Modeling Phage in a Predator-Prey System

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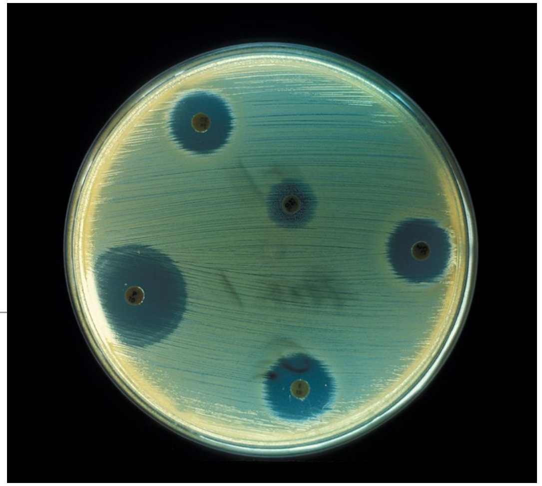
Goal of this workshop

- Expose you to elements of mathematical modeling
- Learn about an interesting biological system
  - Complex enough to be interesting
  - Simple enough to be described by a few equations
- Experience the frustration and elation that math biologists go through!
- Math modeling as an “art”
  - Lots of effects! Which ones do you include?
  - Choice of mathematical expressions
  - Interaction with experimentalists and motivation from their results

What is a Phage?

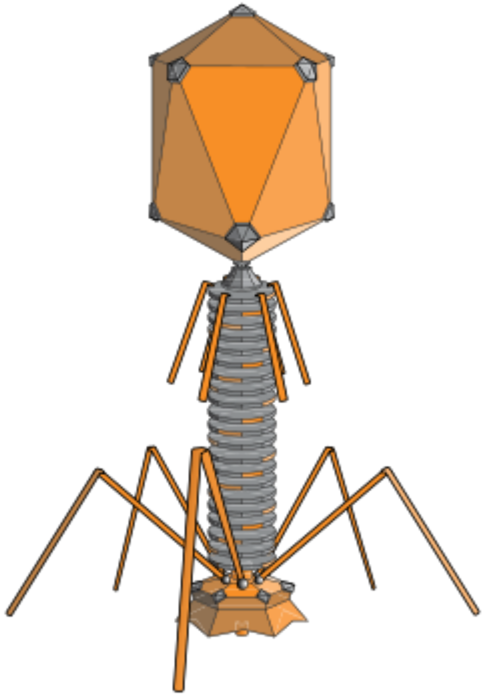


It is a virus that infects bacteria

Examples: T4 phage, Lambda phage

Discovered by Frederick Twort (1915) and Felix d'Herelle (1917)

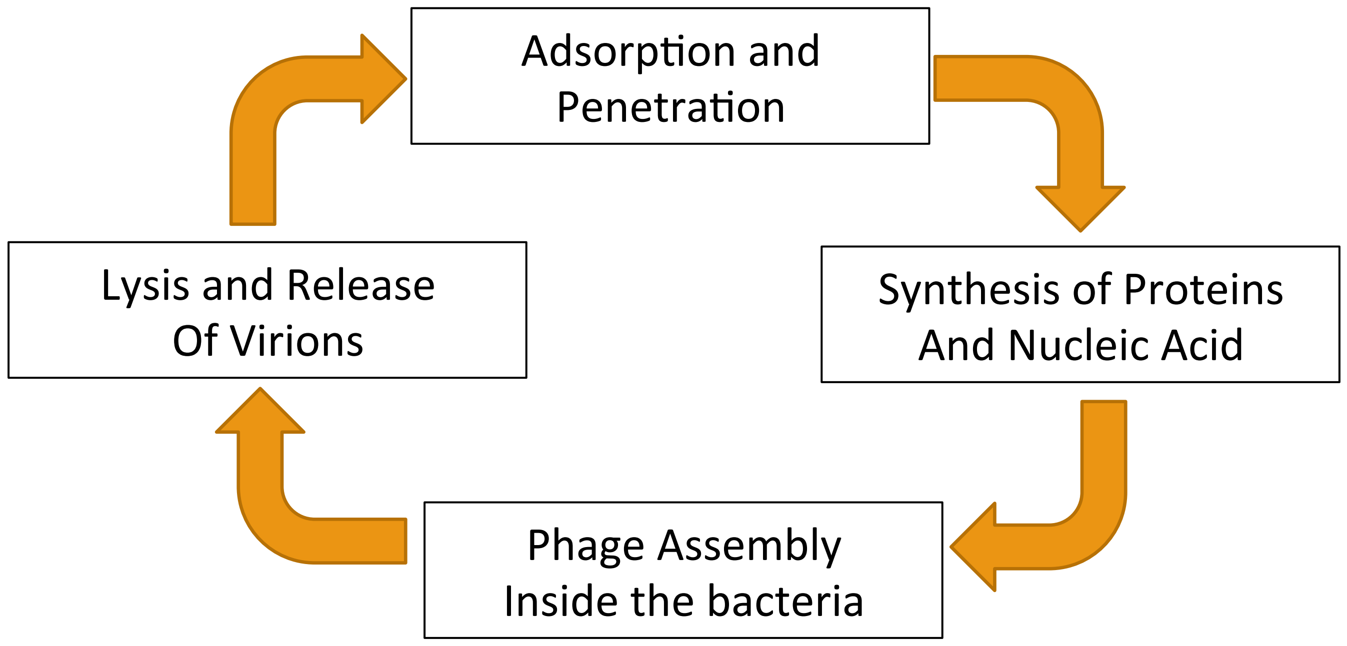
Present in large quantities in sea water (~10^8 virions/ml)



Interesting side note on phage therapy:

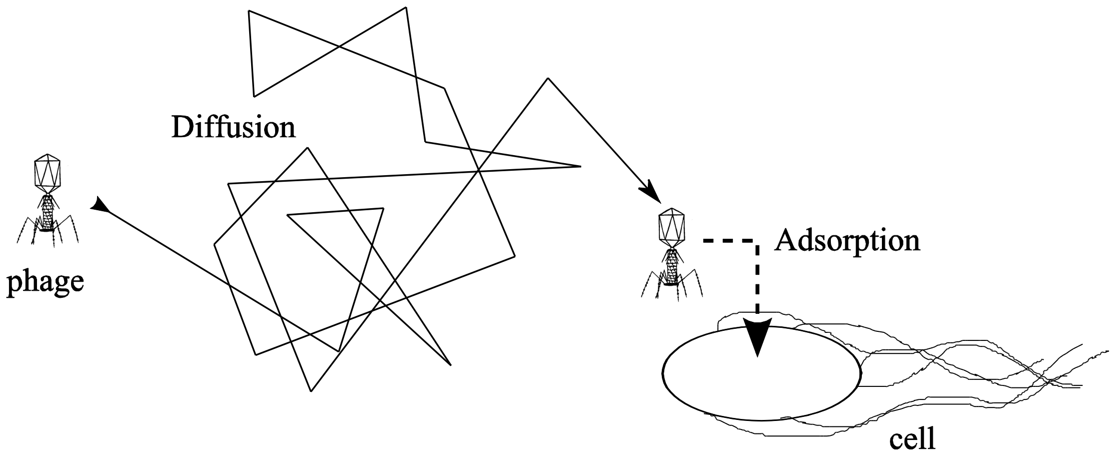
- Used to treat bacterial infections in Russia and Georgia
- Second World War: treatment of bacterial diseases like gangrene and dysentery
- Possible advantages over antibiotics?

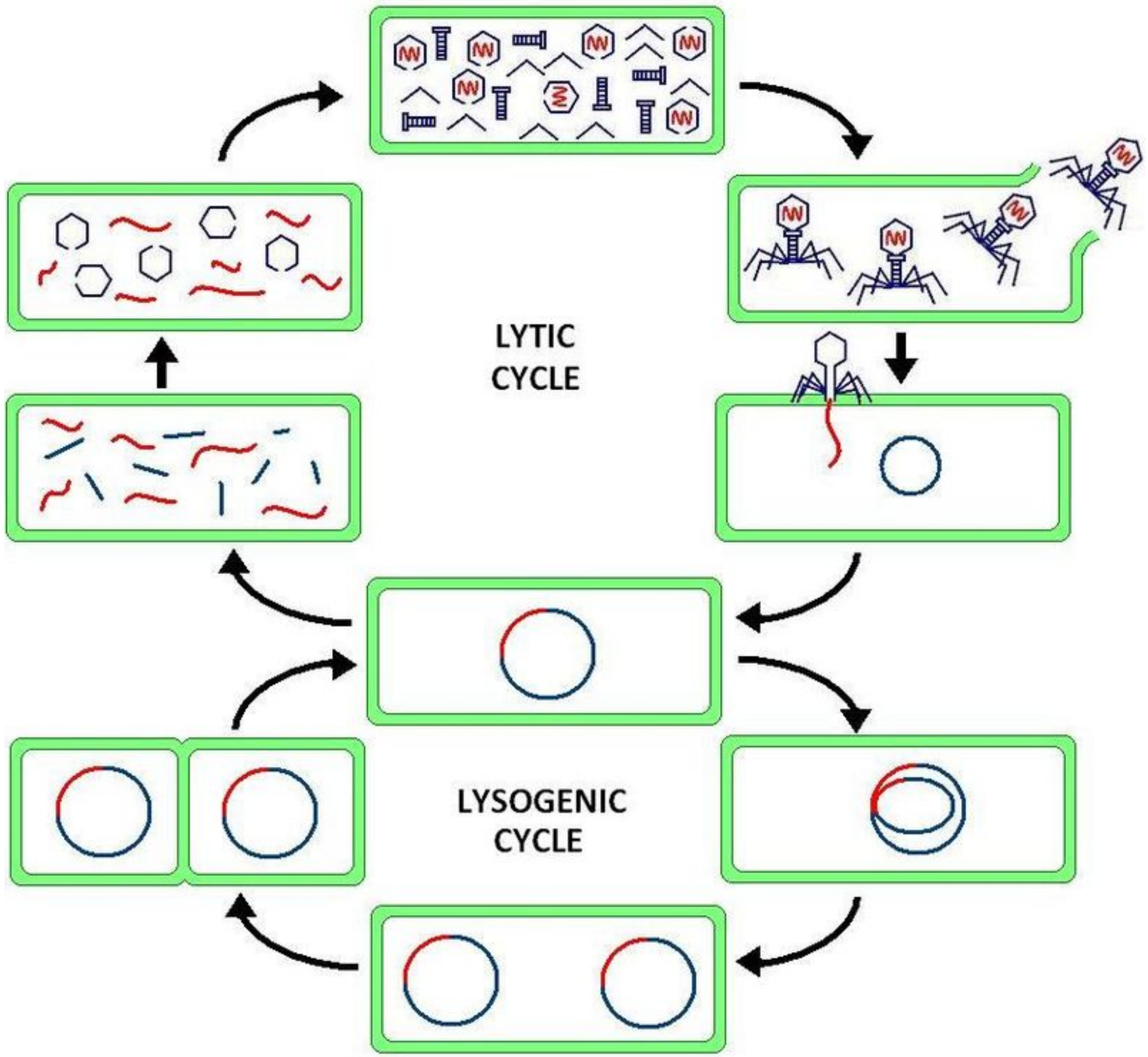
Phage Lifecycle



Lysis vs. lysogeny:

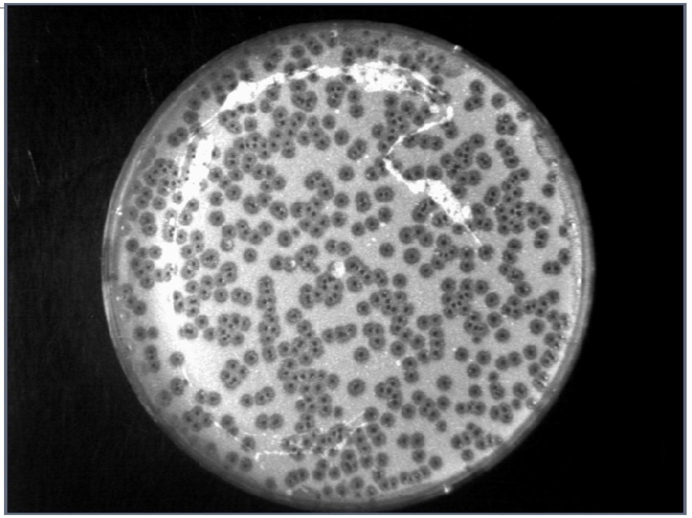
Lysis: bursting/breakdown of cell by bacteriophage
Lysogeny: transmission and proliferation of phage genetic material

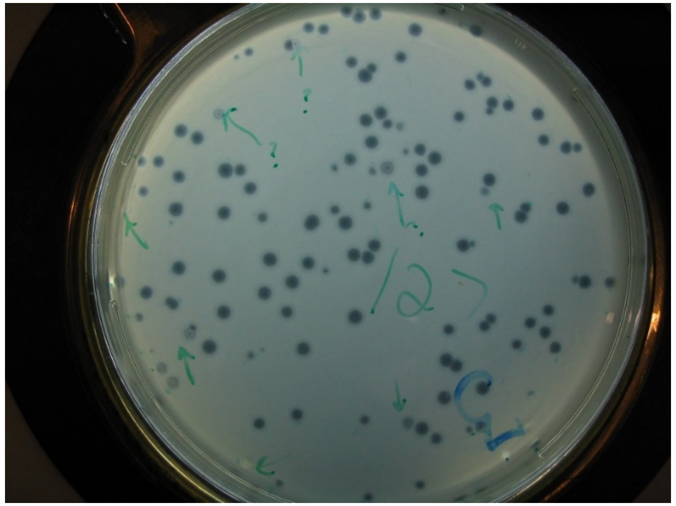


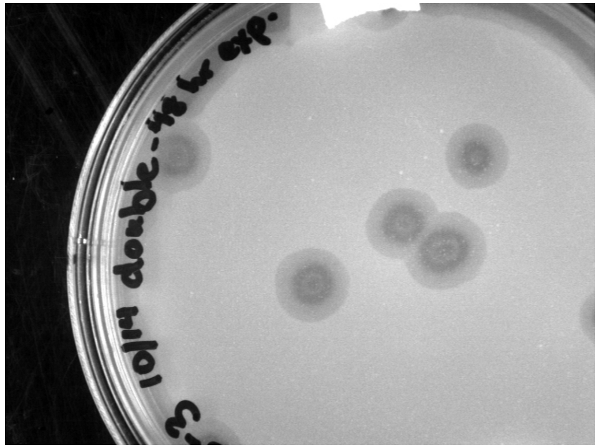


Bullseye Patterns (“plaques”)

- The proliferation of phage can be realized through experiment
- Center of plaque = site of first infection
- Plaques grow in time
- Plaques are radially symmetric
- Plaques with different phages grow at a different rates







Experimental Protocol

Towards a mathematical model

Observations:

1. The spread of the bullseye pattern is mostly deterministic

2. Strong radial symmetry

3. The patterns vary in SPACE and TIME

$$U_n(R) : \text{Density of bacteria at time } n$$

$$V_n(R) : \text{Density of phage at time } n$$

Dependent variables:

R (space), n (time)

Independent variables:

Bacteria density, phage density

Mathematical Formulation

$$V_{n+1}(R) = V_n(R) + F(U_n, V_n)$$
$$U_{n+1}(R) = U_n(R) + G(U_n, V_n)$$

change in phage density between times n and n+1

change of bacteria density between times n and n+1

Can you figure out plausible forms for F and G by thinking about the biology of plaque formation?

What are “good” choices for F and G?

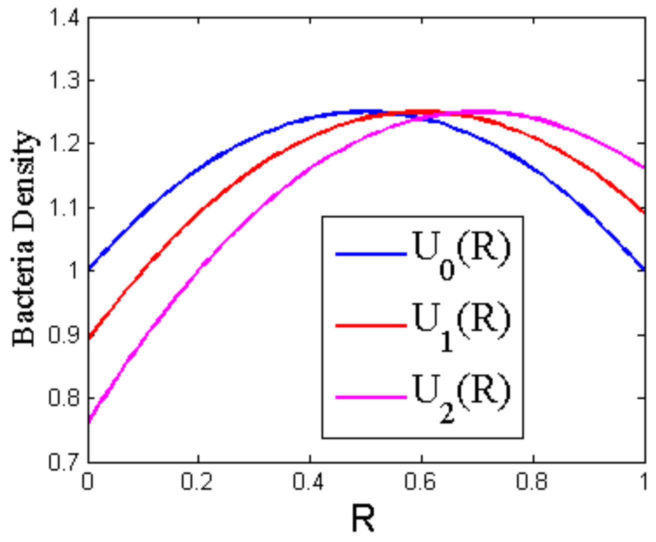
- There are infinitely many choices for F and G.
- Good choices lead to agreement with experiment!
- Physical principles motivate certain functional forms. But biology is messy and often it is unclear if the assumptions underlying the physical laws hold.
- Choosing good F and G is an artform
  - Experience with modeling helps
  - Good knowledge of mathematics, physics and biology helps

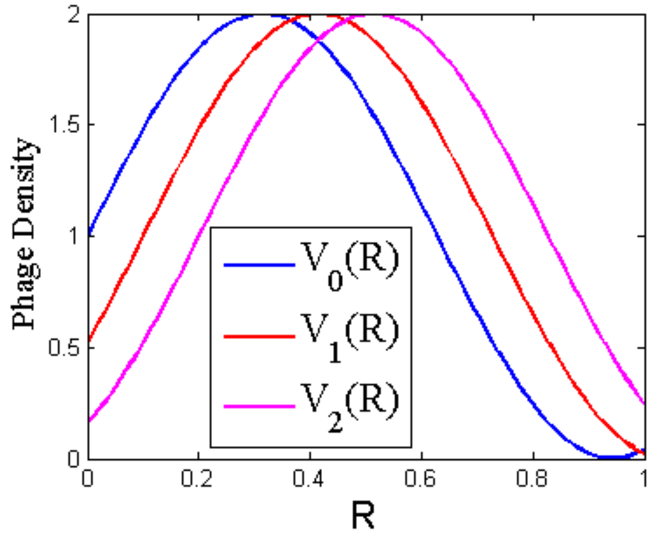
Model Equations

$$V_{n+1}(R) = V_n(R) + F(U_n, V_n)$$
$$U_{n+1}(R) = U_n(R) + G(U_n, V_n)$$
$U_0(R)$ and $V_0(R)$ are given functions (initial conditions)

Iterate in *n*

Find sequence of functions
$\{U_1, U_2, U_3, \ldots\}$
$\{V_1, V_2, V_3, \ldots\}$





Main elements of a mathematical model

1) Diffusion (spreading) of phage from regions of *high* density to *low* density
2) Infection of bacteria by phage and subsequent release of new phages after lysis
3) Growth of bacteria due to nutrients
4) Death of bacteria due to infection and lysis by phage

Work in groups and discuss these points:

1. Which items in 1) – 4) should be incorporated into F, which should be incorporated into G?

2. Are there additional effects that could be incorporated?

3. Should there be explicit dependence on *R* and *n* in F and G?

4. What are reasonable forms for $U_0(R)$ and $V_0(R)$?

My solution

$$V_{n+1}(R) = V_n(R) + (\text{new phages formed} + \text{spread of existing phages})$$
$$U_{n+1}(R) = U_n(R) + (\text{bacteria proliferation} + \text{bacteria death})$$

There are 4 terms to which we need to assign mathematical functions

Guiding principles for constructing a mathematical model

1. Occam's razor: Keep things simple!

2. You should be able to motivate the functional forms of your terms through simple reasoning

3. It's OK to have constants/parameters in your model whose values you don't know (but could be measured by further experiments). But try not to have too many.

4. Complicated functional forms have many unknown parameters, which can make them a poor choice for models.

5. Think about whether each of the terms INCREASE or DECREASE the local density.

Predator-Prey/Lotka-Volterra Models

Classical math bio model for interacting animal populations

Invented by Alfred Lotka (1910-1920) and studied by Vito Volterra (1926):

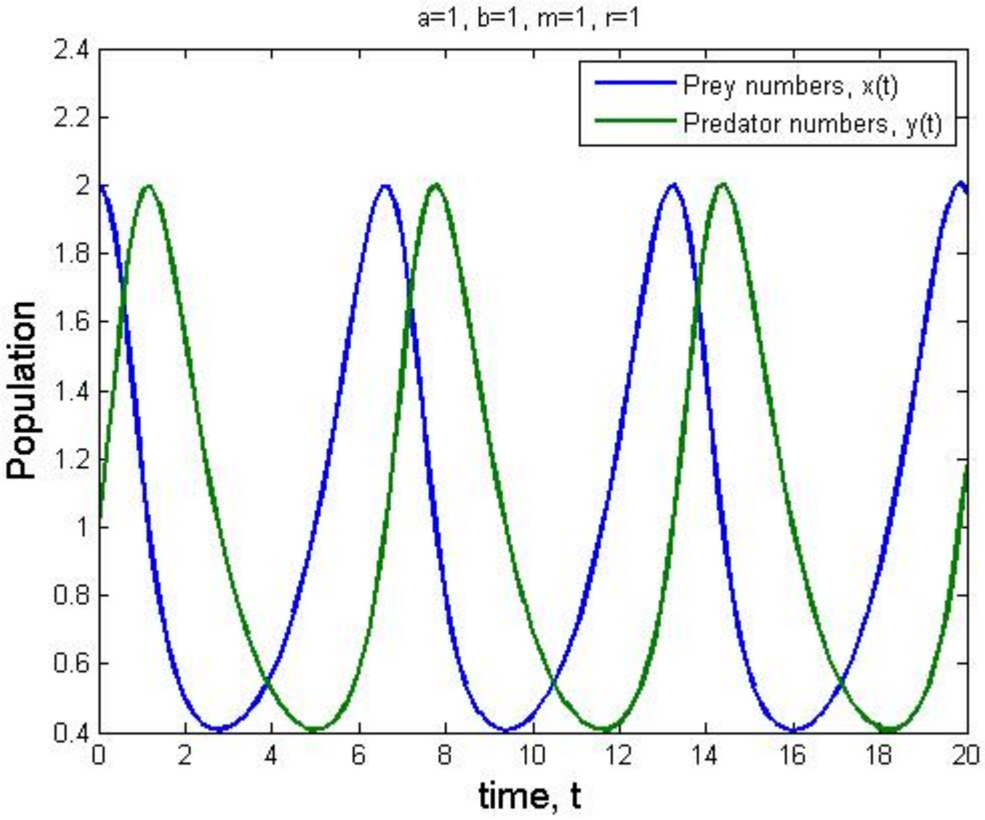
- “Contribution to the Theory of Periodic Reactions,” J. Chem Phys. **14**, 3 (1910)
- “Elements of Physical Biology,” Williams and Wilkins (1925)
- “Variazioni e fluttuazioni del numero d’individui in specie animali conviventi,” Mem. Acad. Lincei Roma (1926)

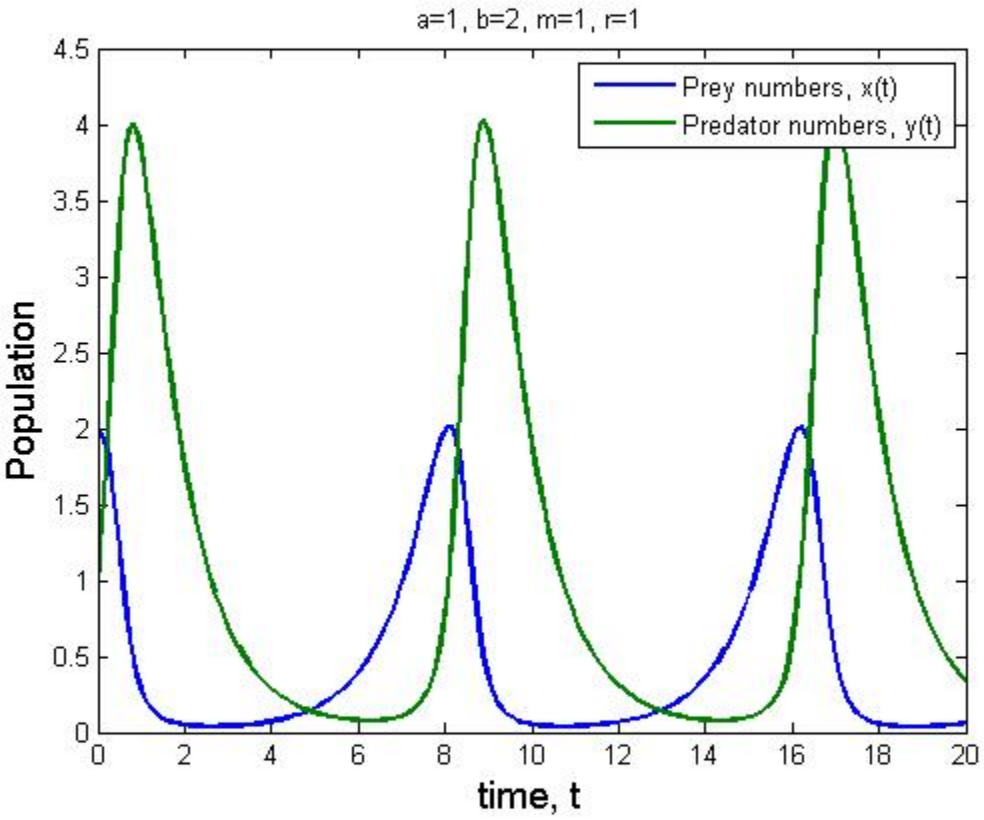
Coupled system of ordinary differential equations:

$$\frac{dx}{dt} = rx - axy$$
$$\frac{dy}{dt} = -my + bxy$$

x(t): population of prey (e.g. rabbits)
y(t): population of predators (e.g. foxes)
r, m, a, b: model parameters

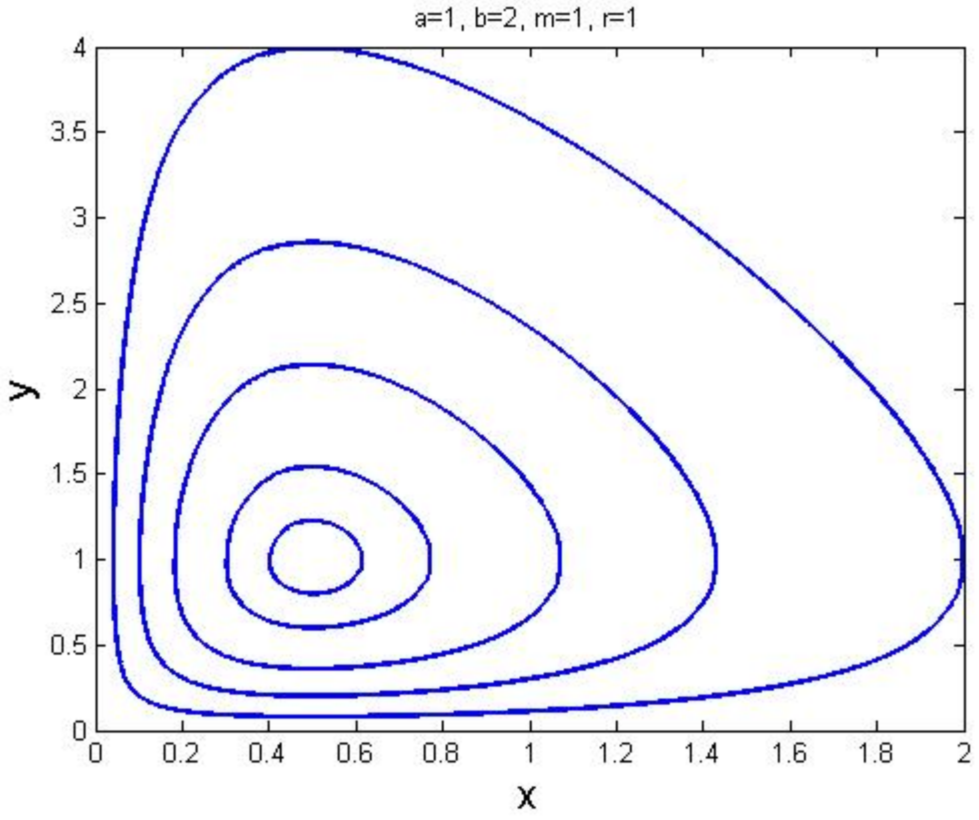
Numerical Solutions to Lotka-Volterra





Phase Plane Diagram

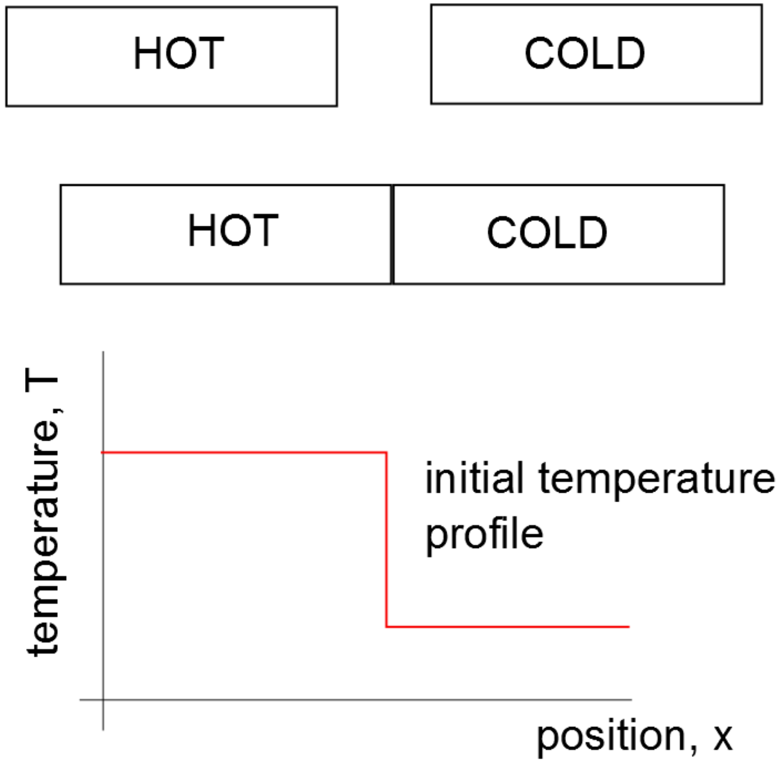
1. Closed orbits in x-y space: extinction is not possible! Unrealistic?
2. Periodic solutions
3. Predator and Prey are out of phase
4. Extensions:
   a) Stochastic Predator-Prey models
   b) Immigration/emigration effects
   c) Multiple species



Read Handout

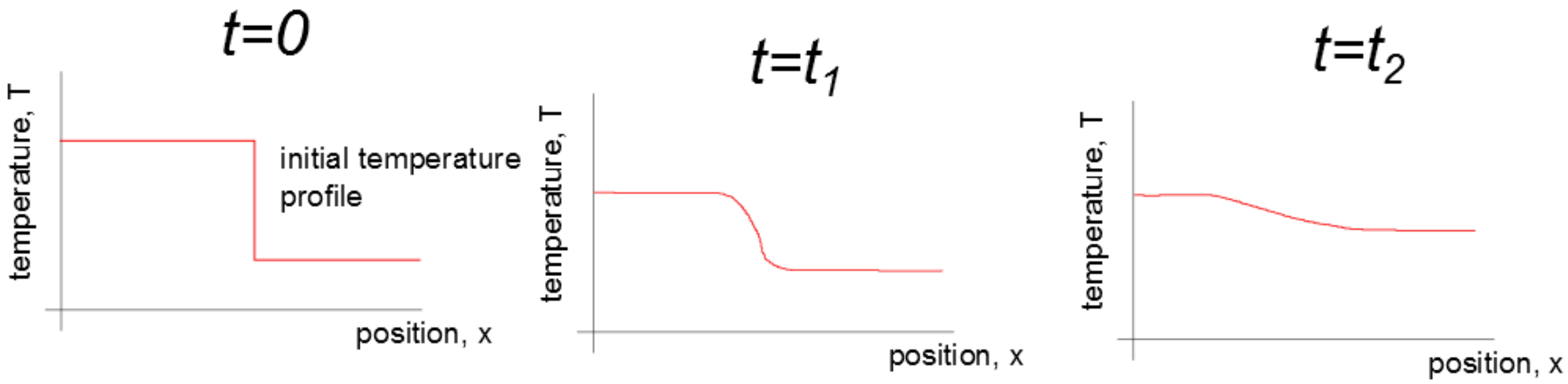
Diffusive spreading

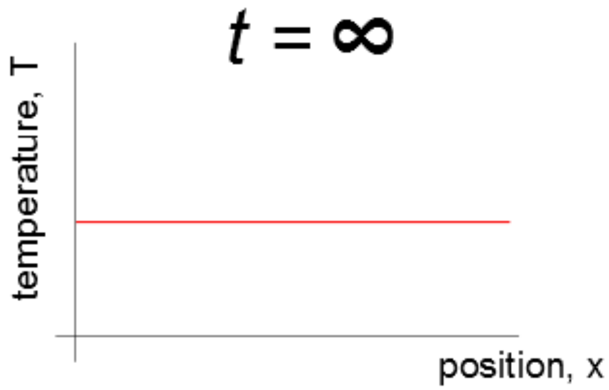
Suppose a hot metal rod is put into thermal contact with a cold metal rod.



What happens at later times?

Smoothing effect of diffusion





1. Diffusion smears out sharp changes in the temperature profile.
2. The more *concave* or *convex* the profile the faster it smooths out!
3. The Laplacian operator (=d^2/dx^2 in 1D) is an indication of convexity/concavity of u(x).