A Markov Chain Monte Carlo Model of Stochastic Gene Expression in Bacteria

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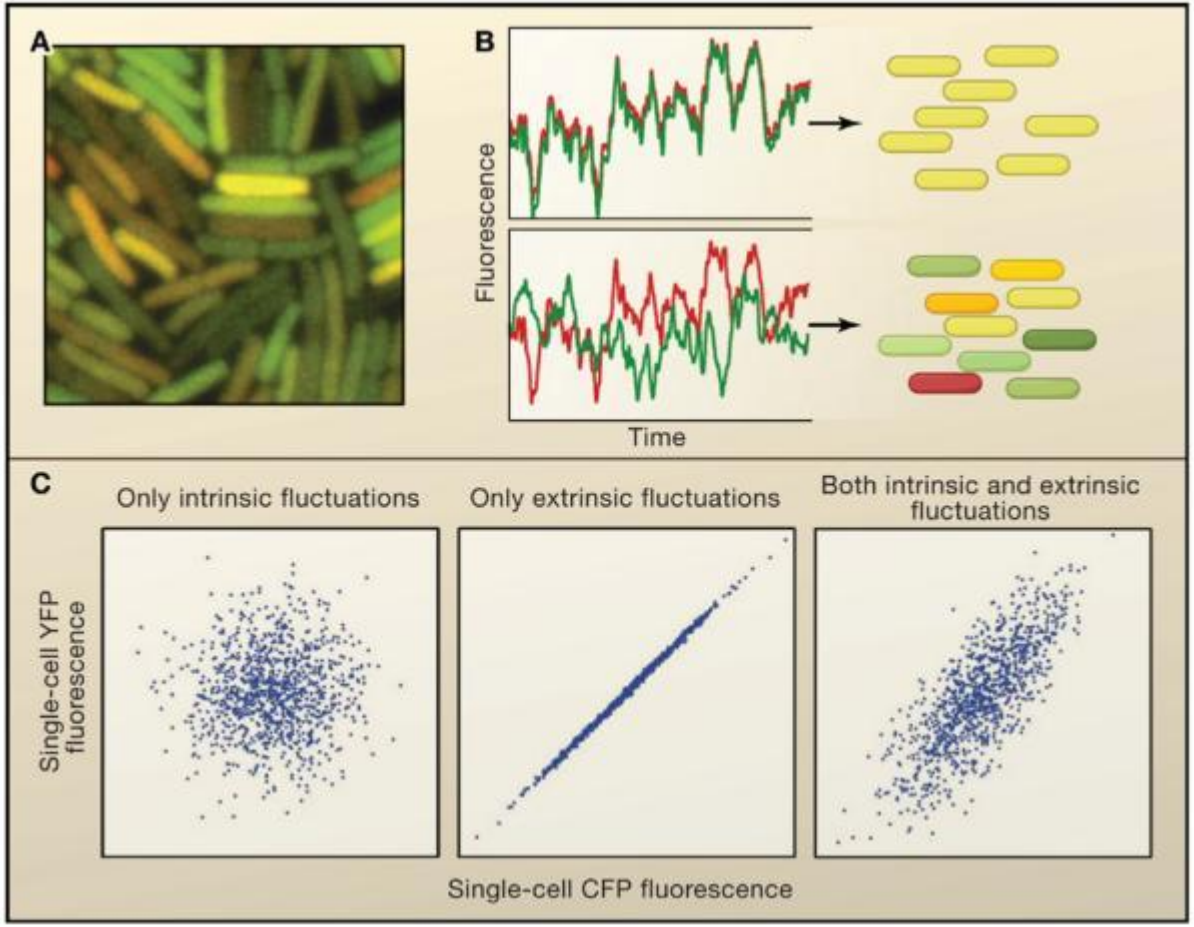
Background: Stochastic Gene Expression

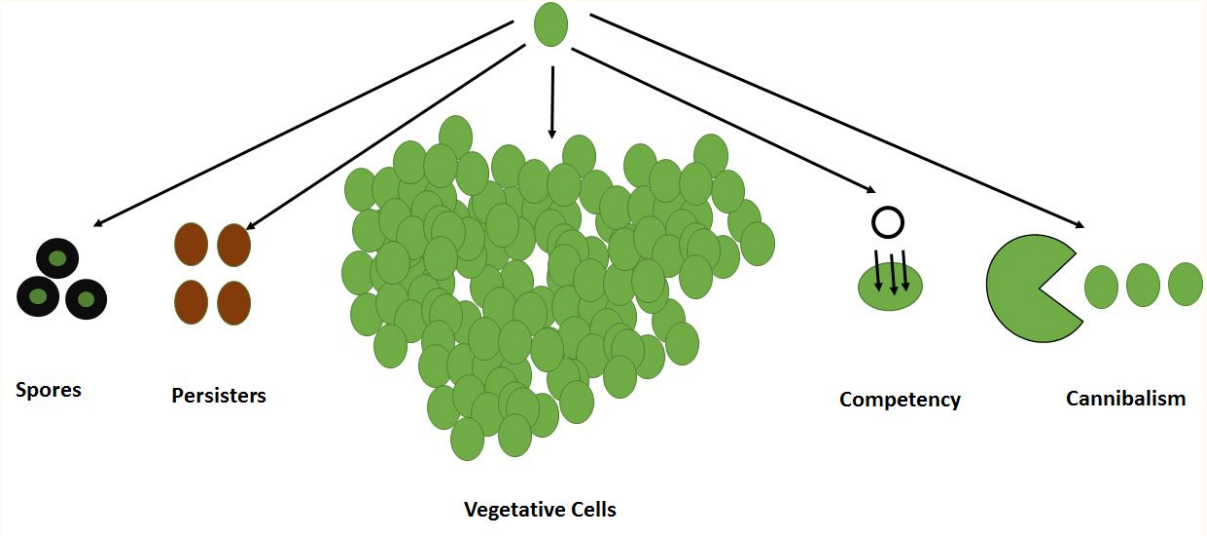
- Gene expression is inherently random
- E. coli two copies of the same promoter integrated into genome with two different fluorescent genes:
  - Cyan FP
  - Yellow FP
- Due to fluctuations in:
  - Transcription factor binding
  - mRNAs
  - Protein synthesis
  - Distribution of products in daughter cells
  - etc.



Raj A, van Oudenaarden A. Stochastic gene expression and its consequences. *Cell*. 2008;135(2):216-226. doi:10.1016/j.cell.2008.09.050.

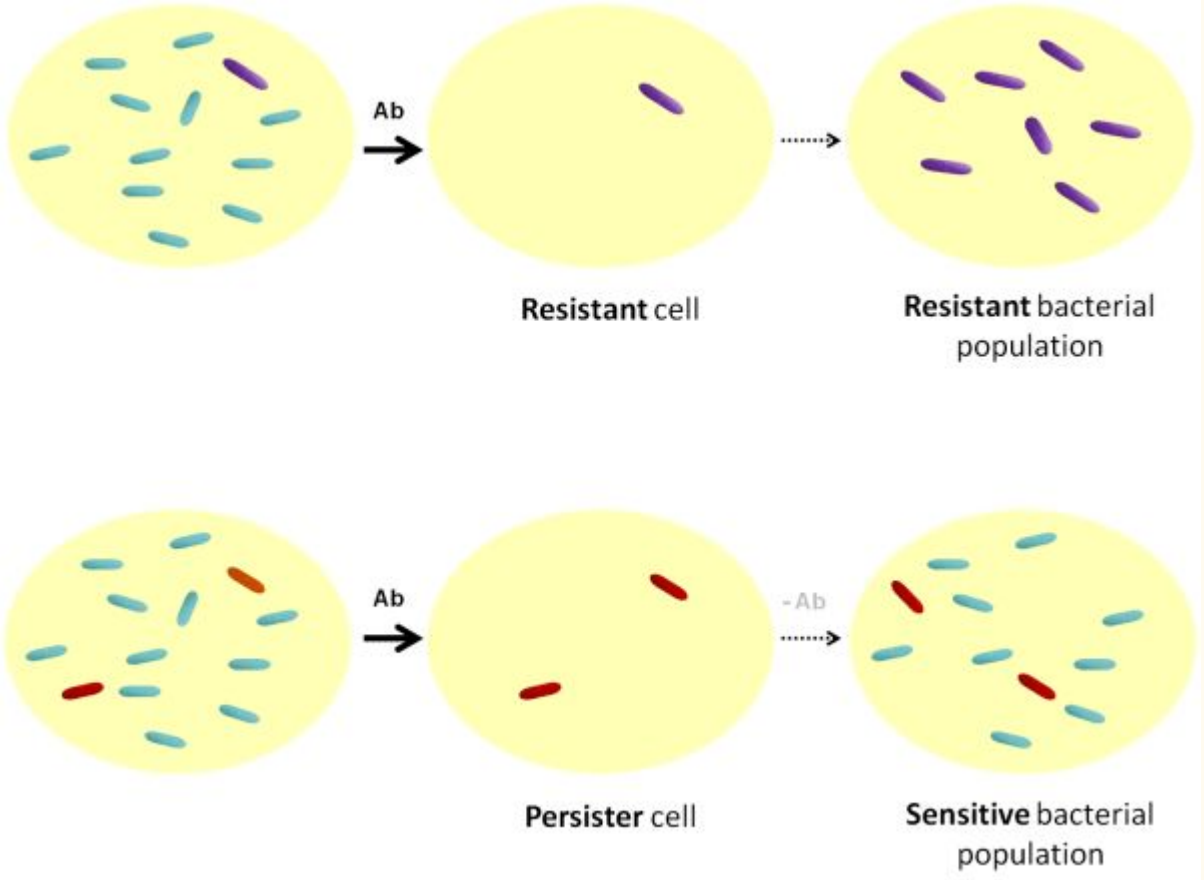
Stochastic Gene Expression Determines Cell Fates

- Stochastic gene expression can lead to dramatic cell changes:
  - Sporulation
  - Competency
  - Suicide
  - Cannibalism
  - Persister formation
- Isogenic population!



Persister Formation

- Stochastic changes in the level of a toxin can halt cellular metabolism, causing persister state
- Randomly generated, resistant subpopulation within isogenic population
- Allows resistance to antibiotics without a resistance gene



https://microbewiki.kenyon.edu/images/b/bd/Suarezfig1final.gif

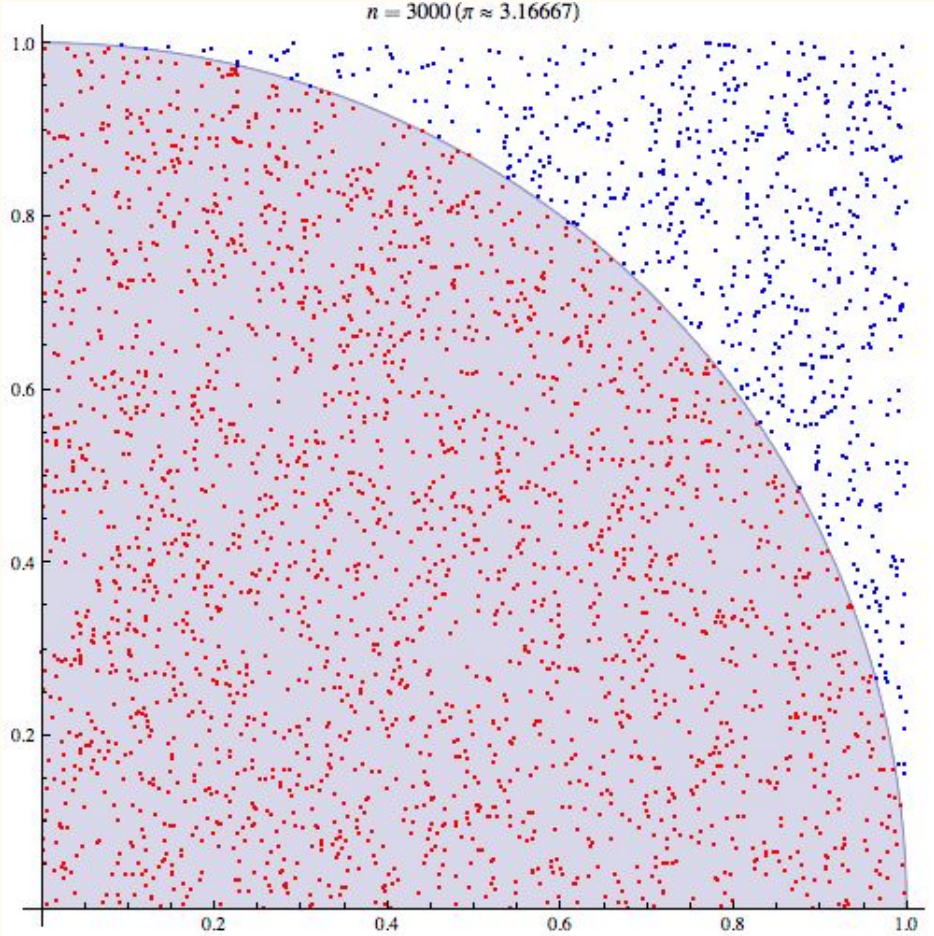
Concept

- Idea: Markov chains could be used to model cell fate transitions
  - Cell fate transitions are memoryless, Markov assumption applies
- Idea: Monte-Carlo approach could simulate randomness in bacterial population

Hypothesis: A Markov Chain Monte-Carlo model could be used to simulate and predict the effect of stochastically mediated persister formation in bacterial endocarditis

Monte-Carlo

- Estimates the value of a variable by random sampling of its distribution
- Example: Estimating pi by sampling from the area of a circle inscribed in a square
- Powered by pseudorandom number generator
- More iterations, more accurate



Simulation Goals

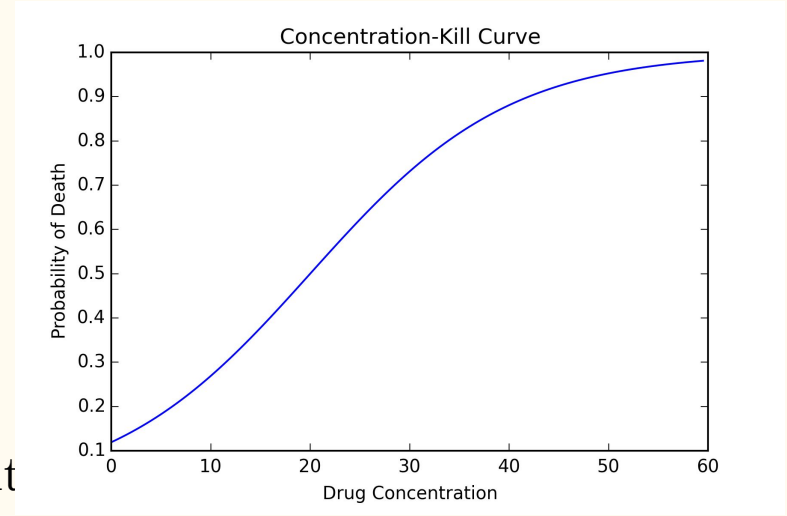
1. Behave according to clinical and laboratory understanding of bacterial endocarditis
2. Reproduce the ability of persister cells to allow resurgence after antibiotic treatment
3. Predict the necessary treatment duration to cure most cases of bacterial endocarditis

Simulation: Endocarditis

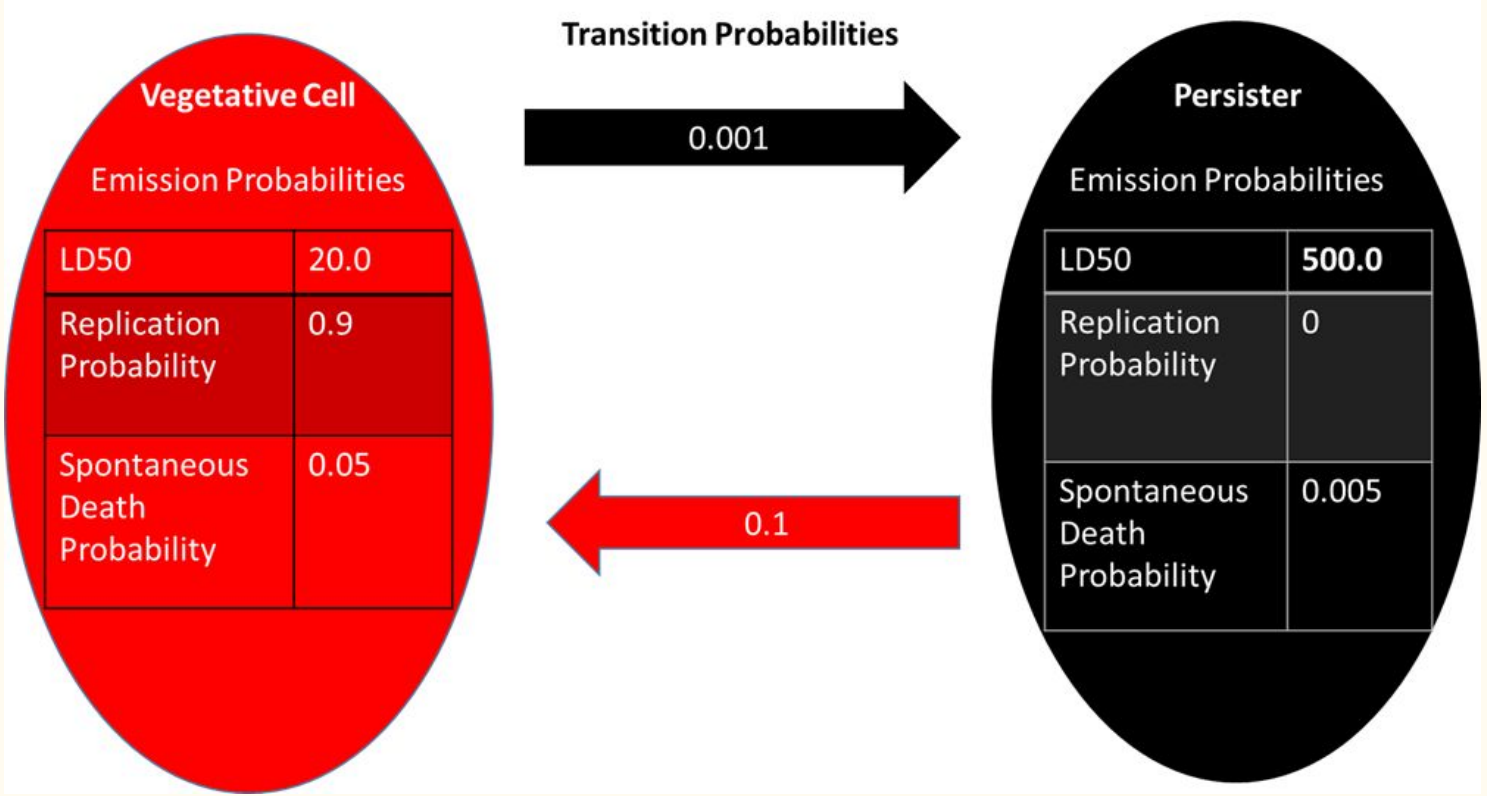
- *Escherichia coli* heart valve infection
- Absent immune response: bacterial population is dependent only on its growth and a bactericidal antibiotic
- *E. coli* can take vegetative and persister states
- Vegetative: Sensitive to cefazolin, but replicates
- Persister: Evades antibiotics, no replication

Methods - Model Design

- Cells have four potential actions per step
  - Replicate
  - Spontaneous Death
  - Spontaneous Transformation
  - Quiescence
- Cells have probabilistic susceptibilities to a drug at a given concentrations
- Vegetative and persister cells have different probabilities to simulate different properties



Persister Transmission/Emission

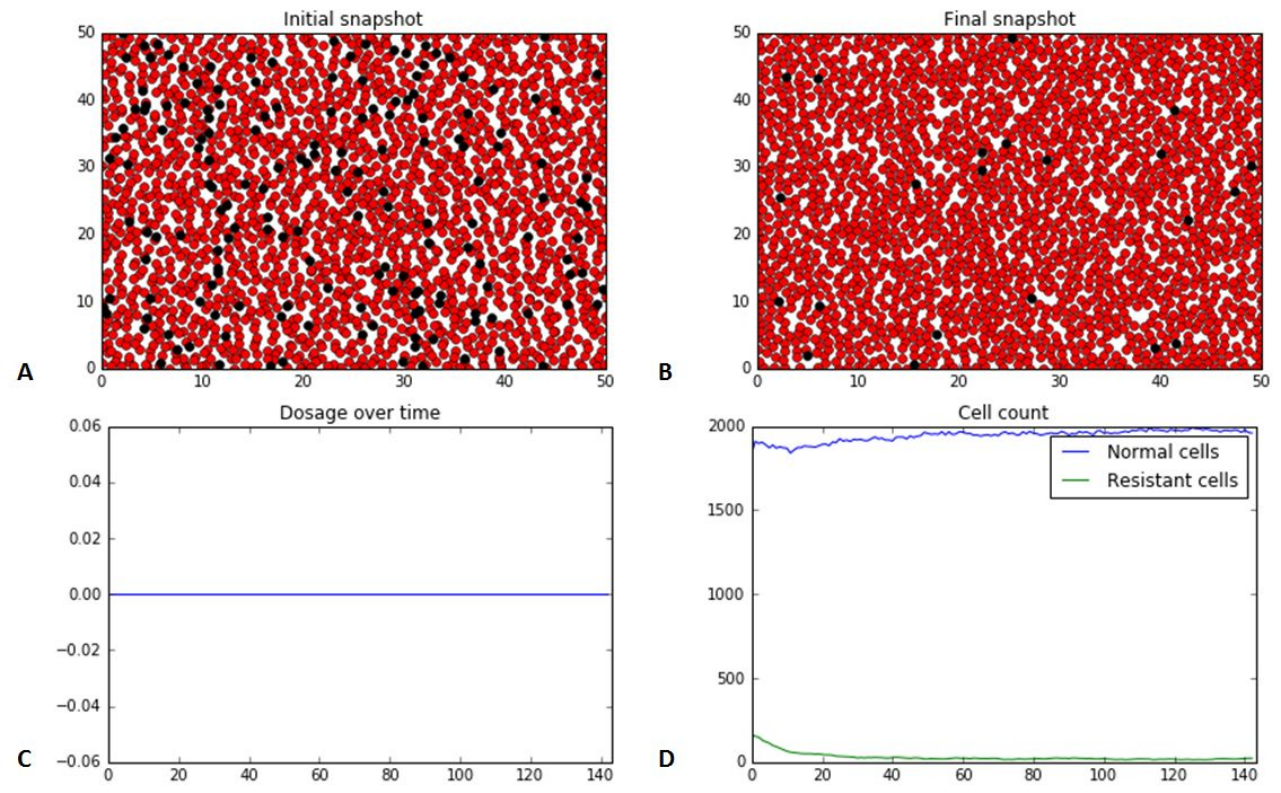


Methods - Simulation Design

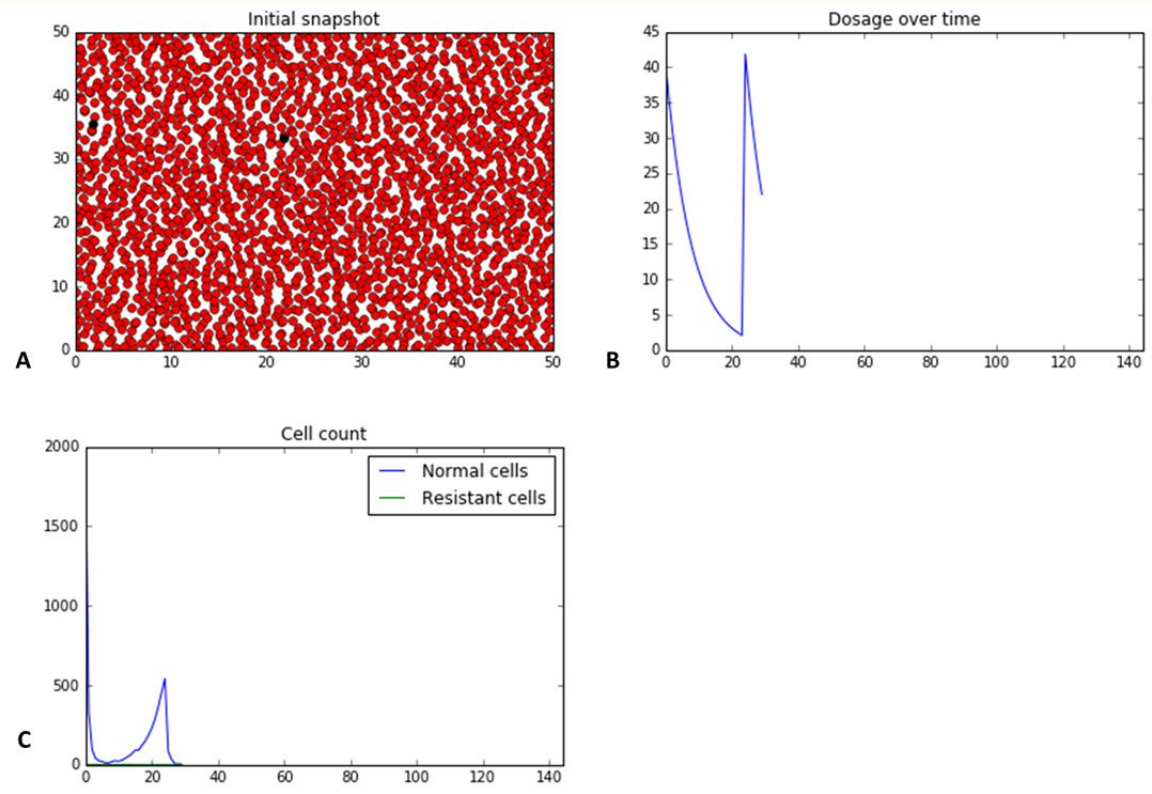
- Populate a grid with bacteria
- Iterate through all bacteria to determine fate for next time step
  - First attempt to kill bacteria with antibiotic if present
  - Use emission probabilities to determine next step if it survives
  - Continue until completion of treatment or until end of simulation
- Time steps are scaled to *E. coli* doubling time
- Drug concentrations modeled using exponential decay

$$C(T) = C_0 e^{-k_e \times T}$$

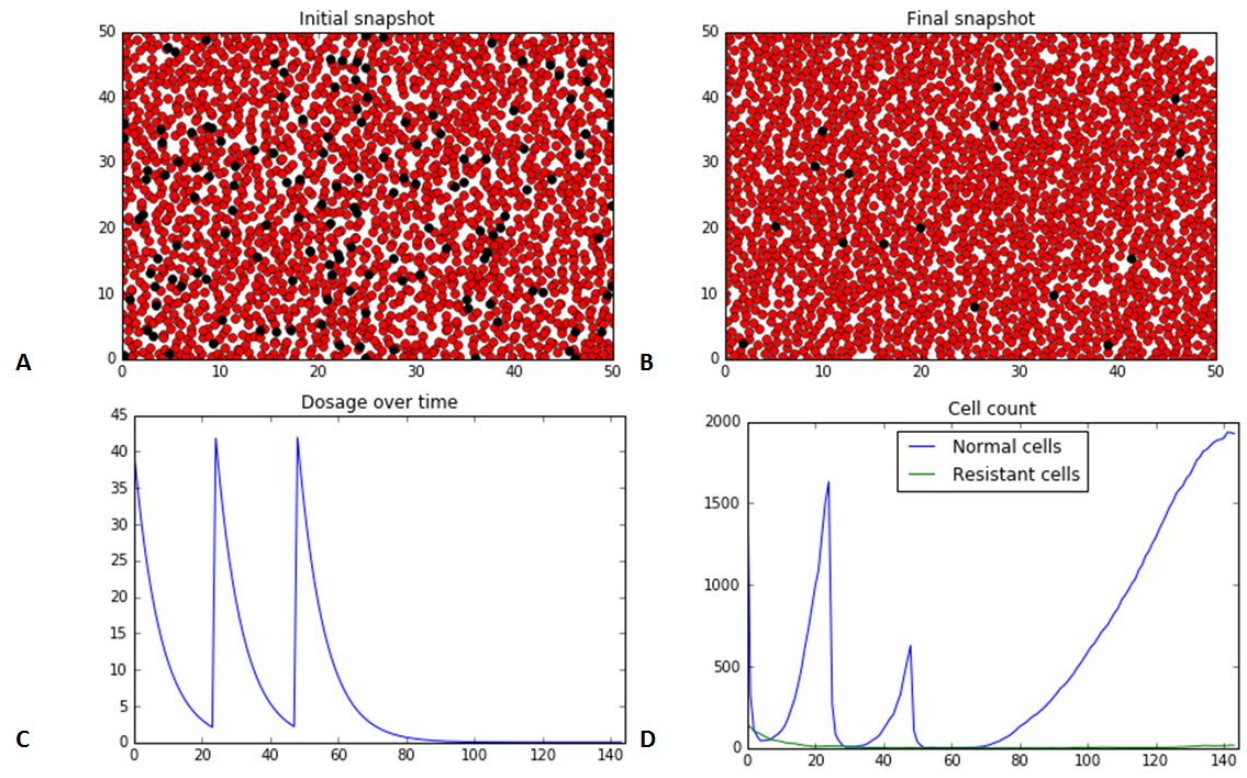
Results: Untreated Endocarditis



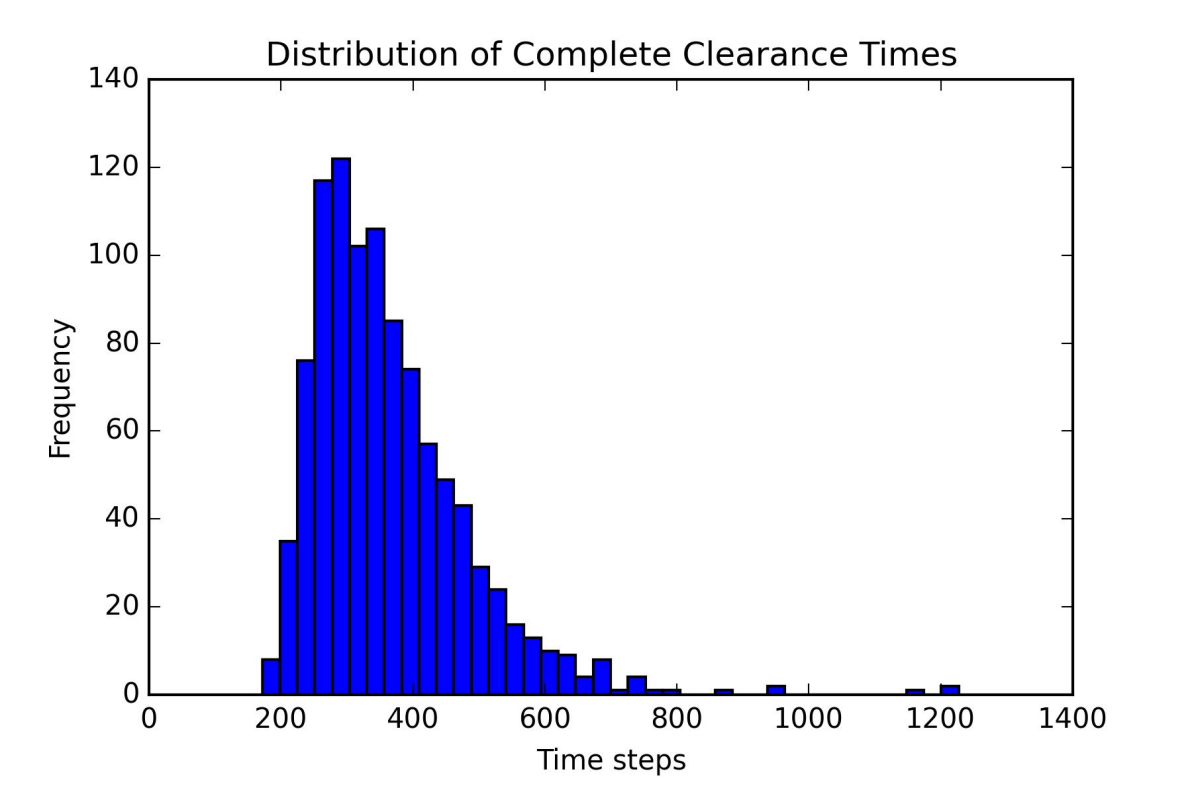
Results: Proper treatment, no persisters



Results: Persisters allow survival of therapy



Results: MCMC predicts probability of resurgence



Conclusions

Developed an MCMC model of endocarditis:

1. Behaves according to clinical and laboratory understanding of bacterial endocarditis
2. Reproduces the ability of persister cells to allow resurgence after antibiotic treatment
3. Predicts the necessary treatment duration to cure most cases of bacterial endocarditis
    - 10.3 days to cure 99% of infections
    - Supported by limited clinical data

Future Applications

- Model different types of infections
- Predict necessary duration of therapy
- Predict outcomes for a given treatment
- Illustrate to patients the value of completing treatment

Any Questions?