Overview

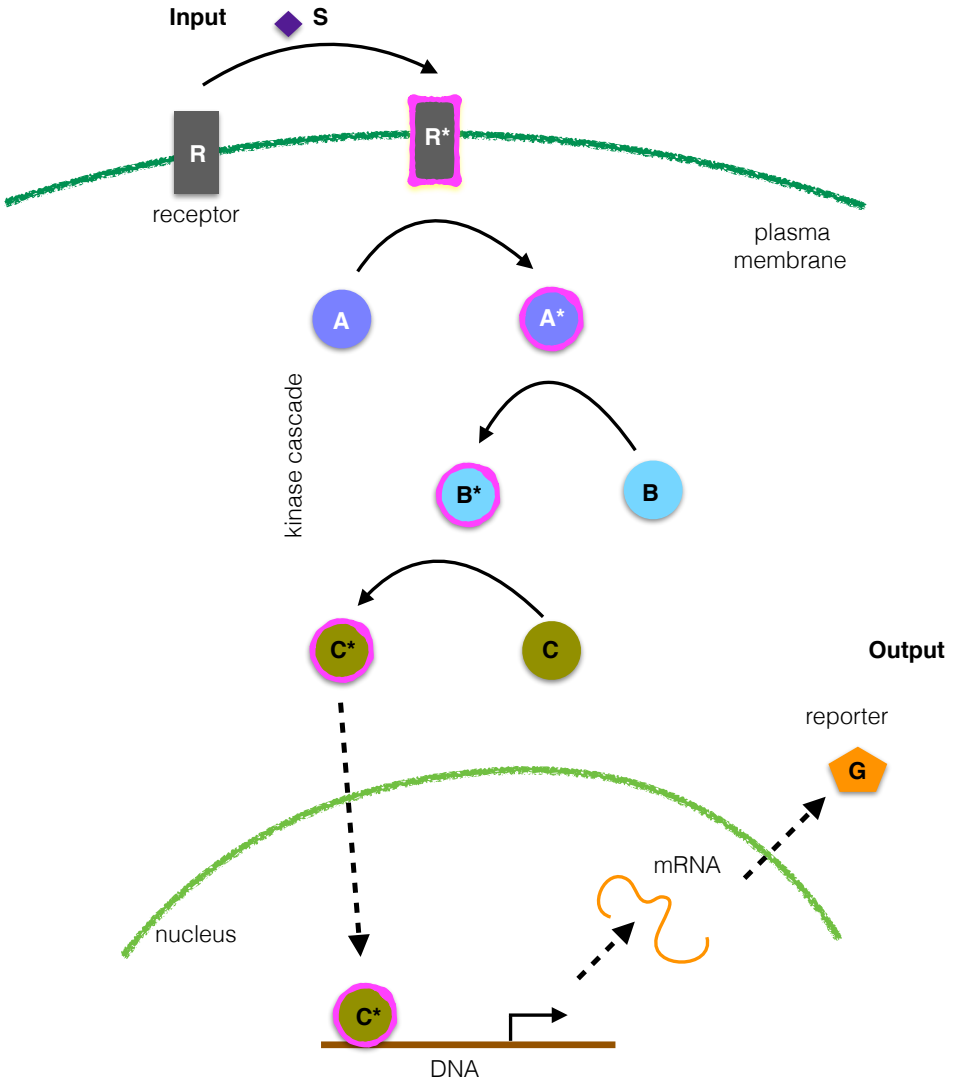
Modelling biochemical reactions

Modelling gene expression

Positive feedback and bistability

Negative feedback and oscillations

I will use a signalling pathway as an example throughout



Modelling biochemical reactions

There are two fundamental types of reactions

$$\mathrm{A} + \mathrm{B} \underset{\tilde{b}}{\overset{\tilde{f}}{\rightleftharpoons}} \mathrm{C}$$

The association rate is determined by two times:

$$\text{time of reaction} = t_{\text{diff}} + t_{\text{reac}}$$

and so

$$\tilde{f} = (t_{\text{diff}} + t_{\text{reac}})^{-1}$$

The dissociation rate is determined by the lifetime of a molecule of *C*:

$$\tilde{b} = \frac{\log(2)}{\text{lifetime of } C}$$

Rate equations describe how number of molecules change with time

$$\mathrm{A} + \mathrm{B} \underset{\tilde{b}}{\overset{\tilde{f}}{\rightleftharpoons}} \mathrm{C}$$

How do the numbers of molecules of, say, species *C* change with time?

$$N_C(t+dt) = N_C(t) + \tilde{f} dt N_A N_B - \tilde{b} dt N_C$$

number of pairs of *A* and *B* associating in time *dt*

number of C disassociating in time *dt*

Or

$$\frac{N_C(t+dt) - N_C(t)}{dt} = \tilde{f} N_A N_B - \tilde{b} N_C$$ and so

$$\boxed{\frac{dN_C}{dt} = \tilde{f} N_A N_B - \tilde{b} N_C}$$

Another example

$$\begin{array}{ccc} \mathrm{A} + \mathrm{B} \underset{\tilde{b}}{\overset{\tilde{f}}{\rightleftharpoons}} \mathrm{C} & & \\ & \downarrow k & \\ & \mathrm{D} + \mathrm{E} \underset{\tilde{h}}{\overset{\tilde{g}}{\rightleftharpoons}} \mathrm{F} & \end{array}$$

We now have

$$\frac{dN_C}{dt} = \tilde{f} N_A N_B - \tilde{b} N_C - k N_C$$

Each reaction that affects C has a corresponding term in the equation.
There is one positive term for the reaction that increases N_C and a negative term for each reaction that decreases N_C.

Interpreting the rates of first-order reactions

$$\mathrm{N} \xrightarrow{k} \mathrm{M}$$

the half life is the time taken for the number of molecules to halve

How does *k* relate to the half-life of *N* ?

The rate equation is

$$\frac{dN}{dt} = -kN \qquad \text{which implies} \qquad N = N_0\,\mathrm{e}^{-kt}$$

$$\text{or} \qquad N = N_0\,2^{-\frac{kt}{\log 2}}$$

$$\mathrm{e}^a = \left(\mathrm{e}^{\log 2}\right)^{\frac{a}{\log 2}} = 2^{\frac{a}{\log 2}}$$

At the half-life, the number of molecules becomes $N_0/2$

$$N_0\,2^{-1} = N_0\,2^{-kt_{\frac{1}{2}}/\log 2}$$

so that

$$1 = \frac{kt_{\frac{1}{2}}}{\log 2} \qquad \text{or} \qquad k = \frac{\log 2}{t_{\frac{1}{2}}}$$

Defining concentrations

The molar concentration of C is defined as

$$[C] = \frac{N_C}{n_A V}$$

molar units are moles per litre

where N_C is the number of molecules of C, n_A is Avogadro's number, and V is the volume of the cell in litres.

$$n_A \simeq 6.02 \times 10^{23}$$ 1 mole

Note that $1\ell = 10^{-3}\mathrm{m}^3$

The rate equation for concentrations

Before we had

$$\frac{dN_C}{dt} = \tilde{f} N_A N_B - \tilde{b} N_C$$

If we divide this equation by $n_A V$

$$\frac{d}{dt} \cdot \frac{N_C}{n_A V} = \tilde{f} \frac{N_A}{n_a V} \cdot \frac{N_B}{n_a V} n_a V - \tilde{b} \frac{N_C}{n_A V}$$

and so using the definition of concentration

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

$$[C] = \frac{N_C}{n_A V}$$

Defining macroscopic rates

$$f = \tilde{f} n_A V$$
$$b = \tilde{b}$$

then

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

Mesoscopic rates govern numbers of molecules, macroscopic rates govern concentrations

For associations, the *mesoscopic* rate depends on the cell's volume – in larger volumes, it takes longer for two molecules to associate – but the *macroscopic* rate does not

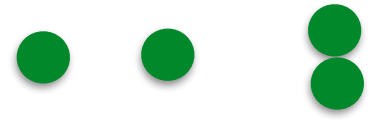
$$f = \tilde{f} n_A V$$
$$b = \tilde{b}$$

the volume terms cancel

For disassociations, the mesoscopic and macroscopic rates are the same – they are determined by the lifetime of molecules.

The difference between mesoscopic and macroscopic rates is important for running stochastic stimulations.

Dimerisation is the only tricky example



$$T + T \underset{b}{\overset{f}{\rightleftharpoons}} T_2$$

association rate: $f\,[T]^2$
disassociation rate: $b[T_2]$

An association reaction removes *two* molecules of *T*, a dissociation reaction creates *two* molecules of *T*

$$\frac{d[T]}{dt} = -2f[T]^2 + 2b[T_2]$$

An association reaction creates *one* molecule of T_2, a dissociation reaction creates *one* molecule of T_2

$$\frac{d[T_2]}{dt} = f[T]^2 - b[T_2]$$

Molecules are conserved during dimerisation

An example

$$T + T \underset{b}{\overset{f}{\rightleftharpoons}} T_2$$

T	T_2
10	0
8	1
6	2
8	1

time ↓

each line shows the number of molecules after one reaction occurs

We have

$$\frac{d[T]}{dt} = -2f[T]^2 + 2b[T_2]$$

$$\frac{d[T_2]}{dt} = f[T]^2 - b[T_2]$$

and so

$$\frac{d[T]}{dt} + 2\frac{d[T_2]}{dt} = 0$$

implying

$$[T] + 2[T_2] = \text{constant}$$

the constant is determined by the initial numbers of monomers and dimers

Association reactions are limited by diffusion

$$f = \frac{n_A V}{t_{\text{diff}} + t_{\text{reac}}} < \frac{n_A V}{t_{\text{diff}}}$$

$f = \tilde{f} n_A V$

The fastest association reaction is one where the two molecules react the instant they come together and so is determined only by diffusion

$$f_{\max} = 4\pi D a$$

from solving the diffusion equation

the sum of the molecules' diffusion coefficients

typical size of a molecule

and for molar concentrations

$$f\ (\text{in M}) < f_{\max} \times n_a \times 10^3$$

1 mole

volume in litres

Association reactions have rates less than approximately 10^9 M^{-1} s^{-1}

$$f\ (\text{in M}) < f_{\max} \times n_a \times 10^3$$

$$f_{\max} = 4\pi Da$$

Assuming D is 1000 μm^2 s^{-1} (100 times faster than the typical diffusion of proteins)

$$\begin{aligned} f &< 4\pi \times \overbrace{10^3 \times 10^{-12}}^{D \text{ in } \mathrm{m^2 s^{-1}}} \times \overbrace{10^{-9}}^{a} \times \overbrace{6 \times 10^{23}}^{n_a} \times \overbrace{10^3}^{\text{for } \ell} \\ &\simeq 7.5 \times 10^9\, \mathrm{M^{-1} s^{-1}}. \end{aligned}$$

What is the lowest possible concentration in a bacterium?

The concentration of 1 molecule is

$$\frac{1}{n_A V}$$

and the volume of a bacterium is 1μm^3

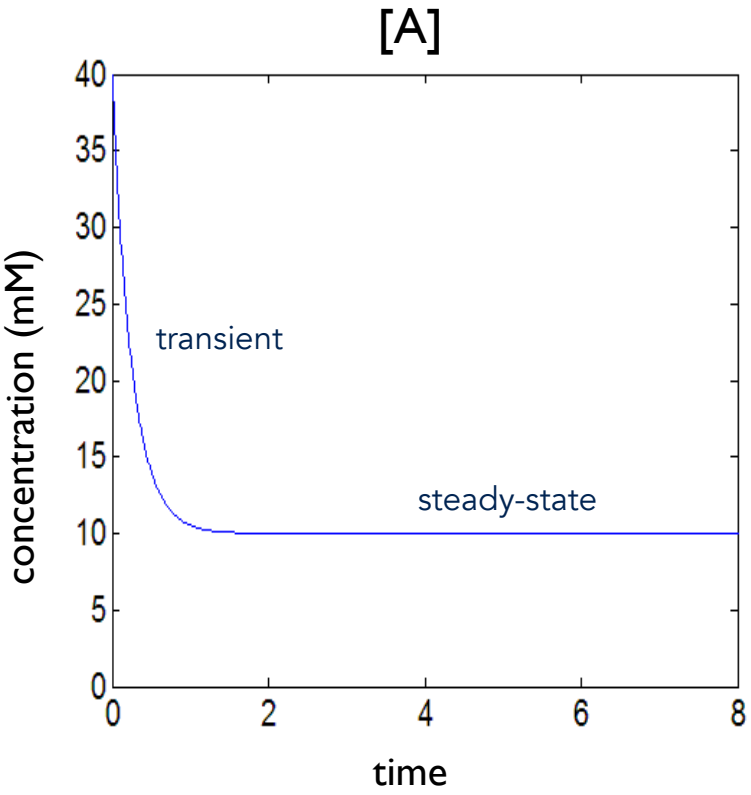
$$\frac{1}{6 \times 10^{23} \times 10^{-18} \times 10^{3}} \simeq \frac{1}{10^9}$$

Avogado volume litres

The lowest possible concentration is 1 nM

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

$$\mathrm{A} + \mathrm{B} \underset{b_1}{\overset{f_1}{\rightleftharpoons}} \mathrm{C}$$

$$C \overset{f_2}{\underset{b_2}{\rightleftharpoons}} D + E$$

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

At steady state

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

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

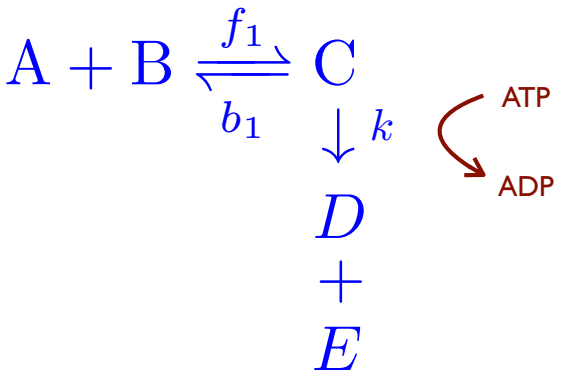
At equilibrium

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

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

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



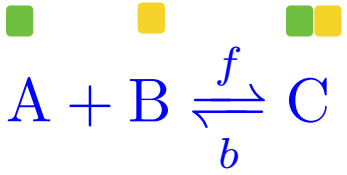
we implicitly assume the free energy preventing a backward reaction, here ATP, is continually re-supplied

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

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

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

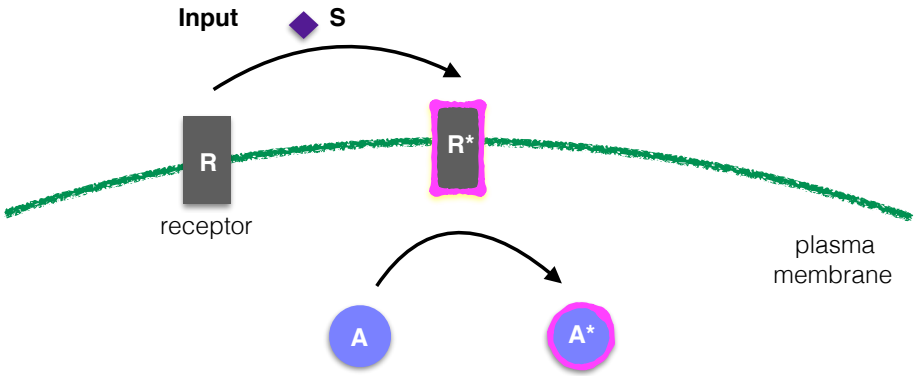
The rate equations are

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

and so we have two further equations

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

Modelling signal transduction I.i



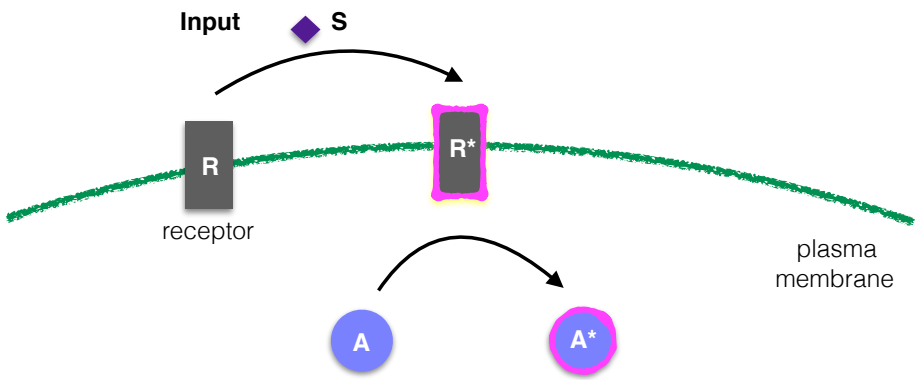
Signal (ligand) binding the receptor

$$[\mathrm{R}] + [\mathrm{S}] \underset{b}{\overset{f}{\rightleftharpoons}} [\mathrm{R}^*]$$

and activated receptors activate a downstream protein *A*

$$[\mathrm{R}^*] + [\mathrm{A}] \xrightarrow{k} [\mathrm{R}^*] + [\mathrm{A}^*]$$

Modelling signal transduction I.ii



$$[\mathrm{R}] + [\mathrm{S}] \underset{b}{\overset{f}{\rightleftharpoons}} [\mathrm{R}^*]$$

$$[\mathrm{R}^*] + [\mathrm{A}] \xrightarrow{k} [\mathrm{R}^*] + [\mathrm{A}^*]$$

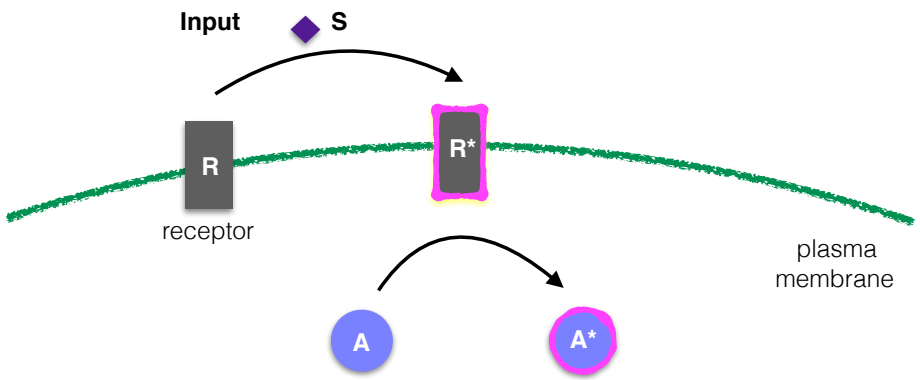
The rate equations are

$$\begin{aligned}
\frac{d[S]}{dt} &= -f[R][S] + b[R^*] \\
\frac{d[R]}{dt} &= -f[R][S] + b[R^*] \\
\frac{d[R^*]}{dt} &= f[R][S] - b[R^*] \\
\frac{d[A]}{dt} &= -k[A][R^*] \\
\frac{d[A^*]}{dt} &= k[A][R^*]
\end{aligned}$$

notice that the number of receptors is conserved

$$\frac{d[R]}{dt} + \frac{d[R^*]}{dt} = 0$$

Modelling signal transduction I.iii



$$[\mathrm{R}] + [\mathrm{S}] \underset{b}{\overset{f}{\rightleftharpoons}} [\mathrm{R}^*]$$

$$[\mathrm{R}^*] + [\mathrm{A}] \xrightarrow{k} [\mathrm{R}^*] + [\mathrm{A}^*]$$

We are interested in downstream effects – the rate of change of activated *A*.

Let's assume the binding of the receptor and signal is at equilibrium

$$f[R][S] \simeq b[R^*]$$

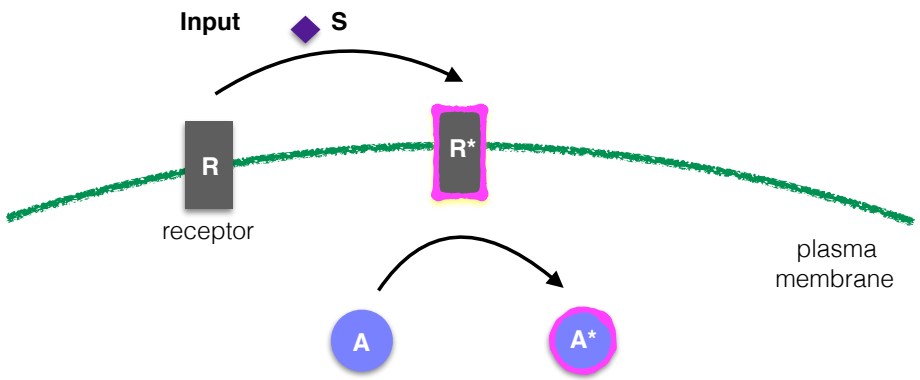
That the receptors are conserved means – for a constant R_0

$$R_0 = [R] + [R^*]$$

and so

$$[R^*] \simeq \frac{[S]R_0}{\frac{b}{f} + [S]}$$

Modelling signal transduction I.iv



$$[\mathrm{R}] + [\mathrm{S}] \underset{b}{\overset{f}{\rightleftharpoons}} [\mathrm{R}^*]$$

$$[\mathrm{R}^*] + [\mathrm{A}] \xrightarrow{k} [\mathrm{R}^*] + [\mathrm{A}^*]$$

We are interested in downstream effects – activated *A*

$$\frac{d[A^*]}{dt} = k[A][R^*]$$

$$[R^*] \simeq \frac{[S]R_0}{\frac{b}{f} + [S]}$$

and so

$$\frac{d[A^*]}{dt} \simeq \frac{k[S]R_0}{\frac{b}{f} + [S]}[A]$$

or

$$\frac{d[A^*]}{dt} \simeq \frac{k[S]R_0}{\frac{b}{f} + [S]}(A_0 - [A^*])$$

because the number of *A* molecules is also conserved