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BRANCHING MODEL WITH STATE DEPENDENT OFFSPRING DISTRIBUTION FOR *CHLAMYDIA* SPREAD

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Abstract. *Chlamydiae* are bacteria with an interesting unusual developmental cycle. Initially, a single bacterium in its infectious form (elementary body, EB) enters the host cell, where it converts into its dividing form (reticulate body, RB), and divides by binary fission. Since only the EB form is infectious, before the host cell dies, RBs start to convert into EBs. After the host cell dies RBs do not survive. We model the population growth by a 2-type discrete-time branching process, where the probability of duplication depends on the state. Maximizing the EB production leads to a stochastic optimization problem. Simulation study shows that our novel model is able to reproduce the main features of the development of the population.

Mathematics Subject Classification. 60J85, 92C70.

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1. Introduction

Chlamydiae are obligate intracellular bacteria which have a unique two-stage developmental cycle, with two forms, the elementary body (EB) and the reticulate body (RB). The EB is the infectious form and it is not capable to multiply. Upon infecting the host cell, the EB differentiates to RB. RBs multiply in the host cell by binary fission. After some time RBs redifferentiate to EBs. The EBs are then released from the host cell ready to infect new host cells.

This unique life-cycle triggered a lot of mathematical work to model the growth of the population. Wilson [1] worked out a deterministic model taking into account the infected and uninfected host cells and the extracellular *Chlamydia* concentration. Wan and Enciso [2] formulated a deterministic model for the quantities of RBs and EBs, and solved an optimal control problem to maximize the quantity of EBs when the host cell dies. The same problem in a stochastic framework was investigated by Enciso *et al.* [3] and Lee *et al.* [4].

RBs divide repeatedly by binary fission expanding the RB population. Then after a period of no conversion, RBs convert into EBs. It was shown recently by Lee *et al.* [4] using 3D electron microscopy method and manual counting that this conversion occurs asynchronously, so that some RBs are converting into EBs, while others continue to divide. Mathematical models suggested up to now are unable to reproduce this asynchronous conversion, since both in the deterministic differential equation model in [2] and in the stochastic model in [3] the optimal conversion strategy is the so-called 'bang-bang' strategy, that is, up to some time the population duplicates, then converts to EBs with the maximal possible rate.

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Branching processes are well-known tools to model cell proliferation, see *e.g.* the monographs by Haccou *et al.* [5], Kimmel and Axelrod [6]. Bogdanov *et al.* [7] used a discrete-time Galton–Watson process to model *chlamydia* growth in the presence of antibiotics. In [3], a continuous time Markov chain model was introduced with time-dependent transition rates, and the cell death was assumed to be independent of the population process. However, as heavily infected cells are more likely to die, the latter independence assumption, while mathematically convenient, is not realistic. In the present paper we use a discrete-time branching process model, where the probability of duplication and the time of the cell death depend on the state of the process. Finding the optimal conversion strategy leads to a stochastic optimization problem, a so-called *discrete-time Markov control process*, see *e.g.* Hernández-Lerma and Lasserre [8]. The only input of the process is a *death-probability function* $d(x, y)$, which determines the probability that the host cell dies when there are x RBs and y EBs. Simulation study shows that with a simple death-probability function our model is able to capture the real behavior described recently in [4].

We emphasize that our aim here is to provide a stochastic model describing the evolution of a bacterium population inside a single host cell. Therefore, the model is different from the 'branching in branching' models, where the host cells divide by binary fission, and they contain proliferating parasites, which after division are distributed between the two offspring cells. Branching in branching models were first introduced by Kimmel [9] in the discrete state space setting. The continuous state space version of such processes was investigated very recently by Marguet and Smadi [10].

The paper is organized as follows. In Section 2, we describe our model. In Sections 3 and 4, we analyze the cases when the host cell's death time is independent of, or depends on the process. The latter case is biologically more relevant. Section 5 contains a simulation study, and we finish with concluding remarks.

2. The theoretical model

Consider a two-type discrete-time Galton–Watson branching process $\mathbf{X}^\pi = (\mathbf{X}_n^\pi)_n = (X_n^\pi, Y_n^\pi)_n$, $n \geq 0$, together with a sequence of probabilities $\pi = (p_n)_n$. We assume that π is adapted to the natural filtration $(\mathcal{F}_n)_n$ generated by $\mathbf{X}$, *i.e.* $\mathcal{F}_n = \sigma(\mathbf{X}_k^\pi, k \leq n)$. Initially $\mathbf{X}_0^\pi = (1, 0)$, and the process evolves as

$$X_{n+1}^\pi = \sum_{i=1}^{X_n^\pi} \xi_{n,i},$$
$$Y_{n+1}^\pi = Y_n^\pi + \sum_{i=1}^{X_n^\pi} \left(1 - \frac{\xi_{n,i}}{2}\right), \quad n \geq 0,$$

where $\xi_n, \xi_{n,i}, n = 1, 2, \ldots, i = 1, 2, \ldots$ are conditionally independent random variables given $(p_n)_n$, for fixed n the variables $\xi_n, \xi_{n,i}$, $i = 1, 2, \ldots$ are identically distributed, such that $\mathbf{P}(\xi_n = 2|p_n) = p_n$, $\mathbf{P}(\xi_n = 0|p_n) = 1 - p_n$.

Here X_n^π stands for the number of RBs and Y_n^π for the number of EBs in generation n. In generation n each RB duplicates with probability p_n and converts into EB with probability $1 - p_n$. If $\xi_{n,i} = 2$, then the ith RB in generation n duplicates, while if $\xi_{n,i} = 0$ then it converts to EB. The process π, the sequence of duplication probabilities, is adapted to $(\mathcal{F}_n)_n$, which intuitively means that based on the whole past of the process the population determines its duplication probabilities. In what follows, we call the random process π a *strategy*.

For the conditional expectations we obtain

$$\begin{aligned}\mathbf{E}[(X_{n+1}^\pi, Y_{n+1}^\pi)|\mathcal{F}_n] &= (2p_n X_n^\pi, Y_n^\pi + (1 - p_n)X_n^\pi) \\ &= \mathbf{X}_n^\pi \begin{pmatrix} 2p_n & 1 - p_n \\ 0 & 1 \end{pmatrix}.\end{aligned}$$

If p_n depends only on the actual state (X_n, Y_n), then the process is Markovian.

The process ends at a random time $T \in \{1, 2, \ldots\}$ when the infected host cell dies. The aim of the bacterial population is to produce as many EBs as possible, that is to maximize $\mathbf{E}(Y_T^\pi)$ over all possible strategies (p_n). Denoting by $\mathcal{P}$ the set of all strategies, a strategy $\mathbf{q}$ is *optimal*, if

$$\sup_{\pi \in \mathcal{P}} \mathbf{E}(Y_T^\pi) = \mathbf{E}(Y_T^{\mathbf{q}}).$$

Note that we do not claim neither existence nor uniqueness in general, see the remark after Theorem 3.1.

The cause of the host cell's death and the distribution of its time is not yet well-understood. Experiments indicate that the lysis times of different host cells vary between 48 and 72 hours post infection (hpi), see Elwell *et al.* [11]. Here we consider two models. If T is independent of the process then we can explicitly calculate the optimal strategy, which turns out to be a deterministic 'bang-bang' strategy. Depending on the distribution of T, the population doubles up to a deterministic time ($p_n = 1$), and then all the RBs convert to EBs immediately ($p_n = 0$). This phenomena is analogous to the findings in the continuous time setup in [3], where independence of T and $\mathbf{X}^\pi$ was tacitly assumed. Therefore, this model cannot explain the asynchronous conversion. In our second model we assume that the host cell dies at time n with a probability depending on $\mathbf{X}_n^\pi$, where more bacteria imply higher death probability. In this more complex and more realistic model we can determine the optimal strategy only numerically. We found that asynchronous conversion happens naturally. In simulations we obtained similar behavior as in real experiments in [4].

3. Death time T is independent of $\mathbf{X}$

Assume that the host cell's death time T is independent of the process $\mathbf{X}^\pi$. Introduce the notation $\pi_\ell = (1, 1, \ldots, 1, 0, 0, \ldots)$, where the first $\ell \geq 0$ components are 1.

Theorem 3.1. *Assume that $T \geq 1$ is bounded and it is independent of $\mathbf{X}^\pi$. Let ℓ be such that*

$$2^\ell \mathbf{P}(T > \ell) = \sup_{k \geq 0} 2^k \mathbf{P}(T > k). \tag{3.1}$$

Then π_ℓ is an optimal strategy, with optimal value

$$\sup_{\pi \in \mathcal{P}} \mathbf{E}(Y_T^\pi) = \sup_{k \geq 0} 2^k \mathbf{P}(T > k).$$

Note that if T is unbounded, then it is possible that $\lim_{k \to \infty} 2^k \mathbf{P}(T > k) = \infty$, in which case it is easy to see that there is no optimal strategy.

Furthermore, one can construct distributions for which ℓ in (3.1) is not unique, showing that the optimal strategy is not necessarily unique. Indeed, the simplest example is a two-valued T, for which $\mathbf{P}(T = 1) = \mathbf{P}(T = 2) = \frac{1}{2}$. Then both π_0 and π_1 are optimal strategies with optimal value 1. Under π_0 the gain is constant 1, *i.e.* deterministically $Y_T^{\pi_0} \equiv 1$, while under π_1 the gain is 2 or 0 with probability $\frac{1}{2} - \frac{1}{2}$.

Proof. To ease notation we suppress π. Since $T \leq N$, for some N, in an optimal strategy $p_{N-1} = 0$. Next, using the independence of T and X

$$\begin{aligned}
&\mathbf{E}\left[Y_T | T > N-2, \mathcal{F}_{N-2}\right] \\
&= Y_{N-2} + 2p_{N-2}X_{N-2}\mathbf{P}(T = N | T > N-2) + X_{N-2}(1 - p_{N-2}) \\
&= Y_{N-2} + X_{N-2}\left(1 + p_{N-2}(2\mathbf{P}(T = N | T > N-2) - 1)\right).
\end{aligned}$$

Thus, the resulting expression is linear in p_{N-2}, therefore choosing $p_{N-2} = 0$ or 1, maximizes the expectation. (We emphasize that there is no uniqueness in general, since if $\mathbf{P}(T = N | T > N-2) = \frac{1}{2}$, then any $p_{N-2} \in [0, 1]$

maximizes the expression.) Since p_{N-2} only depends on the distribution of T, and not on (X_{N-2}, Y_{N-2}), we have

$$\begin{aligned}
&\mathbf{E}\left[Y_T | T > N-3, \mathcal{F}_{N-3}\right] \\
&= Y_{N-3} + X_{N-3}(1-p_{N-3}) + X_{N-3}2p_{N-3}(1-p_{N-2})\mathbf{P}(T > N-2 | T > N-3) \\
&\quad + X_{N-3}4p_{N-3}p_{N-2}\mathbf{P}(T > N-1 | T > N-3) \\
&= Y_{N-3} + X_{N-3}\left(1 + p_{N-3}\left(2(1-p_{N-2})\mathbf{P}(T > N-2 | T > N-3) + 4p_{N-2}\mathbf{P}(T > N-1 | T > N-3) - 1\right)\right).
\end{aligned}$$

Again, the resulting expression is linear in p_{N-3}, therefore choosing $p_{N-3} = 0$ or 1, maximizes the expectation. Iteration gives that there is an optimal strategy for which each p_i is either 0 or 1.

This means that there exists an optimal strategy of the form π_k, for some k. Under π_k the population doubles up to generation k, then all the RBs convert to EBs. These strategies are easy to compare. Under π_k simply $Y_T = \mathbb{I}(T \geq k+1)2^k$, with $\mathbb{I}$ standing for the indicator function, thus

$$\mathbf{E}(Y_T) = \mathbf{P}(T > k)2^k.$$

Taking the maximum in k, we obtain that π_ℓ is indeed an optimal strategy. □

One can consider a more general model, in which each bacterial cell is allowed to wait, that is, neither divides, nor converts. Then instead of a single p_n, we have a vector (p_n, q_n), such that $\mathbf{P}(\xi_n = 2|(p_n, q_n)) = p_n$, $\mathbf{P}(\xi_n = 1|(p_n, q_n)) = q_n$, and $\mathbf{P}(\xi_n = 0|(p_n, q_n)) = 1 - p_n - q_n$. In this more general setting Theorem 3.1 remains true with the identical proof. Intuitively it is clear that the population loses nothing by adding RBs, as T is independent of $\mathbf{X}$. Therefore, in an optimal strategy $q_n \equiv 0$. However, this more general setup might allow us to model stress factors for the bacteria, such as antiobiotic treatment. Then, depending on the antibiotic concentration, there is a minimal probability $q_{\min} > 0$, such that a single bacterium waits, that is $q_n \geq q_{\min}$. This extended model will be the subject of further research.

4. Death time T depends on $\mathbf{X}$

Here we assume that T, the death time depends on the process $\mathbf{X}^\pi$. Given that the host cell is alive in generation $n-1$, the probability that it dies in the next step is $d(X_n^\pi, Y_n^\pi)$, that is

$$\mathbf{P}(T = n | T > n-1, \mathcal{F}_n) = d(X_n^\pi, Y_n^\pi).$$

The deterministic *death-probability* function d describes the effect of RBs and EBs to cell's death. It is not clear which type is more harmful to the host cell, since RB particles are larger, while EB particles secrete chemicals poisoning the host cell, see *e.g.* [11]. Assume that

$$\exists\, C > 0 \;\text{ such that }\; d(x,y) = 1 \;\text{ whenever }\; x + y \geq C. \tag{4.1}$$

That is, if the total number of bacteria exceeds C the host cell necessarily dies. This is biologically a natural assumption.

In this scenario the process is a special *discrete-time Markov control process* (or Markov decision process). For theory and properties of these processes we refer to the monograph [8]. To see that our model fits in the theory we slightly modify our process. Recall that $X_n = X_n^\pi$ depends on the strategy π, however for notational ease we suppress the upper index. Define a Markov chain $(\widetilde{X}_n, \widetilde{Y}_n)_n$ on the state space $\{0, 1, \ldots\}^2$, where the possible controls are given by the duplication probabilities $p_n \in [0,1]$. The transition probabilities are,

for $x > 0$, $y \geq 0$,

$$\begin{aligned}
&\mathbf{P}\left(\widetilde{X}_{n+1} = 2j, \widetilde{Y}_{n+1} = y + x - j | \widetilde{X}_n = x, \widetilde{Y}_n = y, p_n = p\right) \\
&= \binom{x}{j} p^j (1-p)^{x-j} (1 - d(2j, y + x - j)), \quad j = 1, \ldots, x, \\
&\mathbf{P}\left(\widetilde{X}_{n+1} = 0, \widetilde{Y}_{n+1} = y + x - j | \widetilde{X}_n = x, \widetilde{Y}_n = y, p_n = p\right) \\
&= \binom{x}{j} p^j (1-p)^{x-j} d(2j, y + x - j), \quad j = 1, \ldots, x, \\
&\mathbf{P}\left(\widetilde{X}_{n+1} = 0, \widetilde{Y}_{n+1} = y + x | \widetilde{X}_n = x, \widetilde{Y}_n = y, p_n = p\right) \\
&= (1-p)^x,
\end{aligned} \tag{4.2}$$

while if $x = 0$

$$\mathbf{P}(\widetilde{X}_{n+1} = 0, \widetilde{Y}_{n+1} = 0 | \widetilde{X}_n = 0, \widetilde{Y}_n = y, p_n = p) = 1.$$

The first two formulae correspond to the possibility that j bacteria duplicate (with probability $\binom{x}{j} p^j (1-p)^{x-j}$) and the host cell remains alive, or dies, while the third formula corresponds to the possibility that all the RBs convert to EBs, and in this case it does not matter whether the host cell dies or not. The fourth equation states that $(0, 0)$ is the unique absorbing state, which is a convenient condition for the form of the reward function.

The *reward function* (-1 times the cost function in [8]) gives the number of EBs upon cell's death, that is

$$c(x, y) = \begin{cases} y, & x = 0, \\ 0, & \text{otherwise} \end{cases} \tag{4.3}$$

Define the *value function*

$$h(x, y) = \begin{cases} \sup_{\pi \in \mathcal{P}} \mathbf{E}\left[\sum_{n=0}^{\infty} c(\widetilde{X}_n, \widetilde{Y}_n) | (\widetilde{X}_0, \widetilde{Y}_0) = (x, y)\right], & d(x, y) < 1, \\ y, & d(x, y) = 1. \end{cases} \tag{4.4}$$

which is the optimal number of expected EBs upon host cell's death, given that the host cell is alive and $(\widetilde{X}_0, \widetilde{Y}_0) = (x, y)$, if $d(x, y) < 1$. If $d(x, y) = 1$ then the cell cannot be alive at state (x, y), thus the reward is y. Clearly $h(0, y) = y$. Note that since $(0, 0)$ is the only absorbing state, in the infinite sum in (4.4) there is only one non-zero term.

We are looking for the value $h(x, y)$ and the optimal strategy π. This stochastic optimization problem is in fact a finite-horizon problem, see [8], Chapter 3. Indeed, from any state $(\widetilde{X}_n, \widetilde{Y}_n) = (x, y)$ either the total number of bacteria increases ($j \geq 1$ and the host cell survives in (4.2)), or $\widetilde{X}_{n+1} = 0$, meaning that the cell dies. Therefore, by condition (4.1) from any initial state (x, y) the process reaches the absorbing state $(0, 0)$ in at most $C + 1$ steps. So in (4.4) in the summation the upper limit can be changed to C. Using Theorem 3.2.1 in [8] both the value function h and the optimal strategy can be determined by backward induction on time. In our setup, backward induction on the total number of bacteria is more natural, and this goes as follows.

Theorem 4.1. *Assume that (4.1) holds. Then $h(x,y) = y$ if $x+y \geq C$, and $h(0,y) = y$ for any y. Assume that $h(x,y)$ is determined whenever $x+y \geq m$ for some $m \leq C$, and let $x+y = m-1$. Then*

$$h(x,y) = \max_{p\in[0,1]} \sum_{j=0}^{x} \binom{x}{j} p^j (1-p)^{x-j} \times \left[d(2j, y+x-j)(y+x-j) + (1-d(2j,y+x-j))h(2j, y+x-j) \right], \tag{4.5}$$

where all the values of h on the right-hand side are determined. The maximum in p of the continuous function on the right-hand side of (4.5) is attained at $p(x,y)$, which gives the optimal strategy.

Proof. From definition (4.4) we see that $h(x,y) = y$ if $x+y \geq C$ or $x = 0$. Formula (4.5) follows from the Markovian structure and from the transition probabilities in (4.2).

Indeed, from (x,y), $x+y = m-1$, the process can jump to states $(0, y+x-j)$, $j = 0,1,\dots,x$, and $(2j, y+x-j)$, $j = 1,2,\dots,x$, depending on whether the host cell dies or not. In the first case $h(0,y+x-j) = y+x-j$, while in the second case the total number of bacteria equals $y+x+j \geq m$, therefore $h(2j, y+x-j)$ is determined by the induction assumption. Thus all the quantities in (4.5) are known, so $h(x,y)$ can be calculated. □

One could consider again the more general model mentioned at the end of Section 3, where each bacterium is allowed to wait. Then instead of a single p_n, the possible controls are given by a vector (p_n, q_n), with $p_n + q_n \leq 1$. A version of Theorem 4.1 remains true, except in (4.5) the maximum is taken in (p,q). We found that for reasonable death-probability functions (*i.e.* d_2 in (5.2)), the optimal values of q are small, or even 0. However, adding a constraint on q_n leads to a model in the presence of antibiotic, see the comment at the end of Section 3.

5. Simulation studies

For a given death-probability function d, we can determine numerically the value function and the optimal strategy using Theorem 4.1. Then, the process is a simple Galton–Watson branching process with state-dependent offspring distribution, which can be simulated easily. In each example below the empirical mean of RBs and EBs are calculated from 1000 simulations.

First we consider a simple threshold death-probability function, that is for some $C > 0$

$$d_1(x,y) = d_1(x+y) = \begin{cases} 1, & \text{if } x+y \geq C, \\ 0, & \text{otherwise.} \end{cases} \tag{5.1}$$

This is a simple, but biologically very unnatural death-probability function. In this case, typically some bacteria convert to EBs at an early stage, while others still divide. As long as the total number of bacteria is below C, the population is safe, in the sense that the host cell cannot die. Consequently, the population does not rush to expand, rather tries to find a state, from which the optimal value $C-1$ can be obtained deterministically. Indeed, the population exhibits a slow growth, taking numerous generations to eventually reach the optimal value $C-1$. This unnatural behavior is apparent in Figure 2, where we plotted six trajectories of the process, with $C = 300$.

For simulations we choose $C = 300$. The value function is almost constant 299 with $h(1,0) = 298.7$. In Figure 1 we see that the number of RBs is typically small, while the number of EBs starts to increase at an early stage. On Figure 9 (top left) we see the numerical p values. The structure of the death-probability function causes the discontinuity of the p function. Note *e.g.* that $p(x,y) \equiv 1$ on the line $\{(x,y) : 2x+y = 299\}$, since after one duplication the population reaches the maximum possible value 299.

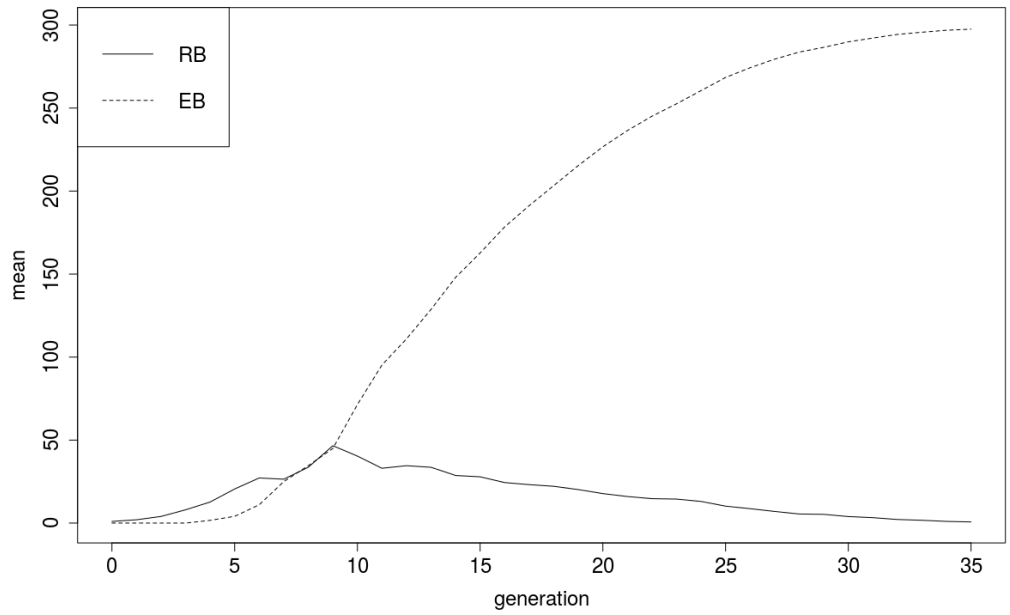

FIGURE 1. The mean number of EBs and RBs for the death-probability (5.1) with $C = 300$.

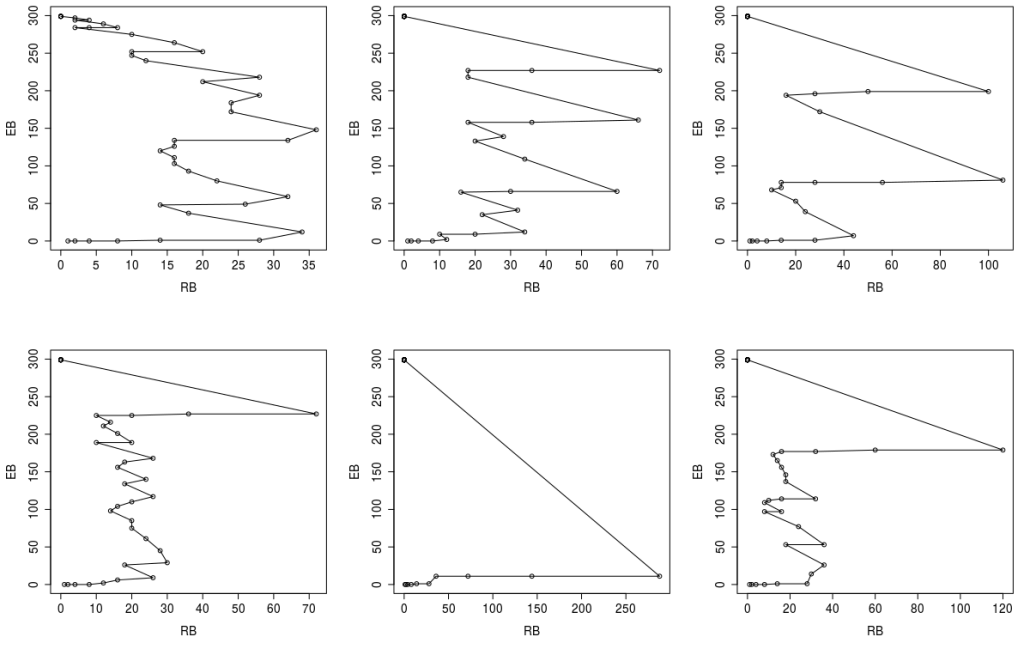

FIGURE 2. Simulations of the process with death-probability (5.1) and $C = 300$.

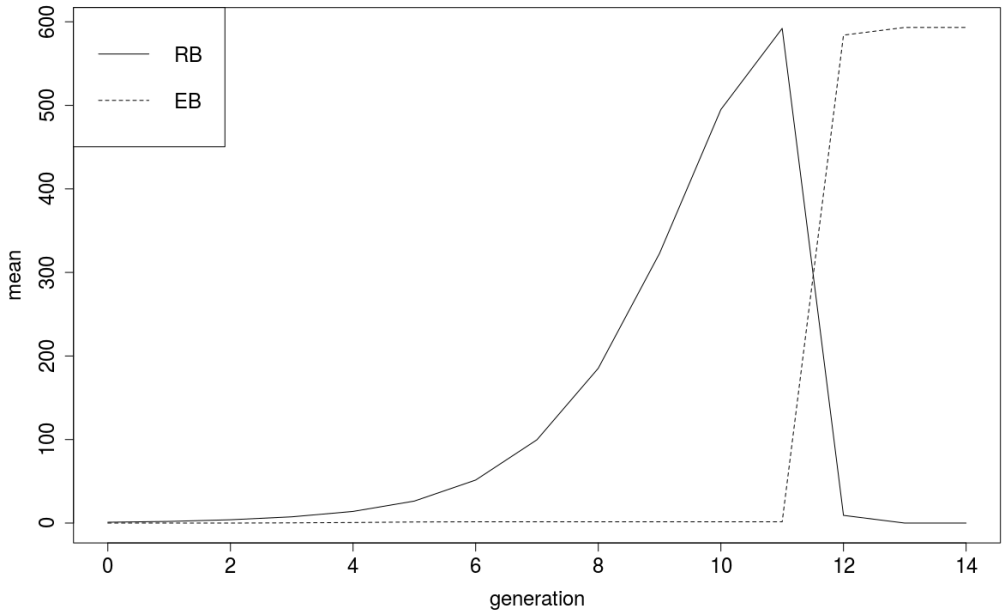

FIGURE 3. The mean number of EBs and RBs for the death-probability (5.2), with $(\alpha, \beta) = (1, 3)$.

Consider a smoother death-probability function

$$d_2(x, y) = \begin{cases} 1 - -\mathrm{e}^{-c_0(\alpha x + \beta y)}, & x + y \leq C - 1, \\ 1, & x + y \geq C. \end{cases} \tag{5.2}$$

When the total number of bacteria is small, it is unlikely that the host cell dies. The parameters α, β allow us to tune the relative effect of EBs and RBs on the host cell's death. On the one hand RBs are much larger than EBs suggesting $\alpha > \beta$, on the other hand EBs secrete chemicals enhancing cell death. Note that biological experiments suggests that *chlamydia* controls host cell survival, see [11], p. 392. We explored three scenarios, with $c_0 = 0.0003$ in each case, and $(\alpha, \beta) = (1, 3)$, $(2, 2)$, and $(3, 1)$, with $C = 2500$, 1500, 3000, respectively. We chose C large enough, so that the optimal strategy does not depend on its specific value, but not too large, to be able compute numerically. That is, C is so large that the process cannot reach a state (x, y), with $x + y \geq C$. For $(\alpha, \beta) = (1, 3)$ we chose $C = 2500$. We have $p(1150, 0) = 1$, so the process jumps from $(1150, 0)$ to $(2300, 0)$, and then to $(0, 2300)$. In this case the p values are either very close to 0, or very close to 1, and there is a sudden change along a line, see Figure 9. Therefore, the process cannot reach (x, y) with $x + y \geq 2500$. For $(\alpha, \beta) = (2, 2)$ the structure of p values are rather different, and for $x \geq 500$ the probability of duplication is small. On the other hand $p(1, 1150) = 1$. In this case a smaller threshold is enough, and we chose $C = 1500$. Finally, for $(\alpha, \beta) = (3, 1)$ the duplication probabilities are large only for $x \leq 200$, while $p(1, 2300) = 1$. In this case we chose $C = 3000$. For the empirical mean of 1000 simulations and some typical trajectories see Figures 3–8.

The population dynamics of RB and EB cells depend strongly on the value (α, β). For $(\alpha, \beta) = (1, 3)$ the relative effect of EBs on cell-death is much larger. Therefore, the process prefer to have only RBs up to some point (generation 11), and then all RBs convert to EBs immediately, resulting a 'bang-bang' strategy. The exponential increase of RBs and the sudden change is clearly visible both on the means (Fig. 3), and on the trajectories (Fig. 4). Here $h(1, 0) = 605$. The optimal p values on Figure 9 (top right) show the same pattern: in each state either all cells duplicate ($p = 1$), or all cells convert ($p = 0$).

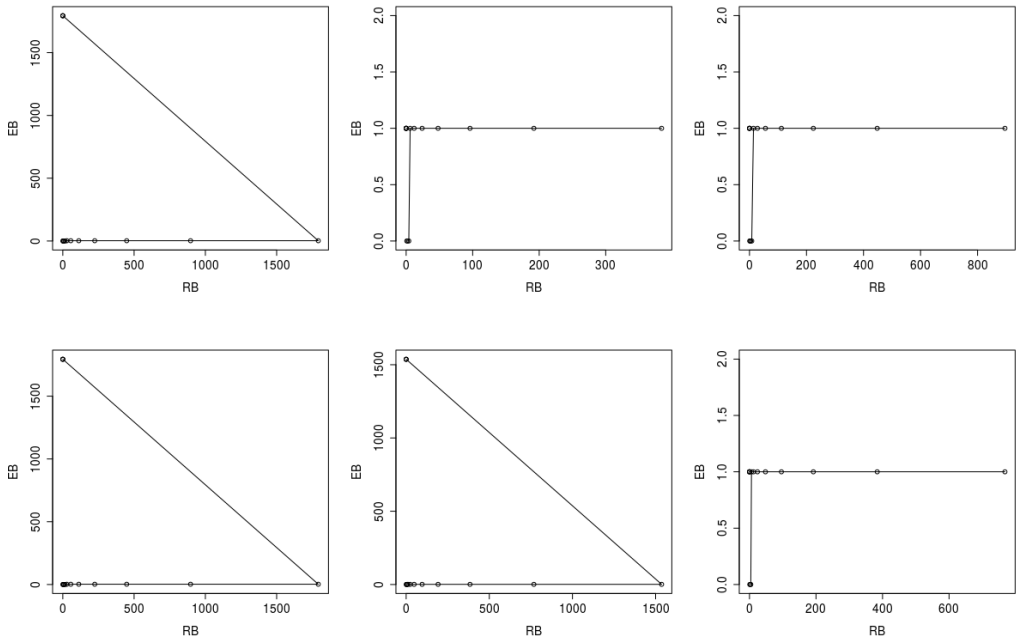

FIGURE 4. Simulations of the process with death-probability (5.2), with $(\alpha, \beta) = (1, 3)$.

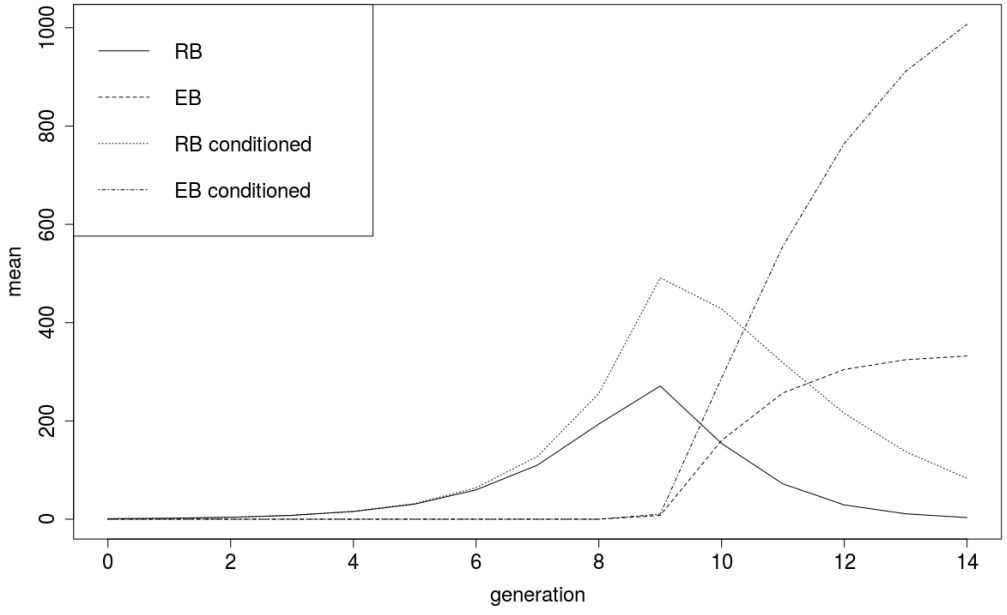

FIGURE 5. The mean and conditional mean of EBs and RBs for the death-probability (5.2), with $(\alpha, \beta) = (2, 2)$.

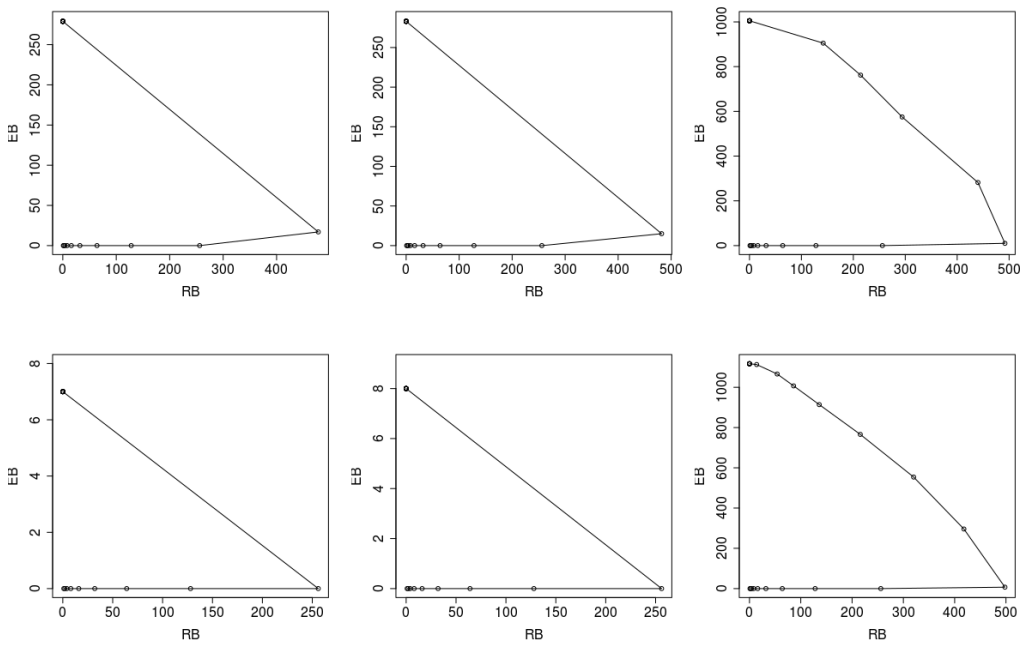

FIGURE 6. Simulations of the process with death-probability (5.2), with $(\alpha, \beta) = (2, 2)$.

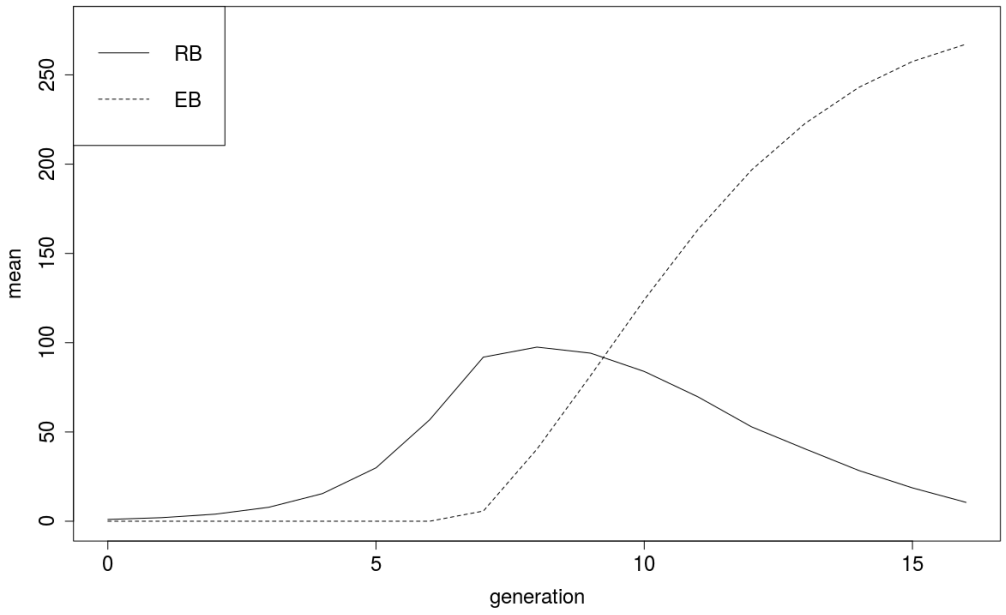

FIGURE 7. The mean number of EBs and RBs for the death-probability (5.2), with $(\alpha, \beta) = (3, 1)$.

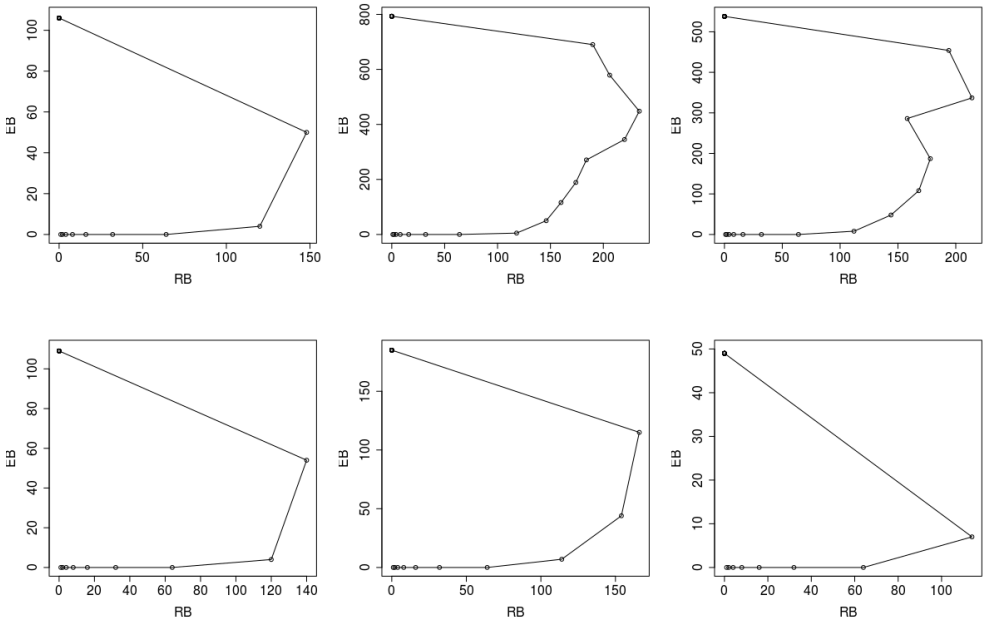

FIGURE 8. Simulations of the process with death-probability (5.2), with $(\alpha, \beta) = (3, 1)$.

TABLE 1. Conditional means for different values of (α, β) in our simulations, and real data from Lee *et al.* [4] (last two rows).

(α, β)	gen	0	3	5	7	10	11	12	13
	hpi	12	16	20	24	28	32	36	40
$(1.8, 2.2)$	RB	1	8	32	128	634	286	286	87
	EB	0	0	0	0	194	687	687	940
$(1.9, 2.1)$	RB	1	8	32	128	500	314	177	104
	EB	0	0	0	0	262	603	825	945
$(2, 2)$	RB	1	8	32	128	429	309	211	136
	EB	0	0	0	0	287	563	768	910
$(2.1, 1.9)$	RB	1	8	32	128	390	323	244	177
	EB	0	0	0	0	268	497	697	858
$(2.2, 1.8)$	RB	1	8	32	128	356	314	256	195
	EB	0	0	0	0	261	460	648	804
measured	RB	1.3	7.6	34	105	385	507	271	171
	EB	0	0	0	3.7	192	656	706	751

For $(\alpha, \beta) = (2, 2)$ the relative effect of RBs and EBs is the same. The RBs duplicate and increase exponentially up to generation 9, then they start to convert to EBs. In Figures 5 and 6, we see that in generations 9–12 the EBs and RBs simultaneously appear, showing the asynchronous conversion obtained in real experiments in [4]. Here $h(1, 0) = 324$.

In Figure 5, we also plotted the empirical means of the EBs and RBs conditioned on the host cell being alive. In the real experiment in Lee *et al.* [4], only those inclusions are counted where the host cell is alive. This clearly causes a bias. We can transform the generation time to real time, hours-post-infection (hpi). After the

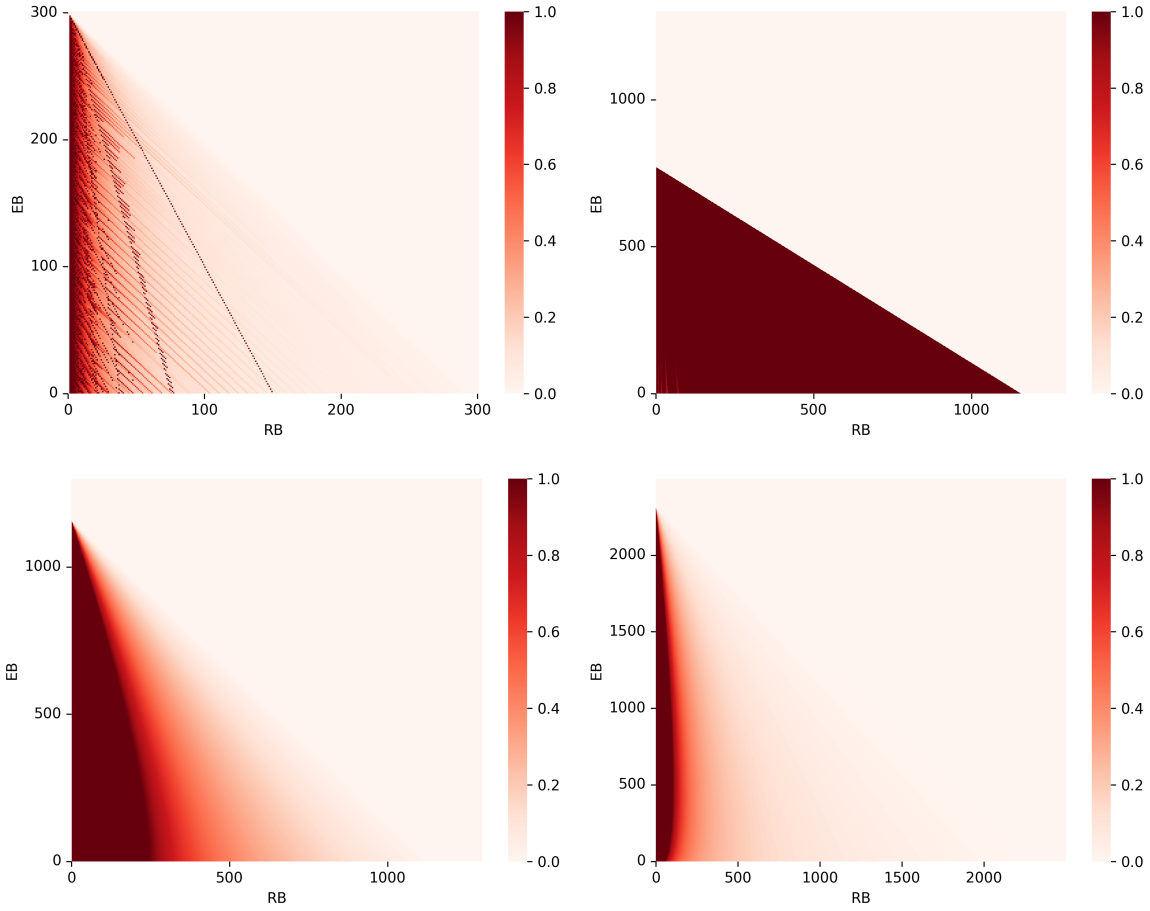

FIGURE 9. The numerical p values corresponding to the death-probability function (5.1) with $C = 300$ (top left), and to (5.2) with $(\alpha, \beta) = (1, 3)$ (top right), $(\alpha, \beta) = (2, 2)$ (bottom left), $(\alpha, \beta) = (3, 1)$ (bottom right).

EB enters the host cell, it takes approximately 12 hours to convert to RB and initiate duplication. Between 12 and 24 hpi, the doubling time is about 1.8 hours. RB-EB conversion starts around 28 hpi, see [4], p. 2. In Table 1 we copied the measurements from [4] together with the simulation results corresponding to different values of (α, β) around $(2, 2)$, to see that our model captures remarkably well the experimental data.

For the optimal p values in Figure 9 (bottom left), we do see values other than 0 and 1. There are no big jumps in the p values, which makes it biologically relevant.

Finally, for $(\alpha, \beta) = (3, 1)$ the relative effect of RBs is much larger, which implies a shorter period of exponential increase in the RB population, and a longer coexistence of RB and EB population, see Figures 7 and 8. These results suggest that the effect of RBs on host cell's death is larger, or at least as large as the effect of EBs. Here $h(1, 0) = 285.7$. The p values in Figure 9 are even smoother than in the previous case, and the population prefers to have not too many RBs.

We note that calculating the optimal probabilities is slow. From (4.5) we see that the runtime is $O(C^3)$. For the death-probability function d_2 in (5.2) with $C = 3000$ it takes about 12 hours on a 5-year-old normal PC. Once we have the optimal probabilities simulations are fast. We calculated the optimal probabilities with the given $c_0 = 0.0003$, in the neighborhood of $(\alpha, \beta) = (2, 2)$. Simulations show that the optimal fit to the measurements is obtained around $(2, 2), (2.1, 1.9)$, see Table 1.

6. Concluding remarks

To model the evolution of *Chlamydia* populations we propose a novel Galton–Watson branching model. In this model, the state-dependent offspring distribution is determined by solving a stochastic optimization problem. The only input of the process is a death-probability function d, describing the probability that the host cell dies in a given state.

Choosing a natural death-probability function, our simulation study shows that the process captures the asynchronous conversion property of the population, which was recently found experimentally in [4]. Moreover, our simulated data fits extremely well to the real measurements in [4], see Table 1. To the best of our knowledge, this is the first mathematical model which reproduces this phenomena.

The exact cause of the host cell's death remains unclear. Experiments suggests that *chlamydia* controls host cell survival, as an early death would be disadvantageous to the bacterial population, see [11], p. 394. However, the quantity of bacteria within the host cell definitely plays a significant role. It is not clear which form of the bacteria is more harmful to the host cell, given that RBs are larger in size, while EBs secrete chemicals. Varying the relative effect of RBs and EBs on the death time of the host cell, our simulation studies suggest that RBs and EBs have the same influence on the host cell's death.

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