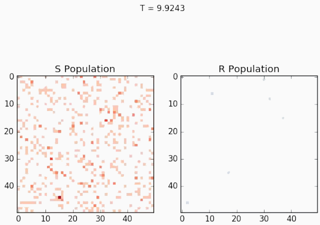
Simulation and Theory of Bacterial Transformation

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

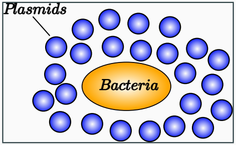
What conditions lead to emergence of antibiotic resistance?

Plasmids

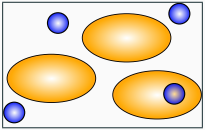
- Small, independently replicating genetic material
- Often include DNA segments encoding antibiotic resistance
- Imposes a fitness cost on host cell

Transformation and Conjugation

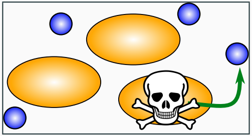
- **Conjugation:** Plasmid transferred between cells
- **Transformation:** Cell incorporates plasmid from environment
  - Three main regimes



Constant α



Linear α



Recycled α

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

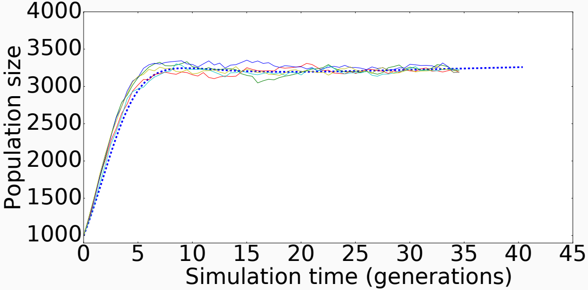
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha S$$

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

Outline

Simulation vs Modeling

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



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

Outline

Population Dynamics Model - Constant

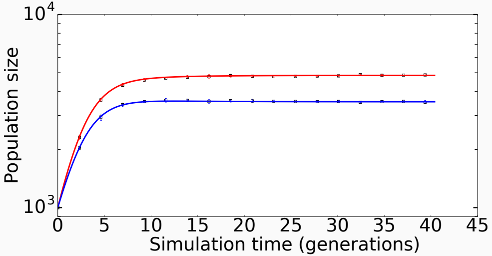
Reactions

$$S \xrightarrow{b_S} 2S$$
$$S \xrightarrow{\alpha} R$$
$$R \xrightarrow{b_R} 2R$$
$$R \xrightarrow{\delta} \varnothing$$

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

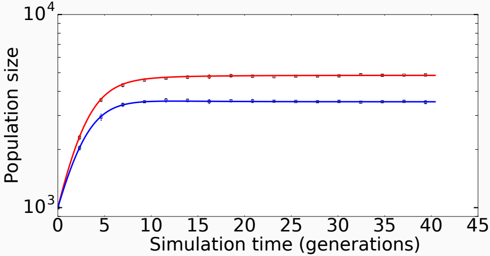


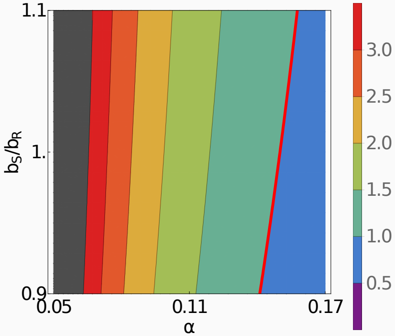
Parameters

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

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

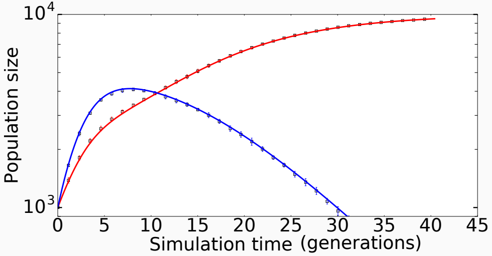
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

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

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

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

Well-Mixed - Linear α



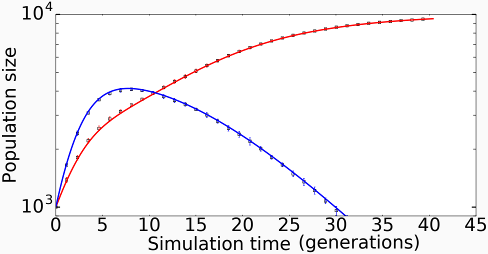
Parameters

α	.13	$\frac{b_S}{b_R}$	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

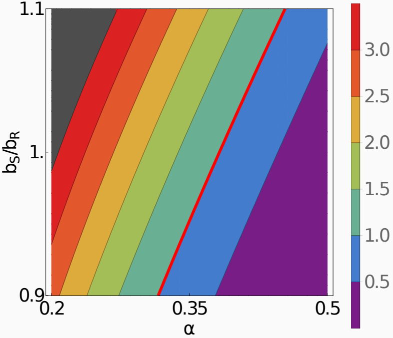


Parameters

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

Susceptible

Resistant



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

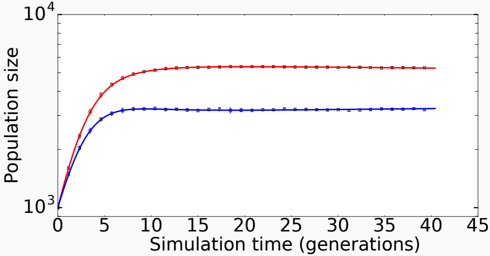
$$\frac{dS}{dt} = b_S \left(1 - \frac{S+R}{K}\right) S - \alpha \left(\frac{P_f}{P}\right) S$$

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

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

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

Well-Mixed - Recycled α

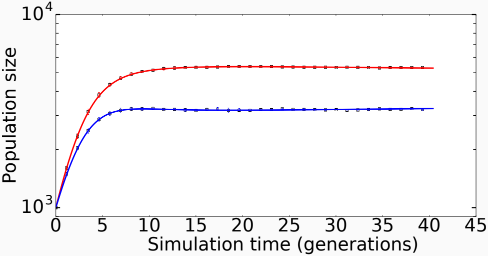


Parameters

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

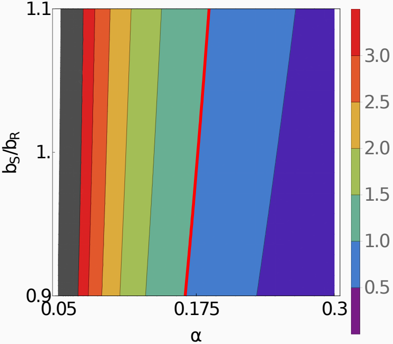
Well-Mixed - Recycled α



Parameters

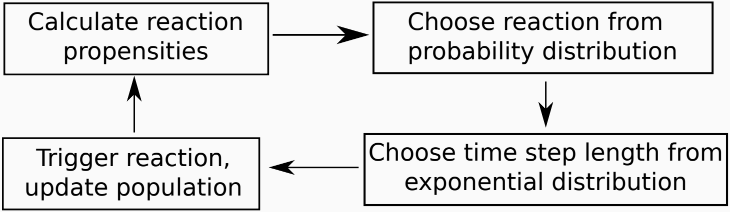
α	.13	$\frac{b_S}{b_R}$	1.07
δ	.3	R_0	10^3
S_0	10^3	K	10^4
P_0	10^4		

● 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



Simulation Details

- Slower plasmid carrier growth rate
- Carrying capacity
- Periodic boundary conditions
- 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

Ongoing Work

- Continue gathering lattice data
- Simulate larger lattices

Future Work

- Incorporate diffusion
- Add conjugation reaction
- Simulate antibiotic dosing

Questions?

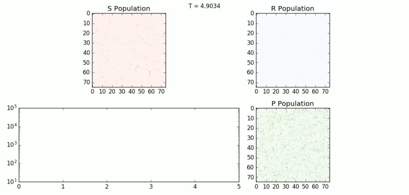
Acknowledgments

- 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

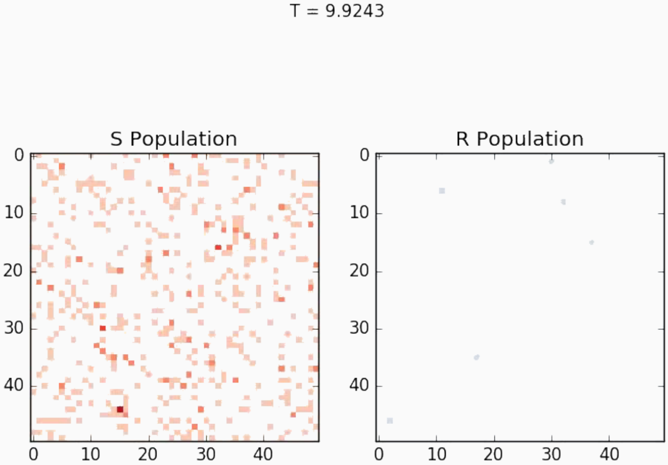
$$\frac{dS}{dt} = b_S S$$

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

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

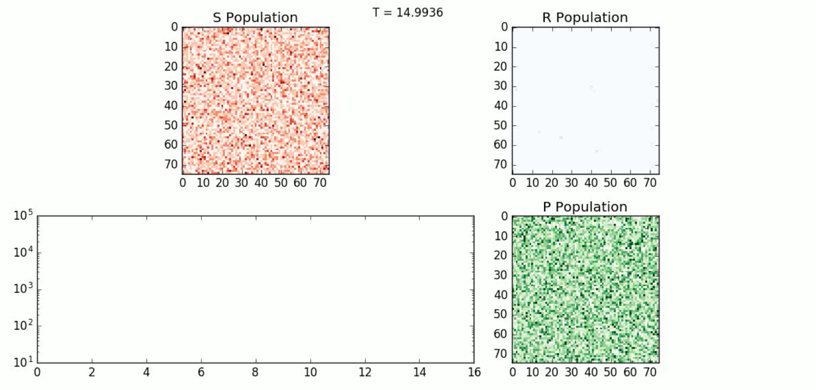
Lattice Simulation Results

Sharp Transition



Lattice Simulation Results

Long Run



Lattice Simulation Results

Large Lattice