Stochastic Model on the Spread of Chlamydia Trachomatis

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August 29, 2017

What is Chlamydia Trachomatis?

A bacterium that causes ocular and genital tract infections in humans. Common diseases are trachoma (blindness) and chlamydia (STD).

Why Do We Care?

- Chlamydia accounts for about 60% of sexually transmitted diseases reported in the U.S.
- 40 million people in underdeveloped countries are affected by trachoma.

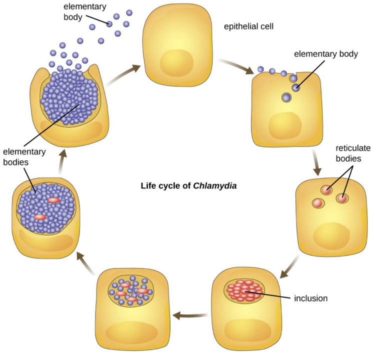
Life Cycle of Chlamydia Trachomatis

Two developmental forms:

- Elementary body (EB)
- Reticulate body (RB)

Stages:

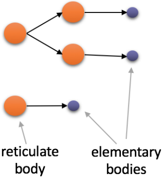
1. EBs infect a cell and form an inclusion
2. EBs convert to RBs
3. RBs divide repeatedly through binary fission
4. RBs convert to EBs asynchronously
5. When host cell dies, only EBs survive



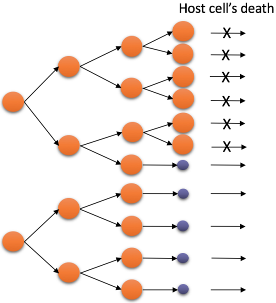
Taken from CDC and Lumen Learning

What if Conversions Occur Too Soon or Too Late?

Too Soon: There will not be many RBs to reproduce. Therefore, there would be few EBs at the time host cell dies.

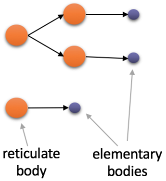


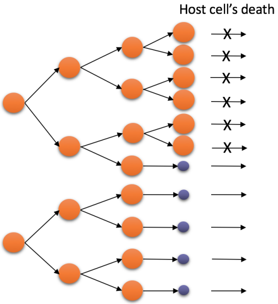
Too Late: By the time the host cell dies, many RBs that haven't converted will die. Therefore, there would be few EBs at the cell death.



There Must Be a Balance!

There must be an optimal rate of conversion in order to have the maximum number of EBs at the time of the host cell's death.





Our Goals

- Create a stochastic mathematical model that describes the behavior of *C. Trachomatis*.
- Understand the optimal behavior to maximize the number of EBs.
- Understand the role that size control has on cell fate regulation
- Run and analyze computer simulations of the models using the Gillespie algorithm

Defining the Birth-Death Model

- Since we gain an RB through a division, we consider this as a "birth" process.
- Likewise, we lose an RB through a conversion, so we consider this as a "death" process.

This model is called a birth-death model

Birth-Death Model: Modeling the RB Population

Assumptions

- Let $P_k(t)$ be the probability of having k RBs at time t.
- Start with an initial population of N RBs.
- Parameters:
  - λ_D - describes the rate of division (birth process)
  - λ_C - describes the rate of conversion (death process)
- Consider the time interval $(t, t + \delta t)$ for small enough δt that at most one conversion or division can occur:
  - One conversion occurs with probability $\delta t \lambda_C$
  - One division occurs with probability $\delta t \lambda_D$
  - Neither occurs with probability $1 - \delta t(\lambda_D + \lambda_C)$

Birth-Death Model (RB): Deriving the ODEs

We have determined that:

$$P_k(t+\delta t) = \underbrace{(1 - k\delta t(\lambda_D + \lambda_C))P_k(t)}_{\text{probability of nothing changing}} + \underbrace{(k+1)\delta t \lambda_C P_{k+1}(t)}_{\text{probability of losing 1 RB - "death"}}$$

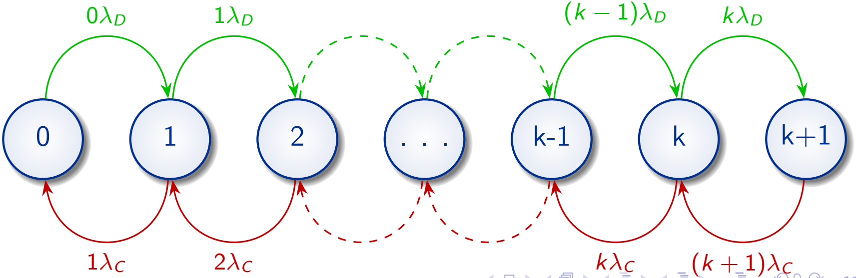
$$+ \underbrace{(k-1)\delta t \lambda_D P_{k-1}(t)}_{\text{probability of gaining 1 RB - "birth"}}$$

Birth-Death Model (RB): ODEs and Diagram

We find that for all nonnegative integers k,

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

with initial conditions $P_k(0) = \begin{cases} 1 & : \quad k = N \\ 0 & : \quad k \neq N \end{cases}$



Birth-Death Model (RB): Expected Value

We solve for the probability generating function by the method of characteristics and derive that

Expected Value of RBs

$$E[RB(t)] = Ne^{(\lambda_D - \lambda_C)t}$$

where N is the initial population of RBs

Birth-Death Model: Modeling the EB Population

Assumptions

- Let $Q_j(t)$ be the probability of having j EBs at time t.
- Start with an initial population of 0 EBs
- Consider the time interval $(t, t + \delta t)$ such that δt is small enough that at most one conversion can occur:
  - Probability of one conversion $\delta t \lambda_C$
  - Probability of no conversion $1 - \delta t \lambda_C$

Birth-Death Model (EB): Deriving the ODE

We have determined that:

$$Q_j(t+\delta t) = \underbrace{[1-\delta t \lambda_C \sum_{k=0}^{\infty} kP_k(t)] Q_j(t)}_{\text{probability of nothing changing}} + \underbrace{[\lambda_C \delta t \sum_{k=0}^{\infty} kP_k(t)] Q_{j-1}(t)}_{\text{probability of gaining 1 EB}}$$

Birth-Death Model (EB): ODE

From this, we derive for all nonnegative integers j,

$$\frac{dQ_j(t)}{dt} + \lambda_C N e^{(\lambda_D - \lambda_C)t} Q_j(t) = \lambda_C N e^{(\lambda_D - \lambda_C)t} Q_{j-1}(t)$$

with initial conditions $Q_j(0) = \begin{cases} 1 & : \quad j = 0 \\ 0 & : \quad j \neq 0 \end{cases}$

Birth-Death Model (EB): Expected Value

We calculated the solution of the ODE using integrating factors and found the solution of the ODE is in the form of a Poisson distribution with

Expected Value of EB's

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

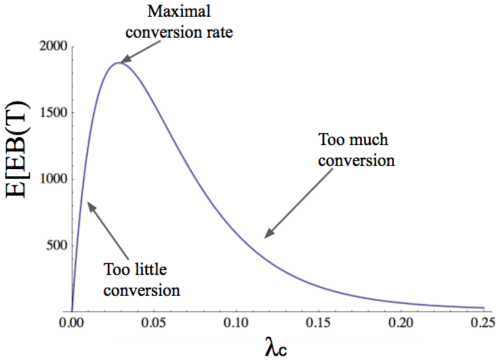
Maximizing the Number of EBs at Terminal Time T

We are interested in obtaining the maximum number of EBs when the host cell dies so that *C. Trachomatis* can spread optimally.

- Assume that T is the time at which the host cell dies.
- We want to maximize $E[EB(T)]$.
- We can find the maximum with respect to either λ_C or λ_D
- Increasing λ_D increases the expected value, so there is no optimal λ_D.

Maximizing with Respect to λ_C

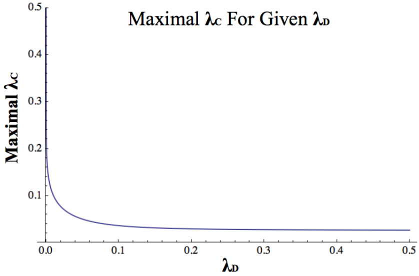
- Assume that λ_D is a given constant.
- The optimal λ_C value has no dependence on N



$E[EB(T)]$ as a function of λ_C with parameter values $\lambda_D = 0.225$, $N = 5$, and $T = 40$

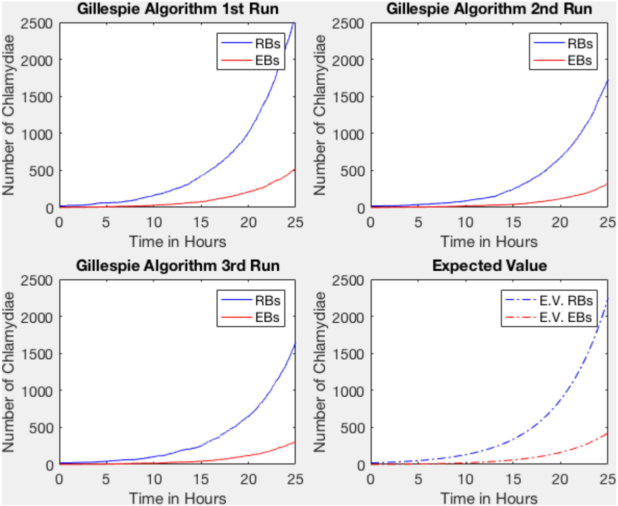
Sample Maximal Conversion Rates

Parameter values used are
$T = 40$ and $N = 5$.
Generated using *Mathematica*.



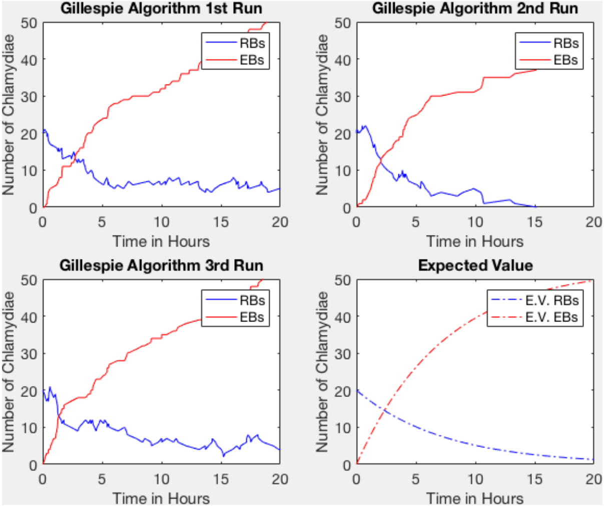
λ_D	Maximal λ_C	E[EB(t)]
0.	2.05569	5.
0.025	0.0698321	6.49213
0.05	0.0499998	10.
0.075	0.0409805	17.4623
0.1	0.0360768	33.5696
0.125	0.0331642	69.3122
0.15	0.0313246	150.769
0.175	0.0301018	340.657
0.2	0.0292511	791.584
0.225	0.0286344	1878.64
0.25	0.0281709	4531.66
0.275	0.0278114	11 072.6
0.3	0.0275249	27 336.2
0.325	0.0272916	68 065.9
0.35	0.0270979	170 694.
0.375	0.0269346	430 660.
0.4	0.0267949	1.09222×10^6
0.425	0.0266741	2.7826×10^6
0.45	0.0265687	7.11725×10^6
0.475	0.0264757	1.82682×10^7
0.5	0.0263932	4.70367×10^7

Birth-Death Model: Gillespie Algorithm for $\lambda_C < \lambda_D$



$\lambda_C = 0.03608$
$\lambda_D = 0.225$
$N = 20$

Birth-Death Model: Gillespie Algorithm for $\lambda_C > \lambda_D$

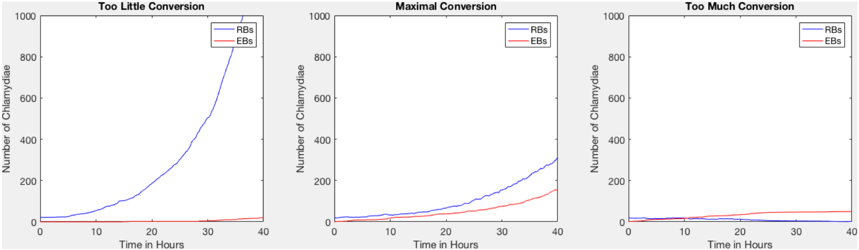


$$\lambda_C = 0.3608$$
$$\lambda_D = 0.225$$
$$N = 20$$

Birth-Death Model: Gillespie Algorithm

Using the *Mathematica* program, we calculated the optimal λ_C value for $N = 20$, $\lambda_D = 0.1$, and $T = 40$.

- Optimal $\lambda_C = 0.03608$, Expected value of EBs ≈ 134



Parameter Values: $N = 20$, $\lambda_D = 0.1$

• left: $\lambda_C = 0.0015$ • middle: $\lambda_C = 0.03608$ • right: $\lambda_C = 0.12$

Defining the Size Control Model

Experimental data suggests that at each RB division, the size of an RB decreases. Only after a certain size threshold RBs begin to convert to EBs.

As a first step, we consider a simpler approach, where we only have 2 sizes of RBs: large RBs and small RBs. Suppose that

- 1 large RB can either divide into 2 large RBs or divide into 2 small RBs
- 1 small RB can either divide into 2 small RBs or convert into an EB

Size Control Model: Modeling the RB Population

Assumptions

- Let $P_{m,n}(t)$ be the probability of having m small RBs and n large at time t.
- Start with an initial population of M small RBs and N large RBs.
- Parameters:
  - μ_L - describes rate of large RB $\rightarrow$ 2 large RBs
  - μ_S - describes rate of large RB $\rightarrow$ 2 small RBs
  - λ_D - describes rate of small RB $\rightarrow$ 2 small RBs
  - λ_C - describes rate of small RB $\rightarrow$ EB

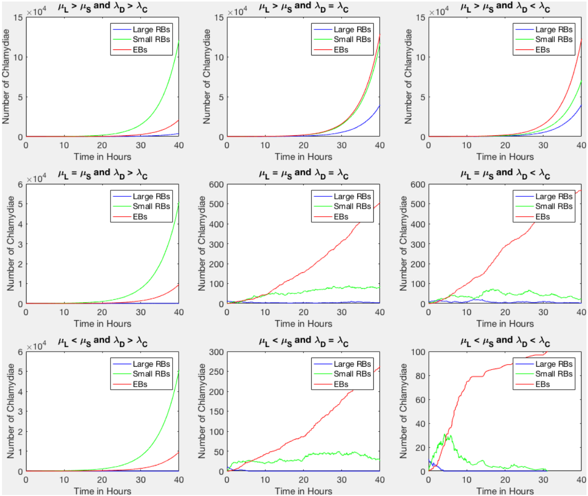
Size Control Model: ODEs

From this, we derive for all nonnegative integers m,n,

$$\frac{dP_{m,n}(t)}{dt} = \underbrace{-(\lambda_D m + \lambda_C m + \mu_L n + \mu_S n)P_{m,n}(t)}_{\text{no event occurs}}$$
$$+ \underbrace{\lambda_C(m+1)P_{m+1,n}(t)}_{\text{1 small RB} \to \text{1 EB}} + \underbrace{\lambda_D(m-1)P_{m-1,n}(t)}_{\text{1 small RB} \to \text{2 small RBs}}$$
$$+ \underbrace{\mu_L(n-1)P_{m,n-1}(t)}_{\text{1 large RB} \to \text{2 large RBs}} + \underbrace{\mu_S(n+1)P_{m-2,n+1}(t)}_{\text{1 large RB} \to \text{2 small RBs}}$$

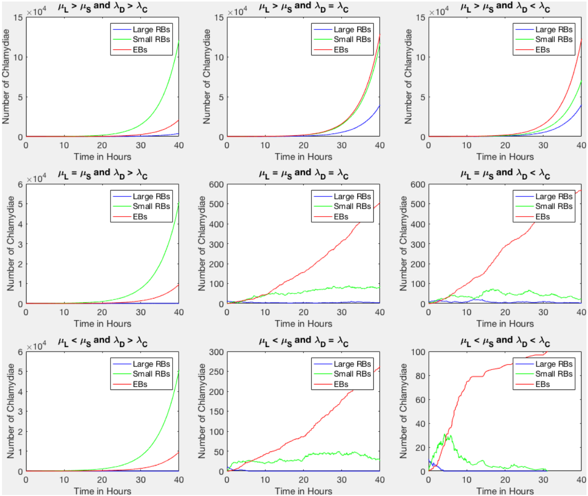
with initial conditions $P_{m,n}(0) = \begin{cases} 1 & : \quad m = M, n = N \\ 0 & : \quad otherwise \end{cases}$

Size Control Model: Gillespie Algorithm



Row 1: $\mu_L > \mu_S$
Row 2: $\mu_L = \mu_S$
Row 3: $\mu_L < \mu_S$
Column 1: $\lambda_D > \lambda_C$
Column 2: $\lambda_D = \lambda_C$
Column 3: $\lambda_D < \lambda_C$

Size Control Model: Predictions



- Large RB population grows exponentially if $\mu_L > \mu_S$; remains constant if $\mu_L = \mu_S$; decays exponentially if $\mu_L < \mu_S$
- Small RB population grows exponentially if $\mu_L > \mu_S$ or if $\lambda_D > \lambda_C$
- EB population always increases; but depends on all four parameters; more division increases

Conclusion

Birth-Death Model:

- RBs: Expected value of RBs at time t
- EBs: Poisson distribution and expected value of EBs at time t
- Maximal conversion rate: built a function in *Mathematica* that calculates λ_C for any λ_D, N, and T.
- Ran Gillespie algorithms in *MATLAB* for $\lambda_C < \lambda_D$ and $\lambda_C > \lambda_D$

Size Control Model:

- ODE for probability of having m small RBs and n large RBs
- Ran Gillespie algorithms in *MATLAB* for varying parameter values

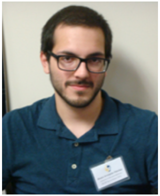
Future Work

- Continue working on size control model
  - Simplify the model if possible
  - Find expected value of large RBs and small RBs
  - Derive an ODE for the EB population
  - Find expected value of EBs
  - Calculate the optimal λ_C that maximizes the expected value of EBs
- Expand the model to include smaller sizes of RBs

Acknowledgements

Germán A. Enciso

Frederic Y.M. Wan



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This material is based upon work supported by the National Science Foundation under Grant No. DMS-1129008

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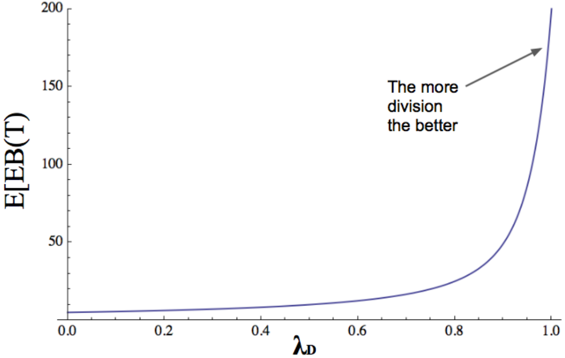
Why a Stochastic Model?

There are not that many RBs at the beginning. Hence, variability is important.
In addition, there is an element of randomness since RBs can either divide or convert. Due to this, we can expect that computer simulations of this model will produce different outputs.

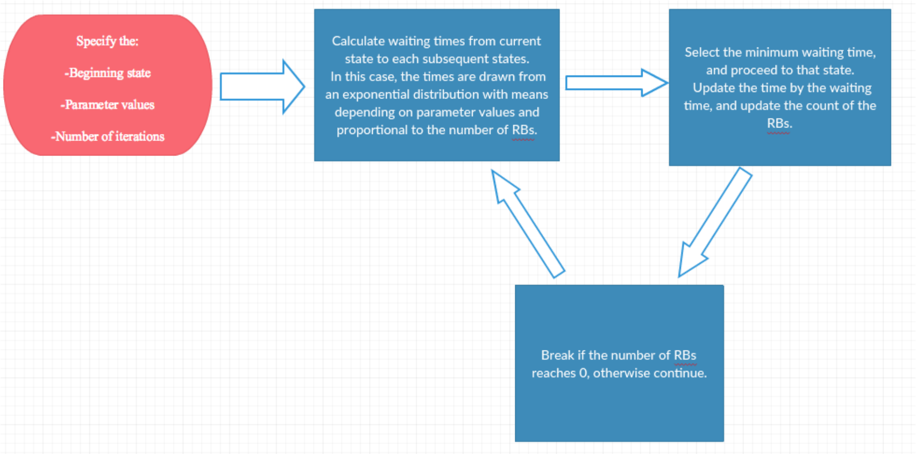
Maximizing with Respect to λ_D

- Assume that λ_C is a given constant.



$E[EB(T)]$ as a function of λ_D with parameter values $\lambda_C = 1$, $N = 5$, and $T = 40$

How the Gillespie Algorithm Works



Size Control Model: Diagram