Ideas on modelling of phage dynamics

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Bioquant

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Definitions

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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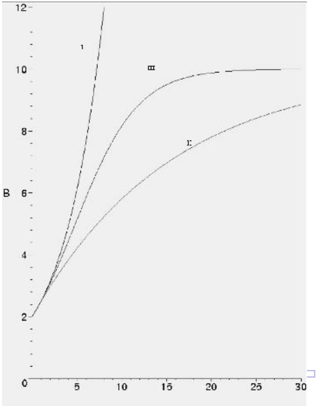
Population model

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

Types of population models

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



Standard balance equation

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

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

$P(t)$ – amount of species at time t

B – normalised birth rate

D – normalised death rate

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

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

Some special cases

- Constant birth and death rates

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

$\Rightarrow P(t) = P_0 e^{kt}$ with initial population size $P(0) = P_0$

- Decreasing birth rate with increasing population

$$\frac{d}{dt}P(t) = B_0 P - B_1 P^2 - D_0 P = (B_0 - D_0) P - B_1 P^2$$

$$\Leftrightarrow B = B_0 - B_1 P, D = D_0$$

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

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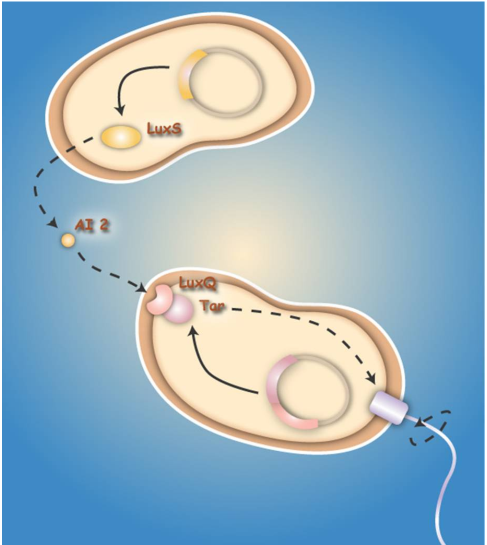
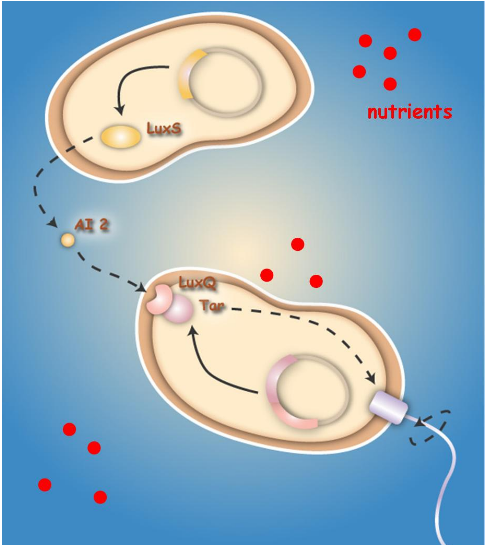
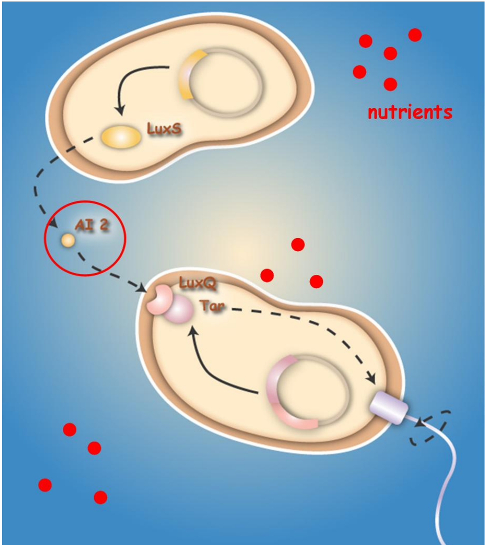
Sensing process



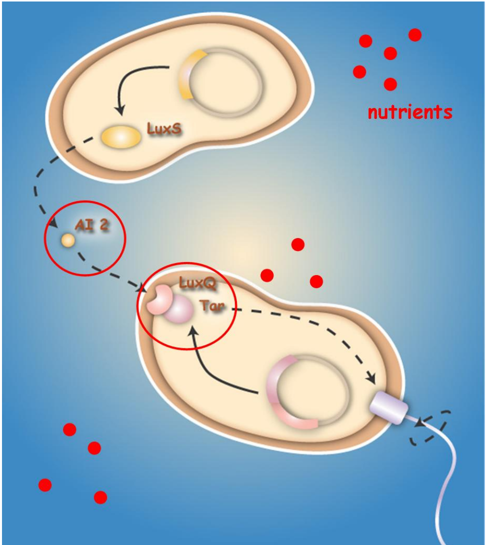
concentration of nutrients



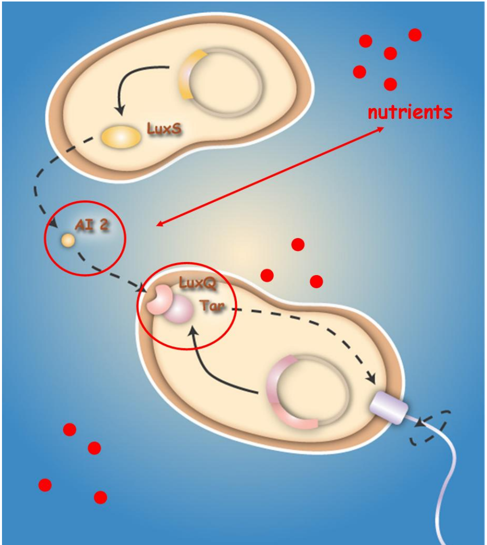
concentration of AI-2



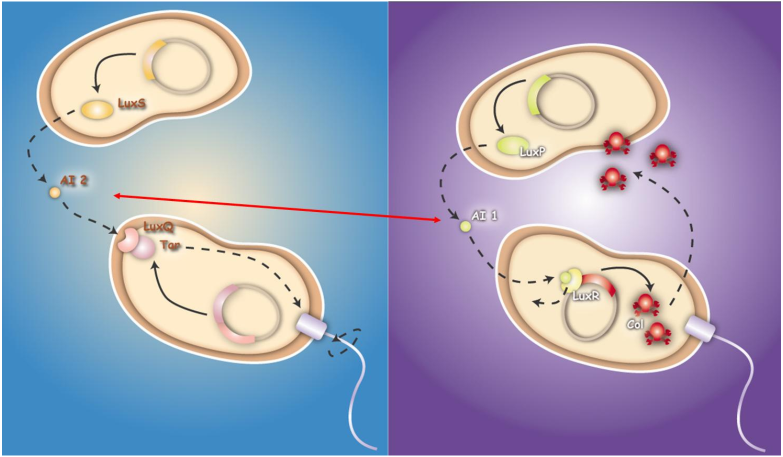
number of LuxQ proteins



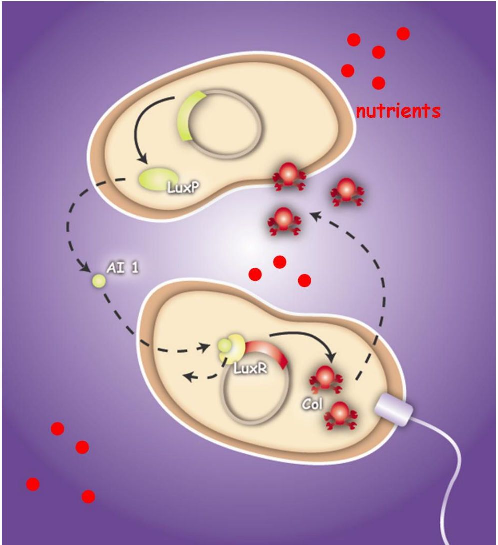
ratio between AI-2 and nutrients



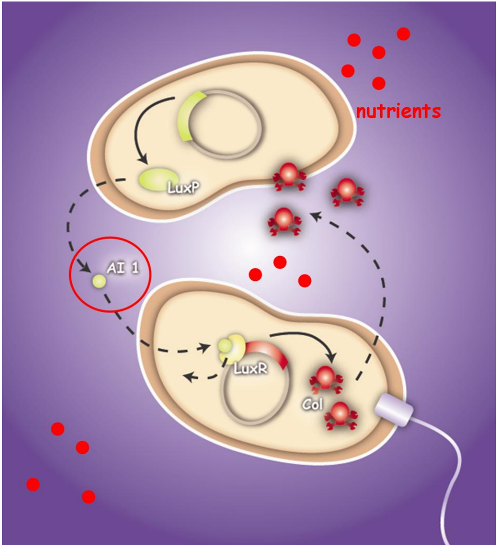
ratio between AI-2 and AI-1



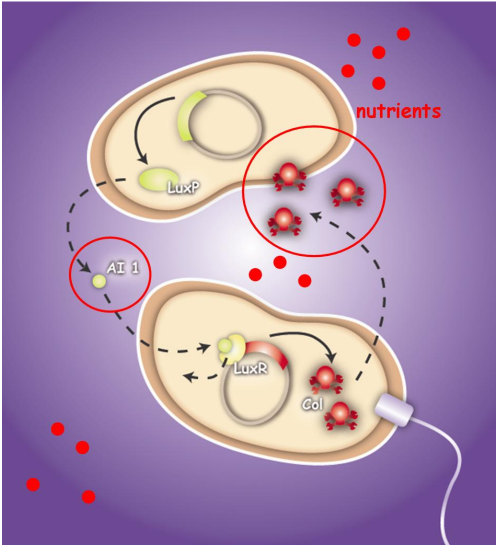
concentration of nutrients



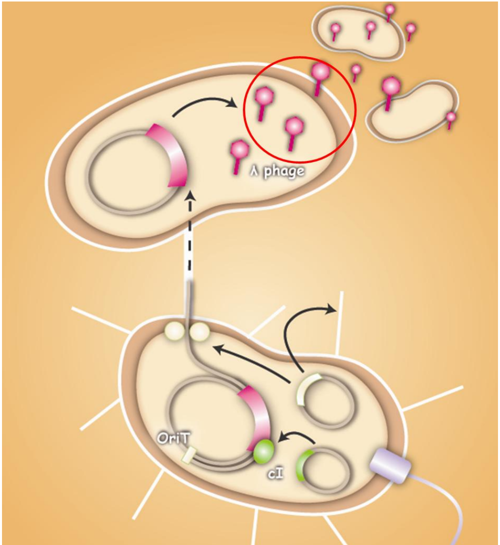
concentration of AI-1



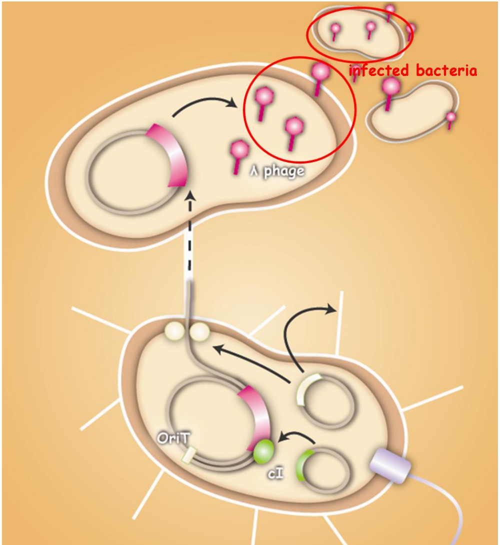
concentration of toxin



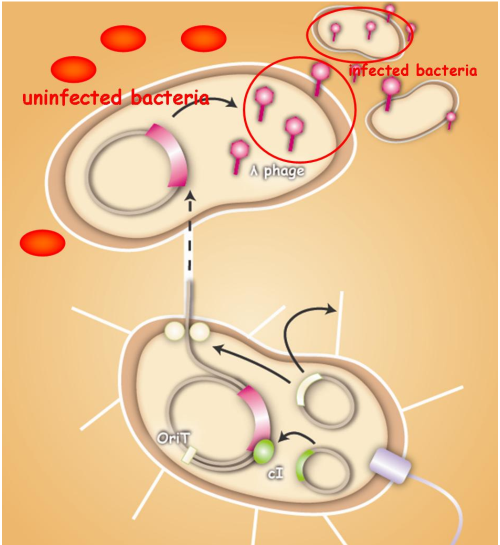
concentration of λ phage



number of infected bacteria

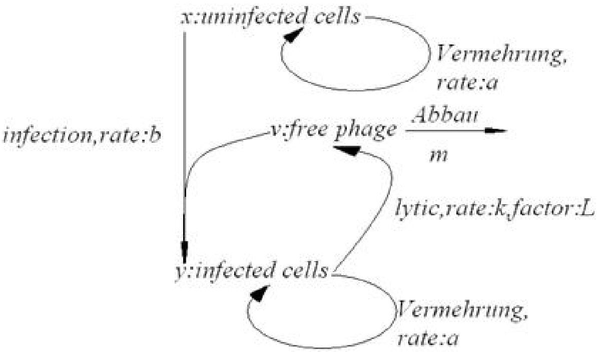


number of uninfected bacteria



Phage basic model

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



Phage basic model

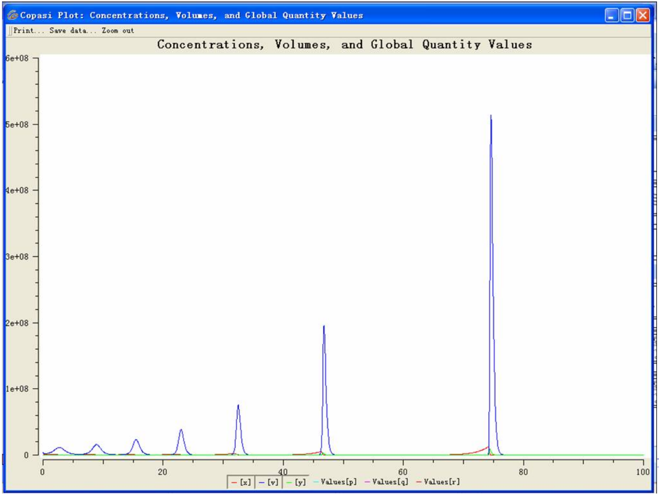
$$\frac{d}{dt}x = ax - bvx - H(t)\,x$$
$$\frac{d}{dt}y = ay + bvx - ky - H(t)\,y$$
$$\frac{d}{dt}v = kLy - bvx - mv - h(t)\,v$$

x	–	uninfected cells
y	–	infected cells (lytic cells)
v	–	free phage
a	–	replication coefficient
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

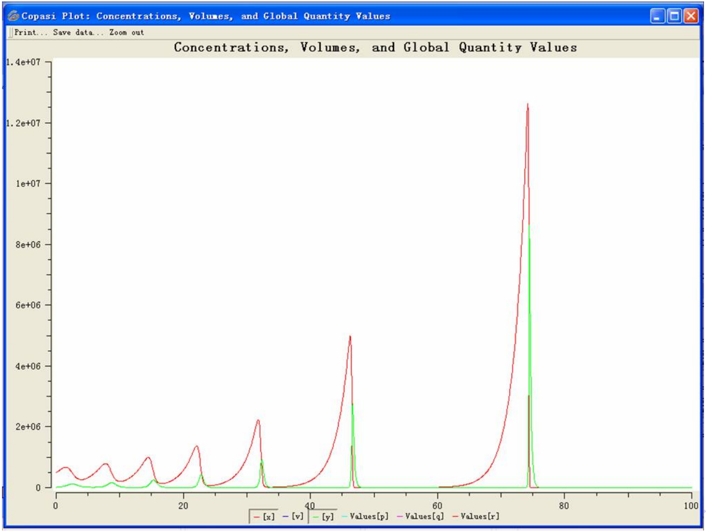
Simplified basic model

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

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



Simulation results



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

Conjugation basic model

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

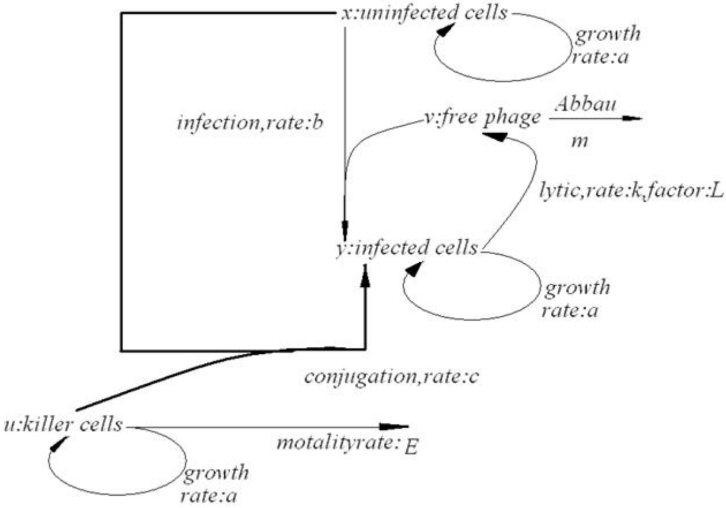
n	–	recipient cells
n_+	–	donor cells
n_*	–	conjugated cells
Ψ	–	replication coefficient
c	–	conjugational transfer rate constant

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

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

Basic test model - scheme



Restrictions

- Does not include secondary infection of phages
- Does not include the time which is needed for conjugation

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

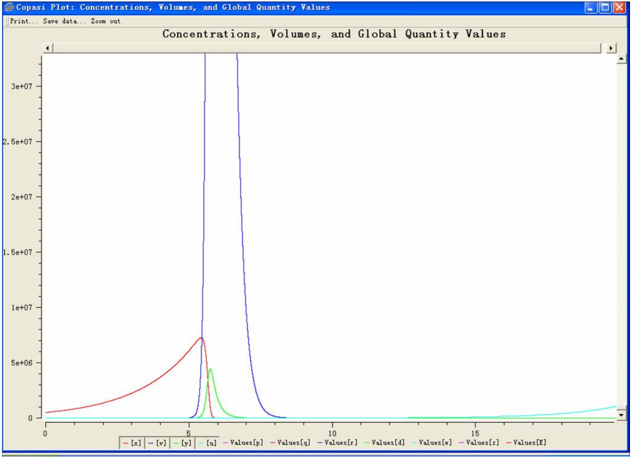
Basic test model

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

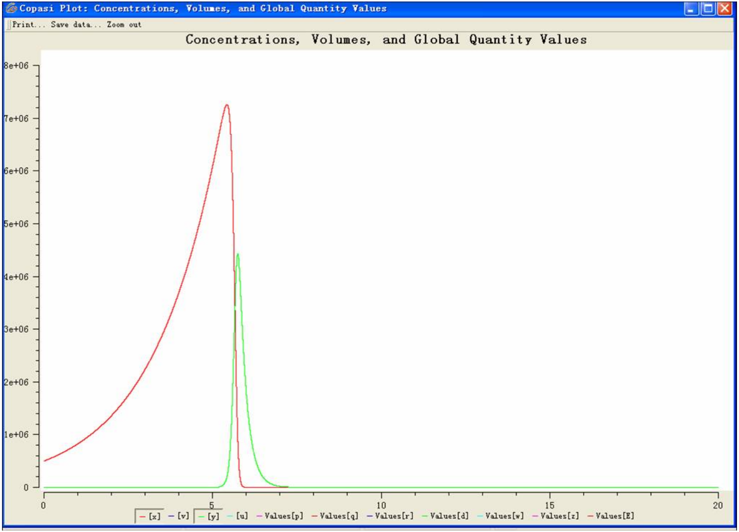
c	–	conjugational transfer rate constant
k	–	lysis rate
L	–	burst size
m	–	decay rate of free phage
E_1	–	normalized death rate
E_2	–	inner stress rate

Simulations

$$a = 0.5, b = 10^{-7}, k = 5, L = 100, m = 5, x(0) = 500000, v(0) = 0, y(0) = 0, u(0) = 50, E = 0, c = 10^{-10}$$



Simulation results



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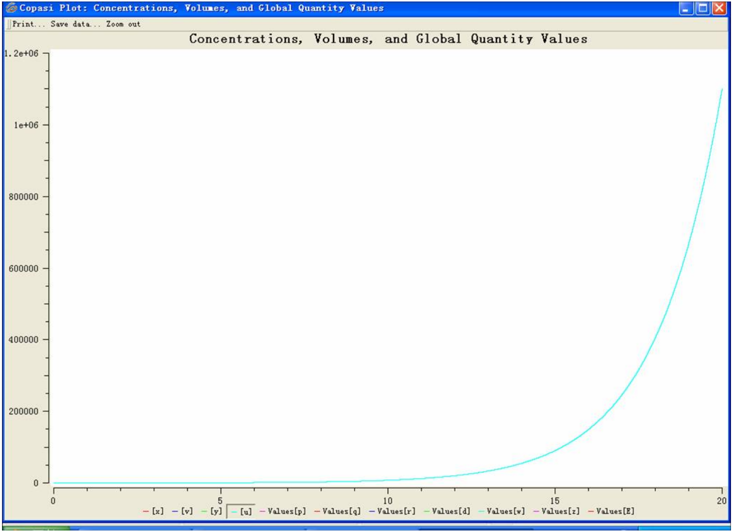

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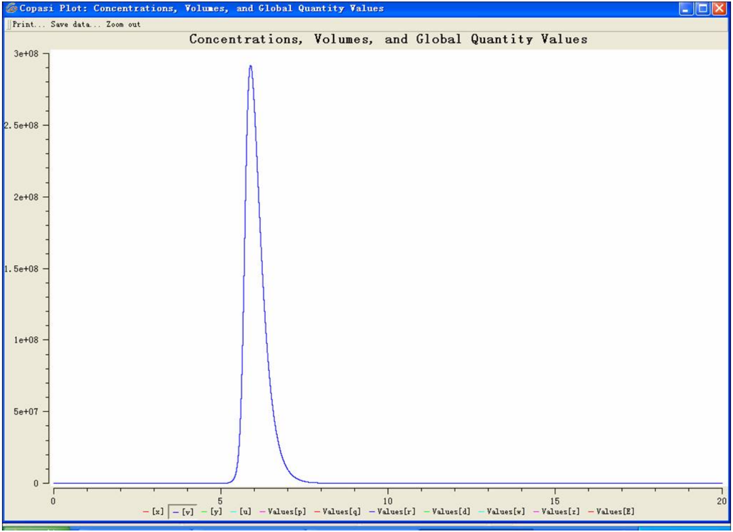
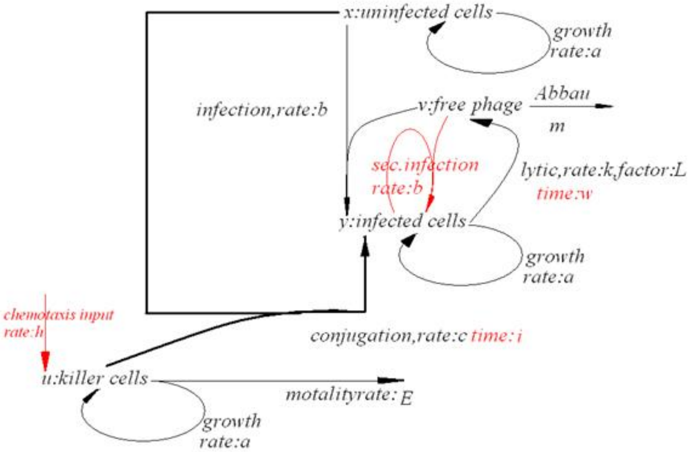


Basic test model: second step



Basic test model: second step

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

w	–	phage maturing time
i	–	conjugation running time
h	–	chemotaxis input rate
j	–	conjugating cells

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