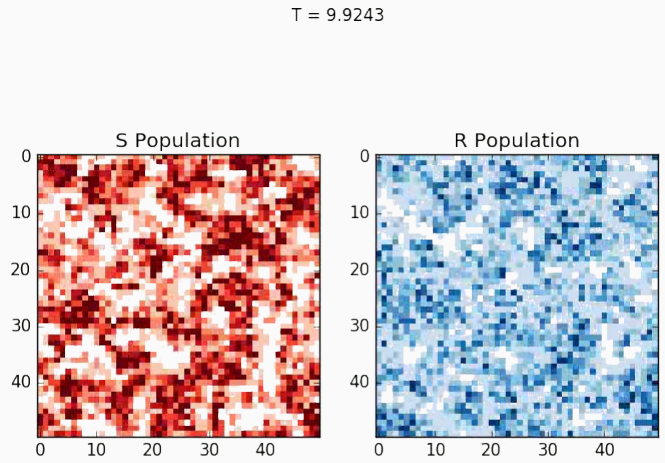
Simulation and Theory of Bacterial Transformation

JD Russo, JJ Dong

August 5, 2016

Department of Physics and Astronomy
Bucknell University



Outline

Motivation

- Ubiquitous threat of antibiotic resistance
- Transmission of resistance via plasmids
- Transformation of susceptible bacteria to resistant
- Identify what most significantly affects resistant cell dominance

Question

What conditions lead to emergence of antibiotic resistance?

- Ubiquitous threat of antibiotic resistance
- Transmission of resistance via plasmids
- Transformation of susceptible bacteria to resistant
- Identify what most significantly affects resistant cell dominance

Question

What conditions lead to emergence of antibiotic resistance?

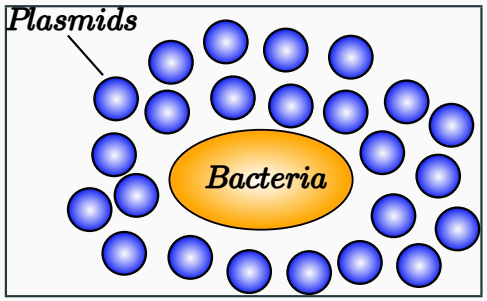
- Threat of resistance even in well-controlled diseases (TB)
- Main mechanisms of transmission are conjugation and transformation

Plasmids

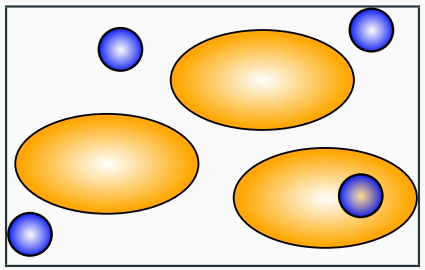
- Small, independently replicating genetic material
- Often include DNA segments encoding antibiotic resistance
- Imposes a fitness cost on host cell

Transformation and Conjugation

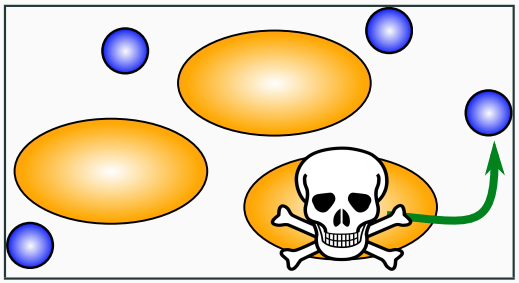
- **Conjugation:** Plasmid transferred between cells
- **Transformation:** Cell incorporates plasmid from environment
  - Three main regimes



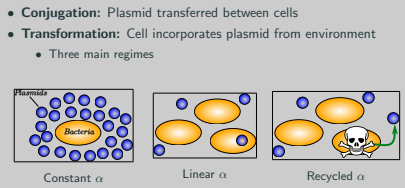
Constant α



Linear α



Recycled α



- 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 only pay attention to now for transformaton. We will investigate conjugation later.
- Describe physical meaning for each case. Constant is abundance of plasmids, linear is a dwindling population of plasmids. Recycled is the same, but with realism.

Population Dynamics Model - Constant

Reactions

$$S \xrightarrow{b_S} 2S$$

$$S \xrightarrow{\alpha} R$$

$$R \xrightarrow{b_R} 2R$$

$$R \xrightarrow{\delta} \varnothing$$

Population Dynamics Model - Constant

Reactions

$$S \xrightarrow{b_S} 2S$$

$$S \xrightarrow{\alpha} R$$

$$R \xrightarrow{b_R} 2R$$

$$R \xrightarrow{\delta} \varnothing$$

Equations

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

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

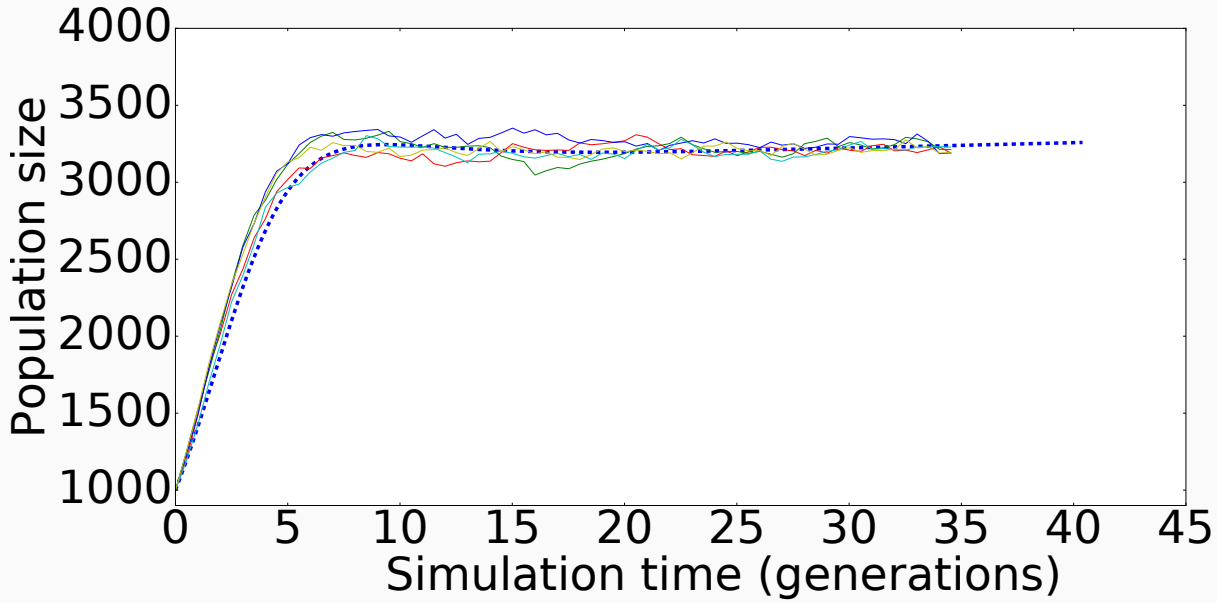
Population Dynamics Model - Constant

Reactions	Equations
$S \xrightarrow{b_S} 2S$	$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha S$
$S \xrightarrow{\alpha} R$	$\frac{dR}{dt} = b_R \left(1 - \frac{S+R}{K}\right) R + \alpha S - \delta R$
$R \xrightarrow{b_R} 2R$	
$R \xrightarrow{\delta} \varnothing$	

We can look to the simplest case of my simulation as a case study of this, and to understand in more depth how I'll be simulating these populations.

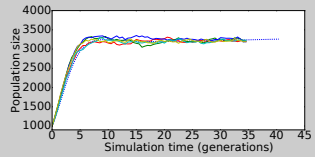
Simulation vs Modeling

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



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

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



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

- 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

Outline

Population Dynamics Model - Constant

Reactions

$$S \xrightarrow{b_S} 2S$$

$$S \xrightarrow{\alpha} R$$

$$R \xrightarrow{b_R} 2R$$

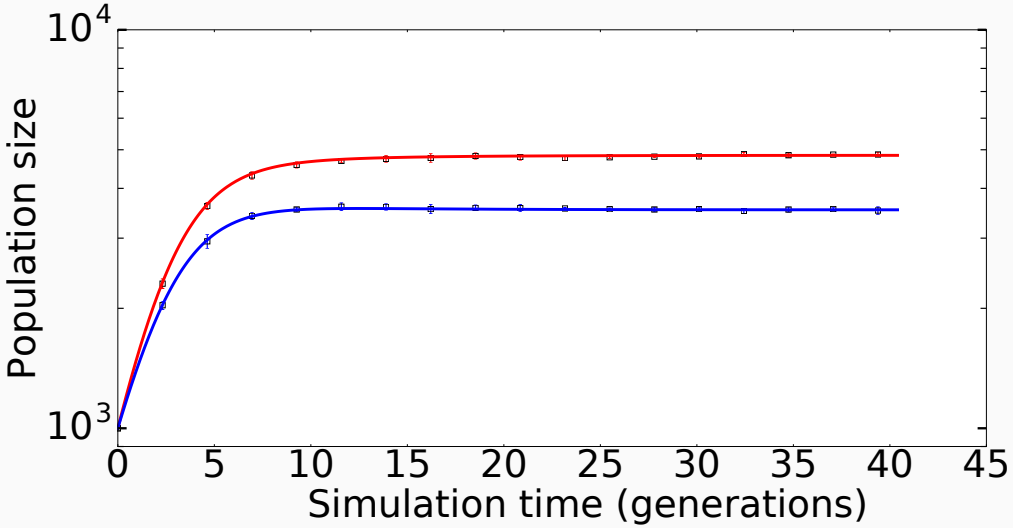
$$R \xrightarrow{\delta} \varnothing$$

Equations

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

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

Well-Mixed - Constant α

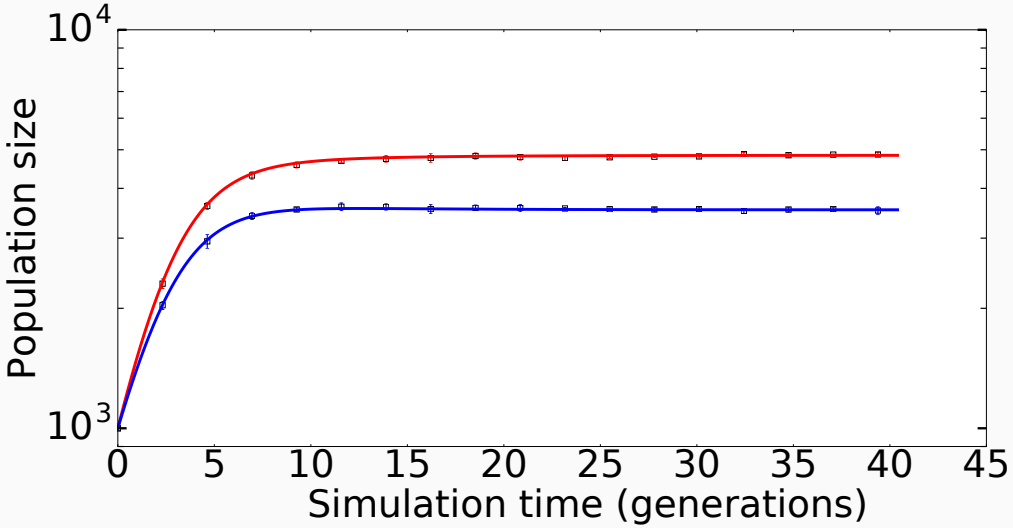


Parameters

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

- Susceptible
- Resistant

Well-Mixed - Constant α

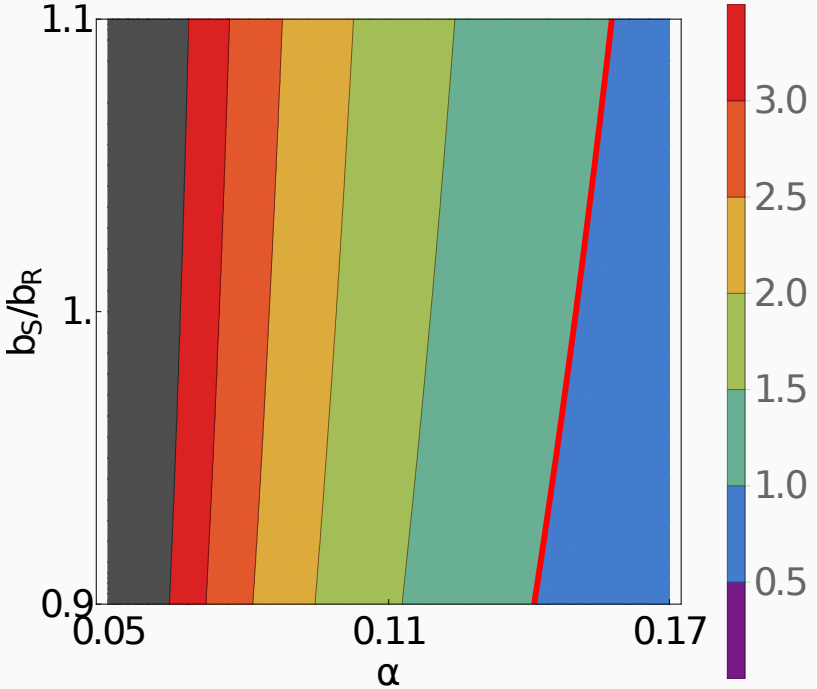


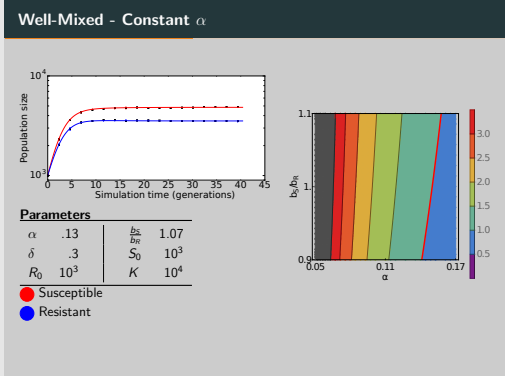
Parameters

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

Susceptible

Resistant





- Red line is where populations break even
- Here we can see the system falls into a steady state
- Contour plot shows after some empirically determined burn-in time has elapsed, which population dominates
- In constant case, difference in population dominance is largely due to rate of transformation, which acts as an additional growth and death term, growth rates, and death rate. Growth freezes when total population reaches carrying capacity

Population Dynamics Model - Linear

Reactions

$$S \xrightarrow{b_S} 2S$$

$$S + P_{free} \xrightarrow{\alpha} R$$

$$R \xrightarrow{b_R} 2R$$

$$R \xrightarrow{\delta} \varnothing$$

Equations

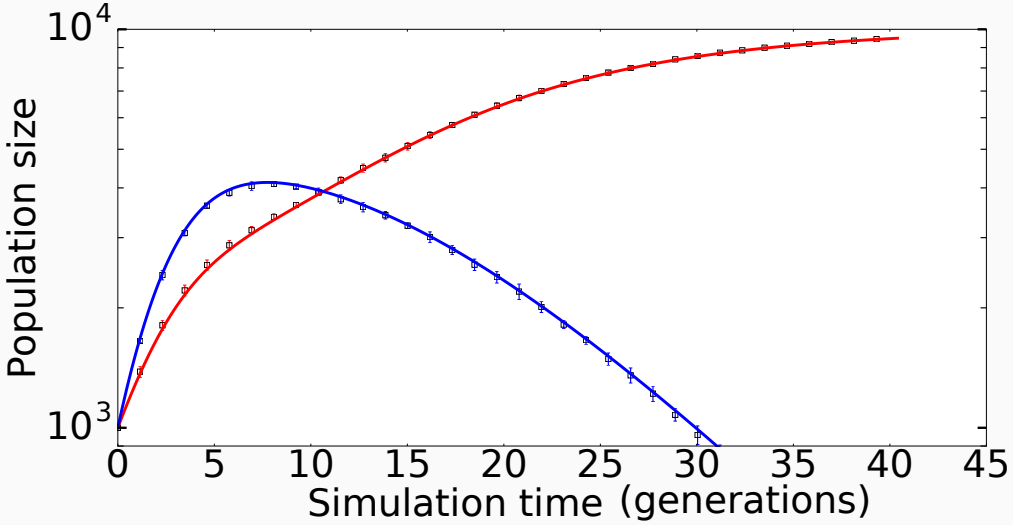
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

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

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

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

Well-Mixed - Linear α

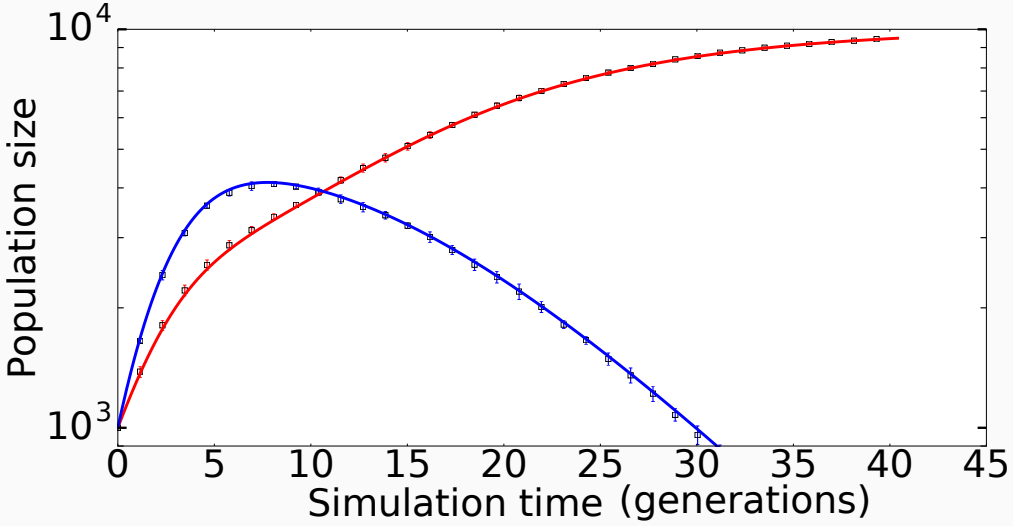


Parameters

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

- Susceptible
- Resistant

Well-Mixed - Linear α

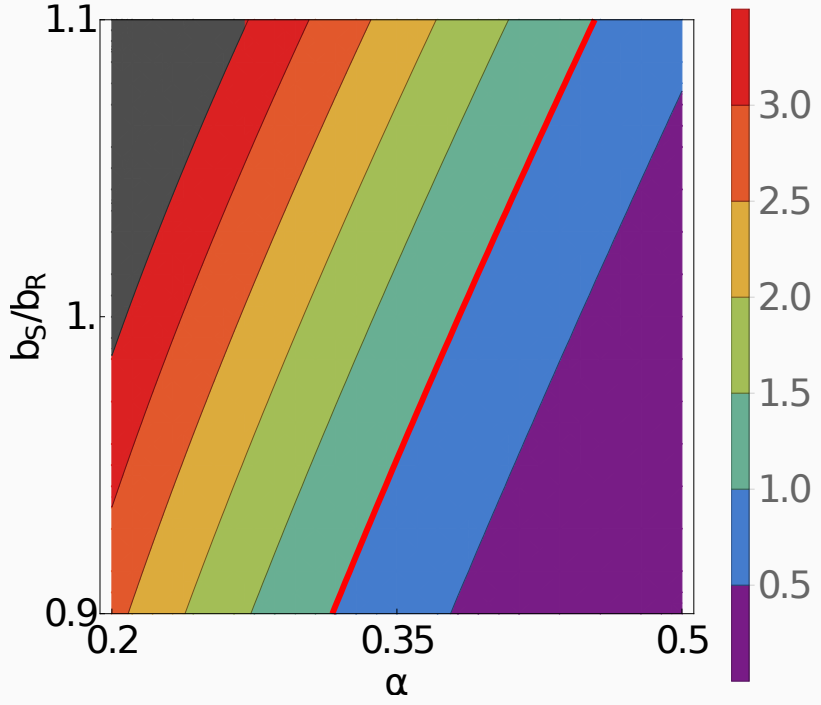


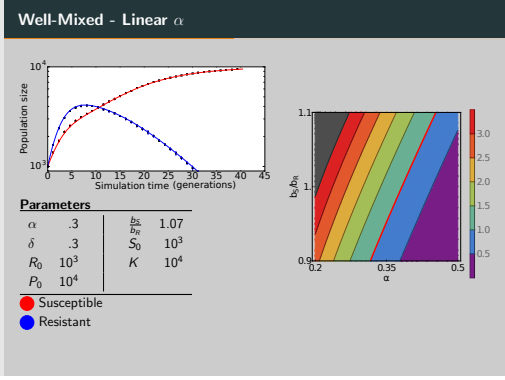
Parameters

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

Susceptible

Resistant





- Reiterate rules
- Most dynamic case
- Susceptible population slows down as R booms, but when all plasmids are exhausted R dies off and S dominates.
- Shows the most dependence on the ratio of growth rates, angled line in contour
- Break even point shifts WAY right, S dominates except for VERY high alphas, where the R population grows fast enough before plasmids are exhausted that it can hit the carrying capacity.

Population Dynamics Model - Recycled

Reactions

$$S \xrightarrow{b_S} 2S$$

$$S + P_{free} \xrightarrow{\alpha} R$$

$$R \xrightarrow{b_R} 2R$$

$$R \xrightarrow{\delta} \varnothing + P_{free}$$

Equations

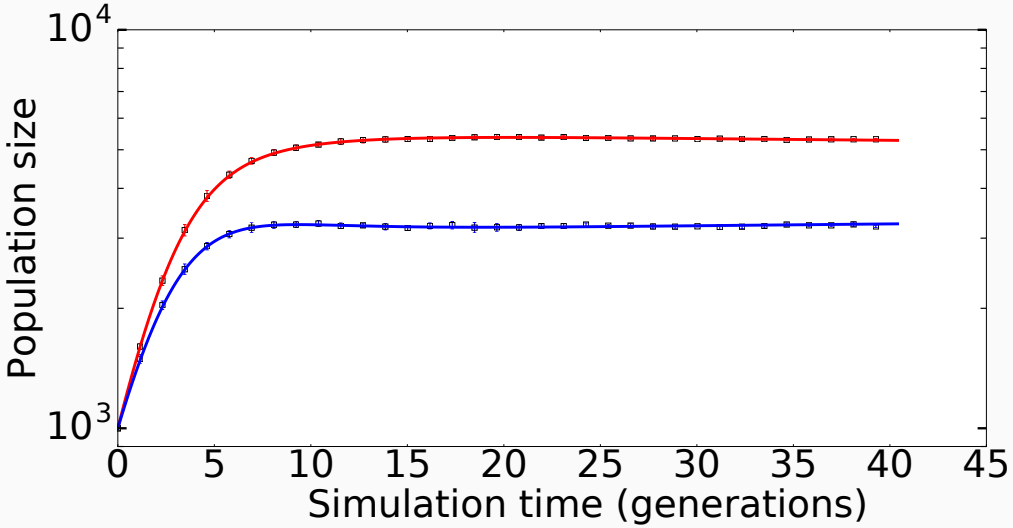
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

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

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

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

Well-Mixed - Recycled α

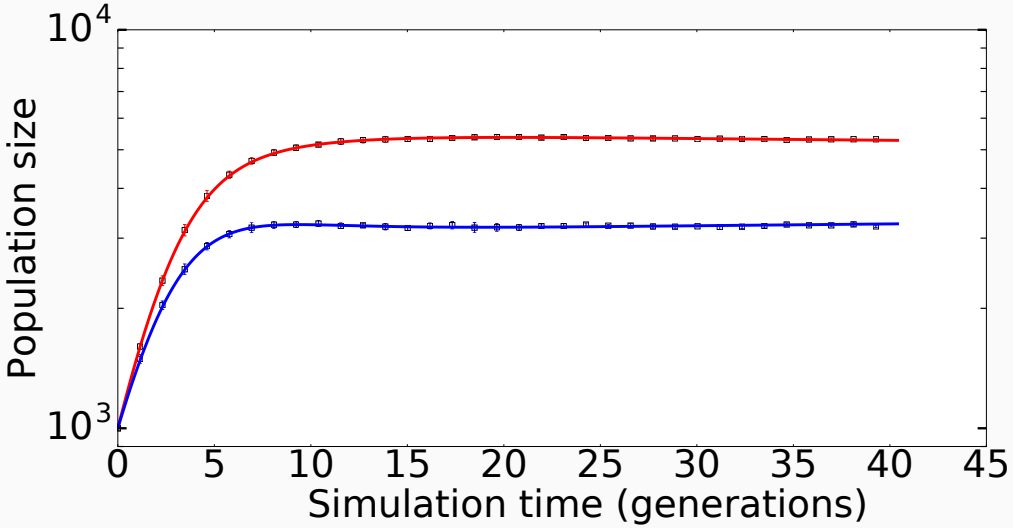


Parameters

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

Resistant Susceptible

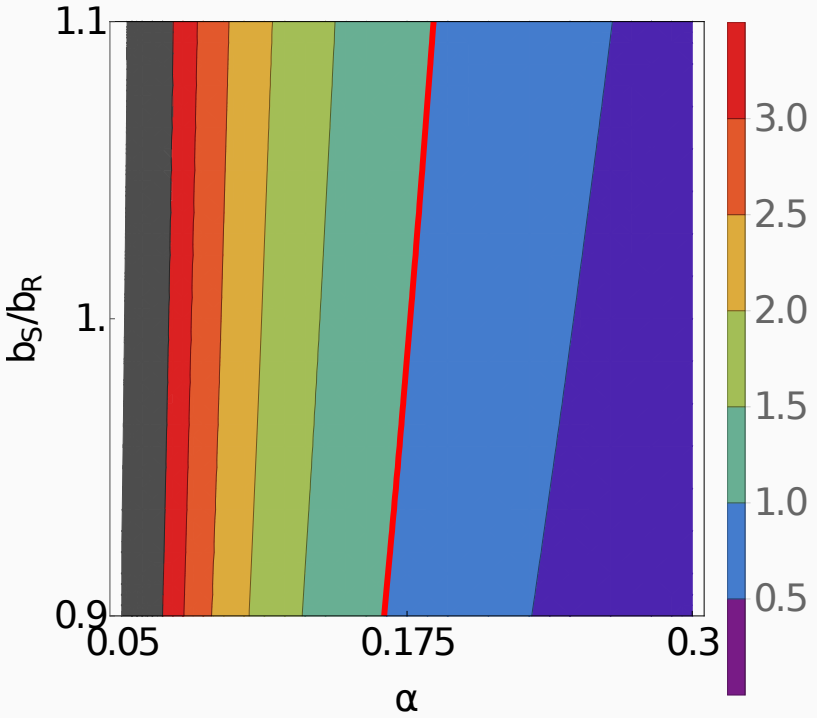
Well-Mixed - Recycled α



Parameters

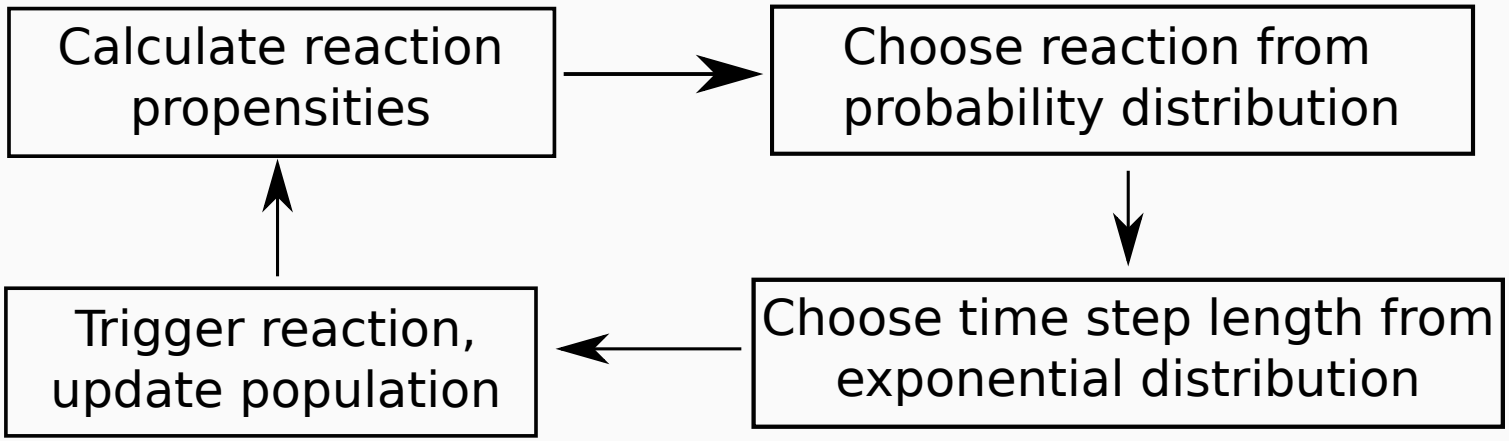
α	.13	$\frac{b_S}{b_R}$	1.07
δ	.3	R_0	10^3
S_0	10^3	K	10^4
P_0	10^4		

Resistant Susceptible



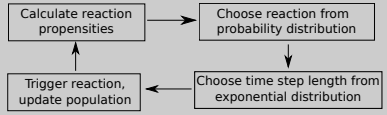
Kinetic Monte Carlo Method

- 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



Kinetic Monte Carlo Method

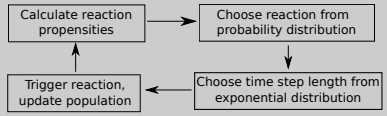
- Initially used to simulate chemical reactions
- Useful for simulating any reaction that occurs with a rate
- Captures information about dynamics of a growing system
- Self-adjusting timescales



- The kinetic monte carlo method, or the Gillespie Algorithm, was originally developed to simulate stochastic chemical reactions.
- If any of you remember, yesterday in her talk Payton mentioned a parameter that had to be tweaked in simulation in order to get the simulation to properly account for simulating bacteria instead of a chemical reaction. What's nice about KMC is that it's 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.

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



- 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
- Fixed death rate
- Mapping simulation time to real time

Outline

Conclusions

Question

What conditions lead to emergence of antibiotic resistance?

- Transition point where population dominance switches
- Transition point heavily dependent on α mechanism, not growth rate ratio
- Little growth rate dependence, except linear case
- Linear case tends to population extinction, with interesting dynamics in between

Question

What conditions lead to emergence of antibiotic resistance?

- Transition point where population dominance switches
- Transition point heavily dependent on α mechanism, not growth rate ratio
- Little growth rate dependence, except linear case
- Linear case tends to population extinction, with interesting dynamics in between

- This is all for the well-mixed case!

Ongoing Work

- Continue gathering lattice data
- Simulate larger lattices

Future Work

- Incorporate diffusion
- Add conjugation reaction
- Simulate antibiotic dosing

Questions?

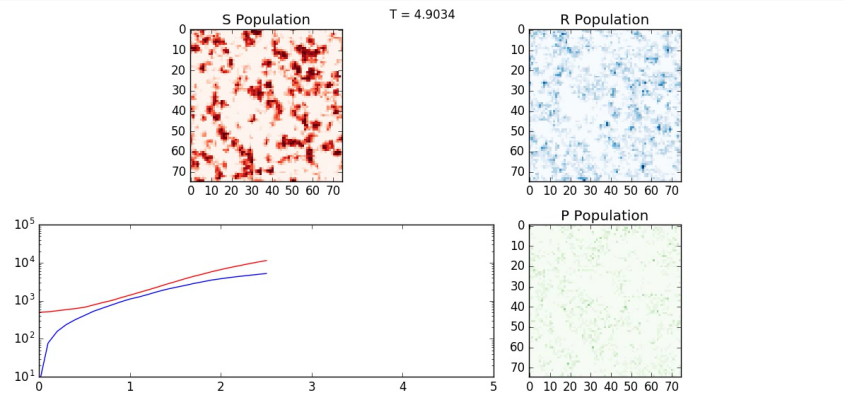
Acknowledgments

- Department of Physics and Astronomy, Bucknell University
- NSF-DMR #1248387
- Sandy!

Optimizations

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

Lattice Results



Gillespie Algorithm[1]

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

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

4. Choose time step length τ according to the distribution

$$\mathrm{P}(\tau) = \left(\sum_i a_i \right) \cdot \exp\left(-\tau \sum_i ai \right)$$

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

[1] Heiko 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.

Mapping Simulation Time to Realtime

$$\frac{dS}{dt} = b_S S$$

$$\begin{aligned} S(t) &= S_0 e^{b_S t} \\ &= S_0 e^{\ln 2 t/\tau} \end{aligned}$$

$$\begin{aligned} b_S &= \ln 2/\tau \\ \tau &= \ln 2/b_S \end{aligned}$$

Mapping Simulation Time to Realtime

$$\frac{dS}{dt} = b_S S$$

$$S(t) = S_0 e^{b_S t} = S_0 e^{\ln 2 t/\tau}$$

$$b_S = \ln 2/\tau$$

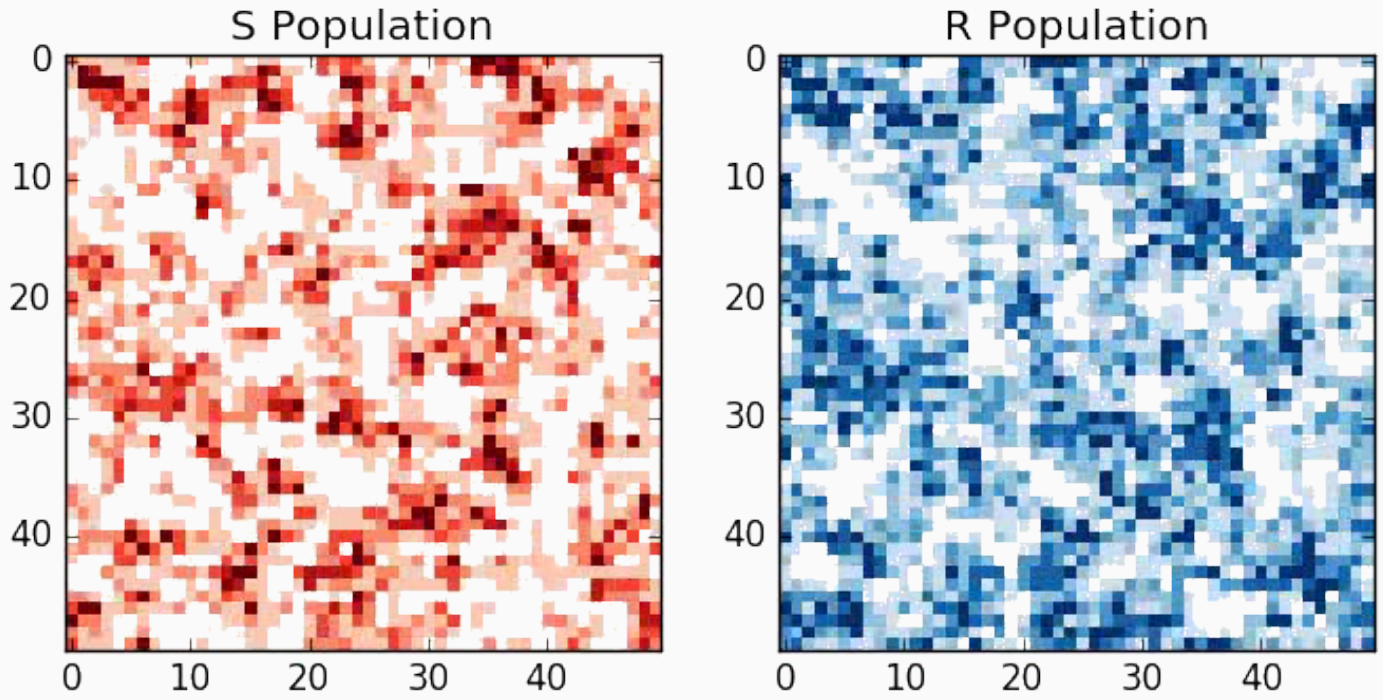
$$\tau = \ln 2/b_S$$

τ is the characteristic timescale for the simulation, in term of generations. Map this to realtime by multiplying by the doubling time.

Lattice Simulation Results

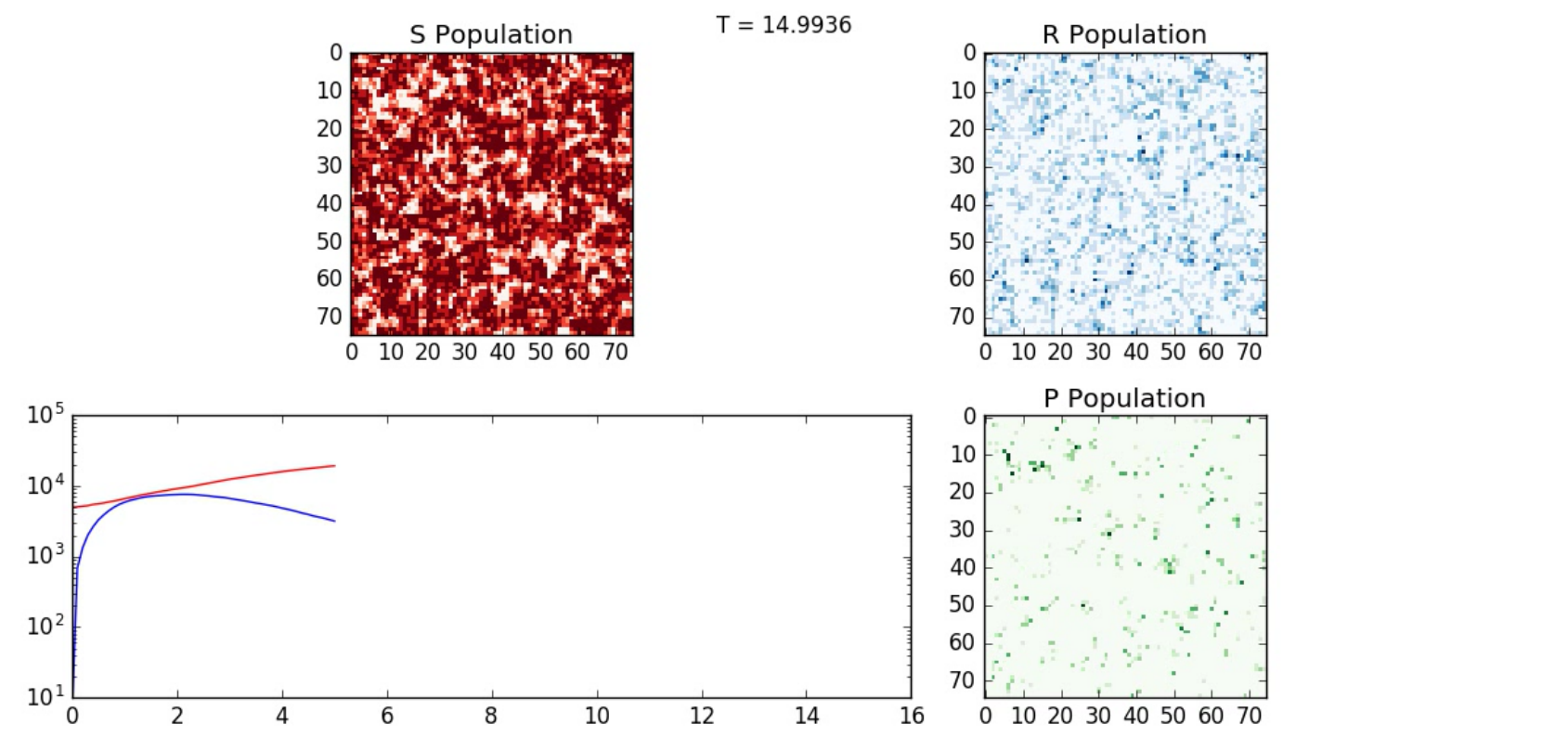
Sharp Transition

T = 9.9243



Lattice Simulation Results

Long Run



Lattice Simulation Results

Large Lattice