Introduction to mathematical modelling with ODEs

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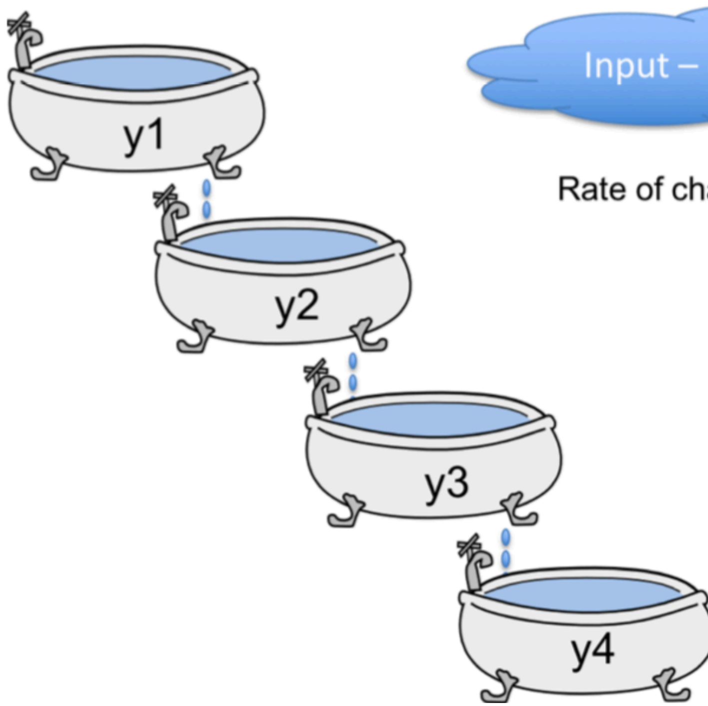
3. Interconnected systems

Biology is the study of the complex things in the Universe. Physics is the study of the simple ones.
Richard Dawkins

Bathtubs

To convert a set of reactions into a system of differential equations we can imagine every reaction species as a bathtub. Every reaction where a species is a reactant represents flow out of the bathtub and every reaction where a species is a product represents flow into the bathtub. The overall rate of change of concentration of the species is the difference between the sum of the inputs and sum of the outputs.



Input – output models

Rate of change = rate input – rate output

$$\frac{dy1}{dt} = -\text{ rate (out) } 1$$

$$\frac{dy2}{dt} = \text{rate (in) } 2 - \text{rate (out) } 2$$

$$\frac{dy3}{dt} = \text{rate (in) } 3 - \text{rate (out) } 3$$

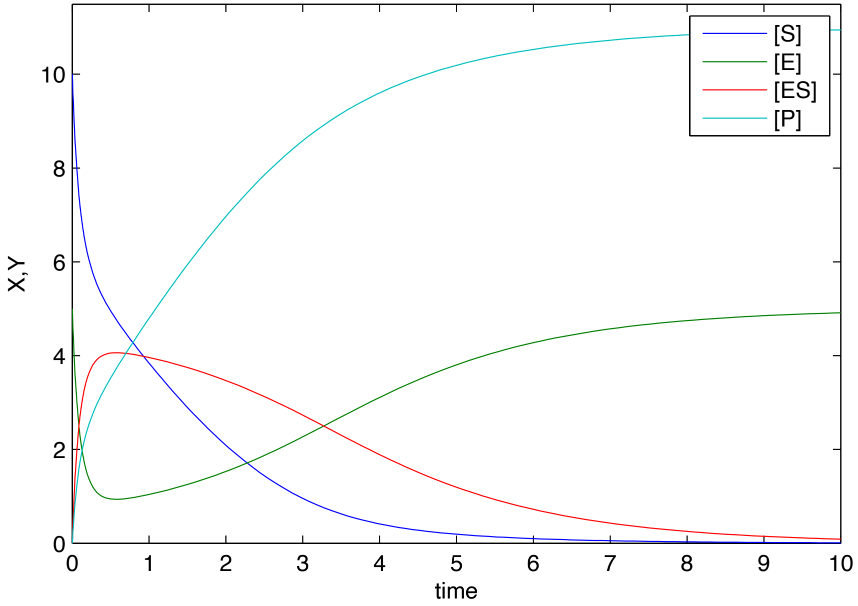
$$\frac{dy4}{dt} = \text{rate (in) } 4$$

Enzymatic reactions

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

How can we model the rates of these reactions:

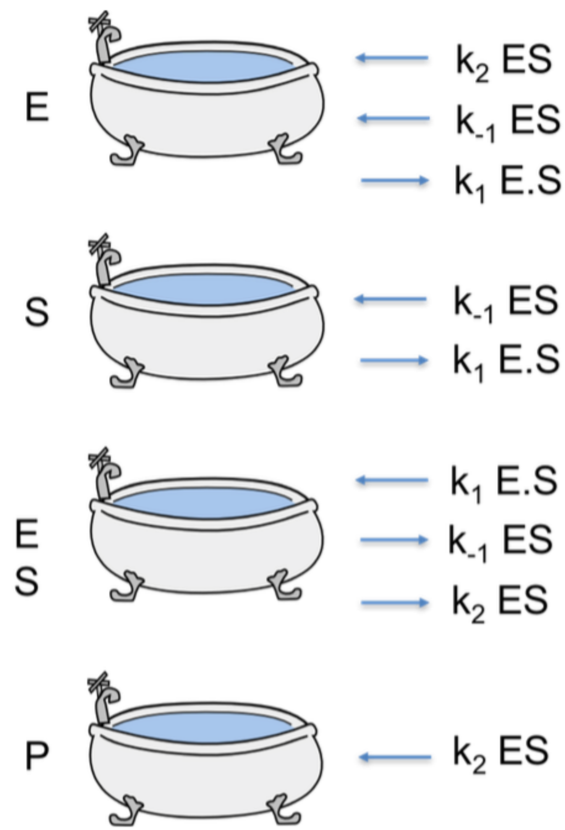
1. Convert the reactions into a system of differential equations
2. Starting from an initial concentration of enzyme, E, substrate, S, complex, ES and product, P, we can solve the system of differential equations using computational methods. This is an initial value problem



Enzymatic system

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

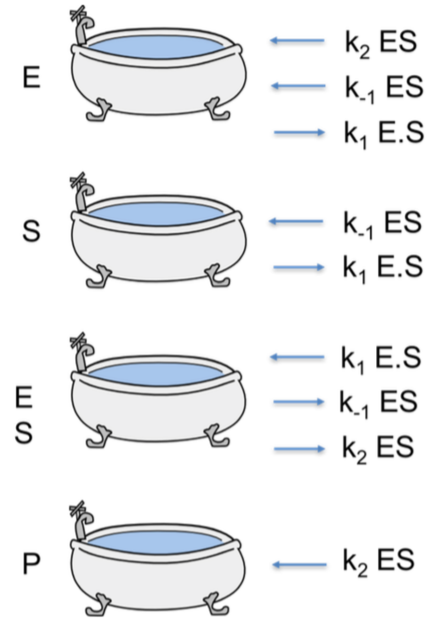
First write down the inputs and outputs of each bathtub



Input-output arguments

Sum the inputs and outputs of each bathtub to get the differential equations

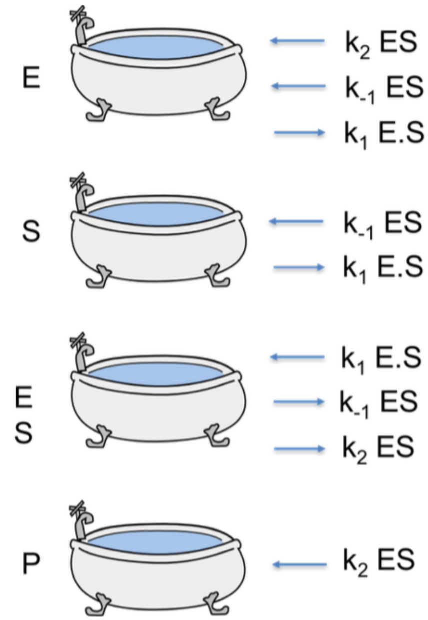
$$\frac{dS}{dt} =$$



$$\frac{dES}{dt} =$$

Input-output arguments

Sum the inputs and outputs of each bathtub to get the differential equations



$$\frac{dS}{dt} = +k_{-1}ES \; - k_1 E.S$$

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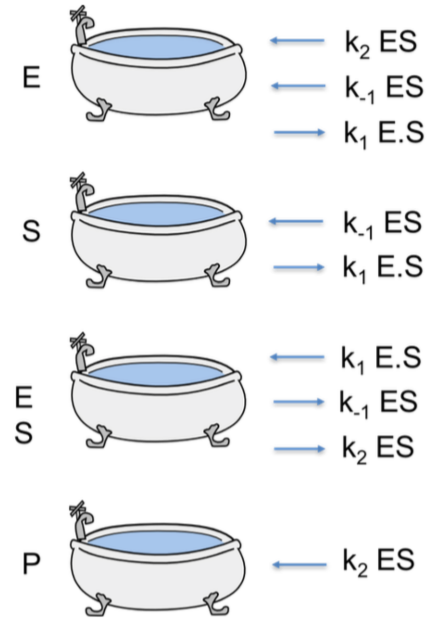
Input-output arguments

Sum the inputs and outputs of each bathtub to get the differential equations

$$\frac{dS}{dt} = +k_{-1}ES\ - k_1E.S$$



$$\frac{dES}{dt} = +k_1ES\ - k_{-1}ES - k_2ES$$

The whole system

reaction	rate	$d[S]/dt$	$d[E]/dt$	$d[ES]/dt$	$d[P]/dt$
$E + S \to ES$	$k_1[E][S]$	$-$	$-$	$+$	0
$ES \to E + S$	$k_{-1}[ES]$	$+$	$+$	$-$	0
$ES \to E + P$	$k_2[ES]$	0	$+$	$-$	$+$

$$\frac{d[S]}{dt} = +k_{-1}[ES] - k_1[E][S]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[ES] + k_2[ES]$$

$$\frac{d[ES]}{dt} = +k_1[E][S] - k_{-1}[ES] - k_2[ES]$$

$$\frac{d[P]}{dt} = +k_2[ES]$$

The whole system

Reaction

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

System of differential equations

$$\frac{d[S]}{dt} = +k_{-1}[ES] - k_1[E][S]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[ES] + k_2[ES]$$

$$\frac{d[ES]}{dt} = +k_1[E][S] - k_{-1}[ES] - k_2[ES]$$

$$\frac{d[P]}{dt} = +k_2[ES]$$

Often, we can use approximations to simplify a system

- E.g. Michaelis-Menten equation for enzyme kinetics

$$\frac{d[S]}{dt} = +k_{-1}[ES] - k_1[E][S]$$

$$\frac{d[E]}{dt} = -k_1[E][S] + k_{-1}[ES] + k_2[ES]$$

$$\frac{d[ES]}{dt} = +k_1[E][S] - k_{-1}[ES] - k_2[ES]$$

$$\frac{d[P]}{dt} = +k_2[ES]$$

$$\longrightarrow$$

$$\frac{d[P]}{dt} = V_{max}\frac{[S]}{K_m + [S]}$$

$$V_{max} = k_2[E]_0$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

- $[E]_0$ is the initial value of enzyme concentration ($t = 0$)
- Here we have simplified four differential equations into one, which makes calculations and analysis easier

How do we solve the differential equations?

- How do we go from $\frac{d[P]}{dt}$ to $[P]$, etc?
  - In general we require integration
  - For most non-trivial problems this cannot be done analytically
  - It must be done numerically

- Initial value problem:

  $[E]_0$ is the initial value of enzyme concentration (t=0)

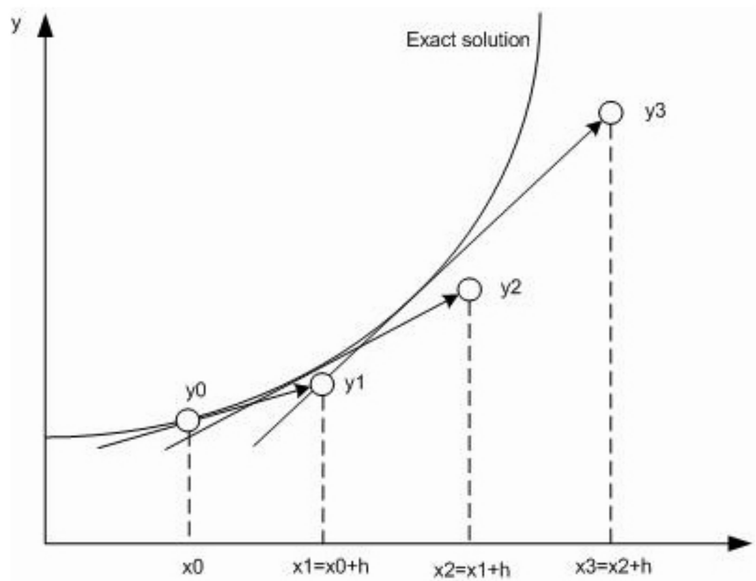
  $$[ES]_0 \; [P]_0 \; [S]_0$$

  What is the state of the system at time t?

Numerical integration

- Integrate the system of differential equations on a computer
- A simple scheme, known as Euler algorithm, is as follows

  – 0 : Start at the initial conditions
  – 1 : Calculate $\frac{d[S]}{dt}, \frac{d[E]}{dt}, \frac{d[ES]}{dt}, \frac{d[P]}{dt}$
  – 2 : Take a small step in time, h
  – 3 : Update $[S], [E], [ES], [P]$ using:
    - $\Delta[S] \approx (\frac{d[S]}{dt})h$
    - $\Delta[E] \approx (\frac{d[E]}{dt})h$
    - etc
  – 4 : If final time reached exit, otherwise go to 1



- In general solvers do more complicated stepping but the principle is the same

Results

parameters: $k_1 = 1, k_{-1} = 0.5, k_2 = 0.6$

initial conditions: $[S]_0 = 10, [E]_0 = 5, [ES]_0 = [P]_0 = 0$