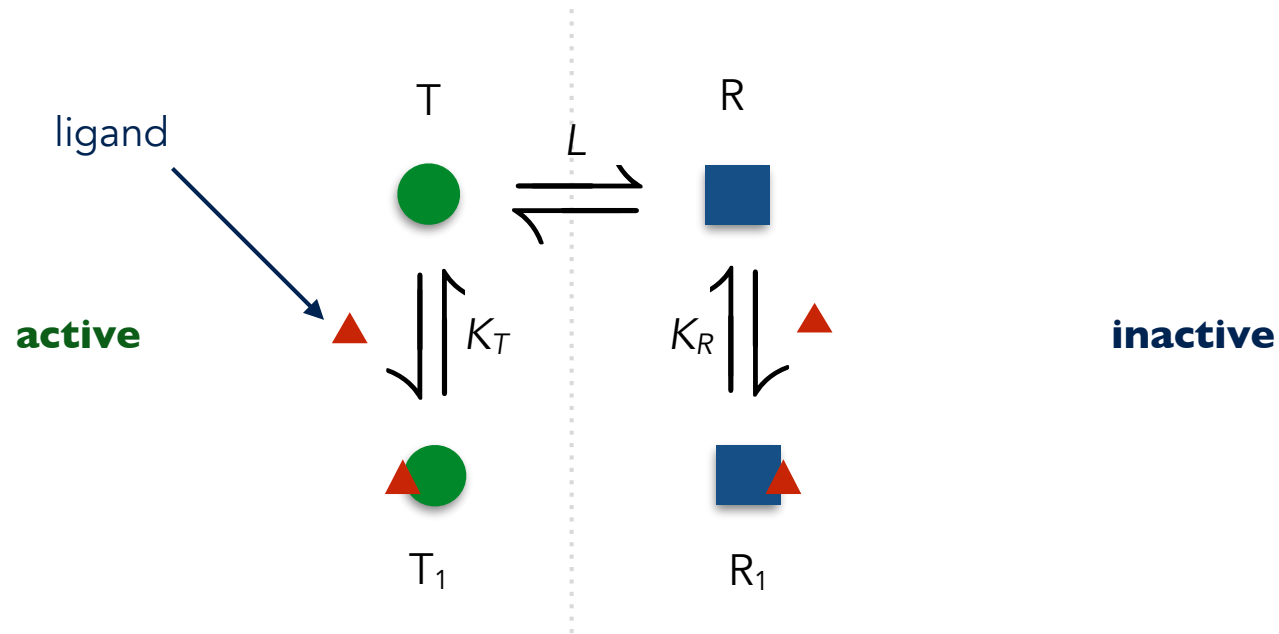


The Monod-Wyman-Changeux model of allostery

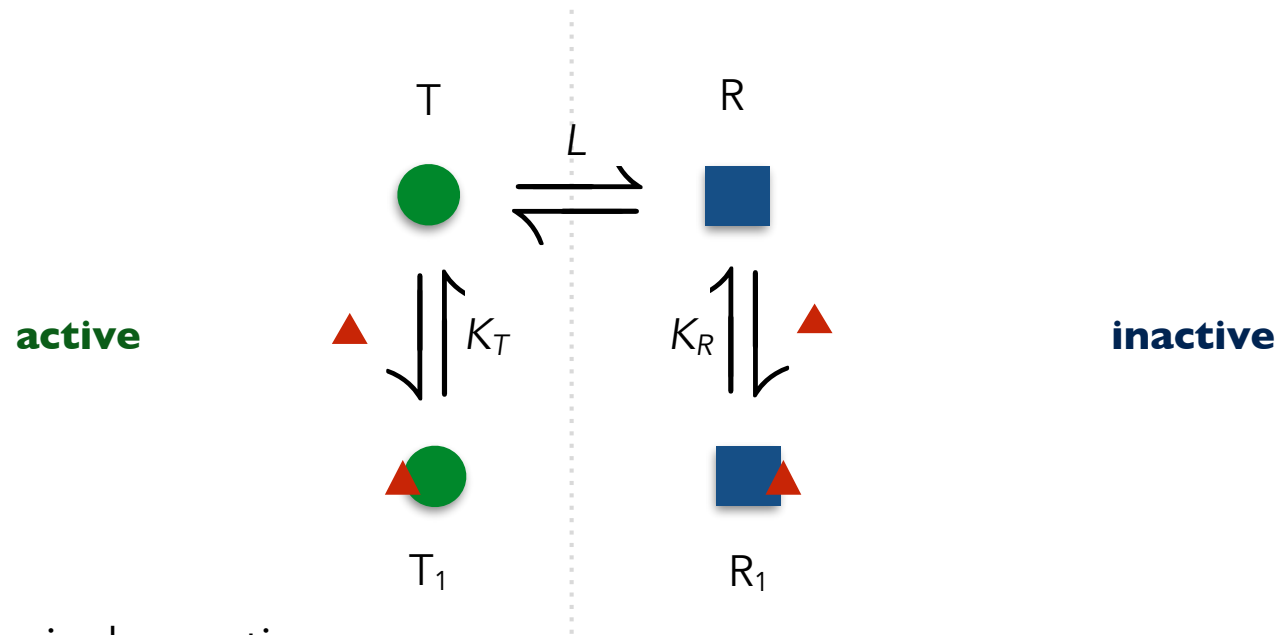
Allostery connects molecules with different structures

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.

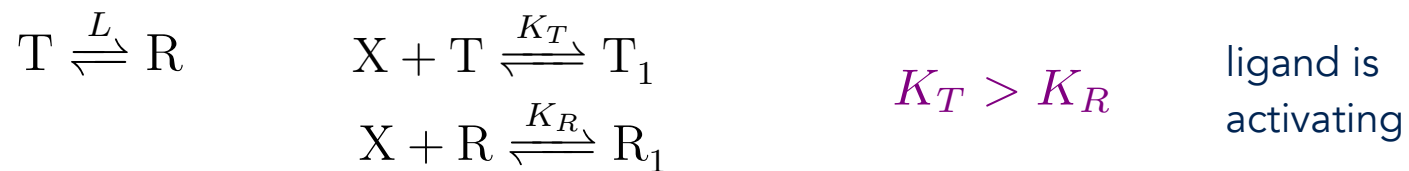


The downstream molecule regulated by the active state of the receptor need not have any structural similarity to the ligand.

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



In terms of chemical equations



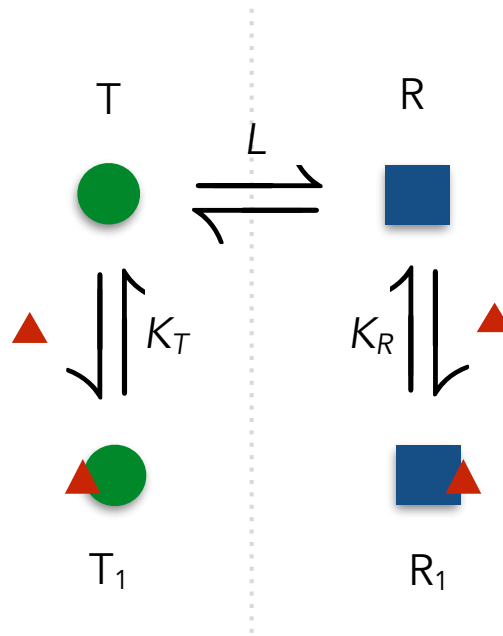
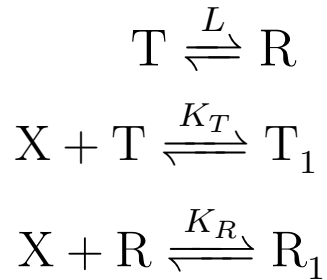
with

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

equilibrium constants

association constants

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



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

$$K_T = \frac{[T_1]}{[X][T]}$$

$$K_R = \frac{[R_1]}{[X][R]}$$

The fraction of activated enzymes is

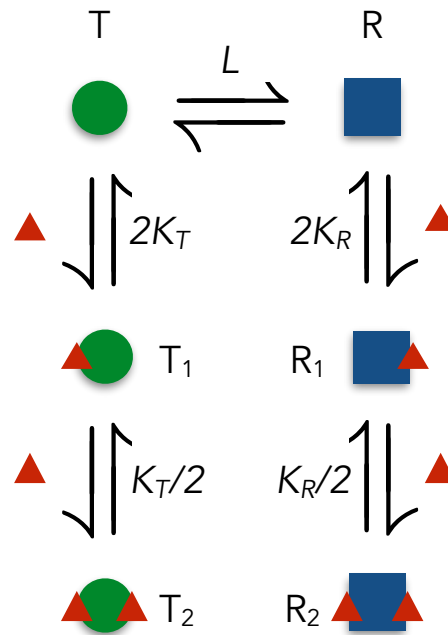
$$f_{\text{on}} = \frac{[T] + [T_1]}{[T] + [T_1] + [R] + [R_1]}$$

$$= \frac{[T] + K_T[X][T]}{[T] + K_T[X][T] + L[T] + K_R[X]L[T]}$$

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

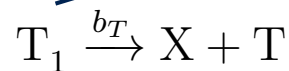
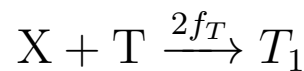
approximately
hyperbolic

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:

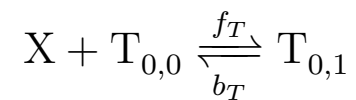
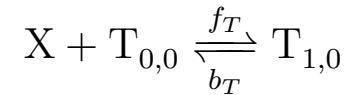
the rate of dissociation is b_T because there is only one X that can dissociate



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

Understanding the factor of two

Consider the binding sites explicitly

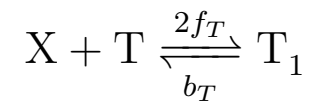


the rate equation is

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

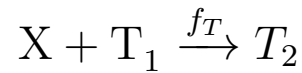
Defining: $[T_1] = [T_{1,0}] + [T_{0,1}]$ then

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

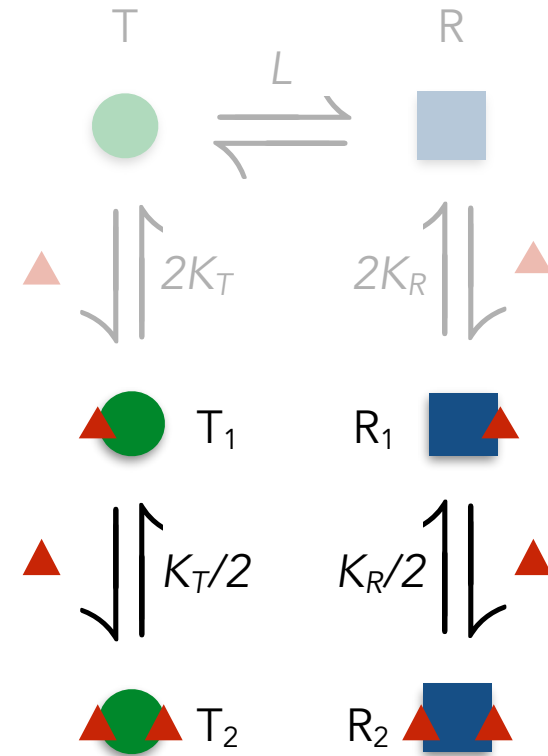
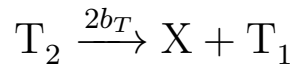


Consider the binding of the second regulator

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



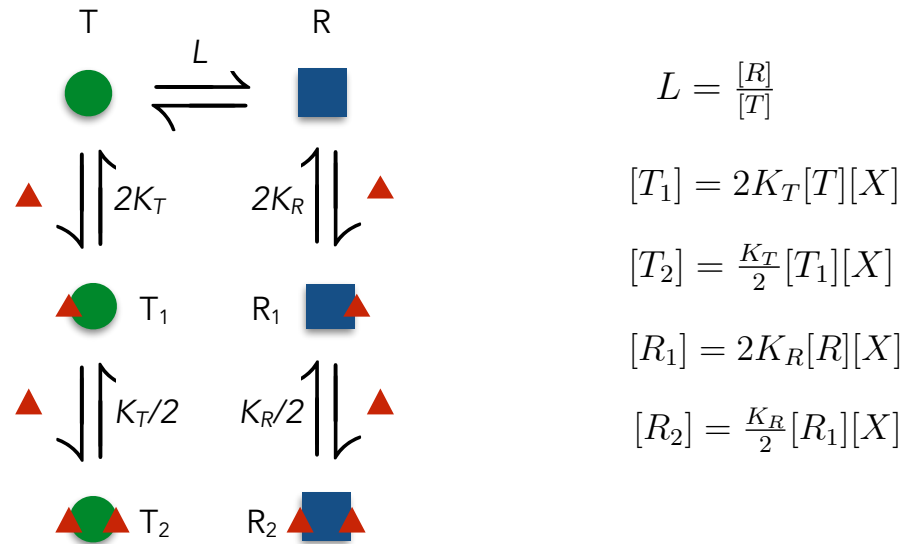
the rate of dissociation is $2b_T$ because there are two X molecules that can dissociate



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



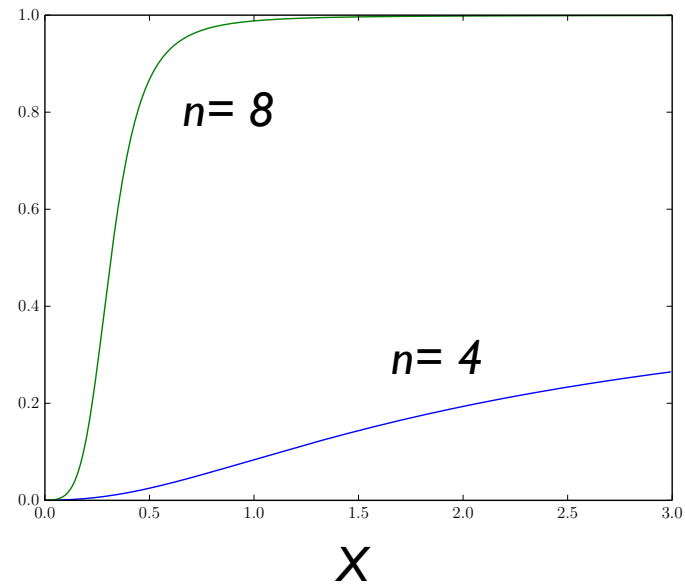
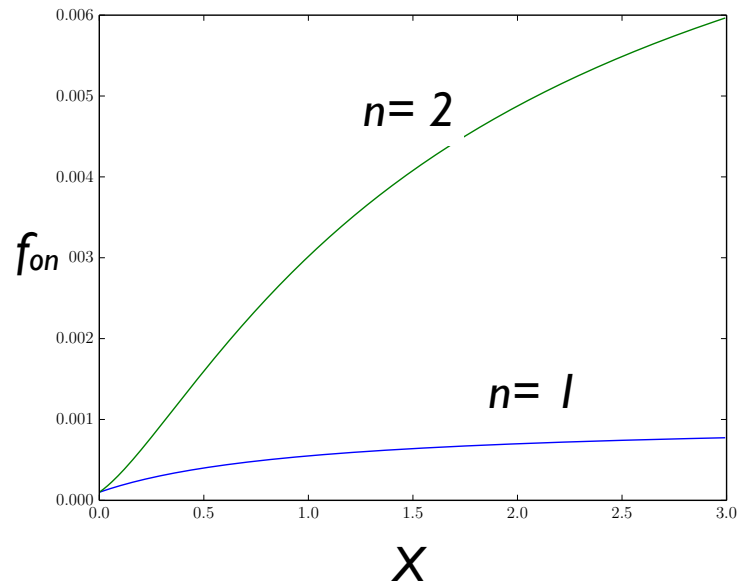
$$\begin{aligned}
 f_{\text{on}} &= \frac{[T] + [T_1] + [T_2]}{[T] + [T_1] + [T_2] + [R] + [R_1] + [R_2]} \\
 &= \frac{[T] + 2K_T[X][T] + \frac{1}{2}K_T[X]2K_T[X][T]}{[T] + 2K_T[X][T] + \frac{1}{2}K_T[X]2K_T[X][T] + L[T] + 2K_R[X]L[T] + \frac{1}{2}K_R[X]2K_R[X]L[T]} \\
 &= \frac{1 + 2K_T[X] + K_T^2[X]^2}{1 + 2K_T[X] + K_T^2[X]^2 + L(1 + 2K_R[X] + K_R^2[X]^2)} \\
 &= \frac{(1 + K_T[X])^2}{(1 + K_T[X])^2 + L(1 + K_R[X])^2}
 \end{aligned}$$

$\underbrace{T_1}$
 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

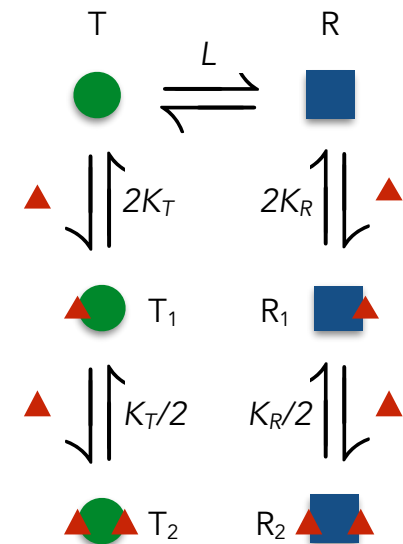


An allosteric enzyme has a basal level of activity in the absence of its regulator

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

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

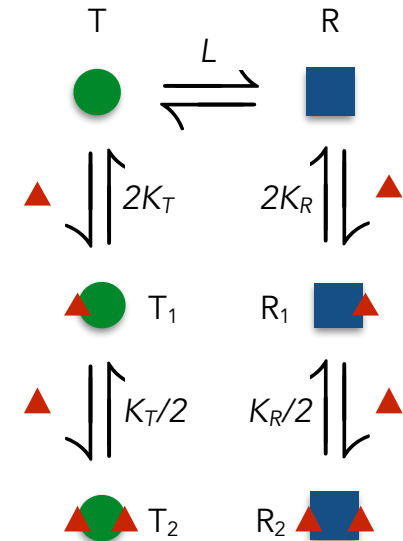
$$f_{\text{on}}(K_R[X] \gg 1) \simeq \frac{K_T^n}{K_T^n + LK_R^n} < 1$$

or

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

defining X 's preference for binding as

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



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

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

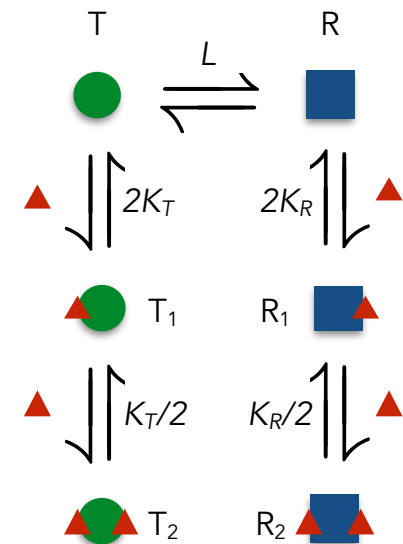
If $c \gg K_T[X]$

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

and if $K_T[X] \gg 1$

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

Hill number of n



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

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

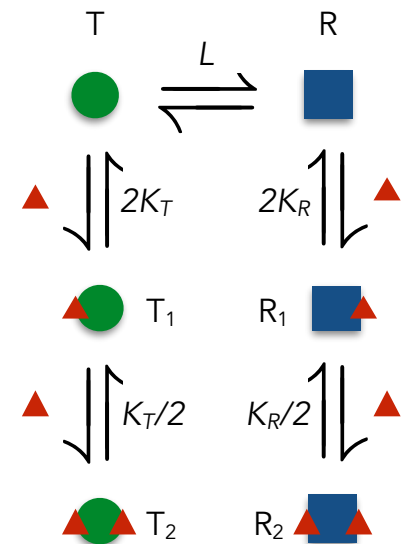
If $c \ll \frac{1}{K_R[X]}$

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

and if $K_R[X] \gg 1$

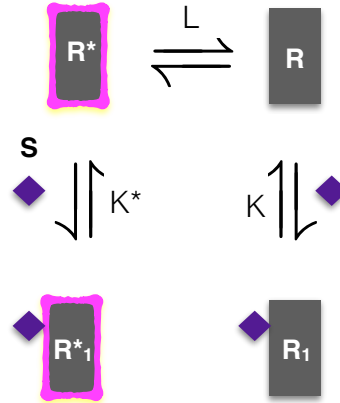
$$\begin{aligned} f_{\text{on}} &\simeq \frac{1}{1 + L(K_R[X])^n} \\ &= \frac{\frac{1}{LK_R^n}}{\frac{1}{LK_R^n} + [X]^n} \end{aligned}$$

Hill number of n



Modelling signal transduction III.i

An allosteric receptor



The fraction of activated receptors is

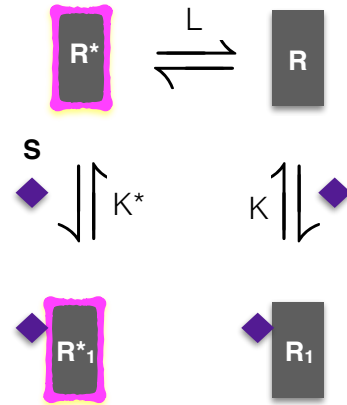
$$f^* = \frac{1 + K^*[S]}{1 + K^*[S] + L(1 + K[S])} \quad \text{with} \quad [R^*] = f^*R_0$$

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