Original Article

Predicting the duration of antibacterial treatment with cell wall synthesis inhibitors using mathematical models

Panit Suavansri, Chidchanok Lursinsap

Department of Mathematics and Computer Science, Faculty of Science, Chulalongkorn University, Phayathai Road, Patumwan, Bangkok, Thailand

Corresponding Author:
Panit Suavansri, Department of Mathematics and Computer Science, Faculty of Science, Chulalongkorn University, Phayathai Road, Patumwan, Bangkok, Thailand.
E-mail: panitsuavansri@gmail.com

Received: July 21, 2016
Accepted: Sept 12, 2016
Published: Sept 26, 2016

Keywords:
Mortality rate, Bacteria, Probability

ABSTRACT

Objective: This paper proposed a new mathematical model of within-host population dynamics of bacteria after cell wall synthesis inhibitors administration for practically predicting treatment duration and drug dosage. The aim of this paper is to predict the duration of antibacterial treatment with cell wall synthesis inhibitors using mathematical models. **Materials and Methods:** Our model deployed various concepts from different fields of probability, biology, physics, chemistry, pharmacology (pharmacokinetics and pharmacodynamics), and medical sciences. The following assumptions and hypotheses were established: (i) Binding or collision rate between drug molecule and bacteria depends on the relative velocity between drug molecule and bacteria, (ii) ability or probability of binding or capturing between drug molecule and bacteria can be evaluated using four probability factors, based on the principal of physics and chemistry, (iii) the number of bacteria dying from antibiotics is equal to the number of drug molecules binding bacteria. Thus, the bacterial death rate is equal to rate of drug molecules binding and killing bacteria (amount of drug molecules per second), and (iv) plasma drug concentration is constant and time-independent. In this paper, *Neisseria meningitidis* and *Pseudomonas aeruginosa* are selected to demonstrate the numerical results. **Conclusion**: In this result, duration of treatment are 2-7 days, which is nearly the same as course of antibacterial therapy.

INTRODUCTION

There have been several researches concerning the growth and mortality rate of bacteria to estimate the recuperation period of a patient in the forms of mathematical models. Those researches generally consist of pharmacodynamics (PD) and pharmacokinetics with drug absorption, drug distribution, metabolism, and drug elimination [1]. However, the factors regarding the vasculature, shapes of bacteria and drug molecule, velocity of blood flow, as well as the probability of binding between drug molecules and bacteria were not comprehensively encompassed.

In this study, the above factors are simultaneously considered to model the temporal interaction between the drug molecules and the bacteria. The drug molecules move toward the bacteria with a relative velocity defined in terms of the diameter of vasculature and blood stream acting as a transporter. Based on the theoretical relative velocities in physics, the velocity of drug molecules in blood flow is assumed to be higher than the velocity of bacterial agents resulting from the convection of blood flow. To effectively kill a bacterium, some drug molecules must be bound with the surface of bacterium. However, it is impossible to control the movement of drug molecules in the blood stream. A practical solution is to have much amount of drug molecules than the number of bacteria so that the probability of binding some drug molecules with the surface of bacterium can be increased. This solution confirms with the actual treatment. Therefore, in this study, it is assumed that the amount of drug molecules is much more than the number of bacteria and only some portions of drug molecules can bind with bacteria.

To consider the mechanism of drugs in molecular level, after cell wall synthesis inhibitors attach Penicillin-binding proteins (PBPs), which are bacterial enzymes for cell wall synthesis and located on bacterial cell wall, N-acetylmuramic acid (NAG) and N-acetylglucosamine (NAM) cannot enter to an active site on PBPs to be substrates for synthesis of peptidoglycan, which are components of cell wall (see details in Section 2). Although both Gram-positive and Gram-negative bacteria consist of cell wall with different amount of peptidoglycan, our model can also apply with both of them by the same mechanism. Hence,

antibiotics with other mechanisms (not cell wall synthesis inhibition), such as DNA or RNA synthesis inhibitors, using Brownian movement for attaching intracellular enzymes, not convection by blood flow, are neglected in this paper. Second, since theoretical background in this paper uses the convective rate by blood flow, this model can apply with only systemic infection (bacteremia or septicemia). Since the most common Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* causing cellulitis or *Streptococcus pneumoniae* causing pneumonia, are local or organ infection, i.e., skin and lung infection, respectively, our model cannot apply with them. Therefore, in this study, *Neisseria meningitidis* in the case of nonresistance and *Pseudomonas aeruginosa*, representing extended spectrum beta-lactamase bacteria in case of resistance, are chosen for simulating numerical results since both of them are systemic infection (bacteremia or septicemia).

With the loss of generality, we assume that the structure of drug molecule and bacteria are sphere and prolate spheroid, respectively, as shown in Figure 1. The size of each drug molecule is smaller than the size of each bacterium, implying that drug molecule can follow bacteria to attach and kill them. First, since the shape and size of each drug molecule as well as bacteria are not exactly the same, the concept of Stokes radius derived from Varani [2] was adopted to define the average radius of prolate spheroid-shaped of the drug molecule and bacteria. The principal is $V^{(sphere)}=V^{(sphere)}$, then $r^{(stoke)}=\left(r_w^{(particle)\,2} r_l^{(particle)}\right)^{1/3}$, where $r_w^{(particle)}$ and $r_l^{(particle)}$ be the half width and half-length of a particle having prolate shape. Thus, we have two average radii of drug molecule and bacteria, denoted as $\bar{r}^{(drug)}=\left(r_w^{(drug)\,2} r_l^{(drug)}\right)^{1/3}$ and $\bar{r}^{(bacteria)}=\left(r_w^{(bacteria)\,2} r_l^{(bacteria)}\right)^{1/3}$, respectively.

MATERIALS AND METHODS

Difference of Velocities of Drug Molecule and Bacteria

To derive the time of chasing bacteria by a drug molecule, the relative velocities of bacteria and drug molecule must be defined first. Since the velocities of the drug molecule and bacteria may be affected by their shapes and sizes, the transportation velocity of a rod-shaped particle in a cylindrical pore with the effect of convective hindrance introduced by Agasanapura *et al*. [3] were adapted to show the velocity difference. This difference is captured by a term called local lag coefficient and it is defined as the ratio of steady state of particle velocity and the fluid velocity in the absence of the particle in a cylindrical tube.

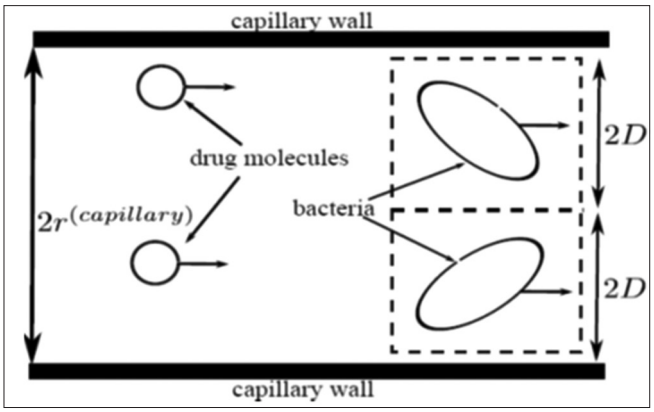

Figure 1: The scenario and assumptions of shape and size of drug molecule and bacteria made in our study. The drug molecules can chase the bacteria to bind and kill them in a lumen of capillary. $r^{(capillary)}$ is a radius of capillary and D is the width of cubic volume such that one bacterium can be found

However, directly measuring the velocity of a drug molecule or bacteria is not simple. To ease this burden, the particle velocity can be transformed and written in terms of relative particle ratio defined as the ratio of known particle radius and tube radius instead. The word particle in this Section may refer to a drug molecule or bacteria depending on the context of discussion. By using the notations from the previous section, the relative particle ratio for drug molecule $\lambda^{(drug)}$ and for bacteria $\lambda^{(bacteria)}$ are defined as

$$\lambda^{(drug)}=\frac{\bar{r}^{(drug)}}{r^{(capillary)}}=\frac{\sqrt[3]{\left(r_w^{(drug)}\right)^2 r_l^{(drug)}}}{r^{(capillary)}}\approx 0.000156 \quad (1)$$

and

$$\lambda^{(bacteria)}=\frac{\bar{r}^{(bacteria)}}{r^{(capillary)}}=\frac{\sqrt[3]{\left(r_w^{(bacteria)}\right)^2 r_l^{(bacteria)}}}{r^{(capillary)}}\approx 0.21 \quad (2)$$

From the relative particle ratios in Equations 1 and 2, it can be seen that the relative drug ratio is much smaller than that of bacteria ($\lambda^{(bacteria)}>\lambda^{(drug)}$). since $G^{(drug)}>G^{(bacteria)}$ and $v^{(particle)}=G^{(particle)}v^{(blood)}$, this implies that the flow velocity of drug molecule $v^{(drug)}$ is obviously much higher than that of bacteria $v^{(bacteria)}$ [3]. Thus, chasing and binding done by a drug molecule against bacteria is possible.

Position Probability Factor

The collision of drug molecules and bacteria can be modeled by modifying the probabilistic model of ship grounding which focused on traveling through a waterway in a straight forward line [4]. In our work, this probability is defined as the ratio of the projection area of bacterium to the contact area. Figure 1 shows different scenarios of how bacteria and drug molecules contact each other from various angles. However, the other human vessels, except capillaries, are not considered for evaluation since the local lag coefficient of drug molecule $G^{(drug)}$ is equal to local lag coefficient of bacteria $G^{(bacteria)}$. This means that drug molecule cannot chase bacteria because both have the same flow speed as discussed in Section 2.1. Thus, our position probability factor is

$$p^{(position)}=\frac{\left(\bar{r}^{(drug)}+r_w^{(bacteria)}\right)\left(\bar{r}^{(drug)}+\bar{d}\right)}{\left(r^{(capillary)}\right)^2} \quad (3)$$

Binding Probability Factor

Once a drug molecule collides with bacteria, the drug molecule must bind with a disk of receptor, i.e., an active site of PBPs, to inhibit the signal transduction pathways for cell wall synthesis by competing with NAG and NAM, as substrates, used for cell

wall synthesis. In this study, binding probability from Berg and Purcell's study [5] must be modified because drug molecules can bind only the half of size of bacteria. Since the current of drug molecules is unidirectional, they can bind only bacterial receptors at one side of bacteria. Then, binding probability in this study is as follows:

$$p^{(\text{binding})}=\frac{1}{2}\left(\frac{r^{(\text{receptor})}N^{(\text{receptor})}}{\left(\pi\bar{r}^{(\text{bacteria})}+r^{(\text{receptor})}N^{(\text{receptor})}\right)}\right) \quad (4)$$

Where $N^{(\text{receptor})}$ is the number of receptors on the cell surface and $r^{(\text{receptor})}$ is the radius of disk of the receptor of bacteria.

Capture Probability Factor

During colliding between drug molecule and bacteria, the drug molecule can deviate or be deviated by some factors. Thus, Berg and Purcell's study [5] defined the probability of ligands capturing the receptor on cell surface. In this paper, since drug molecules can deviate from the straight direction toward the position of bacterial target, capture probability must be calculated from the length between bacteria and drug molecules that drug molecules can follow bacteria to bind is $l^{(\text{capillary})}$, where $l^{(\text{capillary})}$ is the length of capillary and $\bar{r}^{(\text{bacteria})}$ is the average radius of prolate spheroidal bacteria. Thus, our capture probability factor is as follows:

$$p^{(\text{capture})}=\frac{\bar{r}^{(\text{bacteria})}}{\bar{r}^{(\text{bacteria})}+l^{(\text{capillary})}} \quad (5)$$

Orientation Probability Factor

In the aspect of chemical reaction, the reaction of particles will occur when particles collide with their accurate orientations in space. This implies that accurate orientations can increase the probability of collision and rate of reaction. Taroni *et al*. [6] defined the probability of attaching between a binding site of substrate and an active site of enzyme is the ratio of the surface area of amino acid binding to the molecule to the total surface area. In this paper, since drug molecule must bind a disk of receptor or an active site of PBPs with its binding site, i.e. beta-lactam ring of the drug molecule, orientation probability must be evaluated. Hence, our orientation probability factor is the ratio of binding area of drug molecule to the total surface area of drug molecule, i.e.,

$$p^{(\text{orientation})}=\left(\frac{\pi z^2}{4}\right)/\left(2\pi\left(r_w^{(\text{drug})}\right)^2\left(1+\frac{r_l^{(\text{drug})}}{er_w^{(\text{drug})}}\sin^{-1}e\right)\right) \quad (6)$$

Where z is the diameter of binding site of drug molecule (beta-lactam ring) and $e=\sqrt{1-\left(r_w^{(\text{drug})}/r_l^{(\text{drug})}\right)^2}$.

Total Probability

The total probability of drug molecule to interact with bacteria is computed from the probabilities of all factors which are position probability, binding probability, capture probability, and orientation probability.

$$p^{(\text{total})}=p^{(\text{position})}\times p^{(\text{binding})}\times p^{(\text{capture})}\times p^{(\text{orientation})} \quad (7)$$

Each probability in equation (7) can be computed from equations 3-6, respectively.

Duration of Treatment by Dynamic Drug Model

From Section 2.1, the relative velocity with respect to those of drug molecule and bacteria is defined as

$$v^{(\text{relative})}=v^{(\text{drug})}-v^{(\text{bacteria})}=(G^{(\text{drug})}-G^{(\text{bacteria})})v^{(\text{capillary})} \quad (8)$$

Where $G^{(\text{drug})}$ and $G^{(\text{bacteria})}$ are the local lag coefficients of drug molecules and bacteria (with $G^{(\text{drug})} > G^{(\text{bacteria})}$, respectively. Once the relative velocity of drug molecules and bacteria is known, the number of drug molecules within a capillary tube at any unit time must be estimated before the computation of mortality rate of bacteria. The cross-sectional area of capillary $\pi\left(r^{(\text{capillary})}\right)^2$ is multiplied to the relative velocity to get the flow rate of drug molecules by blood volume. The blood volume can be transformed into the mass of drugs by multiplying the blood volume by the function of plasma drug concentration c(t) at time t. The obtained result can be interpreted as the flow rate of drug mass. To link drug mass with the number of drug molecules, the drug mass is divided by the molecular mass of drug molecule M and multiplied by Avogadro's number A. Therefore, the number of drug molecules $N^{(\text{drug})}$ at a given flow rate is equal to:

$$N^{(\text{drug})}=\frac{\pi r^{(\text{capillary})^2}C(t)A(G^{(\text{drug})}-G^{(\text{bacteria})})v^{(\text{capillary})}}{M} \quad (9)$$

To estimate the flow rate of drug molecules in host blood physiology, the capillary transit time τ and the circulatory time γ [7,8] when drug molecules chase a bacteria in capillary must be involved. Then, ratio of time that drug molecules travel only in capillaries is τ/γ. Furthermore, only drug molecules in free form (not bounded with plasma protein) actually binding with the bacteria are taken into account. Thus, free drug fraction, denoted by α and defined as the ratio of free (unbound) drug molecules to all drug molecules, is also considered. Other parameters to be considered are the number of capillaries in human body defined as $N^{(\text{capillary})}$ and the number of drug molecules that can kill only one bacterium defined as $N^{(\text{kill})}$. The number of bacteria killed by drug molecules per second (called bacterial death rate $\phi(t)$ can be computed by the following equation.

$$\varphi(t)=\frac{\pi\alpha N^{(\text{capillary})}\tau r^{(\text{capillary})^2}C(t)Ap^{(\text{total})}\left(G^{(\text{drug})}-G^{(\text{bacteria})}\right)v^{(\text{capillary})}}{N^{(\text{kill})}\gamma M} \quad (10)$$

Thus, the bacterial population at time t, denoted as P(t), can be evaluated from its dynamical system in the form of the first order linear differential equation with the birth-death rate of bacteria itself (denoted as g and μ), and the bacterial death rate due to drug previously computed as $\phi(t)$ in the following equations.

$$\frac{d}{dt}P(t)=(g-\mu)P(t)-\varphi(t) \quad (11)$$

First, to solve Equation (11) for evaluating duration of treatment, assume that the plasma drug concentration C(t) can become a constant k. Then, the bacterial death rate becomes a function of the constant k instead of time t and $\phi(k)$ is used instead of $\phi(t)$. Finally, after solving equation (11), the bacterial population P(t) from equation (11) can be written as follows.

$$P(t)=\exp((g-\mu)t)\left(P(0)-\frac{\varphi(k)}{g-\mu}\right)+\frac{\varphi(k)}{g-\mu} \quad (12)$$

Combination Therapy and Effect of Drug Resistance

Antagonist effect can also be found. We will use this principle of proportion [9] to apply with our bacterial death rate by multiplying $\left(\frac{\kappa^{(\text{agonist})}}{\kappa^{(\text{agonist})}+\kappa^{(\text{antagonist})}}\right)$, where $K^{(agonist)}$ and $K^{(agonist)}$ are two plasma concentrations of agonist and antagonist drugs, respectively. Thus, the bacterial death rate in this case is $\left(\frac{\kappa^{(\text{agonist})}}{\kappa^{(\text{agonist})}+\kappa^{(\text{antagonist})}}\right)\varphi\left(\kappa^{(\text{agonist})}\right)$.

Drug resistance of bacteria can be evaluated by defining the potency of the drug resistance as η $(0<\eta<1)$, then $(1-\eta)K^{(agonist)}$ is the effective plasma drug concentration for killing bacteria without considering drug resistance. In this study, the potency of the drug resistance in our numerical example is $\eta=\frac{N^{(\beta)}}{N^{(\beta)}+N^{(PBP)}}$, where $N^{(PBP)}$ and $N^{(\beta)}$ is the number of two enzymes: PBPs and beta-lactamase, respectively. Note that beta-lactamase is a bacterial enzyme destroying beta-lactams, which is one of the mechanisms of drug resistance of bacteria.

Dual effect contains different drug action such as beta-lactams with beta-lactamase inhibitor for treating in the case of drug resistance. In the case of dual drug action, our numerical example uses clavulanic acid as a dual drug for inhibiting beta-lactamase (beta-lactamase inhibitor). Thus,

Table 1: The parameters used in our numerical example of patient with *N. meningitidis* infection

Parameters	Value	Description	Source
$G^{(drug)}$	1	Lag coefficient of drug molecule	[3]
$G^{(bacteria)}$	0.99	Lag coefficient of bacteria[a]	[3]
$r_l^{(drug)}$	0.8142	Half-length of drug molecule (nm)[b]	c
$r_w^{(drug)}$	0.3552	Half width of drug molecule (nm)[b]	c
z	0.2105	Diameter of binding site of drug molecule (nm)[b]	c, d
$r_l^{(bacteria)}$	1	Half-length of bacteria (μm)[a]	[12]
$r_w^{(bacteria)}$	0.5	Half width of bacteria (μm)[a]	[12]
$r^{(receptor)}$	0.1052	Radius of receptor (nm)[a]	[12]
$N^{(receptor)}$	3,100	Number of receptors of bacteria[a]	[5]
g	0.48	Growth rate of bacteria (/day)	[10]
μ	0.33	Death rate of bacteria (/day)	[8]
γ	60	Blood circulatory time (s)	[8]
$r^{(capillary)}$	0.003	Radius of capillary (mm)	[7]
T	1	Transit time of capillary (s)	[7]
$l^{(capillary)}$	0.2	Length of capillary (mm)	[13]
$v^{(capillary)}$	0.3	Blood velocity in capillary (mm/s)	[7]
$N^{(capillary)}$	10^9	Number of capillaries	[14]
V	5	Whole blood volume (l)	[15]
K	18.18	Average plasma ceftriazone concentration (μg/ml)	[16]
α	0.05	Free drug fraction	[16]
A	6.02×10^{23}	Avogadro's number	[17]
M	661.59	Molecular weight of ceftriazone	[16]
k*	2.55	Average plasma clavulanic acid concentration (μg/ml)	[18]
M*	199.16	Molecular weight of clavulanic acid	[19]

N. meningitides: Neisseria meningitides. [a]Using *Neisseria meningitidis* for our numerical example, [b]Using ceftriazone for our numerical example, [c]Measured by using Accelrys Discovery Studio 3.5 client (DS visualizer) program, [d]Calculated by using a program

the effective plasma ceftriaxone concentration, that can kill bacteria, is $\left(\frac{N^{(PBP)}}{(1-\sigma)N^{(\beta)}+N^{(PBP)}}\right)k$, where $\sigma\frac{k^*/M^*}{(k/M)+\left(k^*/M^*\right)}$ is the potency of dual drug action, k and k* are plasma drug and dual drug concentration, M and M* are molecular weight of drug and dual drug, respectively.

Since our numerical example uses clavulanic acid as dual drug inhibiting beta-lactamase in bacteria [10]. Thus, we construct this probability, named dual action probability and defined as $p^{(dual)}$. By using the fact that the active site of beta-lactam inhibiting enzyme (beta-lactamase) can choose ceftriaxone (beta-lactams) or clavulanic acid (beta-lactam analogs) by proportion of both molecules, then we have

$$p^{(dual)}=\frac{N}{N+N^*}=\frac{\frac{kVA}{M}}{\frac{kVA}{M}+\frac{k^*VA}{M^*}}=\frac{(k/M)}{(k/M)+(k^*/M^*)}. \quad (13)$$

Where A is the Avogadro's number, k and k* are plasma drug and dual drug concentration, respectively, V is patient's whole blood volume, N and N* are the number of drug molecules and dual drug molecules in patient's blood, respectively.

RESULTS AND DISCUSSION

In this study, our first scenario or assumption is that there are patients' infected *N. meningitidis* with their different bacterial loads. These patients are treated by ceftriaxone, derivatives of the 3rd generation cephalosporin. All parameters used in our simulation are summarized in Table 1. The plasma concentration of ceftriaxone is calculated using time-weighted average plasma drug concentration with 0.5 g IV* (first row) of Table 2 in [11]. The results of monotherapy and combination therapy were reported in the following Sections.

Results of Monotherapy, Combination Therapy, and Drug Resistance

Figure 2(b) illustrates the logarithmic plots of different bacterial loads with the fixed plasma drug concentration. It is noticeable that the maximal of the initial bacterial loads of this figure does not decline, but still increases continuously. This means that the given plasma drug concentration cannot diminish or eliminate this initial bacterial density. On the contrary, the other bacterial loads below 1×10^7 copies/ml blood can be cleared within 1-7 days. After the patients have received antibacterial drugs, bacterial load in each patient gradually declines except for the one that still increases since this plasma drug concentration level is not enough to wipe out all bacteria from the patient's blood.

Figure 2(c) demonstrates the normal plots of various bacterial loads. Those initial bacterial loads below 1.5×10^7 copies/ml blood go down and become zero within

Table 2: The parameters for evaluating the local lag coefficient

Description	**r_l (μm)**	**r_w (μm)**	**$\bar{r}$ (μm)**	**ε**	**λ**	**G**	**g (/day)**	**μ (/day)**	**N/A**	**N/A**	**Reference**
Bacteria											
P. aeruginosa	1	0.275	0.57	3.64	0.019	0.995	0.48	0.33	N/A	N/A	[12,10]
Antibiotics	**r_l (μm)**	**r_w (μm)**	**$\bar{r}$ (μm)**	**ε**	**λ**	**G**	**M**	**A**	**K (μg/ml)**	**k (μg/ml)**	**Reference**
Penicillins											
Amoxicillin	0.7768	0.3396	0.4474	2.2876	1.49×10^{-5}	1	365.4042	0.85	5.6	0.21	[19,21]
Ampicillin	0.7265	0.4517	0.5292	1.6084	1.76×10^{-5}	1	349.4048	0.8	4.8	0.18	[19,21]
Cephalosporins											
1st generation											
Cephalexin	0.702	0.3237	0.4190	2.1687	1.40×10^{-5}	1	347.3889	0.895	16	0.598	[19-22]
Cefazolin	0.8931	0.304	0.4353	2.9377	1.45×10^{-5}	1	454.5072	0.26	188	7.031	[19-22]
2nd generation											
Cefuroxime	0.8949	0.4559	0.5709	1.9626	1.90×10^{-5}	1	424.3852	0.7	51	1.907	[20-22]
Cefoxitin	0.9067	0.3372	0.4689	2.6893	1.56×10^{-5}	1	427.4521	0.27	110	4.114	[20-22]
3rd generation											
Cefotaxime	0.8388	0.4600	0.5620	1.8235	1.87×10^{-5}	1	455.4655	0.64	46	1.720	[20-22]
Ceftazidime	0.8299	0.6039	0.6715	1.3742	2.24×10^{-5}	1	546.5761	0.9	69	2.580	[20-22]
4th generation											
Cefepime	0.9549	0.4605	0.5872	2.0738	1.96×10^{-5}	1	480.5611	0.8	70	2.618	[19-21,23]
Phagocytes	**r_l (μm)**	**r_w (μm)**	**(μm)**	**ε**	**λ**	**G**	**N/A**	**N/A**	**N/A**	**N/A**	**Reference**
Neutrophil		8	8.618	1.25	0.2873	0.95	N/A	N/A	N/A	N/A	[24]
Macrophage	10	5	7.937	4	0.2646	0.94	N/A	N/A	N/A	N/A	[24]

P. aeruginosa: Pseudomonas aeruginosa

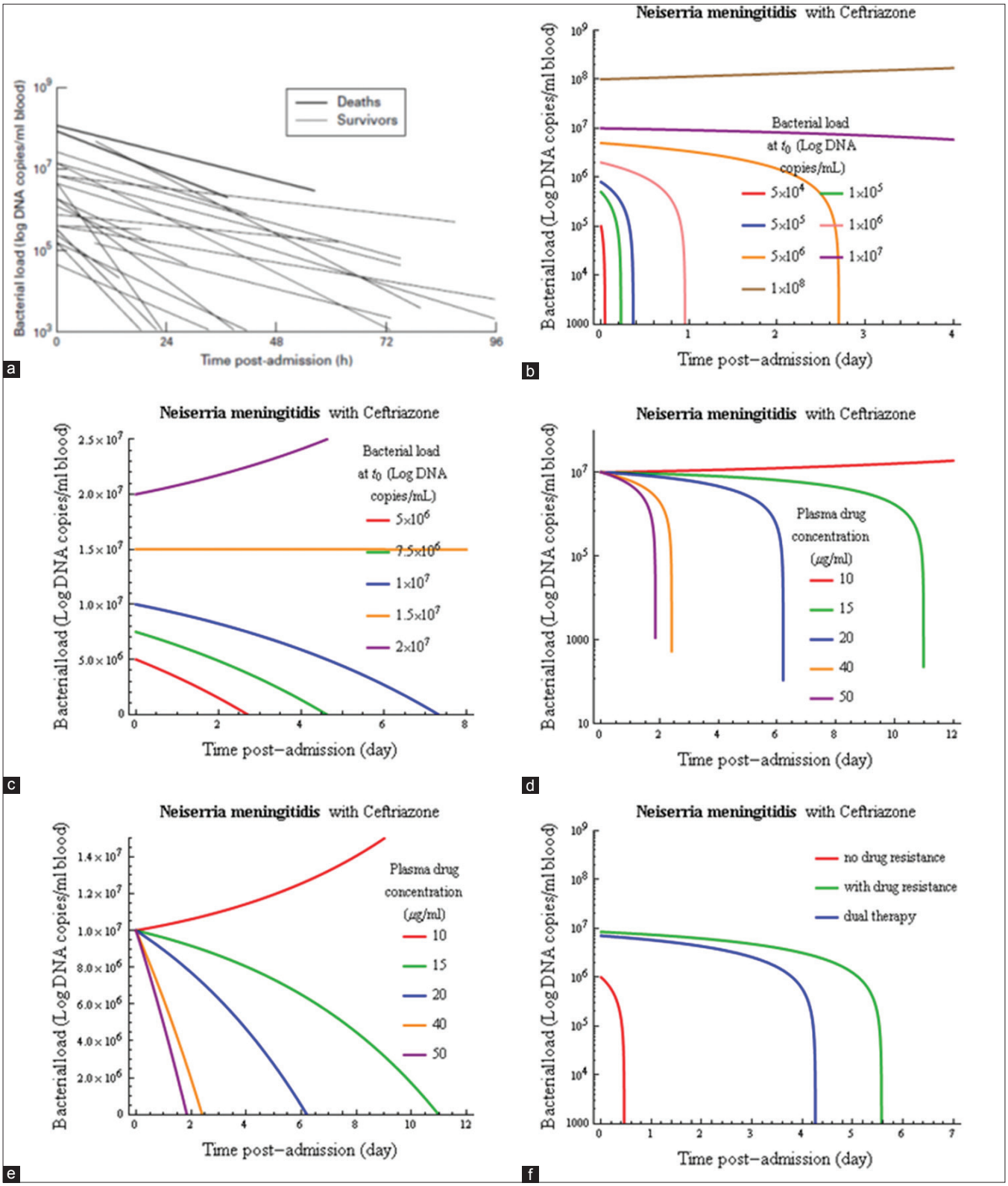

Figure 2: Our estimation results with different values of bacterial load, plasma drug concentration, number of post-admission days. (a) Linear regression analysis showing decline in bacterial DNA load from sequential EDTA samples [20]. (b) The logarithmic plots between time post-admission (day) and different initial bacterial loads with fixed plasma drug concentration. (c) The normal plots between time post-admission (day) and different initial bacterial loads with fixed plasma drug concentration. (d) The logarithmic plots between time post-admission day) and the same initial bacterial load with different plasma drug concentrations. (e) The normal plots between time post-admission (day) and the same initial bacterial load with different plasma drug concentrations. (f) Our results of no drug resistance, drug resistance, and dual therapy

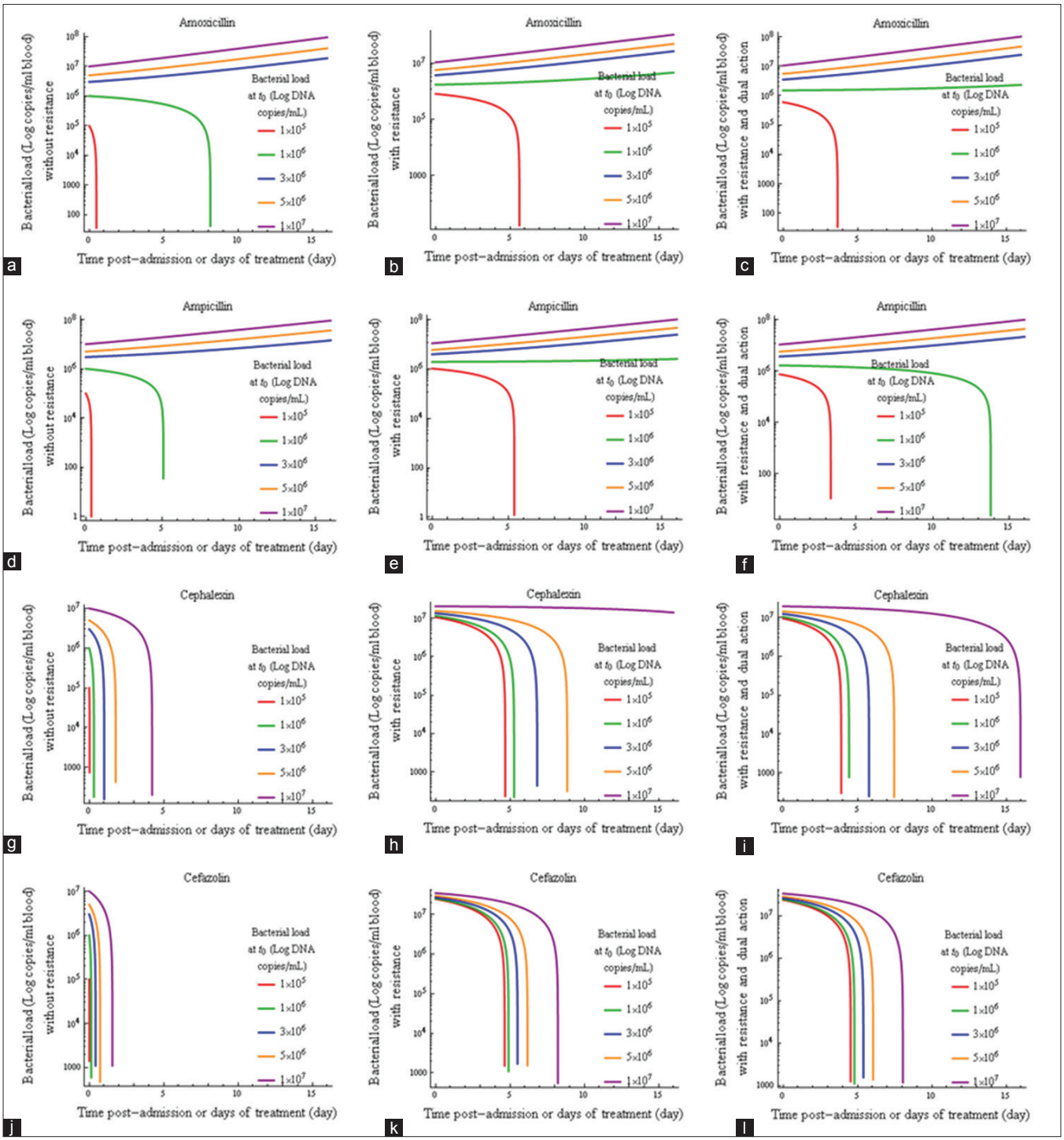

Figure 3: (a-l) show the numerical results between bacterial load of *Pseudomonas aeruginosa* and time after antibiotics administration. Amoxicliin in (a-c) and ampicillin in (d-f) of penicillin group, cephalexin in (g-i) and cefazolin in (j-l), representing 1st generation of cephalosporins were used for these simulations with/without resistance and with dual action of clavulanate as beta-lactamase inhibitors

2-7 days. At the initial bacterial load, 1.5×10^7 copies/ml blood, there is no way for this bacterial load to become zero or be completely eliminated.

In Figure 2(d), the logarithmic plots of different plasma drug concentrations with a fixed initial bacterial load, 10^7 copies/ml blood are considered. It can be observed from these four plots that the time for treatment is about 2-11 days to clear bacteremia while the average plasma drug concentration, 10 μg/ml, cannot reduce the bacterial density.

Peak and Mean Plasma Drug Concentration

All antibiotics, such as penicillins and cephalosporins, are complex to compare with each numerical result due to their

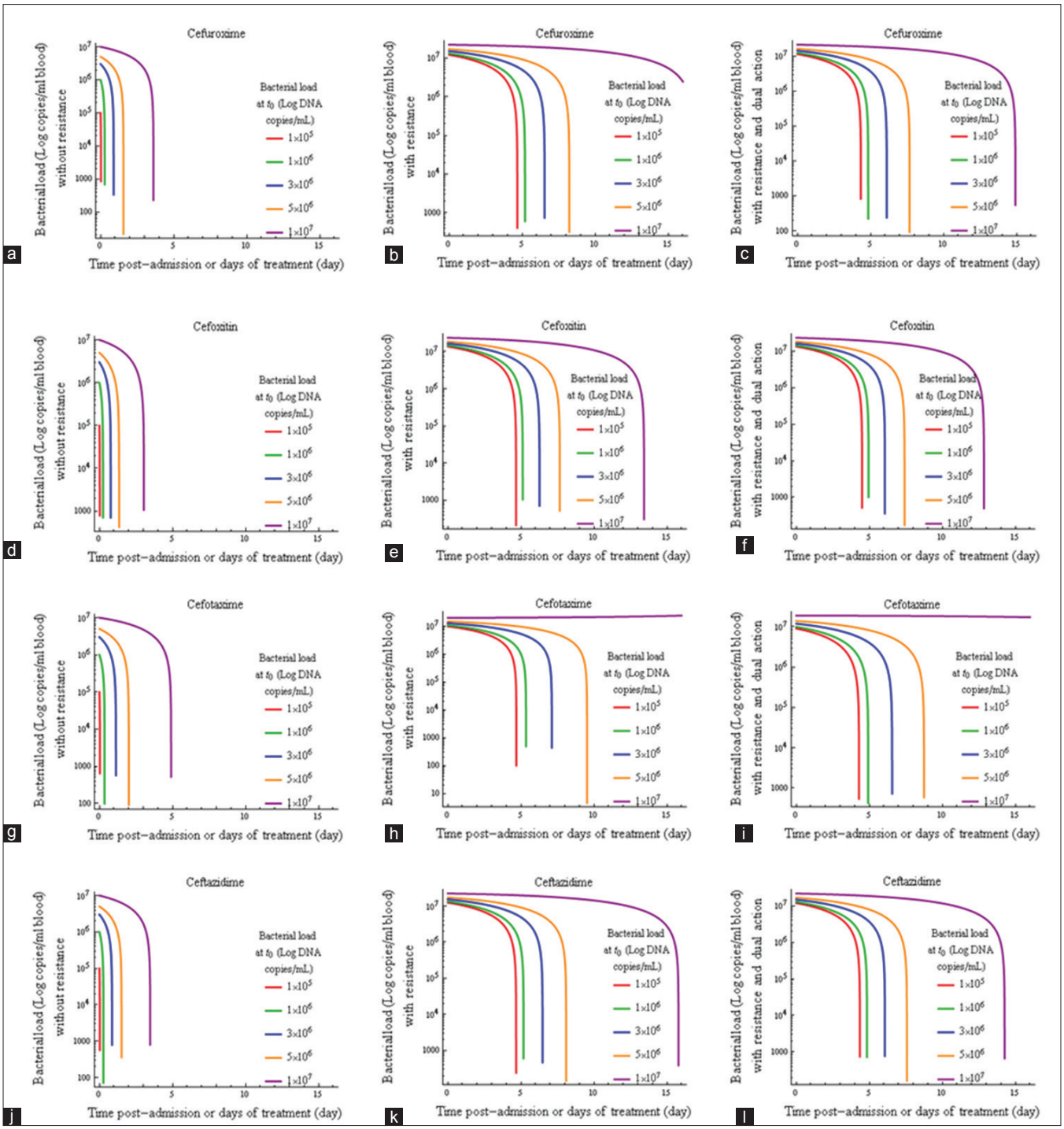

Figure 4: (a-l) shows the numerical results between bacterial load of *Pseudomonas aeruginosa* and time after antibiotics administration. Cefuroxime in (a-c) and cefoxitin in (d-f), representing 2nd generation of cephalosporins, cefotaxime in (g-i) and ceftazidime in (j-l), representing 3rd generation of cephalosporins are used for these simulations with/without resistance and with dual action of clavulanate as beta-lactamase inhibitors

drug dosage and plasma drug concentration. However, the peak plasma drug concentration can be available. Our model is based on the proportion of mean and peak plasma drug concentration of ceftriaxone. The profile of ceftriaxone concentration is given in Table 2 [22]. This section introduces peak plasma drug concentration of penicillins and cephalosporins to use them with other bacteria, *P. aeruginosa* for generating numerical results. Furthermore, these following variables are used for generating results: r_l and r_w are half of length and width, respectively. $\bar{r}=\sqrt[3]{(r_w)^2 r_l}$ is the geometric mean. $\varepsilon=r_l/r_w$ and $\lambda=\bar{r}/r^{(capillary)}$ are the particle aspect ratio and the relative particle radius, respectively, and used for finding the local lag coefficient. $G=v^{(particle)}/v^{(fluid)}$ is

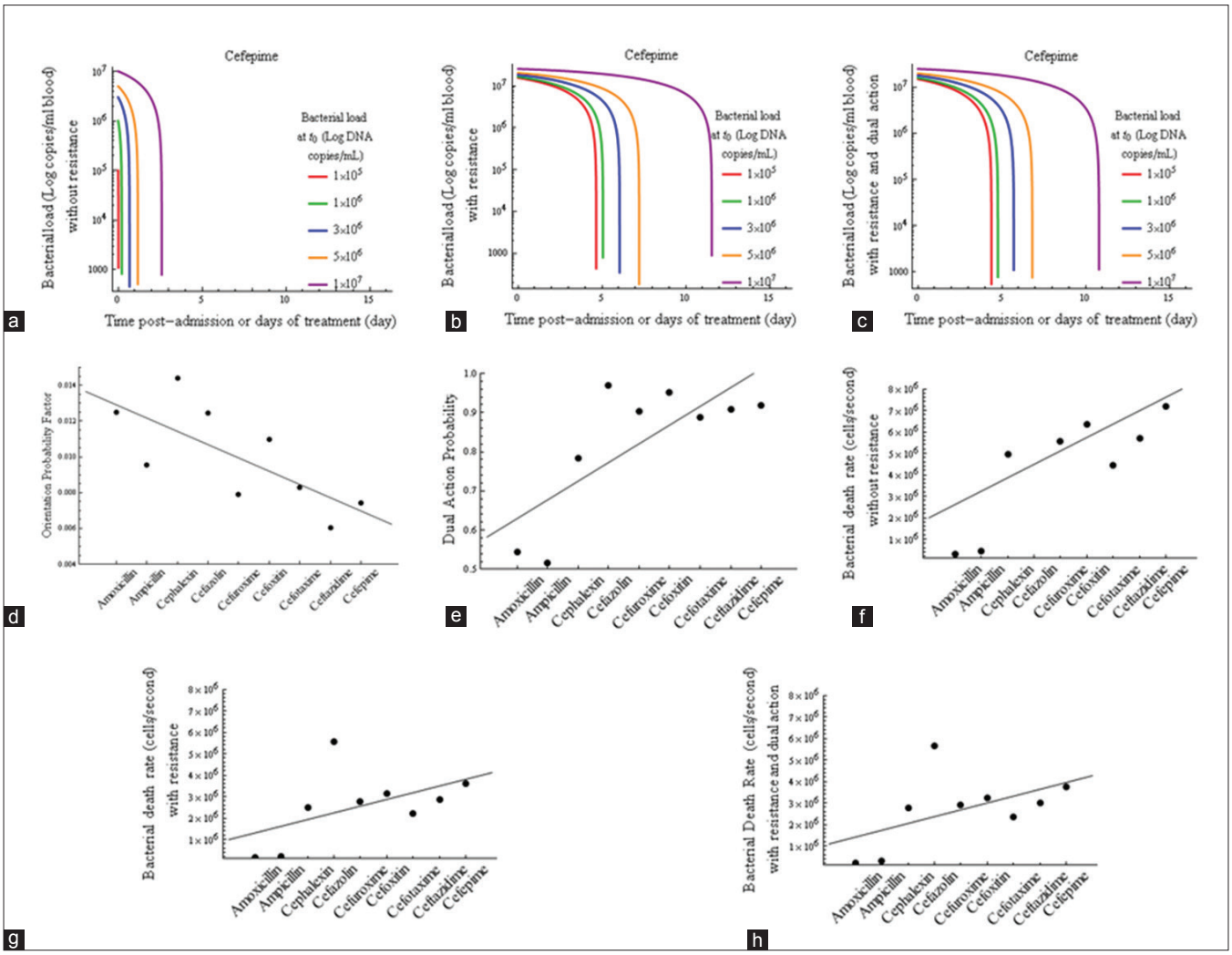

Figure 5: (a-c) The numerical results between bacterial load of *Pseudomonas aeruginosa* and Time after antibiotics administration. Cefepime in (a-c), representing 4th generation of cephalosporins, used for these simulations with/without resistance and with dual action of clavulanate as beta-lactamase inhibitors. (d-h) show the curve fitting of orientation probability factor, dual action probability and bacterial death rate with/without resistance and dual action

the local lag coefficient. $v^{(fluid)}$ and $v^{(particle)}$ are two velocities of fluid and particle, respectively, moving by convection of fluid. K and $k=K\left(\frac{k^{(ceftriazone)}}{K^{(ceftriazone)}}\right)$ are peak and mean plasma drug concentration, where $K^{(ceftriaxone)}=123$ μg/ml and $k^{(ceftriaxone)}=4.6$ μg/ml are peak and mean plasma ceftriaxone concentration, used for calculating k. M and α are the molecular weight and free fraction of drug molecules. N/A is non-applicable. Length and width of drug molecules are measured using Accelrys Discovery Studio 3.5 client (DS Visualizer) program.

Results of Penicillin Group and Generations of Cephalosporin with *P. aeruginosa*

Other cell wall inhibitors, besides ceftriaxone, such as amoxicillin or ampicillin in penicillin group and 1st to 4th generation of cephalosporin are considered with the growth and death rate of *P. aeruginosa*, denoted by g and μ in Table 2, which are, respectively. Figures 3a-l and 4a-l, and 5a-c show the numerical results of both penicillins and cephalosporins with *P. aeruginosa*.

Figure 5d-h shows five the fitting curves for the analysis of penicillin group and 1st to 4th generation of cephalosporin. First, in Figure 5(d), the orientation probability factor from penicillin group to 4th generation goes down, implying that the chance or probability of beta-lactamase for destroying beta-lactams in the mechanism of bacterial resistance decreases. This can be explained by increasing the steric effect of R-group or functional group of beta-lactams and then orientation probability factor decreases. Thus, this result confirms that the development of beta-lactams can prevent from bacterial resistance. Second, in Figure 5(e), the efficacy of dual action is higher by upgrading from penicillin group and 1st to 4th generation of cephalosporin. The reason is that beta-lactamase in bacteria cannot split many classes of beta-lactams with two previous reasons and then beta-lactamase will bind clavulanic acid instead of high beta-lactams.

Finally, beta-lactamase is inactivated by clavulanic acid as beta-lactamase inhibitor. This result also confirms that high developmental beta-lactamase inhibitors can prevent from bacterial resistance. Other three Figures 5f-h show that the high beta-lactams can increase bacterial death rate with/without resistance and with dual action. In conclusion, bacterial death rate in our model, consisting of the orientation probability factor, and dual action factor in this section, satisfies the low to the high potency of penicillin and cephalosporin.

CONCLUSION

In this study, a set of mathematical models of bacteria in patient's blood after antibiotic treatment were focused using PD, physics, and chemistry. The proposed models can capture the recuperation behavior and time of patients treated with antibiotics for clearing bacteria in patient's blood. The probability of drug molecule binding bacteria was determined by assuming drug molecules to be spherical and bacteria to be prolate spheroid. All bacteria have different orientations. Furthermore, the mortality rate of bacteria in blood circulation due to drug, the relationship between the population of bacteria with respect to time, and the duration of treatment were modeled. Finally, we hope that our models will be an alternative choice for evaluating the duration of the treatment of patient with bacterial infection in blood.

ACKNOWLEDGMENTS

The authors would like to thank Professor Dr. Supa Hannongbua and Assistant Professor Dr. Patchreenart Saparpakorn for helping about the measurement of drug molecules which have greatly increased the credit of our paper. We also thank Dr. Panadda Dechadilok for suggesting the theory of convective rate. This research was supported by scholarship 60/40 of Chulalongkorn University.

REFERENCES

1. Austin DJ, White NJ, Anderson RM. The dynamics of drug action on the within-host population growth of infectious agents: Melding pharmacokinetics with pathogen population dynamics. J Theor Biol 1998;194:313-39.
2. Varani G. Diffusion and Molecular Shape and Size, Department of Chemistry; 2013. p. 4-5.
3. Agasanapura BN, Baltus RE, Chellam S. Effect of Convective Hindrance on Microfiltration of Rod Shaped Particles, AIChE Journal, Proceedings of Conference for Annual Meeting. 2011. p. 5-29.
4. Mazaheri A. A review of the literature, probabilistic modeling of ship grounding, Helsinki University of Technology. Faculty of Engineering and Architecture, Department of Applied Mechanics, 2009. p. 26-34.
5. Berg HC, Purcell EM. Physics of chemoreception. Biophys J 1977;20:193-219.
6. Taroni C, Jones S, Thornton JM. Analysis and prediction of carbohydrate binding sites. Protein Eng 2000;13:89-98.
7. Khurana I. Textbook of Medical Physiology; Dynamics of Circulation: Pressure and Flow of Blood and Lymph. New York: Elsevier; 2006. p. 327.
8. Dilsizian V, Pohost GM, Cardiac CT. PET and MR, Multislice Cardiac Tomography: Myocardial Function, Perfusion, and Viability. Chichester: Blackwell Publishing Ltd.; 2010. p. 260.
9. Friedman A, Lungu EM. Can malaria parasite pathogenesis be prevented by treatment with tumor necrosis factor-alpha? Math Biosci Eng 2013;10:609-24.
10. Middelboe M. Bacterial growth rate and marine virus-host dynamics. Microb Ecol 2000;40:114-24.
11. Drugs.com, Ceftriaxone - FDA Prescribing Information, Side Effects and Uses. Available from: http://www.drugs.com/pro/ceftriaxone.html. [Last cited on 2014 Nov 14].
12. Kowalski WJ, Bahnfleth WP, Whittam TS. Filtration of airborne microorganisms: Modeling and prediction. ASHRAE Trans 1999;105:5-6.
13. Krstic RV. Human Microscopic Anatomy: An Atlas for Students of Medicine and Biology. Germany: Springer-Verlag, Berlin Heidelberg; 1997. p. 54-5.
14. Pollak AN. Emergency care and transportation of the sick and injured. The Human Body. 10th ed. Ch. 4. USA: Jones and Bartlett publishers; 2005. p. 108-9.
15. Pocock G, Richards CD, Richards DA. Human physiology. The Properties of Blood. 4th ed. Ch.18. USA: C&C Offset Printing Co. Ltd.; 2013. p. 312-3.
16. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001;47:421-9.
17. Staver JR, Lumpe AT. A content analysis of the presentation of the mole concept in chemistry textbooks. J Res Sci Teaching 1993;30:321-37.
18. Vree TB, Dammers E, Exler PS. Identical pattern of highly variable absorption of clavulanic acid from four different oral formulations of co-amoxiclav in healthy subjects. J Antimicrob Chemother 2003;51:373-8.
19. PubChem Open Chemistry Database, U.S. National Library of Medicine, National Center for Biotechnology Information. Available from: https://www.pubchem.ncbi.nlm.nih.gov/compound/5280980#section=Top. [Last accessed on 2016 Feb 02].
20. Hackett SJ, Guiver M, Marsh J, Sills JA, Thomson AP, Kaczmarski EB, *et al.* Meningococcal bacterial DNA load at presentation correlates with disease severity. Arch Dis Child 2002;86:44-6.
21. Masoud MS, Ali AE, Nasr NM. Chemistry, classification, pharmacokinetics, clinical uses and analysis of beta lactam antibiotics: A review. J Chem Pharm Res 2014;6:28-58.
22. Starlin R, Lin TL, Goodenberger DM. "Antimicrobial Agents", The Washington Manual Infectious Diseases Subspecialty Consult, Department of Medicine. Ch. 27. Washington University School of Medicine; 2005. p. 248-57.
23. Wiskirchen DE, Keel-Jayakumar RA, Nicolau DP. Continuous and intermittent infusion beta-lactam antibiotics. Casebook in Clinical Pharmacokinetics and Drug Dosing. 1st ed. Ch. 3. New York, NY: McGraw-Hill Education/Medical; 2015.
24. Freitas RA Jr. Section 8.5.1 "Cytometrics", Nanomedicine, Volume I: Basic Capabilities, Landes Bioscience, Georgetown, TX; 1999. Available from: http://www.nanomedicine.com/NMIIA/15.4.3.1.htm. [Last cited on 2016 Jan 04].