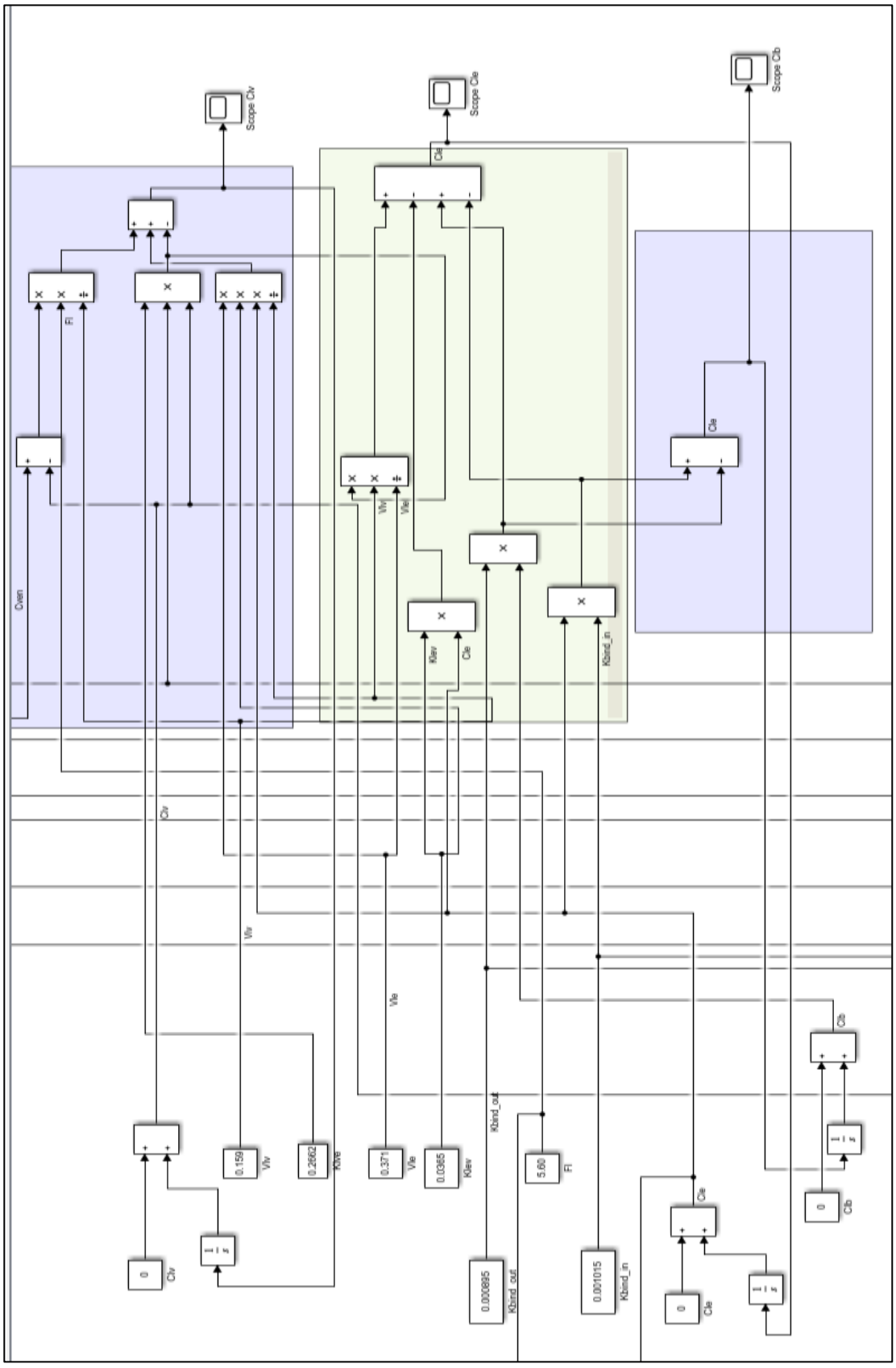


Fig. B.2 Simulink implementation of Lung Compartment of PBPK Model

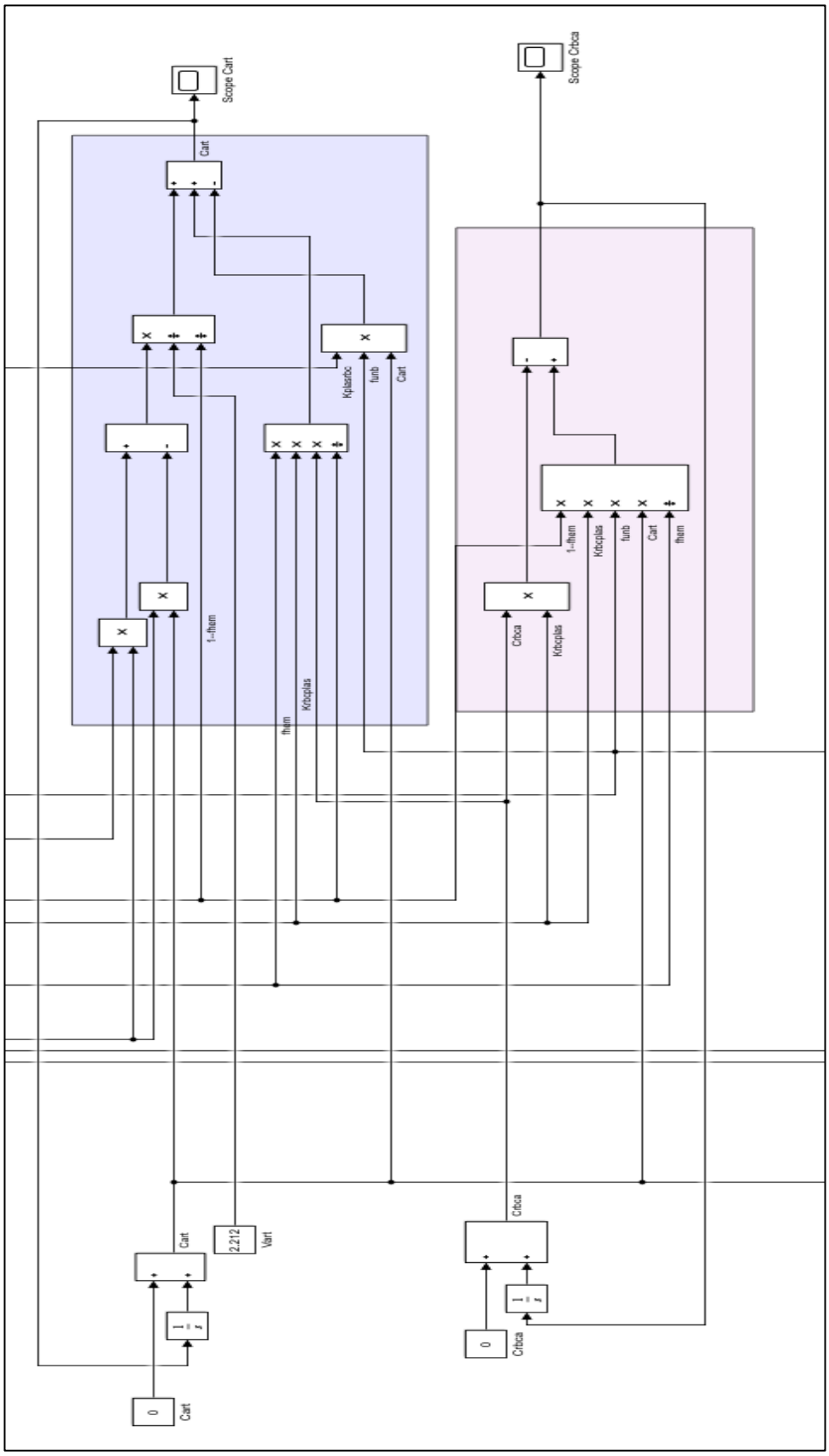


Fig. B.3 Simulink implementation of Arterial Blood Compartment of PBPK Model

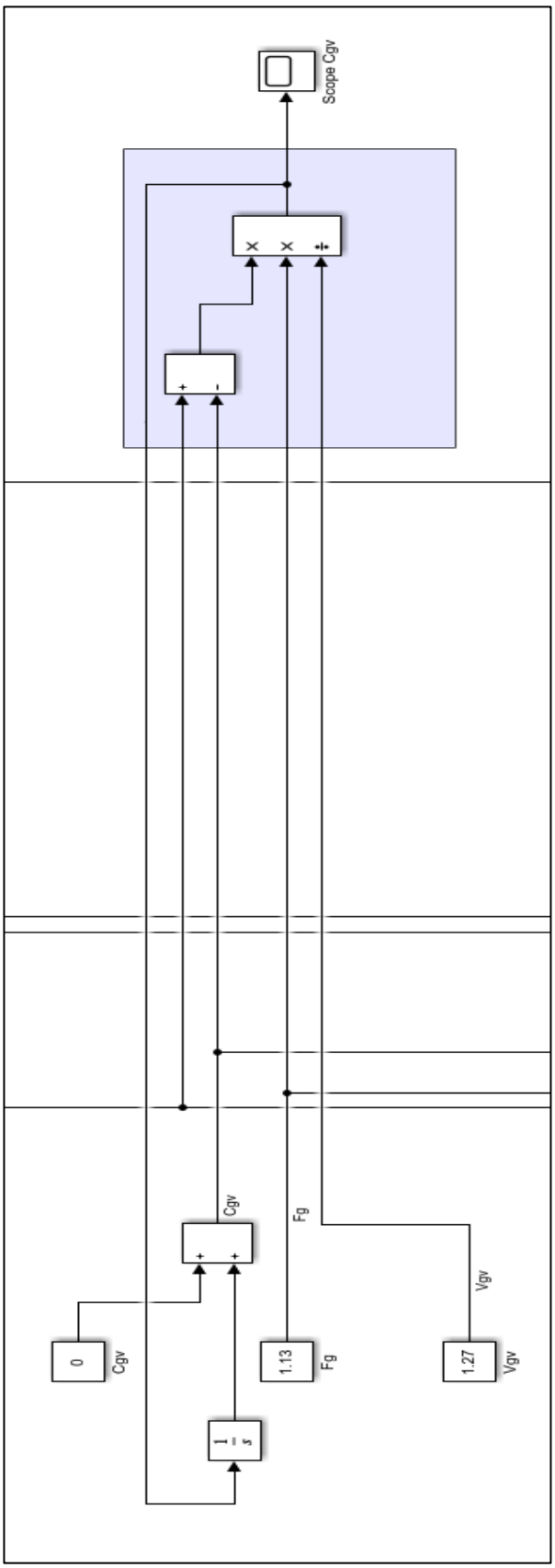


Fig. B.4 Simulink implementation of Gut Compartment of PBPK Model

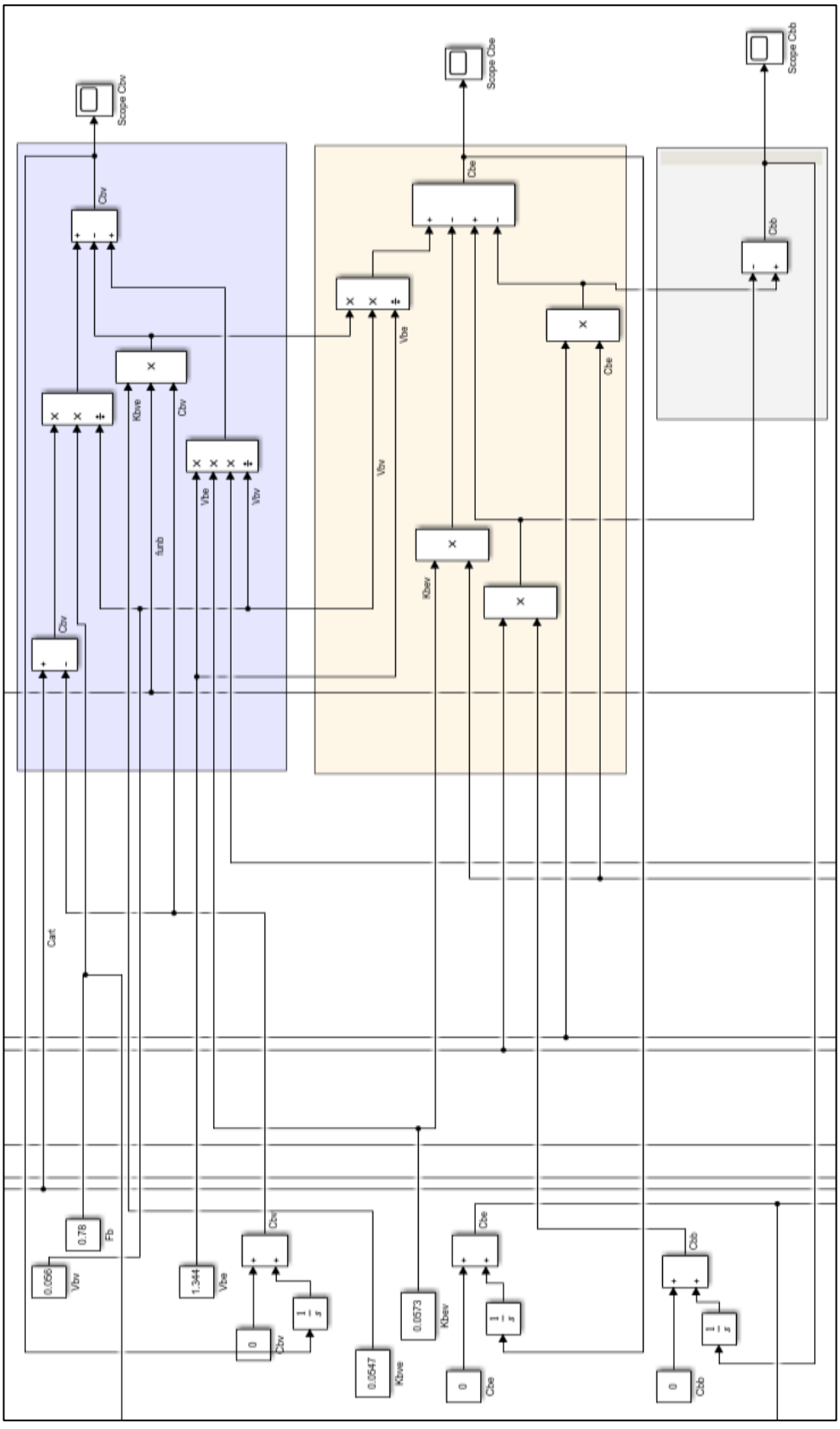


Fig. B.5 Simulink implementation of Brain Compartment of PBPK Model

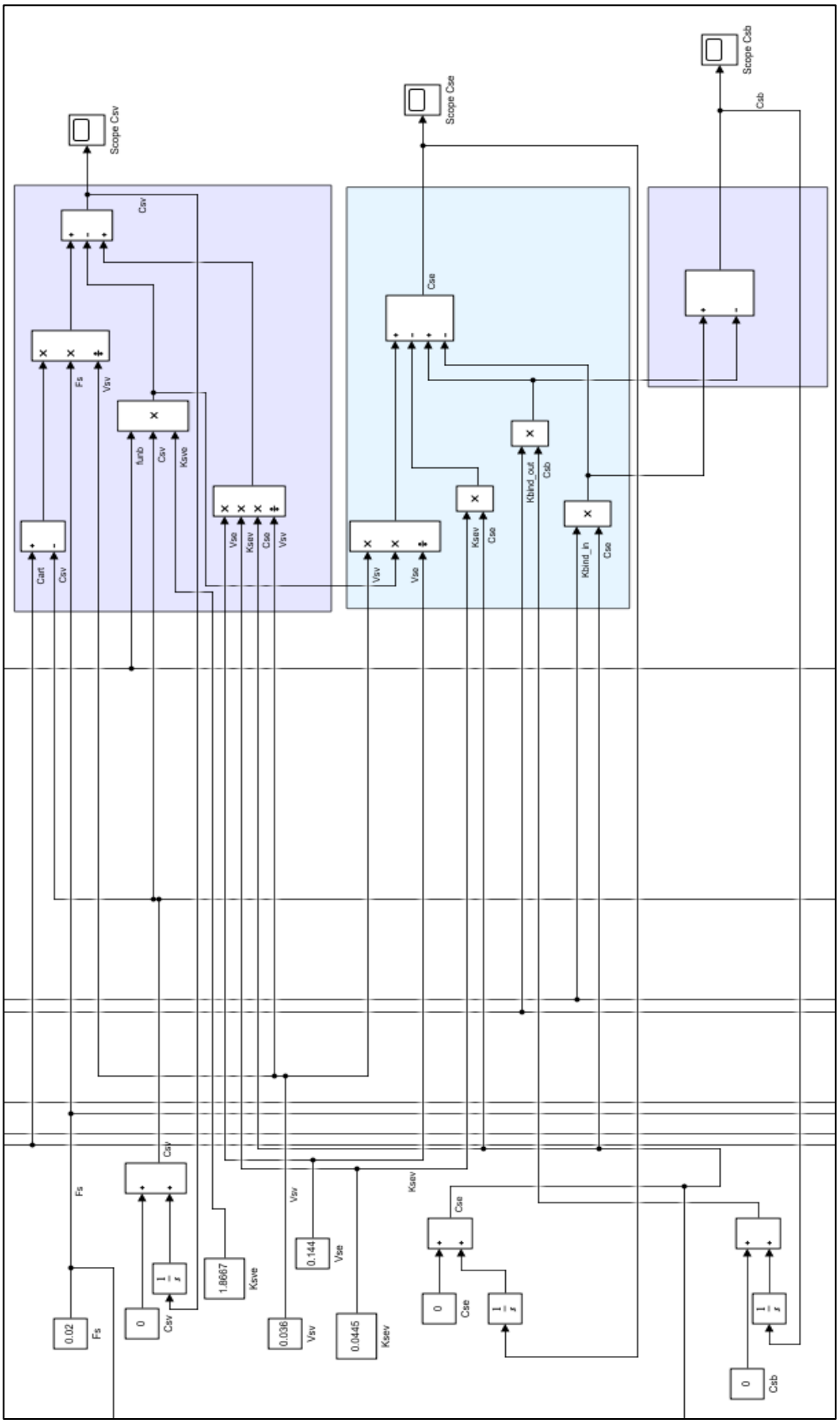


Fig. B.6 Simulink implementation of Spleen Compartment of PBPK Model

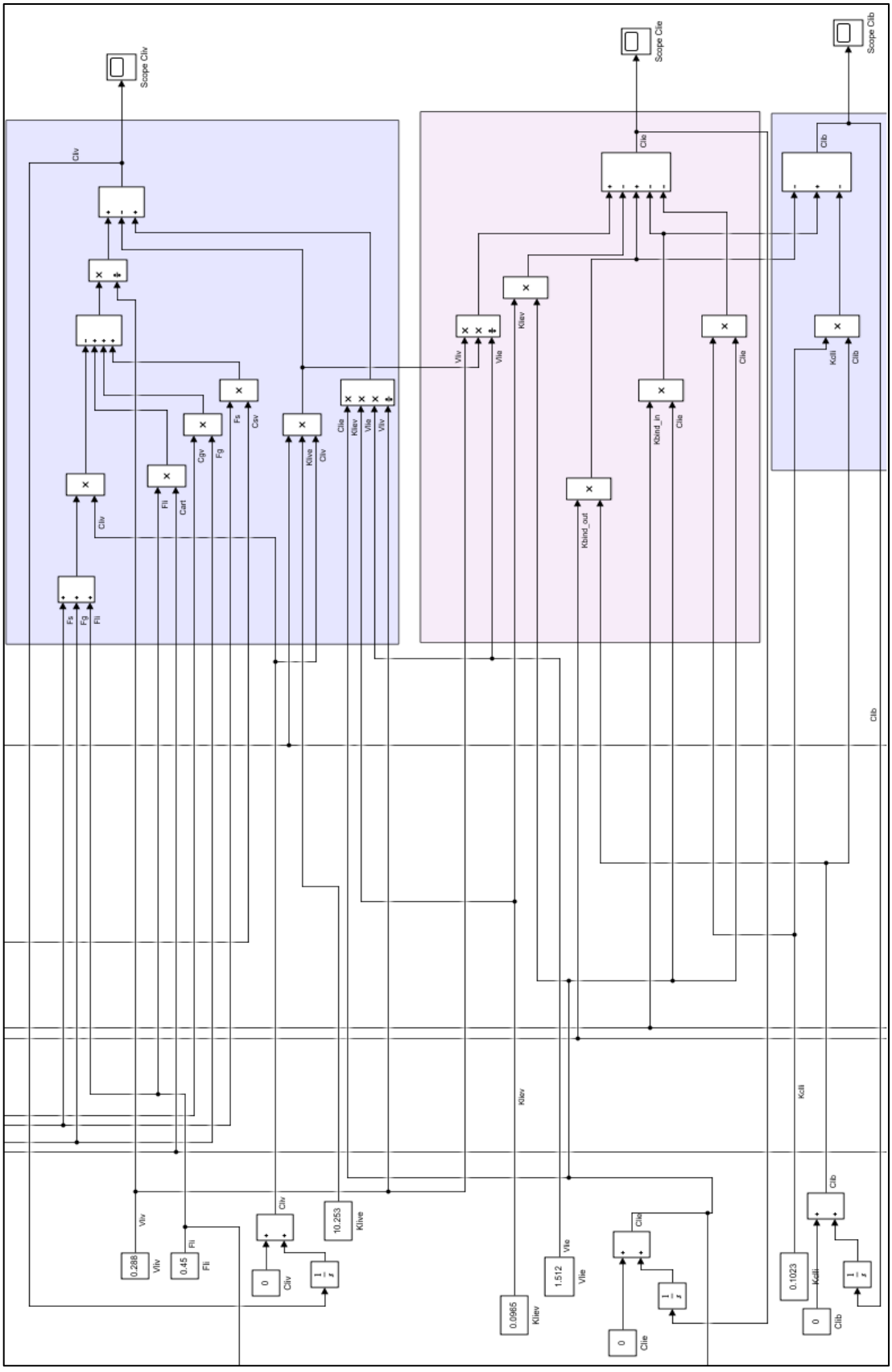


Fig. B.7 Simulink implementation of Liver Compartment of PBPK Model

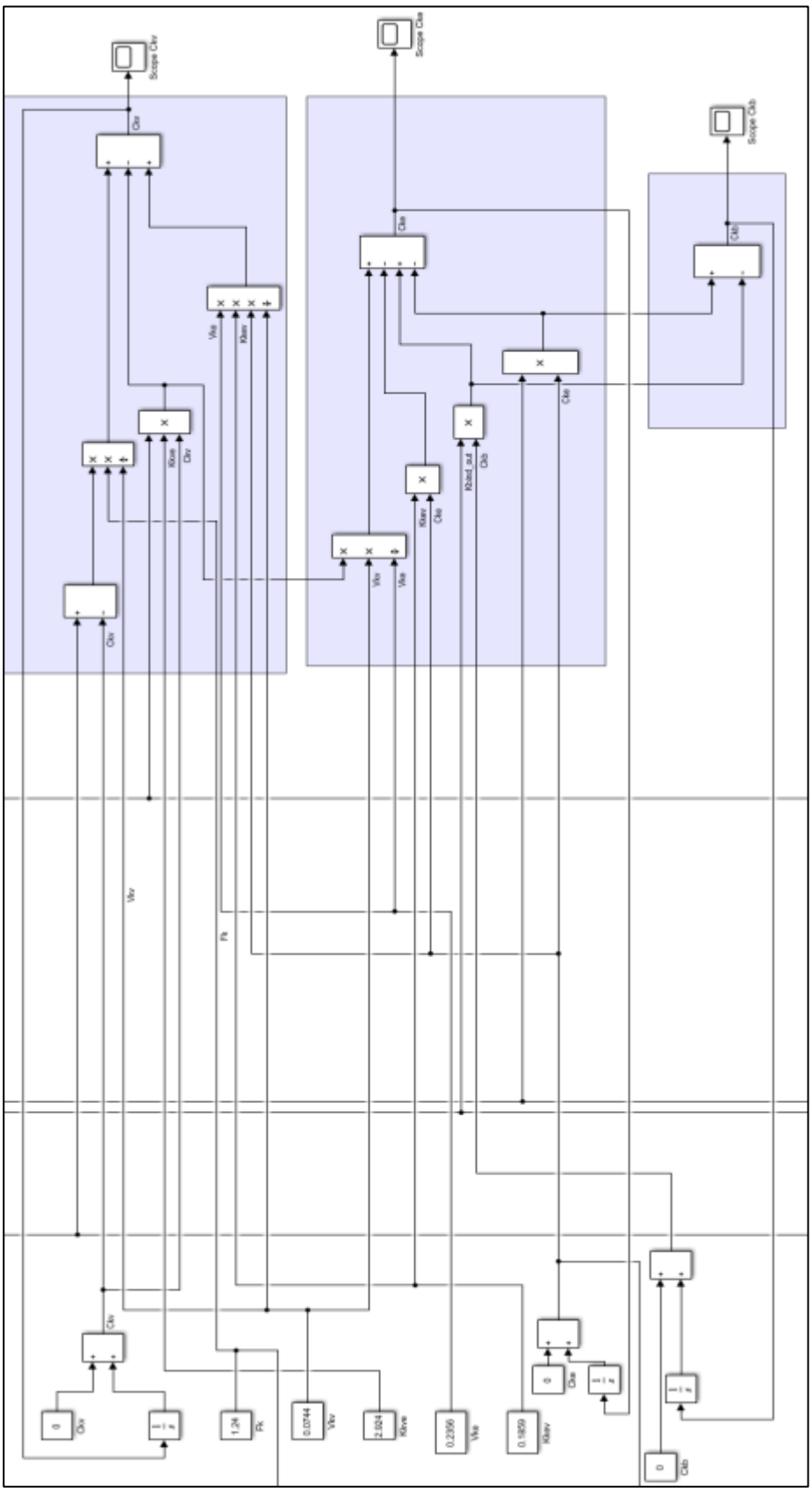


Fig. B.8 Simulink implementation of Kidney Compartment of PBPK Model

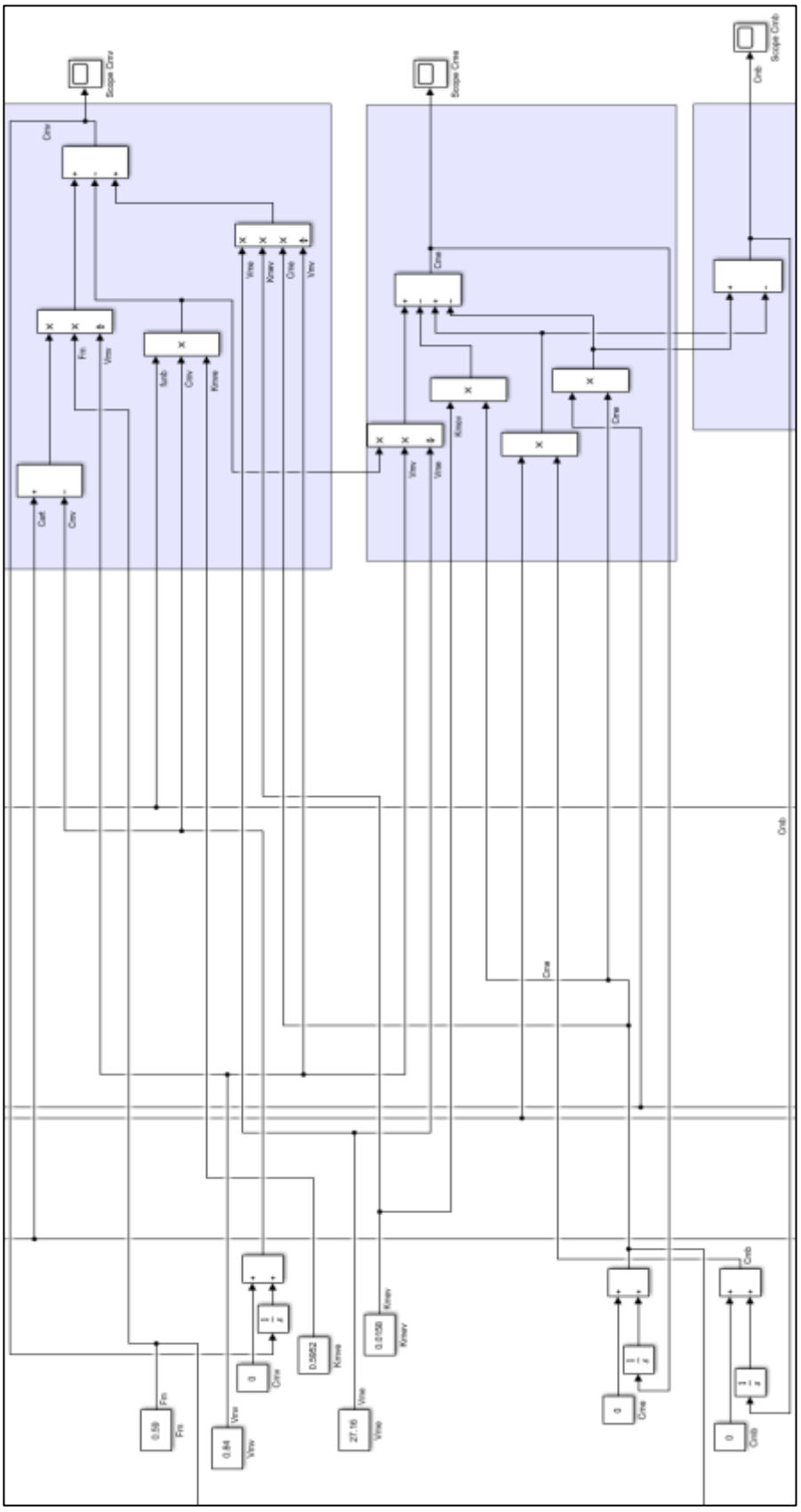


Fig. B.9 Simulink implementation of Muscle Compartment of PBPK Model

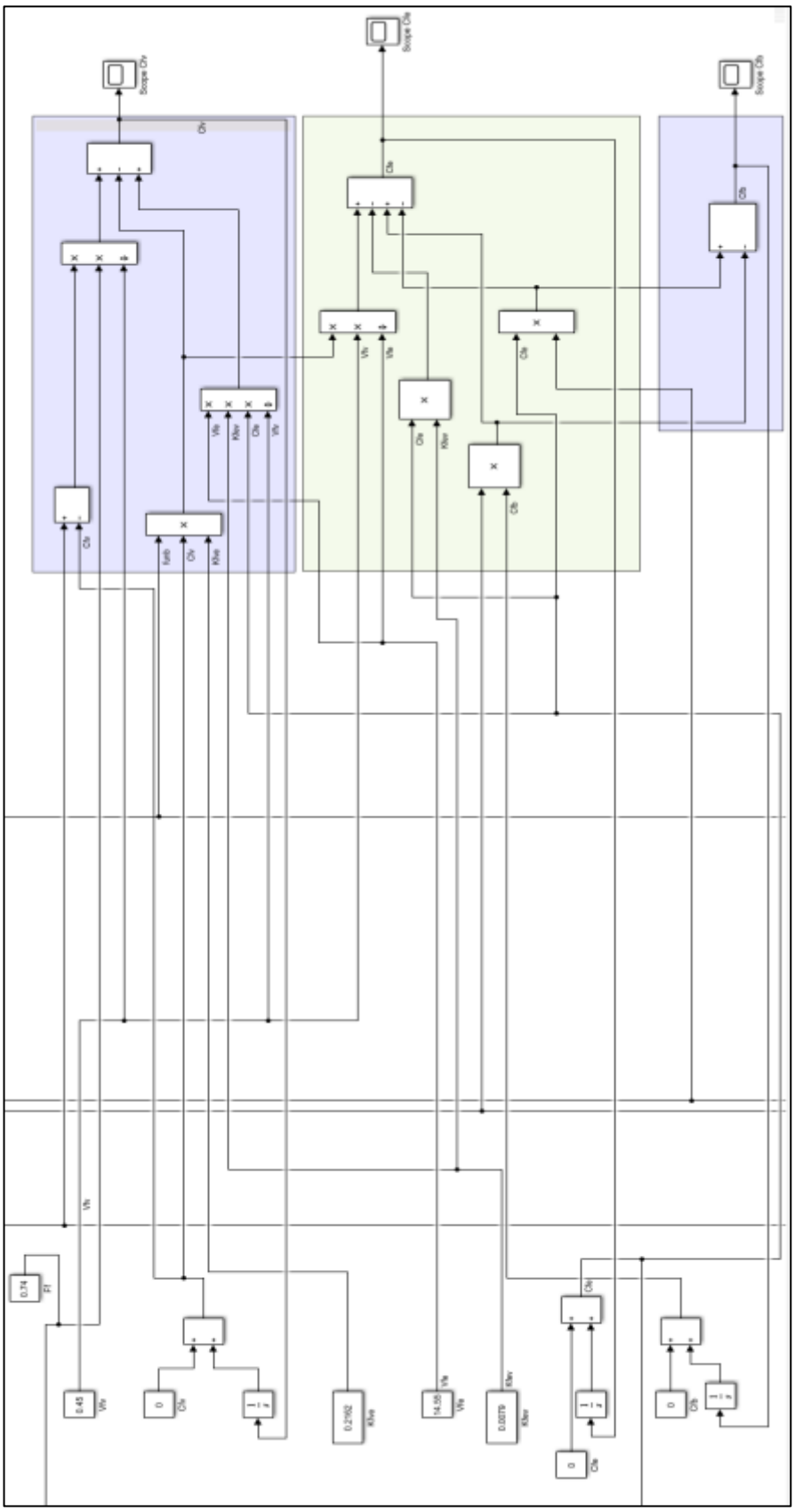


Fig. B.10 Simulink implementation of Fat Compartment of PBPK Model

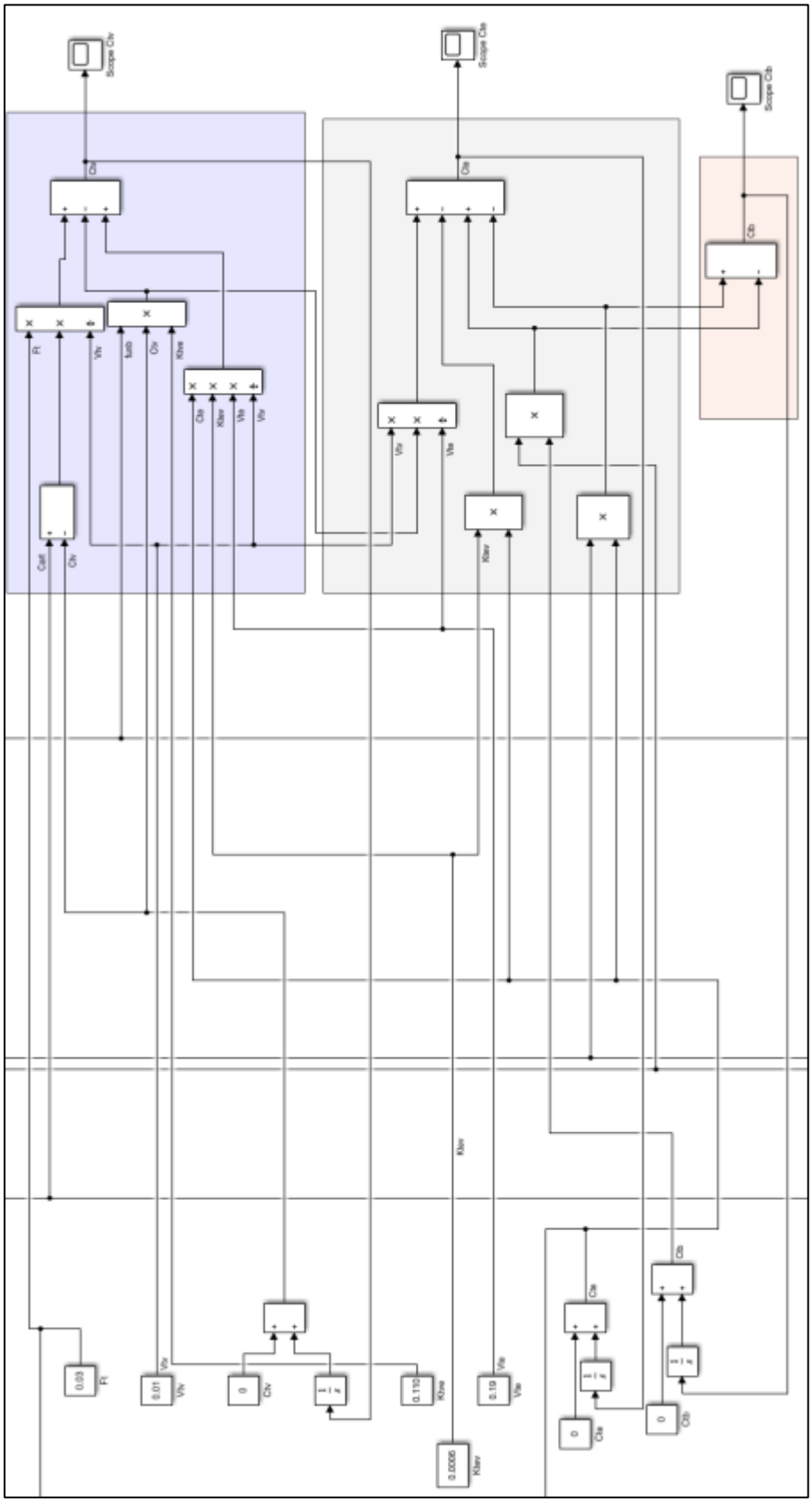


Fig. B.11 Simulink implementation of Tumor Compartment of PBPK Model

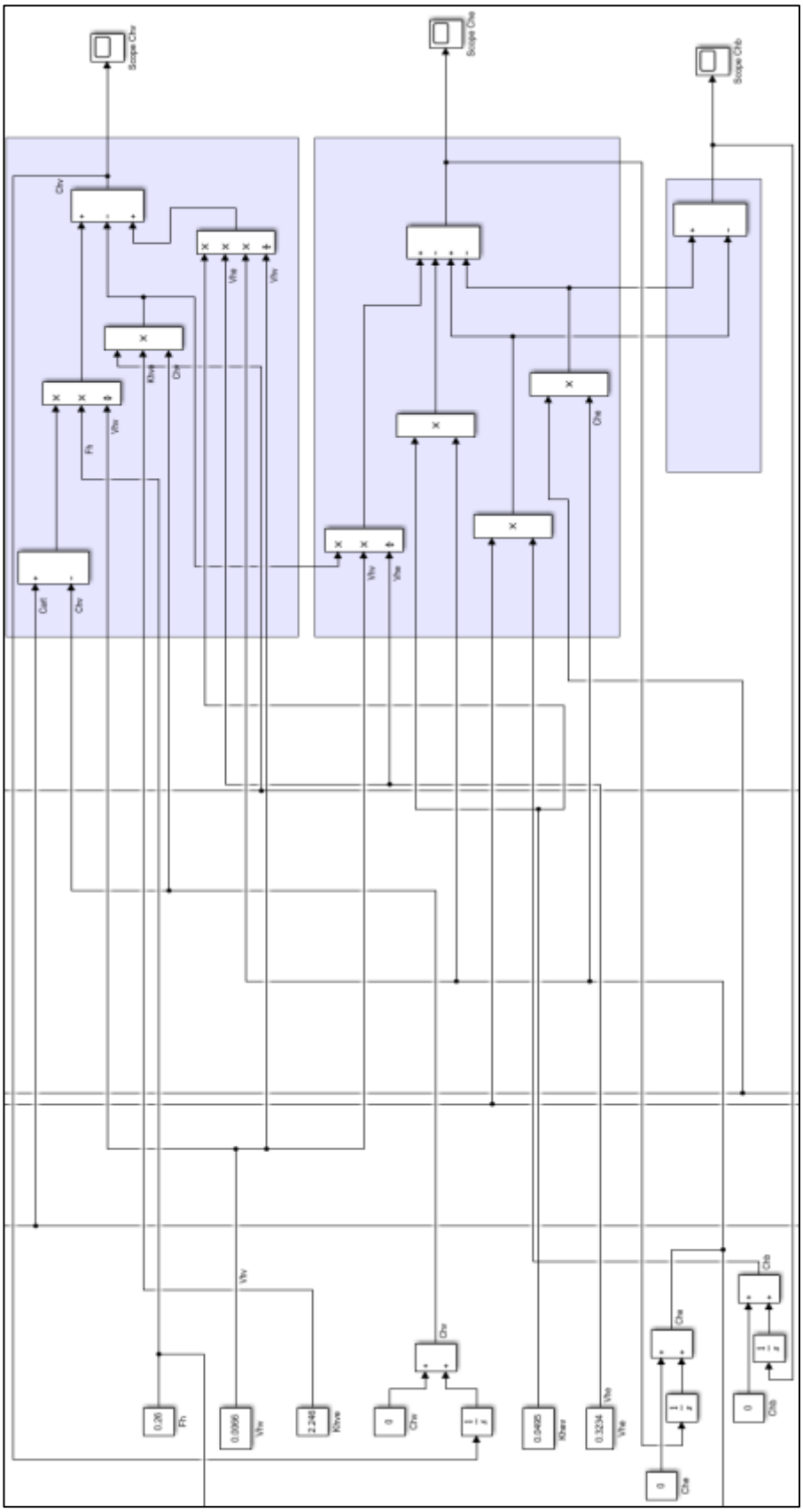


Fig. B.12 Simulink implementation of Heart Compartment of PBPK Model

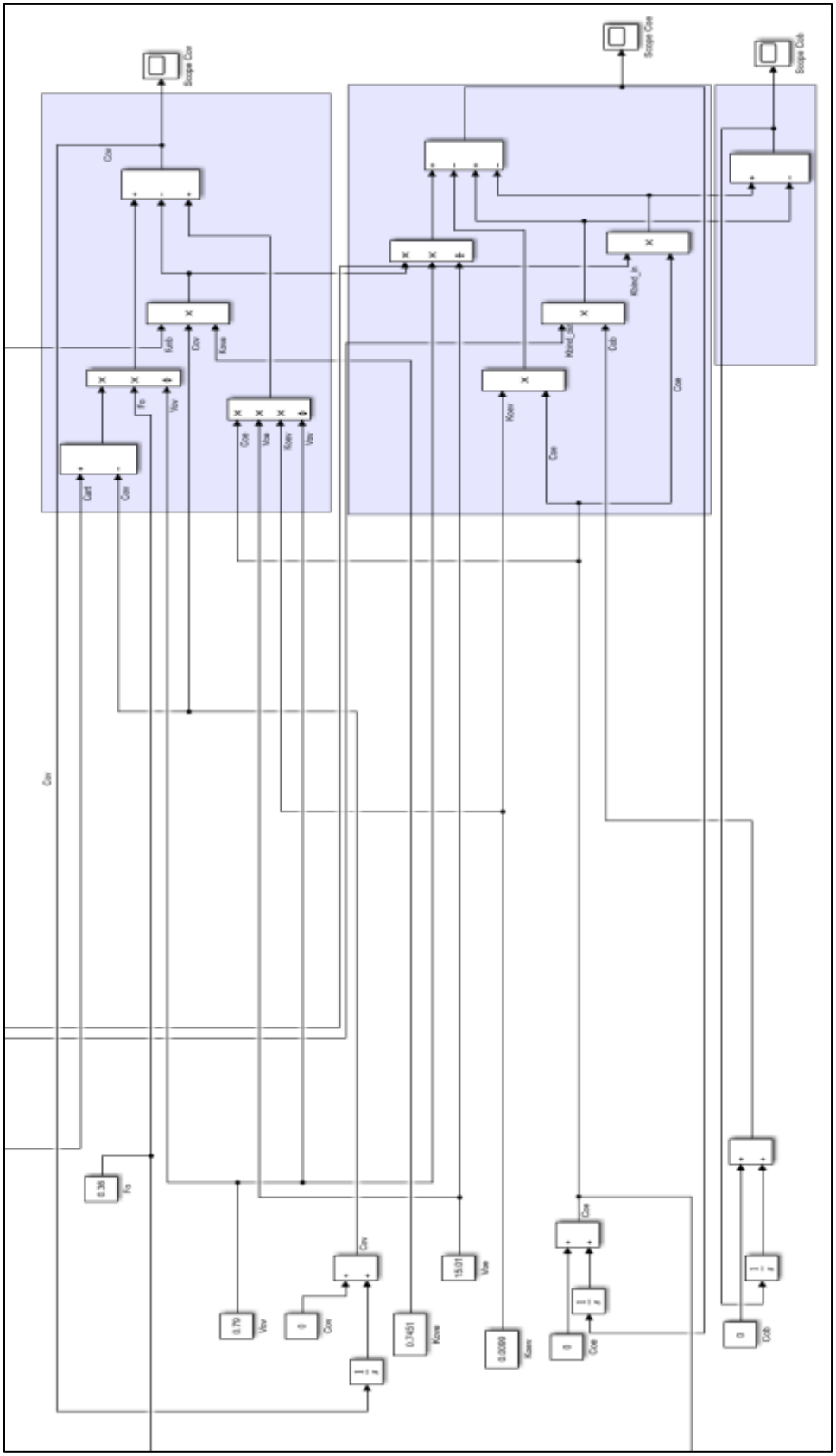


Fig. B.13 Simulink implementation of Other Compartment of PBPK Model

Appendix C

Feedback Controller:

```
def checkVenousBlood(C_ven, C_rbcv, max_dose):

    total = []
    for i in range(0, 48):
        total.append(C_ven[i] + C_rbcv[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkLung(C_lv, C_le, C_lb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_lv[i] + C_le[i] + C_lb[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkArterialBlood(C_art, C_rbca, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_art[i] + C_rbca[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkGut(C_gv, max_dose):
    if max(C_gv) > max_dose:
        return True
    else:
        return False

def checkBrain(C_bv, C_be, C_bb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_bv[i] + C_be[i] + C_bb[i])
```

```
    if max(total) > max_dose:
        return True
    else:
        return False

def checkSpleen(C_sv, C_se, C_sb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_sv[i] + C_se[i] + C_sb[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkLiver(C_liv, C_lie, C_lib, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_liv[i] + C_lie[i] + C_lib[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkHeart(C_hv, C_he, C_hb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_hv[i] + C_he[i] + C_hb[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkKidney(C_kv, C_ke, C_kb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_kv[i] + C_ke[i] + C_kb[i])

    if max(total) > max_dose:
        return True
    else:
        return False
```

```
def checkMuscle(C_mv, C_me, C_mb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_mv[i] + C_me[i] + C_mb[i])

    print("Max: ", max(total), "Max Dose: ", max_dose)

    if max(total) > max_dose:
        return True
    else:
        return False

def checkFat(C_fv, C_fe, C_fb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_fv[i] + C_fe[i] + C_fb[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkTumor(C_tv, C_te, C_tb, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_tv[i] + C_te[i] + C_tb[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def checkOther(C_ov, C_oe, C_ob, max_dose):
    total = []
    for i in range(0, 48):
        total.append(C_ov[i] + C_oe[i] + C_ob[i])

    if max(total) > max_dose:
        return True
    else:
        return False

def check(dose, max_dose):
    venBloodOverDose = checkVenousBlood(dose.y[0], dose.y[1],
max_dose[0])
```

```
    lungOverDose = checkLung(dose.y[2], dose.y[3], dose.y[4],
max_dose[1])
    artBloodOverDose = checkArterialBlood(dose.y[5], dose.y[6],
max_dose[2])
    gutOverDose = checkGut(dose.y[7], max_dose[3])
    brainOverDose = checkBrain(dose.y[8], dose.y[9], dose.y[10],
max_dose[4])
    spleenOverDose = checkSpleen(dose.y[11], dose.y[12], dose.y[13],
max_dose[5])
    liverOverDose = checkLiver(dose.y[14], dose.y[15], dose.y[16],
max_dose[6])
    heartOverDose = checkHeart(dose.y[17], dose.y[18], dose.y[19],
max_dose[7])
    kidneyOverDose = checkKidney(dose.y[20], dose.y[21], dose.y[22],
max_dose[8])
    muscleOverDose = checkMuscle(dose.y[23], dose.y[24], dose.y[25],
max_dose[9])
    fatOverDose = checkFat(dose.y[26], dose.y[27], dose.y[28],
max_dose[10])
    tumorOverDose = checkTumor(dose.y[29], dose.y[30], dose.y[31],
max_dose[11])
    otherOverDose = checkOther(dose.y[32], dose.y[33], dose.y[34],
max_dose[12])


    if venBloodOverDose == True or lungOverDose == True or
artBloodOverDose == True or gutOverDose == True or brainOverDose ==
True or spleenOverDose == True or liverOverDose == True or
heartOverDose == True or kidneyOverDose == True or muscleOverDose ==
True or fatOverDose == True or tumorOverDose == True or otherOverDose
== True:
        return True
    else:
        return False
```

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