Simulation and Theory of Bacterial Transformation

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Introduction

The threat of antibiotic resistant bacteria is becoming more ubiquitous, even among well-controlled diseases such as tuberculosis. Main mechanisms for the emergence of antibiotic resistance include conjugation and transformation. We focus on the effect of transformation.

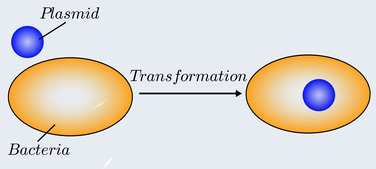
We use a combined approach of Kinetic Monte Carlo simulation and mathematical modeling to explore interplay among **growth** (b), **death** (δ), **transformation** (α), and **plasmid availability** (P). Numerically modelling the populations with their associated differential equations provides information about long-term population behavior, while K.M.C. simulation provides information about dynamics.

We study differential growth and transformation to determine what most affects whether the susceptible or resistant population dominates.

Biological Background

Plasmids are small independently replicating genetic materials, often including DNA segments encoding antibiotic resistance.

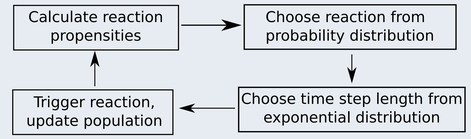
Through **transformation** a cell can incorporate a physical plasmid and translate the encoded genes. However, this often comes with a small fitness cost to the carrying cell, typically manifesting as a longer doubling time.



Simulation Methods

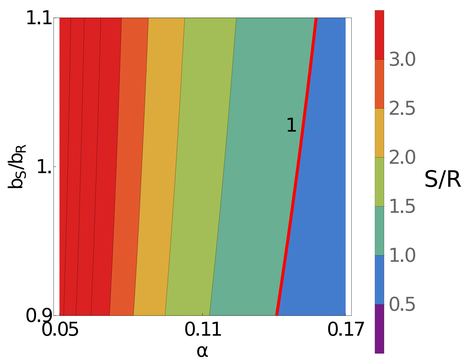
We examine the **susceptible** (S) and **resistant** (R) populations with a combined approach of numerical modeling methods and Kinetic Monte Carlo simulation.

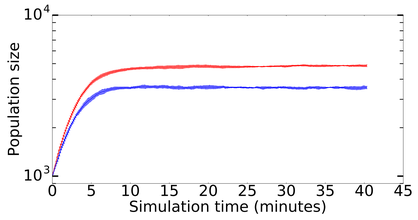
Kinetic Monte Carlo simulation allows us to capture information about the dynamics of the populations. We implement the Gillespie algorithm, which consists of the following steps:



We assume a well-mixed environment, a fixed carrying capacity K, and that reproduction occurs symmetrically for both S and R. This does not conserve total plasmid number.

Constant 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

Reactions

$S \xrightarrow{b_S} 2S$

$S \xrightarrow{\alpha} R$

$R \xrightarrow{b_R} 2R$

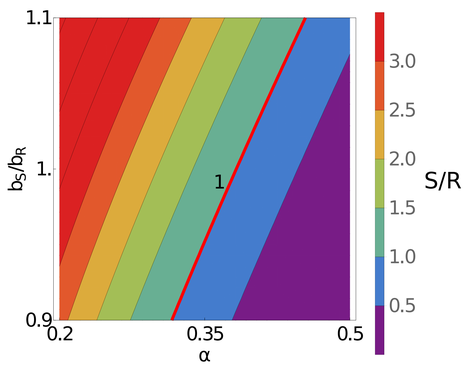
$R \xrightarrow{\delta} \varnothing$

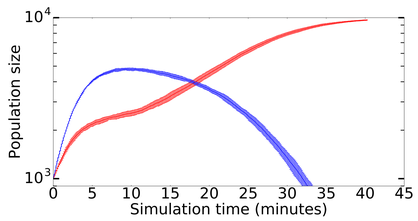
Equations

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

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

Linear α





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P_0	10^4	K	10^4

- Susceptible
- Resistant

Reactions

$S \xrightarrow{b_S} 2S$

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

$R \xrightarrow{b_R} 2R$

$R \xrightarrow{\delta} \varnothing$

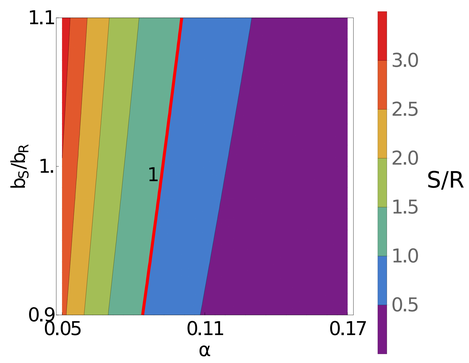
Equations

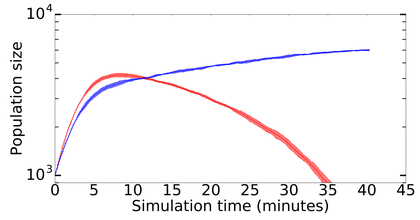
$$\frac{dS}{dt} = b_S\left(1 - \frac{S+R}{K}\right)S - \alpha\left(\frac{P}{P_0}\right)S$$

$$\frac{dR}{dt} = b_R\left(1 - \frac{S+R}{K}\right)R + \alpha\left(\frac{P}{P_0}\right)S - \delta R$$

$$\frac{dP}{dt} = -\alpha\left(\frac{P}{P_0}\right)S$$

Recycled α





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P_0	10^4	K	10^4

- Susceptible
- Resistant

Reactions

$S \xrightarrow{b_S} 2S$

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

$R \xrightarrow{b_R} 2R$

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

Equations

$$\frac{dS}{dt} = b_S\left(1 - \frac{S+R}{K}\right)S - \alpha\left(\frac{P}{P_0}\right)S + +b_R\left(1 - \frac{S+R}{K}\right)R$$

$$\frac{dR}{dt} = \alpha\left(\frac{P}{P_0}\right)S - \delta R$$

$$\frac{dP}{dt} = -\alpha\left(\frac{P}{P_0}\right)S + \delta R$$

Conclusions

We aimed to determine what most heavily impacts R or S population dominance.

We found that the transition point where the dominant population switches depends heavily on both transformation rate and mechanism. In the constant case, long-term steady state behavior can be seen.

Both the linear and recycled cases present examples of population extinction. In the linear case, the S population invariably dominates, as plasmids are never replenished. In the recycled case, plasmid abundance enables the R population to eventually outgrow the S.

In addition, only the linear case shows significant sensitivity to the ratio of growth rates b_S/b_R

Future Work

Currently, this simulation assumes well-mixed populations of S, R, and P. A more realistic simulation could account for spatial configuration by simulating on a lattice.

Simulating adding antibiotics to the environment could reveal situations where increased survivability outweighs the fitness cost of carrying a plasmid.

Changing R division to an asymmetric scheme ($R \to R + S$) would yield a conserved total plasmid number.

Acknowledgements

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