

Simulation and Theory of Bacterial Transformation

JD Russo, JJ Dong

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Department of Physics and Astronomy
Bucknell University

Outline

Introduction

Motivation

Biological Background

Simulation

Results

Conclusions

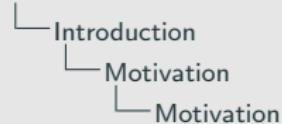
Motivation

- Ubiquitous threat of antibiotic resistance
- Transmission of resistance via plasmids
- Identify what most significantly affects resistant cell dominance.

Question

What conditions lead to emergence of antibiotic resistance?

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Motivation

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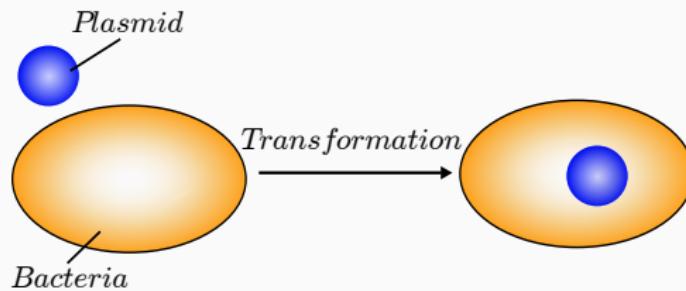
- Threat of resistance even in well-controlled diseases (TB)
- Main mechanisms of transmission are conjugation and transformation

Plasmids

- Small, independently replicating genetic material
- Often include DNA segments encoding antibiotic resistance
- Imposes a fitness cost on host cell

Transformation and Conjugation

- **Transformation:** Cell incorporates plasmid from environment
- **Conjugation:** Plasmid transferred between cells



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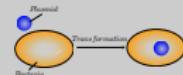
Simulation and Theory of Bacterial Transformation

Introduction

Biological Background

Transformation and Conjugation

- Transformation: Cell incorporates plasmid from environment
- Conjugation: Plasmid transferred between cells



- Transformation is the process where a cell incorporates a plasmid from its environment, translating any encoded genes
- Conjugation is horizontal transfer of a plasmid between two cells
- We assume transformation is the primary mechanism of plasmid transfer because we also assume that when a cell acquires a plasmid, it keeps it.

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Simulation

Population Dynamics Model

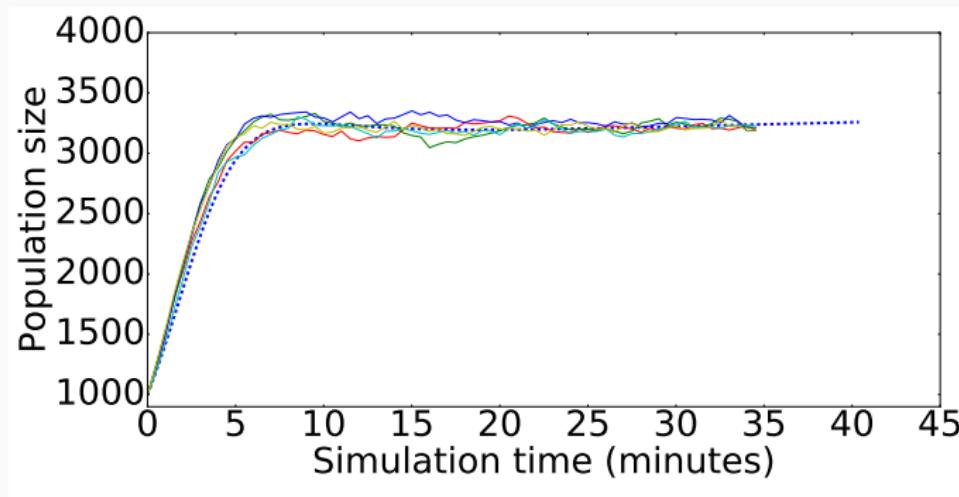
Simulation Methods

Results

Conclusions

Simulation vs Modeling

- Stochastic vs Deterministic
- Information about average behavior vs specific trajectories
- Individual realizations noisily follow model



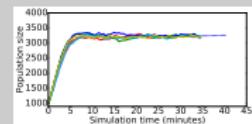
Simulation and Theory of Bacterial Transformation

└ Simulation

└ Simulation vs Modeling

Simulation vs Modeling

- Stochastic vs Deterministic
- Information about average behavior vs specific trajectories
- Individual realizations noisily follow model



- At a very general level... More general discussion of models vs simulations
- Mathematical modeling of populations is deterministic - useful to capture info about average behavios
- Simulations can incorporate stochastic reactions
- If any of you remember, both Jonathan and Josh have mentioned generalizing from discrete to continuum limits. In our case we can get more information about population growth by doing the opposite, moving from a continuous model, the differential equations that describe general behavior of populations, to the discrete simulation, which model behavior of individual populations.
- Individual experiments noisily follow model

Simulation vs Modeling



Simulation vs Modeling



Differential equation $\frac{dR}{dt} = -\delta R$ (2)

$$R(t) = R_0 e^{-\delta t}$$
 (3)

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└ Simulation

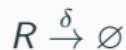
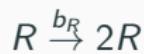
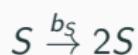
└ Simulation vs Modeling

Reaction	$R \xrightarrow{\delta} \emptyset$	(1)
Differential equation	$\frac{dR}{dt} = -\delta R$	(2)
	$R(t) = R_0 e^{-\delta t}$	(3)

- This reaction describes a basic situation where a resistant cell dies with probability δ .
- You can phrase this mathematically by writing the differential equation
- ... Which you can solve to find the exact solution for the population at any time
- Plotting this equation describes an exponential function that asymptotically approaches zero.
- However, implementing this reaction in simulation, this is not a smooth curve. This is a step-like function, where for instance at some discrete time the population jumps from one to zero and goes extinct.

Population Dynamics Model - Constant

Reactions



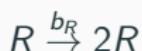
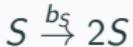
Equations

$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha S$$

$$\frac{dR}{dt} = b_R \left(1 - \frac{S+R}{K}\right) R + \alpha S - \delta R$$

Population Dynamics Model - Linear

Reactions



Equations

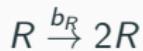
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

$$\frac{dR}{dt} = b_R \left(1 - \frac{S+R}{K}\right) R + \alpha \left(\frac{P_f}{P}\right) S - \delta R$$

$$\frac{dP_f}{dt} = -\alpha \left(\frac{P_f}{P}\right) S$$

Population Dynamics Model - Recycled

Reactions



Equations

$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

$$\frac{dR}{dt} = b_R \left(1 - \frac{S+R}{K}\right) R + \alpha \left(\frac{P_f}{P}\right) S - \delta R$$

$$\frac{dP_f}{dt} = -\alpha \left(\frac{P_f}{P}\right) S + \delta R$$

$$\frac{dP}{dt} = b_R \left(1 - \frac{S+R}{K}\right) R$$

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Simulation

Population Dynamics Model

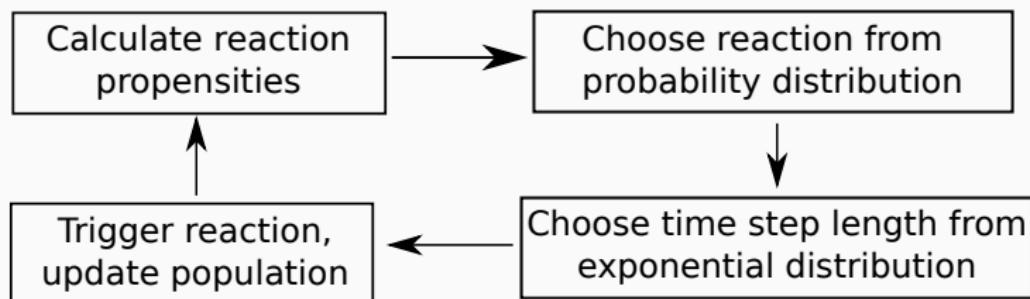
Population Dynamics Model - Constant

Reactions	Equations
$S \xrightarrow{b_1} 2S$	$\frac{dS}{dt} = b_1 \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_r}{P}\right) S$
$S + P_{new} \xrightarrow{\alpha} R$	$\frac{dR}{dt} = b_1 \left(1 - \frac{S+R}{K}\right) R + \alpha \left(\frac{P_r}{P}\right) S - \delta R$
$R \xrightarrow{b_2} 2R$	$\frac{dP_r}{dt} = -\alpha \left(\frac{P_r}{P}\right) S + kR$
$R \xrightarrow{k} \emptyset + P_r$	$\frac{dP}{dt} = b_2 \left(1 - \frac{S+R}{K}\right) R$

- For our research, we simulate three main cases, where the growth rates of the populations vary according to different rules. They all build on each other in complexity.
- The first case is the constant α case, where α is the rate of transformation of resistant into susceptible. So, in this case, resistant cells just transform at a fixed rate.
- Describe reactions
- In the second case, we now add a certain amount of plasmids to the simulation, and only allow a cell to transform by consuming a plasmid. Most importantly, we linearly scale the rate of transformation with the ratio of free plasmids to initial plasmids.
- In the third case, we build on the linear case by adding that whenever a resistant cell dies, so a plasmid carrier, it releases a free plasmid back into the environment.

Kinetic Monte Carlo Method

- Initially used to simulate chemical reactions
- Useful for simulating any reaction that occurs with a rate
- Captures information about dynamics of a growing system
- Self-adjusting timescales



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- The kinetic monte carlo method, or the Gillespie Algorithm, was originally developed to simulate stochastic chemical reactions.
- KMC is agnostic to what you're actually simulating, just cares about rates
-
- Time scale of a KMC step is not fixed and scales with number of reagents being simulated. This is cool because as the system grows, and has more particles, and therefore more frequent interactions, the time step gets shorter. This simulates more reactions in the same amount of time. Conversely, the time step will lengthen as the system shrinks.
- Basic algorithm: Calculate likelihood of reaction happening, given size of system, rates, and number of particles of each type. Use that probability distribution to randomly select one. Choose a random timestep length from an exponential distribution given by the number of particles. Carry out the reaction, updating the simulation with the result of the reaction.

Simulation Details

- Slower plasmid carrier growth rate
- Carrying capacity
- Periodic boundary conditions
- Fixed death rate
- Mapping simulation time to real time

Simulation Detailed (cont'd)

Well-Mixed Case

- System-wide carrying capacity
- Most closely follows the model

Lattice Case

- Clustering
- Discrete sites with per-site carrying capacity

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Simulation

Simulation Methods

Simulation Detailed (cont'd)

Well-Mixed Case

- System-wide carrying capacity
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Lattice Case

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- Discrete sites with per-site carrying capacity

Optimizations

- Occupancy lists
- Sets vs. lists
- imshow vs. plcolor

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Optimizations

- Occupancy lists
- Sets vs. lists
- inshor vs. plcolor

- When implemented for a lattice, the KMC algorithm goes pick a reaction THEN pick a random site. So, we have to know which sites actually have the reagents necessary for that reaction. Instead of searching through the whole lattice, which is very slow, I just track a list of sites occupied by each type of particle. Then I can just randomly pick from the appropriate list.
- Sometimes it's hard to avoid searching through the array. For instance when a transformation reaction happens, I need a site that's occupied by both an S and a P. In order to get a list of those, I have to check which lattice sites exist in both lists. However, that's a very slow operation. The way python implements lists under the hood means that the time it takes to do that increases with the square of the length of the lists, or the square of the lattice dimensions. I use something called sets instead of lists, which are implemented in such a way that the time it takes to do that same operation just goes linearly with the length of the lists. (20x

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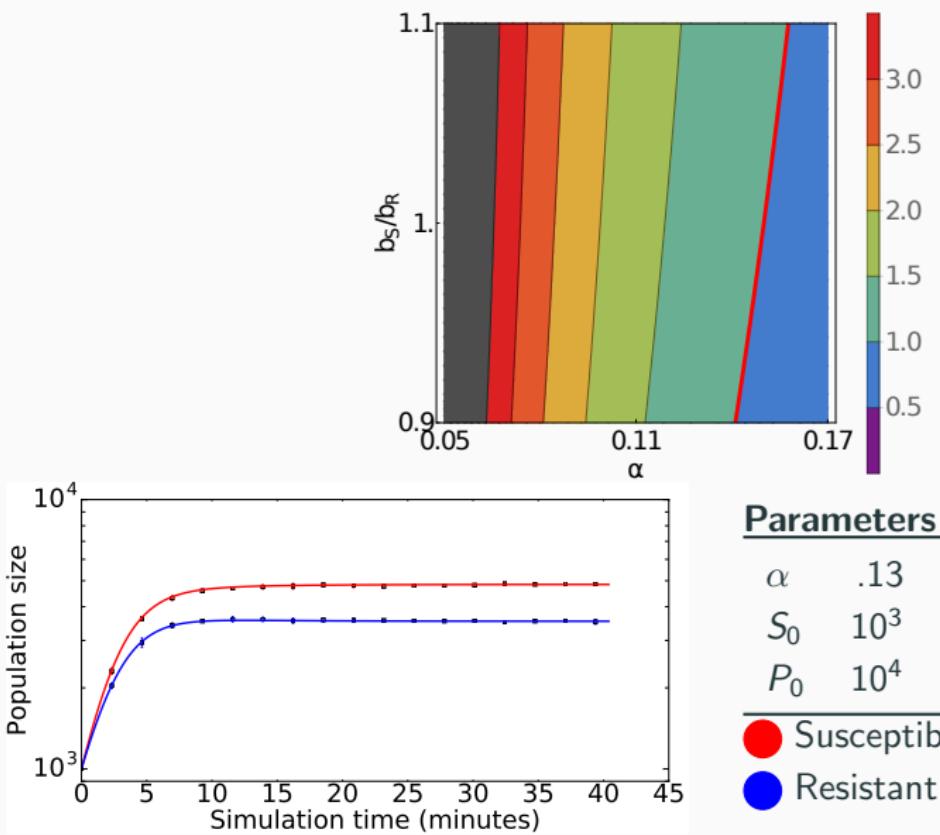
Results

Well-Mixed

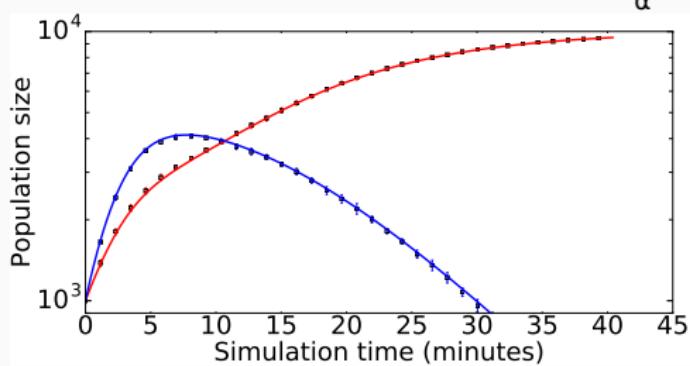
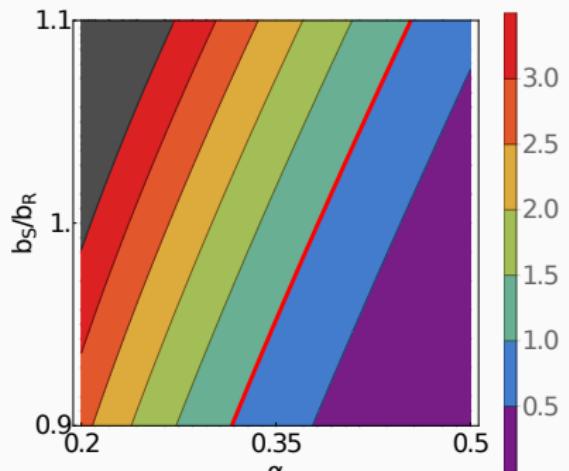
Lattice

Conclusions

Constant α



Linear α

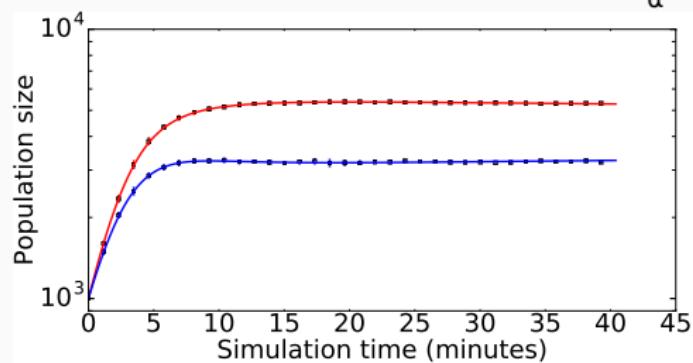
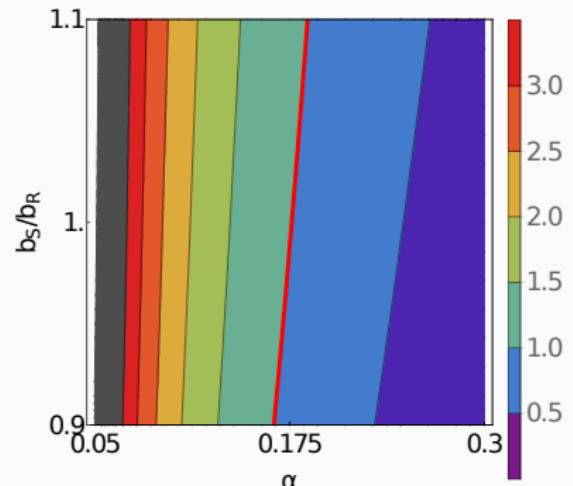


Parameters

α	.3	$\frac{b_S}{b_R}$	1.07
S_0	10^3	R_0	10^3
P_0	10^4	K	10^4

- Susceptible
- Resistant

Recycled α



Parameters

α	.13	$\frac{b_S}{b_R}$	1.07
S_0	10^3	R_0	10^3
P_0	10^4	K	10^4

● Susceptible

● Resistant

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What most heavily affects R or S dominance?

- Transition point heavily dependent on α
- Little growth rate dependence, except linear case

Future Work

- Larger lattice simulations
- Simulate antibiotic dosing
- Incorporate diffusion reaction

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Questions?

Gillespie Algorithm¹

1. Initialize simulation
2. Calculate propensity a for each reaction
3. Choose reaction μ according to the distribution

$$P(\text{reaction } \mu) = a_\mu / \sum_i a_i$$

4. Choose time step length τ according to the distribution

$$P(\tau) = \left(\sum_i a_i \right) \cdot \exp \left(-\tau \sum_i a_i \right)$$

5. Update populations with results of reaction
6. Go to Step 2

¹Heiko Rieger. *Kinetic Monte Carlo*. Powerpoint Presentation. 2012. URL:
https://www.uni-oldenburg.de/fileadmin/user_upload/physik/ag/compphys/download/Alexander/dpg_school/talk-rieger.pdf.

References i