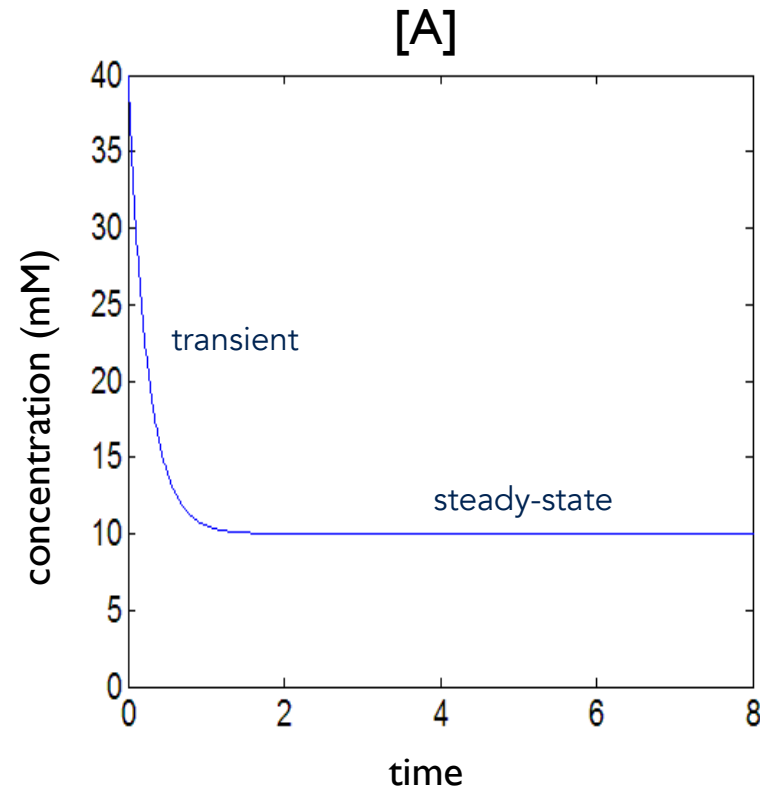


Steady state and equilibrium

A system is at *steady-state* when concentrations do not change with time – they are fixed, or steady



At steady-state

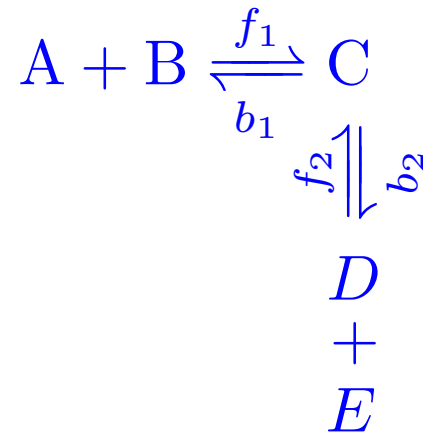
$$\frac{d[A]}{dt} = 0$$

We will often study systems at steady-state because their behaviour is then simpler.

Equilibrium is a special steady state where detailed balance holds

A system is in *detailed balance* if the rate of every forward reaction balances the rate of every backward reaction.

Consider



$$\frac{d[C]}{dt} = f_1[A][B] - b_1[C] + f_2[D][E] - b_2[C]$$

At steady state

$$\frac{d[C]}{dt} = f_1[A][B] - b_1[C] + f_2[D][E] - b_2[C] = 0$$

$$f_1[A][B] + f_2[D][E] = b_1[C] + b_2[C]$$

At equilibrium

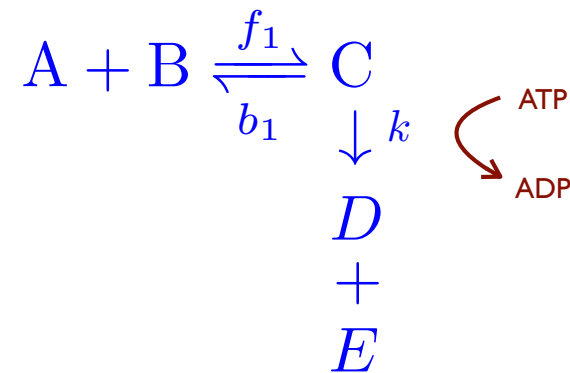
$$\frac{d[C]}{dt} = \overbrace{f_1[A][B] - b_1[C]}^0 + \overbrace{f_2[D][E] - b_2[C]}^0 = 0$$

$$f_1[A][B] = b_1[C]$$

$$f_2[D][E] = b_2[C]$$

Detailed balance means that the system is at a minimum of free energy and is in a “dead” state

We often model systems that can never equilibrate



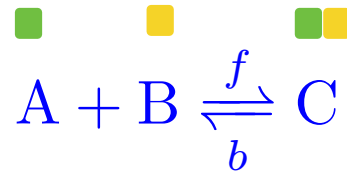
we implicitly assume the free energy, here ATP, preventing a backward reaction is continually re-supplied

Now

$$\frac{d[C]}{dt} = f_1[A][B] - b_1[C] - k[C]$$

which is able to reach steady state but never equilibrium because the  $k$  reaction cannot be balanced.

We use detailed balance and conservations to find equilibrium concentrations



Detailed balance implies

$$f[A][B] = b[C]$$

or

$$[A][B] = K_{\text{eq}}[C].$$

$$K_{\text{eq}} = \frac{b}{f}$$

The rate equations are

$$\frac{d[A]}{dt} = \frac{d[B]}{dt} = -f[A][B] + b[C] = -\frac{d[C]}{dt}$$

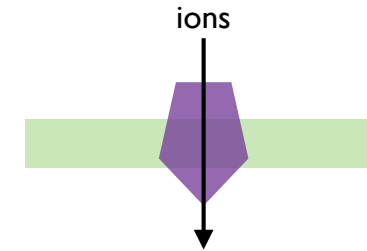
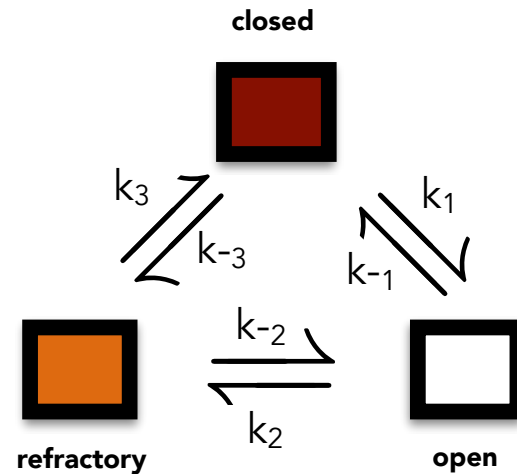
and so we have two further equations

$$[A] + [C] = A_0 \quad [B] + [C] = B_0$$

# Thermodynamic cycles

Allowing reactions to go to equilibrium can restrict the values of rate constants

Ion channels often have multiple states



Detailed balance implies

$$k_1 C = k_{-1} O \quad ; \quad k_2 O = k_{-2} R \quad ; \quad k_3 R = k_{-3} C.$$

equilibrium

or

$$C = \frac{k_{-1}}{k_1} O = \frac{k_{-1}}{k_1} \cdot \frac{k_{-2}}{k_2} R = \frac{k_{-1}}{k_1} \cdot \frac{k_{-2}}{k_2} \cdot \frac{k_{-3}}{k_3} C$$

and so

$$k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$$

if this constraint is broken, the system must use energy to bias the cycle to move in a particular direction

Hill functions



# Empirical input-output relationships are often approximated as Hill functions

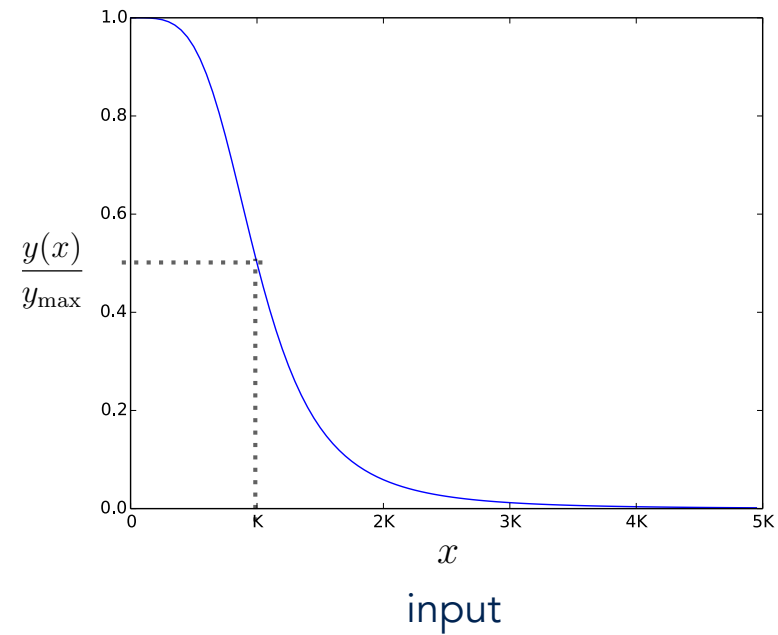
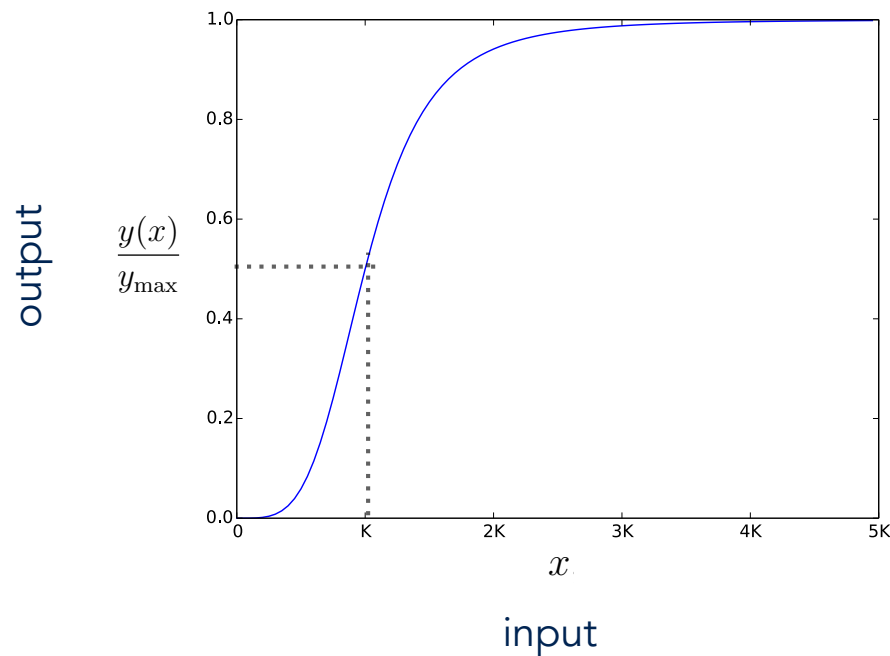
Hill number: determines the steepness of the response

$$y(x) = \frac{y_{\max} x^n}{K^n + x^n}$$

EC<sub>50</sub>

$$y(x) = \frac{y_{\max} K^n}{K^n + x^n}$$

IC<sub>50</sub>



$$y(x = K) = \frac{y_{\max}}{2}$$

## Some terminology

$$y(x) = \frac{y_{\max} x^n}{K^n + x^n}$$

$n = 1$ : *hyperbolic* or Michaelis-Menten response

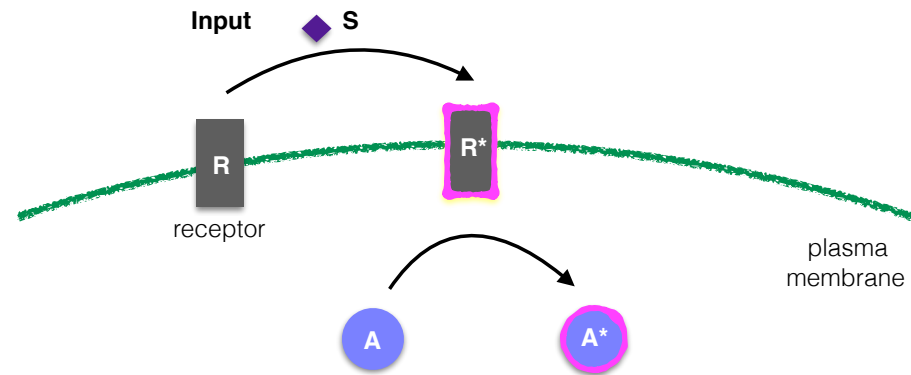
$n > 1$ : *sigmoidal* or S-shaped response

$n > 1$ : *ultrasensitive* response for signalling

$n < 1$ : *subsensitive* response

$n > 1$ : *cooperative* response for gene expression

# Modelling signal transduction II



Rather than

$$[R^*] \simeq \frac{[S]R_0}{\frac{b}{f} + [S]} \quad \text{use} \quad [R^*] \simeq \frac{R_0[S]^n}{K^n + [S]^n}$$

so that

$$\frac{d[A^*]}{dt} \simeq \frac{kR_0[S]^n}{K^n + [S]^n} (A_0 - [A^*])$$

eg  $n$  molecules of  $S$   
are needed to  
activate a receptor