Introduction	Possible substances for models	Model for phage dynamics	Conjugation model	Test model	Literature
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Ideas on modelling of phage dynamics

Yin Cai and Maria Münch

Bioquant

August 14th, 2008

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Definitions and overview

elementary steps of mathematical modelling

1 definition of the purpose of the model

2 biological basics, observations of the real system

3 development of a first system approach

④ draft of simulation tools

6 analysis of simulation results

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Definitions and overview

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Definitions and overview

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Definitions and overview

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Definitions and	Definitions and overview								



Population

group of individuals that belong to the same species, live in the same area, and breed with others in the group

Population model

hypothetical population that attempt to exhibit the key characteristics of a real population

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Population

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Population model

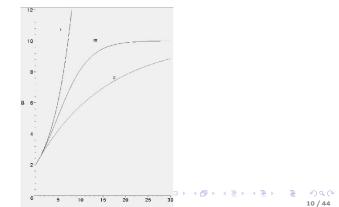
hypothetical population that attempt to exhibit the key characteristics of a real population

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Definitions and overview

Types of population models

- Linear growth
- Exponetial growth (I)
- Bounded growth (II)
- Logistic growth (III)



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General equations

Standard balance equation

rate of change of quantity = production rate of quantity - loss rate of quantity

$$\frac{d}{dt}P(t) = BP - DP = (B - D)P$$

- $P\left(t
 ight)$ amount of species at time t
 - $B \ \ {\rm normalised}$ birth rate

 $B = \frac{\text{birth rate}}{P} = \text{ number of births per unit time per unit population}$ $D = \frac{\text{death rate}}{P} = \text{ number of deaths per unit time per unit population}$

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General equati	General equations							

Some special cases

Constant birth and death rates

$$\frac{d}{dt}P\left(t\right) = kP \Leftrightarrow k = (B - D)$$

 $\Rightarrow P\left(t\right)=P_{0}e^{kt}$ with initial population size $P\left(0\right)=P_{0}$

• Decreasing birth rate with increasing population

$$\frac{d}{dt}P(t) = B_0P - B_1P^2 - D_0P = (B_0 - D_0)P - B_1P^2$$

$$\Leftrightarrow B = B_0 - B_1P - D_0$$

substitution:

 $k = B_1, M = \frac{B_0 - D_0}{B_1} \Rightarrow \text{Logistic equation } \frac{d}{dt} P(t) = kMP - kP^2$ $\Rightarrow P(t) = \frac{MP_0}{P_0 + (M - P_0)e^{-kMt}} \text{ with initial population size } P(0) = P_0$

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General equati	ons				

Some special cases

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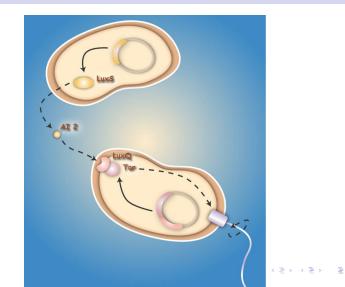
$$\Leftrightarrow B = B_0 - B_1P, D = D_0$$

substitution:

 $\begin{aligned} k &= B_1, M = \frac{B_0 - D_0}{B_1} \Rightarrow \textit{Logistic equation } \frac{d}{dt} P(t) = kMP - kP^2 \\ \Rightarrow P(t) &= \frac{MP_0}{P_0 + (M - P_0)e^{-kMt}} \text{ with initial population size } P(0) = P_0 \end{aligned}$

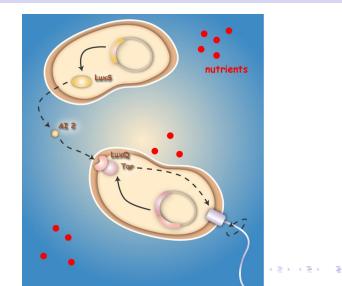
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Sensing					

Sensing process



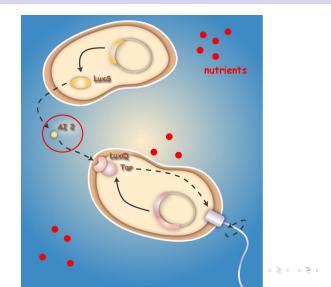
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Sensing					

concentration of nutrients



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Sensing					

concentration of AI-2

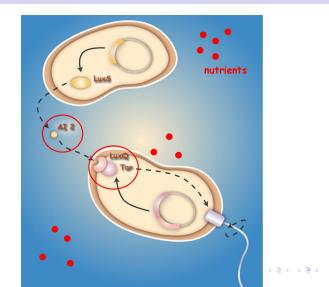


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Sensing

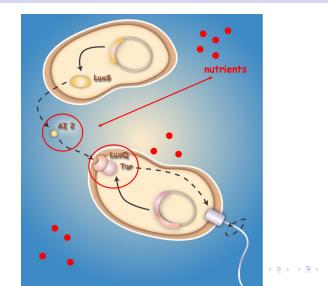
number of LuxQ proteins



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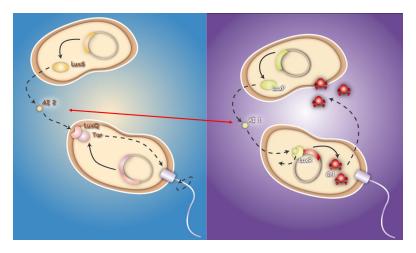
ratio between AI-2 and nutrients



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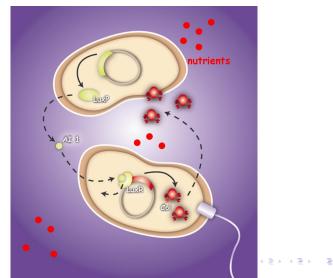
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Sensing					

ratio between AI-2 and AI-1



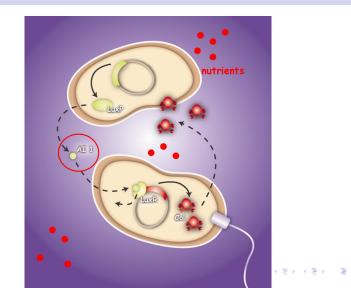
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Killing I					

concentration of nutrients



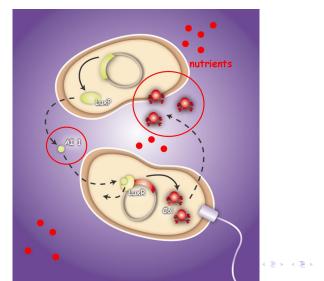
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Killing I					

concentration of AI-1



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Killing I					

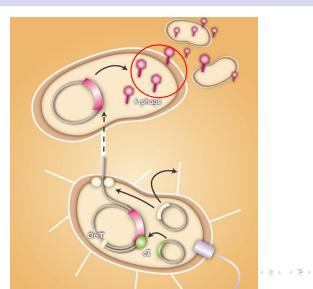
concentration of toxin



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Killing II					

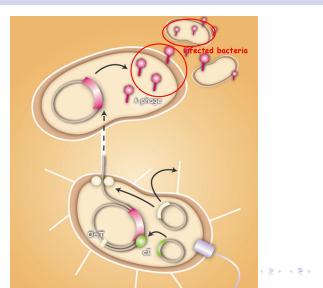
concentration of λ phage



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Killi	ng II					

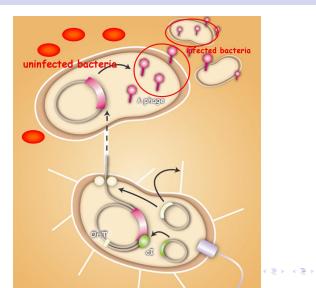
number of infected bacteria



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Introduction	Possible substances for models	Model for phage dynamics	Conjugation model	Test model	Literature
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Killing II					

number of uninfected bacteria

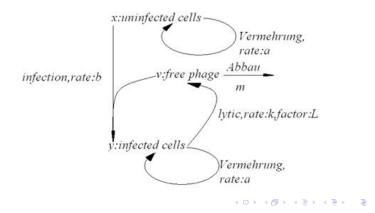


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Equations					

Phage basic model

- model for lytic phage
- model does not include the possibility of bacterial growth constrained by target cell limitation



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Equations	000			00	

Phage basic model

$$\frac{d}{dt}x = ax - bvx - H(t) x$$
$$\frac{d}{dt}y = ay + bvx - ky - H(t) y$$
$$\frac{d}{dt}v = kLy - bvx - mv - h(t) v$$

$$x$$
 – uninfected cells

$$y - \text{infected cells (lytic cells)}$$

$$v$$
 – free phage

- replication coefficient a
- b transmission coefficient
- k lysis rate
- L burst size
- m decay rate of free phage

h/H – responses against the bacteria or against the phage 27/44

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Equations					

Simplified basic model

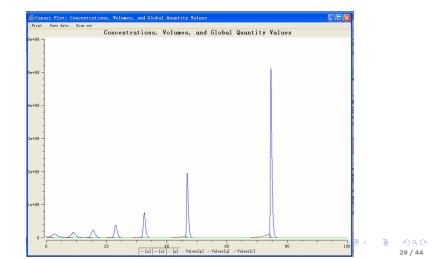
$$\frac{d}{dt}x = ax - bvx$$
$$\frac{d}{dt}y = ay + bvx - ky$$
$$\frac{d}{dt}v = kLy - bvx - mv$$

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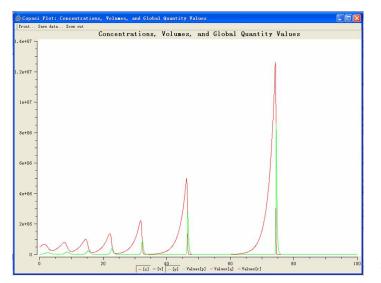
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Simulations

$$a = 0.5, b = 10^{-7}, k = 5, L = 100, m = 5, x (0) = 500000, v (0) = 4000000, y (0) = 0$$



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Simulations					



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Assumptions

- mating occurs at random with a frequency that is jointly proportional to the concentrations of plasmid-free and plasmid-bearing cells
- plasmid loss by segregation occurs at a negligible rate
- there is no significant delay between the time a transconjugant receives the plasmid and the time when it can begin to transmit it
- the original donors and the transconjugants transfer the plasmid at the same rate
- all bacterial clones grow at the same rate

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Conjugation basic model

$$\frac{d}{dt}n = \Psi n - c (n_+ + n_*) n$$
$$\frac{d}{dt}n_+ = \Psi n_+$$
$$\frac{d}{dt}n_* = \Psi n_* + c (n_+ + n_*) n$$

- n recipient cells
- n_+ donor cells
- n_{*} conjugated cells
- Ψ replication coefficient
- $c \ -$ conjugational transfer rate constant

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Simplified basic model

In our system: n_* cells does not have the helper plasmid with genes coding pilli etc. $\Rightarrow n_*$ is not conjugation donor

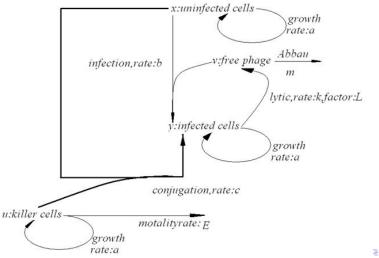
$$\frac{d}{dt}n = \Psi n - cn_{+}n$$
$$\frac{d}{dt}n_{+} = \Psi n_{+}$$
$$\frac{d}{dt}n_{*} = \Psi n_{*} + cn_{+}n$$

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Equations					

Equations

Basic test model - scheme



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• Does not include secondary infection of phages

• Does not include the time which is needed for conjugation

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Equations					

Basic test model

$$\frac{d}{dt}x = ax - bvx - cux$$
$$\frac{d}{dt}y = ay + bvx - ky + cux$$
$$\frac{d}{dt}v = kLy - bvx - mv$$
$$\frac{d}{dt}u = au - E_1u - E_2u^2$$

- x uninfected cells
- y infected cells (lytic cells)
- v free phage
- u killer cells, conjugation donor
- a replication coefficient
- b transmission coefficient

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Equations					

Basic test model

$$\frac{d}{dt}x = ax - bvx - cux$$
$$\frac{d}{dt}y = ay + bvx - ky + cux$$
$$\frac{d}{dt}v = kLy - bvx - mv$$
$$\frac{d}{dt}u = au - E_1u - E_2u^2$$

c – conjugational transfer rate constant

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$$k$$
 – lysis rate

L – burst size

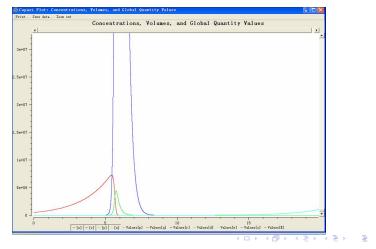
- m decay rate of free phage
- E_1 normalized death rate
- E_2 inner stress rate

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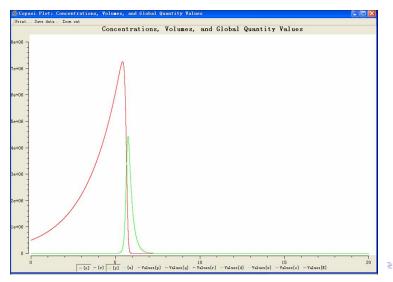
Simulations

$$a = 0.5, b = 10^{-7}, k = 5, L = 100, m = 5, x (0) =$$

500000, $v (0) = 0, y (0) = 0, u (0) = 50, E = 0, c = 10^{-10}$

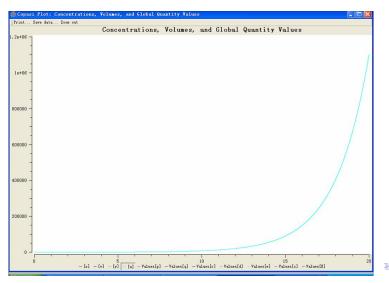


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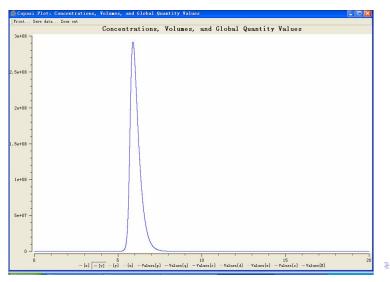
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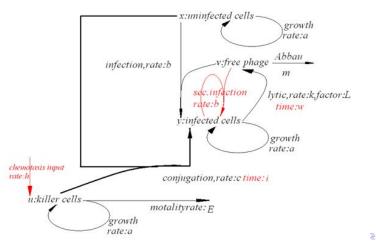
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Extended test model					

Basic test model: second step



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Extended test model					

Basic test model: second step

$$\begin{aligned} \frac{d}{dt}x &= ax(t) - bv(t)x(t) - cu(t)x(t) \\ \frac{d}{dt}y &= ay(t) + bv(t)x(t) - ky(t-w) + cu(t-i)x(t-i) \\ \frac{d}{dt}v &= kLy(t-w) - bv(t)(x(t) + y(t)) - mv(t) \\ \frac{d}{dt}u &= au(t) - E_1u(t) - E_2u^2(t) + h - cu(t)x(t) + cu(t-i)x(t-i) \\ \frac{d}{dt}j &= cu(t)x(t) - cu(t-i)x(t-i) \end{aligned}$$

- w phage maturing time
- i~-~ conjugation running time
- h chemotaxis input rate
- j conjugating cells $(\Box) (\Box$

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Papers						

- Understanding Bacteriophage Therapy as a Density-dependet Kinetic Process, Robert J. H. Payne and Vincent A. A. Jansen, 2001
- The Kinetics of Conjugative Plasmid Transmission: Fit of a Simple Mass Action Model, Bruce R. Levin, Frank M. Stewart and Virginia A. Rice, December 1978
- Stochastic Receptor Expression Allows Sensitive Bacteria to Evade Phage Attack. Part II: Theoretical Analyses, E. Chapman-McQuiston and X. L. Wu, June 2008