공학석사 학위논문

A Bayesian Approach to Robust Parameter Estimation of Physiologically Based Pharmacokinetics Model with Drug Dissolution Model

약물 용해 모델이 포함된 생리학적 약동학 모델의 베이즈 접근을 통한 강건한 변수 추정

2014년 1월

서울대학교 대학원
화학생물공학부
김대식

A Bayesian Approach to Robust Parameter Estimation of Physiologically Based Pharmacokinetics Model with Drug Dissolution Model

지도교수 이종민

이 논문을 공학석사 학위논문으로 제출함

2014년 1월

서울대학교 대학원

화학생물공학부

김대식

김대식의 석사 학위논문을 인준함

2014년 1월

위 원 장 김 병 기 (인)

부위원장 이 종 민 (인)

위 원 황 석 연 (인)

Abstract

A Bayesian Approach to Robust Parameter Estimation of Physiologically Based Pharmacokinetics Model with Drug Dissolution Model

Dae Shik Kim
Chemical and Biological Engineering
The Graduate School
Seoul National University

Physiologically based pharmacokinetics (PBPK) model can predict absorption, degradation, execration and metabolism in drug delivery system. Thus, it can be useful for regulating dose and estimating drug concentration at a particular time during the clinical demonstration. While PBPK model is generally expressed as a set of ordinary differential equations with a large number of parameters, in-vivo experimental data are often noisy and sparse. This makes it difficult to estimate parameters with conventional least squares approaches. Therefore, maximum a posteriori method from Bayesian approach that is the robust parameter estimation technique can be used to estimate parameters of PBPK model. However, the scheme of maximum a posteriori method by using Markov Chain Monte Carlo sampling is hard to use for parameter estimation of PBPK model because of the

large number of parameters. This work introduces the Bayesian approach estimation method for parameter estimation of PBPK model. In addition, a scheme of maximum a posteriori method is proposed to find maximum of the posterior distribution without using Markov Chain Monte Carlo sampling.

To regulate the concentration of drug and prevent side effect, the studies of drug dosage form are developed. However, since PBPK models and drug dissolution models are studied independently, there is no consideration of the drug dissolution dynamics in PBPK model. Therefore, accurate description of oral administrated drug delivery system requires an improved PBPK model. This work proposes a PBPK model that can describe orally administrated drug dissolution model by combining the drug dissolution model and PBPK model.

This thesis simulates parameter estimation of PBPK model to compare the performance of least squares method and maximum a posteriori method. In addition, the case study for Tegafur delivery system is conducted with in-vivo data and drug dissolution model included PBPK model to predict concentration profile of Tegafur, and to evaluate the proposed PBPK model.

Keywords: Bayesian approach, Parameter estimation, PBPK model, Pharmacokinetics, Drug delivery system, Maximum a posteriori
Student Number: 2012-20933

Contents

List of Figures

List of Tables

Chapter 1

Introduction

The drug discovery process and clinical demonstration take an enormous amount of time, money, and effort. Nevertheless, to prevent side effect of drug and to find optimal dosage, a large number of demonstrations is conducted to various subjects. Especially, the repetitive experiments of new drug have a great risk in human trial phase because the informations of toxicity and side-effect of the new drug are unknown. Mathematical models describing drug delivery mechanism in terms of drug concentrations in each organ over the time course can be of significant help in reducing the cost of development and risk of failure. Therefore, time-course data are collected to construct physiologically based pharmacokinetics (PBPK) models during animal and human trials (Phases I-III) [1]. Pharmacokinetics is the study of absorption, distribution, metabolism, and excretion of chemicals in a living body and plays an important role in the development of drugs [2]. The PBPK model combines pharmacokinetic dynamics in organs involved drug delivery pathway to describe drug delivery system of a biological entity [3]. If a PBPK model is constructed, not only can we use it for prediction of dynamics of drug delivery but can also apply it to dose regulation as in feedback control strategies [1]. Therefore, the PBPK model can also help to decide

optimal dosage and administration time [4].

Because PBPK models are only observing dynamics inside body, they commonly consist of a number of organs and blood vessel and have no consideration of drug dissolution dynamics. In the past, most of medicines contain serious side effects or dosage sensitivity were usually in the form of liquid because they need to be activated quickly [5]. Therefore, since the drug is absorbed with high absorption rate or injected directly, drug dissolution dynamics can be ignored. However, with the recent development of various drug dosage forms, particular medicines are produced in the form of tablet or capsule to control dissolution rate [6, 7]. Since the dissolution dynamics of non-liquid dosage form of medicine can be an important part of drug delivery system, a model describing dissolution dynamics is also necessary to set up the PBPK model for that kind of drug. Nevertheless, the studies for PBPK model and drug dissolution model are developed independently. Therefore, a model that combines PBPK and drug dissolution dynamics is necessary to describe the dynamics of non-liquid dosage form and perform the accurate prediction of concentration.

Various parameters exist in PBPK model, physical parameters and kinetic parameters. Physical parameters are related physical properties of individual such as organ volume, blood flow rate, blood volume. Kinetic parameters are related pharmacokinetics dynamics, such as absorption rate constant, Michaelis-Menten constant. Although values of physical parameters can be measured easily, values of kinetic parameters are hard to know [8]. Therefore, to construct PBPK model, unknown parameters should be estimated with experimental

data. However, experiments to collect in-vivo data are expensive and often have poor repeatability [9]. Estimating parameters of a PBPK model with such data set is further complicated by the concentration profiles showing a pattern of declining exponential functions, with amplitudes and decay times [10]. In addition, since each individual may have different parameter values depending on its own physical and properties, its concentration profile of drug can be different. Therefore, the values of parameter are distributed, they should be estimated by stochastic method. The widely used estimation method, least squares method, estimates parameters by minimizing squares error between data and measurements. Since there is no probabilistic structure in least squares method, if the data are collected from unusual case, the estimation result can not describe general concentration profile. Moreover, since it is hard to collect a large number of in-vivo data, the estimation accuracy of least squares method is decreased [11]. Therefore, robust estimation method is necessary for parameter estimation of PBPK model.

This study presents a Bayesian approach scheme for robust parameter estimation of PBPK model to address the difficulties, and demonstrates its advantages over the least squares method. In addition, this work introduces a drug dissolution model to describe dissolution dynamics of non-liquid dosage form, and combines the dissolution model and PBPK model for oral administrated drug delivery system to perform accurate concentration prediction. The proposed estimation scheme and improved PBPK model are illustrated on the Tegafur delivery system.

Chapter 2

Background

2.1 Physiologically Based Pharmacokinetics Model

The mathematical model based on physiological reaction describes pharmacokinetics in the body is called PBPK model [12]. When the medicine is taken into the body, it is dissolved and absorbed into the blood vessel. In a particular organ, it can be degraded or transformed to a new structure by enzymes. It is also cleared out from the body during the circulation of the blood. Those dynamics occurring inside the body generate medicinal effects to the target place. However, if concentration of the medicine in a certain organ exceeds a threshold value, it can cause serious side-effects. In addition, if the concentration cannot reach a particular value, the medicine can not work effectively. Therefore, the optimum dosage should be determined to control the concentration inside the body.

PBPK models involve two kinds of differential equations. The first describes the transportation and metabolism of the medicine based on mass balance.

$$V \cdot \frac{dC}{dt} = Q \cdot (C_{in} - \frac{C}{P}) - R_e \tag{2.1}$$

where V is the organ volume, Q is the volumetric flow rate of blood in the organ, C_{in} is drug concentration into the organ and C is drug concentration in the the organ. P is the tissue/blood partition coefficient of organ that describes the proportion of blood volume in the organ. R_e is the consumption term due to the metabolism in the organ such as degradation, transformation and excretion. Since a drug is transformed by a certain enzyme, transformation metabolism can be described with Michaelis-Menten equation [13]. Michaelis-Menten equation is the mathematical model of enzyme kinetics [14].

$$v = \frac{V_{max} \cdot C}{K_m + C} \tag{2.2}$$

where v is the reaction rate of the enzyme, V_{max} is a kinetic parameter that represents maximum reaction rate, K_m is Michaelis-Menten constant that represents concentration of substrate when the reaction rate is $\frac{V_{max}}{2}$ and C is the substrate concentration. Another metabolism, clearance effect, is the rate of elimination to drug concentration in the blood vessel [15]. Clearance effect can be described as below.

$$v_{cl} = CL \cdot C \tag{2.3}$$

where v_{cl} is the rate of elimination, CL is the kinetic parameter of clearance effect and C is the drug concentration. The consumption term, R_e, can be expressed with these two equations.

The second describes absorption of medicine to the capillary blood vessel. The drug is absorbed into the organ from the capillary blood vessel and circulates the body. This absorption dynamics can

be described as

$$\frac{dC}{dt} = \begin{cases} 0 & C = 0, \\ k_{abs} \cdot C & C > 0. \end{cases} \tag{2.4}$$

where k_{abs} is the absorption rate of the medicine into the organ from the capillary blood vessel. If there are particular organs playing an important role in the metabolisms, we can set up a dynamic model like (2.1) and (2.4) for each organ. The other organs can be neglect or are considered a combined organ. The concentration of drug at each time can be predicted by solving the set of differential equations.

2.2 Drug Dissolution Model

Noyes-Whitney equation is traditionally used for drug dissolution modelling [16]. Although this model equation is simple, it can describe drug dissolution dynamics well. The equation assumes that there are a diffusion layer with between the surface of drug and the bulk solution whose drug concentration is uniformly distributed as shown in Figure 1.

The driving force of the mass transfer is the concentration gradient between the solid surface and bulk phase. For simplification, 1-D mass transfer is assumed, and the resulting Noyes-Whitney equation takes the following form [17].

$$\frac{dW}{dt} = \frac{D \cdot A \cdot (C_s - C_b)}{L} \tag{2.5}$$

where W is the mass of drug, D is the diffusion coefficient, A is the surface area of the drug, L is the diffusion layer thickness, C_s is the

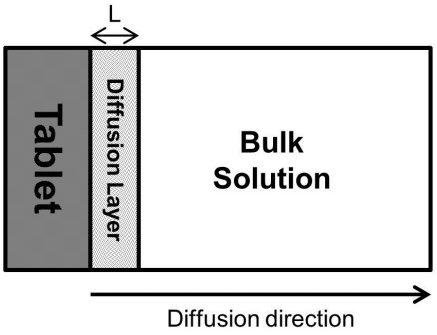

Figure 1: The first order drug dissolution model for drug delivery system.

concentration of the boundary, and C_b is the concentration of bulk solution.

2.3 Least Squares Method

Least squares method is an estimation technique to find the parameters that minimize the sum of squared difference between given data and measurements [18]. This method is introduced by Gauss to study planetary motions [19].

$$S = \sum_{i=1}^{n} {r_i}^2 \tag{2.6}$$

where i is the number of data points and r is residual between estimation result and data point. If an model function has a parameter a and b, the residual can be described below.

$$r_i = y_i - f(x_i, a, b) \tag{2.7}$$

where y_i is the ith data point and $f(x_i, a, b)$ is the ith model output. The estimated values of a and b minimize the sum of squares error, S.

The advantage of least squares method is the broad range of application because of its simplicity [18]. However, there are no claims about optimality and the statistical performance can not be assessed about the probabilistic structure of the data [11].

2.4 Bayesian Estimation Methods

Bayes' rule is the equation about conditional probability of event θ for given X [20]. Bayes' rule can be described as (2.8).

$$P(\theta|X) = \frac{P(\theta) \cdot P(X|\theta)}{\int P(\theta) \cdot P(X|\theta) d\theta} \tag{2.8}$$

$P(\theta)$ is called 'Prior distribution' describing the probability of θ, $P(X|\theta)$ is called 'Likelihood function' describing the conditional probability of X for given θ and $P(\theta|X)$ is called 'Posterior distribution' describing the conditional probability of θ for given X. The denominator term is constant called 'Normalizing factor' which adjust the maximum value of posterior probability that is equal to 1 [21]. In parameter estimation problem, since θ is the vector of parameters and X is the given data, the posterior distribution describes the conditional probability of parameters for given data. Therefore, the parameter vector that has maximum value of posterior distribution is the optimal parameter set of the objective model.

2.4.1 Maximum Likelihood Method

The maximum likelihood estimation (MLE) method is to find parameters that maximize the likelihood function, $P(X|\theta)$. In MLE method, there is no consideration about probabilistic structure of parameters, only consideration about probabilistic structure of data. Since the prior distribution $P(\theta)$ and the normalizing factor have constant value, $P(\theta|X)$ is maximized by maximizing the likelihood function.

$$\hat{\theta}_{mle} = arg \max_{\theta} P(X|\theta) \tag{2.9}$$

Therefore, if there is no information about the parameters or the parameters have deterministic values, MLE method can be used [11].

2.4.2 Maximum a Posteriori Method

When the parameters have probabilistic structure, $P(\theta|X)$ is maximized by the product of likelihood function and prior distribution because the normalizing factor is constant. The estimation method by maximizing the product of likelihood and prior distribution is called 'Maximum a posteriori' (MAP) method.

$$\hat{\theta}_{map} = arg \max_{\theta} P(\theta) \cdot P(X|\theta) \tag{2.10}$$

Because the prior knowledge is incorporated into the estimation, MAP method is the more robust estimation method than least squares and MLE method [22, 23]. Therefore, MAP method can perform more accurate estimation when the data have serious noise [11].

Chapter 3

Drug Dissolution Included PBPK Model for Tegafur Delivery System

Tegafur is widely used in the treatment of a range of cancers, especially of colorectal cancer[24]. Tegafur is the oral administrated drug and transform to 5-fluorouracil by CYP450 enzyme in liver, thereby it can perform pharmacological action[25]. To set up the PBPK model for Tegafur drug delivery system, human body is split into each organ part. The most important parts of the body from the viewpoint of the drug delivery are liver and tumor where transformation from Tegafur to 5-fluorouracil occurs. In addition, oral administrated Tegafur is dissolve in the body and absorbed from lumen to gut. Drug is delivered by blood and also cleared out at blood. The other organs are combined into well perfused organ and poorly perfused organ. Therefore, the PBPK model can be constructed as in Figure 2 [26].

The Tegafur PBPK model consists of phamracokinetic model in each organ. The Pharmacokinetic models in the organs from Figure 2 are (3.1) $\sim$ (3.13). The transformation and degradation by enzymes, CYP450 and DPD, are described with Michaelis-Menten equation. The notations are in Table 1 $\sim$ 3. The kinetic parameters, that is un-

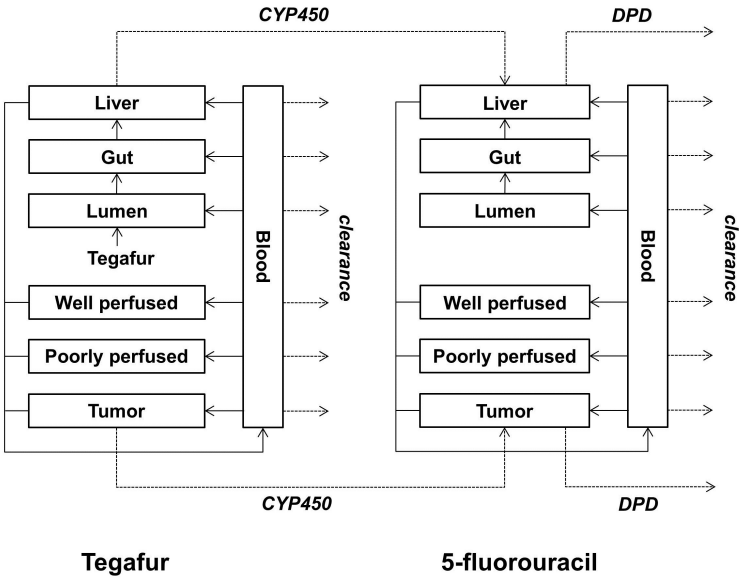

Figure 2: The PBPK model for Tegafur delivery system

known parameters, are in Table 1 and the physical parameters are in Table 2 and 3.

$$V_{lmn} \cdot \frac{dC_{lmn}}{dt} = -k_{abs} \cdot C_{lmn} \cdot V_{lmn} \tag{3.1}$$

$$V_g \cdot \frac{dC_{g,T}}{dt} = k_{abs} \cdot V_{lmn} \cdot C_{lmn} + Q_g \cdot C_{b,T} - Q_g \cdot \frac{C_{g,T}}{P_{g,T}} \tag{3.2}$$

$$V_l \cdot \frac{dC_{l,T}}{dt} = (Q_l - Q_g) \cdot C_{b,T} - Q_l \cdot \frac{C_{l,T}}{P_{l,T}} - \frac{V_{ml,T} \cdot C_{l,T} \cdot V_l}{K_{ml,T} \cdot C_{l,T}} \tag{3.3}$$

$$V_t \cdot \frac{dC_{t,T}}{dt} = Q_t \cdot C_{b,T} - Q_t \cdot \frac{C_{t,T}}{P_{t,T}} - \frac{V_{mt,T} \cdot C_{t,T} \cdot V_t}{K_{mt,T} \cdot C_{t,T}} \tag{3.4}$$

$$V_w \cdot \frac{dC_{w,T}}{dt} = Q_w \cdot C_{b,T} - Q_w \cdot \frac{C_{w,T}}{P_{w,T}} \tag{3.5}$$

$$V_p \cdot \frac{dC_{p,T}}{dt} = Q_p \cdot C_{b,T} - Q_p \cdot \frac{C_{p,T}}{P_{p,T}} \tag{3.6}$$

$$\begin{aligned} V_b \cdot \frac{dC_{b,T}}{dt} &= Q_l \cdot \frac{C_{l,T}}{P_{l,T}} + Q_t \cdot \frac{C_{t,T}}{P_{t,T}} + Q_w \cdot \frac{C_{w,T}}{P_{w,T}} \\ &+ Q_p \cdot \frac{C_{p,T}}{P_{p,T}} - Q_b \cdot C_{b,T} - CL_T \cdot C_{b,T} \end{aligned} \tag{3.7}$$

$$V_g \cdot \frac{dC_{g,FU}}{dt} = Q_g \cdot C_{b,FU} - Q_g \cdot \frac{C_{g,FU}}{P_{g,FU}} \tag{3.8}$$

$$\begin{aligned} V_l \cdot \frac{dC_{l,FU}}{dt} &= (Q_l - Q_g) \cdot C_{b,FU} - Q_l \cdot \frac{C_{l,FU}}{P_{l,FU}} \\ &+ \frac{V_{ml,T} \cdot C_{l,T} \cdot V_l}{K_{ml,T} \cdot C_{l,T}} - \frac{V_{ml,FU} \cdot C_{l,FU} \cdot V_l}{K_{ml,FU} \cdot C_{l,FU}} \end{aligned} \tag{3.9}$$

$$\begin{aligned} V_t \cdot \frac{dC_{t,FU}}{dt} &= Q_t \cdot C_{b,FU} - Q_t \cdot \frac{C_{t,FU}}{P_{t,FU}} \\ &+ \frac{V_{mt,T} \cdot C_{t,T} \cdot V_t}{K_{mt,T} \cdot C_{t,T}} - \frac{V_{mt,FU} \cdot C_{t,FU} \cdot V_t}{K_{mt,FU} \cdot C_{t,FU}} \end{aligned} \tag{3.10}$$

$$V_w \cdot \frac{dC_{w,FU}}{dt} = Q_w \cdot C_{b,FU} - Q_w \cdot \frac{C_{w,FU}}{P_{w,FU}} \tag{3.11}$$

$$V_p \cdot \frac{dC_{p,FU}}{dt} = Q_p \cdot C_{b,FU} - Q_p \cdot \frac{C_{p,FU}}{P_{p,FU}} \tag{3.12}$$

$$\begin{aligned} V_b \cdot \frac{dC_{b,FU}}{dt} &= Q_l \cdot \frac{C_{l,FU}}{P_{l,FU}} + Q_t \cdot \frac{C_{t,FU}}{P_{t,FU}} + Q_w \cdot \frac{C_{w,FU}}{P_{w,FU}} \\ &+ Q_p \cdot \frac{C_{p,FU}}{P_{p,FU}} - Q_b \cdot C_{b,FU} - CL_{FU} \cdot C_{b,FU} \end{aligned} \tag{3.13}$$

Table 1: Notations of unknown parameters

Parameter	Description
$K_{ml,T}(nmol/min/g$ tissue)	V_{max} for CYP450 enzyme in liver
$V_{ml,T}(nmol/ml)$	Michaelis-Menten constant for CYP450 enzyme in liver
$K_{mt,T}(nmol/min/gtissue)$	V_{max} for CYP450 enzyme in tumor
$V_{mt,T}(nmol/ml)$	Michaelis Menten-constant for CYP450 enzyme in tumor
$K_{ml,FU}(nmol/min/gtissue)$	V_{max} for DPD enzyme in liver
$V_{ml,FU}(nmol/ml)$	Michaelis-Menten constant for DPD enzyme in liver
$K_{mt,FU}(nmol/min/gtissue)$	V_{max} for DPD enzyme in liver
$V_{mt,FU}(nmol/ml)$	Michaelis Menten-constant for DPD enzyme in tumor
$k_{abs}(min^{-1})$	Absorption coefficient of Tegafur
$K(min^{-1})$	Dissolution coefficient of Tegafur
$CL_T(ml/min)$	Clearance rate of Tegafur from plasma
$CL_{FU}(ml/min)$	Clearance rate of 5-flourouracil from plasma

The Tegafur PBPK model, however, has no consideration of the drug dissolution dynamics. Since Tegafur is oral administration drug, the drug dissolution dynamics can effect the drug delivery system. The drug dissolution model for PBPK model can be derived from

Table 2: Notations about organ volume and blood flow rate

Organ	Organ volume(ml)	Blood flow rate(ml/min)
Blood	V_b	Q_b
Gut	V_g	Q_g
Liver	V_l	Q_l
Tumor	V_t	Q_t
Well perfused organs	V_w	Q_w
Poorly perfused organs	V_p	Q_p

Table 3: Notations about tissue/blood partition coefficient

Organ	Tegafur(T)	5-fluorouacil(FU)
Blood	$P_{b,T}$	$P_{b,FU}$
Gut	$P_{g,T}$	$P_{g,FU}$
Liver	$P_{l,T}$	$P_{l,FU}$
Tumor	$P_{t,T}$	$P_{t,FU}$
Well perfused organs	$P_{w,T}$	$P_{w,FU}$
Poorly perfused organs	$P_{p,T}$	$P_{p,FU}$

(2.5). Since W of (2.5) is

$$W = C_s \cdot V \cdot M_w \tag{3.14}$$

where V is the volume of drug and M_w is molecular weight of the drug. Since V and C_s are the functions of time, the derivative of W is

$$\frac{dW}{dt} = M_w \cdot V \cdot \frac{dC_s}{dt} + C_s \cdot M_w \cdot \frac{dV}{dt} \tag{3.15}$$

Because the volume of drug is much smaller than the organ, the volume change of drug can be negligible. Therefore (2.5) can be written as

$$\begin{aligned}\frac{dC_s}{dt} &= \frac{D \cdot A}{M_w \cdot V \cdot L}(C_s - C_b) \\ &= K \cdot (C_s - C_b)\end{aligned} \tag{3.16}$$

where K is the dissolution parameter equals to $\frac{D \cdot A}{M_w \cdot V \cdot L}$. Using (3.16), The drug dissolution model (DDM) included PBPK model can be constructed as Figure 3, and each pharmacokinetic models are (3.17) $\sim$ (3.30). The notations are also in Table 1 $\sim$ 3.

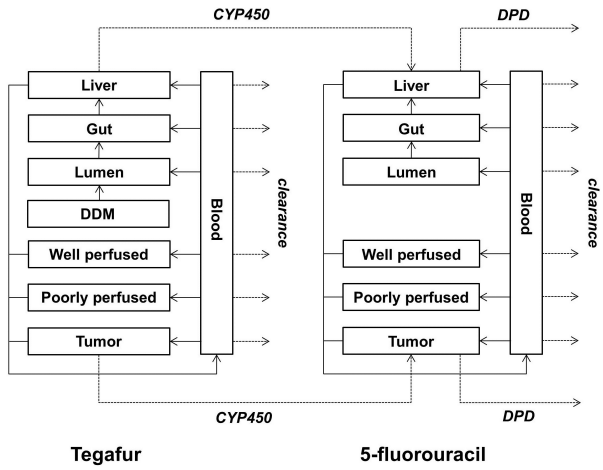

Figure 3: The DDM included PBPK model for Tegafur delivery system

$$\frac{dC_{tab}}{dt} = -K \cdot (C_{tab} - C_{lmn}) \tag{3.17}$$

$$\frac{dC_{lmn}}{dt} = K \cdot (C_{tab} - C_{lmn}) - k_{abs} \cdot C_{lmn} \cdot V_{lmn} \tag{3.18}$$

$$V_g \cdot \frac{dC_{g,T}}{dt} = k_{abs} \cdot V_{lmn} \cdot C_{lmn} + Q_g \cdot C_{b,T} - Q_g \cdot \frac{C_{g,T}}{P_{g,T}} \tag{3.19}$$

$$V_l \cdot \frac{dC_{l,T}}{dt} = (Q_l - Q_g) \cdot C_{b,T} - Q_l \cdot \frac{C_{l,T}}{P_{l,T}} - \frac{V_{ml,T} \cdot C_{l,T} \cdot V_l}{K_{ml,T} \cdot C_{l,T}} \tag{3.20}$$

$$V_t \cdot \frac{dC_{t,T}}{dt} = Q_t \cdot C_{b,T} - Q_t \cdot \frac{C_{t,T}}{P_{t,T}} - \frac{V_{mt,T} \cdot C_{t,T} \cdot V_t}{K_{mt,T} \cdot C_{t,T}} \tag{3.21}$$

$$V_w \cdot \frac{dC_{w,T}}{dt} = Q_w \cdot C_{b,T} - Q_w \cdot \frac{C_{w,T}}{P_{w,T}} \tag{3.22}$$

$$V_p \cdot \frac{dC_{p,T}}{dt} = Q_p \cdot C_{b,T} - Q_p \cdot \frac{C_{p,T}}{P_{p,T}} \tag{3.23}$$

$$\begin{aligned} V_b \cdot \frac{dC_{b,T}}{dt} &= Q_l \cdot \frac{C_{l,T}}{P_{l,T}} + Q_t \cdot \frac{C_{t,T}}{P_{t,T}} + Q_w \cdot \frac{C_{w,T}}{P_{w,T}} \\ &\quad + Q_p \cdot \frac{C_{p,T}}{P_{p,T}} - Q_b \cdot C_{b,T} - CL_T \cdot C_{b,T} \end{aligned} \tag{3.24}$$

$$V_g \cdot \frac{dC_{g,FU}}{dt} = Q_g \cdot C_{b,FU} - Q_g \cdot \frac{C_{g,FU}}{P_{g,FU}} \tag{3.25}$$

$$V_l \cdot \frac{dC_{l,FU}}{dt} = (Q_l - Q_g) \cdot C_{b,FU} - Q_l \cdot \frac{C_{l,FU}}{P_{l,FU}} + \frac{V_{ml,T} \cdot C_{l,T} \cdot V_l}{K_{ml,T} \cdot C_{l,T}} - \frac{V_{ml,FU} \cdot C_{l,FU} \cdot V_l}{K_{ml,FU} \cdot C_{l,FU}} \tag{3.26}$$

$$V_t \cdot \frac{dC_{t,FU}}{dt} = Q_t \cdot C_{b,FU} - Q_t \cdot \frac{C_{t,FU}}{P_{t,FU}} + \frac{V_{mt,T} \cdot C_{t,T} \cdot V_t}{K_{mt,T} \cdot C_{t,T}} - \frac{V_{mt,FU} \cdot C_{t,FU} \cdot V_t}{K_{mt,FU} \cdot C_{t,FU}} \tag{3.27}$$

$$V_w \cdot \frac{dC_{w,FU}}{dt} = Q_w \cdot C_{b,FU} - Q_w \cdot \frac{C_{w,FU}}{P_{w,FU}} \tag{3.28}$$

$$V_p \cdot \frac{dC_{p,FU}}{dt} = Q_p \cdot C_{b,FU} - Q_p \cdot \frac{C_{p,FU}}{P_{p,FU}} \tag{3.29}$$

$$V_b \cdot \frac{dC_{b,FU}}{dt} = Q_l \cdot \frac{C_{l,FU}}{P_{l,FU}} + Q_t \cdot \frac{C_{t,FU}}{P_{t,FU}} + Q_w \cdot \frac{C_{w,FU}}{P_{w,FU}} + Q_p \cdot \frac{C_{p,FU}}{P_{p,FU}} - Q_b \cdot C_{b,FU} - CL_{FU} \cdot C_{b,FU} \tag{3.30}$$

Chapter 4

Parameters Estimation Method for PBPK Model

4.1 Parameter Estimation Schemes of Least Squares, MLE, and MAP Method

PBPK model includes various parameters, and the number of differential equations is equal to the number of organs. If there is a PBPK model consists n differential equations with m parameters and q measurements in l organs, the PBPK model can be described as below.

$$\frac{dC_i}{dt} = f_i\left[C(t),\ P,\ \omega(t)\right] \tag{4.1}$$

$$y(t) = g\left[C(t)\right] + \nu(t) \tag{4.2}$$

In (4.1) and (4.2), $C(t) \in \mathbb{R}^{n\times 1}$ is the vector of the concentrations of drug contains $C_1(t), C_2(t), \cdots, C_n(t)$. $P \in \mathbb{R}^{m\times 1}$ is the vector of unknown parameters, $y(t) \in \mathbb{R}^{l\times 1}$ is the vector of measurements contains $y_1(t), y_2(t), \cdots, y_l(t)$. $\omega(t) \in \mathbb{R}^{n\times 1}$ is the noise vector describing model mismatch and $\nu(t) \in \mathbb{R}^{l\times 1}$ is the measurement noise

vector.

To predict the concentration profile of the drug, the parameter estimation with experiment data is needed. Least squares method is easy to apply to the estimation problem of PBPK model because of its simplicity. However, Bayesian estimation methods, especially MAP method, is hard to apply since the posterior distribution, described as the product of probability density functions, is complicated. Because it is hard to know about the posterior distribution, Markov Chain Monte Carlo (MCMC) sampling method can be used to find the maximum value [27]. The posterior distribution calculated from sampling method is described as joint distributions of all parameters. From the joint distributions, the parameter that maximize the posterior distribution can be found. However, since there are 11 or 12 parameters in the PBPK model for Tegafur delivery system, 55 or 66 joint distributions are generated. Therefore, it is impossible to find the parameters from the joint distributions. This study proposes a objective function based parameter estimation scheme for MAP method for PBPK model that has a large number of parameters.

4.1.1 Least Squares Method

Least squares method is to find parameters minimizing the sum of squares error. The objective function of least squares method is (4.3) which depends on the given data set and parameters.

$$J_{lse}[\hat{y}(t),\theta] = \sum_{k=1}^{l} [y_k(t) - \hat{y}_k(t)]^T \cdot [y_k(t) - \hat{y}_k(t)] \qquad (4.3)$$

where the $y_k(t) \in \mathbb{R}^{q\times 1}$ is the measurements in kth organ, $\hat{y}_k(t) \in \mathbb{R}^{q\times 1}$ is the data points in kth organ and θ is the parameters in PBPK model. When the experimental data is given, the parameter set $\hat{\theta}$, which minimizes objective function $J_{lse}[\hat{y}(t), \theta]$, is the estimation result of least squares method.

$$\hat{\theta}_{lse} = arg \min_{\theta} J_{lse}[\hat{y}(t), \theta] \tag{4.4}$$

Since there are 11 or 12 parameters in PBPK model for Tegafur delivery system and differential equations need to be solved to estimate the parameters, the minimum of objective function can be found by heuristic optimization tool, genetic algorithm.

4.1.2 MLE Method

From (4.2), $g[C(t)]$ is the unknown concentration vector and $y(t)$ is the vector of measurements. The difference between $g[C(t)]$ and $y(t)$ is measurements noise from sensors. Because the unbiased sensor noise can be assumed to follow a normal distribution, the likelihood function can be described as below.

$$p[\hat{y};\ \theta] = \prod_{k=1}^{l} \frac{1}{\sqrt{2\pi \cdot det(\Sigma)}} \cdot e^{-\frac{1}{2}\cdot[y_k(t)-\hat{y}_k(t)]^T \cdot \Sigma^{-1} \cdot [y_k(t)-\hat{y}_k(t)]} \tag{4.5}$$

where Σ is the q-by-q covariance matrix of $y_k(t) - \hat{y}_k(t)$. Since the concentrations in each organ are measured independently, the sensor noises are uncorrelated. Therefore, the off-diagonal entries of the co-

variance matrix are zero. In addition, because the measurements are from the same type of sensors, the diagonal entries of covariance matrix can be assumed as same value. To derive the objective function, minus logarithm is taken to the likelihood function.

$$\begin{aligned} J_{mle}[\hat{y}(t),\theta] &= \frac{l}{2}\ln(2\pi\sigma^2) + \frac{1}{2\sigma^2}\sum_{k=1}^{l}[y_k(t)-\hat{y}_k(t)]^T \cdot [y_k(t)-\hat{y}_k(t)] \\ &= \frac{n}{2}\ln(2\pi\sigma^2) + \frac{1}{2\sigma^2}\cdot J_{lse}[\hat{y}(t),\theta] \end{aligned} \tag{4.6}$$

where σ^2 is diagonal entries of the covariance matrix. From (4.6), The minimizing J_{mle} is the same as minimizing J_{lse}. Therefore, maximum likelihood estimator is equal to least squares estimator when the data noise follows the normal distribution. If there is a different distribution of data noise, the objective function of maximum likelihood method can be changed, also the estimation result from maximum likelihood method can be different.

4.1.3 MAP Method

For the estimation of the large number of parameters, finding maximum of the posterior distribution from the joint posterior distributions is impossible. However, since the objective of MAP method is finding the parameters maximizing the posterior distribution, the exact probability value of maximum point is unnecessary. Since the posterior distribution is proportional to the product of the prior distribution and likelihood function, and those equations can be derived,

this work proposed a scheme for the MAP method by deriving an objective function.

Because the likelihood function is derived in the previous section, the objective function from taking minus logarithm to the product of the prior distribution and likelihood function is

$$J_{map}[\hat{y}(t),\theta] = -\sum \ln P(\theta) + \frac{l}{2}\ln(2\pi\sigma^2) + \frac{1}{2\sigma^2}\sum_{k=1}^{l}[y_k(t)-\hat{y}_k(t)]^T \cdot [y_k(t)-\hat{y}_k(t)] \quad (4.7)$$

The estimated parameters can be found by minimizing the objective function. The genetic algorithm is used to find the parameters at minimum value of the objective function.

$$\hat{\theta}_{map} = arg \min_{\theta} J_{map}[\hat{y}(t),\theta] \quad (4.8)$$

The prior probability term, $-\sum \ln P(\theta)$, depends on how the prior distribution is defined. If there is a reliable deterministic parameter value from the literatures, the prior distribution can be defined as a normal distribution. If there is a certain probability distribution for prior term from the repetitive experimental results, the optimal parameter set minimizing objective function is calculated by numerical method. However, if there is no information about the model parameter, the bootstrap method can be used. The bootstrap method is to calculate unknown statistical knowledge of variables by the samples from the target variables [28, 29]. In this estimation problem, the sim-

ple bootstrap method by using samples from the result of least squares method with random data is used.

4.2 Comparison Between Least Squares Method and MAP Method

Least squares method and MAP method have different advantages. Since PBPK model has a number of parameters, the simplicity of least squares method can be strong advantage for this estimation problem. However, because the size of the experimental data is limited, the accuracy of least squares method can be poor. With this limited size data set, if we have information of parameter set, MAP method can perform better. To see how these two estimation techniques work in the estimation problem of PBPK model, the parameter estimation of PBPK model for Tegafur is conducted with arbitrary noisy data sets.

Table 4: The arbitrary values of the parameters

Parameter	Arbitrary value	Parameter	Arbitrary value
$K_{ml,T}$	2700 $nmol/min/gtissue$	$K_{mt,FU}$	2 $nmol/min/gtissue$
$V_{ml,T}$	997 $nmol/ml$	$V_{mt,FU}$	16.2 $\times 10$ $nmol/ml$
$K_{mt,T}$	40$nmol/min/gtissue$	k_{abs}	1.29$\times 10$ min^{-1}
$V_{mt,T}$	250.7 $nmol/ml$	k	128 min^{-1}
$K_{ml,FU}$	2700 $nmol/min/gtissue$	CL_T	1 ml/min
$V_{ml,FU}$	504 $nmol/ml$	CL_{FU}	0.1 ml/min

The arbitrary literature value of unknown parameters is shown

in Table 4. The values of physical parameters are arbitrarily given. the arbitrary data sets are assumed that they measured from gut, liver, tumor cell and blood vessel. 700 data sets are made which have $4 \sim 10$ data points of each organ and they have different mean squares error compared with the concentration profile in Table 4. The prior distributions of parameters are assumed as a normal distribution, and the mean of the each distribution has 10% error compared with the arbitrary literaturevalue. The PBPK model which includes DDM is used and the proposed schemes for least squares method and MAP method are used to compare which estimation method yields better performance. Since the objective function depends on 12 parameters and data, the heuristic optimization algorithm, genetic algorithm, can be used effectively to find the global minimum [30, 31].

From the Figure 4, regardless of the mean squares error and the size of data, the result of MAP method is closer to arbitrary literature value. The mean squares errors of 622 estimation results of Bayesian approach have lower value than the results of least squares method, and only 78 least squares method results are better performed than MAP method. Thus, the MAP method can perform the robust estimation even if there is noise, and limited size of experimental data.

If the prior result is untrustworthy, the accuracy of the estimation result by MAP method would be poor. In this case, the mean of the each prior distribution is assumed that it has 50% error compared with the arbitrary literature parameter values and the same procedure is performed.

From the Figure 5, the estimation performance of MAP method is lower than previous case, only the mean squares errors of 172 re-

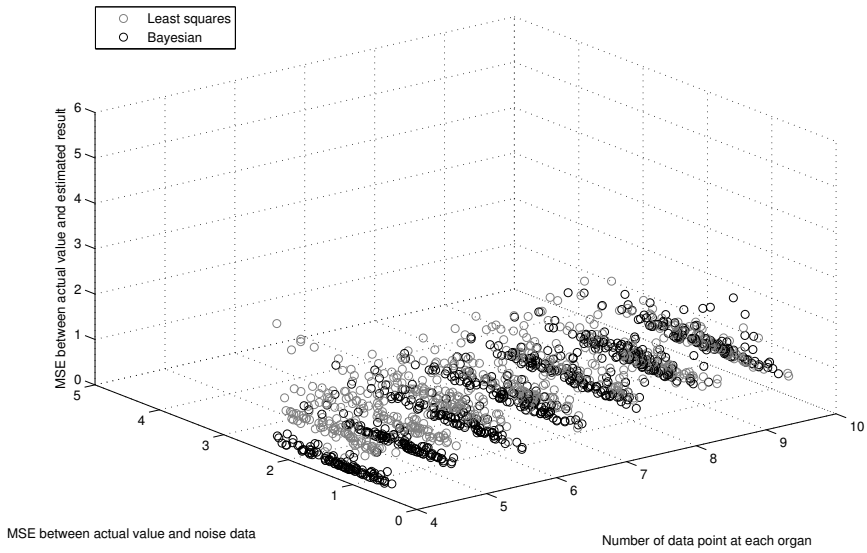

Figure 4: The result of parameter estimation with MAP method and least squares method with the reliable prior knowledge.

sults are lower than the results by least squares method. However, when the number of data points is small, 4 or 5 data points, mean squares errors of 78 results and 51 results by MAP method have the lower values than by least squares method. Consequently, when the number of data points is small, the estimation performance of MAP method are still better than that of least squares method even if the prior knowledge is unreliable.

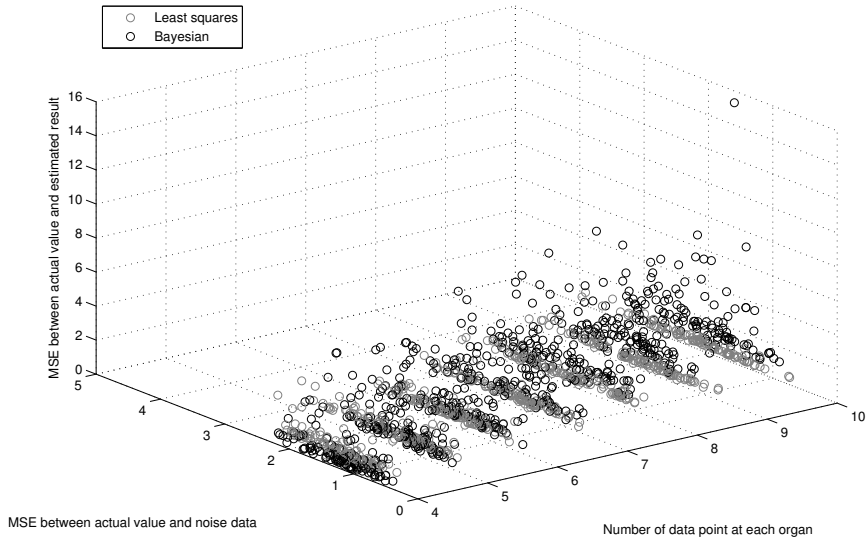

Figure 5: The result of parameter estimation with MAP method and least squares method with the untrustworthy prior knowledge.

Chapter 5

Comparison Between The PBPK Model and DDM Included PBPK Model

With a set of in-vivo experimental data, the parameters of PBPK model are estimated to predict real concentration profile inside living body. A 0.22 kg rat used for this experiment, and the concentration of Tegafur and 5-fluorouracil are measured at 30 miniutes, an hour, 2 and 4 hours in gut, liver, tumor cell and blood vessel. Initial dose is 15 mg/kg of Tegafur and administrated at time 0. From the literature, the information of physical parameters are in table 3 and 4 [26].

Table 5: Organ volumes and blood volumetric flow rates

Organ	Volume (ml)	Blood flow rate (ml/min)
Blood (V_b, Q_b)	13.2	76.45
Gut (V_g, Q_g)	7.92	17.1
Liver (V_l, Q_l)	8.8	19
Tumor (V_t, Q_t)	1.0	0.25
Well perfused organs (V_w, Q_w)	8.5	38.9
Poorly perfused organs (V_p, Q_p)	165	18.3

Since there is only one set of in-vivo data, and no available information of parameters, the bootstrap method is needed to find the prior distribution for Tegafur delivery system. To make a reliable prior dis-

Table 6: Tissue/blood partition coefficients

Organ	Tegafur (T)	5-fluorouacil (FU)
Blood (P_b)	0.808	0.794
Gut (P_g)	0.768	0.759
Liver (P_l)	0.895	0.5
Tumor (P_t)	0.336	0.169
Well perfused organs (P_w)	0.834	0.826
Poorly perfused organs (P_p)	0.8	0.795

tribution, 1000 sets of random data sets based on the experimental data are generated randomly. With these random data, the information of parameters is collected as a form of normal distribution by using result of least squares estimation, $P(\theta) \sim N(\overline{\theta}, \Omega^2)$. Now, the objective function of MAP method can be described below.

$$\begin{aligned} J_{map}[\hat{y}(t), \theta] =& \frac{1}{2} \ln [2\pi \cdot det(\Omega)] + \frac{1}{2} \cdot [\theta - \overline{\theta}]^T \cdot \Omega^{-1} \cdot [\theta - \overline{\theta}] \\ &+ \frac{l}{2} \ln (2\pi\sigma^2) + \frac{1}{2\sigma^2} \sum_{k=1}^{l} [y_k(t) - \hat{y}_k(t)]^T \\ &\cdot [y_k(t) - \hat{y}_k(t)] \end{aligned} \tag{5.1}$$

where θ is the m by 1 vector of parameters, $\overline{\theta}$ is the m by 1 vector of the means of parameters and Ω is the m by m covariance matrix. The estimation result is the parameter set which minimizes this objective function.

By using MAP method, unknown parameters of for the PBPK model without DDM and include DDM are estimated. With estima-

tion result, the ordinary differential equations of each PBPK model are solved to observe concentration profiles at each organ. The predicted concentration profiles at each organ are in Figure 6 $\sim$ 13. The solid line is the DDM included PBPK model, dotted line is the PBPK model without DDM, and circle is in-vivo experimental data. From the Figure 6 $\sim$ 13, although the MAP method is used to both of models, the result of DDM included PBPK model is more accurate. The mean squares error of the DDM include model is 1.817 and that of the model without DDM is 6.765 in log scale. In addition, from Table 7, the mean squares error of the DDM included PBPK model is lower than the mean squares error of the PBPK model without DDM in all organs. Consequently, for oral administrated drug delivery system, DDM helps to improve accracy of concentration prediction.

Table 7: The log scaled mean squares error of estimation result in each organ

	The DDM included model	The model without DDM
Tegafur in gut	0.042	0.674
Tegafur in liver	0.285	0.582
Tegafur in tumor	2.131	17.719
Tegafur in blood	0.049	1.093
5-fluorouacil in gut	1.915	6.428
5-fluorouacil in liver	1.548	14.917
5-fluorouacil in tumor	1.748	7.767
5-fluorouacil in blood	2.814	4.937

The estimation results from MAP method have probabilistic informations. Table 8 shows 95% confidence intervals and variances for each parameter. Based on these informations, the difference of concentration profile for each individual can be predicted.

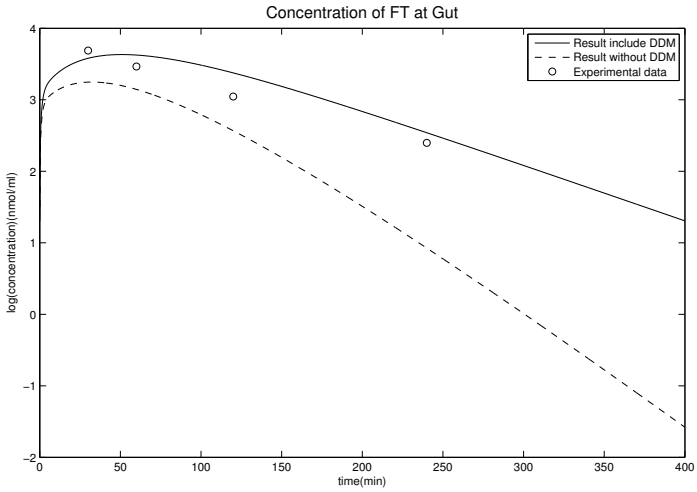

Figure 6: Estimated Tegafur concentration profile at Gut.

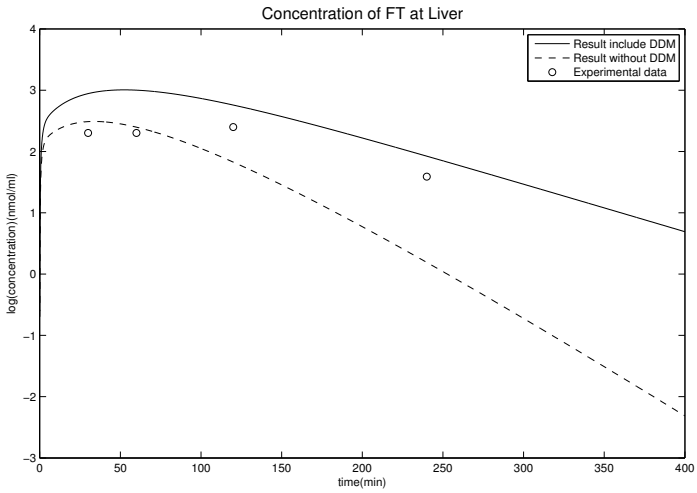

Figure 7: Estimated Tegafur concentration profile at Liver.

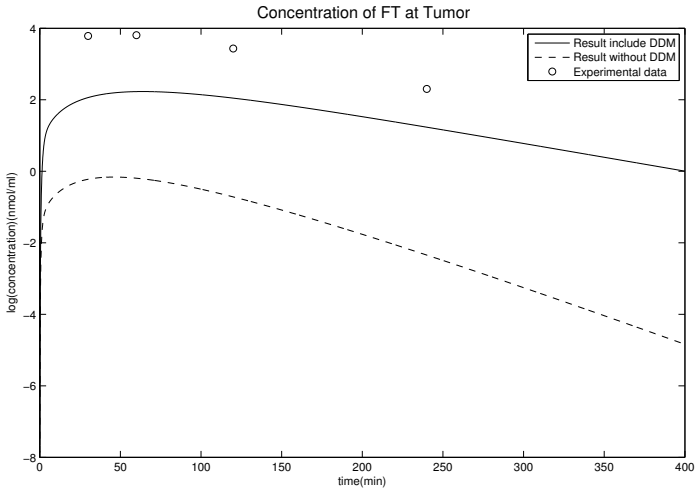

Figure 8: Estimated Tegafur concentration profile at Tumor.

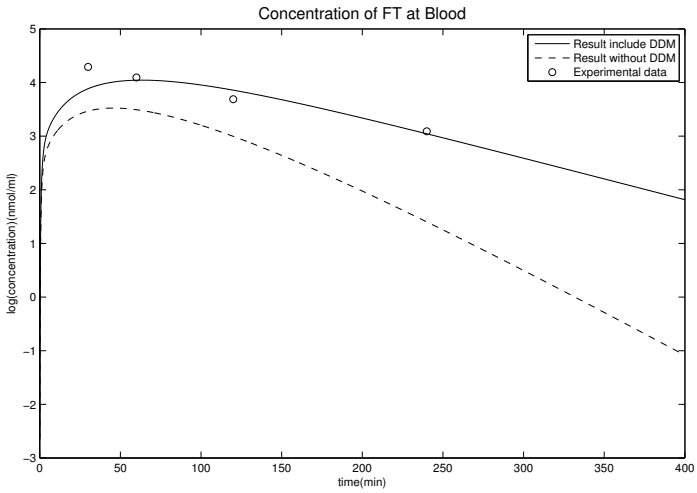

Figure 9: Estimated Tegafur concentration profile at Blood vessel.

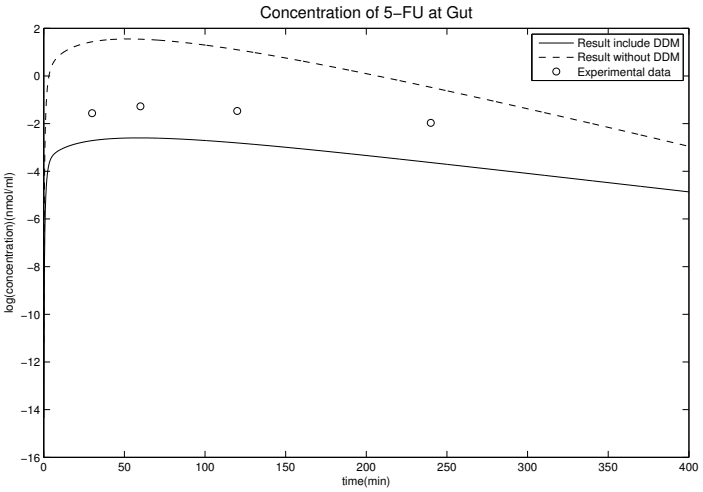

Figure 10: Estimated 5-fluorouracil concentration profile at Gut.

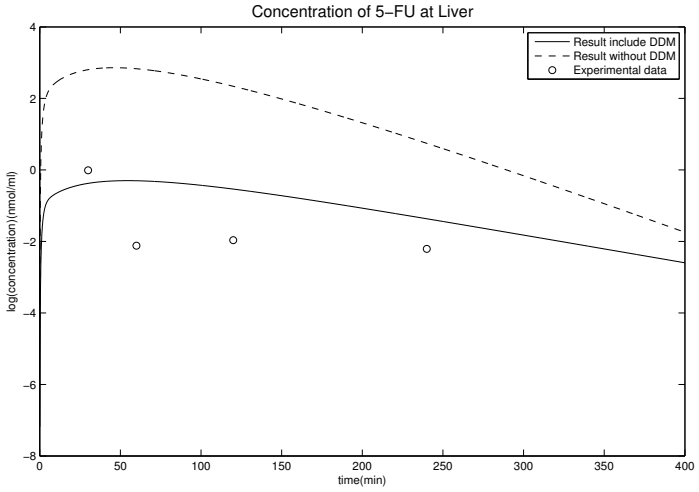

Figure 11: Estimated 5-fluorouracil concentration profile at Liver.

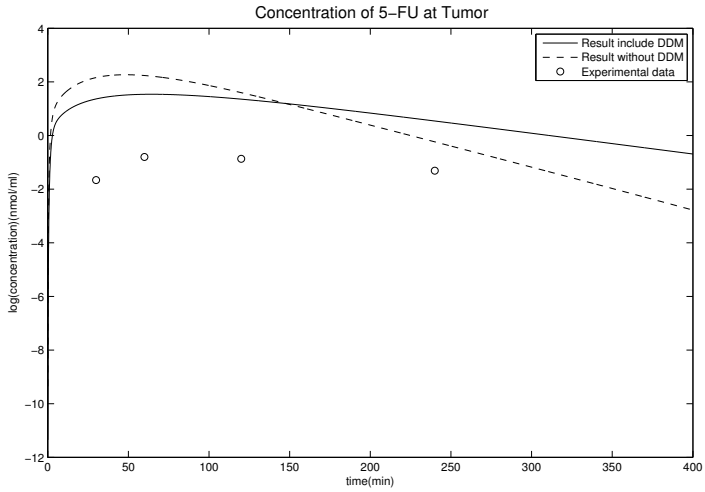

Figure 12: Estimated 5-fluorouracil concentration profile at Tumor.

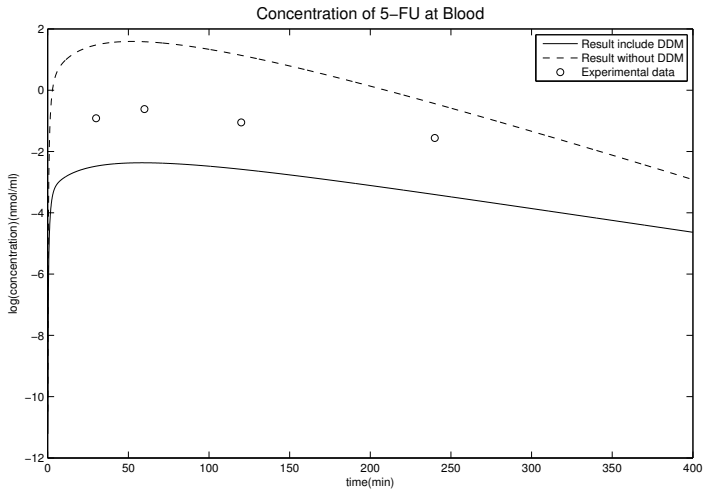

Figure 13: Estimated 5-fluorouracil concentration profile at Blood vessel.

Table 8: 95% confidence intervals and variances for the estimated parameters

Parameter	Lower bound	Upper bound	Variance
$K_{ml,T}(nmol/min/g$ tissue)	7.485×10^3	7.726×10^3	1.626×10^3
$V_{ml,T}(nmol/ml)$	1.886×10^3	2.041×10^3	1.048×10^3
$K_{mt,T}(nmol/min/gtissue)$	5.090	9.204	2.772×10
$V_{mt,T}(nmol/ml)$	3.081×10^3	3.321×10^3	1.609×10^2
$K_{ml,FU}(nmol/min/gtissue)$	1.416×10^3	1.463×10^3	3.181×10^2
$V_{ml,FU}(nmol/ml)$	1.602×10	2.337×10	4.955×10
$K_{mt,FU}(nmol/min/gtissue)$	7.610	9.130	1.024×10
$V_{mt,FU}(nmol/ml)$	2.720×10	3.048×10	2.211×10
$k_{abs}(min^{-1})$	1.685	2.191	3.409
$K(min^{-1})$	5.608×10^2	5.971×10^2	2.452×10^2
$CL_T(ml/min)$	2.104	2.211	0.721
$CL_{FU}(ml/min)$	1.840	2.040	1.35

Chapter 6

Concluding Remarks

In this thesis, the drug dissolution model (DDM) included PBPK model is proposed to describe oral administrated drug delivery system, the maximum a posteriori (MAP) method is introduced to robust parameter estimation, and the scheme of MAP method is proposed to find the maximum of posterior distribution without using the joint distribution. The scheme of MAP method is simulated with 700 random data sets, and compared with least squares method. The case study for Tegafur delivery system is conducted with in-vivo data to compare the PBPK model and DDM included PBPK model.

The PBPK model is useful to predict concentration in drug delivery system. To predict concentration, since there are various parameters in PBPK model, the parameter estimation with the experimental data will be needed. However, because of the limitation of collecting in-vivo concentration data, the robust estimation method should be introduced for the estimation problem of the PBPK model. MAP method can be used as a robust estimation technique even if there is the small number of data points. To compare MAP method and least squares method, parameters of PBPK model are estimated with 700 sets of random data. When there is the prior knowledge with 10%

error, the 88% of estimation results are more accurate by using the MAP method and only 12% of estimation results are more accurate by using the least squares method. Even if the prior information has 50% error, despite of the lack of reliability for the prior knowledge, 64.5% of the estimation results are more accurate by MAP method when the data points are only 4 and 5.

While a direct injected drug delivery system can be well described by PBPK model, the drug dissolution dynamics of oral administrated drug delivery system is not considered in PBPK model. To describe the oral administration case, DDM is introduced and the DDM included PBPK model is constructed by combining DDM and PBPK model. When predict the concentration profile of drug delivery system for Tegafur with in-vivo data, mean squares error of the DDM included model is 1.817 in log sclae, that is the 73% less than the mean squares error of the PBPK model without DDM. Consequentially, for oral administrated drug delivery system, the DDM included PBPK model has more accurate prediction performance than the PBPK model without DDM.

참고 문헌

[1] P. J. Gehring, P. G. Watanabe, G. E. Blau, Risk assessment of environmental carcinogens utilizing pharmacokinetic parameters, Annals of the New York Academy of Sciences 329 (1979) 137–152.

[2] J. K. Lindsey, W. D. Byrom, J. Wang, P. Jarvis, B. Jones, Generalized nonlineaer models for pharmacokinetic data, Biometrics 56 (2000) 81–88.

[3] K. B. Bischoff, Physiologically based pharmacokinetic modeling, Pharmacokinetics in Risk Assessment, Drinking Water and Health 8 (1987) 36–61.

[4] P. Zhao, L. Zhang, J. Grillo, Q. Liu, J. Bullock, Y. Moon, P. Song, S. Brar, R. Madabushi, T. Wu, et al., Applications of physiologically based pharmacokinetic (pbpk) modeling and simulation during regulatory review, Clinical Pharmacology & Therapeutics 89 (2) (2010) 259–267.

[5] L. Lasgna, H. K. Beecher, The optimal dose of morphine, The Journal of the American Medical Association 18 (1954) 230–234.

[6] J. B. Dressman, G. L. Amidon, C. Peppas, V. P. Shah, Dissolution testing as a prognostic tool for oral drug absorption: Immediate release dosage forms, Pharmaceutical Resarch 15 (1998) 11–22.

[7] S. S. Davis, J. G. Hardy, J. W. Fara, Transit of pharmaceutical dosage forms through the small intestine, Gut 27 (1986) 886–892.

[8] R. Brown, M. Delp, S. Lindstedt, L. Rhomberg, R. Beliles, Physiological parameter values for physiologically based pharmacokinetic models, Toxicol. Ind. Health 13407 (1997) 484.

[9] M. C. Coleman, D. E. Block, Bayesian parameter estimation with informative priors for nonlinear systems, AIChE Journal 52 (2006) 651–667.

[10] A. Gelman, F. Bois, J. M. Jiang, Physiological pharmacokinetic analysis using population modeling and informative prior distribution, Journal of the American Statistical Association 91 (1996) 1400–1412.

[11] S. M. Kay, Fundamentals of statistical signal processing, Prentice Hall PTR, New Jersey, 1993.

[12] K. J. Himmelstein, R. J. Lutz, A review of the applications of physiologically based pharmacokinetic modeling, Journal of Pharmacokinetics and Biopharmaceutics 7 (1979) 127–145.

[13] J. B. Houston, K. E. Kenworthy, In vitro-in vivo scaling of cyp kinetic data not consistent with the classical michaelis-menten model, Drug Metabolism and Disposition 28 (3) (2000) 246–254.

[14] M. L. Shuler, F. Kargi, Bioprocess engineering, Prentice Hall New York, 2002.

[15] M. Rowland, Protein binding and drug clearance, Clinical pharmacokinetics 9 (1) (1984) 10–17.

[16] A. Dokoumetzidisa, P. Macherasb, A century of dissolution research: From noyes and whitney to the biopharmaceutics classification system, International Journal of Pharmaceutics 321 (2006) 1–11.

[17] A. Noyes, W. Whitney, The rate of solution of solid substances in their own solutions, Journal of American Chemical Society 19 (1897) 930–934.

[18] S. C. Chapra, R. Canale, Numerical methods for engineers, McGraw-Hill, Inc., 2005.

[19] J. Aldrich, Doing least squares: Perspectives from gauss and yule, International Statistical Review 66 (1) (1998) 61–81.

[20] S. E. Fienberg, When did bayesian inference become" bayesian"?, Bayesian analysis 1 (1) (2006) 1–40.

[21] P. L. Bonate, Pharmacokinetic-Pharmacodynamic Modeling and Simulation, Springer Science+Business Media, San Antonio, 2006.

[22] P. J. Harrison, C. F. Stevens, Bayesian forecasting, Journal of the Royal Statistical Society 38 (1976) 205–247.

[23] G. Marrelec, H. Benali, P. Ciuciu, M. Pelegrini-Issac, J.-B. Poline, Robust bayesian estimation of the hemodynamic response function in event-related bold fmri using basic physiological information, Human Brain Mapping 19 (2003) 1–17.

[24] F. Jonsson, G. Johanson, The bayesian population approach to physiological toxicokinetic-toxicodynamic models–an example using the mcsim software, Toxicology Letters 138 (2003) 143–150.

[25] Y. Sakata, A. ohtsu, N. Horikoshi, K. Sugimachi, Y. Mitachi, T. Taguchi, Late phase ii study of novel oral fluoropyrimidine anticancer drug s-1 (1m tegafur±0.4m gimestat±1m otastat potassium) in advanced gastric cancer patients, European Journal of Cancel 34 (1998) 1715–1720.

[26] J. H. Sung, A. Dhiman, M. L. Shuler, A combined pharmacokinetic-pharmacodynamic(pk–pd) model for tumor growth in the rat with uft administration, Journal of Pharmaceutical science 98 (2009) 1885–1904.

[27] S. Jang, R. Gopaluni, Parameter estimation in nonlinear chemical and biological processes with unmeasured variables form small data sets, Chemical Engineering Scinece 66 (2011) 2774–2787.

[28] B. Efron, R. Tibshirani, An introduction to the bootstrap, Vol. 57, CRC press, 1993.

[29] D. B. Rubin, The bayesian bootstrap, The annals of statistics 9 (1) (1981) 130–134.

[30] D. Broadhursta, R. Goodacrea, A. Jonesa, J. J. Rowlandb, D. B. Kell, Genetic algorithms as a method for variable selection in multiple linear regression and partial least squares regression, with applications to pyrolysis mass spectrometry, Analytica Chimica Acta 348 (1997) 71–86.

[31] C. Lucasius, G. Kateman, Genetic algorithms for large-scale optimization in chemometrics: An application, Trends in Analytical Chemistry 10 (1991) 254–261.

초 록

생리학적 약동학 모델은 약물 전달 시스템에서 일어나는 대사작용을 예측하는데 유용하게 쓰이는 기법이다. 따문에 특정 시간의 약물의 농도를 예측하여 약물의 복용량을 조절하는데 매우 효과적으로 사용되여 약물의 임상실험 단계에 도움을 줄 수 있다. 생리학적 약동학 모델은 여러 변수를 포함한 미분방정식들로 이루어져 있는 반면에, 생체 내 실험 데이터는 매우 오차가 심하고, 측정횟수를 늘리는 것 역시 한계가 있다. 이러한 이유로 최소자승법을 이용한 변수 추정에는 어려움이 따른다. 따라서 강건한 변수 추정 기법인 최대 사후 확률법을 생리학적 약동학 모델의 변수 추정에 사용할 수 있다. 하지만 마르코프 연쇄 몬테 카를로 방법을 통한 최대 사후 확률 기법은 많은 수의 변수가 존재하는 생리학적 약동학 모델에서 사용하기 힘들다. 따라서 이 연구는 베이지안 접근을 기반으로 한 생리학적 약동학 모델의 변수 추정 기법을 도입하고자 한다. 또, 마르코프 연쇄 몬테 카를로 기법을 이용하지 않는 새로운 최대 사후 확률 기법을 제안한다.

약물의 농도를 조절하고 부작용을 막기 위해 약물 제형에 관한 연구가 발전되어 왔다. 하지만 약물 제형에 관한 연구와 생리학적 약동학 모델의 연구는 서로 독립적으로 진행되었기 때문에, 생리학적 약동학 모델에서는 약물의 용해에 관한 동역학이 고려되지 않는다. 따라서, 구강을 통해 복용되는 약물 전달 시스템을 정확히 표현하기 위해서는 새로운 생리학적 약동학 모델이 필요하다. 이 연구는 약물 용해 모델과 생리학적 약동학 모델을 결합하여 구강을 통해 복용되는 약물 전달 시스템을 표현하는

생리학적 약동학 모델을 제안하고자 한다.

이 논문은 모의 실험을 통해 최소 자승법과 최대 사후 확률 기법의 성능을 비교하였다. 또, 체내에서 수집된 데이터와 약물 용해 모델이 포함된 생리학적 약동학 모델을 이용하여 Tegafur의 약물 전달 시스템의 약물 농도를 예측하는 연구를 진행하였고 이를 통해 제안된 생리학적 약동학 모델의 성능을 실험하였다.

주요어 : 베이지안 접근, 변수 추정, 생리학적 약동학 모델, 약동학, 약물 전달 시스템, 사후 최대 확률법
학번 : 2012-20933