ModelMEMS tutorial: Modelling phage-bacteria interactions

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This tutorial allows you to explore the dynamics of the phage - bacteria - arbitrium model of the paper "Repeated outbreaks drive the evolution of bacteriophage communication". It consists of three parts: (i) dynamics of a single phage and bacterial population; (ii) dynamics of competing and mutating strains of bet-hedging phages (no arbitrium communication); and (iii) dynamics of competing and mutating strains of communicating phages. Each subsection contains a short introduction to the specific model and how to run it, followed by recommendations of what to explore and play around with.

Scripts for this tutorial are made available through `https://octave-online.net` (direct links to the different models below). The full Matlab code used for the manuscript is available from GitHub: `https://github.com/hiljedoekes/PhageCom`.

Model parameters

Parameter	*Description (dimension)*	*Default*
r	Net replication rate of bacteria (hour^{-1})	1.0
K	Carrying capacity of bacteria (cells mL^{-1})	10^9
a	Adsorption rate of phages to bacteria (hour^{-1} (cells per mL)$^{-1}$)	10^{-8}
b	Proportion of adsorptions of a phage to a susceptible cell that leads to infection (cells phage^{-1})	0.01
B	Burst size (phages)	200
α	Rate of spontaneous lysogen induction (hour^{-1})	10^{-3}
δ	Spontaneous decay rate of free phages (hour^{-1})	0.01
u	Scaled uptake rate of arbitrium by cells (arbitrium mL^{-1} (cells per mL)$^{-1}$)	0.1

1. Single Phage Strain

Scripts: `https://https://octav.onl/202108ModelMEMS-SingleStrain`

Model equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \underbrace{rS(1-N/K)}_{\text{logistic growth}} - \underbrace{baSP}_{\text{infection}}, \tag{1}$$

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \underbrace{rL(1-N/K)}_{\text{logistic growth}} + \underbrace{\varphi(A)baSP}_{\text{lysogenic infection}} - \underbrace{\alpha L}_{\text{induction}}, \tag{2}$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \underbrace{B\alpha L}_{\text{burst from induction}} + \underbrace{B(1-\varphi(A))baSP}_{\text{burst from lytic infection}} - \underbrace{\delta P}_{\text{phage decay}} - \underbrace{aNP}_{\text{adsorption}}, \tag{3}$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \underbrace{baSP}_{\text{production upon infection}} - \underbrace{uNA}_{\text{adsorption and degradation}}, \tag{4}$$

$$N = S + L \tag{5}$$

$$\varphi(A) = \begin{cases} 0 & \text{if } A \leq \theta, \\ \phi_{\max} & \text{if } A > \theta \end{cases}. \tag{6}$$

These equations describe the dynamics of a single phage strain (P), infecting susceptible bacteria (S). Depending on the arbitrium concentration (A), lysogens (L) may be produced. Lysogens grow with the same reproduction rate as susceptible bacteria, but are immune to superinfection by new phage particles. Lysogens are only produced if the arbitrium concentration is larger than the phage's response threshold θ. Each infection then leads to production of a lysogen with probability $\phi_{\max}$, and to cell lysis with probability $(1-\phi_{\max})$. The arbitrium concentration in the model is scaled such that $0 \leq \theta \leq 1$. To simulate the dynamics of a bet-hedging phage (*i.e.*, a phage with a constant φ-value), set $\theta = 0$.

Serial passages are simulated by taking a sample from the phage population and introducing that to a "fresh" population of bacteria, diluting it by a fixed dilution factor. The time between serial passages is given by `Ttransfer`.

The model consists of three scripts:

ShortTerm_dyn.m Run this script to simulate the dynamics for a couple of passaging cycles. Parameters and model settings can be changed at the top of the script.

solve_ode.m Called by `ShortTerm_dyn.m`. Here the differential equations are defined.

phi.m Called by `solve_ode.m`. Here the arbitrium response function $\varphi(A)$ is defined.

To run the model, go to the Octave-online folder, open `ShortTerm_dyn.m` and press "Run". When changing parameters, make sure to first save the changes before running again.

Suggestions:

Study the dynamics without serial passaging (set `Ttransfer` > `Tmax`). For default parameters, the system has only one stable equilibrium at which $S = 0$ (*i.e.*, all susceptible cells are depleted).

- First consider bet-hedging phages (with $\theta = 0$). How quickly does the system converge to the equilibrium for different values of ϕ? Can you understand these results?
- Then consider a communicating phage strain (*e.g.*, $\theta = 0.6$, $\phi_{\max} = 1$). Try to understand the dynamics of S, A, L, and P.

2. Bet-hedging phages

Scripts: `https://https://octav.onl/202108ModelMEMS-NoComm`

Model equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \underbrace{rS(1-N/K)}_{\text{logistic growth}} - \underbrace{baS\sum_i P_i}_{\text{infection}}, \tag{7}$$

$$\frac{\mathrm{d}L_i}{\mathrm{d}t} = \underbrace{rL_i(1-N/K)}_{\text{logistic growth}} + \underbrace{\phi_i baSP_i}_{\text{lysogenic infection}} - \underbrace{\alpha L_i}_{\text{induction}}, \tag{8}$$

$$\frac{\mathrm{d}P_i}{\mathrm{d}t} = \underbrace{B\alpha L_i}_{\text{burst from induction}} + \underbrace{B(1-\phi_i)baSP_i}_{\text{burst from lytic infection}} - \underbrace{\delta P_i}_{\text{phage decay}} - \underbrace{aNP_i}_{\text{adsorption}}, \tag{9}$$

$$N = S + \sum_i L_i. \tag{10}$$

This model includes multiple phage variants, that differ in their fixed propensity for lysogeny ϕ_i. For legibility, mutations are not included in these equations, but they are included in the model: whenever a new phage particle is produced, it may mutate to a different variant than its parent with a small probability μ.

The model scripts are structured the same as before. There are two scripts you can run:

ShortTerm_dyn.m Simulates the dynamics over a few serial passages. Plots the dynamics within a passaging cycle.

LongTerm_dyn.m Simulates many serial passages. Plots the frequency of different variants at the end of each cycle.

The second script takes a while to run. You might need to refresh your waiting time in octave online to get its results (click "Add 15 seconds" when your simulation time is running out).

Suggestions:

- Study which variant becomes dominant (*i.e.*, which ϕ-value is selected) for varying times between serial passages. Start with very frequent passages (`Ttransfer`= 1 hour) and work your way up to longer and longer waiting times.
- In the paper, we derive an analytical estimate for the evolutionarily stable strategy ϕ^* if the time between passages is sufficiently long (*e.g.*, 12 hours):

$$\phi^* = \frac{1-(bB)^{-1}}{\log(\frac{BK}{P_0}}.$$

  Vary parameters to investigate the validity of this approximation. For instance, phages are known to have widely varying burst sizes. What happens if you change B?

3. Communicating phages

Scripts: `https://https://octav.onl/202108ModelMEMS-Comm`

Model equations:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \underbrace{rS(1-N/K)}_{\text{logistic growth}} - \underbrace{baS\sum_i P_i}_{\text{infection}}, \tag{11}$$

$$\frac{\mathrm{d}L_i}{\mathrm{d}t} = \underbrace{rL_i(1-N/K)}_{\text{logistic growth}} + \underbrace{\varphi_i(A)baSP_i}_{\text{lysogenic infection}} - \underbrace{\alpha L_i}_{\text{induction}}, \tag{12}$$

$$\frac{\mathrm{d}P_i}{\mathrm{d}t} = \underbrace{B\alpha L_i}_{\text{burst from induction}} + \underbrace{B(1-\varphi_i(A))baSP_i}_{\text{burst from lytic infection}} - \underbrace{\delta P_i}_{\text{phage decay}} - \underbrace{aNP_i}_{\text{adsorption}}, \tag{13}$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \underbrace{baS\sum_i P_i}_{\text{production upon infection}} - \underbrace{uNA}_{\text{adsorption and degradation}}, \tag{14}$$

$$N = S + \sum_i L_i, \tag{15}$$

$$\varphi_i(A) = \begin{cases} 0 & \text{if } A \le \theta_i, \\ \phi_{\max_i} & \text{if } A > \theta_i \end{cases}. \tag{16}$$

This model includes multiple communicating phage variants. Mutations are once again excluded from the equations, but included in the model. Note that all variants produce the same signal (arbitrium) and hence also respond to each other's signals. The model thus describes very closely related phage variants, not different phage species. We can use this model to study which communication strategy is selected under which conditions.

There are three scripts to run:

ShortTerm_dyn.m Simulates the dynamics over a few serial passages. Plots the dynamics within a passaging cycle.

LongTerm_dyn.m Simulates many serial passages. Plots the frequency of different variants at the end of each cycle.

Competition_BetHedging_Communication.m Simulates the competition between two phage variants: an invader phage that enters a resident phage population at low frequency. For default settings, the invader uses communication while the resident has a bet-hedging strategy (fixed ϕ).

NOTE: Phages can now vary in two characteristics: their $\phi_{\max}$-value and their θ-value. The `ShortTerm_dyn` and `LongTerm_dyn` scripts automatically produce variants with all combinations, so do not include too many values of each in your analysis (or you'll end up with hundreds of strains).

Suggestions:

- Consider phages that switch from only causing lytic infections to only causing lysogenic infections (*e.g.*, fix $\phi_{\max} = 1$). Study which response strategy (*i.e.*, which θ-value) is selected for varying times between the serial passages.
- For a fixed value of θ (*e.g.*, $\theta = 0.5$), find the optimal value of $\phi_{\max}$. Does this depend on your θ-value? Try to understand your results.
- In the paper, we derived an analytical estimate for the evolutionarily stable response strategy θ^* (for $\phi_{\max} = 1$ and large `Ttransfer`):

  $$\theta^* = \frac{1}{2 - (bB)^{-1}}.$$

  Vary parameters to study how well this approximation holds.
- (ADVANCED) In the model, the environment is very predictable: each passaging cycle takes a fixed time, after which the phages are transferred to a "fresh" population of susceptible bacteria at always the same density. Of course, in natural systems we would expect such a process to be noisy. Adjust the model to introduce noise. For instance, you could vary the bacterial carrying capacity from cycle to cycle. Or you could introduce variation in the time between transfers. Or ...