Modeling the Mechanism of Post Antibiotic Effect

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Abstract

In this paper a stochastic model for describing one of the possible underlying biological mechanisms of postantibiotic effect (PAE) (the delayed regrowth of the bacteria after complete removal of an antibiotic) is formulated. The model is based on the theory of penicillin binding proteins (PBPs), where the PAE is the time required by the bacteria to synthesize new PBPs before growth. Newly synthesized PBPs are unsaturated and becomes saturated under antibiotic pressure and eventually removed due to death.

The model assumes that unsaturated PBPs are attached (synthesized) to a bacterium according to a Poisson process and that these are saturated with an intensity proportional to the antibiotic concentration of the treatment. The calculations and results are divided into three simplifying steps toward a more realistic approach. At first, we assume constant antibiotic concentration and no initial PBPs. Secondly, we assume constant antibiotic concentration, but with an initial set of unsaturated PBPs (no saturated PBPs). Thirdly, we assume exponentially declining antibiotic concentration and the same initial set of unsaturated PBPs.

The stochastic models are solved using a set of Kolmogorov equations and exact solutions with interesting properties can be derived for all three steps. The results are useful for giving a better understanding of the time properties of PAE.

1. Introduction

The rapid evolution of antibiotic resistance in pathogenic bacteria, due to overuse and misuse of antibiotics, is today a major public health problem. While the antibiotic resistance is increasing, the research for development of new antimicrobial agents is decreasing. As a result, activities to maintain the effect of existing antibiotics and thereby prolong their useful lifespan have a high priority. The knowledge though, of how to use existing antibiotics to minimize the emergence of resistance without compromising efficacy is today inadequate.

The clinical implication of long postantibiotic effects (PAEs) lies in the possibility of increasing the intervals between drug administrations, thus allowing for fewer daily doses and thereby potentially reducing treatment costs, increasing patient compliance and decreasing drug exposure [1][2].

In spite of the increasing interest in the PAE as an important parameter for the dosage and frequency of administration of a drug, knowledge on this phenomenon is still incomplete. One possible explanation for the PAE is that it represents the time required for synthesis of new penicillin binding proteins (PBP), before growth of bacteria [3][4].

In this work a stochastic model for describing the dynamics behind PAE was derived. The results are useful for giving a better understanding of the time properties of PAE.

2. Model

The models describe how new PBPs are being created, going from unsaturated to saturated and finally being removed. This process takes place independently for all existing PBPs. We will assume that there are a number of unsaturated PBPs at the start and that new PBPs are created according to a Poisson process during the time of study. The unsaturated PBPs become saturated at a rate that depends on the concentration, while the saturated is removed at a different rate. We will first consider constant concentration and later declining concentration:

$$\begin{cases} c(t) = C_0 & \texttt{(Constant antibiotic concentration)} \\ c(t) = C_0 e^{-kt} & \texttt{(Declining antibiotic concentration)} \end{cases}$$

Assume that PBPs can be in either of two states: 1) unsaturated or 2) saturated with antibiotics. Let $X(t)$ denote the number of PBPs that are unsaturated (in state 1) at time t and $Y(t)$ the number saturated PBPs (in state 2) at time t. If we assume that a PBP stays in an unsaturated state for an exponentially distributed time, the model implies that $(X(t), Y(t))$ is a Markov process with transition rates as listed in Table 1. A schematic picture of this model is given in Figure 1.

From	To	Rate
(x, y)	$(x+1, y)$	β
(x, y)	$(x-1, y+1)$	$\gamma c(t) x$
(x, y)	$(x, y-1)$	μy

Table 1: Transition rates of the Markov process

Let $p_{j,k}(t) = P(X(t) = j, Y(t) = k)$ be the joint probability of sizes j and k at time t. The Kolmogorov equations can then be written as

$$p_{j,k}(t + \Delta t) \quad = \quad p_{j,k}(t)[1 - (\beta + \gamma c(t) j + \mu k)\Delta t] + p_{j-1,k}(t)[\beta \Delta t] +$$

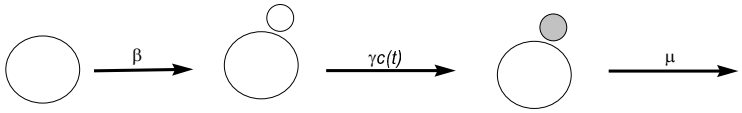

Figure 1: A schematic picture of the model. Initially a new PBP is created (left arrow) with an intensity β. When antibiotics is added to the system, the PBP becomes saturated (middle arrow) with an intensity $\gamma c(t)$ and later the PBP is removed (right arrow) from the bacteria with an intensity μ.

$$p_{j+1,k-1}(t)[\gamma c(t)(j+1)\Delta t] + p_{j,k+1}(t)[\mu(k+1)\Delta t] + o(\Delta t). \quad (1)$$

It follows that

$$\begin{aligned} \frac{\partial p_{j,k}(t)}{\partial t} &= -(\beta + \gamma c(t) j + \mu k) p_{j,k}(t) + \beta p_{j-1,k}(t) + \\ &\quad \gamma c(t)(j+1) p_{j+1,k-1}(t) + \mu(k+1) p_{j,k+1}(t). \end{aligned} \quad (2)$$

Consider the probability generating function for x and y defined as

$$P(s_1, s_2, t) = \sum_{j,k} s_1^j s_2^k p_{j,k}(t). \quad (3)$$

By multiplying both sides in Equation 2 with $s_1^j s_2^k$ and summing over j and k together with the definition in Equation 3, we get the partial differential equation (PDE) for the generating function:

$$\frac{\partial P}{\partial t} = (s_1 - 1)\beta P + (s_2 - s_1)\gamma c(t)\frac{\partial P}{\partial s_1} + (1 - s_2)\mu \frac{\partial P}{\partial s_2} \quad (4)$$

2.1. Constant antibiotic concentration and no initial PBPs

With the initial conditions $X(0) = 0$ and $Y(0) = 0$ which yields $P(s_1, s_2, 0) = 1$, we get the solution to the PDE in Equation 4,

$$P(s_1, s_2, t) = e^{(s_1-1)\lambda_1(t) + (s_2-1)\lambda_2(t)} \quad (5)$$

where

$$\begin{cases} \lambda_1(t) = \frac{\beta[1 - e^{-\gamma C_0 t}]}{\gamma C_0} \\ \lambda_2(t) = \frac{\beta[e^{-\gamma C_0 t} - 1 - \frac{\gamma C_0}{\mu}(e^{-\mu t} - 1)]}{\gamma C_0 - \mu}. \end{cases}$$

This is the product of the generating functions of two Poisson distributions, which means that X and Y are statistically independent random variables.

2.2. Constant antibiotic concentration and an initial set of unsaturated PBPs (no saturated PBPs)

It is more realistic to assume that the initial conditions are $X(0) = n$ and $Y(0) = 0$, which yields $P(s_1, s_2, 0) = s_1^n$.

Since each PBP develop independently, the n unsaturated PBPs which are already in the process from start and the newly created PBPs can be treated separately, with the latter part following independent Poisson distributions with a bivariate density function in Equation 5.

The n unsaturated PBPs that are in the process from start will move independently with equal probabilities between the different states: From unsaturated to saturated and from saturated to removed. Let $\pi_{11}(t)$ denote the probability that a PBP that was unsaturated (in state 1) at time 0 will still be unsaturated at time t and furthermore $\pi_{21}(t)$ the probability that the PBP is instead saturated (in state 2) at time t. Thus, (X, Y) will have a trinomial distribution with parameters n, $\pi_{11}(t)$ and $\pi_{21}(t)$. In this process $(n - X - Y)$ PBPs are removed.

Now the products of the two parts of probability generating functions for the PBPs starting in the process at time 0 and the PBPs arriving after time 0 yields the following distribution

$$P(s_1, s_2, t)e^{(s_1-1)\lambda_1(t)+(s_2-1)\lambda_2(t)}(1 + (s_1 - 1)\pi_{11}(t) + (s_2 - 1)\pi_{21}(t))^n, \quad (6)$$

where the occupation probabilities $\pi_{11}(t)$ and $\pi_{21}(t)$ can be derived from the Kolmogorov equation in Equation 2. In this equation the bivariate probabilities $p_{10}(t)$ and $p_{01}(t)$ corresponds to $\pi_{11}(t)$ and $\pi_{21}(t)$, respectively. Since we are are looking at the process for the n PBPs which started as unsaturated (in state 1), it follows that $\beta = 0$. Hence,

$$\begin{cases} \frac{d\pi_{11}(t)}{dt} = -\gamma C_0 \pi_{11}(t) \\ \frac{d\pi_{21}(t)}{dt} = \gamma C_0 \pi_{11}(t) - \mu \pi_{21}(t). \end{cases} \quad (7)$$

>From the assumption that the time in the unsaturated state is exponential, it follows with the initial conditions $\pi_{11}(0) = 1$ and $\pi_{21}(0) = 0$ that

$$\begin{cases} \pi_{11}(t) = e^{-\gamma C_0 t} \\ \pi_{21}(t) = \frac{\gamma C_0}{\mu - \gamma C_0}(e^{-\gamma C_0 t} - e^{-\mu t}) \\ \pi_{01}(t) = 1 - \pi_{11}(t) - \pi_{21}(t), \end{cases}$$

where $\pi_{01}(t)$ is the probability that a PBP has been removed.

2.3. Exponentially declining antibiotic concentration and an initial set of unsaturated PBPs (no saturated PBPs)

The most realistic model for human kinetics, is when we assume that the concentration of an initial dose is declining exponentially rather than being constant.

Again, we can split the problem into two parts: 1) Describing the PBPs existing already at $t = 0$ and 2) describing PBPs that develops at time t. It can be shown that the distribution do not change from the result in the previous section, apart from different parameters. The probabilities for the already existing PBPs at $t = 0$ are

$$\begin{cases} \pi_{11}(t) = \frac{e^{\frac{\gamma C_0 e^{-kt}}{k}}}{e^{\frac{\gamma C_0}{k}}} e^{-C_0\gamma \int_0^t e^{-ks}ds} \\ \pi_{21}(t) = e^{-mt} \int_0^t \frac{\gamma C_0 e^{\frac{\gamma C_0 e^{-kv}}{k} - v(k-m)}}{e^{\frac{\gamma C_0}{k}}} dv. \end{cases}$$

Hence, (X, Y) have a trinomial distribution with parameters n, $\pi_{11}(t)$ and $\pi_{21}(t)$. In order to derive the expressions for $\lambda_1(t)$ and $\lambda_2(t)$, let us introduce

$$c(u, s) = C_0 e^{-k(u+s)} = C_0 e^{-ku} e^{-ks}$$

for the concentration when a PBP created at time u and exposed to antibiotics after a time s. Furthermore, let

$$C(u, s) = \int_0^s c(u, x)dx = \frac{1}{k} C_0 e^{-ku}(1 - e^{-ks})$$

be the cumulative antibiotic pressure. Now, the density function of the lifetime distribution can be written as

$$\gamma c(u, s) e^{-\gamma C(u,s)}$$

and the survival function (the probability that a PBP created at time u and still unsaturated at time T) can be written as

$$e^{-\gamma C(u,T-u)}. \tag{8}$$

Note that $u = 0$ gives $\pi_{11}(T)$, as defined earlier.

Integrating Equation 8 over the time period when PBPs are created and multiplying with the intensity, β, yields

$$\lambda_1(t) = \beta \int_0^T e^{-\gamma C(u,T-u)} du = \beta e^{\frac{\gamma}{k} C_0 e^{-kT}} \int_0^T e^{-\frac{\gamma}{k} C_0 e^{-ku}} du. \tag{9}$$

In order to derive $\lambda_2(t)$, we assume that a PBP is created at time $u < T$ and later saturated after time v, where $u + v < T$. The probability that the PBP is

still alive at time T, i.e. the probability that a PBP created at time u survives a time $T-u-v$ is then

$$r(u,t) = \int_0^{T-u} e^{-\mu(T-v-u)}\gamma C_0 e^{-ku} e^{-kv} e^{-\frac{\gamma C_0}{k}e^{-ku}(1-e^{-kv})} dv. \qquad (10)$$

Again, inserting $u = 0$ in Equation 10 yields $\pi_{21}(T)$ as defined earlier.

Integrating Equation 10 over the time period when PBPs are born and multiplying with the intensity, β, yields

$$\lambda_2(t) = \beta \int_0^T r(u,t)du. \qquad (11)$$

The solutions $\lambda_1(t)$ and $\lambda_2(t)$ can, as with the constant concentration, be verified by checking that Equation 9 and Equation 11 are solutions to the following differential equation system

$$\begin{cases} \frac{d\lambda_1(t)}{dt} = \beta - \gamma C_0 e^{-kt}\lambda_1(t) \\ \frac{d\lambda_2(t)}{dt} = \gamma C_0 e^{-kt}\lambda_1(t) - \mu\lambda_2(t). \end{cases}$$

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3. Bibliography

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