Stochastic Modeling on the Spread of Chlamydia Trachomatis

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Abstract

The purpose of this research is to develop and analyze stochastic models to obtain a better understanding of the behavior of C. trachomatis, a bacterium that causes ocular and genital tract infections in humans. C. trachomatis has two developmental forms: the infectious elementary body (EB) and the reticulate body (RB), the latter of which divides into other RBs or converts into EBs. Studying a stochastic model of this system allows us to take into account the importance of variability at the beginning of the bacterium's life cycle. By analyzing the models, we determine expected values of RBs and EBs at any given time and optimal conversion rates to maximize the terminal EB population by the time the host cell dies. Knowing the maximum number of elementary bodies at the time of host cell death allows us to determine the speed at which C. trachomatis spreads and may help us to find the minimal time window to begin treatment for the diseases caused by this bacterium.

1 Introduction

Chlamydia Trachomatis is a bacterium that causes ocular and genital tract infections in humans. The most common diseases are chlamydia (the sexually transmitted disease) and trachoma, the leading infectious cause of blindness in the world. Normally, this infection is spread by sexual activity, flies, and contaminated towels in areas with poor sanitation. In fact, in underdeveloped countries, approximately 40 million people suffer from trachoma. In addition, chlamydia accounts for approximately 60% of sexually transmitted diseases reported in the United States [1].

C. Trachomatis has two developmental forms: the elementary body (EB) and the reticulate body (RB). Figure 1 shows that the EBs infect a cell and form an inclusion, in which the EBs undergo a conversion to RBs. This is the beginning of the life cycle. RBs then begin to divide repeatedly through binary fission. Approximately after 24 hours post infection (hpi), the RBs begin converting into EBs asynchronously. The entire process culminates at 40-48 hpi, at which time the host cell dies. Only EBs survive the death of the host cell, which then continue to infect other cells, and repeat the process [2].

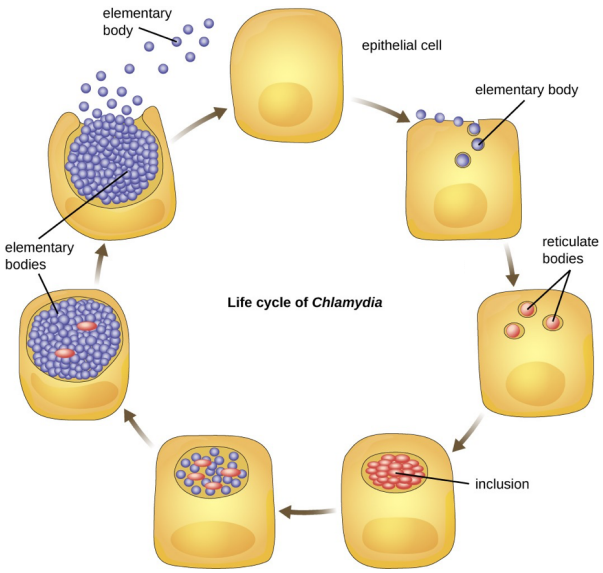

Figure 1: *Life Cycle of C. Trachomatis [3, 4]*

In this paper, we carry out an analysis of two stochastic models to study the behavior of *C. trachomatis*. At the beginning of the life cycle, there are few RBs that can divide or convert. Thus, variability is important. If RBs convert into EBs too soon, then there would be few RBs to reproduce. If RBs convert too late, then at the time of the cell death, any RBs that did not yet divide would die. In both cases, the terminal EB population would not be at its maximum. Therefore, there must exist an optimal rate of conversion in order to have the maximum number of EBs at the time of host cell death. Moreover, knowing the maximal spread of the chlamydia also enables us to find the minimal time window to begin treatment.

The report begins with an analysis of a birth-death model in Section 2. We assume that the choice of an RB dividing or converting is mutually exclusive. When one RB divides, one RB is added to the population. When one RB converts, one RB is subtracted from the

population. Therefore, division can be thought of as a birth process, and conversion as a death process. We first consider the RB population in Section 2.1. Then, in Section 2.2, we consider the EB population. The derivations and analyses are based on notes written by Frederic Y.M. Wan [5]. In Section 2.3, we then undertake the optimization problem of maximizing the expected number of EBs. Finally, in Section 2.4, we run computer simulations using the Gillespie algorithm.

Experimental data suggests that at each RB division the size of an RB decreases. It is hypothesized that the size of an RB influences the choice of whether or not an RB will convert to an EB. The next model expands upon the previous model by adding in the role of size control in Section 3. However, the model is simplified so that only two sizes of RBs are taken into consideration: large and small. We assume that large RBs are only capable of dividing into large RBs or into small RBs. Furthermore, we assume that small RBs can divide into small RBs or convert into EBs. These choices are mutually exclusive. The derivation of the ODEs for the large and small RB population, based on notes written by Frederic Y.M. Wan [5], is carried out in Section 3.1. Using this ODE, we then run computer simulations using the Gillespie algorithm to make predictions regarding the populations of large RBs, small RBs, and EBs in Section 3.2. Further investigation of this model is needed in order to calculate the expected values of each of the populations and to find the optimal conversion rate for a given set of parameter values.

2 Birth-Death Model

2.1 Modeling the RB Population

We first want to model the RB population. We assume that the life cycle of *C. Trachomatis* begins when the EBs that infect a cell convert into RBs. When an RB divides, we gain one RB. When an RB converts, we lose one RB. Therefore, we consider division and conversion as a birth and death process, respectively.

Suppose at time $t = 0$ there is a population of N RBs, each one capable of dividing (+1 RB) or converting (-1 RB). Let $P_k(t)$ be the probability for the population of RBs, $X(t)$, to be of size k at time t:

$$P_k(t) = Pr\{X(t) = k\}$$

Hence, we have that $P_k(0) = \delta_{kN}$, where δ_{kN} is the Kronecker delta. Consider a time interval $(t, t + \delta t)$ for small enough δt such that at most one conversion or division can occur. Then the probability of having k RBs by the time $t + \delta t$ is

$$\begin{aligned} P_k(t + \delta t) &= Pr\{X(t + \delta t) = k\} \\ &= Pr\{X(t) = k, \Delta X(t) = 0\} + Pr\{X(t) = k - 1, \Delta X(t) = 1\} \\ &\quad + Pr\{X(t) = k + 1, \Delta X(t) = -1\} \end{aligned}$$

where $\Delta X(t) = X(t + \delta t) - X(t)$.

2.1.1 Kolmogorov Differential Equations

Let λ_C be the rate of a conversion and λ_D be the rate of a division. The intervals $(0, t)$ and $(t, t + \delta t)$ do not overlap. The independent increment assumption can be made to rewrite $P_k(t + \delta t)$ as

$$\begin{aligned} P_k(t+\delta t) &= Pr\{X(t+\delta t) = k\} \\ &= Pr\{X(t) = k\} \cdot Pr\{\Delta X(t) = 0\} + Pr\{X(t) = k-1\} \cdot Pr\{\Delta X(t) = 1\} \\ &\quad + Pr\{X(t) = k+1\} \cdot Pr\{\Delta X(t) = -1\} \\ &= (1 - k\delta t(\lambda_D + \lambda_C))P_k(t) + (k+1)\delta t\lambda_C P_{k+1}(t) + (k-1)\delta t\lambda_D P_{k-1}(t) \end{aligned}$$

with

- $Pr\{\Delta X(t) = 0\} = 1 - k\delta t(\lambda_D + \lambda_C)$ since there are k RBs that do not divide nor convert, each with probability $1 - \delta t(\lambda_D + \lambda_C)$
- $Pr\{\Delta X(t) = 1\} = (k+1)\delta t\lambda_C$ since there are $k+1$ RBs that can convert, each with probability $\delta t\lambda_C$, and
- $Pr\{\Delta X(t) = -1\} = (k-1)\delta t\lambda_D$ since there are $k-1$ RBs that can divide, each with probability $\delta t\lambda_D$.

Now we calculate

$$\lim_{\delta t \to\ 0} \frac{P_k(t+\delta t) - P_k(t)}{\delta t}$$

and obtain

$$\frac{dP_k(t)}{dt} = -(\lambda_D + \lambda_C)kP_k(t) + \lambda_C(k+1)P_{k+1}(t) + \lambda_D(k-1)P_{k-1}(t) \tag{1}$$

with initial conditions $P_k(0) = \delta_{kN}$ for all nonnegative integers k.

2.1.2 Probability Generating Function

The probability generating function of this sequence of probabilities is

$$G(x, t) = \sum_{k=0}^{\infty} P_k(t)x^k \tag{2}$$

With (2) we have the following properties:

- If $x = 1$, then
$$G(1, t) = \sum_{k=0}^{\infty} P_k(t) = 1$$
so that the sum of all the probabilities is 1, as we expect.
- If $t = 0$, then
$$G(x, 0) = x^N$$
where N is the initial population.

- To recover $P_k(t)$ from the probability generating function, calculate

$$P_k(t) = \frac{1}{k!} \cdot \frac{\partial^k G}{\partial x^k}\Big|_{x=0} \tag{3}$$

To solve for the probability generating function, we convert this problem into a partial differential equation. Take the partial derivative of G with respect to t

$$\begin{aligned}\frac{\partial G}{\partial t} &= \frac{\partial}{\partial t}\sum_{k=0}^{\infty} P_k(t)x^k \\ &= \sum_{k=0}^{\infty}\frac{dP_k(t)}{dt}x^k\end{aligned}$$

Substitute (1) into the sum

$$\begin{aligned}\sum_{k=0}^{\infty}\frac{dP_k(t)}{dt}x^k &= -(\lambda_D+\lambda_C)\sum_{k=0}^{\infty}kP_k(t)x^k + \lambda_C\sum_{k=0}^{\infty}(k+1)P_{k+1}(t)x^k + \lambda_D\sum_{k=0}^{\infty}(k-1)P_{k-1}(t)x^k \\ &= -(\lambda_D+\lambda_C)x\sum_{k=1}^{\infty}kP_k(t)x^{k-1} + \lambda_C\sum_{k=1}^{\infty}kP_k(t)x^{k-1} + \lambda_D x^2\sum_{k=1}^{\infty}kP_k(t)x^{k-1} \\ &= -(\lambda_D+\lambda_C)x\frac{\partial G}{\partial x} + \lambda_C\frac{\partial G}{\partial x} + \lambda_D x^2\frac{\partial G}{\partial x} \\ &= [-(\lambda_D+\lambda_C) + \lambda_C + \lambda_D x^2]\frac{\partial G}{\partial x}\end{aligned}$$

We may rewrite this result as

$$\frac{\partial G}{\partial t} + [(\lambda_D+\lambda_C) - \lambda_C - \lambda_D x^2]\frac{\partial G}{\partial x} = 0$$

The solution of this first order PDE can be obtained by the method of characteristics that solves the following system of two ODEs:

$$\frac{dx}{dt} = (\lambda_D+\lambda_C) - \lambda_C - \lambda_D x^2, \qquad \frac{dG}{dt} = 0$$

Solving the two separable ODEs gives us

$$\frac{1}{\lambda_D-\lambda_C}ln\left(\frac{\lambda_D x - \lambda_C}{1-x}\right) = t + c_0, \qquad G(t) = G_0$$

The initial conditions are $x(0) = x_0$ (not yet specified) and $G(0) = x_0^N$ given $P_k(0) = \delta_{kN}$:

$$c_0 = \frac{1}{\lambda_D-\lambda_C}ln\left(\frac{\lambda_D x_0 - \lambda_C}{1-x_0}\right), \qquad G_0 = x_0^N$$

Thus, it follows that

$$x_0 = \frac{(\lambda_D x - \lambda_C)e^{(\lambda_C-\lambda_D)t} + \lambda_C(1-x)}{(\lambda_D x - \lambda_C)e^{(\lambda_C-\lambda_D)t} + \lambda_D(1-x)}$$

and

$$G(x,t) = x_0^N = \left[\frac{(\lambda_D x - \lambda_C)e^{(\lambda_C-\lambda_D)t} + \lambda_C(1-x)}{(\lambda_D x - \lambda_C)e^{(\lambda_C-\lambda_D)t} + \lambda_D(1-x)}\right]^N \tag{4}$$

We can verify that

$$G(1,t) = \left[\frac{(\lambda_D - \lambda_C)e^{(\lambda_C-\lambda_D)t}}{(\lambda_D - \lambda_C)e^{(\lambda_C-\lambda_D)t}}\right]^N = 1$$

Now having solved for the probability generating function, we may now calculate $P_0(t)$ using (3) where $\frac{\partial^k G}{\partial x^k}$ is defined to be the function G itself at $k = 0$

$$P_0(t) = \frac{1}{0!} \cdot G(x,t)\Big|_{x=0} = \left[\frac{-\lambda_C e^{(\lambda_C-\lambda_D)t} + \lambda_C}{-\lambda_C e^{(\lambda_C-\lambda_D)t} + \lambda_D}\right]^N$$

. Then we may determine the probability of extinction:

- If $\lambda_D < \lambda_C$, then
$$\lim_{t\to\infty} P_0(t) = 1$$
- If $\lambda_D > \lambda_C$, then
$$\lim_{t\to\infty} P_0(t) = \left[\frac{\lambda_C}{\lambda_D}\right]^N$$

2.1.3 Expected Value of RBs

The expected value of the population size of RBs for initial size N is

$$\begin{aligned} E[RB(t)] = E[X(t)] &= \sum_{k=0}^{\infty} kP_k(t) \\ &= \frac{\partial G}{\partial x}\Big|_{x=1} = Ne^{(\lambda_D-\lambda_C)t} \end{aligned} \tag{5}$$

Therefore, we expect that the population of RBs will:

- Exponentially grow if $\lambda_D > \lambda_C$,
- Exponentially decay toward 0 if $\lambda_D < \lambda_C$, or
- Equal N if $\lambda_D = \lambda_C$.

2.2 Modeling the EB Population

Now we model the EB population. Since we assume that the life cycle begins when the EBs that infect a cell convert into RBs, there are no EBs at the start. We gain EBs only when an RB converts. Thus, we expect that the EB population will depend on the RB population. We further assume that EBs do not die, so that the number of EBs increases over time.

Suppose at time $t = 0$, there is a population of 0 EBs. Let $Q_j(t)$ be the probability for the population of EBs, $Y(t)$, to be of size j at time t:

$$Q_j(t) = Pr\{Y(t) = j\}$$

We have that $Q_j(0) = \delta_{j0}$, where δ_{j0} is the Kronecker delta. Again, we consider a time interval $(t, t+\delta t)$ for small enough δt such that at most one conversion can occur. Then the probability of having j EBs by the time $t+\delta t$ is

$$\begin{aligned} Q_j(t+\delta t) &= Pr\{Y(t+\delta t) = j\} \\ &= Pr\{Y(t) = j, \Delta Y(t) = 0\} + Pr\{Y(t) = j-1, \Delta Y(t) = 1\} \end{aligned}$$

where $\Delta Y(t) = Y(t+\delta t) - Y(t)$.

2.2.1 Kolmogorov Differential Equations

The intervals $(0, t)$ and $(t, t+\delta t)$ do not overlap. The independent increment assumption can be made to rewrite $Q_j(t+\delta t)$ as

$$\begin{aligned} Q_j(t+\delta t) &= Pr\{Y(t+\delta t) = j\} \\ &= Pr\{Y(t) = j\} \cdot Pr\{\Delta Y(t) = 0\} + Pr\{Y(t) = j-1\} \cdot Pr\{\Delta Y(t) = 1\} \\ &= \big[1 - \delta t \lambda_C \sum_{k=0}^{\infty} k P_k(t)\big] Q_j(t) + \big[\delta t \lambda_C \sum_{k=0}^{\infty} k P_k(t)\big] Q_{j-1}(t) \end{aligned}$$

with

- $Pr\{\Delta Y(t) = 0\} = 1 - \delta t \lambda_C \sum_{k=0}^{\infty} k P_k(t)$ since there are on average $\sum_{k=0}^{\infty} k P_k(t)$ RBs that do not convert, each with probability $1 - \delta t \lambda_C$
- $Pr\{\Delta Y(t) = 1\} = \delta t \lambda_C \sum_{k=0}^{\infty} k P_k(t)$ since there are on average $\sum_{k=0}^{\infty} k P_k(t)$ RBs that can convert, each with probability $\delta t \lambda_C$

Now we calculate

$$\lim_{\delta t \to 0} \frac{Q_j(t+\delta t) - Q_j(t)}{\delta t}$$

and with (5) we obtain

$$\begin{aligned} \frac{dQ_j(t)}{dt} &= \lambda_C \sum_{k=0}^{\infty} k P_k(t)[-Q_j(t) + Q_{j-1}(t)] \\ &= \lambda_C N e^{(\lambda_D - \lambda_C)t}[-Q_j(t) + Q_{j-1}(t)] \end{aligned}$$

Let $I'(t) = \lambda_C N e^{(\lambda_D - \lambda_C)t}$. Then, after some algebraic manipulation, we can derive

$$\frac{dQ_j(t)}{dt} + I'(t) Q_j(t) = I'(t) Q_{j-1}(t) \tag{6}$$

with initial conditions $Q_j(0) = \delta_{j0}$, for all nonnegative integers j.

2.2.2 Expected Value of EBs

By using the method of integrating factor for $Q_0(t), Q_1(t), Q_2(t)$ and so on, we can recursively determine that

$$Q_j(t) = e^{-I(t)} \frac{[I(t)]^j}{j!} \tag{7}$$

for all nonnegative integers j, where $I(t) = \frac{\lambda_C N}{\lambda_D - \lambda_C}[e^{(\lambda_D - \lambda_C)t} - 1]$.
Notice that $Q_j(t)$ in (7) has the form of a Poisson distribution which is illustrated in Figure 2.

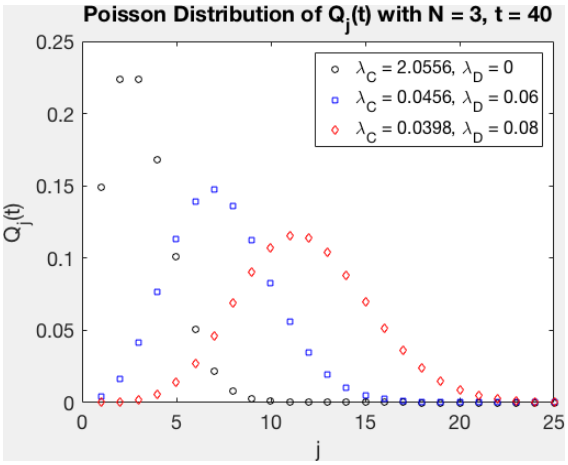

Figure 2: *MATLAB plot showing Poisson distributions of $Q_j(t)$ for given parameter values*

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Therefore, we can determine that the expected value of the population size of EBs with an initial size of N RBs is

$$\begin{aligned} E[EB(t)] &= E[Y(t)] = I(t) \\ &= \frac{\lambda_C N}{\lambda_D - \lambda_C}[e^{(\lambda_D - \lambda_C)t} - 1] \end{aligned} \tag{8}$$

Notice that the expected value is an increasing function of time t. We expect that the population of EBs will:

- Exponentially grow if $\lambda_D > \lambda_C$, or
- Increase and asymptotically approach $\frac{\lambda_C N}{\lambda_D - \lambda_C}$ if $\lambda_D < \lambda_C$.

2.3 Optimizing Expected Value of the EB Population

We want to know the maximal spread of *C. Trachomatis*. Therefore, we want to optimize the expected value of EBs, since the EBs are what spread and infect cells. If experimental data coincides with the model's predictions, then this suggests that *C. Trachomatis* has evolved to the point where it can spread at its fastest rate.

Let T be the time at which the host cell dies. We want to maximize,

$$E[EB(T)] = \frac{\lambda_C N}{\lambda_D - \lambda_C}[e^{(\lambda_D - \lambda_C)T} - 1] \tag{9}$$

Since we have two parameters, λ_D and λ_C, we can choose either one as the variable to maximize (9). Notice when taking the derivative with respect to either λ_D or λ_C that N is a coefficient. When we set the derivative equal to 0, we immediately can divide out N from the equation. Thus, the optimal λ_D or λ_C value will not depend on N.

2.3.1 Maximizing with respect to λ_D

In this case, we choose λ_D to be the variable and assume λ_C is a given constant.

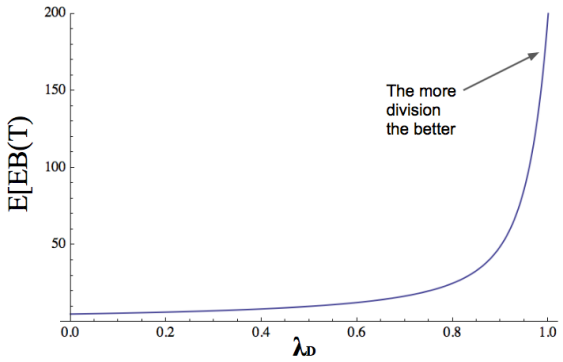

Figure 3: *(9) as a function of λ_D with parameter values $\lambda_C = 1$, $N = 5$, and $T = 40$*

The graph in Figure 3 suggests that (9) is an increasing function of λ_D. The more division there is, the more EBs we should expect by the terminal time T. Hence, there does not exist an optimal value of λ_D that maximizes (9) for given λ_C, N, and T.

2.3.2 Maximizing with respect to λ_C

In this case, we choose λ_C to be the variable and assume λ_D is a given constant.

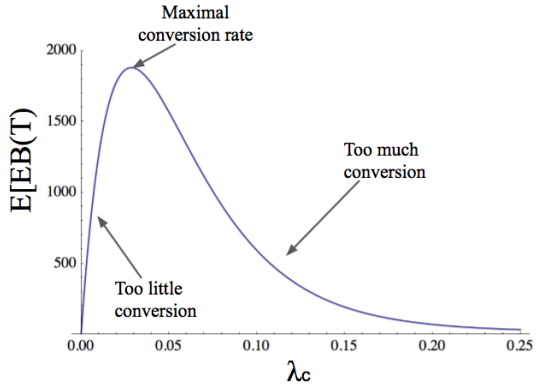

Figure 4: *(9) as a function of λ_C with parameter values $\lambda_D = 0.225$, $N = 5$, and $T = 40$*

The graph in Figure 4 suggests that there exists an optimal value of λ_C that maximizes (9). We have written a *Mathematica* program that calculates the maximal λ_C value and the expected value for given parameter values λ_D, N, and T.

2.4 Gillespie Algorithm for Birth-Death Model

To see how the population of RBs and EBs changes with time visually, we run computer simulations using the Gillespie algorithm. We run the algorithm three times and compare it to the expected values of RBs (5) and EBs (8). Figure 5 and Figure 6 below differ in the choice of the value for λ_C.

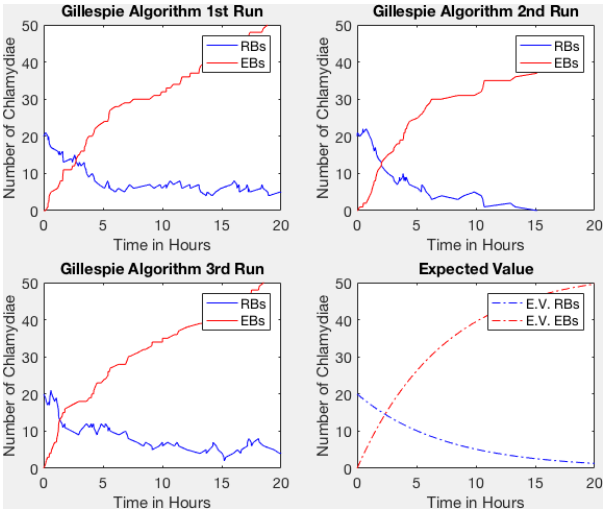

Figure 5: $\lambda_D < \lambda_C$
Parameter values: $N = 20$, $\lambda_D = 0.225$, $\lambda_C = 0.3608$

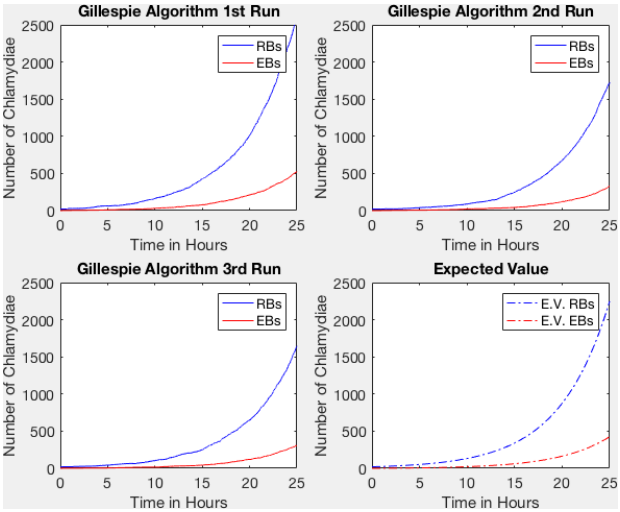

Figure 6: $\lambda_D > \lambda_C$
Parameter values: $N = 20$, $\lambda_D = 0.225$, $\lambda_C = 0.03608$

In both cases, the algorithm closely simulates the expected value. In the case where $\lambda_D < \lambda_C$, the algorithm correctly predicts that the RB population is tending toward 0 and the EB population is increasing toward $\frac{\lambda_C N}{\lambda_D - \lambda_C}$ asymptotically. Similarly in the case where $\lambda_C > \lambda_D$, the algorithm correctly predicts that both the RB and EB population grow exponentially.

We have said that with too little or too much conversion there will be few EBs at the time of host cell death. We can use the Gillespie algorithm to visually confirm this. For $\lambda_D = 0.1$, $N = 20$, and $T = 40$, we calculate that the optimal conversion rate is $\lambda_C = 0.03608$. We then take a smaller conversion rate, $\lambda_C = 0.0015$, and a larger conversion rate, $\lambda_C = 0.12$. We then run the Gillespie algorithm for each of these λ_C values in Figue 7 below:

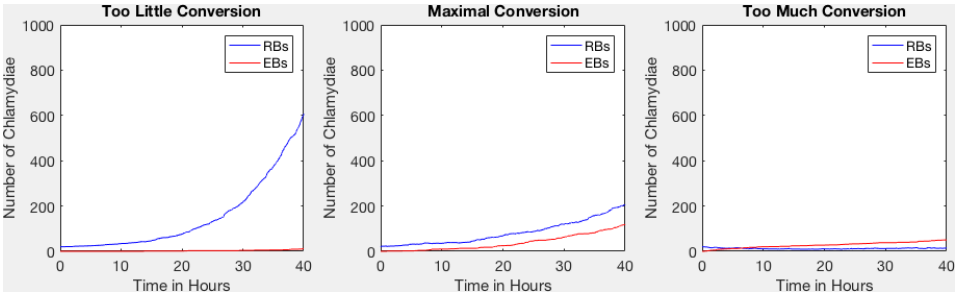

Figure 7: *Left:* $\lambda_C = 0.0015$, *Middle:* $\lambda_C = 0.03608$, *Right:* $\lambda_C = 0.12$

As expected, with smaller or larger conversion rates we have fewer EBs than with the optimal conversion rate. The Gillespie algorithm correctly predicts this as well. The number of EBs at time $T = 40$ for the middle graph is greater than the other two graphs, and is close to the expected value of 134 EBs.

3 Size Control Model

3.1 Modeling the RB Population

Experimental data has suggested that the size of an RB determines whether it can divide or not, which implies that size is a catalyst for conversion [2]. Throughout the birth-death model, we took no consideration of the size of the RBs. Expanding on the previous model, now we take into account the role of size control to model the RB population. Consider two sizes of RBs: large RBs and small RBs. We make the following two assumptions:

- A large RB can either divide into two large RBs or divide into two small RBs
- A small RB can either divide into two small RBs or convert into one EB

Suppose at time $t = 0$ there is a population of M small RBs and N large RBs. Let $P_{m,n}(t)$ be the probability for the population of RBs to consist of m small RBs, $X_S(t)$, and n large RBs, $X_L(t)$, at time t:

$$P_{m,n}(t) = Pr\{X_S(t) = m, X_L(t) = n\}$$

Hence, we have that $P_{m,n} = 1$ when $m = M$ and $n = N$ and $P_{m,n} = 0$ otherwise. Consider a time interval $(t, t + \delta t)$ for small enough δt such that at most one event can occur. Then the probability of having m small RBs and n large RBs by the time $t + \delta t$ is

$$\begin{aligned}
P_{m,n}(t+\delta t) &= Pr\{X_S(t+\delta t) = m, X_L(t+\delta t) = n\} \\
&= Pr\{X_S(t) = m, X_L(t) = n; \quad \Delta X_S(t) = 0, \Delta X_L(t) = 0\} \\
&\quad + Pr\{X_S(t) = m-1, X_L(t) = n; \quad \Delta X_S(t) = 1, \Delta X_L(t) = 0\} \\
&\quad + Pr\{X_S(t) = m+1, X_L(t) = n; \quad \Delta X_S(t) = -1, \Delta X_L(t) = 0\} \\
&\quad + Pr\{X_S(t) = m, X_L(t) = n-1; \quad \Delta X_S(t) = 0, \Delta X_L(t) = 1\} \\
&\quad + Pr\{X_S(t) = m-2, X_L(t) = n+1; \quad \Delta X_S(t) = 2, \Delta X_L(t) = -1\}
\end{aligned}$$

where $\Delta X_S(t) = X_S(t + \delta t) - X_S(t)$ and $\Delta X_L(t) = X_L(t + \delta t) - X_L(t)$.

3.1.1 Kolmogorov Differential Equations

Let μ_L be the rate of one large RB dividing into two large RBs and let μ_S be the rate of one large RB dividing into two small RBs. Furthermore, let λ_D be the rate of one small RB dividing into two small RBs and let λ_C be the rate of one small RB converting into one EB. The intervals $(0, t)$ and $(t, t + \delta t)$ do not overlap. The independent increment assumption can

be made to rewrite $P_{m,n}(t+\delta t)$ as

$$\begin{aligned}
P_{m,n}(t+\delta t) &= Pr\{X_S(t+\delta t)=m, \quad X_L(t+\delta_t)=n\} \\
&= Pr\{X_S(t)=m, X_L(t)=n\}\cdot Pr\{\Delta X_S(t)=0, \Delta X_L(t)=0\} \\
&\quad + Pr\{X_S(t)=m-1, X_L(t)=n\}\cdot Pr\{\Delta X_S(t)=1, \Delta X_L(t)=0\} \\
&\quad + Pr\{X_S(t)=m+1, X_L(t)=n\}\cdot Pr\{\Delta X_S(t)=-1, \Delta X_L(t)=0\} \\
&\quad + Pr\{X_S(t)=m, X_L(t)=n-1\}\cdot Pr\{\Delta X_S(t)=0, \Delta X_L(t)=1\} \\
&\quad + Pr\{X_S(t)=m-2, X_S(t)=n+1\}\cdot Pr\{\Delta X_S(t)=2, \Delta X_L(t)=-1\} \\
&= [1-m\delta t(\lambda_D+\lambda_C)-n\delta t(\mu_L+\mu_S)]P_{m,n}(t)+(m-1)\delta t\lambda_D P_{m-1,n}(t) \\
&\quad + (m+1)\delta t\lambda_C P_{m+1,n}(t)+(n-1)\delta t\mu_L P_{m,n-1}(t)+(n+1)\delta t\mu_S P_{m-2,n+1}(t)
\end{aligned}$$

with

- $Pr\{\Delta X_S(t)=0, \Delta X_L(t)=0\} = 1-m\delta t(\lambda_D+\lambda_C)-n\delta t(\mu_L+\mu_S)$ since there are m small RBs that do not divide nor convert, each with probability $1-m(\lambda_D+\lambda_C)$, and n large RBs that do not divide, each with probability $1-n(\mu_L+\mu_S)$;
- $Pr\{\Delta X_S(t)=1, \Delta X_L(t)=0\} = (m-1)\delta t\lambda_D$ since there are $m-1$ small RBs that can divide into more small RBs, each with probability $\delta t\lambda_D$;
- $Pr\{\Delta X_S(t)=-1, \Delta X_L(t)=0\} = (m+1)\delta t\lambda_C$ since there are $m+1$ small RBs that can convert into EBs, each with probability $\delta t\lambda_C$;
- $Pr\{\Delta X_S(t)=0, \Delta X_L(t)=1\} = (n-1)\delta t\mu_L$ since there are $n-1$ large RBs that can divide into more large RBs, each with probability $\delta t\mu_L$;
- $Pr\{\Delta X_S(t)=2, \Delta X_L(t)=-1\} = (n+1)\delta t\mu_S$ since there are $n+1$ large RBs that can divide into small RBs, each with probability $\delta t\mu_S$.

Now we calculate

$$\lim_{\delta t\to 0}\frac{P_{m,n}(t+\delta t)-P_{m,n}(t)}{\delta t}$$

and obtain

$$\begin{aligned}
\frac{dP_{m,n}(t)}{dt} &= -(m\lambda_D+m\lambda_C+n\mu_L+n\mu_S)P_{m,n}(t)+(m+1)\lambda_C P_{m+1,n}(t)+(m-1)\lambda_D P_{m-1,n}(t) \\
&\quad + (n-1)\mu_L P_{m,n-1}(t)+(n+1)\mu_S P_{m-2,n+1}(t) \qquad (10)
\end{aligned}$$

for all nonnegative integers m and n, with initial conditions $P_{m,n}(0)=1$ if $m=M$ and $n=N$, $P_{m,n}(0)=0$, otherwise.

3.2 Gillespie Algorithm for Size Control Model

Similar to the birth-death model, we want to see how the population of large RBs, small RBs, and EBs change over time using the Gillespie algorithm. Figure 7 below shows the numbers of large RBs, small RBs, and EBs as functions of time t with varying parameter values. Each row corresponds to different inequalities between μ_L and μ_C and each column corresponds to different inequalities between λ_D and λ_C:

- Row 1: $\mu_L > \mu_C$
- Row 2: $\mu_L = \mu_C$
- Row 3: $\mu_L < \mu_C$

- Column 1: $\lambda_D > \lambda_C$
- Column 2: $\lambda_D = \lambda_C$
- Column 3: $\lambda_D < \lambda_C$

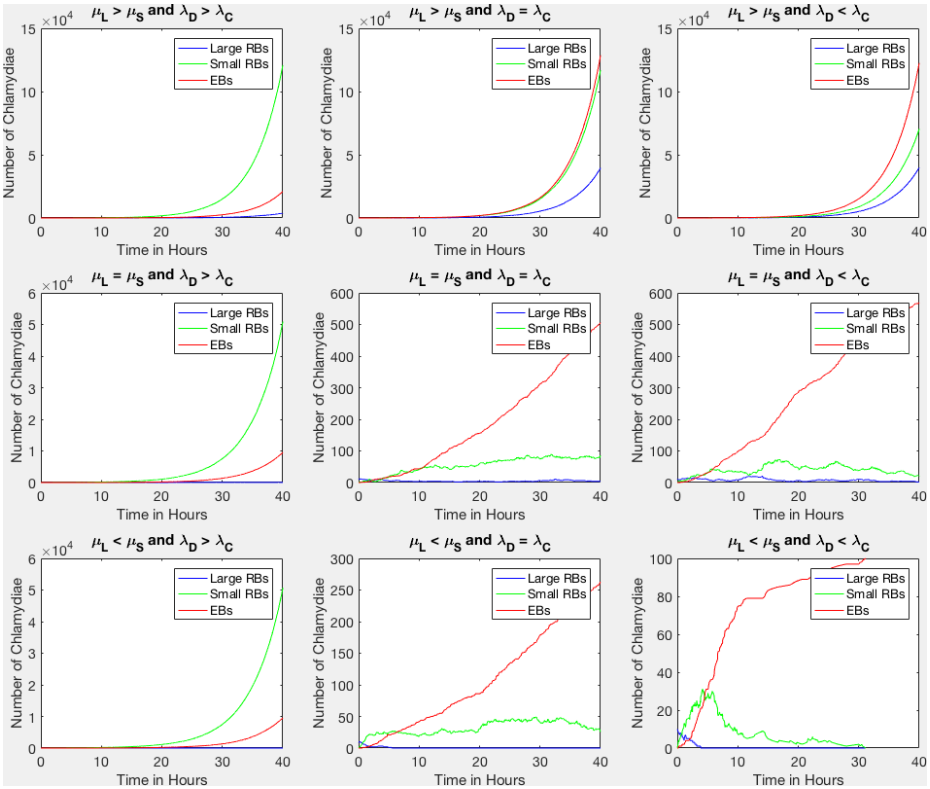

Figure 8: *Gillespie algorithm showing the size control model*

Using the graphs above, we can predict the following:

- The large RB population grows exponentially if $\mu_L > \mu_S$; remains constant if $\mu_L = \mu_S$; decays exponentially if $\mu_L < \mu_S$. There is no dependence on the the parameters λ_C and λ_D.
- The small RB population will grow exponentially if $\mu_L > \mu_S$ or if $\lambda_D > \lambda_C$. The population will decrease or remain constant if there is too much conversion and not enough division.
- The EB population will always increase. This will depend on all four parameters. In addition, the greater the division rates are, the greater the EB population will be.

4 Conclusion

In the first model, we consider division and conversion as a birth and death process, respectively. From this, we are able to derive Kolmogorov differential equations (1) for the RB population and solve for the probability generating function using the method of characteristics (4). With this, we determine that the expected value of the RB population is an

exponential function of time t (5) with behavior dependent on parameter values. In addition, we derive the Kolmogorov differential equations (6) for the EB population, which depend on the expected value of the RB population at time t. The solution (7) of the ODE is in the form of a Poisson distribution. Due to this, deducing the expected value of the EB population follows immediately. The expected value is an increasing function of time t whose behavior depends on parameter values.

We begin an optimization problem, where we want to maximize the expected value of EBs at the time of the host cell death T. There are two parameters to choose from in order to maximize (9) with respect to. Maximizing with respect to λ_D shows that there is no optimal λ_D value for any values of λ_C, N, and T. Thus, we maximize with respect to λ_C. Biological intuition supports the idea that there exists some optimal value of λ_C for given values of λ_D, N, and T. We are unable to solve this analytically, and thus we created a program in *Mathematica* that calculates the optimal λ_C value for given parameters and the expected value with this optimal value.

With this information, we run computer simulations using the Gillespie algorithm. We run the simulations for different parameter values and compare it to the respective expected values with the same parameter values. The simulations closely resemble the expected values. In addition, we use the *Mathematica* program to calculate the optimal λ_C value for a particular set of parameter values and find that the Gillespie algorithm correctly predicts that the expected value of EBs at the end of the simulation is near its maximum value.

In our second model, we consider the role of size control. Experimental data suggests that the size of an RB determines whether or not it can convert into an EB. We consider a system where we have two types of RBs: small and large. We assume that large RBs are only capable of dividing and that only small RBs are able to convert into EBs. For this model, we derive the Kolmogorov differential equations (10) and run computer simulations using the Gillespie algorithm. From these simulations, we predict some behaviors of the populations of the large RBs, small RBs, and EBs.

In order to further analyze the size control model, an analysis similar to what was done in the birth-death model needs to be carried out. The expected values of the number of large RBs and small RBs at time t needs to be calculated, perhaps again using the probability generating function and method of characteristics. Similarly, the Kolmogorov differential equations for the EB population would have to be derived and from this deduce the expected value of the EB population at time t. Then, another optimization problem would need to be solved in order to find the optimal λ_C for given parameter values of M, N, T, λ_D, μ_L, and μ_S that maximizes the expected value of EBs at time T. Computer simulations using the Gillespie algorithms then should be used again to graphically interpret the model.

Since experimental data suggests that after, on average, six divisions RBs become sufficiently small enough to begin to convert into EBs, additional sizes of RBs can be introduced into the model to add complexity. Then, an analysis similar to the birth-death model may be carried out. In addition, computer simulations using the Gillespie algorithm may also be used.

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