

Computational models of natural systems - II

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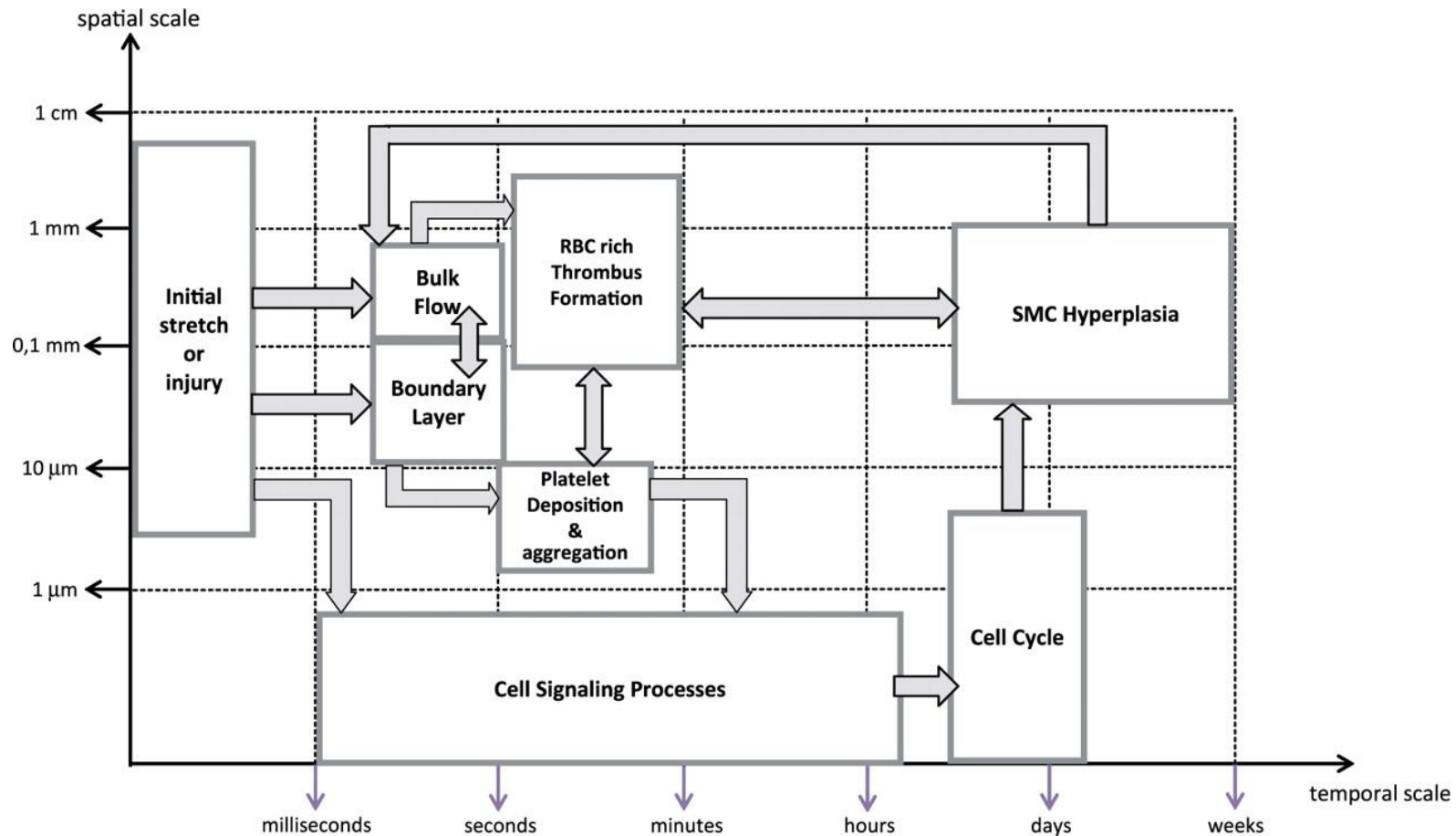


The
University
Of
Sheffield.

Complexity in biology

Scale separation map (SSM) for re-stenosis of coronary stents

PMA Sliot and A G Hoekstra, *Briefings in Bioinformatics* 2010 11(1):142-152;





Outline

Predator prey model

Copasi

Simple example – predator and prey

- Total change in prey population in a short time dt is given by births minus deaths:
- $d\text{Prey} = A * \text{prey} * dt - B * \text{prey} * \text{predator} * dt$
(note that if there are no predators, the population will continue to increase)
- Total change in predator population in a short time dt is also given by births minus deaths:
- $d\text{Pred} = D * \text{predator} * \text{prey} * dt - C * \text{predator} * dt$
(note that if there are no prey, the population will decrease to 0)
- These can be expressed as **differential equations**, where x represents the prey population and y the predator population:

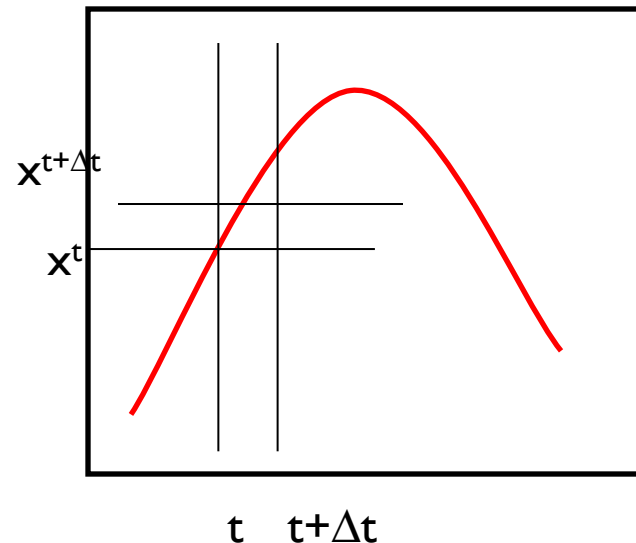
$$\frac{dx}{dt} = Ax(t) - Bx(t)y(t),$$

$$\frac{dy}{dt} = Dx(t)y(t) - Cy(t)$$

Simple example – predator and prey

- How does the system behave in time?
- For this we need to have **initial values** of x and y (prey and predator), as well as values of the rate constants A , B , C , and D .
- From this information we can calculate a **numerical solution** of the system of equations.
- One way we can do this is to approximate dx/dt over a short time step Δt

$$\frac{dx}{dt} \cong \frac{x^{t+\Delta t} - x^t}{\Delta t}$$



Simple example – predator and prey

- By re-arranging the equations, we can arrive at an expression where the value of x and y at $t+\Delta t$ is described in terms of x and y at t
- Once we know the initial conditions for x and y , we can keep calculating new values of x and y

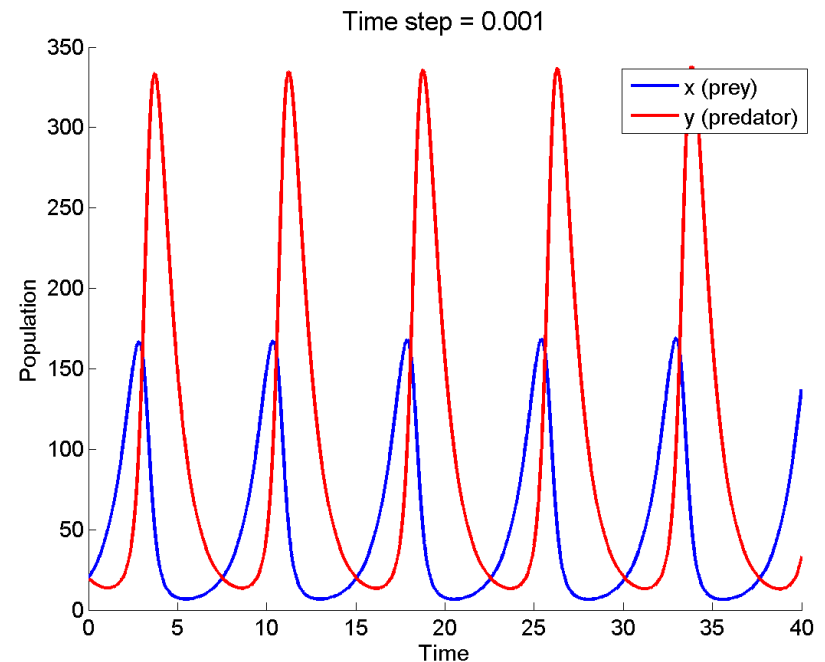
$$\frac{dx}{dt} = Ax(t) - Bx(t)y(t) \cong \frac{x^{t+\Delta t} - x^t}{\Delta t} = Ax^t - Bx^t y^t$$

$$x^{t+\Delta t} = x^t + \Delta t(Ax^t - Bx^t y^t)$$

$$y^{t+\Delta t} = y^t + \Delta t(Dx^t y^t - Cy^t)$$

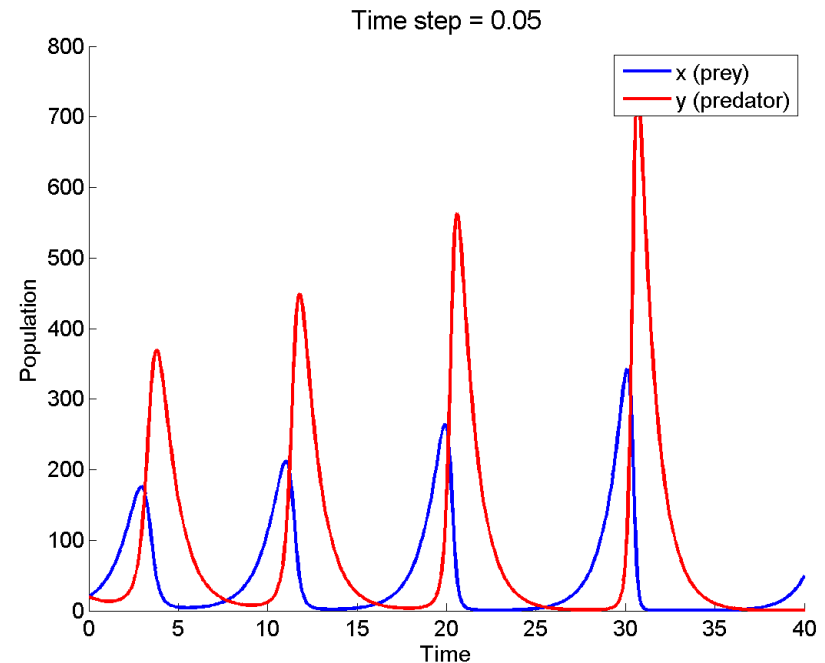
Simple example – predator and prey

- This approach gives us estimates of x and y at discrete times $t, t+\Delta t, t+2\Delta t, \dots$
- For $A = 1, B = 0.01, C = 1, D = 0.02$, initial values of x and y of 20, and $\Delta t = 0.001$, we get an oscillation in predator and prey



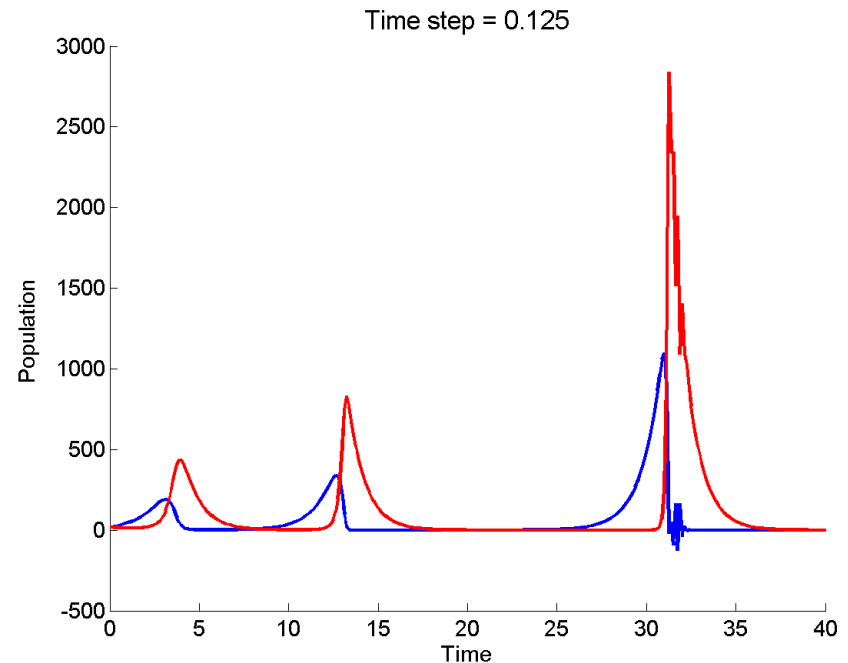
Simple example – predator and prey

- This approach gives us estimates of x and y at discrete times $t, t+\Delta t, t+2\Delta t, \dots$
- For $A = 1, B = 0.01, C = 1, D = 0.02$, initial values of x and y of 20, and $\Delta t = 0.001$, we get an oscillation in predator and prey
- Increasing Δt to 0.05, we get different behaviour, with an increase in amplitude



Simple example – predator and prey

- This approach gives us estimates of x and y at discrete times $t, t+\Delta t, t+2\Delta t, \dots$
- For $A = 1, B = 0.01, C = 1, D = 0.02$, initial values of x and y of 20, and $\Delta t = 0.001$, we get an oscillation in predator and prey
- Increasing Δt further to 0.125, we get a major problem, with negative populations!
- Increasing Δt beyond 0.125 results in major numerical instability.



Problems with the Euler method

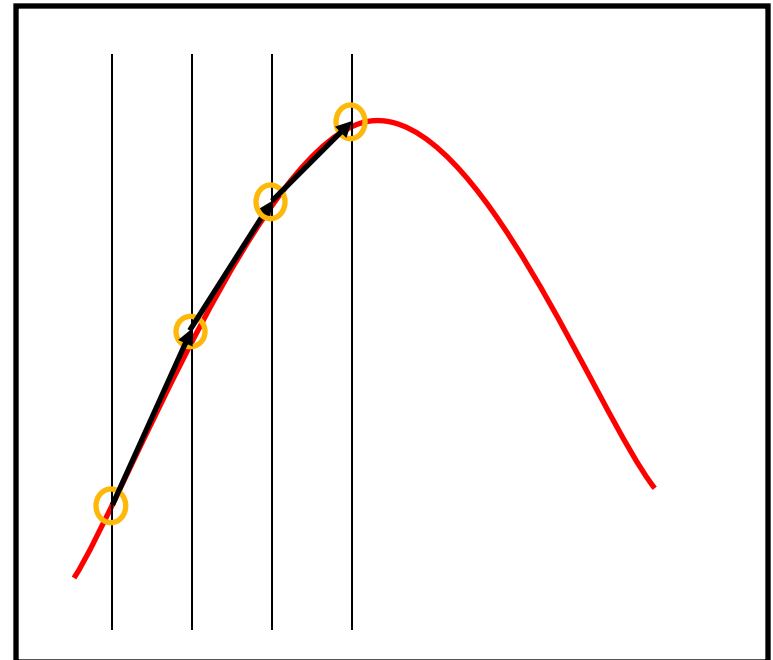
What has gone wrong?

$$\frac{dx}{dt} = f(x) \approx \frac{x_t - x_{t-1}}{dt} = f(x) , \text{ so } x_t \approx x_{t-1} + dt \cdot f(x)$$

The Euler approximation has some serious limitations because it uses the gradient at the current point x_t to predict the value of the next point x_{t+1} .

If the time step dt is small compared with changes in gradient the method works quite well.

If not then it is prone to serious errors.



Problems with the Euler method

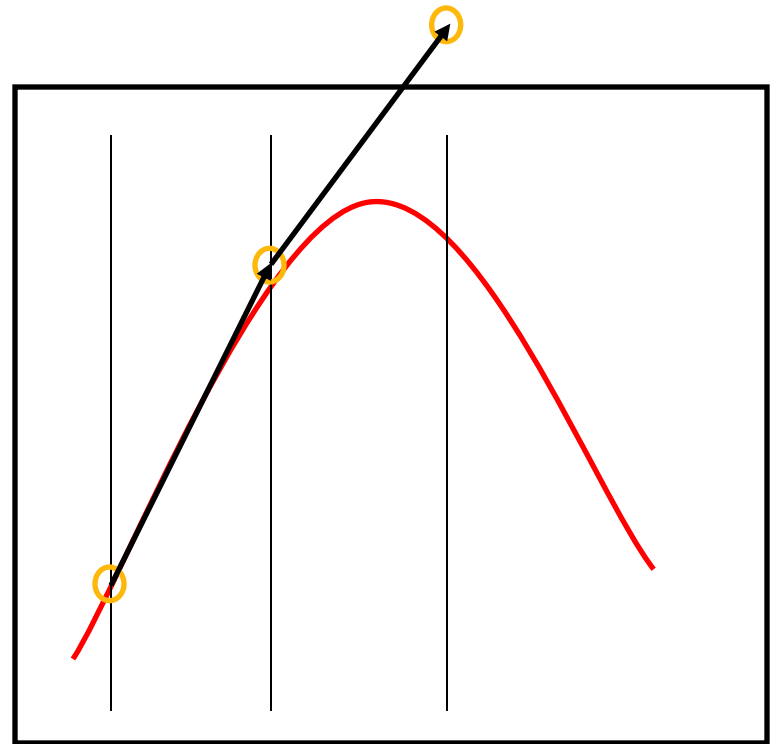
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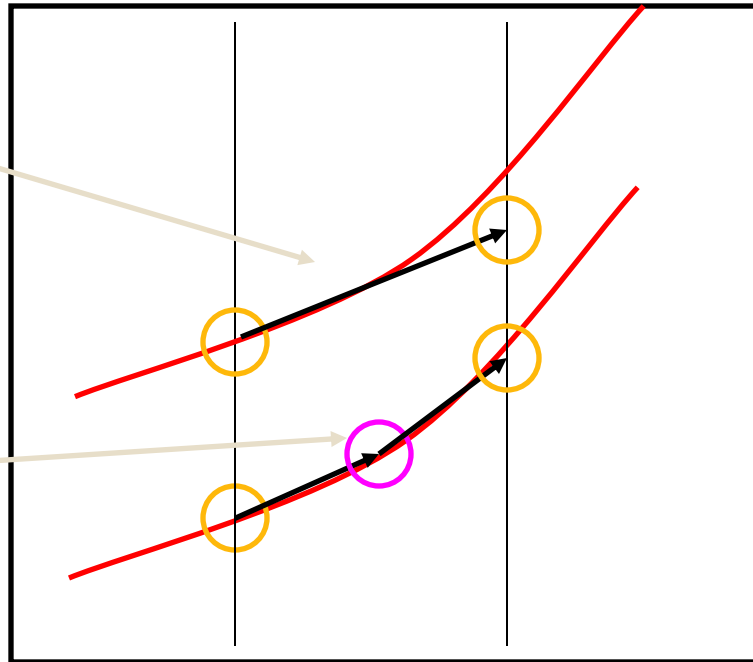
Alternative numerical methods

A vast subject.

A modified Euler method finds a point midway across the interval.

Euler method.

Modified Euler
method
(midpoint).



There are a host of other numerical approaches for solving differential equations – each have advantages and disadvantages.

Good news

- There are many software applications that will solve these kind of equations for you.
- These applications will often choose an appropriate numerical solver,
- **But**, you need to be aware that sometime numerical errors can occur

Copasi – Complex Pathway Simulator

- COPASI is a simulator for biochemical networks.
- It is a tool for solving systems of equations representing chemical reactions.
- It is freely available, and implements stable and fast numerical techniques.

Predator prey model in Copasi

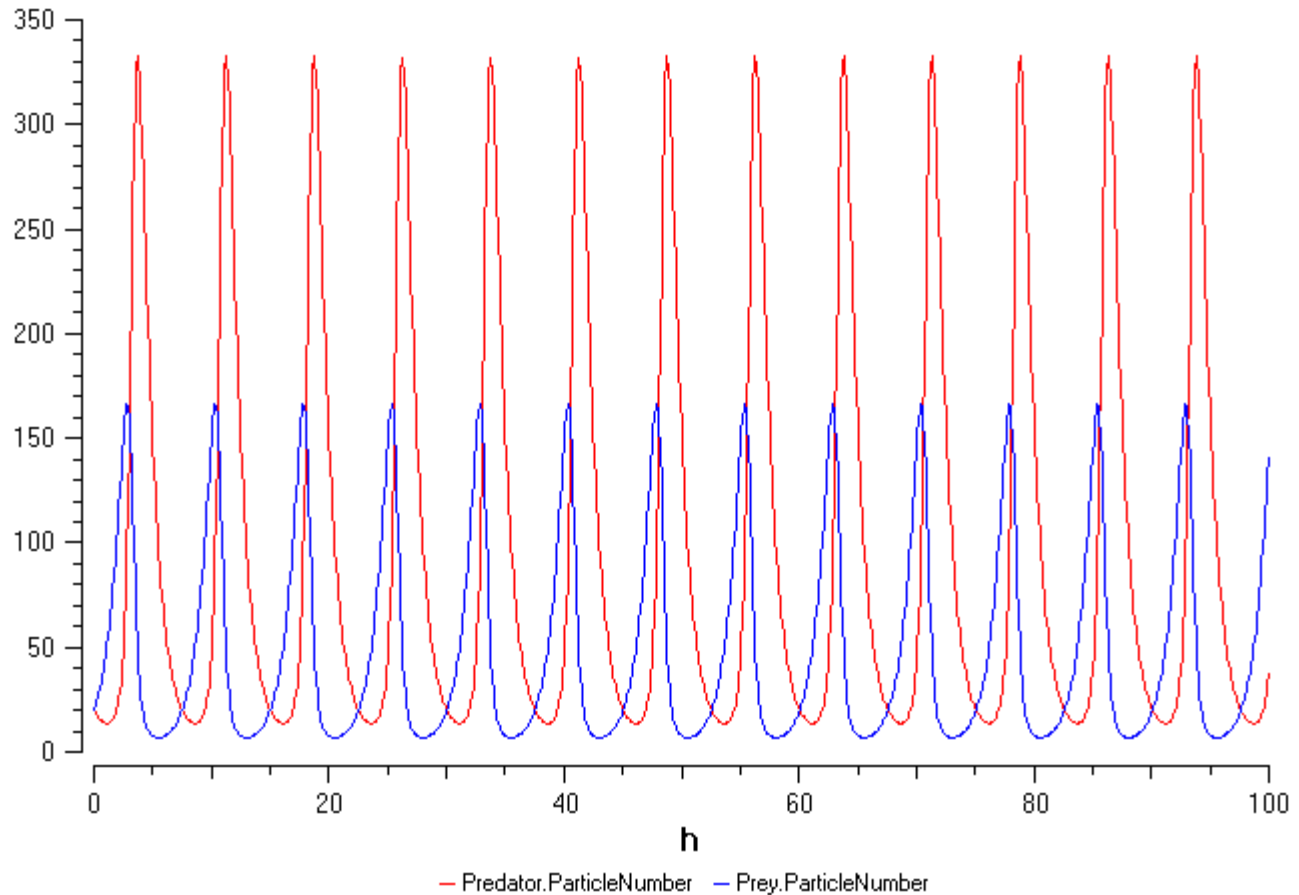
- Thanks to Ion PETRE and Andrzej MIZERA Turku, Finland
- File → New
- Model
 - time units: *hours (h)*
 - volume unit: m^3
 - quantity unit: #
- Biochemical → Compartments: *forest*
- Biochemical → Species: *predator, prey*
 - *Initial concentrations 20*
- Biochemical → Reactions (include spaces):
 - growth of prey population (A): *prey -> 2 prey*
 - consumption of prey (B): *predator + prey -> predator*
 - death of predators (C): *predator ->*
 - increase of predator population (due to prey consumption) (D):
predator + prey -> 2 predator + prey

Predator prey model in Copasi

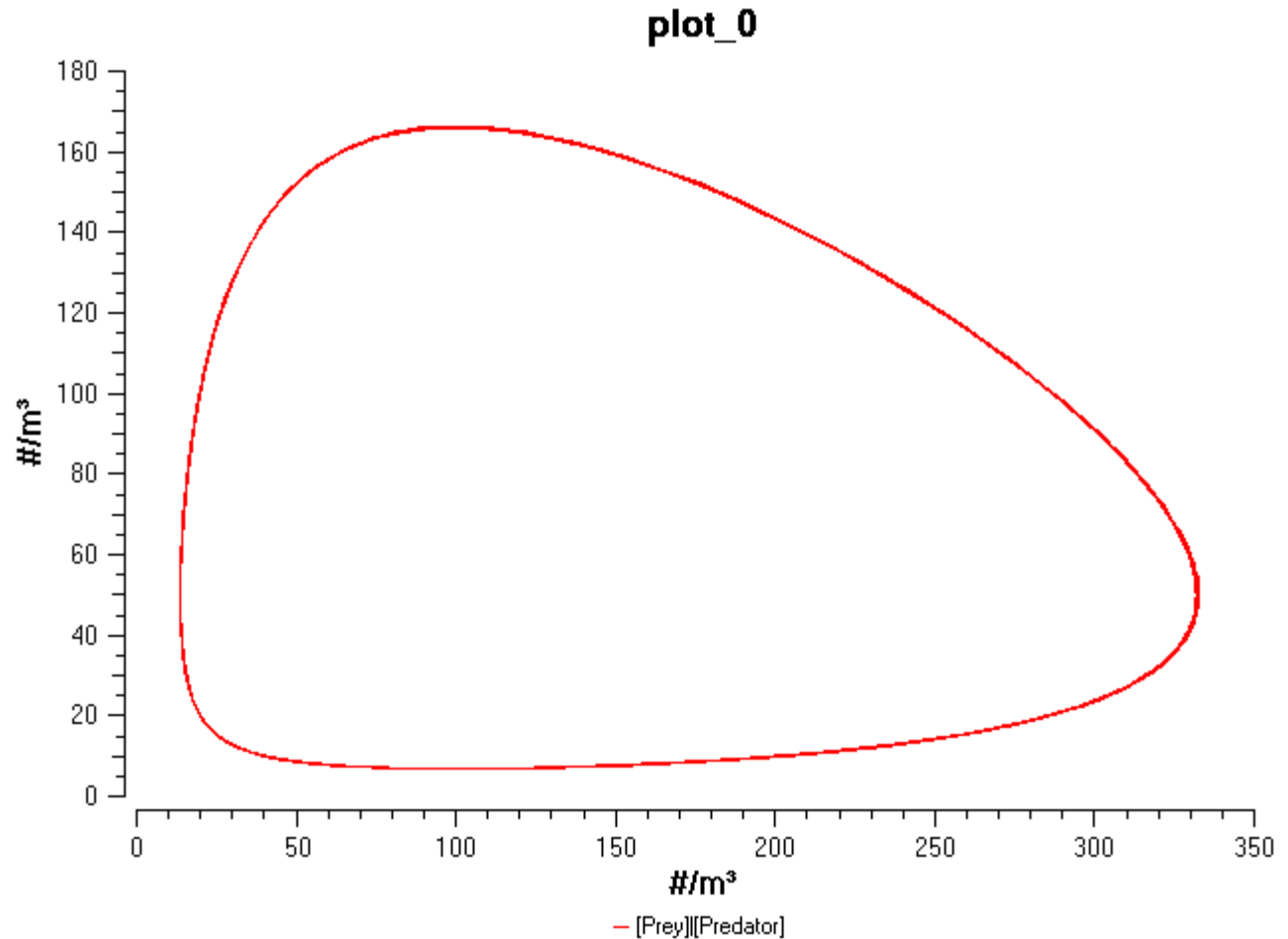
- Biochemical → Reactions A, B, C, D
- Enter parameters
 - $A = 1$;
 - $B = 0.01$;
 - $C = 1$;
 - $D = 0.02$;
- Tasks → Time Course
 - Duration 40
 - Interval size 0.1
- Hit the Run button

Predator prey model in Copasi

Particle Numbers, Volumes, and Global Quantity Values_1



Predator prey model in Copasi

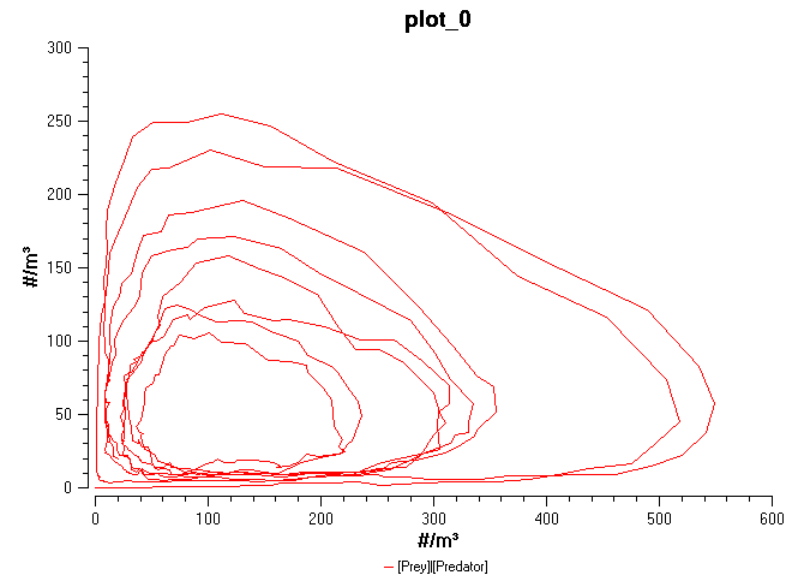
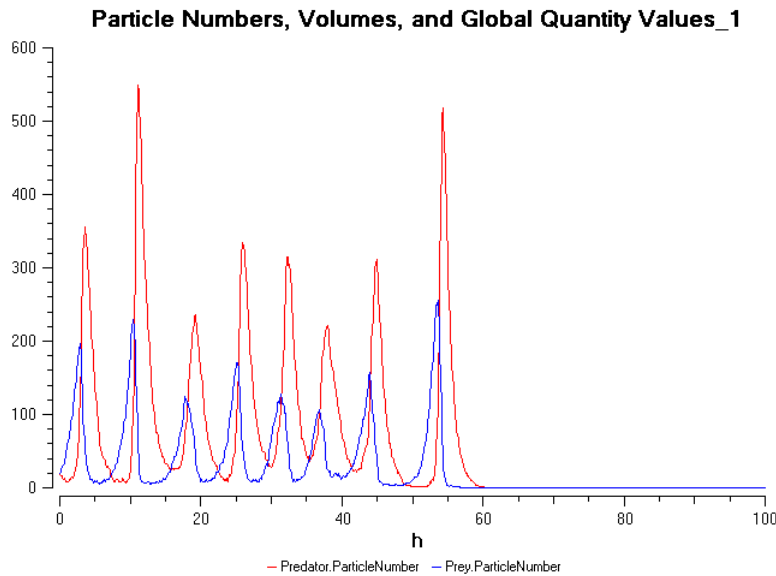


Predator prey model in Copasi

- The default numerical method is deterministic, and assumes that reagents for chemical reactions are well mixed
- This is not always true in biology, especially when concentrations are very low
- In Time Course → Method select Hybrid (Runge-Kutta)
- This will solve the model equations assuming the reagents (rabbits and foxes) are well mixed if the numbers are high, but using a stochastic (random) method when numbers are low.

Predator prey model in Copasi

- The outcome is now rather more uncertain



Simple example – predator and prey

$$\frac{dx}{dt} = Ax(t) - Bx(t)y(t),$$

$$\frac{dy}{dt} = Dx(t)y(t) - Cy(t)$$

- These equations can immediately tell us something about the system.
- If $dx/dt = 0$ and $dy/dt = 0$, then the system is in equilibrium, i.e. the numbers of predator and prey are exactly balanced.
- This occurs when

$$0 = Ax(t) - Bx(t)y(t), \quad 0 = Dx(t)y(t) - Cy(t)$$

- And there are solutions for $x=0$ and $y = 0$, and for $x = C/D$ and $y = A/B$
- Set initial values of Predator = $A/B = 100$,
- Prey = $C/D = 50$

Summary

- Models are widely used in physical science and engineering to
 - Organise knowledge
 - Make predictions
- Often these models are expressed as differential equations
- Systems of equations can be solved, so that the time course of a particular natural system can be examined.

Simple example – predator and prey

- Total change in prey population in a short time dt is given by births minus deaths:
- $d\text{Prey} = A * \text{prey} * dt - B * \text{prey} * \text{predator} * dt$
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Simple example – predator and prey

- What about other effects such as spatial variations in population density?
- What if we don't know the values for the rate constants A , B , C , and D ?
- What if our numbers of predator and prey are very small?
- How do we choose sensible initial conditions for x and y ?
- How do we know when our model is complete?

Context

- Many problems in physics and engineering involve continuous properties.
- For example heat transfer in a conducting bar.
- If $T_1 > T_2$, then a temperature gradient becomes established.
- The distribution of temperature is continuous, with a continuous change in temperature from one end to the other.



Heat transfer

- The transfer of heat energy in this situation is described by the heat equation.

$$\frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2}$$

Where T = temperature, t = time, k a heat transfer coefficient, and x is distance.

This is an example of a continuous model expressed as a ***partial differential equation***.



Heat transfer

$$\frac{\partial T}{\partial t} = k \frac{\partial^2 T}{\partial x^2}$$

This term describes the rate of change of temperature at a particular point.

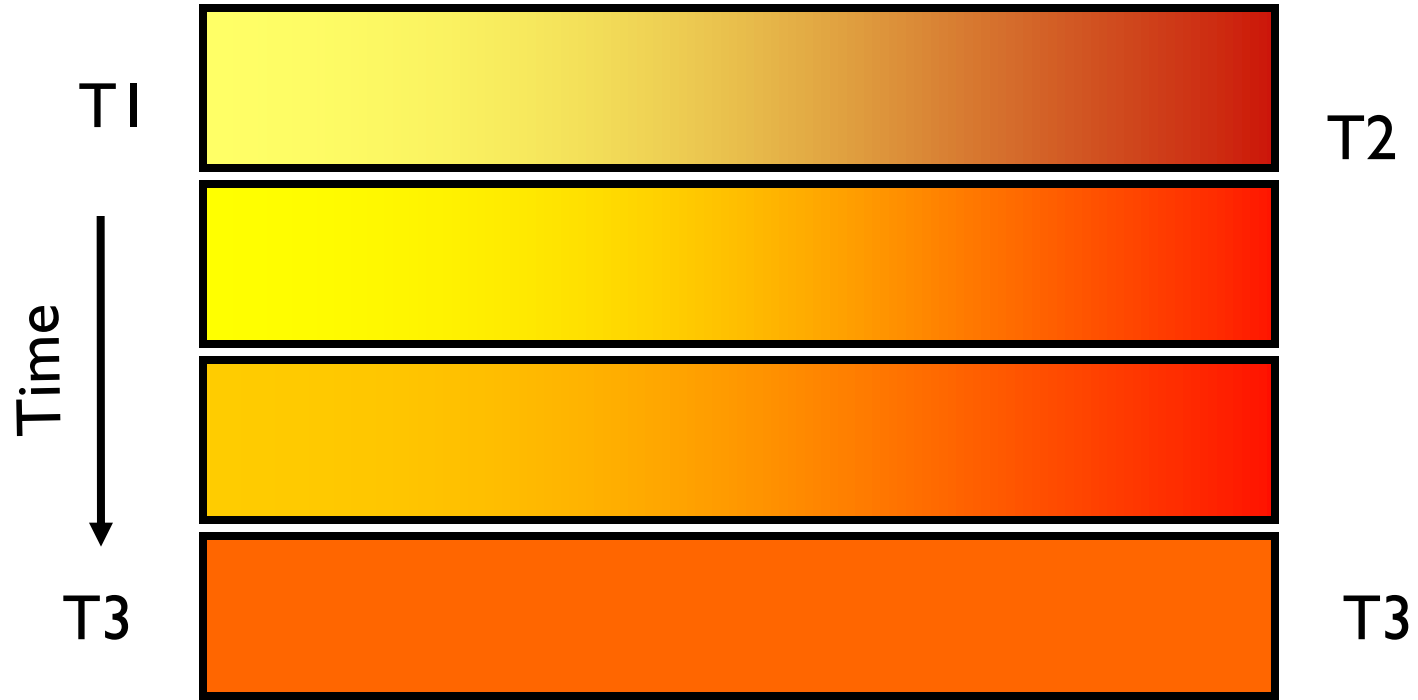
This term describes the temperature gradient at a particular point.

T1



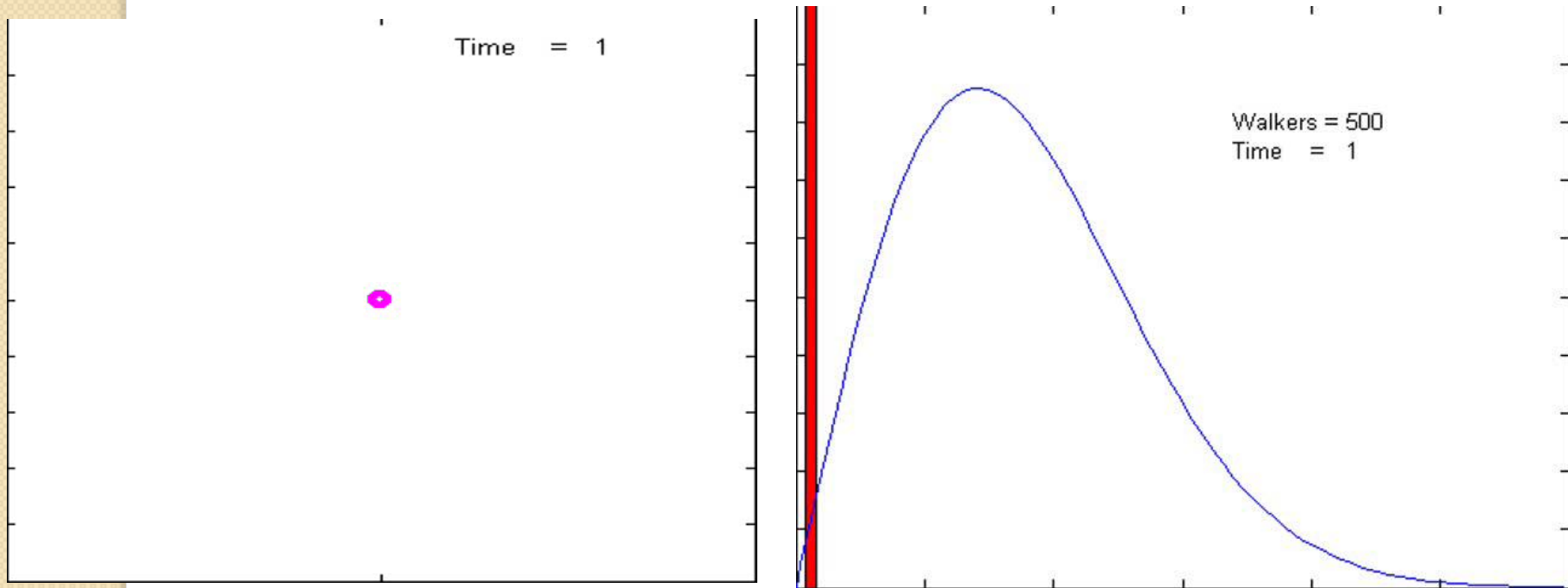
T2

Heat transfer



Diffusion

Molecules have kinetic energy, and so they tend to diffuse from regions with high concentration to regions with lower concentrations.



Fick's law – the diffusion equation

$$\frac{du}{dt} = D\nabla^2 u, \quad (\text{in 1D } \nabla^2 u = \frac{d^2 u}{dx^2})$$

- The quantity u describes the concentration of species u , which changes in both space and time, in 1D $u(x,t)$.
- The quantity du/dt is the rate of change of u at a single spatial point.
- The *Laplacian* of u ($\nabla^2 u$) is an index of the concentration gradient.
- Thus u flows down the concentration gradient, $du/dt > 0$ if $\nabla^2 u > 0$.
- This law is analogous to the heat equation.

Analytical solution to Fick's law

$$\frac{du}{dt} = D\nabla^2 u, \quad (\text{in 1D } \nabla^2 u = \frac{d^2 u}{dx^2})$$

- For an equation like this, we can produce an **analytical** solution.
- To do this we select a function $u(x,t)$ that fits the partial differential equation

$$u(x,t) = \frac{1}{\sqrt{4\pi D t}} e^{(-x^2 / 4Dt)}$$

Analytical solution to Fick's law

$$\frac{du}{dt} = D\nabla^2 u, \quad (\text{in 1D } \nabla^2 u = \frac{d^2 u}{dx^2})$$

An **analytical** solution in 1D is given by

$$u(x, t) = \frac{1}{\sqrt{4\pi D t}} e^{(-x^2/4Dt)}$$

Diffusion acts to smooth out discontinuities.

Spreading occurs over a distance of about \sqrt{Dt}

In many biological systems D is very small ($10^{-13} \text{ m}^2\text{s}^{-1}$), so diffusion is very slow.

