Pharmacokinetics/Pharmacodynamics Modeling and Simulation with MATLAB

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Abstract

Population pharmacokinetics has taken off with an exponential increase in published papers in the last decade. This has revolutionized how data from clinical studies is analyzed. Population pharmacokinetics methods are used almost exclusively for phase II and III studies and to summarize data across a drug development program. Advances in pharmacokinetic and pharmacodynamic modeling will allow fewer, more focused and informative clinical trials, and lead to significant cost savings. However, despite these advances, population methods are not routinely easy to employ. A major hindrance to implementing population methods is that it is mathematically and statistically complex, and compared to the number of pharmacokineticists in general there are few modelers who specialize in the methodology. Hence, in this study, we have used MATLAB computer program to obtain information on effective dosage regimens of doripenem by a modeling and simulation approach based on pharmacokinetic (PK)/pharmacodynamic (PD) theory. We have introduced a modification to the PK/PD model which explains in-vitro bactericidal kinetics of doripenem for several Pseudomonas aeruginosa strains. Time-course profiles of bacterial counts in patients infected with P. aeruginosa were simulated for typical clinical dosage regimens considering the variability of PK and the patients' backgrounds by a Monte Carlo simulation. Moreover, time-course profiles of probability achieving the criterion ($\log(CFU/mL) < 0$) were predicted for the evaluation of antibacterial efficacy by renal function. The in-vitro bacterial profiles at various dosage regimens could be well explained by the PK/PD model. The simulations suggested the dependence of antibacterial efficacy on the frequency of administration, indicating time-dependent antibacterial activity. It was also suggested that 500 mg t.i.d. showed significant bacterial reduction in patients for any degree of renal function and any severities in two weeks after the start of treatment. Our approach to simulate time-course profiles of bacterial counts should be useful for determining and examining effective dosage regimens, including the treatment period in drug development.

Keywords: PK/PD model, MATLAB computer program, doripenem, Monte Carlo simulation, development.

Introduction

Pharmacokinetics and pharmacodynamics are the two main areas of pharmacology a branch of medicine and biology concerned with the study of drug action, where a drug can be broadly defined as any man-made, natural, or endogenous (within the body) molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism. Pharmacokinetics and pharmacodynamics were both first introduced by F. H. Dost in 1953. However, some of the subject matter was published before the words were coined. The first English language review of the subject matter pharmacokinetics, published in 1961, was entitled kinetics of Drug Absorption, Distribution, Metabolism and Excretion and did not include the word pharmacokinetics (Nelson, 1961). Pharmacokinetics has been defined in numbers of ways. Literally, the word means the application of kinetics to pharamako, the Greek word for drugs and poisons and “what the body does to the drug”. Kinetics is that branch of physics which involves

the change of one or more variables as a function of time. The purpose of pharmacokinetics is to study the time course of drug and metabolite concentrations or amounts in biological fluids, tissues and excreta, and also of pharmacological response, and to construct suitable models to interpret such data. Broadly then, the purposes of pharmacokinetics are to reduce data to a number of meaningful parameter values, and to use the reduced data to predict either the results of a host of studies which would be too costly and time-consuming to complete (Wagner, 1968).

A similar definition has been given by other authors (Gibaldi and Levy, 1976) as follows: Pharmacokinetics is concerned with the study and characterization of the time course of drug absorption, distribution, metabolism, excretion, and with the application of mathematical and biochemical techniques in a physiologic and pharmacologic context. Therefore Pharmacokinetics (PK) describes the quantitative relationship of concentration-time profiles in different body fluids (plasma, blood, urine, and saliva etc).

Pharmacokinetics (PK) Processes

Basically there are four essential processes of pharmacokinetics, Absorption, Distribution, Metabolism and Excretion (ADME). Usually pharmacokinetics (PK) processes are referred to as PK phases (figure 1.1). All this four processes are important for controlling drug levels and tissue exposure, and they are therefore critical for determining the performance and the activity of a drug. The four processes are;

First Phase Absorption: Absorption is the movement of a drug from its site of administration into the blood stream, most drugs are absorbed by passive absorption but some drugs need carrier mediated transport. Is it important to note that Small molecules diffuse more rapidly than large molecules, and most of the absorption of the drug takes place in the small intestine, since the surface area of the stomach is much smaller than that of the intestine, Since drugs are absorbed in the small intestine, the amount of time that the drugs spend in the stomach is less and also the surface area of the stomach is small.

Second Phase Distribution: This is the dispersion or dissemination of substances throughout the fluids and tissues of the body. Distribution causes the movement of drugs throughout the body, determined by the blood flow to the tissues; it's also the ability of the drug to enter the vasculature system and the ability of the drug to enter the cell if required. Distribution of drugs (in-) to tissues depends on: Perfusion of tissues (blood flow), biological barriers, uptake of drugs into tissues, and protein binding.

Third Phase Metabolism or Biotransformation: The recognition by the organism that a foreign substance is present is the process of transformation of a drug within the body to make it more hydrophilic so that it can be excreted out from the body by the kidneys. (Figure 1.3) This needs to be done since drugs and chemicals are foreign substances in our body. If the drug continues to be in the lipohilic state and is going to be filtered by the glomerulus then it will be

reabsorbed and remain in the body for prolonged periods. Hence metabolism deals with making the drug more hydrophilic such that it can be excreted out from the body. In some cases the metabolites can be more active than the drug itself e.g. anxiolytic benzodiazepines. Some enzymes are highly specific and will breakdown only compounds that they recognize for e.g. glucose dehydrogenase. But there are some enzymes such as pepsin which are not specific and will breakdown most soluble proteins into smaller polypeptides or amino acids. This enzyme and many other proteolytic enzymes attack the peptide bond that joins the amino acids to make proteins, and in this way break the protein down into phase I and II metabolism by enzymes.

Fourth Phase Excretion: Excretion is the removal of the substance from the body. Some drugs are either excreted out unchanged or some are excreted out as metabolites in urine or bile. Drugs may also leave the body by natural routes such as tears, sweat, breath and saliva. Patients with kidney or liver problem can have elevated levels of drug in the system and it may be necessary to monitor the dose of the drug appropriately since a high dose in the blood can lead to drug toxicity. Though, the kidney is the main organ responsible for elimination via; glomerular filtration (passive) and tubular secretion (active).

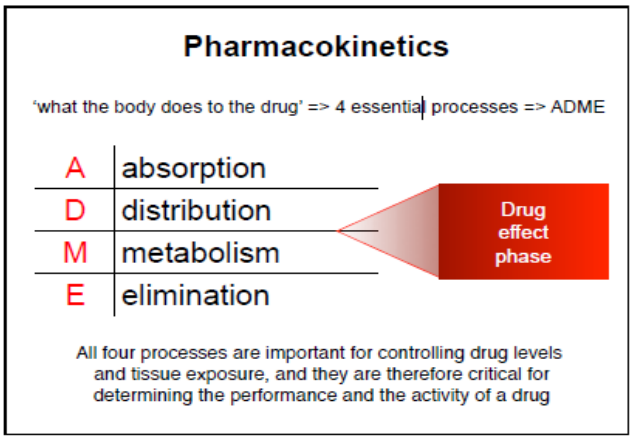


Figure 1: Pharmacokinetics processes.

Pharmacokinetics Models

The handling of a drug by the body can be very complex, as several processes (such as absorption, distribution, metabolism, and elimination) work to alter drug concentrations in tissues and fluids. Simplifications of body processes are necessary to predict a drug's behavior in the body. One way to make these simplifications is to apply mathematical principles to the various processes. To apply mathematical principles, a model of the body must be selected. A basic type of model used in pharmacokinetics is the compartmental model. Compartmental models are categorized by the number of compartments needed to describe the drug's behavior in the body. There are one compartment, two compartment, and multi-compartment models. The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids. These models can be used to predict the time course of drug concentrations in the body (Figure 2). Compartmental models are termed deterministic because the observed drug concentrations determine the type of compartmental model required to

describe the pharmacokinetics of the drug. This concept will become evident when we examine one- and two-compartment models. To construct a compartmental model as a representation of the body, simplifications of body structures are made. Organs and tissues in which drug distribution is similar are grouped into one compartment. For example, distribution into adipose tissue differs from distribution into renal tissue for most drugs. Therefore, these tissues may be in different compartments. The highly perfused organs (e.g., heart, liver, and kidneys) often have similar drug distribution patterns, so these areas may be considered as one compartment. The compartment that includes blood (plasma), heart, lungs, liver, and kidneys is usually referred to as the central compartment or the highly blood perfused compartment (Figure 3). The other compartment that includes fat tissue, muscle tissue, and cerebrospinal fluid is the peripheral compartment, which is less well perfused than the central compartment. Another simplification of body processes concerns the expression of changes in the amount of drug in the body over time. These changes with time are known as rates of elimination, rate describes the change in the amount of drug in the body due to drug elimination over time. Most pharmacokinetic models assume that elimination does not change over time. The value of any model is determined by how well it predicts drug concentrations in fluids and tissues. Generally, it is best to use the simplest model that accurately predicts changes in drug concentrations over time. If a one-compartment model is sufficient to predict plasma drug concentrations (and those concentrations are of most interest to us), then a more complex (two-compartment or more) model is not needed. However, more complex models are often required to predict tissue drug concentrations.

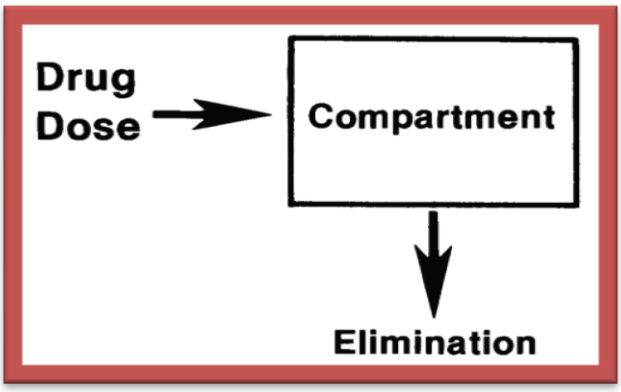


Figure 2: Simple compartmental model

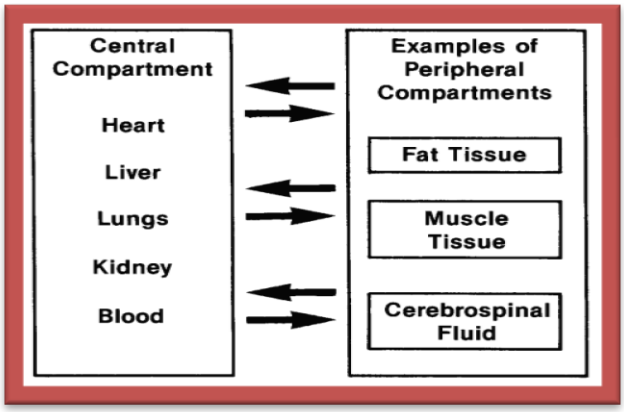
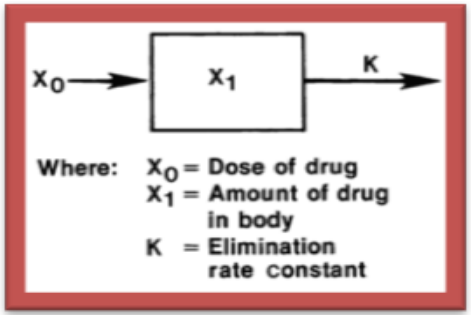


Figure 3: Typical organ groups for central and peripheral compartments.

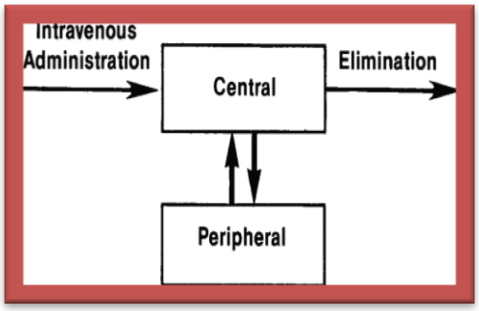
Compartment Models

The one compartment model is the most frequently used model in clinical practice. In structuring the model, a visual representation is helpful. The compartment is represented by an enclosed square or rectangle, and rates of drug transfer are represented by straight arrows (Figure 1.4a). The arrow pointing into the box simply indicates that drug is put into that compartment. And the arrow pointing out of the box indicates that drug is leaving

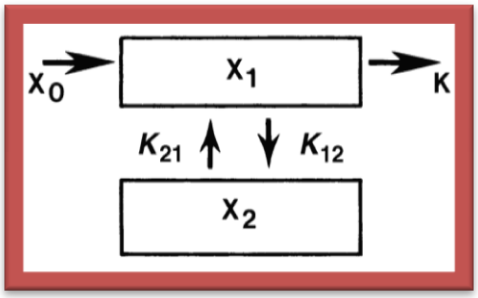
the compartment. This model is the simplest because there is only one compartment. All body tissues and fluids are considered a part of this compartment. Furthermore, it is assumed that after a dose of drug is administered, it distributes instantaneously to all body areas. Common abbreviations are shown in (Figure 1.4b and c). Some drugs do not distribute instantaneously to all parts of the body, however, even after intravenous bolus administration. Intravenous bolus dosing means administering a dose of drug over a very short time period. A common distribution pattern is for the drug to distribute rapidly in the bloodstream and to the highly perfuse organs, such as the liver and kidneys. Then, at a slower rate, the drug distributes to other body tissues. This pattern of drug distribution may be represented by one or two compartment model. Drug moves back and forth between these compartments to maintain equilibrium (Figure 1.5) simplifies the difference between one and two compartment models. Again, the one compartment model assumes that the drug is distributed to tissues very rapidly after intravenous administration.



(a)



(b)



(c)

Figure 4: Illustration of (a) one compartmental model (b) two compartmental model (c) two compartmental flows

where: X_0= Dose of drug, X_1 = Amount of drug in central compartment, X_2 = Amount of drug in peripheral compartment, K = Elimination rate constant of drug from central compartment to outside the body, K_{12} = Elimination rate constant of drug from central compartment to peripheral compartment, K_{21} = Elimination rate constant of drug from peripheral compartment to central compartment.

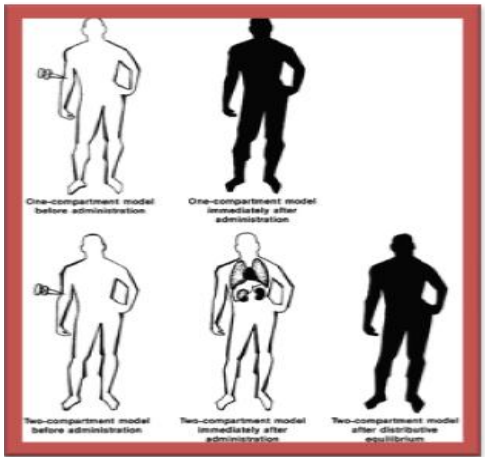


Figure 5: Drug Distribution in one and two Compartment models.

Pharmacodynamics

Pharmacodynamics “what the drug does to the body” sometimes abbreviated as "PD", is often studied in conjunction with pharmacokinetics “what the body does to the drug” is also a discipline within pharmacology that studies the biochemical and the physiological effects of drugs and their mechanisms of action, it encompasses how the drug produces the required pharmacological effect by identifying how the drug is acting, how we can measure that effect and whether there is a dose response. There are also processes involved in pharmacodynamics; and these processes are responsible for the mode of action of the drugs in the body. The pharmacodynamics processes are grouped into two; Drugs Receptor Action and Direct Physiological Action.

Factors Affecting Drug Response

i. Age: either very young or very old may not be able to process the drug efficiently.
ii. Gender: different body compositions and the amount of fat to lean tissue can influence the action of drugs as well as its passage through the body.
iii. Body weight: Increased body weight might lead to an increased amount of drug that needs to be taken to achieve the same response.
iv. Effects of diet: food in the gut will prove to be competition for the drug and hence the amount of drug would actually be lowered. Lipid soluble drugs are less affected as compared to water soluble drugs. The activity of the microsomal enzyme cytochrome P450 depends on the amount of minerals and vitamins present. It needs vitamins A, B1 and B2, essential fatty acids, proteins and minerals like copper, zinc and calcium for proper functioning. If there is an imbalance in any of the above there is an imbalance in the activity of the enzyme.
v. Effects of pregnancy.

Therapeutic Applications of PK/PD Modeling and Simulation

PK/PD modeling and simulation approaches applied in different therapeutic areas such as application in anti ineffective therapy, cancer chemotherapy etc.

1. Application in anti ineffective therapy: Antibacterial and Antiviral both face a constant threat of resistance development, which eventually can lead to therapeutic failure, in this area PK/PD indices are intended to normalize the drug exposure and the susceptibility of the respective pathogens to clinically relevant breaking points, for this study mechanism based linkage of PK/PD used. In drug development process of anti-infective, protein binding and tissue distribution are main PK parameters, minimum inhibitory concentration (MIC) used as major PD parameter to estimate efficacy of compound. Free concentration of antibacterial and antiviral in almost all tissue distribution can be done by microdialylsis technique and MIC of compound can be estimated and PK/PD has been linked to find the effective dose against the pathogens (Schmidt et al. 2008).

2. Application in cancer chemotherapy: Anticancer treatment with the paclitaxel and etoposide results not only in beneficial therapeutic effects also in adverse conditions like leucopenia and neutropenia. To describe such condition a physiological indirect response model was established. This model was successfully relates the drug concentrations vs. time curve to the time course of leucopenia. (Levy, 1998).

Software Approaches in PK/PD Modeling and Simulation

The discipline of pharmacokinetics/ pharmacodynamic has been advanced by the general availability of iterative computer methods for nonlinear regression analysis. In the pre-computer era, only the simplest modeling problems could be solved by approximation, usually after data transformation or linearization. Now, complex problems involving simultaneous determination of a number of clinically relevant pharmacokinetic variables can be rapidly solved, including numerical estimates of the statistical strength of the solution. Iterative nonlinear regression procedures expeditiously solve the problems of fitting theoretical models to actual data.

On the other hand, PK/PD models are usually complicated by the need to jointly consider the time-course of drug concentration, nonlinear equations that relate effect to concentration, and the usual requirement of two or three dose levels of drug. Thus, the use of computers for fitting experimental data is essential. The various softwares available for PK/PD modeling in drug development processes; they include MATLAB, PHOENIX WINONLIN, P-PHARM, PH\EDSIM etc.

Drug discovery and development is still associated with high attrition rates of dose-concentration relationship problem. Recent research and analysis has shown that this high attrition is largely caused due to the lack of efficacy and unsafe concerns of PK/PD-concepts in clinical therapy. The unsafe concerns of PK/PD concepts now lead to numerous challenges' on how to improve the prediction of models to describe the relation between drug dosing, concentration, and efficacy known as "PK/PD modeling". That's why this study was considered to be carried out, in order to see how several predicted models has helped in improving the prediction of the relation between drug dosing, concentration, efficacy and safety, through mathematical modeling resulting to ordinary differential equations (ODEs) and graphs. Expanded use of PK/PD modeling and simulation is assumed to be highly beneficial in drug development as well as applied pharmacotherapy, to give promising approach that provides better understanding of the question "prediction of drug efficacy and safety".

The objective of this study is to review the PK/PD modeling and simulation approaches, see how it has contributed to the drug development world and describe the concepts to achieve the modeling and simulation results.

This study will significantly yield more awareness of how PK/PD modeling and simulation has enormously contributed to the drug development world, pharmacologic and therapeutic disciplines. Also to show how PK/PD parameters interacts mathematically and graphically yielding to the understanding of the two physics terms KINETICS 'to do with motion of drug' and DYNAMICS 'to do with change that drug caused to the body'. This study mainly focused on the relation between drug dosing, concentration, and efficacy using mathematical modeling and simulation. The study was carried out by using MATLB software.

Methods

Matlab/Simbiology

MATLAB is a high-level language and interactive environment for numerical computation, visualization, and programming. Using MATLAB, you can analyze data, develop algorithms, and create models and applications. The language, tools, and built-in math functions enable you to explore multiple approaches and reach a solution faster than with spreadsheets or traditional programming languages, such as C/C++ or Java®. You can use MATLAB for a range of applications, including signal processing and communications, image and video processing, control systems, test and measurement, computational finance, and computational biology. More than a million engineers and scientists in industry and academia use MATLAB, the language of technical computing.

SIMBIOLOGY is a MATLAB package that automates and simplifies the process of modeling biological systems. Simbiology provides a graphical environment and programmatic tools to model, simulate, and analyze dynamic systems, focusing on pharmacokinetic/pharmacodynamic (PK/PD) and systems biology applications. It provides a block diagram editor for building models, or you can create models programmatically using the MATLAB language. Simbiology includes a library of common PK models, which you can customize and integrate with mechanistic systems biology models. A variety of model exploration techniques let you identify optimal dosing schedules and putative drug targets in cellular pathways. Simbiology uses ordinary differential equations (ODEs) and stochastic solvers to simulate the time course profile of drug exposure, drug efficacy, and enzyme and metabolite levels. You can investigate system dynamics and guide experimentation using parameter sweeps and sensitivity analysis.

You can also use single subject or population data to estimate model parameters.

Model Expressions/Quantities

A Simbiology model is composed of a set of expressions (reactions, differential equations, discrete events), and sets of quantities (compartments, species, parameters) which together describe the dynamics of a biological system. We write the expressions in terms of quantities (compartments, species, parameters), which are also enumerated in the model.

1. COMPARTMENTS: A compartment defines a physically bounded region that contains species. A compartment is characterized by a capacity expressed as volume, area, or length.

2. SPECIES: A species characterizes the state of the biological system by representing the amounts (or concentration) present in the system for that entity. Species' amounts (or concentrations) vary during a simulation as a result of their participation in reactions, differential equations, and events. Therefore, species represent the dynamical state of a biological system.

3. PARAMETER: A parameter is a quantity that is referred to by expressions. It typically remains constant during a simulation.

4. REACTION: A reaction describes a process such as a transformation, transport, or binding/unbinding process between reactants and products.

5. RULE: A rule is a mathematical expression that modifies a species amount, compartment capacity, or a parameter value. There are four types of Simbiology rules

6. EVENT: An Event describes an instantaneous change in the value of a quantity (compartment, species, and parameter). The discrete transition occurs when a user-specified condition becomes true. The condition can be a specific time or a specific time-independent condition.

7. DOSES: The Doses feature in Simbiology allows users to easily create different dosing schedules, and test their effect on model behavior. Doses can be applied to the model at simulation time that enables one to test different dosing options without altering the properties of the base model. When a dose is applied during a simulation, the value of the dosed component (as specified by Target Name) is appropriately varied during the simulation according to the specified dosing parameters.

8. VARIANTS: Variants are sets of alternative values for model components that can be applied to the model during simulation. Variants can store values of: Species Initial Amount, Parameter Value and Compartment Capacity.

Work Definition

The example to illustrate this research work is titled PK/PD Modeling and Simulation to Guide Dosing Strategy for Antibiotics This example shows how to perform a Monte Carlo simulation of a pharmacokinetic/pharmacodynamic (PK/PD) model for an antibacterial agent and also shows how to use the Simbiology exported model to perform parameter scans in parallel. This example is adapted from Katsube et al.

Work Definition Objectives

PK/PD modeling and simulation approach was used to determine the most effective dosage regimens for doripenem, a carbapenem antibiotic with the following objectives to

a. Develop a PK/PD model to describe the antibacterial effect of doripenem against several Pseudomonas aeruginosa strains.

b. Use Monte Carlo simulations to compare the efficacy of four common antibiotic dosage regimes, and to determine the most effective dosing strategy.

c. Investigate the effect of renal function on the antibacterial efficacy of the treatments.

The PK/PD Model

Here we assumed a two-compartment infusion model with linear elimination from the central compartment to describe the pharmacokinetics of the doripenem. For the bacterial growth model, and assumed that the total bacterial population is comprised of drug susceptible growing cells and drug-insensitive resting cells. The antibacterial effect of the drug was included in the killing rate of the bacteria via a simple E_{max} type model:

$$Killing\ Rate = \frac{K\,max * [Drug] * [Growing]}{KC50 + [Drug]} \quad (1)$$

where [Drug] is the concentration (ug/ml) of the drug in the central compartment, and [Growing] is the count of the growing bacterial population in CFU/ml (CFU = Colony Forming Units).

K_{max} is the maximal killing rate constant (1/hour) and KC50 is the Michaelis-Menten rate constant (ug/ml).

Steps/Procedures

Here, we will show steps that lead to the achievement of the work on PK/PD Modeling and Simulation to Guide Dosing Strategy for Antibiotics.

The Software was installed according to the installation guides of the software/version.

- Locate the software package on the computer PC and double click, wait a while for the program to come up, showing the COMMAND window.
- Open the Simbiology desktop by typing 'Simbiology' (lower case) in the MATLAB Command Window as shown in Figure 6.

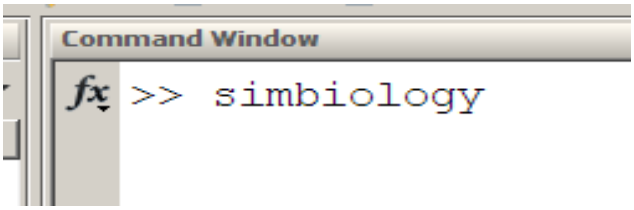


Figure 6: MATLAB Command Window

The simbiology desktop appeared, in the Simbiology desktop that appeared locate 'ADD MODEL' and click, in the drop down menu List, click on 'CREATE NEW BLANK MODEL' a small prompt box appeared with a default name 'untitled' type "ANTIBACTERIALPKPD MODELING" to replace the untitled model and click on OK. The model simbiology desktop appeared, showing the graphical user interface, made up of a set of integrated tools, designed to build, simulate, and analyze dynamic models (Figure 7).

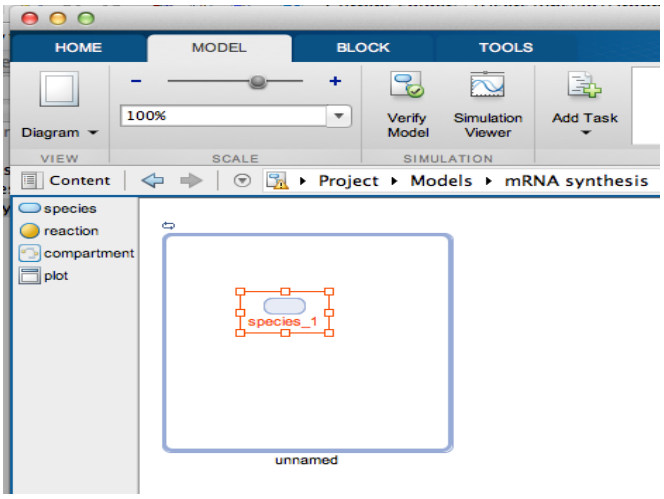


Figure 7: Modeling Work Area.

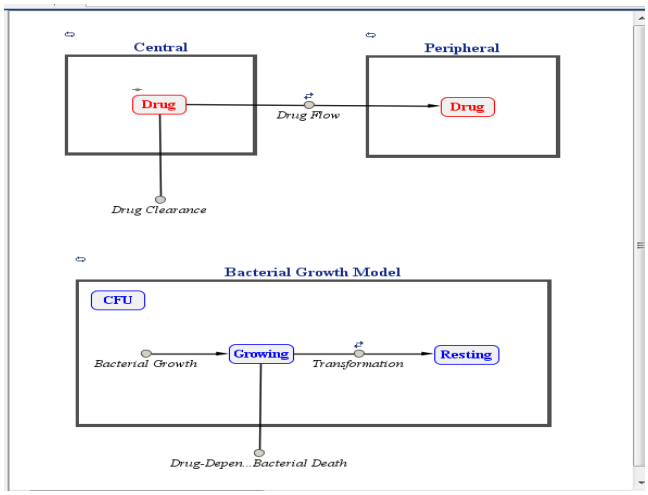


Figure 8: Graphical view of the Simbiology of the model implemented.

Model Parameters

The parameter used for this is research is from the Katsube et al model, we define the parameters to the model by:

i. Changing the from model diagram view to table view.

ii. The table view shows the components of the table view and model components that were not defined in the diagram view of the model.

iii. Click on each of the component in table view and edit as shown in the figure (10-19).

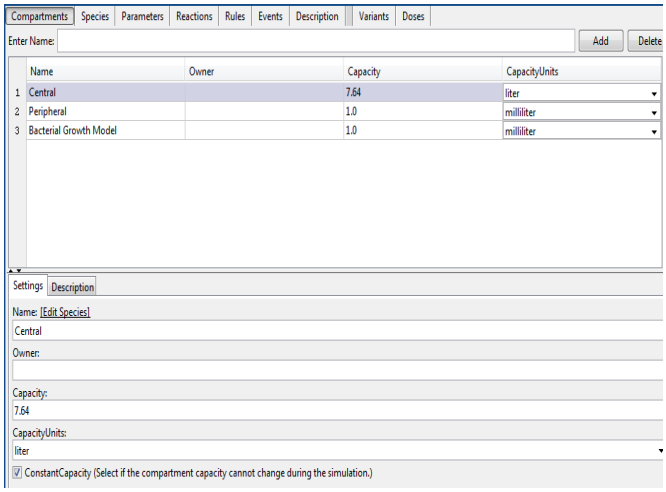


Figure 9: Compartment properties

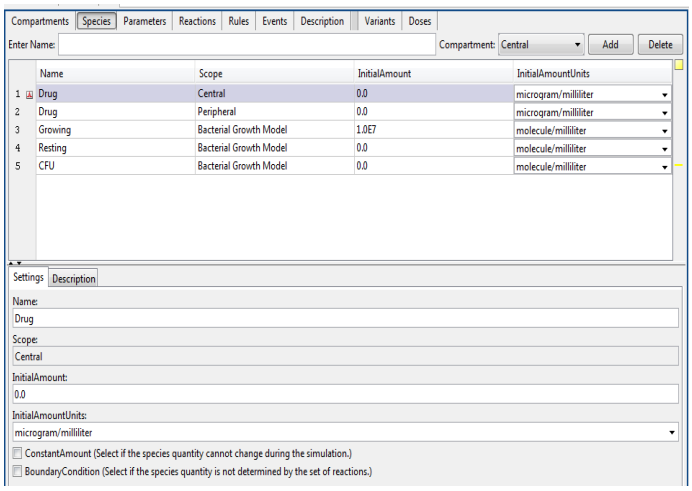


Figure 10: Species properties

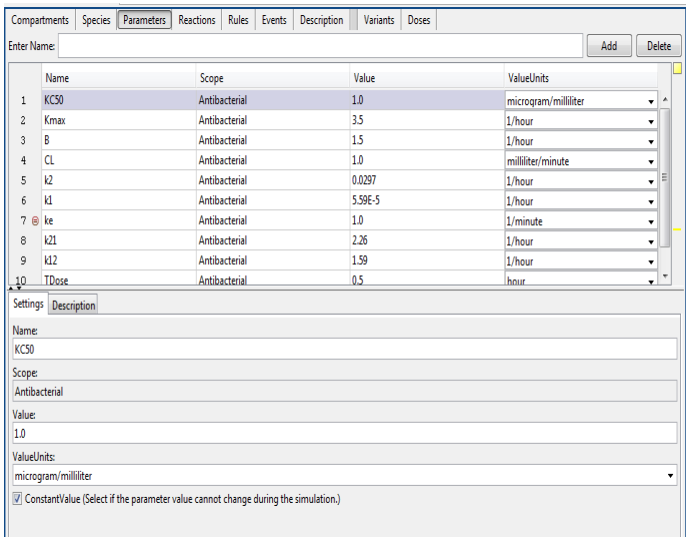


Figure 11: Parameter used in the simulations

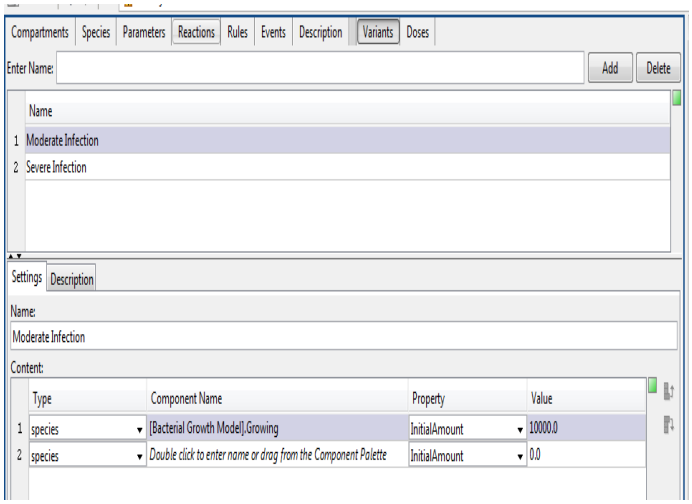


Figure 12: Applied Variants

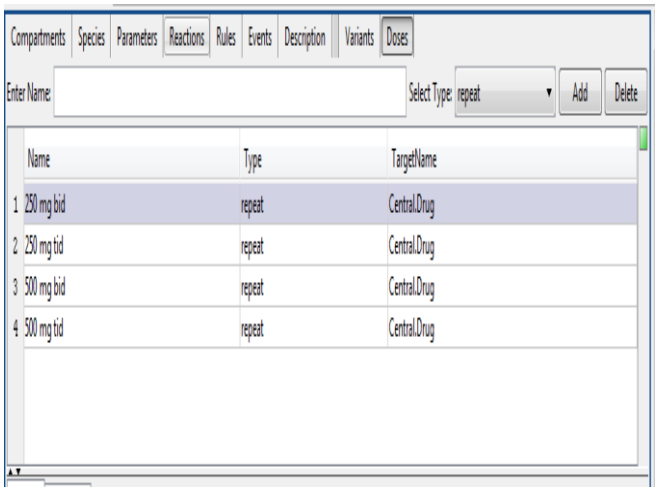


Figure 13: Applied doses in the simulations

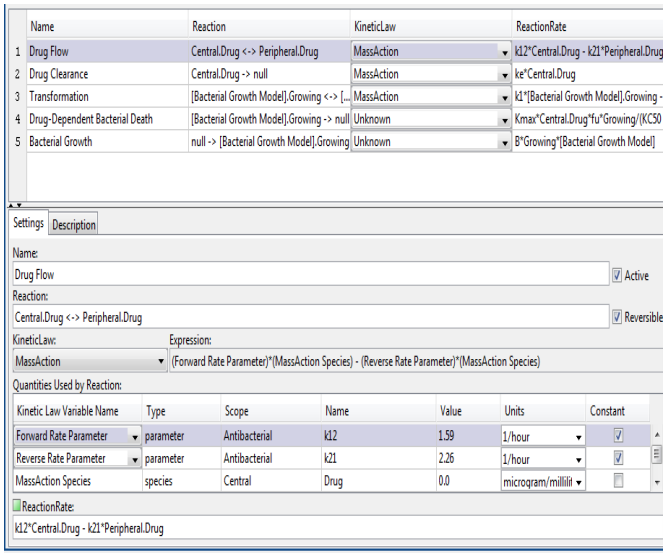


Figure 14: Drug flow reaction properties

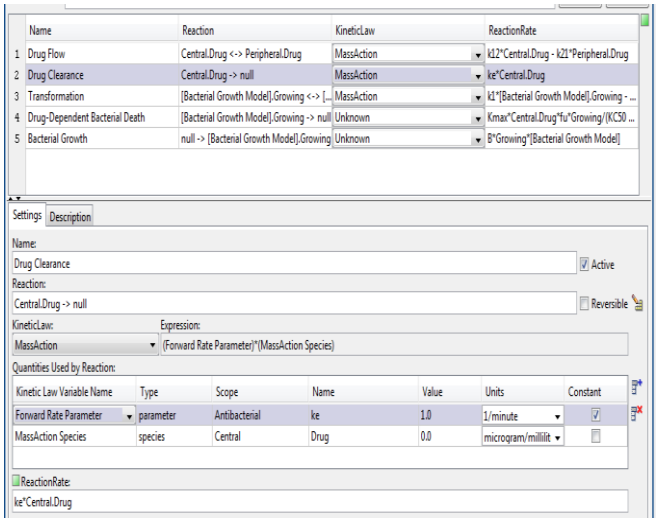


Figure 16: Drug clearance reaction properties

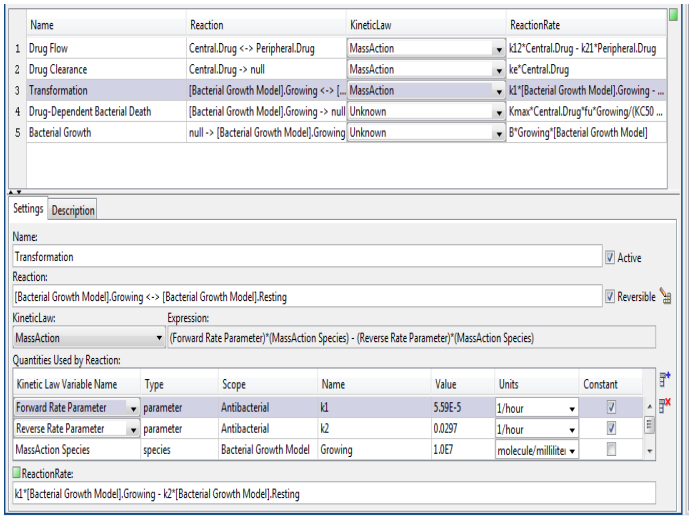


Figure 17: Transformation reaction properties

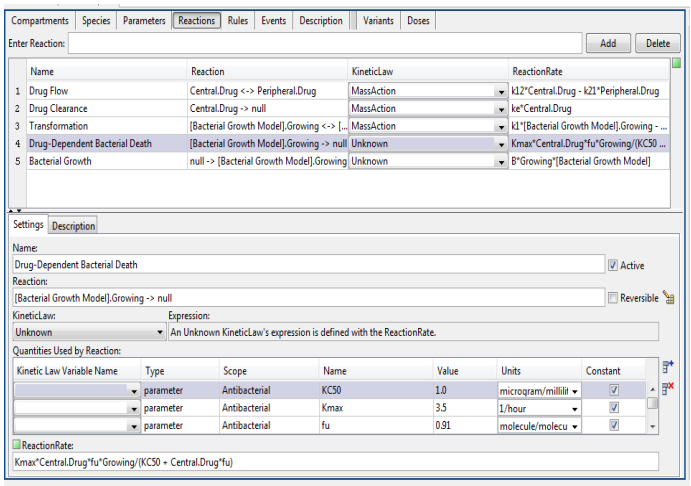


Figure 18: Drug-Dependent reaction properties

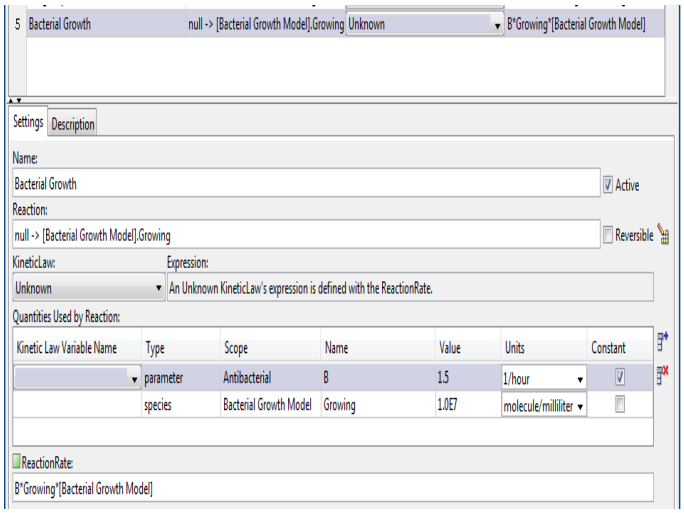


Figure 19: Bacterial Growth reaction properties

Results and Discussions

Now, that we have developed a PK/PD model describing the antibacterial effect of doripenem against several Pseudomonas aeruginosa strains as shown in figure 8, and defined the model quantities, we have to encode the model using MATLAB codes developed by Katsube et al.

Exporting the Built Model in MATLAB Codes

Load the model the antibacterialPKPD model

```
% Load model
sbioloadproject('AntibacterialPKPD.sbproj', 'm1') ;
```

Dosage Regimes

We will simulate the model using four common antibiotic dosage strategies as follows;

- 250 mg two times a day (b.i.d.)
- 250 mg three times a day (t.i.d.)
- 500 mg two times a day (b.i.d.)
- 500 mg three times a day (t.i.d.)

Infusion dosing was used in all four dosages regimens, and infusion time was set to 30 minutes. In Simbiology, these dosage regimens have been implemented as dose objects.

```
% Select dose objects in the model
doseNames = {'250 mg bid', '250 mg tid', '500 mg bid', '500 mg tid'};
for iDoseGrp = 1:length(doseNames)
   doseRegimens(iDoseGrp) = sbioselect(m1, 'Name', doseNames{iDoseGrp}) ;
end
```

Description of the Virtual Population

A virtual population of individuals was generated based on the distribution of demographic variables and PK/PD parameters. The type of distribution and the values of the distribution parameters were based on data from earlier clinical trials of doripenem conducted in Japan. In this example, we will use 1,000 patients in each group. To simulate a different population size, change the value of nPatients below.

```
% Setup
nPatients = 1000 ; % Number of patients per dosage group
nDoseGrps = 4 ; % Number of tested dosage regimens
```

Distribution of Demographic Variables

Weight (Wt) and age (Age) were sampled from a normal distribution with a mean of 51.6 kg and 71.8 years, respectively, and a standard deviation of 11.8 kg and 11.9 years, respectively. 26% of the population was assumed to be female. Serum creatinine levels (Scr) were sampled from a lognormal distribution with a typical value of 0.82 mg/dL, and coefficient of variation (CV) of 32%. The creatinine clearance rates (CrCL) were calculated using the Cockcroft-Gault equation.

```
 % Note: The inputs to the lognrnd function are the mean (mu) and standard
% deviation (sigma) of the associated normal distribution. Here and
% throughout the example, mu and sigma were calculated from the reported
```

% typical value and coefficient of the lognormal distriution. See the
% lognstat documentation for more information.

% Patient demographics
Wt = normrnd(51.6 , 11.8 , nPatients , nDoseGrps) ; % units: kg
Age = normrnd(71.8 , 11.9 , nPatients , nDoseGrps) ; % units: years
Scr = lognrnd(-0.2485 ,0.3197 , nPatients , nDoseGrps) ; % units: ml/minute
% Gender ratio
id = 1:nPatients*nDoseGrps ;
idFemale = randsample(id , round(0.26*nDoseGrps*nPatients)) ; % 26% Female

% Creatinine Clearance (using Cockcroft-Gault equation)
CrCL = (140 - Age).*Wt./(Scr*72) ; % units: ml/minute
CrCL(idFemale) = CrCL(idFemale)*0.85 ; % multiply by 0.85 for females

Distribution of Pharmacokinetics (PK) Parameters
PK parameters, Central, k12 and k21, were sampled from a lognormal distribution with typical values of 7.64 liters, 1.591/hour and 2.261/hour, respectively, and a 20% coefficient of variation (CV). Central is the distribution volume of the central compartment, and k12 and k21 are transfer rate constants between the Central and the Peripheral compartments.
% PK parameters
Central = lognrnd(2.01 , 0.2 , nPatients, nDoseGrps) ; % units: liter
k12 = lognrnd(0.4441 , 0.2 , nPatients, nDoseGrps) ; % units:1/hour
k21 = lognrnd(0.7958 , 0.2 , nPatients, nDoseGrps) ; % units:1/hour
CL = 1.07*CrCL + 45.6 + normrnd(0,22,nPatients,nDoseGrps); % units: ml/minute

Distribution of Pharmacodynamics (PD) Parameters
Growing-to-resting transformation rate constants, K1 and K2, were sampled from a lognormal distribution with typical value of 5.59e-5 and 0.0297 1/hour respectively, each with a CV of 20%. Kmax was sampled from a lognormal distribution with a typical value of 3.5 1/hour and 15.9% CV. Katsube et al. assumed that values K1, K2 and Kmax were independent of the bacterial strain being treated. The value of Beta, the net growth rate constant, was fixed at 1.5 1/hour.
Discrete distribution of MIC values based on 71 P. aeruginosa strains
micValue = [0.0625, 0.125, 0.25, 0.5 , 1 , 2 , 4 , 8 , 16 , 32] ;
micFreq = [5 , 8, 9, 14, 7, 8, 9, 5, 2, 4] ;
k1 = lognrnd(-9.8116, 0.2 , nPatients, nDoseGrps) ; % units: 1/hour
k2 = lognrnd(-3.5362, 0.2 , nPatients, nDoseGrps) ; % units: 1/hour
Kmax = lognrnd(1.2332, 0.159, nPatients, nDoseGrps) ; % units: 1/hour

% Sample MIC values from a discrete distribution using randsample
MIC = nan(nPatients, nDoseGrps) ; % preallocate

```
for iDoseGrp = 1:nDoseGrps
   MIC(:, iDoseGrp) = randsample(micValue , nPatients, true , micFreq);
end

KC50 = exp(-1.91 + 0.898*log(MIC) + 1.06*randn(nPatients , nDoseGrps)) ; % units: microgram/milliliter
```

Simulation Setup and Design

The model will be converted to a Simbiology exported model, which facilitates performing parameter, scans in parallel. When you export the model, you choose which species, parameters, or compartments can be varied. In this example, you will vary 8 parameters, central, k12, k21, CL, k1, k2, Kmax, and KC50.

```
   % Select the parameters you want to vary.
paramNames = {'Central', 'k12', 'k21', 'CL', 'k1', 'k2', 'Kmax', 'KC50'};
for iParam = 1:length(paramNames)
   parameters(iParam) = sbioselect(m1, 'Name', paramNames{iParam});
end

% Created the exported model, using the selected parameters and doses
exportedModel = export(m1, parameters, doseRegimens);
% Accelerate the model
accelerate(exportedModel);
```

For all dosage scenarios, the model was simulated until t = 2 weeks from the time of the first dose. Total bacterial count, CFU, was sampled every 24 hours (once a day) for the entire duration of the dosage regimen.

```
tObs      = 0:24:336      ; % hour
nTPoints  = length(tObs)   ; % Number of sampling points

% Specify that the simulation should report these output times
exportedModel.SimulationOptions.OutputTimes = tObs;
```

Monte Carlo Simulation of Patients with Severe Infection

The antibacterial efficacy of a drug can be measured using different PK/PD indices. Katsube et al. set the criterion for bacterial elimination at log10(CFU) < 0, where CFU is the total bacterial count. The efficacy of each dose regimen was measured as the fraction of the population that achieved the success criteria in the dosage group. This efficacy metric, Pr{log10(CFU) < 0}, was tracked as a function of time for each dosage group. In this simulation studies, the authors investigated the efficacy of the dosage regimens on two classes of patients:

- Moderate infection (Initial bacterial count = 1e4 CFU/ml)
- Severe infection (Initial bacterial count = 1e7 CFU/ml)

In this example, we will replicate the results for the severe infection case only. Note that you can easily simulate the other scenario, patients with moderate infection, by changing the initial amount of bacterial count in the model to 1e4 CFU/ml.

```
% Preallocate
```

```
log10CFU     = cell(1,nDoseGrps) ;
for iDoseGrp = 1:nDoseGrps
   % Select the exported doess
   currentDose        =        getdose(exportedModel,
doseNames{iDoseGrp});
   cfu = nan(nTPoints , nPatients)    ; % preallocate
   disp(['Simulating group ',   num2str(iDoseGrp), '
... '])
   parfor iPatient = 1:nPatients
      % Use parameter values for current patient
      % Define the parameters in the same order used
when exporting
      parameterValues = [
         Central(iPatient , iDoseGrp)
         k12(iPatient, iDoseGrp)
         k21(iPatient, iDoseGrp)
         CL(iPatient , iDoseGrp)
         k1(iPatient , iDoseGrp)
         k2(iPatient , iDoseGrp)
         Kmax(iPatient, iDoseGrp)
         KC50(iPatient, iDoseGrp)
         ];
      % Simulate
      simData        =        simulate(exportedModel,
parameterValues, currentDose) ;
      % Extract bacterial count data for Growing and
Resting population
      [~,   bactCount]     =     selectbyname(simData,
{'Growing', 'Resting'}) ;
      % Sum of growing and resting bacterial
      cfu(:, iPatient) = sum(bactCount, 2) ;
   end
   % Calculate log10(CFU)
   log10CFU{iDoseGrp}  = log10(cfu) ;
end
% Save results
log10CFU_250bid = log10CFU{1} ;
log10CFU_250tid = log10CFU{2} ;
log10CFU_500bid = log10CFU{3} ;
log10CFU_500tid = log10CFU{4} ;
Simulating group 1 ...
Simulating group 2 ...
Simulating group 3 ...
Simulating group 4 ...
```

Time Course Profile of Bacterial Counts

We plot the median (in red) and percentile (shaded) profiles of the log10 (CFU) levels for all four dosage regimens. Observe that in all four groups, the median time course profile shows that bacterial eradication is complete before the end of the treatment period (336 hours). However, it is evident from the higher percentile profiles that the treatments are not successful for all patients. The 95th and 90th percentile profiles also indicate that dosing a lower amount with a higher frequency (250 tid) is more effective than less frequent dosing with higher amount (500 bid).

```
hax1(1) = subplot(2,2,1) ; plotCFUCount(tObs,
log10CFU_250bid, 'a. Dose 250 bid' )
hax1(2) = subplot(2,2,2) ; plotCFUCount(tObs,
log10CFU_250tid, 'b. Dose 250 tid' )
hax1(3) = subplot(2,2,3) ; plotCFUCount(tObs,
log10CFU_500bid, 'c. Dose 500 bid' )
hax1(4) = subplot(2,2,4) ; plotCFUCount(tObs,
log10CFU_500tid, 'd. Dose 500 tid' )
% Link subplot axes
linkaxes(hax1)
```

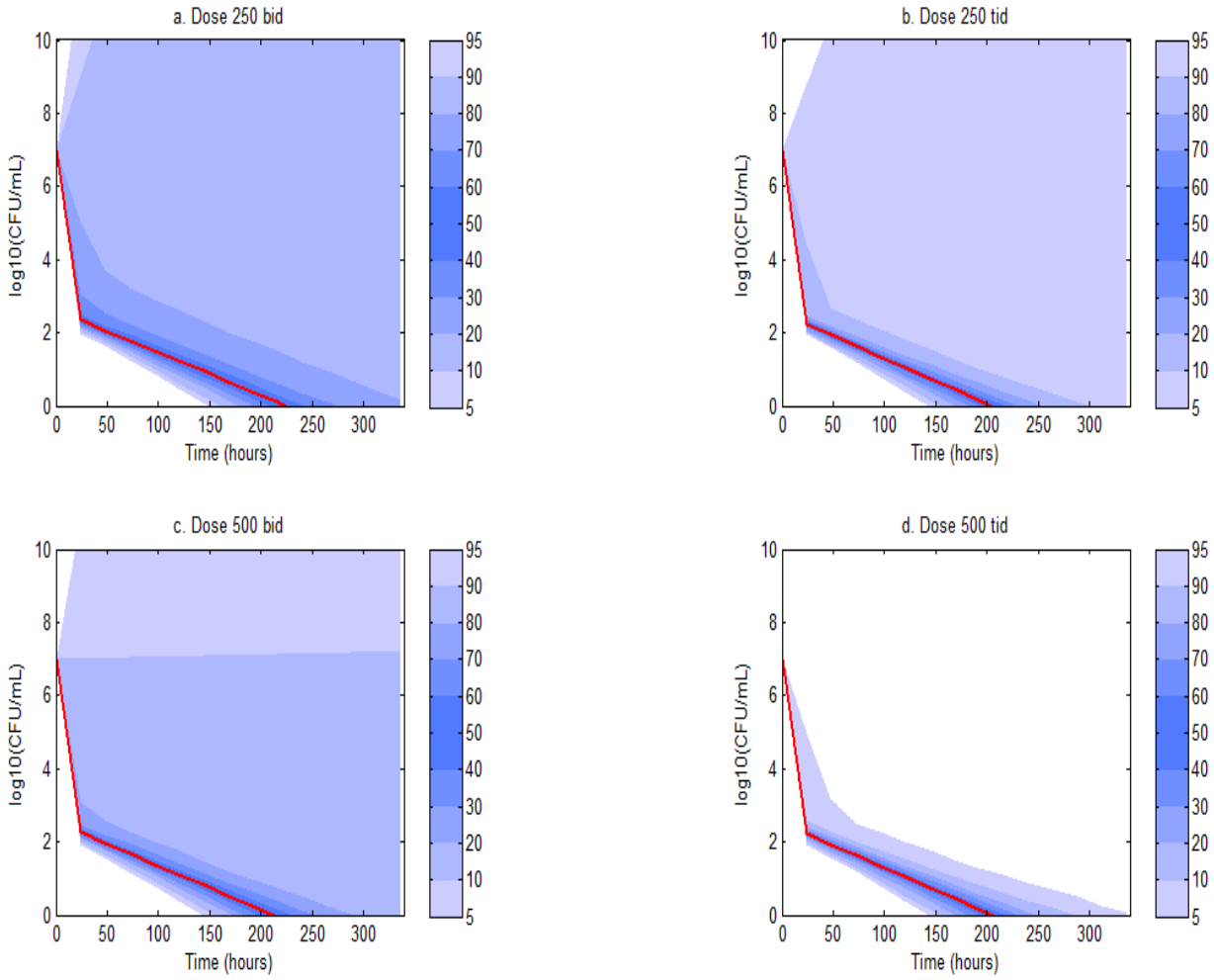


Figure 20: Effect of Renal Function on Antibacterial Activity

Finally, we compared the efficacy profiles of the dosages regimens as a function of the renal function. They classified the patients into four renal function groups based on the creatinine clearance rates (CrCL):

i. Creatinine Clearance Group 1: CrCL < 30
ii. Creatinine Clearance Group 2: 30 <= CrCL < 50
iii. Creatinine Clearance Group 3: 50 <= CrCL < 70
iv. Creatinine Clearance Group 4: CrCL >= 70

The next figure shows the effect of renal function (creatinine clearance rate) on the antibacterial efficacy of the four dosage regimens. Observe that in the normal renal function group (CrCL >= 70), the efficacy profiles of the four treatment strategies are significantly different from each other. In this case, the 500 mg t.i.d. dose is much more effective than the other regimens. In contrast, simulations involving patients with renal dysfunction (CrCL < 30 and 30 <= CrCL < 50), we don't see much difference between the treatment groups. This indicates that for patients with a renal dysfunction, a less intense or less frequent dosing strategy would

work almost as well as a dosing strategy with higher frequency or dosing amount.

```
% Preallocate
idCrCLGrp   = false(nPatients, nDoseGrps) ;
% Line Style
ls = {'bd:', 'b*:', 'rd:', 'r*:'} ;
titleStr = {'CL_c_r < 30'          , ...
          '30 <= CL_c_r < 50'     , ...
          '50 <= CL_c_r < 70'     , ...
          'CL_c_r > 70'           };
f = figure;
set(f, 'Color', 'w')
for iCrCLGrp = 1:4 % Creatinine Clearance Groups
   hax2(iCrCLGrp) = subplot(2,2, iCrCLGrp) ;
   title( titleStr{iCrCLGrp}   ) ;
   ylabel('Prob(log10CFU < 0)' ) ;
   xlabel('Time (hours)'       ) ;

end
% Set axes properties
set(hax2,   'XTick'       , 0:48:336      , ...
          'XTickLabel'   , 0:48:336      , ...
          'Ylim'         , [0 1]         , ...
          'Xlim'         , [0 336]       , ...
          'NextPlot'     , 'add'         , ...
          'Box'          , 'on'          );
% Plot results by renal function group:
for iDoseGrp = 1:nDoseGrps
   % Extract indices for renal function
   idCrCLGrp(:,  1) = CrCL(:,iDoseGrp) < 30
;
   idCrCLGrp(:, 2) = CrCL(:,iDoseGrp) >= 30 &
CrCL(:,iDoseGrp) < 50          ;
   idCrCLGrp(:, 3) = CrCL(:,iDoseGrp) >= 50 &
CrCL(:,iDoseGrp) < 70          ;
   idCrCLGrp(:,  4) = CrCL(:,iDoseGrp) >= 70
;

   for iCrCLGrp = 1:4 % Creatinine Clearance
Groups

      % Calculate probability
      Pr = sum( ( log10CFU{iDoseGrp}(:,
idCrCLGrp(:,  iCrCLGrp)') < 0) , 2
)/sum(idCrCLGrp(:,iCrCLGrp)) ;

      % Plot
      plot(hax2(iCrCLGrp), tObs, Pr , ls{iDoseGrp},
'MarkerSize', 7)
   end

end

legend(hax2(4), {'250 b.i.d.', '250 t.i.d.', '500 b.i.d.',
'500 t.i.d.'} )
legend location NorthWest
legend boxoff

linkaxes(hax2)
```

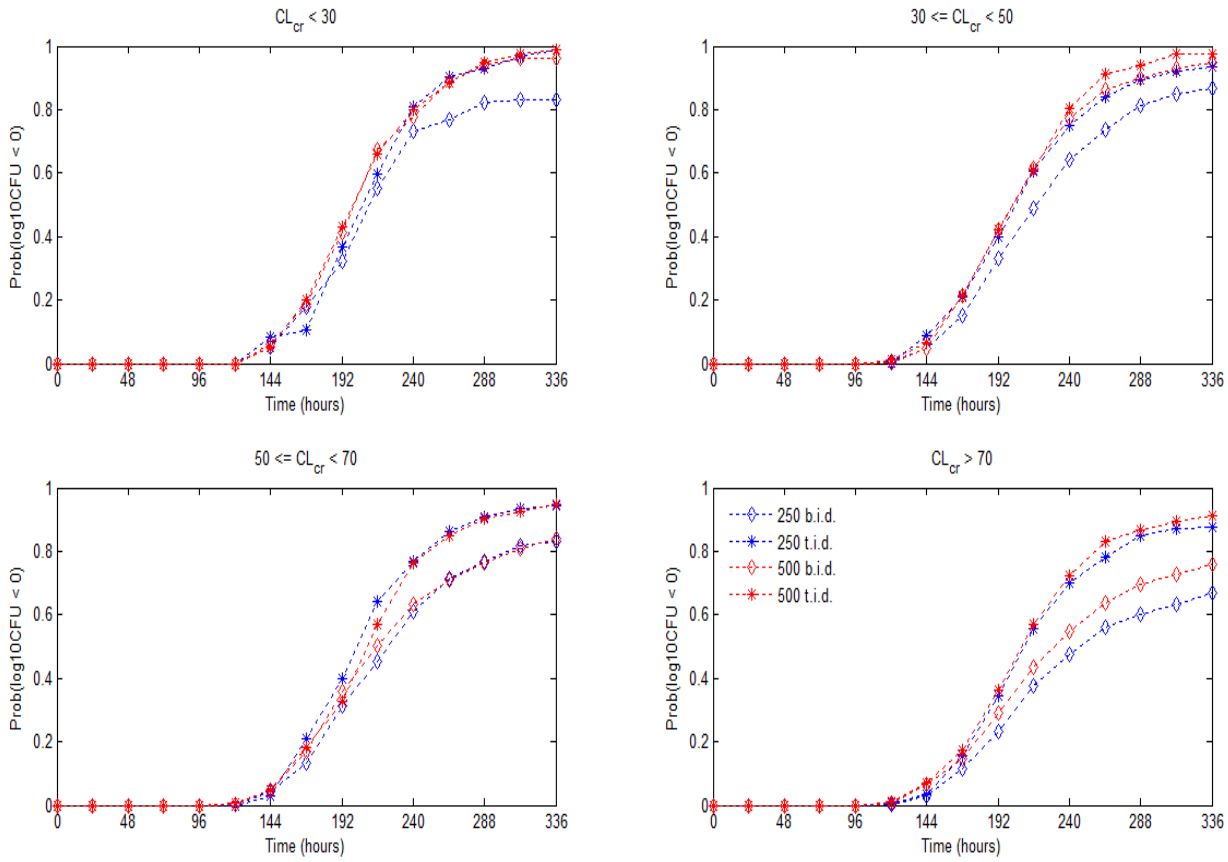


Figure 21: Effect of Renal Function (creatinine clearance rate) on the Antibacterial Efficacy of the Four Dosage Regimens

Model Analysis

Two compartmental models resolve the body into a central compartment and a peripheral compartment (Figure 22). Although these compartments have no physiological or anatomical meaning, it is assumed that the central compartment comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. The two compartment model assumes that, following drug administration into the central compartment, the drug distributes between the central compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution. But after a time interval (*t*), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment as shown by drug clearance reaction in the central compartment of figure 22.

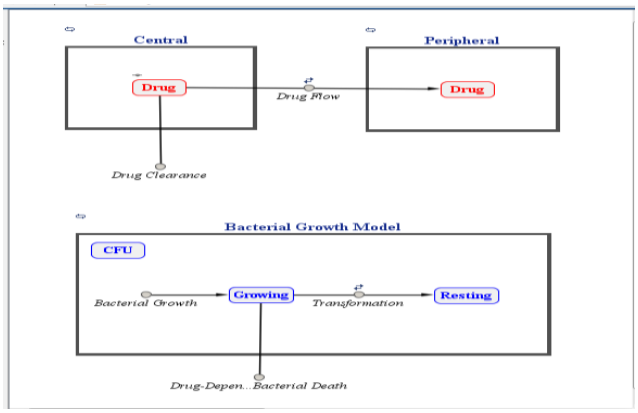


Figure 22: Graphical view of the Simbiology model implemented.

Simulation Results Analysis

The results obtained for the PK/PD modeling and simulation to guide dosing strategy for antibiotics are:

- The plot in red: shows the median
- The shaded percentiles profiles of the log10
- (CFU): shows the level of all four dosages.

We observe that in all four groups, the median time course profile shows that bacterial eradication is complete before the end of the treatment period (336 hours). However, it is evident from the higher percentile profiles that the treatments are not successful for all patients. The 95th and 90th percentile profiles also indicate that dosing a lower amount with a higher frequency (250 tid) is more effective than less frequent dosing with higher amount (500 bid).

Also the graph shows that initially there is a rapid decline in the drug concentration owing to elimination from the central compartment and distribution to the peripheral compartment. Hence during this rapid initial phase the drug concentration will decline rapidly from the central compartment, rise to a maximum in the peripheral compartment, and then decline. After a time interval (*t*), distribution equilibrium is achieved between the central and peripheral compartments.

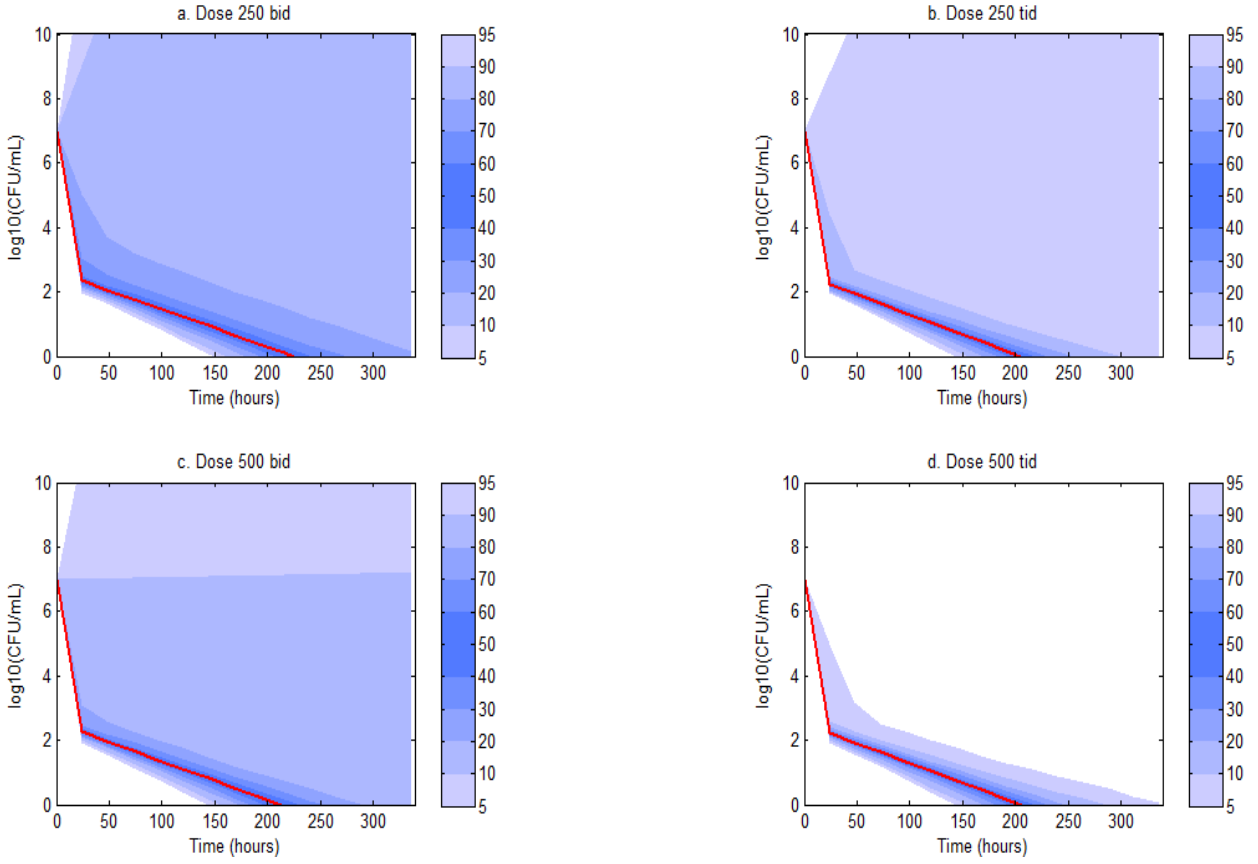


Figure 23: The Drug-Concentration–time profile

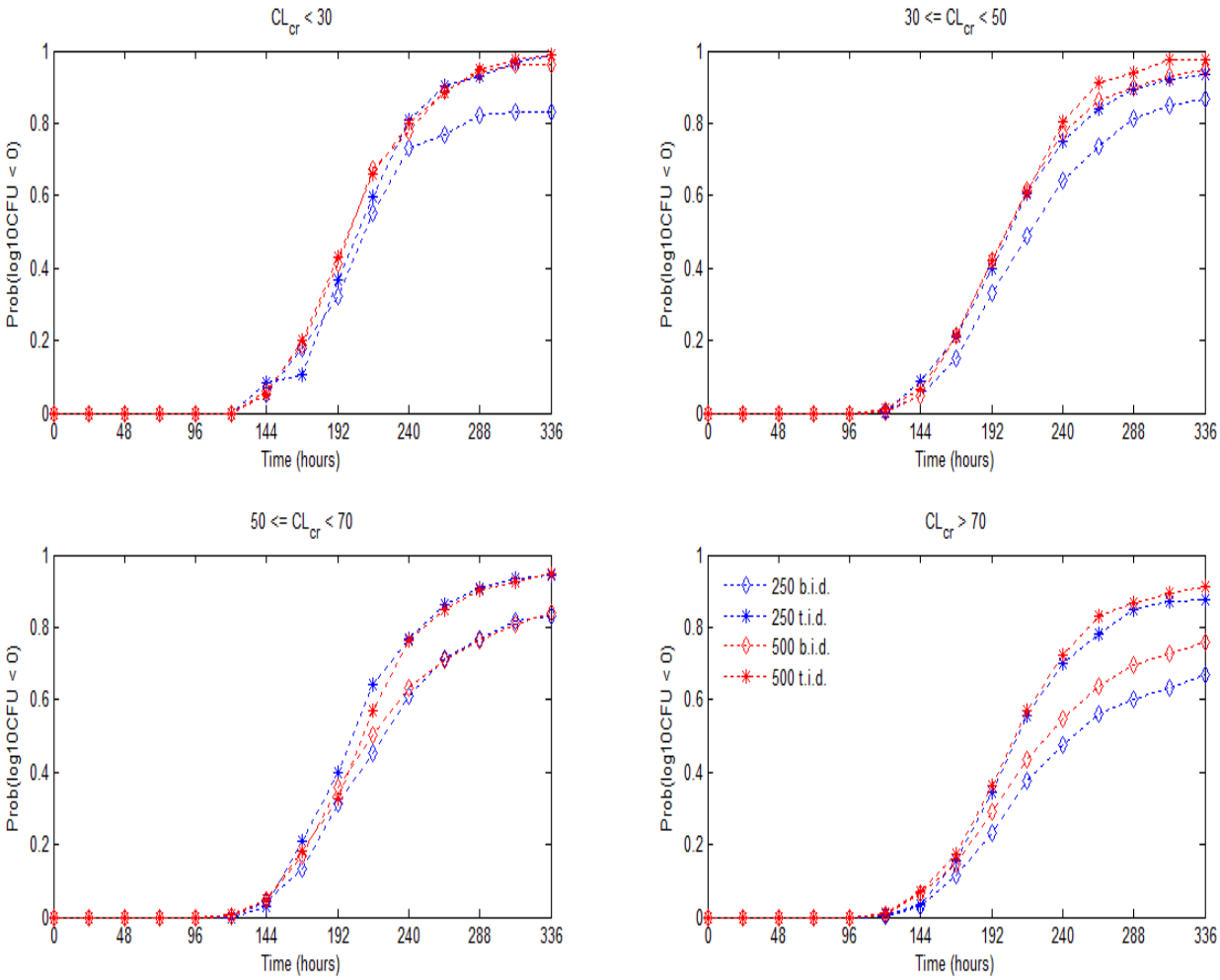


Figure 24: Effect of Renal Function (creatinine clearance rate) on the Antibacterial Efficacy of the Four Dosage Regimens.

In figure 23 and 24, it is observed that in the normal renal function group (CrCL >= 70), the efficacy profiles of the four treatment strategies are significantly different from each other. In this case, the 500 mg t.i.d. dose is much more effective than the other regimens. In contrast, simulations involving patients with renal dysfunction (CrCL < 30 and 30 <= CrCL < 50), we don't see much difference between the treatment groups. This indicates that for patients with a renal dysfunction, a less intense or less frequent dosing strategy would work almost as well as a dosing strategy with higher frequency or dosing amount.

Conclusion

The interpretation of the results obtained in this research have shown that, Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation can be used as an 'applied science' tool to provide answers on efficacy and

safety of new drugs faster and at a lower cost. PK/PD modeling can be used from the preclinical phase through all clinical phases of drug development. For PK/PD modeling and simulation to fulfill its potential in drug development, it needs to be embraced across the industry and regulatory agencies, and more education on this topic is required.

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