Fighting Disease with Maths

Sara Jabbari

School of Mathematics & Institute of Microbiology and Infection, University of Birmingham

9th January 2014

UNIVERSITY OF BIRMINGHAM

MRC Medical Research Council

IMI INSTITUTE OF MICROBIOLOGY AND INFECTION

Outline

Antibiotics and Disease

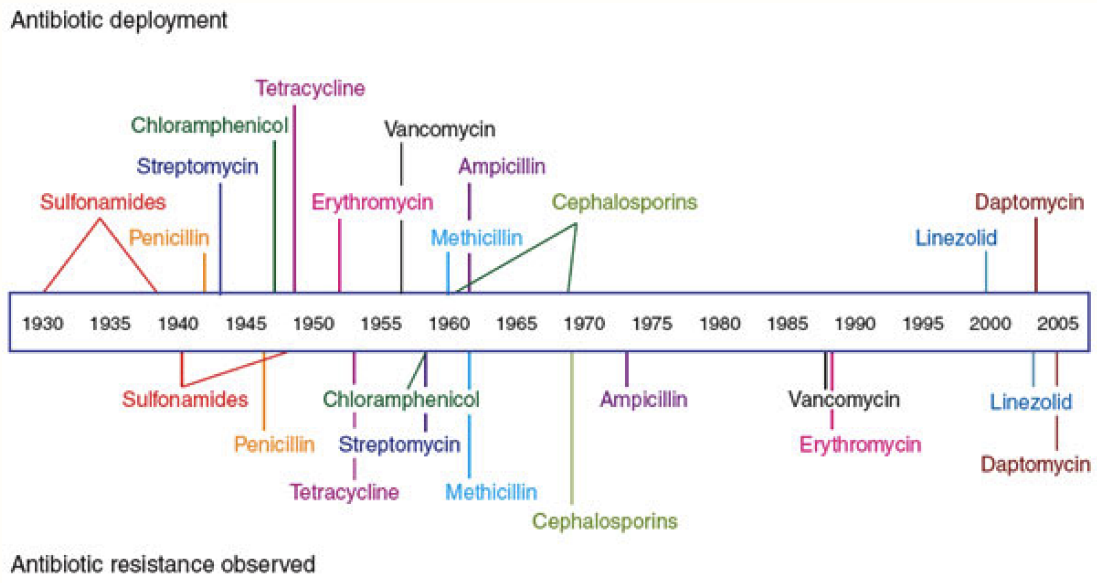
- Antibiotics are widely used to treat bacterial infections
- They act by killing the bacteria, or inhibiting their growth
- First discovered in the early 20th Century

Emergence of resistance

- The emergence of antibiotic resistance is becoming an increasing problem in modern society.

Emergence of resistance

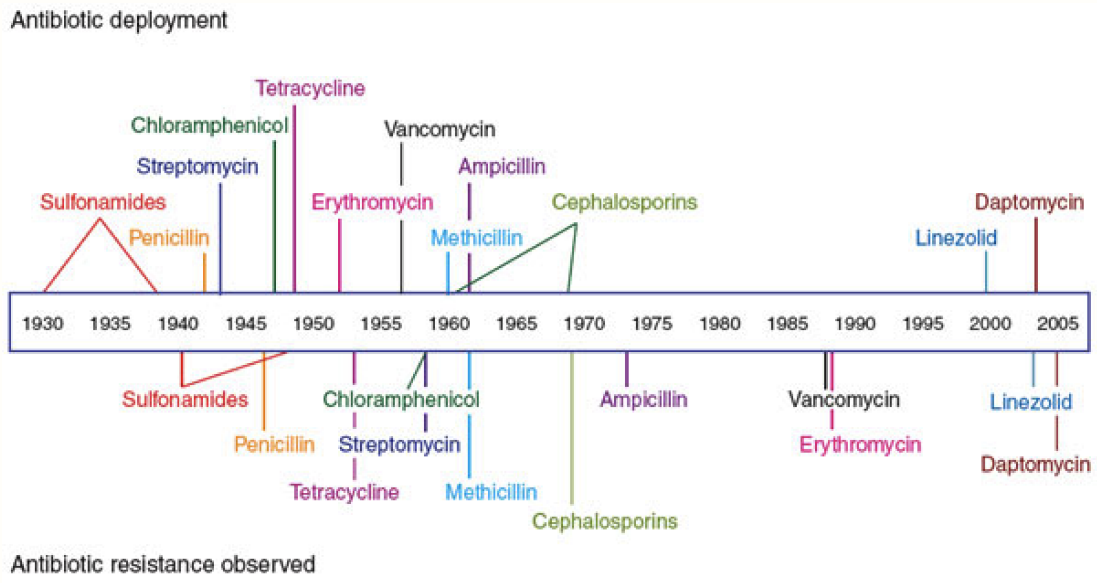
- The emergence of antibiotic resistance is becoming an increasing problem in modern society.



From: Clatworthy *et. al*, *Nat. Chem. Biol.*, 3(9), 541-548 2007.

Emergence of resistance

- The emergence of antibiotic resistance is becoming an increasing problem in modern society.



From: Clatworthy *et. al*, *Nat. Chem. Biol.*, 3(9), 541-548 2007.

- In the USA, resistant bacteria cause an estimated
  - ~2 million illnesses p.a.
  - 23,000 deaths p.a.

Acquisition of resistance

There are two principal methods for the acquisition of resistance in bacteria:

- Vertical evolution
- Horizontal evolution

Acquisition of resistance

There are two principal methods for the acquisition of resistance in bacteria:

- Vertical evolution
  - Spontaneous chromosomal mutation
- Horizontal evolution

Acquisition of resistance

There are two principal methods for the acquisition of resistance in bacteria:

- Vertical evolution
  - Spontaneous chromosomal mutation
- Horizontal evolution
  - Acquiring genetic material from other resistant organisms

Acquisition of resistance

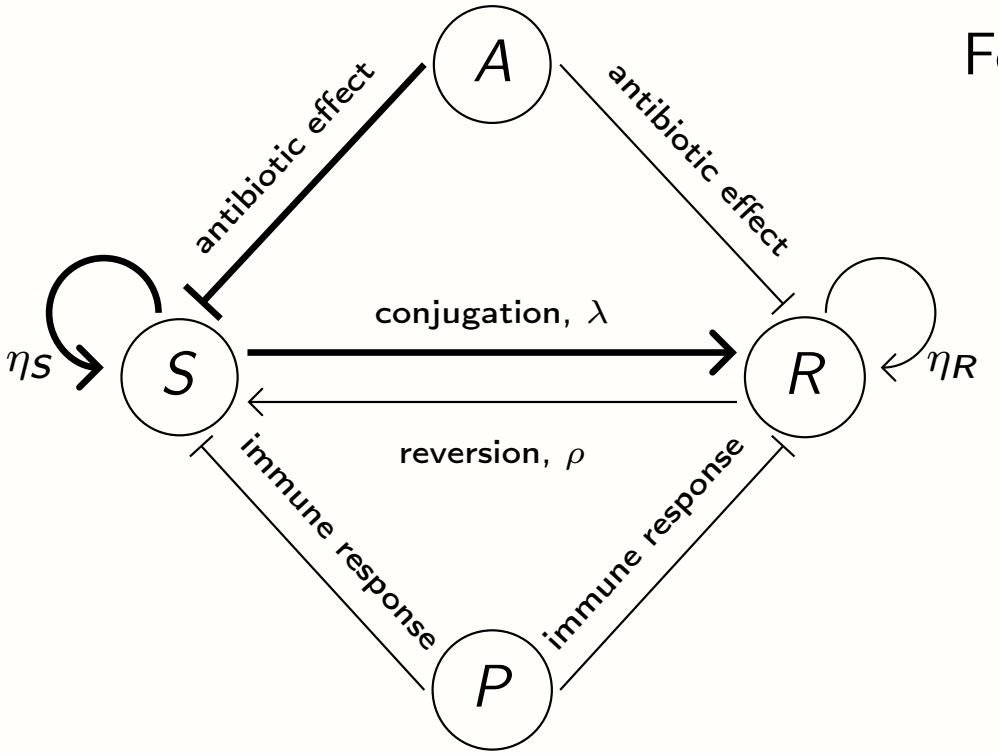
There are two principal methods for the acquisition of resistance in bacteria:

- Vertical evolution
  - Spontaneous chromosomal mutation
- Horizontal evolution
  - Acquiring genetic material from other resistant organisms

Horizontal evolution is thought to be more common, can result in multi-drug resistance and spreads rapidly, hence it is thought to be the main concern for antibiotic resistance in a hospital setting.

Modelling the emergence of antibiotic resistance in-host

Modelling the emergence of resistance



Four variables:

- A - antibiotic
- P - number of phagocytes (immune response)
- S - number of susceptible bacteria
- R - number of resistant bacteria

Construction of a mathematical model

In its simplest form, a mathematical model looks something like:

$$\frac{dN}{dt} = \text{births} - \text{deaths},$$

where N is the number of some biological species.

Construction of a mathematical model

In its simplest form, a mathematical model looks something like:

$$\frac{dN}{dt} = \text{births} - \text{deaths},$$

where N is the number of some biological species.

In terms of an antibiotic-resistance model:

$$\frac{dR}{dt} = \text{birth} + \text{conjugation} - \text{death} - \text{loss of resistance},$$

where R is the number of antibiotic-resistant bacteria.

Construction of each term: Mass Action Kinetics

Construction of each term: Mass Action Kinetics

The rate of a reaction is proportional to the concentrations of the reacting substances.

Construction of each term: Mass Action Kinetics

The rate of a reaction is proportional to the concentrations of the reacting substances.

$$e.g. \quad A + B \rightarrow C$$

Construction of each term: Mass Action Kinetics

The rate of a reaction is proportional to the concentrations of the reacting substances.

$$e.g. \quad A + B \to C$$

$$\Longrightarrow \quad \frac{dC}{dt} = rAB,$$

Construction of each term: Mass Action Kinetics

The rate of a reaction is proportional to the concentrations of the reacting substances.

$$e.g. \quad A + B \to C$$

$$\implies \frac{dC}{dt} = rAB,$$
$$\frac{dA}{dt} = -rAB,$$
$$\frac{dB}{dt} = -rAB.$$

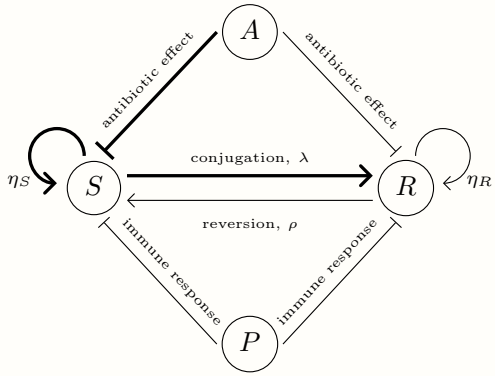
The Model

$$\frac{dA}{dt} = -\alpha A,$$

$$\frac{dP}{dt} =$$

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

$$\frac{dR}{dt} =$$



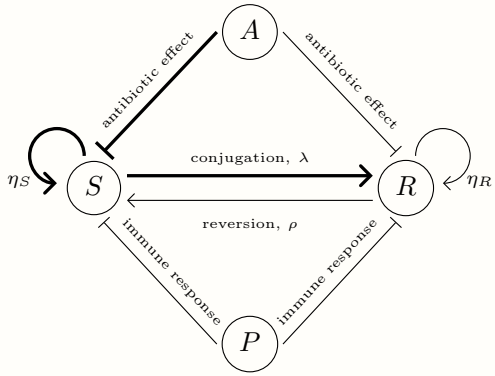
The Model

$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} =$$

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

$$\frac{dR}{dt} =$$



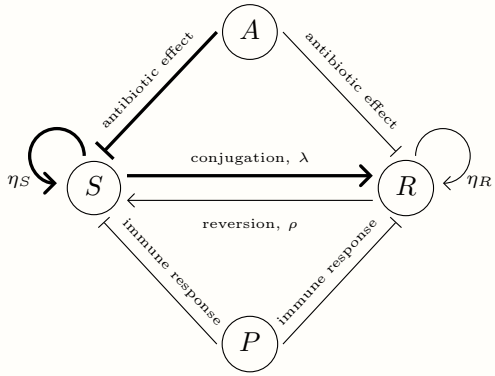
The Model

$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} = \beta(S+R)\left(1 - \frac{P}{P_{\max}}\right)$$

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

$$\frac{dR}{dt} =$$



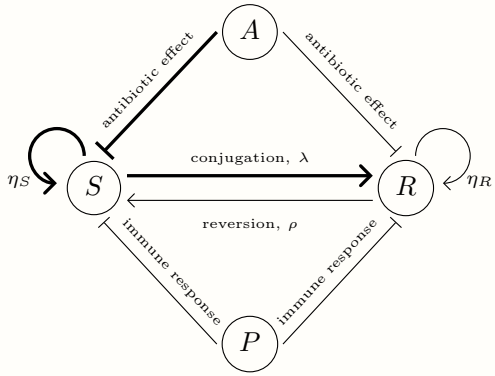
The Model

$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} = \beta(S+R)\left(1-\frac{P}{P_{\max}}\right) - \gamma(S+R)P$$

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

$$\frac{dR}{dt} =$$



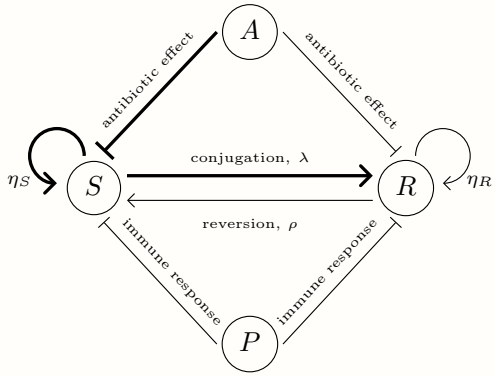
The Model

$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} = \beta(S+R)\left(1-\frac{P}{P_{\max}}\right) - \gamma(S+R)P$$

$$\frac{dS}{dt} = - \gamma SP$$

$$\frac{dR}{dt} = - \gamma RP$$



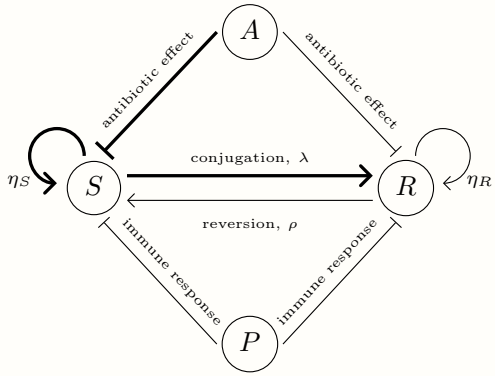
The Model

$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} = \beta(S+R)\left(1-\frac{P}{P_{\max}}\right) - \gamma(S+R)P - \psi P,$$

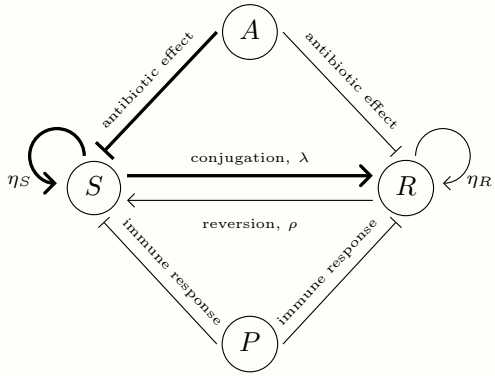
$$\frac{dS}{dt} = - \gamma SP - \psi S,$$

$$\frac{dR}{dt} = - \gamma RP - \psi R,$$



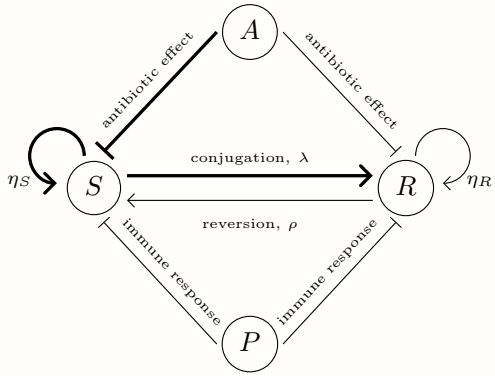
The Model

$$
\begin{aligned}
\frac{dA}{dt} &= 0, \\
\frac{dP}{dt} &= \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P, \\
\frac{dS}{dt} &= \eta_S S\left(1-\frac{S}{S_{max}}\right) - \gamma SP \\
&\quad - \psi S, \\
\frac{dR}{dt} &= - \gamma RP \\
&\quad - \psi R,
\end{aligned}
$$



The Model

$$
\begin{aligned}
\frac{dA}{dt} &= 0, \\
\frac{dP}{dt} &= \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P, \\
\frac{dS}{dt} &= \eta_S S\left(1-\frac{S}{S_{max}}\right) - \frac{\epsilon^S_{max} A}{\theta + A} S - \gamma SP \\
&\quad - \psi S, \\
\frac{dR}{dt} &= - \frac{\epsilon^R_{max} A}{\theta + A} R - \gamma RP \\
&\quad - \psi R,
\end{aligned}
$$



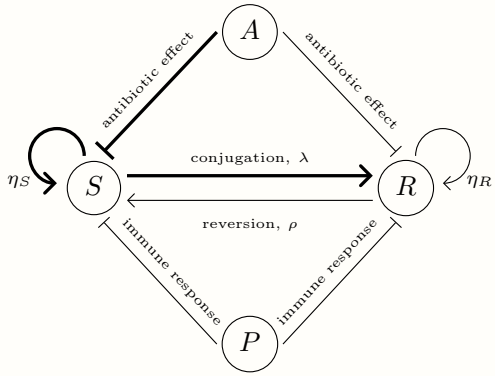
The Model

$$\frac{dA}{dt} = 0,$$

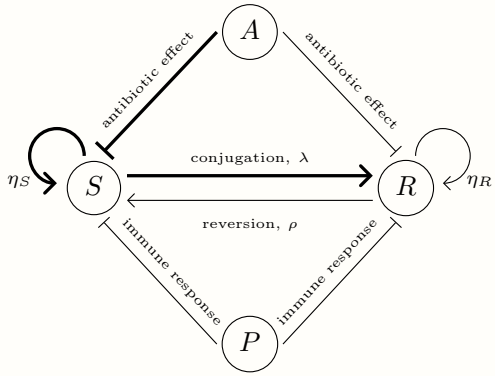
$$\frac{dP}{dt} = \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P,$$

$$\frac{dS}{dt} = \eta_S S\left(1-\frac{S}{S_{max}}\right) - \frac{\epsilon^S_{max} A}{\theta + A}S - \gamma SP - \lambda SR - \psi S,$$

$$\frac{dR}{dt} = - \frac{\epsilon^R_{max} A}{\theta + A}R - \gamma RP + \lambda SR - \psi R,$$



The Model



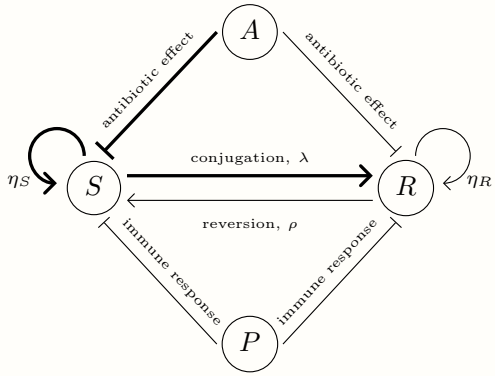
$$\frac{dA}{dt} = 0,$$

$$\frac{dP}{dt} = \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P,$$

$$\frac{dS}{dt} = \eta_S S\left(1-\frac{S}{S_{max}}\right) - \frac{\epsilon^S_{max} A}{\theta + A}S - \gamma SP - \lambda SR + \rho R - \psi S,$$

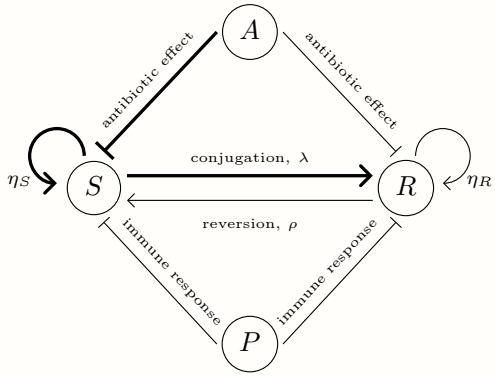
$$\frac{dR}{dt} = - \frac{\epsilon^R_{max} A}{\theta + A}R - \gamma RP + \lambda SR - \rho R - \psi R,$$

The Model



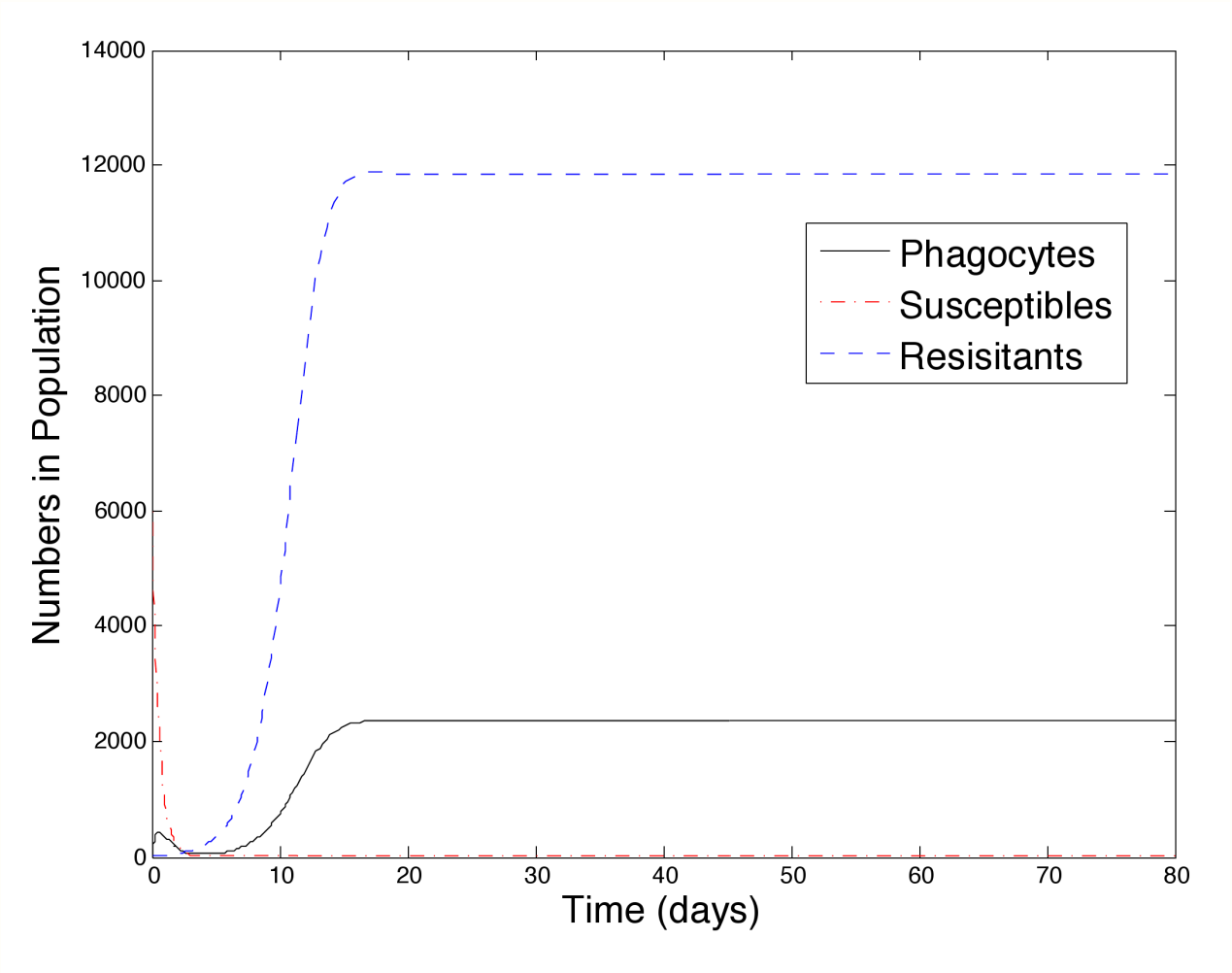
$$
\begin{aligned}
\frac{dA}{dt} &= 0, \\
\frac{dP}{dt} &= \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P, \\
\frac{dS}{dt} &= \eta_S S\left(1-\frac{S}{S_{max}}\right) - \frac{\epsilon^S_{max} A}{\theta + A}S - \gamma SP - \lambda SR + \rho R \\
&\quad - \psi S, \\
\frac{dR}{dt} &= c\eta_S R\left(1-\frac{R}{K}\right) - \frac{\epsilon^R_{max} A}{\theta + A}R - \gamma RP + \lambda SR \\
&\quad - \rho R - \psi R,
\end{aligned}
$$

The Model

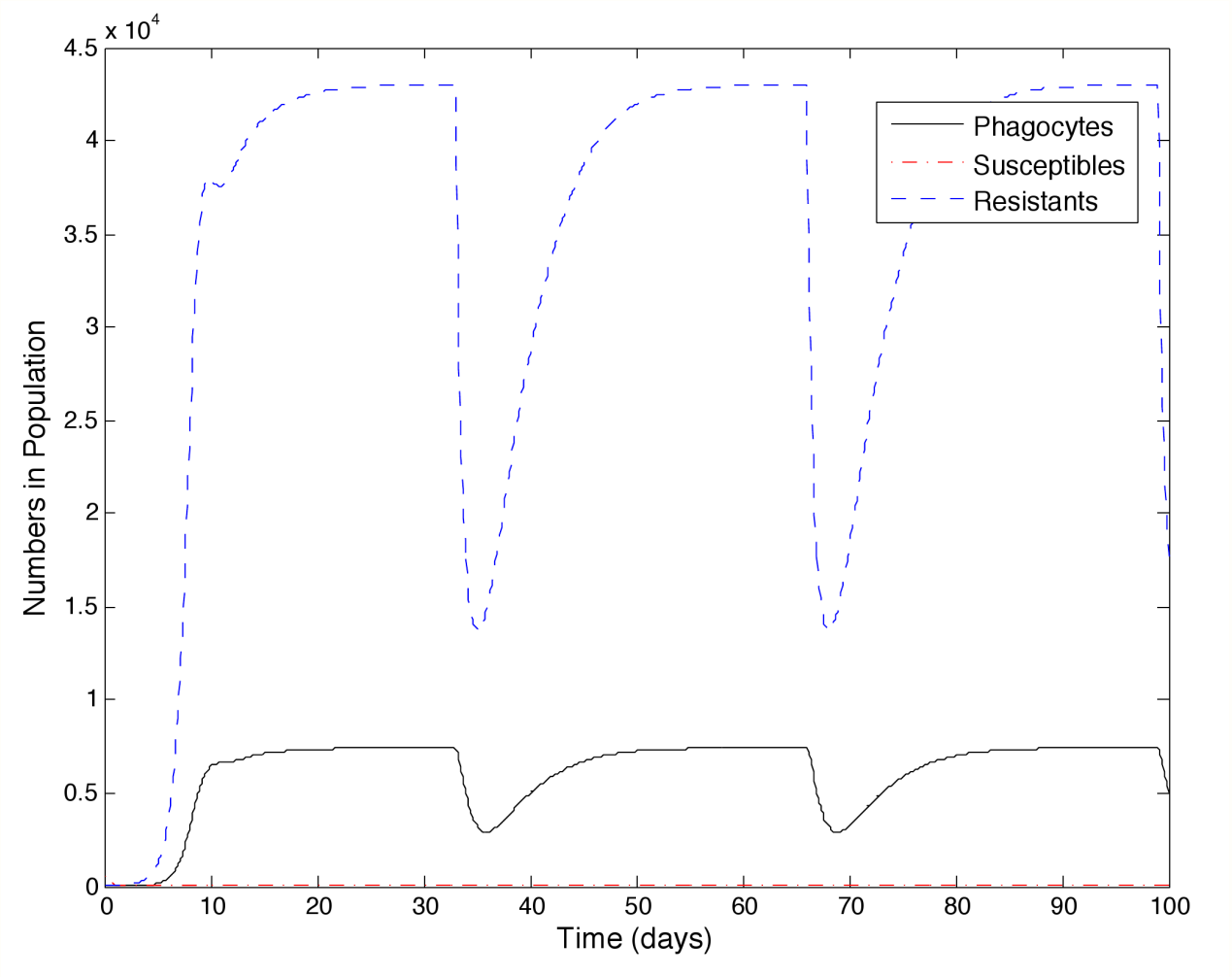


$$
\begin{aligned}
\frac{dA}{dt} &= 0, \\
\frac{dP}{dt} &= \beta(S+R)\left(1-\frac{P}{P_{max}}\right) - \gamma(S+R)P - \psi P, \\
\frac{dS}{dt} &= \eta_S S\left(1-\frac{S}{S_{max}}\right) - \frac{\epsilon^S_{max} A}{\theta + A}S - \gamma SP - \lambda SR + \rho R \\
&\quad - \psi S, \\
\frac{dR}{dt} &= c\eta_S R\left(1-\frac{R}{K}\right) - \frac{\epsilon^R_{max} A}{\theta + A}R - \gamma RP + \lambda SR \\
&\quad - \rho R - \psi R,
\end{aligned}
$$

Model Simulation - constant antibiotic



Model Simulation - antibiotic dosing



Anti-virulence drugs

Alternatives to antibiotics

- Conventional antibiotics act on bacterial growth, imposing selective pressure on the bacteria, leading to the emergence of resistance.

Alternatives to antibiotics

- Conventional antibiotics act on bacterial growth, imposing selective pressure on the bacteria, leading to the emergence of resistance.
- How do we get round this?

Targeting virulence

- Prevent the bacteria from being able to cause harm in the host until cleared via natural defences:

Targeting virulence

- Prevent the bacteria from being able to cause harm in the host until cleared via natural defences:
  - Flushed out of the system
  - Cleared by the host's immune response

Targeting virulence

- Prevent the bacteria from being able to cause harm in the host until cleared via natural defences:
  - Flushed out of the system
  - Cleared by the host's immune response
- In theory this should exert little to no selective pressure on the organism.

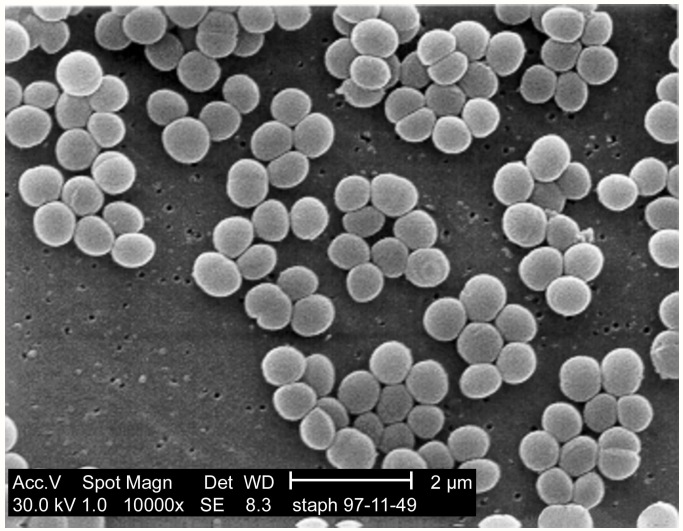
Targeting virulence

- Prevent the bacteria from being able to cause harm in the host until cleared via natural defences:
  - Flushed out of the system
  - Cleared by the host's immune response
- In theory this should exert little to no selective pressure on the organism.
- Possible mechanisms to target:
  - cell adhesion
  - toxin delivery
  - virulence gene regulation
  - toxin function

Staphylococcus aureus
(MRSA)

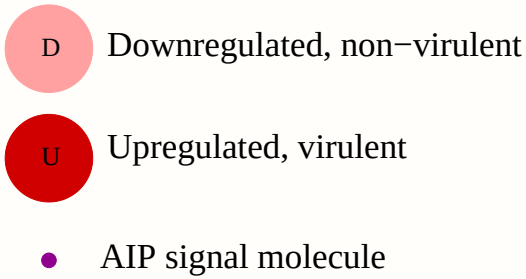
Staphylococcus aureus

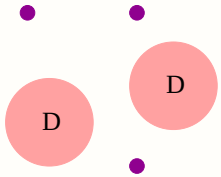
- Methicillin Resistant *Staphylococcus Aureus* (antibiotic resistant)
- skin infections, pneumonia, sepsis, toxic shock syndrome...
- new therapies needed – one target is the quorum sensing system

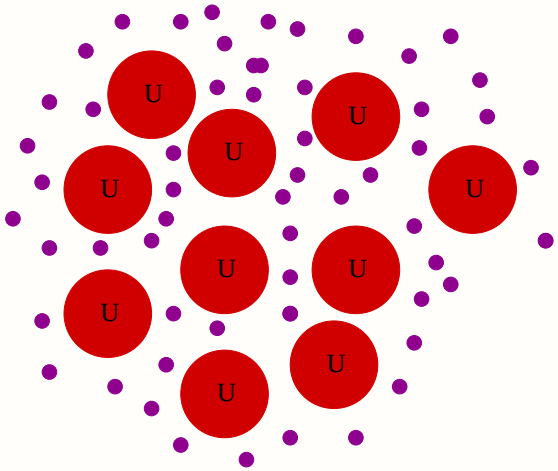


Quorum sensing

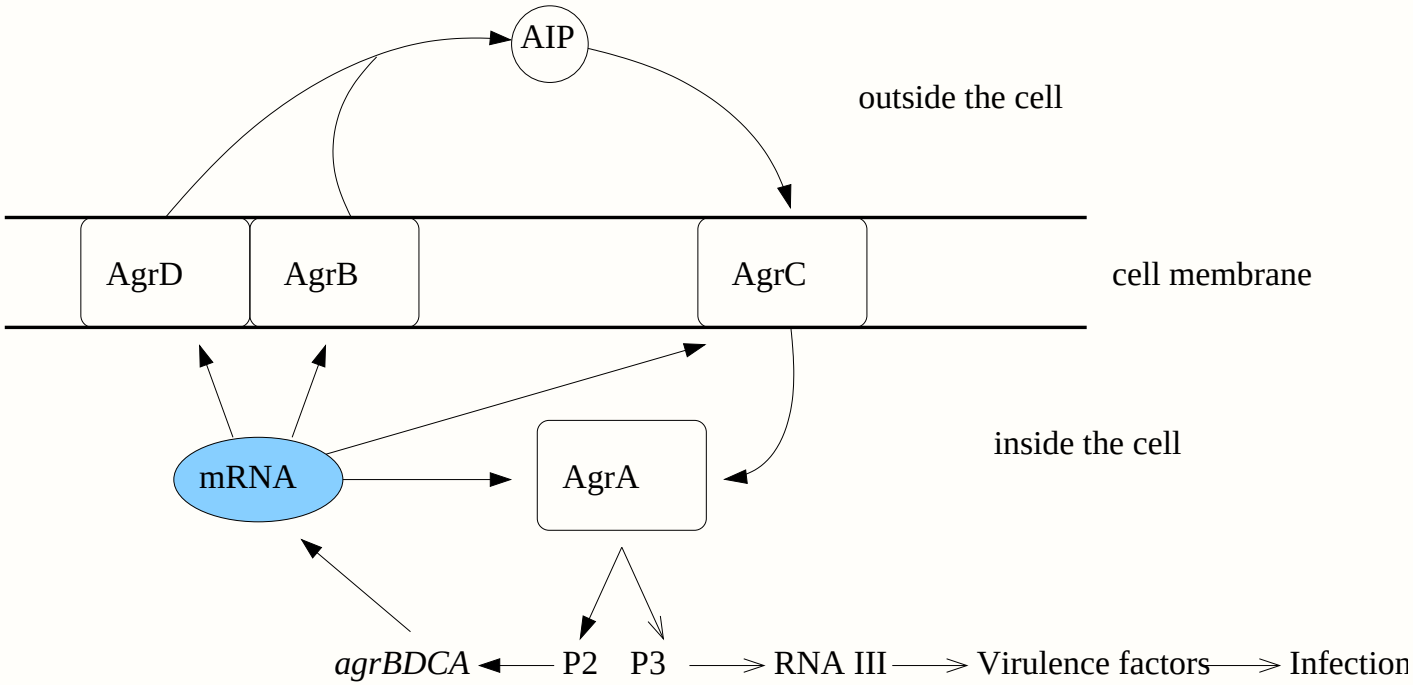
- cell-cell signalling mechanism
- population density dependent behaviour
- used in pathogenesis, biofilm formation sporulation, ...



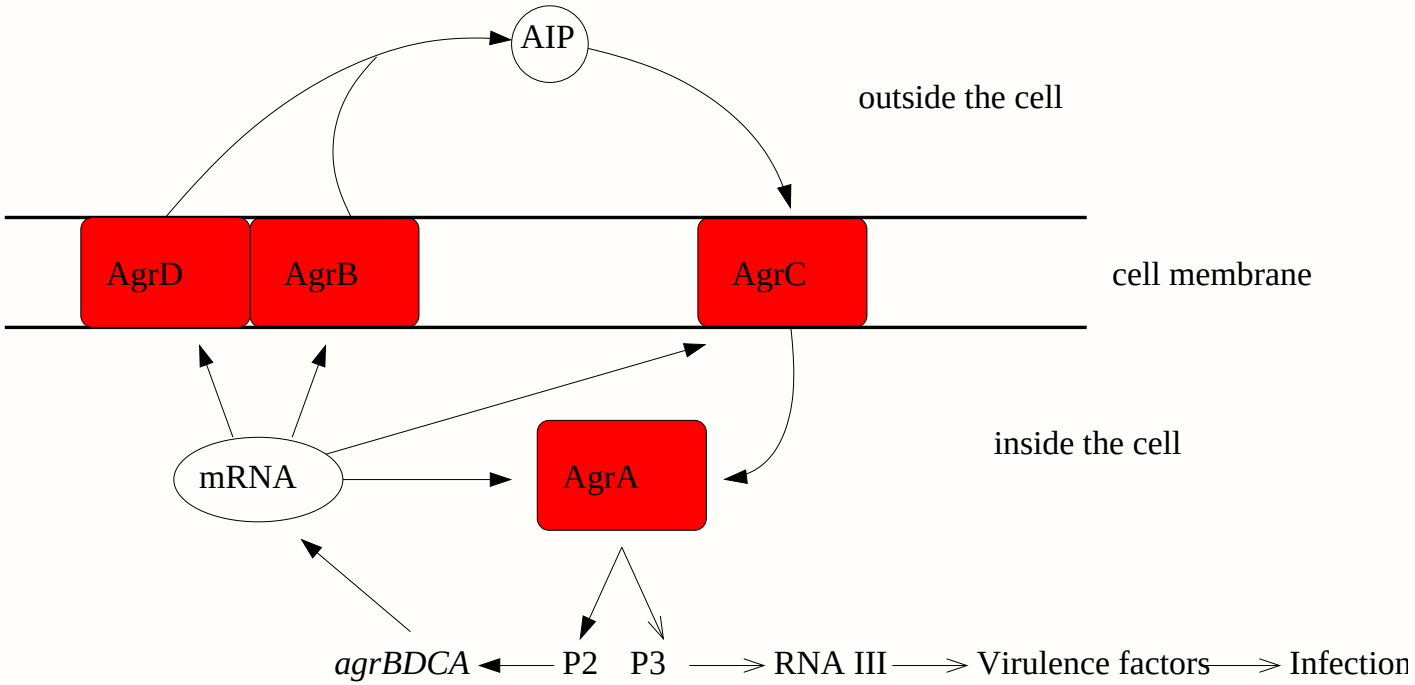




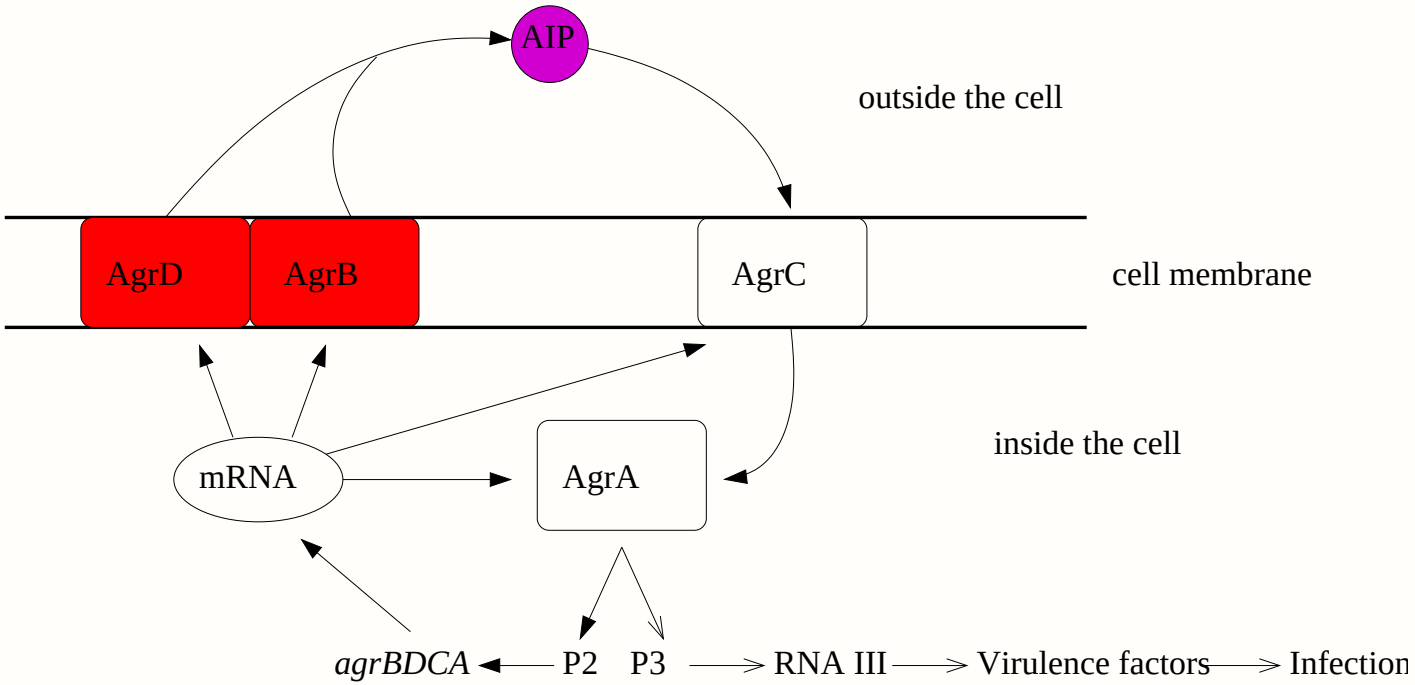
Quorum sensing in *S. aureus*



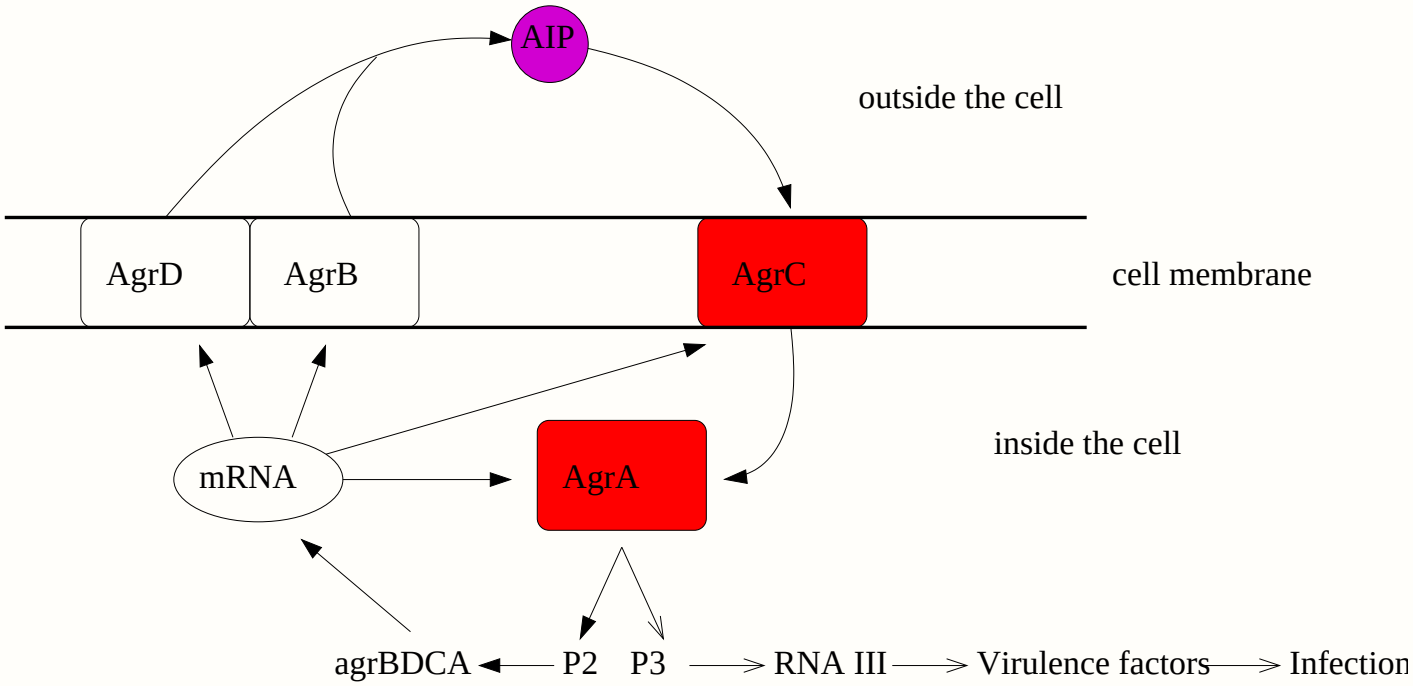
Quorum sensing in *S. aureus*



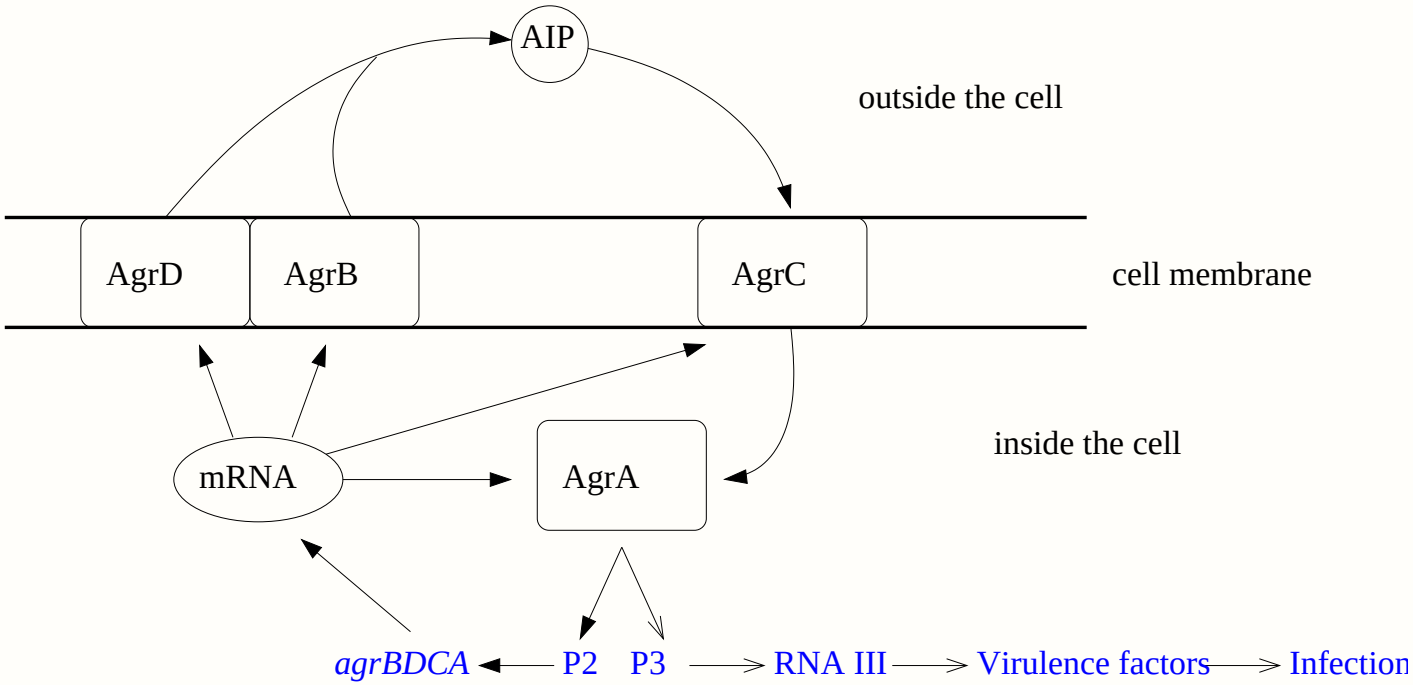
Quorum sensing in *S. aureus*



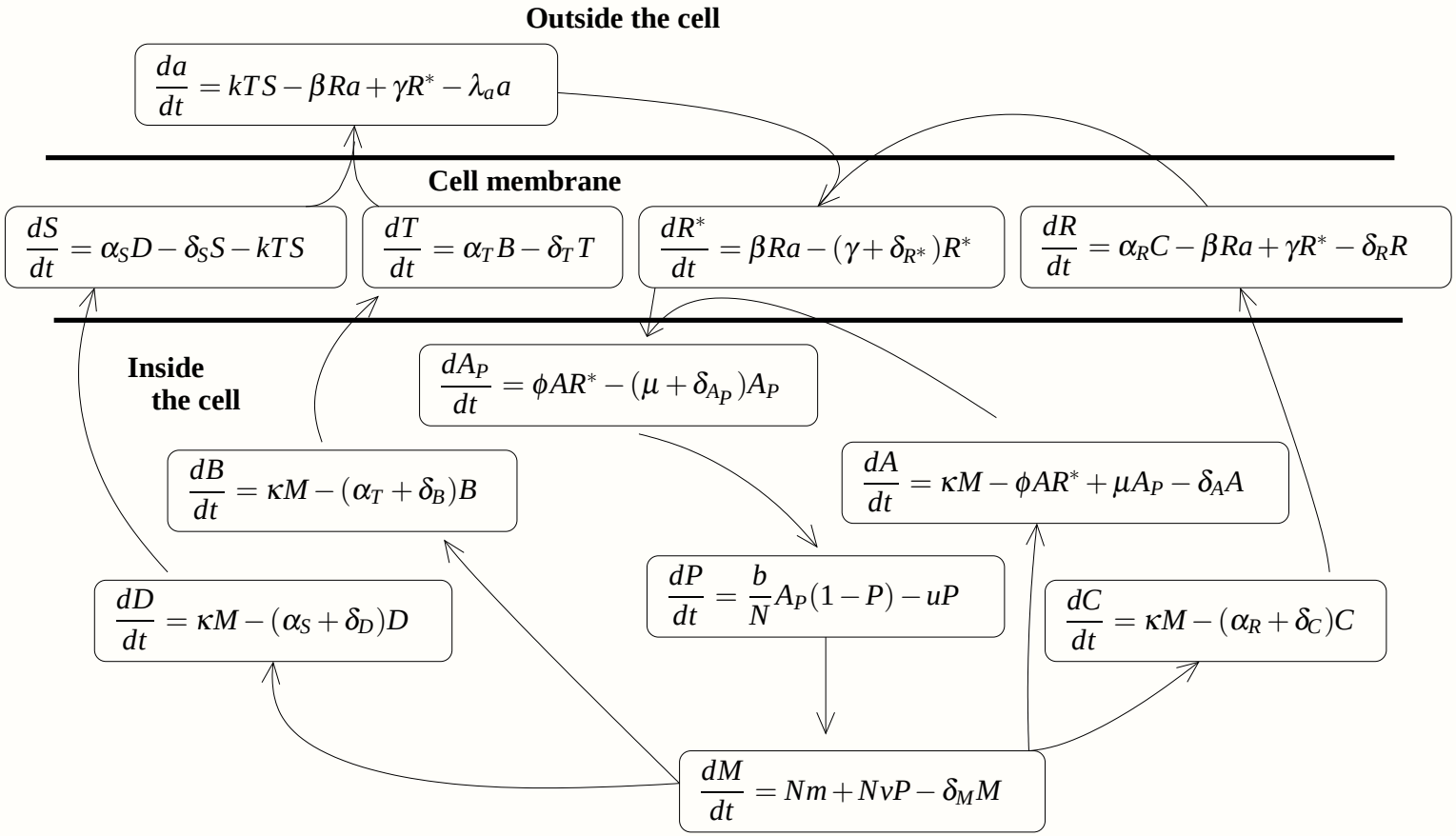
Quorum sensing in *S. aureus*

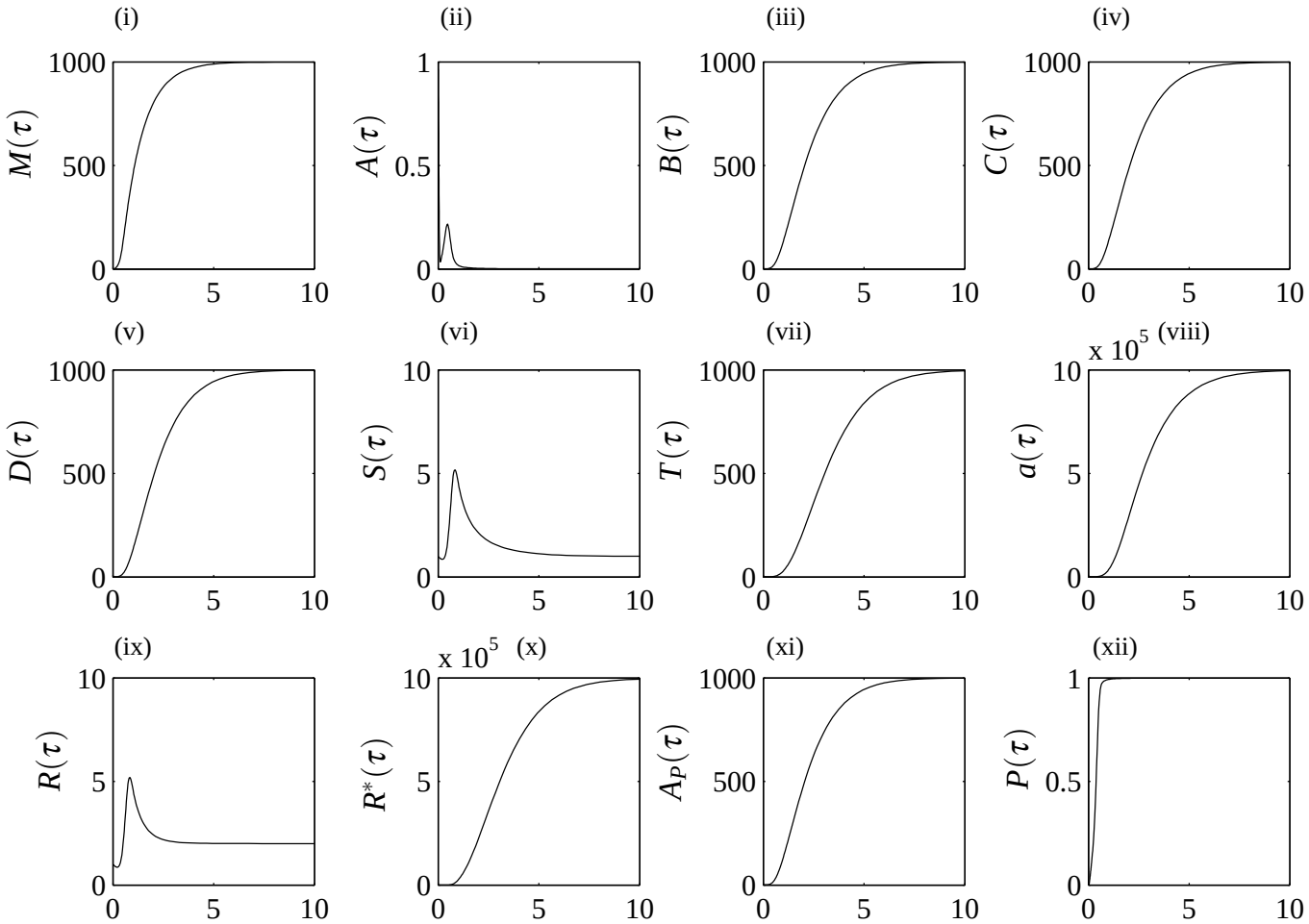


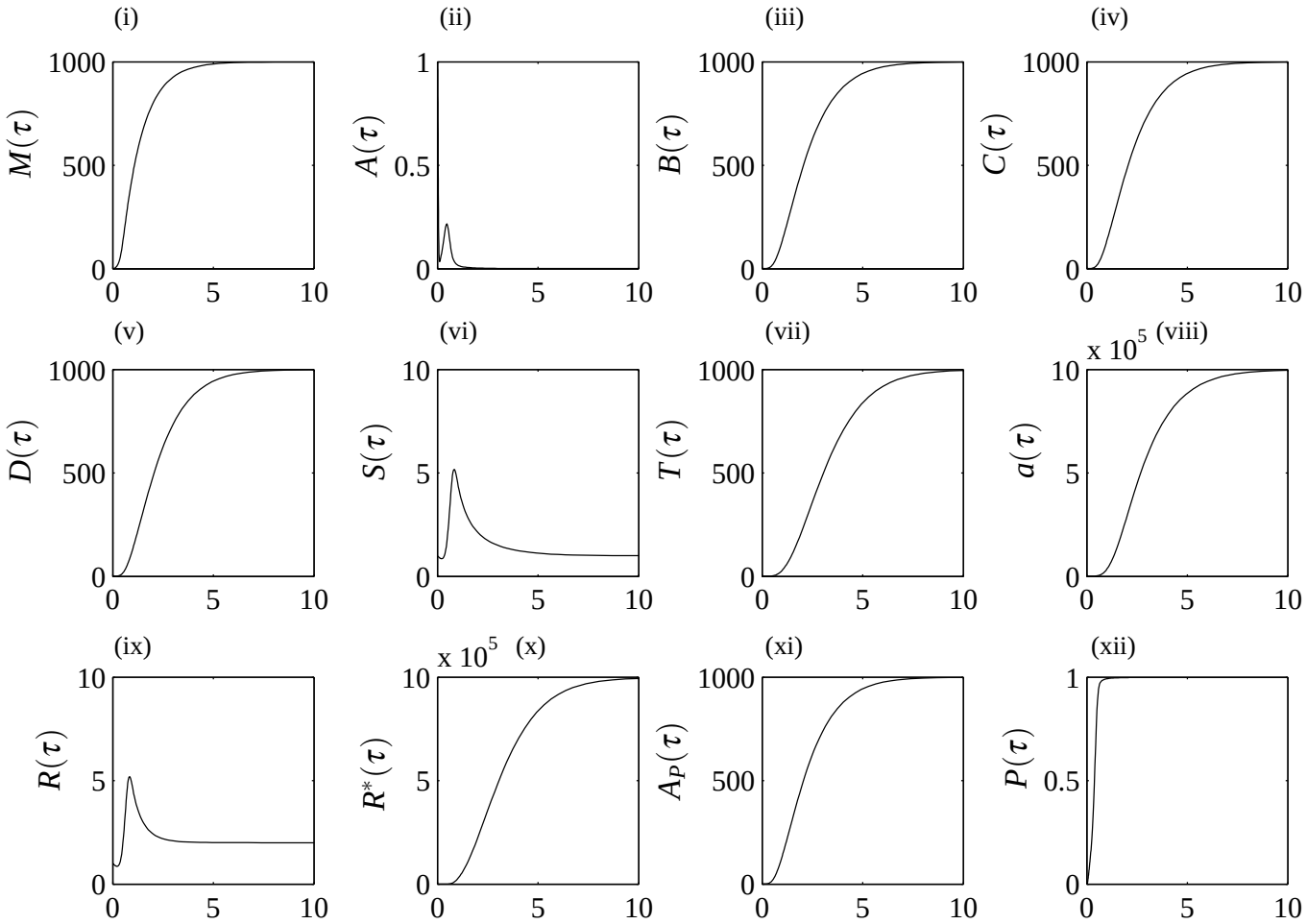
Quorum sensing in *S. aureus*



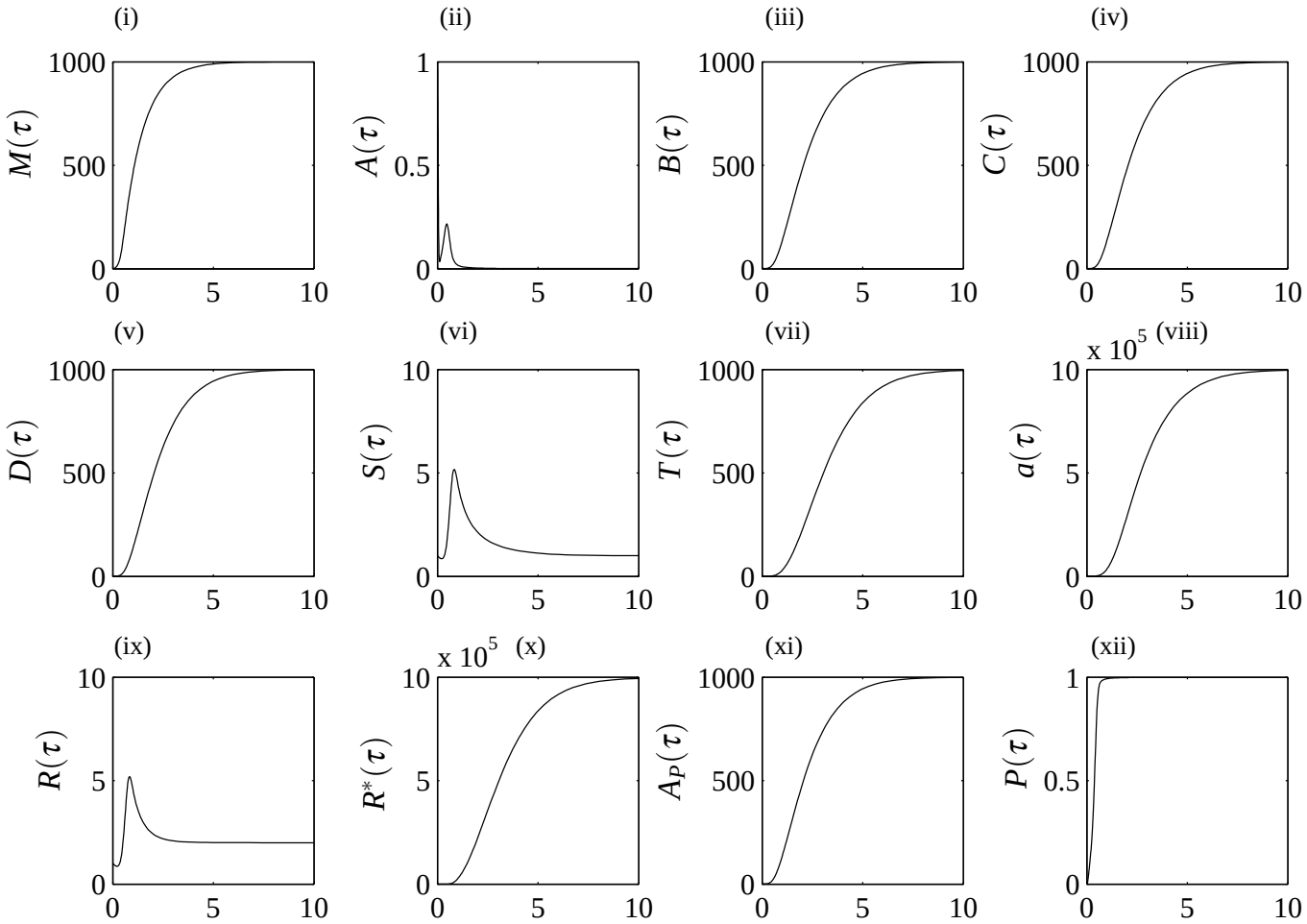
Mathematical model




(i)
$M(\tau)$
1000
500
0
0
5
10
(ii)
$A(\tau)$
1
0.5
0
0
5
10
(iii)
$B(\tau)$
1000
500
0
0
5
10
(iv)
$C(\tau)$
1000
500
0
0
5
10
(v)
$D(\tau)$
1000
500
0
0
5
10
(vi)
$S(\tau)$
10
5
0
0
5
10
(vii)
$T(\tau)$
1000
500
0
0
5
10
(viii)
x 10^5
$a(\tau)$
10
5
0
0
5
10
(ix)
$R(\tau)$
10
5
0
0
5
10
(x)
x 10^5
$R^*(\tau)$
10
5
0
0
5
10
(xi)
$A_P(\tau)$
1000
500
0
0
5
10
(xii)
$P(\tau)$
1
0.5
0
0
5
10



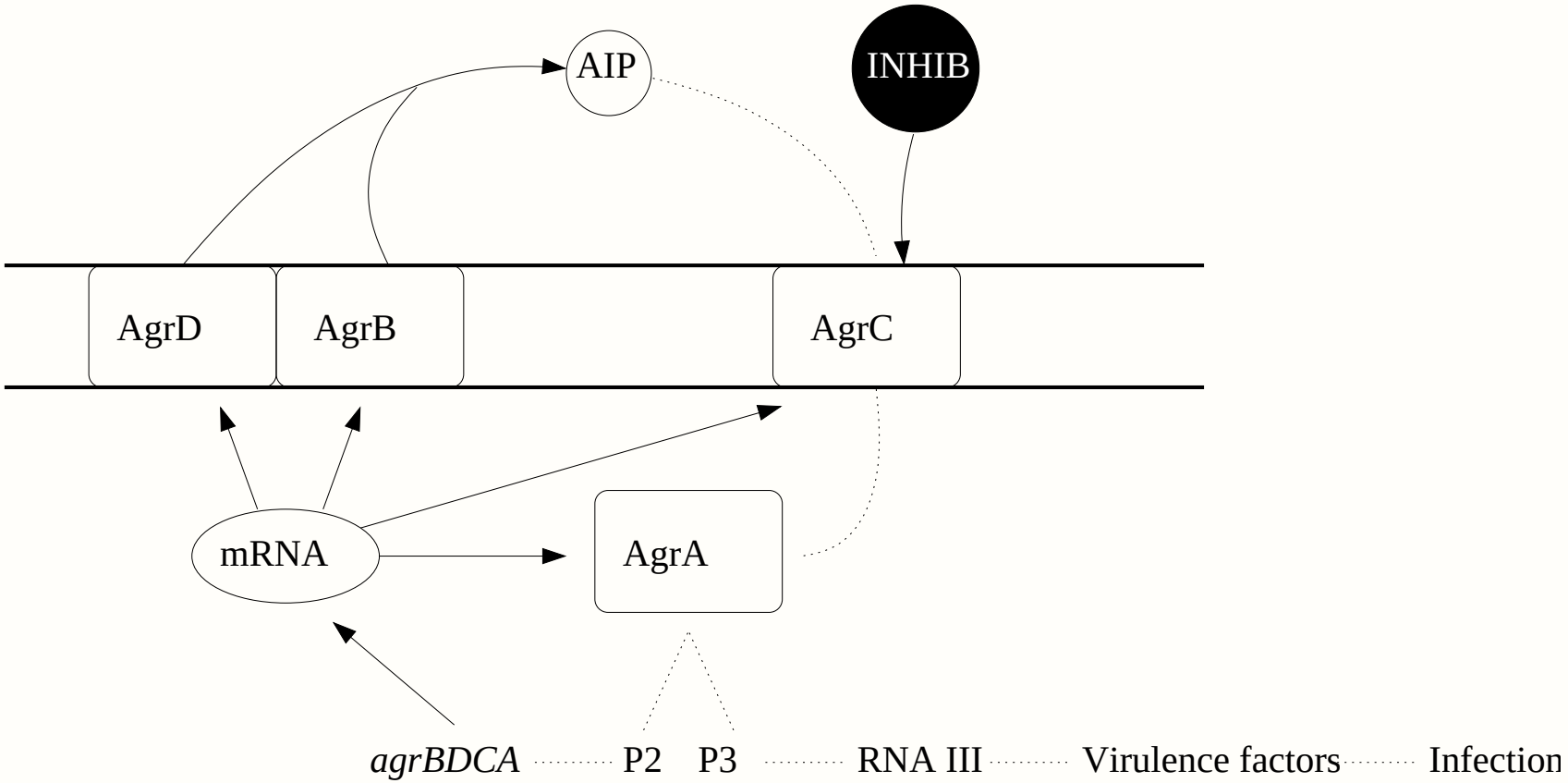
A population of cells will quickly become up-regulated (i.e. virulent)



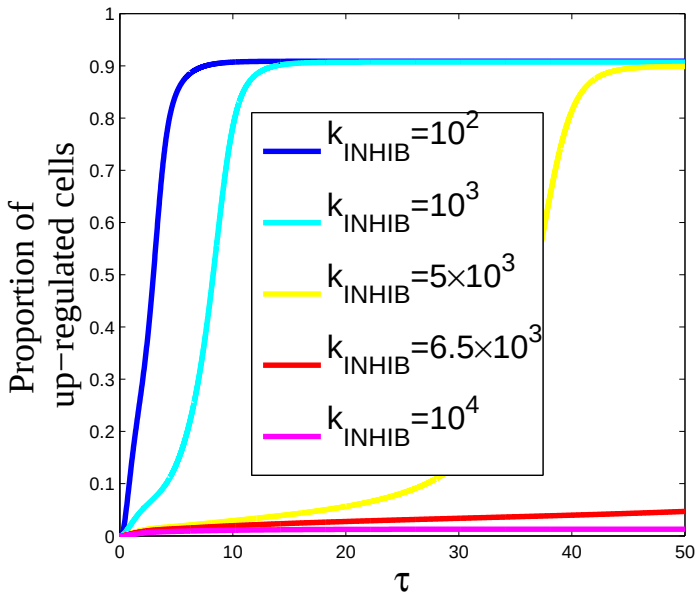
A population of cells will quickly become up-regulated (i.e. virulent)

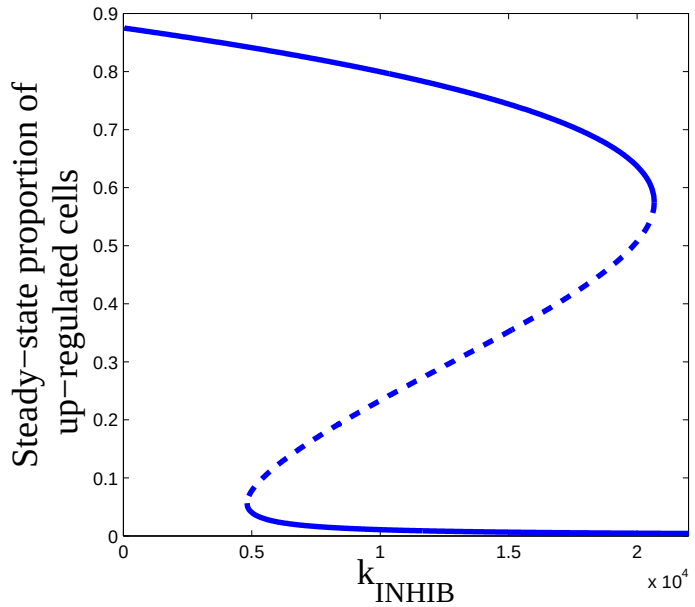
How can we prevent this?

Synthetic inhibition

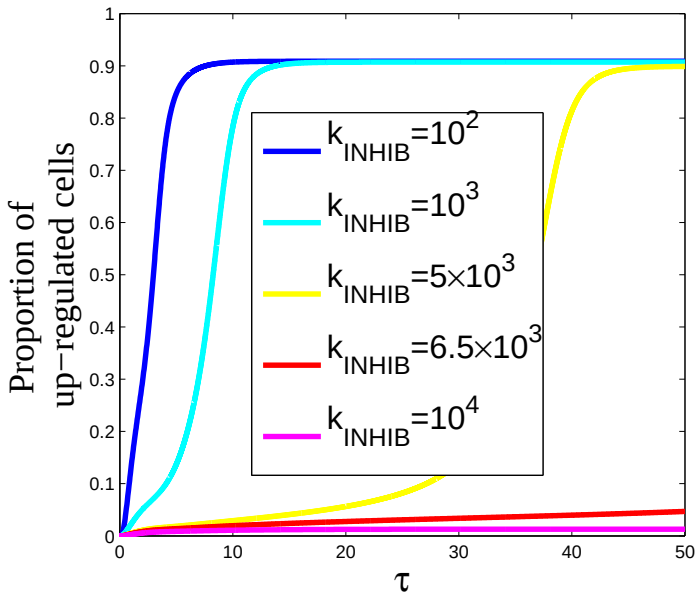


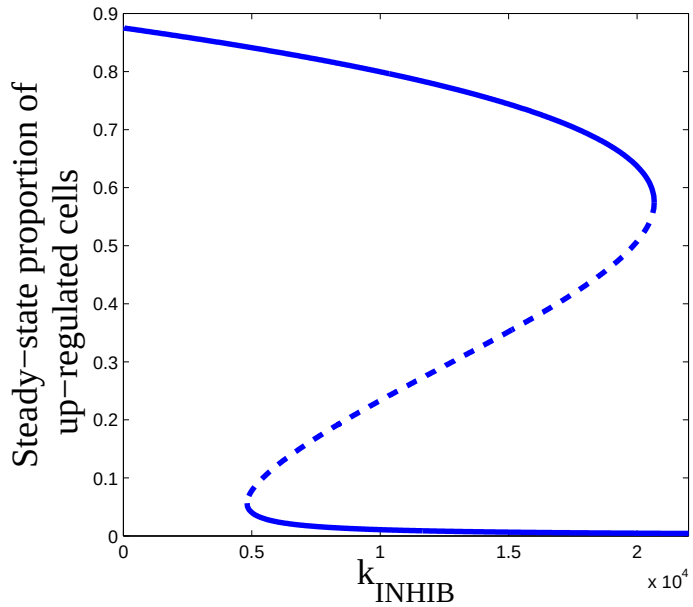
Synthetic inhibition - numerical solutions





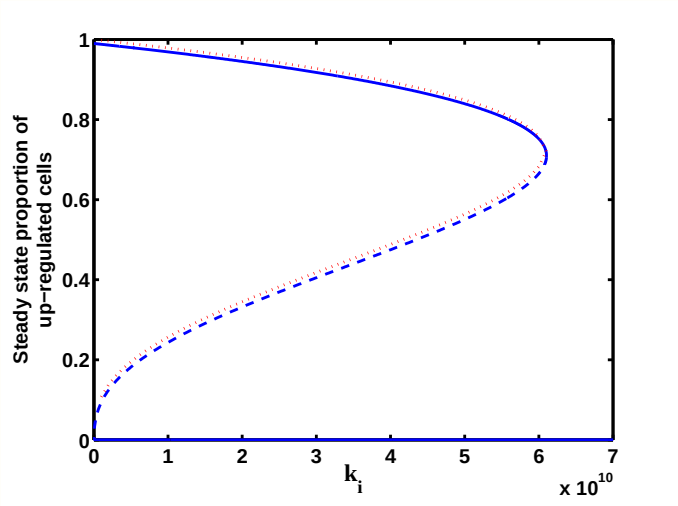
Synthetic inhibition - numerical solutions





For sufficiently large dosage, synthetic inhibitor therapy can successfully downregulate the cells, but the outcome may be dependent upon the initial conditions.

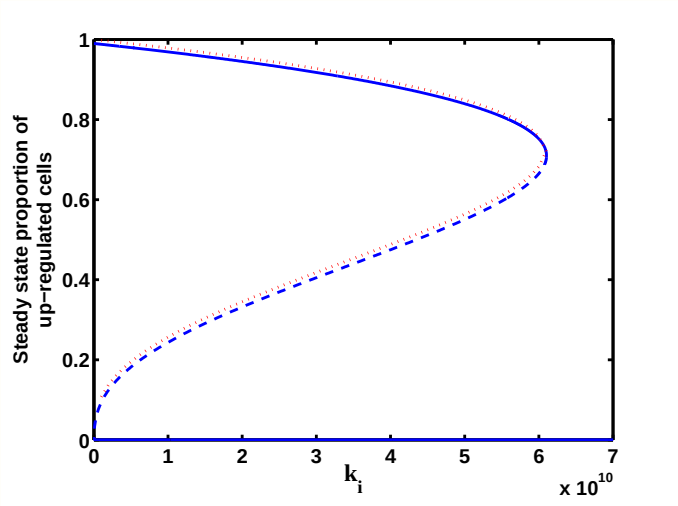
How can we improve this?



What are the key properties of a successful inhibitor?

$k_{\text{crit}} =$

How can we improve this?

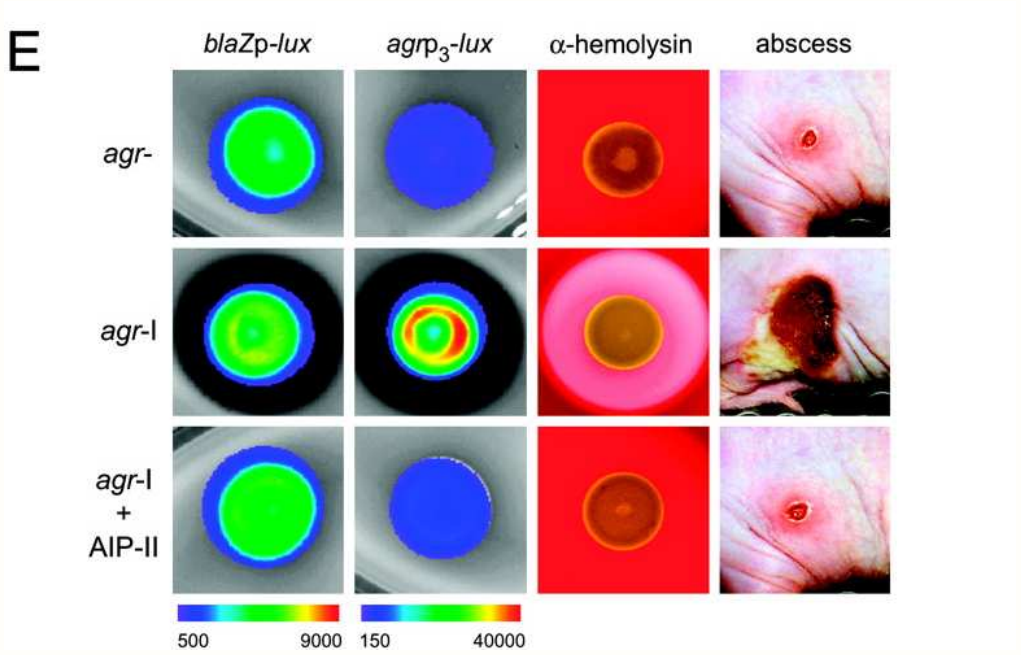


What are the key properties of a successful inhibitor?

Minimise the rate of separation.

$$k_{\text{crit}} = \frac{(\lambda+\gamma_{\mathbf{i}})\lambda_i\gamma_{\mathbf{i}}\hat{k}_a\hat{v}^4(\bar{P}_U^{\dagger 3} - \bar{P}_U^{\dagger 4})}{(\lambda+\gamma)\lambda_a u(\hat{k}_S\hat{v}\bar{P}_U^{\dagger} + \lambda)}$$

Consistent with experimental results



From: J.S. Wright *et al.* (2005) PNAS 102: 1691-1696

MRSA: a summary

- MRSA controls production of its virulence factors in accordance with its population size (quorum sensing)

MRSA: a summary

- MRSA controls production of its virulence factors in accordance with its population size (quorum sensing)
- We can block quorum sensing to reduce virulence factor production

MRSA: a summary

- MRSA controls production of its virulence factors in accordance with its population size (quorum sensing)
- We can block quorum sensing to reduce virulence factor production
- BUT this may only be successful if the infection is caught sufficiently early

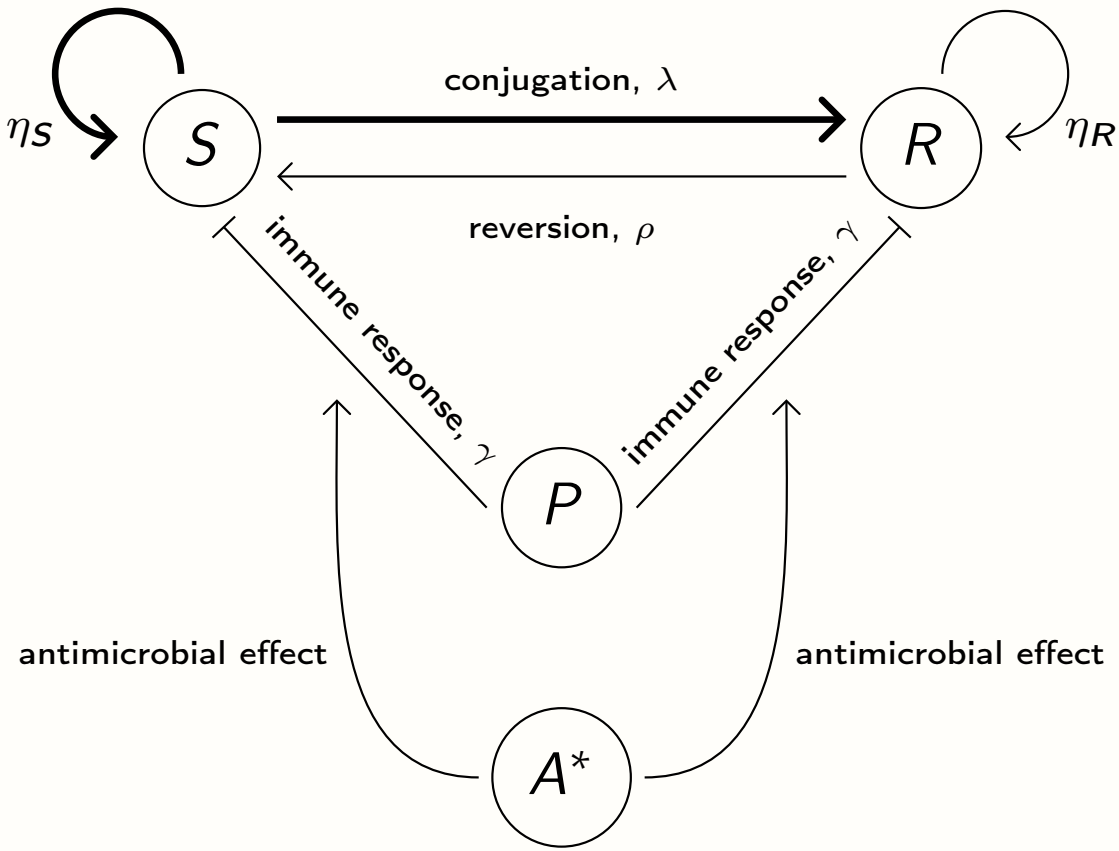
MRSA: a summary

- MRSA controls production of its virulence factors in accordance with its population size (quorum sensing)
- We can block quorum sensing to reduce virulence factor production
- BUT this may only be successful if the infection is caught sufficiently early

Will this help combat antibiotic resistance?

A general model of antibiotics and anti-virulence drugs

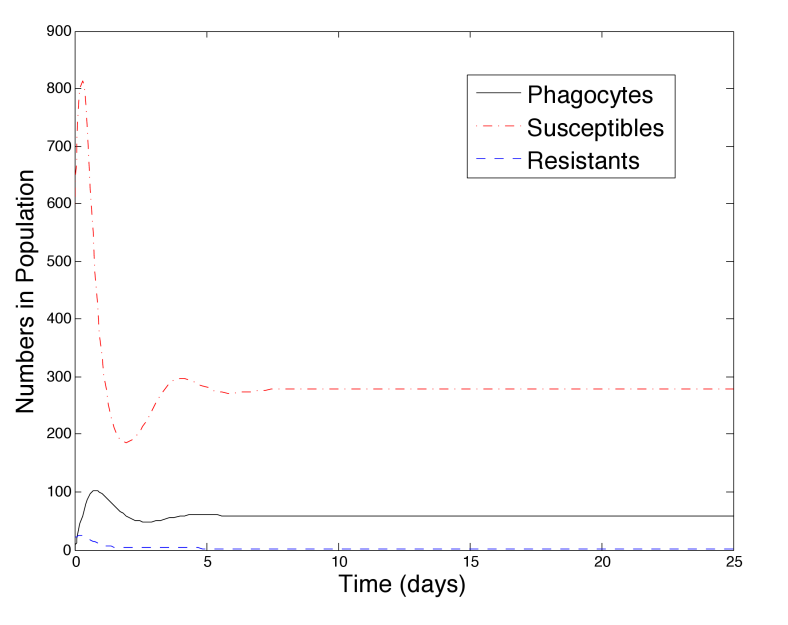
Anti-virulence drugs



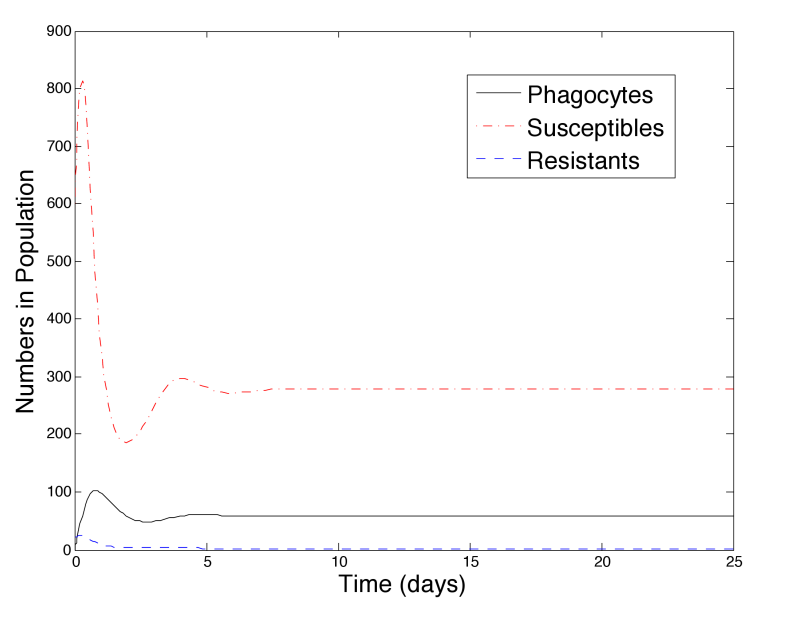
A mathematical model for anti-virulence drugs

$$
\begin{aligned}
\frac{\mathrm{d}A^*}{\mathrm{d}t} &= 0, \\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \beta\left(S+R\right)\left(1-\frac{P}{P_{\max}}\right) - \delta_{SR}\left(S+R\right)P - \delta_P P, \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= \eta_S S\left(1-\frac{S}{K}\right) - \left(\gamma+\frac{\gamma_{\max}{A^*}^h}{{\gamma_{50}}^h+{A^*}^h}\right)PS - \lambda SR + \rho R \\
&\quad - \psi S, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= (1-c)\,\eta_S R\left(1-\frac{R}{K}\right) - \left(\gamma+\frac{\gamma_{\max}{A^*}^h}{{\gamma_{50}}^h+{A^*}^h}\right)PR + \lambda SR \\
&\quad - \rho R - \psi R.
\end{aligned}
$$

Anti-virulence drugs simulation

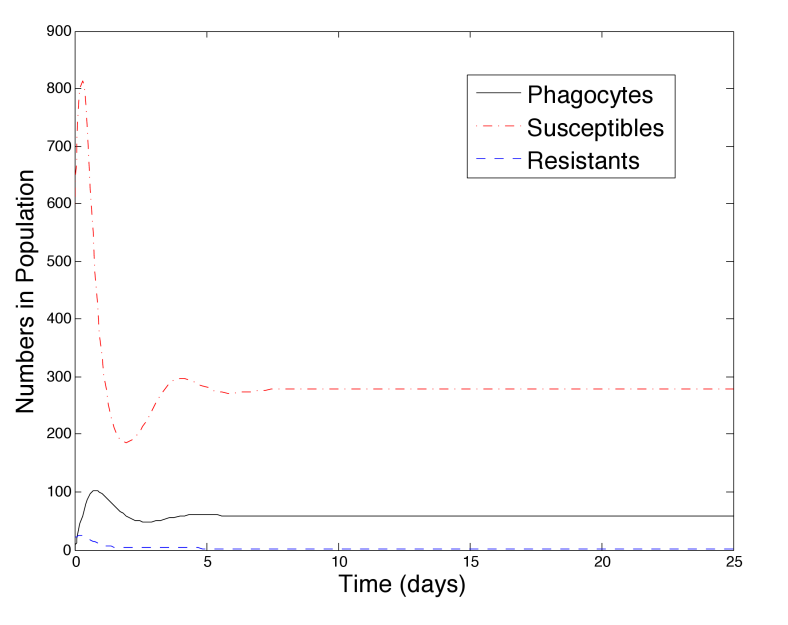


Anti-virulence drugs simulation



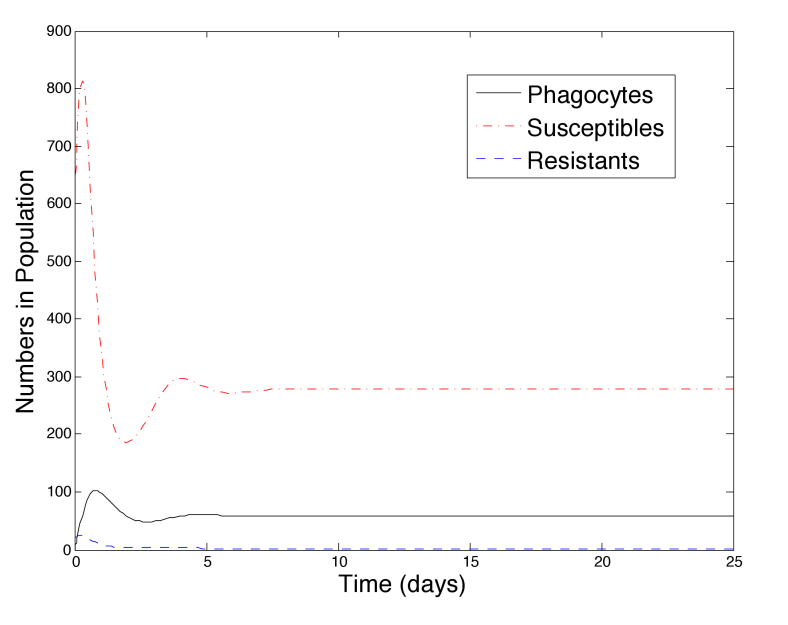
- Resistant bacteria eliminated.

Anti-virulence drugs simulation



- Resistant bacteria eliminated.
- Small level of susceptible bacteria remain at infection site.

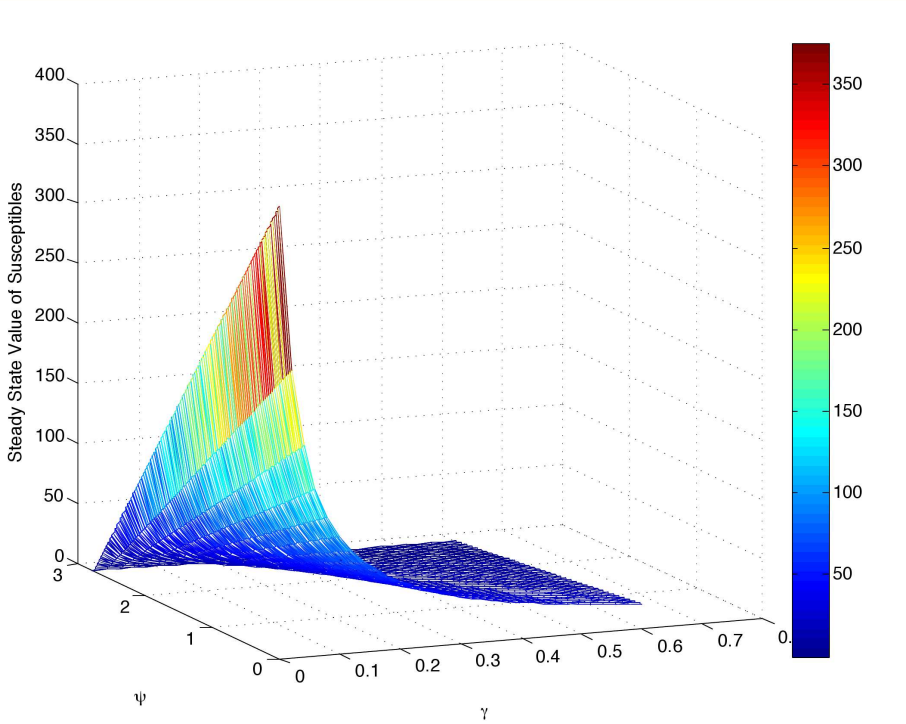
Anti-virulence drugs simulation



- Resistant bacteria eliminated.
- Small level of susceptible bacteria remain at infection site.

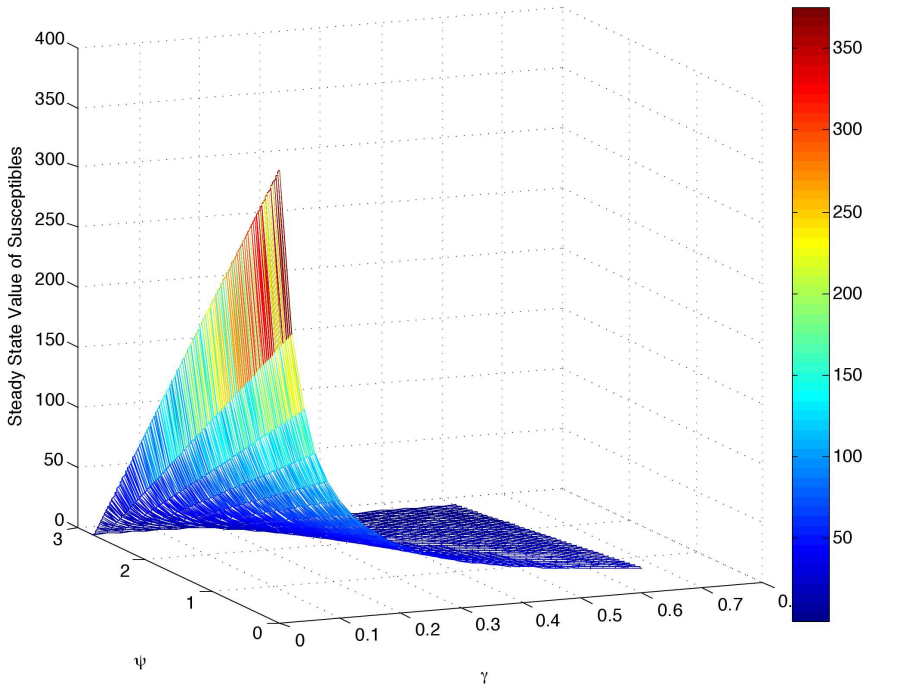
Why?

Patient-specific parameters



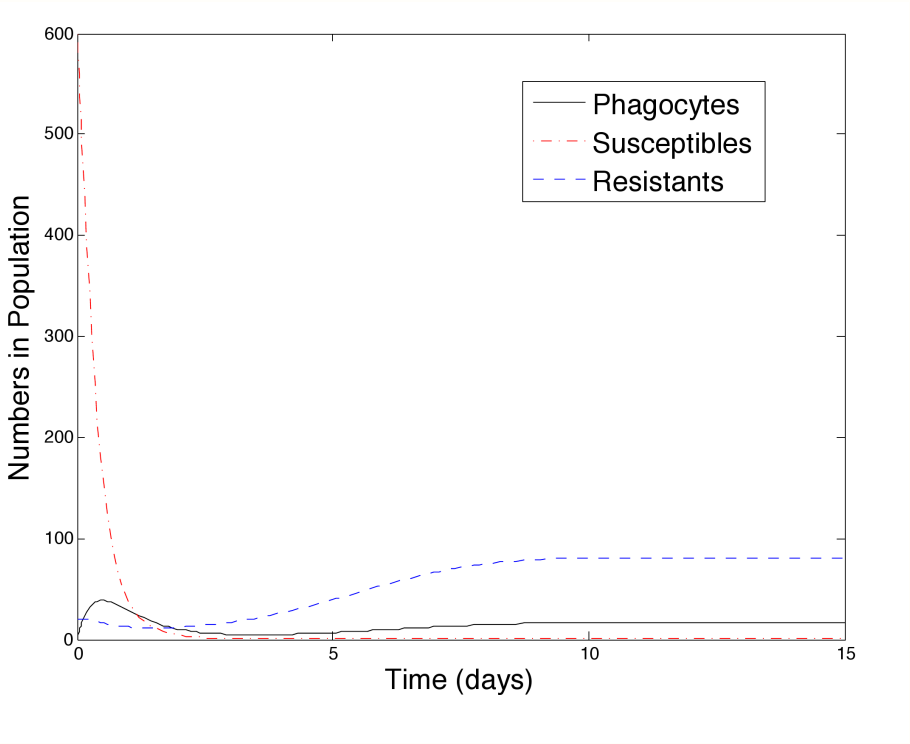
- ψ, general clearance rate
- γ, baseline immune response
- With strong host clearance mechanisms treatment can be completely effective.

Patient-specific parameters

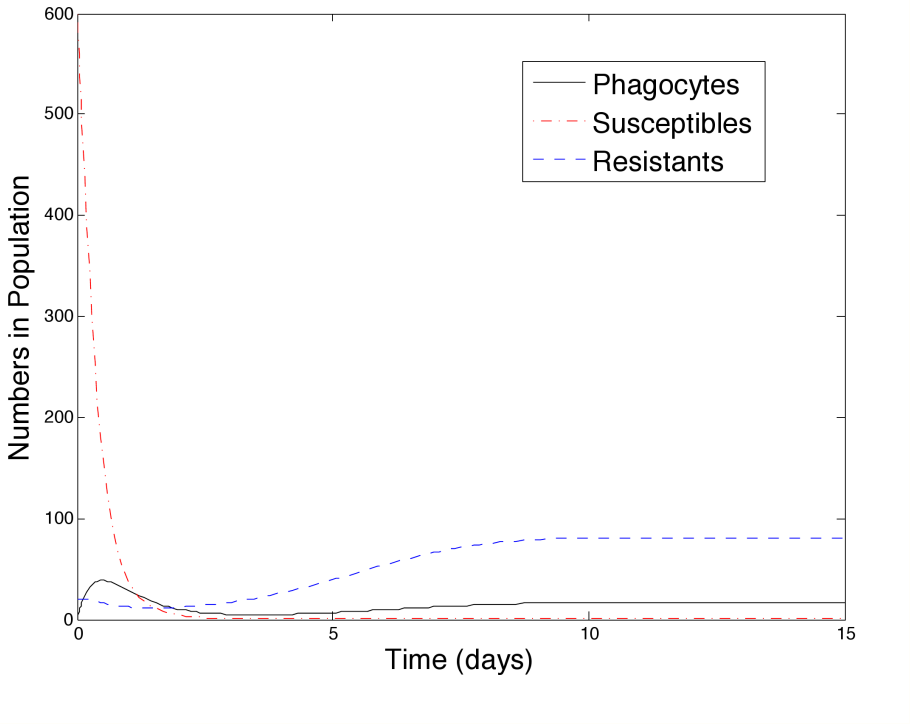


- ψ, general clearance rate
- γ, baseline immune response
- With strong host clearance mechanisms treatment can be completely effective.
- Not suitable therefore for already hospitalised patients?

Combining Antibiotics and Anti-Virulence Drugs

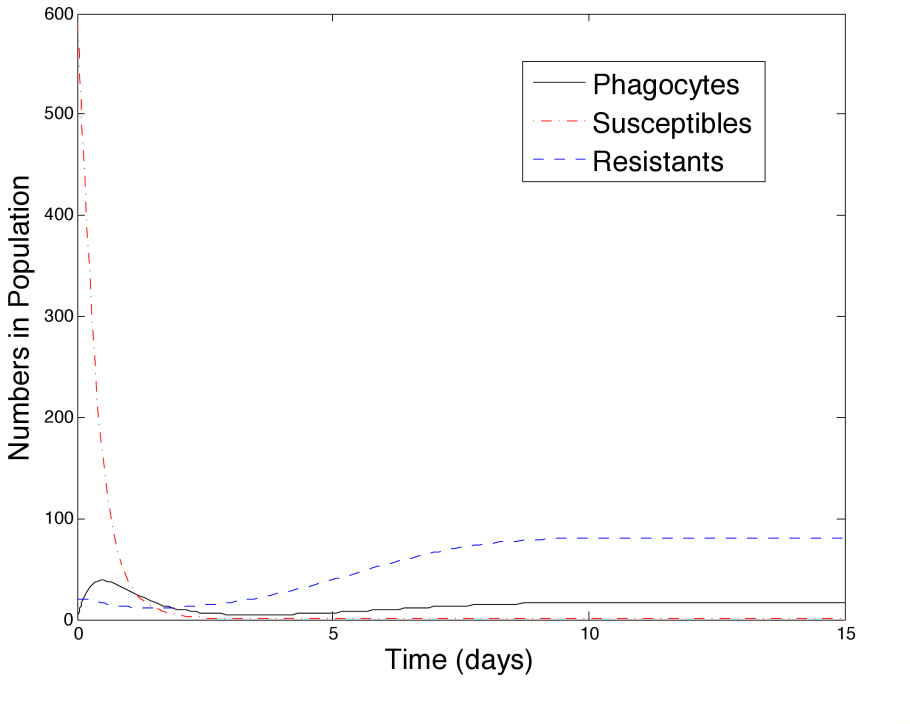


Combining Antibiotics and Anti-Virulence Drugs



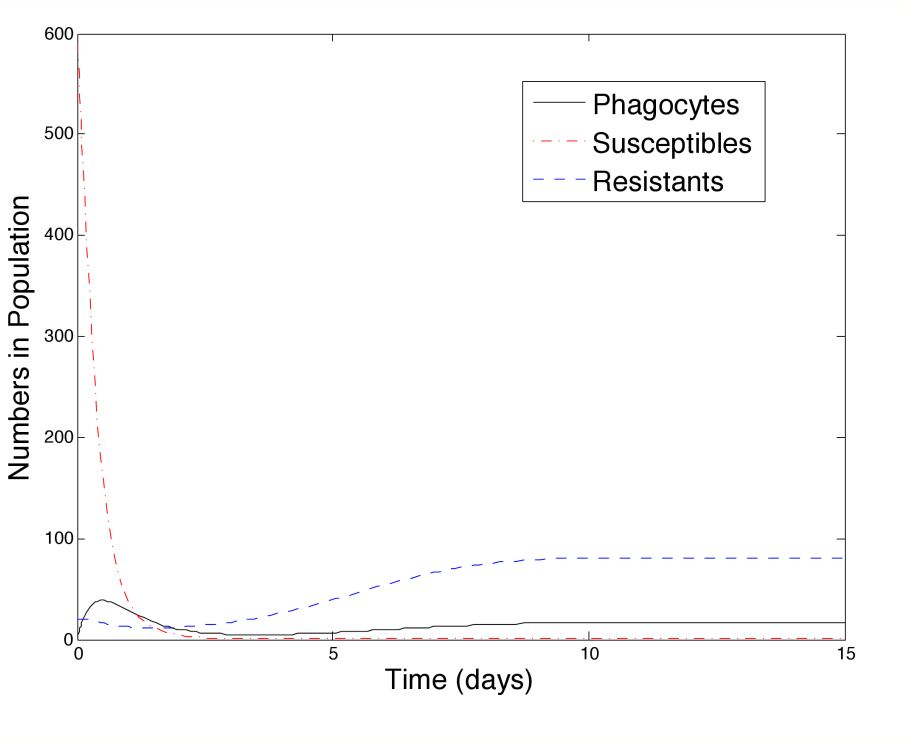
- Both drugs administered simultaneously

Combining Antibiotics and Anti-Virulence Drugs



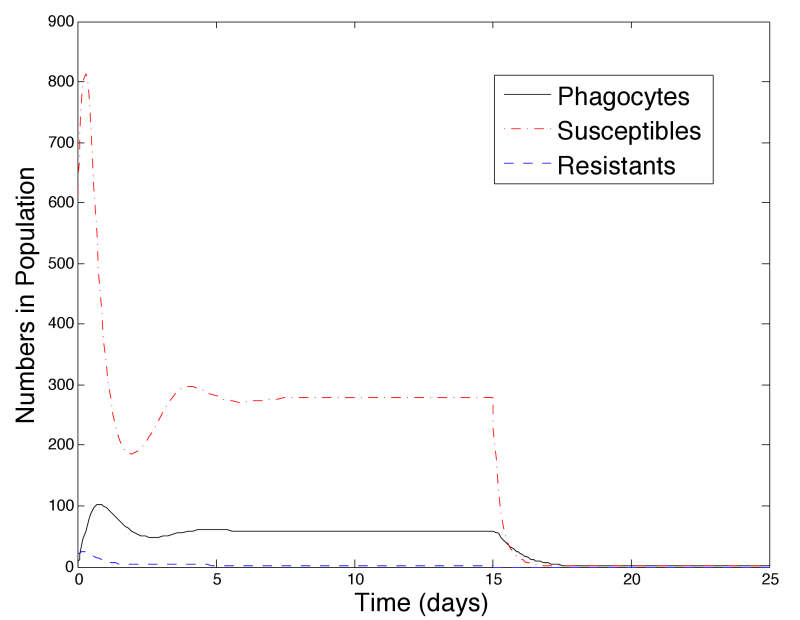
- Both drugs administered simultaneously
- Susceptible bacteria cleared

Combining Antibiotics and Anti-Virulence Drugs



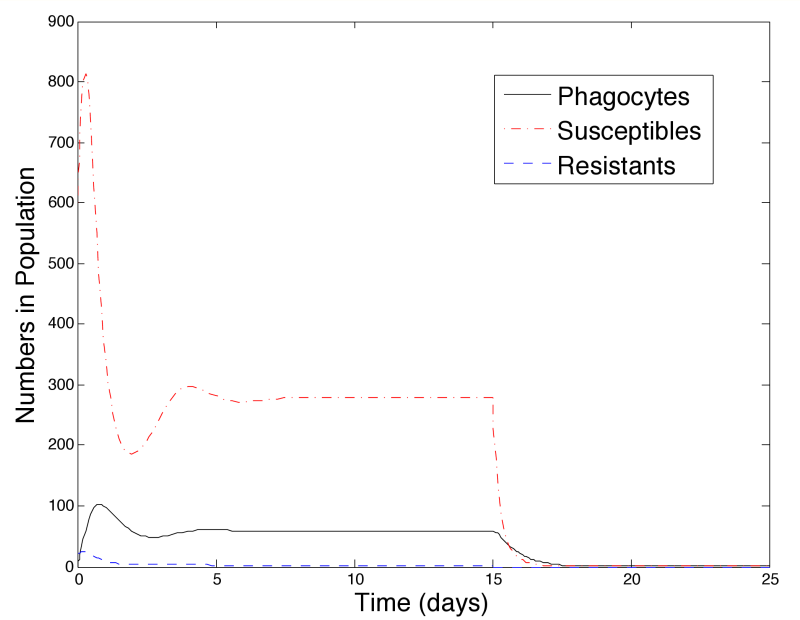
- Both drugs administered simultaneously
- Susceptible bacteria cleared
- Small population of resistant bacteria remain

Combining drugs with a time delay

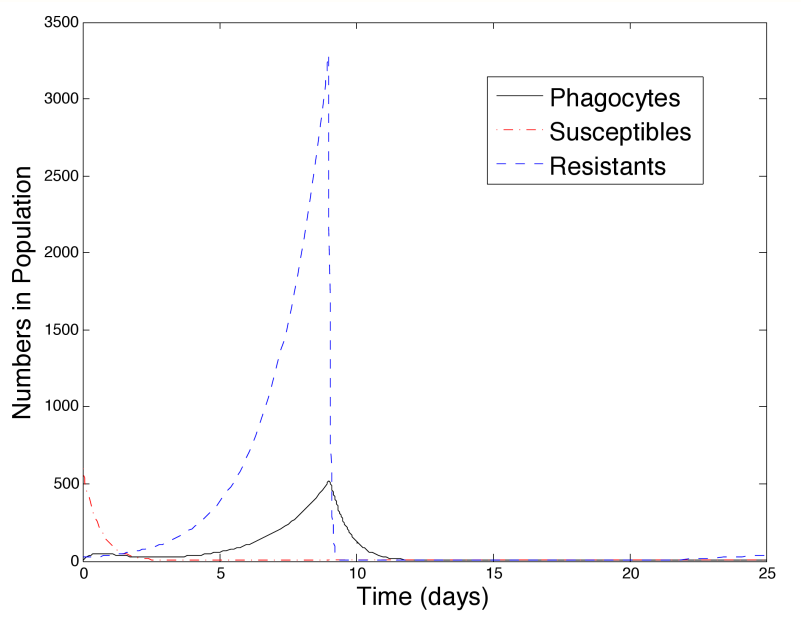


Introduction of antimicrobial first followed by antibiotic after $t = 15$ days.

Combining drugs with a time delay

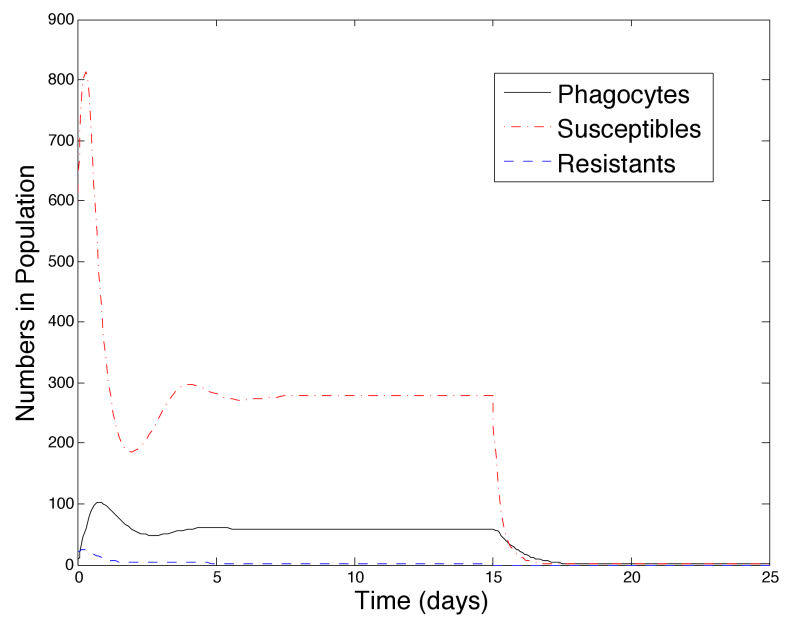


Introduction of antimicrobial first followed by antibiotic after $t = 15$ days.

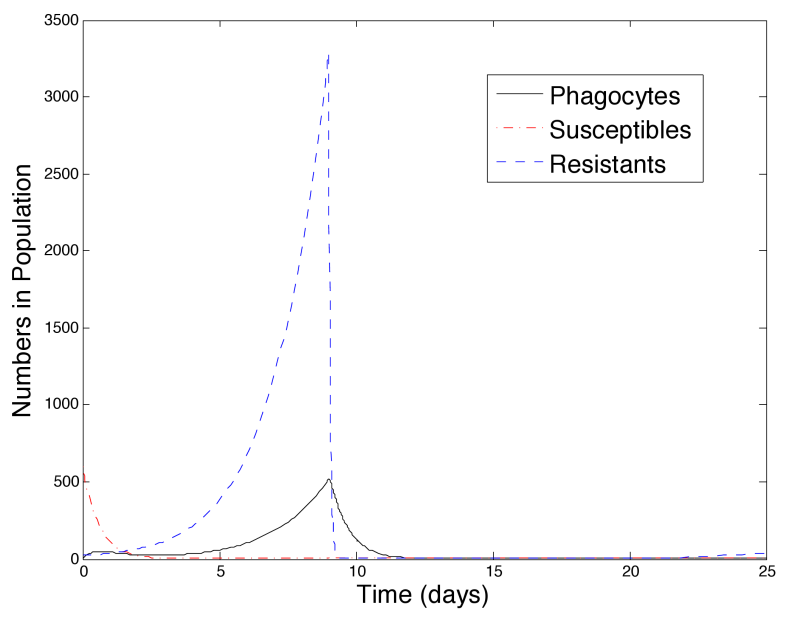


Introduction of antibiotic first followed by antimicrobial after $t = 9$ days.

Combining drugs with a time delay



Introduction of antimicrobial first followed by antibiotic after $t = 15$ days.



Introduction of antibiotic first followed by antimicrobial after $t = 9$ days.

Complete bacterial elimination achieved

Summary

- Mathematical modelling and differential equations can be used to represent the inner-workings of bacteria, infection and the effects of drugs

Summary

- Mathematical modelling and differential equations can be used to represent the inner-workings of bacteria, infection and the effects of drugs
- Anti-virulence drugs show promise for the future, but possibly only either in combination with antibiotics, or for the prevention of treatment

Summary

- Mathematical modelling and differential equations can be used to represent the inner-workings of bacteria, infection and the effects of drugs
- Anti-virulence drugs show promise for the future, but possibly only either in combination with antibiotics, or for the prevention of treatment

Future work:

- Refine the models for specific bacteria and infections, e.g. *E. coli* in urinary tract infections

Summary

- Mathematical modelling and differential equations can be used to represent the inner-workings of bacteria, infection and the effects of drugs
- Anti-virulence drugs show promise for the future, but possibly only either in combination with antibiotics, or for the prevention of treatment

Future work:

- Refine the models for specific bacteria and infections, e.g. *E. coli* in urinary tract infections
- Use the models to determine which aspects of the anti-virulence drugs should be improved and the optimal treatment strategies

Summary

- Mathematical modelling and differential equations can be used to represent the inner-workings of bacteria, infection and the effects of drugs
- Anti-virulence drugs show promise for the future, but possibly only either in combination with antibiotics, or for the prevention of treatment

Future work:

- Refine the models for specific bacteria and infections, e.g. *E. coli* in urinary tract infections
- Use the models to determine which aspects of the anti-virulence drugs should be improved and the optimal treatment strategies
- Develop to account for the possibility of resistance to anti-virulence drugs

What can maths do for biology?

- Investigate systems that are impractical in the lab
  - e.g. the potential for drugs that haven't yet been developed

What can maths do for biology?

- Investigate systems that are impractical in the lab
  - e.g. the potential for drugs that haven't yet been developed
- Accelerate and reduce experimental work
  - e.g. identify most promising aspects on which to focus

What can maths do for biology?

- Investigate systems that are impractical in the lab
  - e.g. the potential for drugs that haven't yet been developed
- Accelerate and reduce experimental work
  - e.g. identify most promising aspects on which to focus
- Predict optimal strategies
  - e.g. dosing strategies

Thank you!

Any questions??