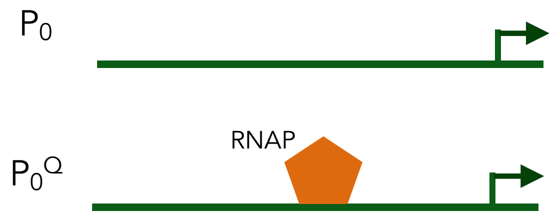
Modelling gene expression

To model gene expression, we start by considering the possible states of the promoter

Constitutive (unregulated) gene expression



We assume binding of RNA polymerase, Q, to the promoter, P_0, is at equilibrium

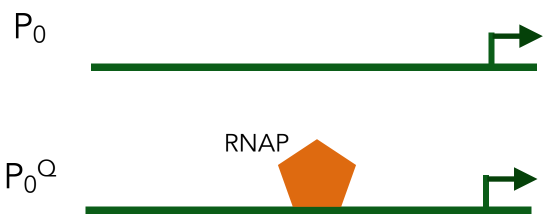
$$P_0^Q = K_Q Q P_0 \qquad \mathrm{P}_0 + \mathrm{Q} \rightleftharpoons \mathrm{P}_0^{\mathrm{Q}}$$

There is a fixed number, n, of promoters

$$P_0 + \overset{K_Q Q P_0}{P_0^Q} = n$$

$$P_0 = \frac{n}{1 + K_Q Q} \qquad \boxed{P_0^Q = \frac{n K_Q Q}{1 + K_Q Q}}$$

Only the promoter state bound by RNAP initiates transcription



$$\mathrm{P_0^Q} \xrightarrow{u} \mathrm{P_0^Q} + \mathrm{M}$$
$$\mathrm{M} \xrightarrow{d_M} \varnothing$$

The rate equation for mRNA *M* is

$$\frac{dM}{dt} = uP_0^Q - d_M M$$

maximum rate of transcription

reciprocal of the half-life of mRNA

$$\boxed{\frac{dM}{dt} = \frac{nuK_Q Q}{1 + K_Q Q} - d_M M}$$

Translation is modelled as a first-order process

$$\boxed{\begin{aligned} &\mathrm{M} \xrightarrow{v} \mathrm{M} + \mathrm{P} \\ &\mathrm{P} \xrightarrow{d_P} \varnothing \end{aligned}}$$

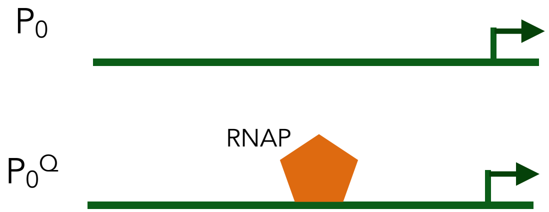
The rate equation for protein *P* is

$$\frac{dP}{dt} = vM - d_P P$$

rate of translation

reciprocal of the half-life of protein

The complete model for a constitutive promoter is then:



$$\mathrm{P}_0^{\mathrm{Q}} \xrightarrow{u} \mathrm{P}_0^{\mathrm{Q}} + \mathrm{M}$$

$$\mathrm{M} \xrightarrow{d_M} \varnothing$$

$$\mathrm{M} \xrightarrow{v} \mathrm{M} + \mathrm{P}$$

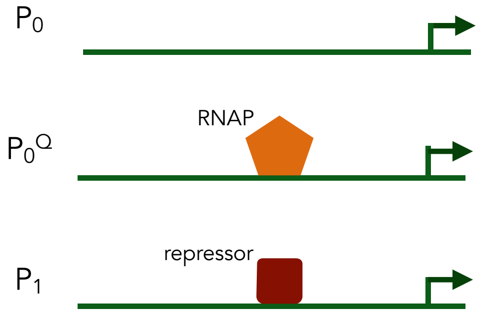
$$\mathrm{P} \xrightarrow{d_P} \varnothing$$

$$\frac{dM}{dt} = uP_0^Q - d_M M$$

$$\frac{dP}{dt} = vM - d_P P$$

$$\boxed{P_0^Q = \frac{nK_Q Q}{1 + K_Q Q}}$$

Modelling repression by a single repressor competing with RNA polymerase for the promoter



$$\mathrm{P}_0 + \mathrm{R} \rightleftharpoons \mathrm{P}_1$$

$$\mathrm{P}_0 + \mathrm{Q} \rightleftharpoons \mathrm{P}_0^{\mathrm{Q}}$$

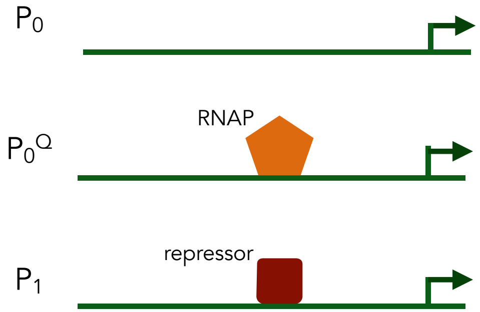
We assume that binding of all proteins at the promoter is at equilibrium

$$P_1 = K_R R P_0 \quad ; \quad P_0^Q = K_Q Q P_0$$

and that the total number of promoters is conserved

$$P_0 + P_0^Q + P_1 = n$$

The higher the number of repressors, the less RNAP binds to the promoter



$$P_1 = K_R R P_0$$
$$P_0^Q = K_Q Q P_0$$

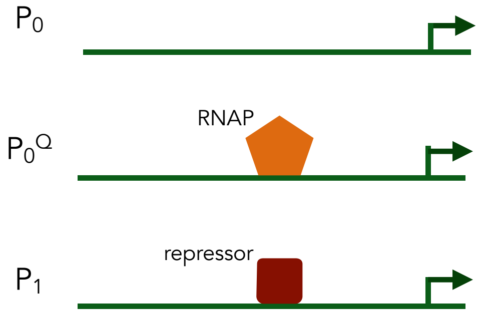
The total number of promoters is conserved

$$P_0 + K_Q Q P_0 + K_R R P_0 = n$$

and so

$$P_0 = \frac{n}{1 + K_Q Q + K_R R} \quad \text{and} \quad \boxed{P_0^Q = \frac{n K_Q Q}{1 + K_Q Q + K_R R}}$$

The model for gene expression from a repressed protein is then



$$\frac{dM}{dt} = \frac{nuK_Q Q}{1 + K_Q Q + K_R R} - d_M M$$

$$\frac{dP}{dt} = vM - d_P P$$

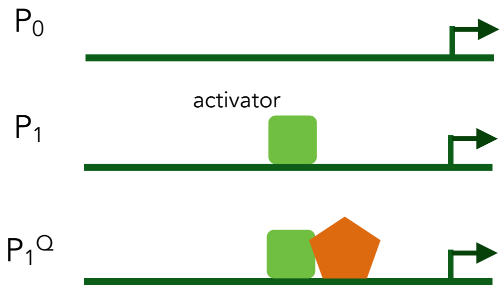
$$u_{\max} = \frac{nuK_Q Q}{1+K_Q Q}$$

$$K_1 = \frac{1+K_Q Q}{K_R}$$

If the concentration of RNAP is constant

$$\frac{dM}{dt} = u_{\max}\left[\frac{1}{1+\frac{R}{K_1}}\right] - d_M M$$

Modelling activation by an activator recruiting RNA polymerase



$$\mathrm{P}_0 + \mathrm{A} \rightleftharpoons \mathrm{P}_1$$

$$\mathrm{P}_1 + \mathrm{Q} \rightleftharpoons \mathrm{P}_1^{\mathrm{Q}}$$

We assume that the binding of all proteins at the promoter is at equilibrium

$$P_1 = K_A A P_0 \quad ; \quad P_1^Q = K'_Q Q P_1$$

and that the total number of promoters is conserved

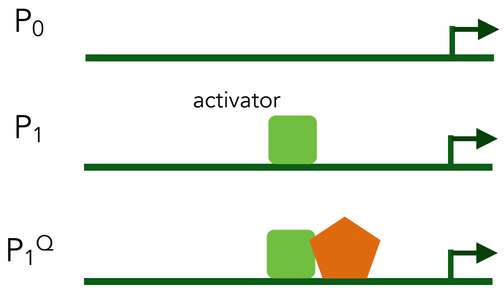
$K'_Q Q K_A A P_0$

$$P_0 + P_1 + P_1^Q = n$$

implying

$$\boxed{P_1^Q = \frac{n K'_Q K_A A Q}{1 + K_A A + K'_Q K_A A Q}}$$

The rate of transcription is an activating Hill function of the number of activators



The rate equation for mRNA

$$\frac{dM}{dt} = \frac{uK'_Q Q K_A A}{1 + K_A A + K_A K'_Q Q A} n - d_M M$$

or for constant RNAP

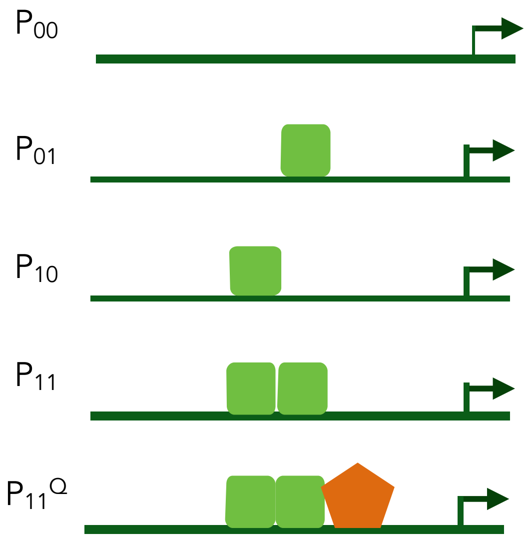
$$\boxed{\frac{dM}{dt} = u_{\max}\left[\frac{\frac{A}{K_1}}{1 + \frac{A}{K_1}}\right] - d_M M}$$

$$u_{\max} = \frac{nuK'_Q Q}{1+K'_Q Q}$$

$$K_1 = \frac{1}{(1+K'_Q Q)K_A}$$

The formalism extends to more than one transcription factor

Two activators



$$\mathrm{P}_{00} + \mathrm{A} \rightleftharpoons \mathrm{P}_{10}$$

$$\mathrm{P}_{00} + \mathrm{A} \rightleftharpoons \mathrm{P}_{01}$$

$$\mathrm{P}_{01} + \mathrm{A} \rightleftharpoons \mathrm{P}_{11}$$

$$\mathrm{P}_{10} + \mathrm{A} \rightleftharpoons \mathrm{P}_{11}$$

$$\mathrm{P}_{11} + \mathrm{Q} \rightleftharpoons \mathrm{P}_{11}^{\mathrm{Q}}$$

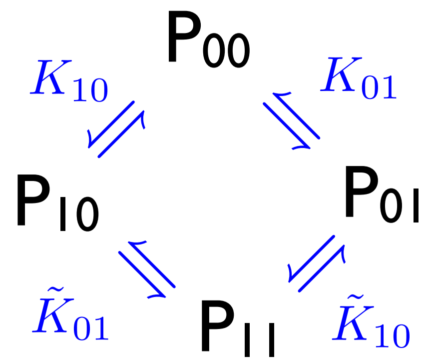
Equilibrium

$$P_{10} = K_{10} A P_{00} \quad ; \quad P_{01} = K_{01} A P_{00}$$

$$P_{11} = \tilde{K}_{10} A P_{01} \quad ; \quad P_{11} = \tilde{K}_{01} A P_{10}$$

$$P_{11}^{Q} = K'_{Q} Q P_{11}$$

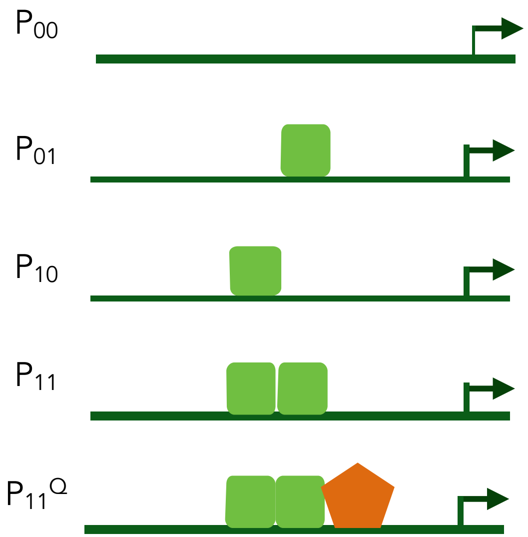
The thermodynamic cycle restricts the equilibrium constants



Detailed balance implies

$$K_{01}\tilde{K}_{10} = K_{10}\tilde{K}_{01}$$

We solve assuming equilibrium and a fixed number of promoters



$$P_{10} = K_{10} A P_{00} \quad ; \quad P_{01} = K_{01} A P_{00}$$

$$P_{11} = \tilde{K}_{10} A P_{01} \quad ; \quad P_{11} = \tilde{K}_{01} A P_{10}$$

$$P_{11}^{Q} = K'_Q Q P_{11}$$

$$P_{00} + P_{10} + P_{01} + P_{11} + P_{11}^{Q} = n$$

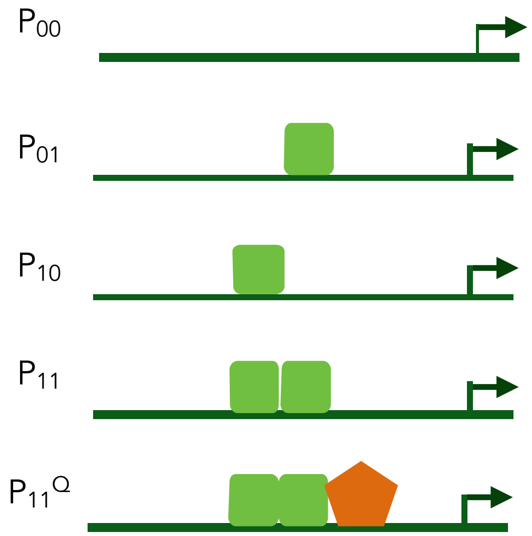
and so

$$P_{00} + K_{10} A P_{00} + K_{01} A P_{00} + \tilde{K}_{10} K_{01} A^2 P_{00} + \tilde{K}_{10} K_{01} K'_Q Q A^2 P_{00} = n$$

giving

$$\boxed{P_{11}^{Q} = \frac{n K'_Q \tilde{K}_{10} K_{01} Q A^2}{1 + K_{10} A + K_{01} A + \tilde{K}_{10} K_{01} A^2 + \tilde{K}_{10} K_{01} K'_Q Q A^2}}$$

Modelling transcription



K_{01}

K_{10}

Let

set by energy of interaction between activators

$$K_i = \mathrm{e}^{-\Delta G_{\text{int}}/kT}$$

$$\tilde{K}_{10} = K_i K_{10}$$

so

$$P_{11} = \tilde{K}_{10} K_{01} \cdot A^2 P_{00} = K_i K_{10} K_{01} \cdot A^2 P_{00}$$

then

$$\frac{dM}{dt} = \frac{unK'_Q Q K_i K_{10} K_{01} A^2}{1 + K_{10}A + K_{01}A + K_i K_{10} K_{01} A^2 + K_i K_{10} K_{01} K'_Q Q A^2} - d_M M$$

or

$$\boxed{\frac{dM}{dt} = u_{\max} \left[\frac{\frac{A^2}{K_2^2}}{1 + \frac{A}{K_1} + \frac{A^2}{K_2^2}} \right] - d_M M}$$

$$u_{\max} = \frac{unK'_Q Q}{1+K'_Q Q}$$

$$K_1^{-1} = K_{01} + K_{10}$$

$$K_2^{-2} = K_i K_{10} K_{01}(1 + K'_Q Q)$$

Multiple transcriptional active states may be included

Let RNAP bind without the activator too

$$\mathrm{P}_0 + \mathrm{Q} \underset{}{\overset{K_Q}{\rightleftharpoons}} \mathrm{P}_\mathrm{Q} \qquad u_\ell \qquad \text{leakage rate}$$

$$\mathrm{P}_{11} + \mathrm{Q} \underset{}{\overset{K'_Q}{\rightleftharpoons}} \mathrm{P}_{11}^{\mathrm{Q}} \qquad u \qquad \text{transcription rate}$$

then

$$\frac{dM}{dt} = n \frac{u_\ell K_Q Q + u K'_Q Q K_i K_{10} K_{01} A^2}{1 + K_Q Q + K_{10} A + K_{01} A + K_i K_{10} K_{01} A^2 + K_i K_{10} K_{01} K'_Q Q A^2} - d_M M$$

or

$$\boxed{\frac{dM}{dt} = \frac{u_{\mathrm{basal}} + u_{\mathrm{max}} \times \frac{A^2}{K_2^2}}{1 + \frac{A}{K_1} + \frac{A^2}{K_2^2}} - d_M M}$$

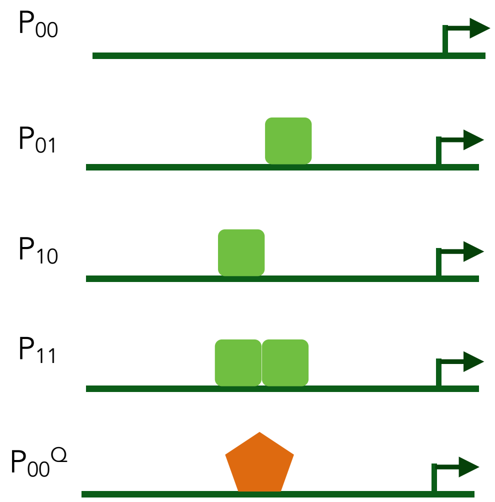
$$u_{\mathrm{basal}} = \frac{u_\ell n K_Q Q}{1+K_Q Q}$$

$$u_{\mathrm{max}} = \frac{u n K'_Q Q}{1+K'_Q Q}$$

From the states of the promoter, we are able to write the rate of transcription

The denominator has one term for each state of the promoter; the numerator has one term for each transcriptionally active state of the promoter.

E.g., for a repressor



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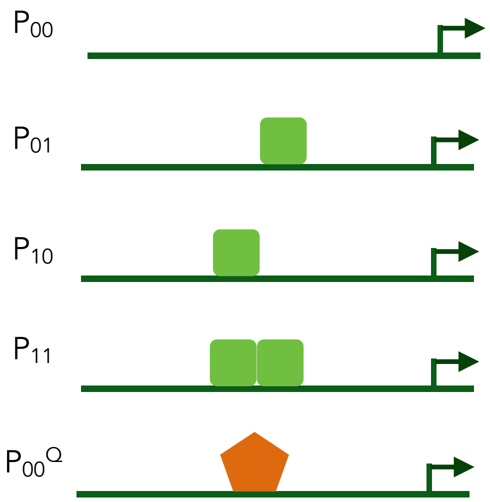
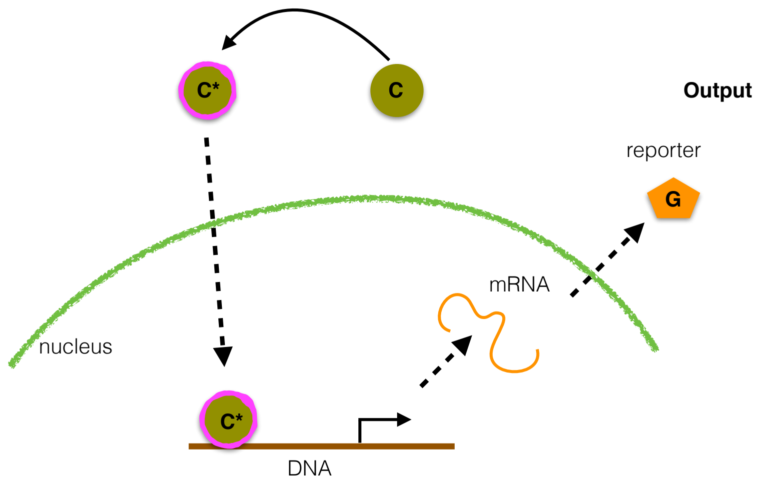


$$\frac{dM}{dt} = nu \frac{\overset{P_{00}^{Q}}{K_Q Q}}{\underset{P_{00}}{1} + \underset{P_{00}^{Q}}{K_Q Q} + \underset{P_{01}}{K_{01} R} + \underset{P_{10}}{K_{10} R} + \underset{P_{11}}{K_i K_{10} K_{01} R^2}} - d_M M$$

Modelling signal transduction V



assuming entry and exit from the nucleus is at equilibrium

$$\mathrm{C}^* \underset{b_n}{\overset{f_n}{\rightleftharpoons}} \mathrm{C}_\mathrm{n}^*$$

$$[C_n^*] = \frac{f_n}{b_n}[C^*]$$

Assume that C* is an activator with a single binding site on G's promoter

mRNA

$$\frac{d[m_G]}{dt} = u_G \frac{\frac{[C_n^*]}{K_{C^*}}}{1 + \frac{[C_n^*]}{K_{C^*}}} - d_m[m_G]$$

using

$$u_{\max}\left[\frac{\frac{A}{K_1}}{1+\frac{A}{K_1}}\right] - d_M M$$

protein

$$\frac{d[G]}{dt} = v[m_G] - d_G[G]$$