Finding Optimal Conversion Rate from Reticulate Bodies to Elementary Bodies of Chlamydia in a Cell

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Abstract: Finding the maximum population of Chlamydia Trachomatis at known host cell death time T is a problem of optimal control. By constructing a logistic growth model, the interior control is ruled out and a bang-bang control is preferred. The method of least squares can also be used to find the optimal conversion rate and switch point, provided that certain assumptions are met.

0.1 Introduction

Motivation: Most Chlamydial bacteria cause human disease. While most of them are not life-threatening, an exception to this is Chlamydia Trachomatis. In developing countries, Chlamydia Trachomatis is still a problem. Chlamydia Trachomatis causes eye infection that leads to blindness and possibly death. At one point, it was the leading cause of blindness worldwide, accounting for 15 percent of all cases. Today, it has dropped to less than 4 percent of such cases due to a worldwide effort for its eradication. For Chlamydia Trachomatis to be fully eradicated, it is useful to gain some insight on the reproductive and infectious aspects of this bacteria strain. Chlamydia Trachomatis can be found in the form of an elementary body (EB) and a reticulate body (RB). The elementary body is the non-replicating infectious particle that is released when the infected cell ruptures. Similar to a spore, it is responsible for the bacteria's ability to spread from person to person. The RB is involved in the process of replication and growth of these bacteria. However the RB cannot survive outside of the cell. In order for Chlamydia to spread, the RB must convert into EB before the cell ruptures. Our goal is to find the optimal conversion rate that RBs turn into EBs to maximize yield of EBs before the cell ruptures.

0.2 Problem Statement

Objectives: The mathematical model given below is an example of an exponential growth model. However, the exponential model is only a good approximation for a short period of time. For longer periods of time, such as our case, it is not too practical. This is where we make use of the logistic model. Unlike the exponential growth model, the logistic growth model takes into account the carrying capacity of the population.

Exponential Model:

$$R(t) = (\alpha - \mu)R \qquad\qquad R(0) = R_0$$

$$E'(t) = \mu R \qquad\qquad E(0) = E_0 \qquad 0 \leq \mu(t) \leq \mu_{max}$$

Given a time T (this is the time that the RBs have converted to EBs), we can deduce that the equation for the number of EBs should look like this:

$$E(T) = \int_0^T (\mu R)\, dt + E_0 \tag{1}$$

Logistic Model:

$$R'(t) = \alpha R(1-\frac{R}{K}) - \mu R, \qquad R(0) = R_0 \qquad K = carrying\ capacity$$

$$E'(t) = \mu R \qquad E(0) = E_0 \qquad 0 \leq \mu(t) \leq \mu_{max}$$

$$E(T) = \int_0^T (\mu R)\, dt + E_0$$

Let us first designate $R'(t)$ as $f(t,\mu,R)$. To find the optimal μ, we apply the Maximum Principle:

$$J[\mu] = \int_0^T \mu R\, dt \qquad 0 \leq \mu(t) \leq \mu_{max}$$

$$I[\mu] = J[\mu] + \int_0^T \lambda(t)\Big\{f(t,\mu,R) - R'\Big\}\, dt$$

$\lambda(t)$ is called the adjoint variable. Notice that since $R'(t)$ equals $f(t,\mu,R)$, $f(t,\mu,R) - R'$ becomes 0.

$$I[\mu] = \int_0^T \mu R + \lambda\Big\{\alpha R(1-\frac{R}{K}) - \mu R\Big\} - \lambda R'\, dt,$$

We can introduce this because we are not adding anything new to our equation. Although it seems like we are adding nothing, it becomes significant later on. It is also worth noting that $H = \mu R + \lambda\Big\{\alpha R(1-\frac{R}{K}) - \mu R\Big\}$ is the Hamiltonian. Now, we apply the method of calculus of variations by letting $R = \bar{R} + \epsilon r(t)$ and $\mu = \bar{\mu} + \epsilon v(t)$. The reason why it is called calculus of variations is because we are introducing variations of our optimal control. The only caveat is that $r(0)$ must be equal to 0 so that the initial condition $R(0) = R_0$ still holds.

Substituting R and μ into I[u] yields:

$$I(\epsilon) = \int_0^T (\bar{R}+\epsilon r(t))(\bar{\mu}+\epsilon v(t)) + \lambda\Big\{\alpha(\bar{R}+\epsilon r(t))(1-\frac{\bar{R}+\epsilon r(t)}{K}) \tag{2}$$

$$-(\bar{\mu}+\epsilon v(t))(\bar{R}+\epsilon r(t))\Big\} - (\bar{R}'+\epsilon r'(t))\, dt$$

After much simplifying this becomes a simple calculus I problem. In order to find the stationary condition, we derive (2) with respect to ϵ and set $\epsilon = 0$ as well as the entire equation equal to 0. Afterwards, we proceed to analyze what we get from it :

$$0 = \frac{dI}{d\epsilon}\bigg|_{\epsilon=0} = \int_0^T v(\bar{R} - \lambda\bar{\mu}) + r(\bar{\mu} + \alpha\lambda - \frac{2\alpha\lambda\bar{R}}{K} - \lambda\bar{\mu} + \lambda')dt - [\lambda r]_0^T \quad (3)$$

Afterwards, we choose λ (the adjoint variable) to eliminate the term involving r, where r(0)=0. With $\lambda(T) = 0$, we get the following equations and theorems:

$$\lambda' = \bar{\mu}(1 - \lambda) + \alpha(\frac{2\bar{R}}{K} - \lambda) = -H_R \quad (4)$$

$$\bar{R}(1 - \lambda) = H_\mu \quad (5)$$

Theorem 1. There exists a t_0, such that $\mu(t) = \mu_{max}$ at $t \in [t_0, T]$, where $t_0 \leq T$.

Proof of Theorem 1: $H(T) = \mu(T)R(T)$ and $0 \leq R(T)$ because $0 < R_0$ and $0 \leq R'(t)$ for all t. To maximize H, we let $\mu = \mu_{max}$ on the interval $[t_0, T]$. Since $H = \mu R(1 - \lambda) + \alpha\lambda R(1 - \frac{R}{K})$, λ is continuous and smaller than 1 on the interval $[t_0, T]$ so that $0 < 1 - \lambda$. Thus, to maximize H on the interval $[t_0, T]$, the optimizing μ is μ_{max}.

Theorem 2. No interior control in $0 < \mu(t) < \mu_{max}$ for t on $[0, T]$ is optimal.

Proof of Theorem 2: Since $0 \leq \mu(t) \leq \mu_{max}$,and $\frac{d^2 H_\mu}{dt^2} = 0$, we get $\mu(t) = \alpha$ for all t. Since $\mu = \mu_{max}$ on $[t_0, T]$ in Thm 1., we cannot end with an upper corner control since we assume $\alpha < \mu_{max}$.

Unfortunately, due to time constraints we were not able to finish solving for λ. However, we were simultaneously using Matlab in order to find a reasonable fit for data given to us by our experimental colleagues.

0.2.1 Method of Least Squares

For simplicity, we assume that the system is a bang-bang control such that

$$\mu(t) = \begin{cases} 0, & for \quad 0 \leq t \leq t_0 \\ \mu_{max}, & for \quad t_0 \leq t \leq T \end{cases},$$

where switch point $t_0 \leq T$

By the method of least squares, we have a function of the error:

$$error = \sqrt{\sum_{i=1}^{N}(R(t_i) - R_i)^2 + \sum_{i=1}^{N}(E(t_i) - E_i)^2} \tag{6}$$

where $R(t_i)$ and $E(t_i)$ are the solutions of the logistic model and R_i and E_i are the experimental data of RB and EB cells. Our goal is to optimize the parameters, μ_{max} and t_0 by using ode45 package in MATLAB. First, we assume that the carrying capacity K is the largest value that the numbers of RBs can reach. Since RB grows exponentially when $t < t_0$, we can solve for α. We entered the initial assumptions of α and K into MATLAB in order to find the minimal error to get the optimal μ_{max} and switch point t_0. When the minimal error is found, the least squares function returns us the optimal value of t_0 and μ_{max}.

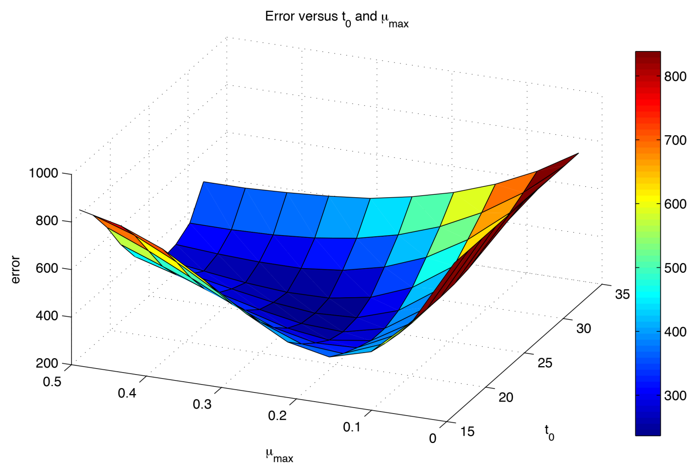

Figure 1: The surface of the error is plotted by evaluating the function of the error. The solution of the least squares problem gives us the location of the minimum error. The lowest point on the surface is where the minimum is located.

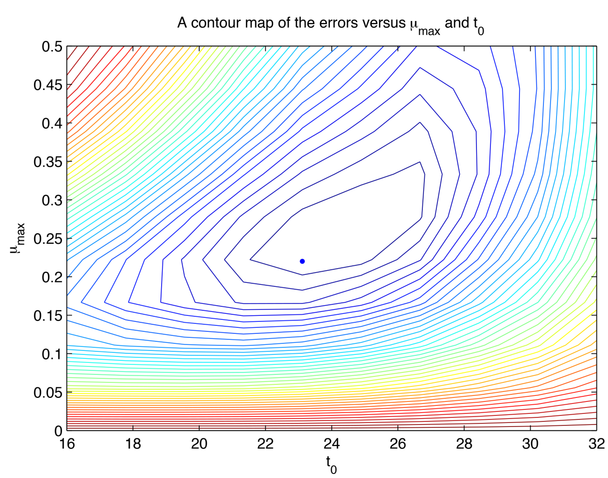

Figure 2: Another way to indicate the minimum error and optimal parameters is to plot a contour map. The map shows us the approximation of minimum and MATLAB gives us the location of the optimal (t_0, μ_{max})

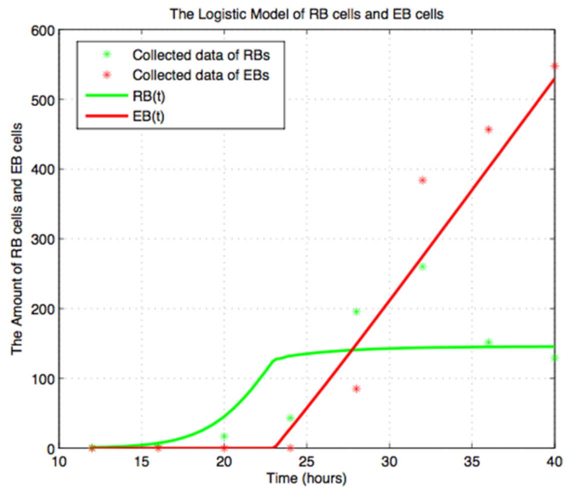

Figure 3: Fitting the optimal t_0 and μ_{max} to logistic growth model

0.2.2 Finding the maximal E(T)

Another experiment is to verify whether the switch point t_0 gives us the maximized E(T). From a vector containing five different values of t_0, where $0 < t_0 < T$, we iterate each t_0 from the vector to the model and get the solutions of EB. However, regardless the values of t_0 is larger or smaller than the optimal one, E(T) are always smaller than the optimal E(T) and data EB. Thus only the optimal t_0 results the best-fitted model to the experimental data. If the RB cells convert too soon, there are not enough RB cells for the conversion. If RB cells convert too late, there are not enough time for it to convert into EB cells.

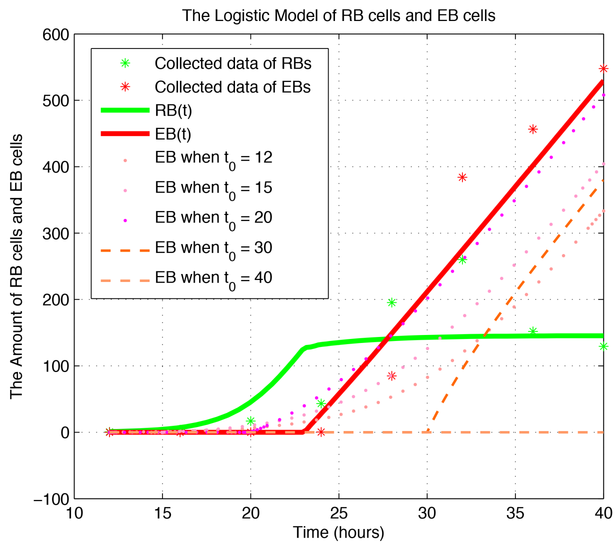

Figure 4: Finding the optimal E(T) when t_0 has different values

0.3 Conclusion

The logistic growth model is more reasonable comparing to the exponential growth model for longer periods of time because it takes into account a carrying capacity. However, the exponential model is still a reasonable approximation for shorter periods of time. We can conclude there exists a t_0, such that $u(t) = \mu_{max}$ at $t \in [t_0, T]$, where $t_0 \leq T$.. We have also proved that there is no interior control in $0 < \mu(t) < \mu_{max}$ for t on $[0, T]$ for which the system is optimal.

0.3.1 Research Tasks

1)Learning about the life cycle of Chlamydia

2)Interpreting graphs/data from our biologist collaborators

3)Working under the supervision of MCB student Cynthia Sanchez-Tapia

4)Regularly meet up with our research advisors, German Enciso and Frederic

Wan about the progress of our research

5)Gaining hands on experience of mathematical modeling using:

a.Mathematica

b.MATLAB

0.3.2 Timeline

Week 1: MATLAB/Mathematica Training

Week 2: Proofreading previous research publications

Week 3: Latex Training

Week 4: Proposal

Week 5: Computation/Analysis

Week 6: Computation/Analysis

Week 7: Computation/Analysis

Week 8: Editing

Week 9: Final draft

Week 10: Presentation

0.4 Collaborators

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