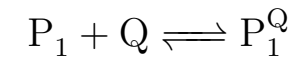
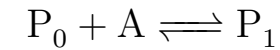
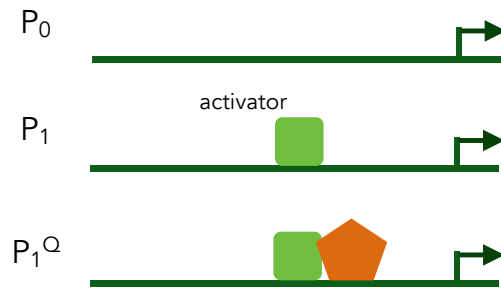


Modelling activation by an activator recruiting RNA polymerase



We assume that 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

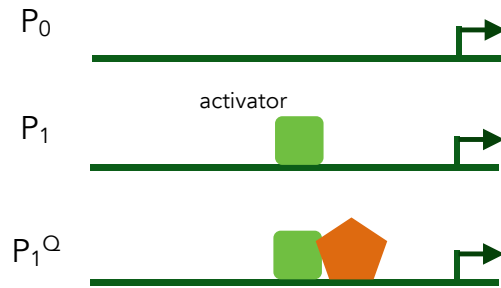
$$P_0 + P_1 + P_1^Q = n$$

$K'_Q Q K_A A P_0$

implying

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

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

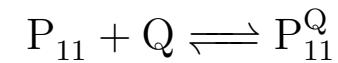
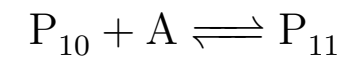
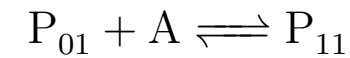
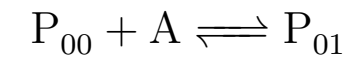
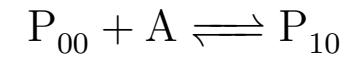
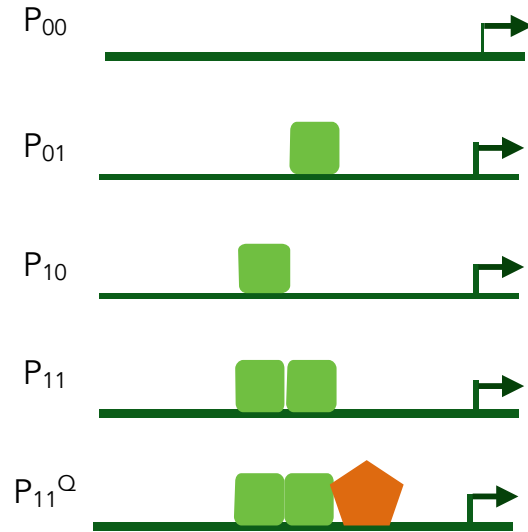
$$\frac{dM}{dt} = u_{\max} \left[\frac{\frac{A}{K_1}}{1 + \frac{A}{K_1}} \right] - d_M M$$

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

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

The formalism extends to more than one transcription factor

Two activators



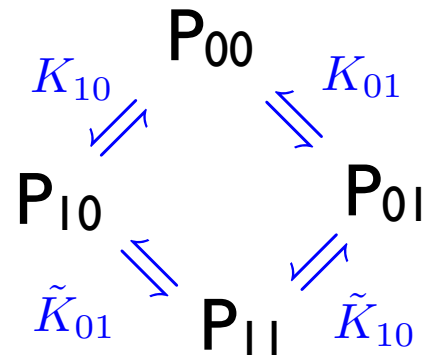
Equilibrium

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

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

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

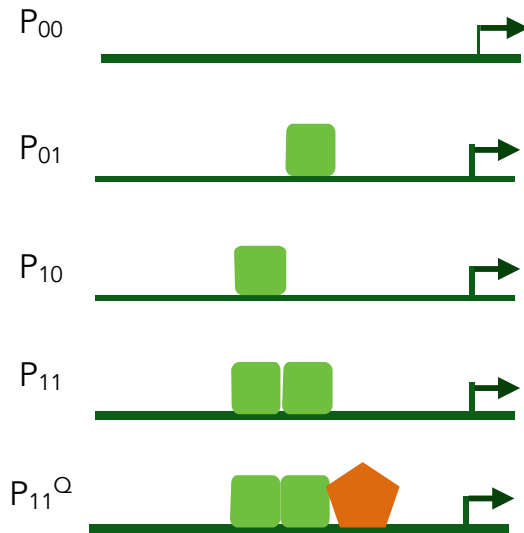
The thermodynamic cycle restricts the equilibrium constants



Detailed balance implies

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

We solve assuming equilibrium and a fixed number of promoters



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

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

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

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

and so

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

giving

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

Modelling transcription

Let

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

set by energy of interaction
between activators

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

so

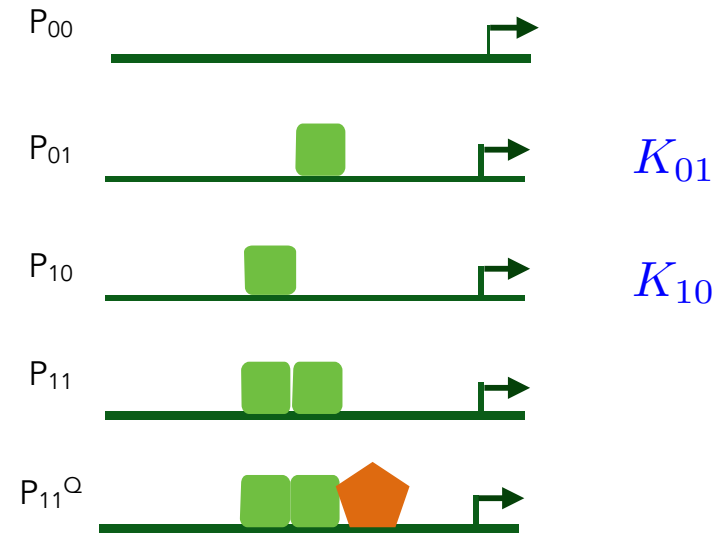
$$P_{11} = \tilde{K}_{10} K_{01} \cdot A^2 P_{00} = K_i K_{10} K_{01} \cdot A^2 P_{00}$$

then

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

or

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



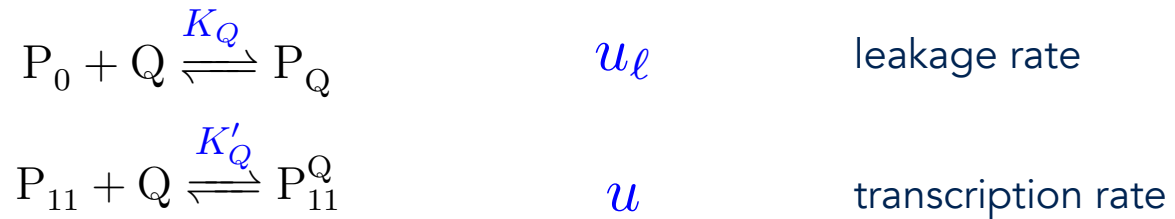
$$u_{\text{max}} = \frac{u n K'_Q Q}{1 + K'_Q Q}$$

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

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

Multiple transcriptional active states may be included

Let RNAP bind without the activator too



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

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

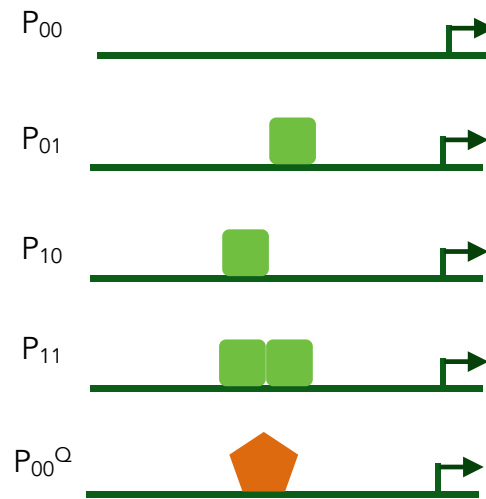
$$u_{\text{basal}} = \frac{u_\ell n K_Q Q}{1 + K_Q Q}$$

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

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

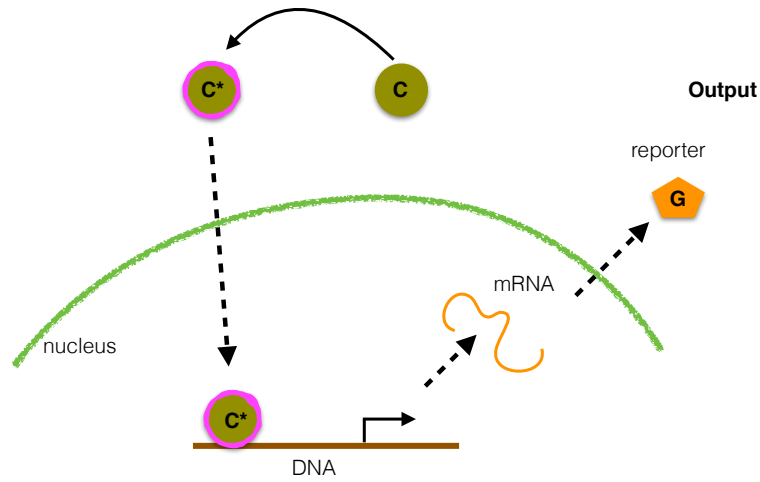
The denominator has one term for each state of the promoter; the numerator has one term for each transcriptionally active state of the promoter.

Eg, for a repressor



$$\frac{dM}{dt} = nu \frac{P_{00}^Q K_Q Q}{1 + P_{00}^Q + P_{01} + P_{10} + P_{11}} - d_M M$$

Modelling signal transduction V



assuming entry and exit from the nucleus is at equilibrium

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

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

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

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