Multi-Scale Modelling of Bacterial Infections

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When developing mathematical models that describe bacterial infections in a host, being able to incorporate the mechanisms by which bacteria replicate within the body would allow these models to be more realistic. However, if bacterial replication occurs intra-cellularly, it is not then feasible to model single-cell dynamics for each individual in the population; the model would simply become too complicated. Creating simpler models that avoid this problem by bridging multiple scales is a known challenge within mathematical biology. A potential approach is to construct individual models for the intracellular, within-host and population-level infection dynamics, to define key quantities characterising infection at each level, and then to use these quantities to link dynamics across scales.

Here we outline the main mathematical concepts involved in the development of a multi-scale model of bacterial infections, and show the applicability of this approach by focusing on the mathematical and computational description of *Francisella tularensis* infection. *Francisella tularensis* is a gram-negative, facultative bacteria and the causative agent of tularemia. Due to its high infectivity it is considered a potential bioterrorism agent. Recent efforts by Carruthers et al. [1] and Gillard et al. [2] have focused on the development of a mathematical model of *Francisella tularensis* infection dynamics across scales.

Intra-cellular model

When bacteria infect and replicate within individual cells, they deprive the cell of resources necessary for its survival. The outcome for the cell is often fatal, and thus, for the bacteria to survive, they must find a way to exit the cell. In one case, bacteria are released continuously while the cell remains alive; however, the more interesting case involves the instantaneous release of bacteria in a single 'burst' that coincides with the cell's death.

To model bacterial replication and cell bursting mathematically, we can make use of a continuous time Markov process, a specific type of stochastic process in which the next state of the system depends only on its current state and not on any past behaviour. Let the state of our Markov process represent the number of bacteria in a single infected cell, and let us introduce an additional state, B, which represents the bursting of the cell. In this way the state from which B is entered is the number of bacteria that are released when the cell bursts. As this could be any number of bacteria, the process can transition to state B from any other state (see Figure 1).

More formally, let $\mathcal{X} = \{X(t) : t \geq 0\}$ be our continuous time Markov process. Then $\mathcal{X}$ is a random process whose path through the states is not fixed but is instead determined by a set of probabilities. If $X(t)$ is the state of the process at time t, then after a short interval of length, Δt, we say that the state of the process is:

- $X(t)+1$, with probability $\lambda X(t)\Delta t$,
- B, with probability $\delta X(t)\Delta t$,
- $X(t)$, with probability $1-(\lambda+\delta)X(t)\Delta t$.

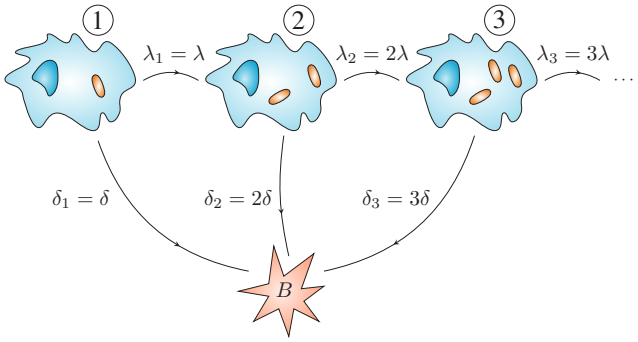

Figure 1: The continuous time Markov process, $\mathcal{X}$, used to model the bacterial load of a single infected cell (blue). Birth and rupture rates are linearly proportional to the number of intra-cellular bacteria, depicted here in orange.

We note that the transition $X(t) \to X(t+\Delta t) = X(t)+1$ represents the replication of bacteria within the infected cell, $X(t) \to X(t+\Delta t) = B$ represents the rupture of the infected cell, releasing $X(t)$ bacteria to the extra-cellular environment within the host, and $X(t) \to X(t+\Delta t) = X(t)$ represents nothing happening at all during the time interval $[t, t+\Delta t)$.

In each of these cases, the transition probability is proportional to $X(t)$. From a biological perspective, this reflects our belief that cells containing a greater number of bacteria are more likely to burst or to further replicate bacteria. To be able to link this model of a single cell with a cell-population model, we need to define the bacteria burst distribution. This probability distribution tells us how likely it is that a cell releases R bacteria when it bursts.

For simplicity, let us assume that the cell is always initially infected by a single bacterium; that is, $X(0) = 1$. Then, let us first consider the probability that the cell releases just a single bacterium when it bursts. In our model, this is possible only if the first transition $\mathcal{X}$ makes is from state 1 to state B. If $\mathcal{X}$ moves to state 2, there is no way for the process to return to state 1, and at least two bacteria will be released. Therefore, the probability that the cell releases just a single bacterium when it bursts is given by

$$\mathbb{P}(R=1) = \frac{\delta_1}{\lambda_1+\delta_1} = \frac{\delta}{\lambda+\delta}.$$

For a cell to release exactly two bacteria when it bursts, $\mathcal{X}$ must first transition from state 1 to state 2, and then from state 2 to state B. The probability of this is

$$\mathbb{P}(R=2) = \frac{\lambda_1}{\lambda_1+\delta_1}\frac{\delta_2}{\lambda_2+\delta_2} = \frac{\lambda}{\lambda+\delta}\frac{\delta}{\lambda+\delta}.$$

In general, there is only one possible combination of transitions that allows $\mathcal{X}$ to enter state B from state $k \in \mathbb{N}$. This first requires a total of $k-1$ transitions from state 1 to state k, each with probability $\lambda/(\lambda+\delta)$, followed by a single transition from state k to state B, with probability $\delta/(\lambda+\delta)$. The distribution of R is then given fully by

$$\mathbb{P}(R=k) = \left(\frac{\lambda}{\lambda+\delta}\right)^{k-1}\frac{\delta}{\lambda+\delta}.$$

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If we think of a replication event as flipping a coin and getting tails, and a burst event as flipping a coin and getting heads, then finding the number of bacteria released when a cell bursts is analogous to asking how many times I have to flip a coin until I get heads. This idea of looking at the number of failures before the first success is often how the geometric distribution is defined. Thus, the burst distribution can be defined more succinctly as: $R \sim \text{Geometric}\,(\delta/(\lambda+\delta))$.

Within-host model

A within-host model aims to make use of our knowledge of infection at a single-cell level to study populations of infected cells and bacteria within an individual. With the previously obtained burst size distribution, we are able to do this in a more realistic manner by allowing for variability between infected cells in terms of how many bacteria are released when they burst. In the results that follow, a more detailed intra-cellular model has been used than that presented in the previous section, although the idea of using the burst size distribution still remains the same.

Within an individual, we assume that three events dictate infection dynamics (see Figure 2):

(i) extra-cellular bacteria can infect uninfected cells with rate α,

(ii) extra-cellular bacteria can be killed by host immune defences with rate μ, and

(iii) infected cells can burst with rate δ. The number of bacteria released is determined by the previously defined burst size distribution, $\mathbb{P}(R=k)$.

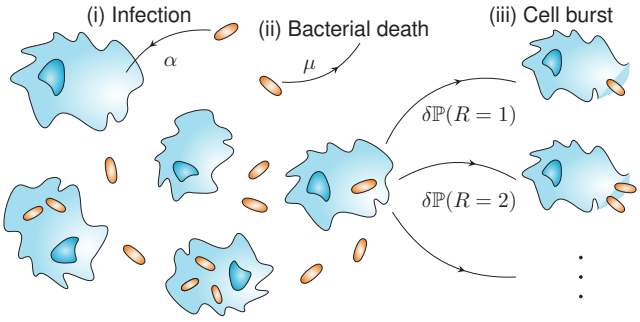

Figure 2: The key events described by the within-host model. Macrophages (blue) can engulf bacteria (orange), and thus, become infected. Intra-cellular replication leads to cell rupture, so that bacteria are released to the extra-cellular environment.

If an individual becomes infected with bacteria, it is possible that their immune system will be capable of clearing the infection. However, in some cases the infection cannot be contained and treatment will be required.

Given a known initial dose of bacteria, the within-host model can be used to predict the likelihood that symptom onset occurs before recovery, and more importantly, how long this will take. To do so, we assume that symptoms will develop once a threshold of bacteria has been reached. We refer to this as a response.

Figure 3 shows the probability and average time of response for inhalational infection with the bacterium *Francisella tularensis*. Particularly important here is how successfully the model predictions agree with the results of existing human trials. The probability of a response is obtained by simulating 10^4 realisations of the stochastic model and considering the fraction of times a simulation ended with a response.

For those realisations that end in a response, the corresponding time taken is then used in the calculation of the average response time. For each realisation, the threshold necessary for a response is sampled from a log-normal distribution, $\log N(26.2, 6.04)$ [1]. Varying this threshold accounts for the expected heterogeneity within a population, with those individuals more susceptible to infection having a lower threshold, whilst more resistant individuals have a higher threshold.

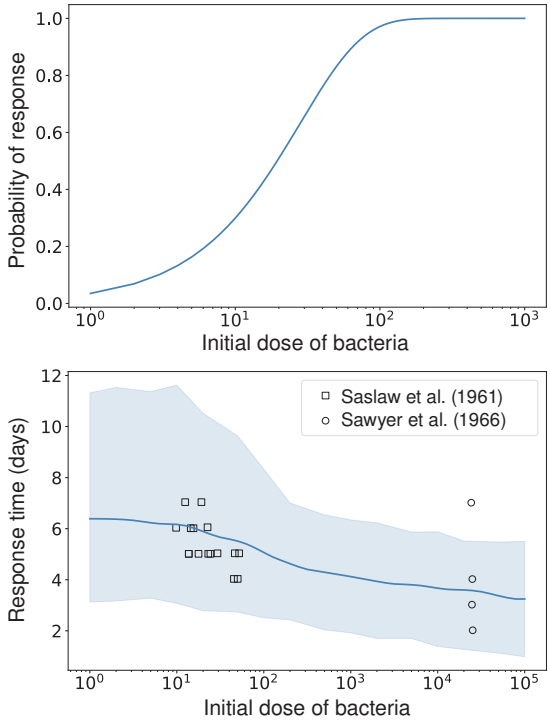

Figure 3: For different initial doses, the probability of symptom onset (top) and time until symptom onset (bottom – see [1]). Curves represent model predictions, while dots represent experimental data (see [3, 4]). For response times, the solid curve is the mean and shaded regions are 95% quantiles.

Population-level model

To link the within-host model to the population-level dynamics, let us consider a group of individuals who are exposed to a release of bacteria. If we know the initial dose of bacteria that each individual receives, we can enter this into the within-host model to obtain a probability that they develop symptoms. From here, a distribution of the number of individuals who respond can be constructed. Although this idea can be applied to any scenario, we demonstrate it here in the case of an accidental release of bacteria in a microbiology laboratory.

Let us suppose that our laboratory consists of three rooms, where the air in each room is assumed to be well mixed. If air is extracted from each room at an equal rate, then the rate of air flow between rooms is also equal. A depiction of a laboratory with this setup is provided in Figure 4. Here, the individuals in each room are represented by circles, whilst the coloured squares indicate three different scenarios for the accidental release of bacteria. For example, the red square indicates that the source of bacteria occurs within Room 1. Following the release of bacteria in one of the rooms, let $C_i(t)$ denote the concentration of bacteria in room i, and $p_j(t)$ be the cumulative amount of bacteria an individual

in room j has inhaled. Given the laboratory description provided in Figure 4, the change in these variables through time may be described using this system of ODEs:

$$V_1\frac{\mathrm{d}}{\mathrm{d}t}C_1 = -(Q_1+\beta_{12}+n_1\rho)C_1+\beta_{21}C_2,$$
$$V_2\frac{\mathrm{d}}{\mathrm{d}t}C_2 = -(Q_2+\beta_{21}+\beta_{23})C_2+\beta_{12}C_1+\beta_{32}C_3,$$
$$V_3\frac{\mathrm{d}}{\mathrm{d}t}C_3 = -(Q_3+\beta_{32}+n_3\rho)C_3+\beta_{23}C_2,$$
$$\frac{\mathrm{d}}{\mathrm{d}t}p_1 = \rho C_1,$$
$$\frac{\mathrm{d}}{\mathrm{d}t}p_3 = \rho C_3,$$

where $\beta_{i,j}$ is the rate of air flow from room i to room j, Q_i is the rate of air extraction from room i, n_i is the number of individuals in room i, V_i is the volume of room i and ρ is the pulmonary rate or the rate at which individuals inhale air.

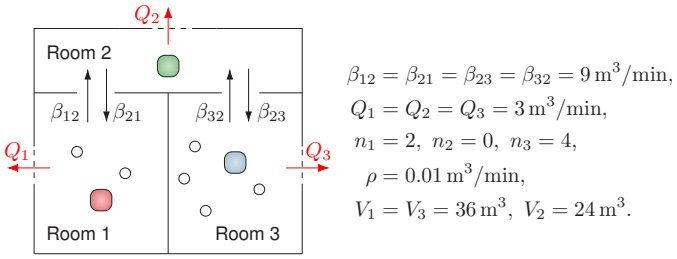

Figure 4: In this laboratory coloured squares represent different source rooms for the initial release of bacteria.

When setting up equations for our population model as the ones above, one should make sure that the dimensions are consistent. For example, since V_i is a volume (of the corresponding room) and C_i represents the concentration of bacteria in the air in this room, the left-hand side of the first equation above has units

$$\left[\mathrm{m}^3\cdot\frac{\mathrm{bact}}{\mathrm{m}^3\cdot\mathrm{hour}}\right]=\left[\frac{\mathrm{bact}}{\mathrm{hour}}\right],$$

representing the change in the (absolute) number of bacteria in the room over time. The right-hand side of this equation has units

$$\left[\left(\frac{\mathrm{m}^3}{\mathrm{hour}}+\frac{\mathrm{m}^3}{\mathrm{hour}}+\frac{\mathrm{m}^3}{\mathrm{hour}}\right)\frac{\mathrm{bact}}{\mathrm{m}^3}+\frac{\mathrm{m}^3}{\mathrm{hour}}\frac{\mathrm{bact}}{\mathrm{m}^3}\right]=\left[\frac{\mathrm{bact}}{\mathrm{hour}}\right],$$

so that our equations are dimensionally consistent.

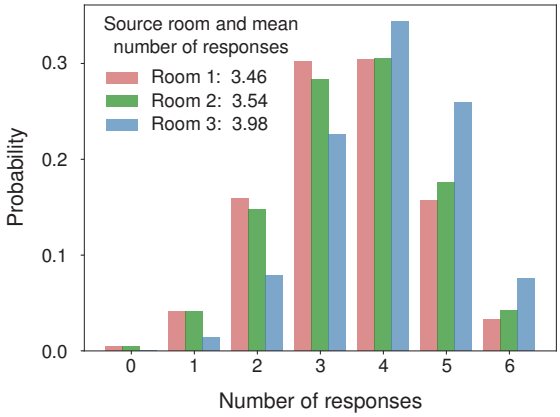

Figure 5: Distributions of the number of individuals who will develop symptoms. The colour of the histogram corresponds to the different source rooms, as indicated in Figure 4.

Once the equations above have been proposed, steady-state values of p_1 and p_3 can then act as initial doses for the within-host model. Figure 5 shows the distribution of the number of individuals who respond for three different scenarios, where the colour of the histogram corresponds to the coloured squares used to denote the location of the initial release of bacteria. As Room 3 is the most populated room, the number of individuals developing symptoms is greatest when the release of bacteria occurs here. The minimum number of responses occurs when the release is in Room 1; even though this is not the least populated room, bacteria in the air must travel further to reach Room 3, and thus, there is a greater chance that the bacteria will first be extracted.

Conclusion

In this article we have introduced a multi-scale mathematical framework for modelling bacterial infections, with specific reference to *Francisella tularensis* infection. The benefit of multi-scale modelling is highlighted through the use of individual models, each representing the dynamics at a different scale, that are linked by key quantities. Given here by the rupture distribution and probability of response, these key quantities allow us to characterise infection at lower levels to simplify the model in subsequent levels. Combining this amount of detail into a single mathematical model would result in one that is both difficult to analyse and time-consuming to simulate; therefore, multi-scale approaches like this must be adopted if we want to incorporate greater detail into our models.

Whilst the example of a microbiology laboratory is used to study population-level dynamics, this framework is also applicable to any situation where the initial dose of bacteria can be estimated, for example, in outdoor dispersion models that consider how meteorological and geographical factors affect the dissemination of bacteria across much larger areas.

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