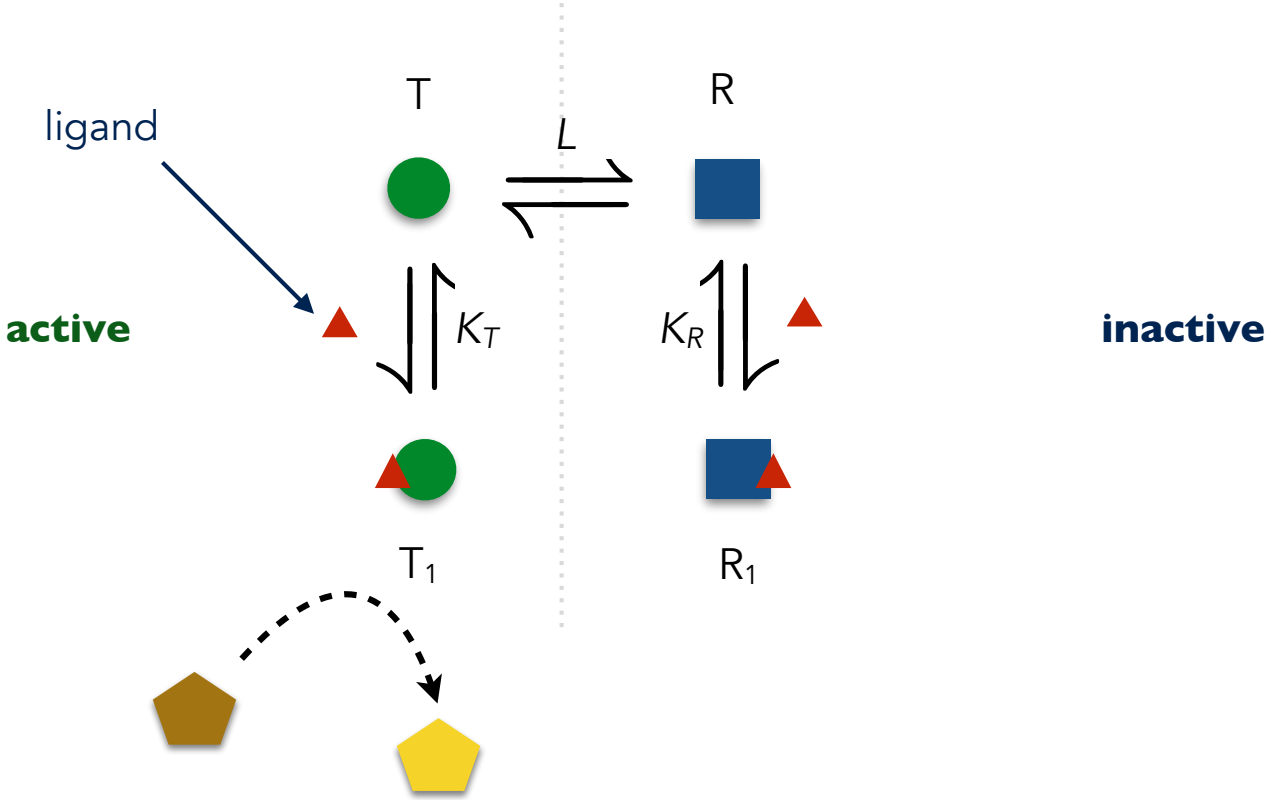
The Monod-Wyman-Changeux model of allostery

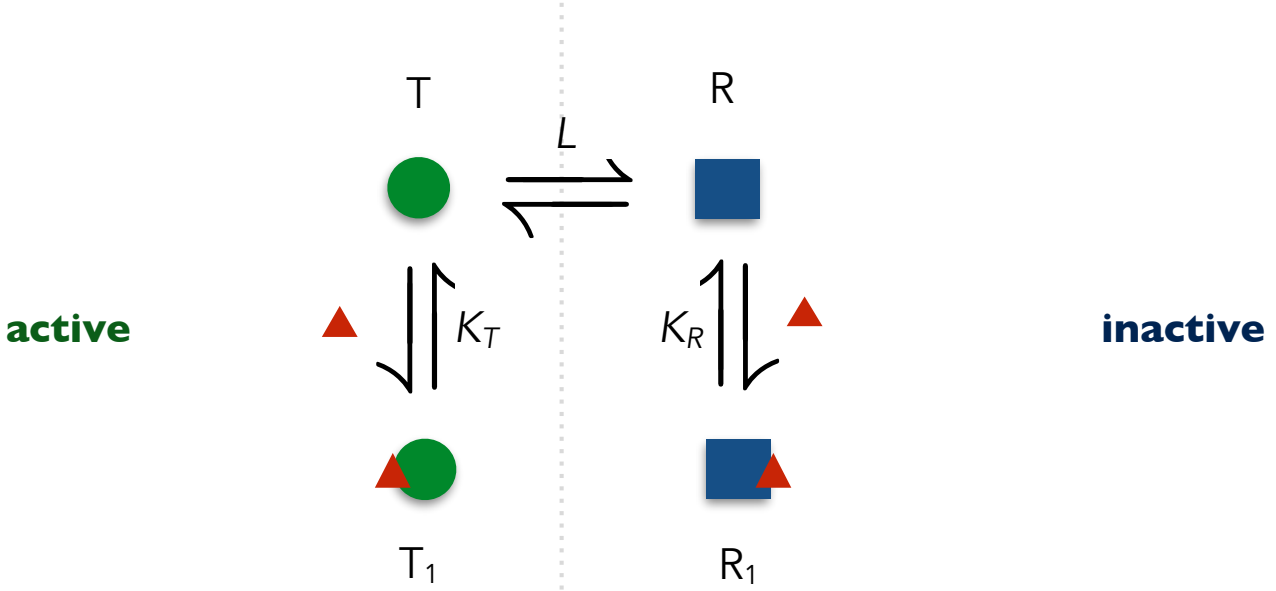
Allostery connects molecules with different structures

An enzyme is *allosteric* if its activity is modified through the binding of a regulator to a site on the enzyme that is not the enzyme's functional site.



The downstream molecule regulated by the active state of the receptor can have a completely different structure to the ligand.

An allosteric enzyme that binds a single regulator has a hyperbolic response



In terms of chemical equations

$$\mathrm{T} \overset{L}{\rightleftharpoons} \mathrm{R} \qquad \mathrm{X} + \mathrm{T} \overset{K_T}{\rightleftharpoons} \mathrm{T}_1 \qquad \mathrm{X} + \mathrm{R} \overset{K_R}{\rightleftharpoons} \mathrm{R}_1$$

$K_T > K_R$ ligand is activating

with

$$L = \frac{[R]}{[T]} \qquad K_T = \frac{[T_1]}{[X][T]} \qquad K_R = \frac{[R_1]}{[X][R]}$$

equilibrium constants

association constants

An allosteric enzyme that binds a single regulator has a hyperbolic response

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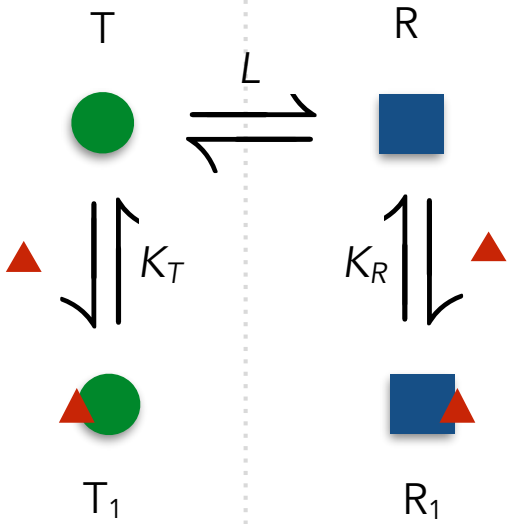
$$\mathrm{X} + \mathrm{T} \overset{K_T}{\rightleftharpoons} \mathrm{T}_1$$
$$\mathrm{X} + \mathrm{R} \overset{K_R}{\rightleftharpoons} \mathrm{R}_1$$



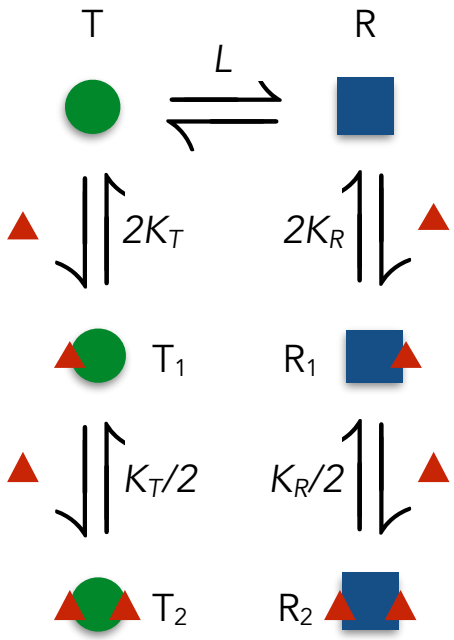
$$L = \frac{[R]}{[T]}$$
$$K_T = \frac{[T_1]}{[X][T]}$$
$$K_R = \frac{[R_1]}{[X][R]}$$

The fraction of activated enzymes is

$$\begin{aligned} f_{\text{on}} &= \frac{[T] + [T_1]}{[T] + [T_1] + [R] + [R_1]} \\ &= \frac{[T] + K_T[X][T]}{[T] + K_T[X][T] + L[T] + K_R[X]L[T]} \\ &= \frac{1 + K_T[X]}{1 + K_T[X] + L(1 + K_R[X])} \end{aligned}$$

approximately hyperbolic

We will assume that an allosteric enzyme that binds more than one regulator is symmetric



There are two identical binding sites for *X* on the enzyme, and f_T is the association rate for binding to one site in the *T* state:

$$\mathrm{X} + \mathrm{T} \xrightarrow{2f_T} T_1$$

the association rate is twice f_T because there are two binding sites

$$\mathrm{T}_1 \xrightarrow{b_T} \mathrm{X} + \mathrm{T}$$

the rate of dissociation is b_T because there is only one *X* that can dissociate

Understanding the factor of two

Consider the binding sites explicitly

$$\mathrm{X} + \mathrm{T}_{0,0} \underset{b_T}{\overset{f_T}{\rightleftharpoons}} \mathrm{T}_{1,0}$$

$$\mathrm{X} + \mathrm{T}_{0,0} \underset{b_T}{\overset{f_T}{\rightleftharpoons}} \mathrm{T}_{0,1}$$

the rate equation is

$$\begin{aligned}\frac{d[X]}{dt} &= -f_T[X][T_{0,0}] - f_T[X][T_{0,0}] + b_T[T_{1,0}] + b_T[T_{0,1}] \\ &= -2f_T[X][T_{0,0}] + b_T[T_{1,0}] + b_T[T_{0,1}]\end{aligned}$$

Defining $[T_1] = [T_{1,0}] + [T_{0,1}]$ then

$$\frac{d[X]}{dt} = -2f_T[X][T_{0,0}] + b_T[T_1]$$

$$\mathrm{X} + \mathrm{T} \underset{b_T}{\overset{2f_T}{\rightleftharpoons}} \mathrm{T}_1$$

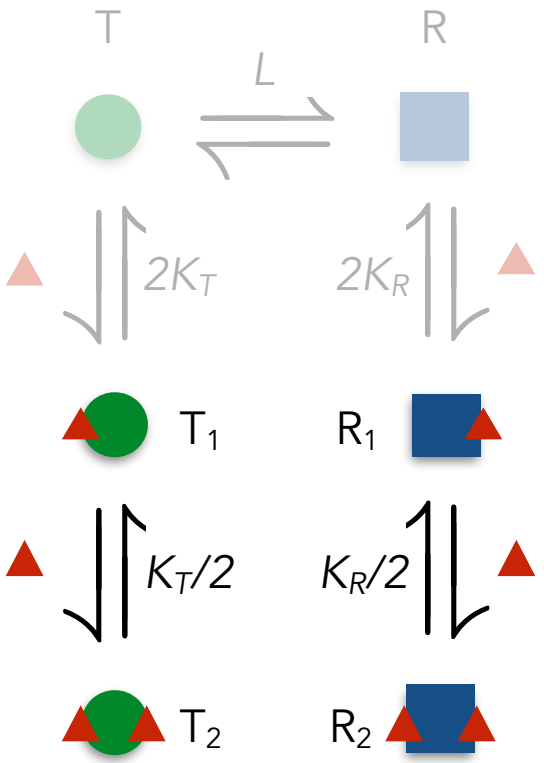
Consider the binding of the second regulator

the association rate is f_T because there is one free binding site

$$\mathrm{X} + \mathrm{T}_1 \xrightarrow{f_T} T_2$$

the rate of dissociation is $2b_T$ because there are two *X* molecules that can dissociate

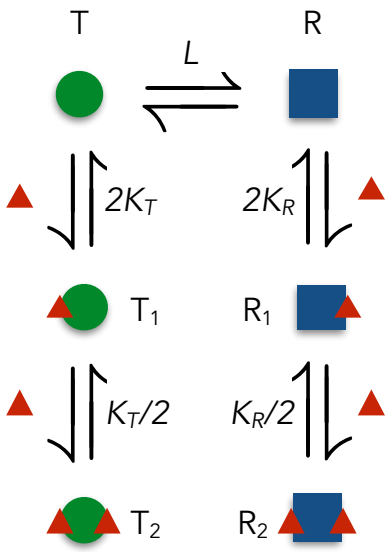
$$\mathrm{T}_2 \xrightarrow{2b_T} \mathrm{X} + \mathrm{T}_1$$



The overall association constant is

$$\frac{f_T}{2b_T} = \frac{K_T}{2}$$

An allosteric enzyme that binds more than one regulator has a sigmoidal response



$$L = \frac{[R]}{[T]}$$

$$[T_1] = 2K_T[T][X]$$

$$[T_2] = \frac{K_T}{2}[T_1][X]$$

$$[R_1] = 2K_R[R][X]$$

$$[R_2] = \frac{K_R}{2}[R_1][X]$$

$$f_{\text{on}} = \frac{[T] + [T_1] + [T_2]}{[T] + [T_1] + [T_2] + [R] + [R_1] + [R_2]}$$

$$= \frac{[T] + 2K_T[X][T] + \overbrace{\frac{1}{2}K_T[X]2K_T[X][T]}^{T_1}}{[T] + 2K_T[X][T] + \frac{1}{2}K_T[X]2K_T[X][T] + L[T] + 2K_R[X]L[T] + \frac{1}{2}K_R[X]2K_R[X]L[T]}$$

$$= \frac{1 + 2K_T[X] + K_T^2[X]^2}{1 + 2K_T[X] + K_T^2[X]^2 + L(1 + 2K_R[X] + K_R^2[X]^2)}$$

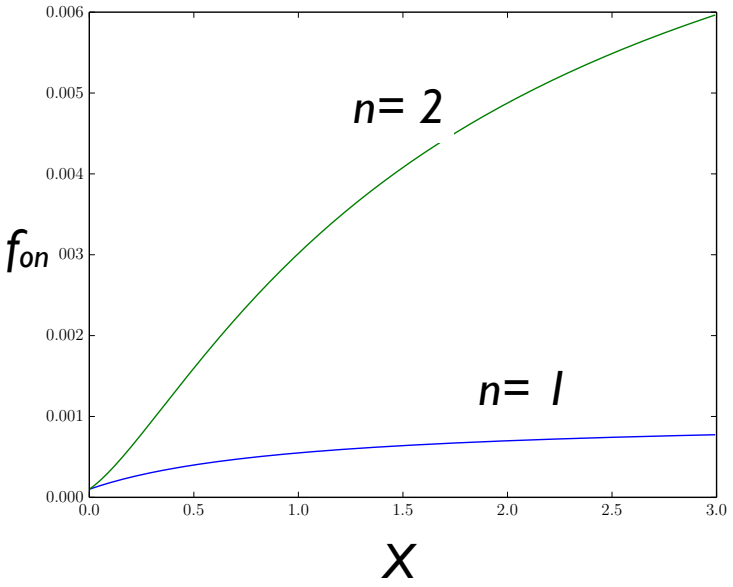
$$= \frac{(1 + K_T[X])^2}{(1 + K_T[X])^2 + L(1 + K_R[X])^2}$$

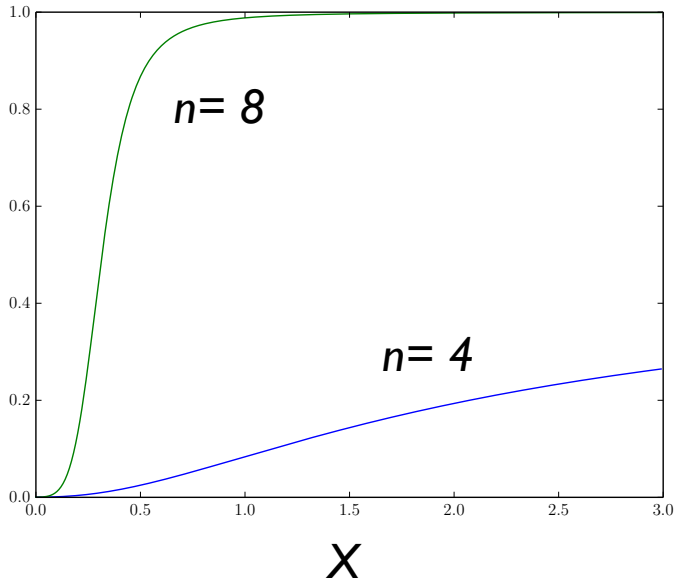
sigmoidal

The more regulators bind, the steeper the response

$$f_{\text{on}} = \frac{(1 + K_T[X])^n}{(1 + K_T[X])^n + L(1 + K_R[X])^n}$$

n is the number of regulators that bind

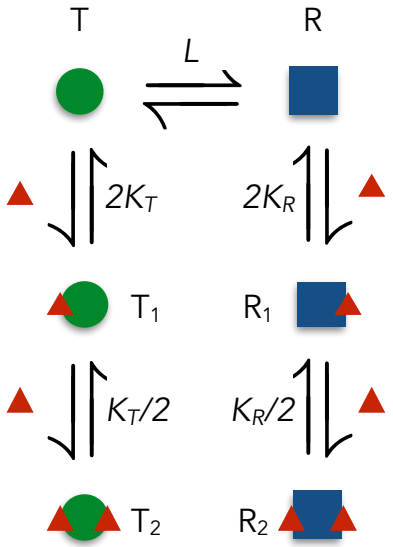




An increases in [X] causes a sharp change in f_{on} when $[X]$ is near $[X_{50}]$ because all reactions involving X shift their equilibrium.

At $X = [X_{50}]$ when $f_{on} = 0.5$, the total concentration of tense molecules equals the total concentration of relaxed molecules

$$[R]\left(1 + K_R\left[X_{50}\right]\right)^n = [T]\left(1 + K_T\left[X_{50}\right]\right)^n$$



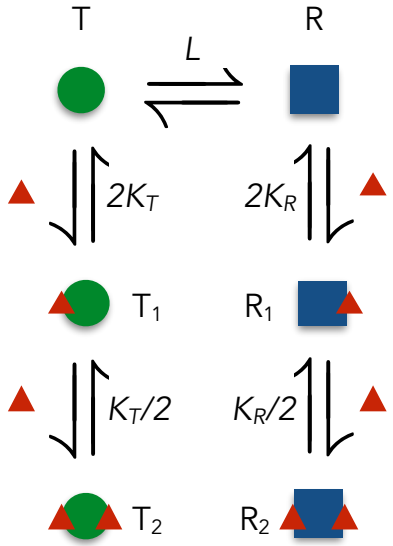
The rate at which f_{on} changes with $[X]$ is

$$\left.\frac{\partial f_{\text{on}}}{\partial [X]}\right|_{[X_{50}]} = \frac{n}{4} \cdot \frac{K_T - K_R}{\left(1 + K_R\left[X_{50}\right]\right)\left(1 + K_T\left[X_{50}\right]\right)}$$

All reactions involving binding to the tense state contribute a term proportional to $+ n K_T$.
All reactions involving binding to the relaxed state contribute a term proportional to $- n K_R$.

An allosteric enzyme has a basal level of activity in the absence of its regulator

$$f_{\text{on}} = \frac{(1 + K_T[X])^n}{(1 + K_T[X])^n + L(1 + K_R[X])^n}$$



When *X= 0*

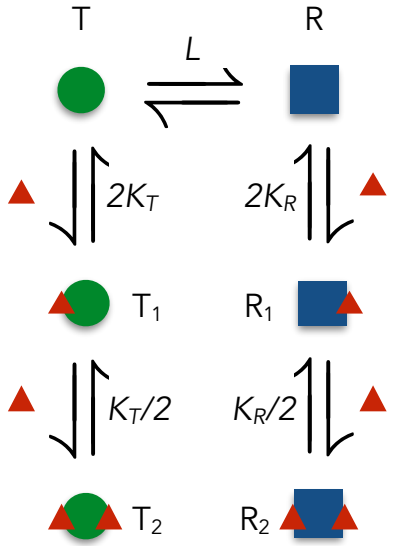
$$f_{\text{on}}([X] = 0) = \frac{1}{1 + L}$$

Basal activation is lost for large *L*, ie *[R]* much bigger than *[T]*

$$[R] = L[T]$$

An allosteric enzyme never reaches maximal activity

$$f_{\text{on}} = \frac{(1 + K_T[X])^n}{(1 + K_T[X])^n + L(1 + K_R[X])^n}$$



For large *X*

$$f_{\text{on}}(K_R[X] \gg 1) \simeq \frac{K_T^n}{K_T^n + LK_R^n} \quad < 1$$

or

$$f_{\text{on}} \simeq \frac{c^n}{c^n + L}$$

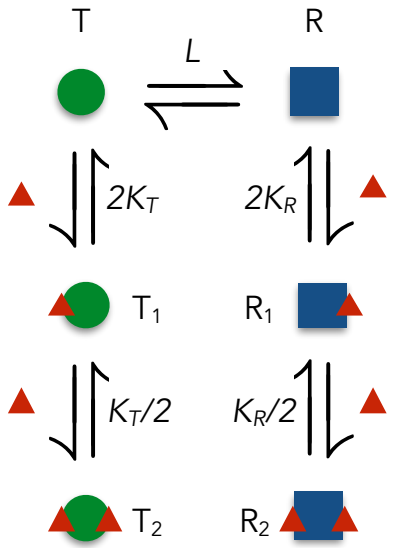
defining *X*'s preference for binding as

$$\text{bias} \quad c = \frac{K_T}{K_R}$$

a high bias – *X* strongly prefers the *T* to the *R* state – brings f_{on} close to 1

With high bias and sufficient *X*, an allosteric enzyme's response is an activating Hill function

$$f_{\text{on}} = \frac{(1 + K_T[X])^n}{(1 + K_T[X])^n + L(1 + K_T[X]/c)^n}$$



If $c \gg K_T[X]$

$$f_{\text{on}} \simeq \frac{(1 + K_T[X])^n}{(1 + K_T[X])^n + L}$$

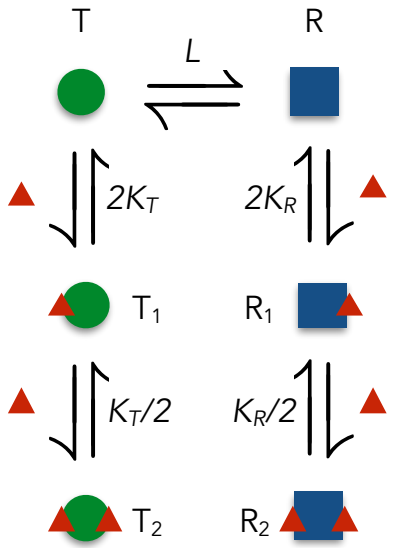
and if $K_T[X] \gg 1$

$$f_{\text{on}} \simeq \frac{(K_T[X])^n}{(K_T[X])^n + L} = \frac{[X]^n}{\frac{L}{K_T^n} + [X]^n}$$

Hill number of *n*

With low bias and sufficient *X*, an allosteric enzyme's response is an inhibiting Hill function

$$f_{\text{on}} = \frac{(1 + cK_R[X])^n}{(1 + cK_R[X])^n + L(1 + K_R[X])^n}$$



If $c \ll \frac{1}{K_R[X]}$

$$f_{\text{on}} \simeq \frac{1}{1 + L(1 + K_R[X])^n}$$

and if $K_R[X] \gg 1$

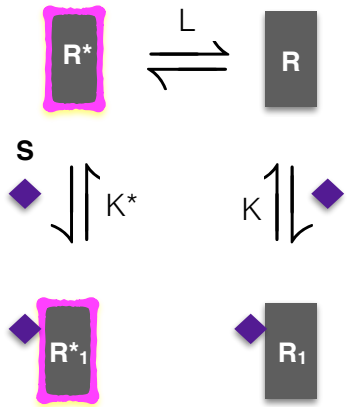
$$f_{\text{on}} \simeq \frac{1}{1 + L(K_R[X])^n}$$

$$= \frac{\frac{1}{LK_R^n}}{\frac{1}{LK_R^n} + [X]^n}$$

Hill number of *n*

Modelling signal transduction III.i

An allosteric receptor



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

The fraction of activated receptors is

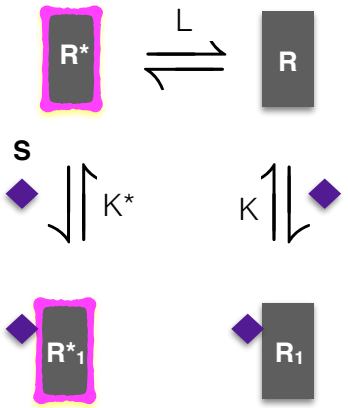
$$f^* = \frac{1 + K^*[S]}{1 + K^*[S] + L(1 + K[S])} \qquad \text{with} \qquad [R^*] = f^* R_0$$

and so

$$\frac{d[A^*]}{dt} \simeq \frac{kR_0(1 + K^*[S])}{1 + K^*[S] + L(1 + K[S])}(A_0 - [A^*]).$$

Modelling signal transduction III.i

An allosteric receptor



$$\frac{d[A^*]}{dt} \simeq \frac{kR_0(1+K^*[S])}{1+K^*[S]+L(1+K[S])}(A_0-[A^*]).$$

If $[S]=0$

$$\frac{d[A^*]}{dt} \simeq \frac{kR_0}{1+L}(A_0-[A^*])$$

basal activation

If $K^*[S] \gg 1$

$$\frac{d[A^*]}{dt} \simeq \frac{kR_0K^*[S]}{L+(K^*+KL)[S]}(A_0-[A^*])$$

with most active receptors in R_1*, we recover the non-allosteric equation

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