The following questions consider binding of a transcription factor protein, denoted X, to a gene promoter with N binding sites. The number of transcription factors bound is denoted n, and in the general case

$$n \in \{0, 1, 2, 3, \ldots, N\}.$$

The number of copies of the gene with n sites bound is denoted G_n. The total number of copies of the gene is the constant

$$G_T = \sum_{n=0}^{N} G_n,$$

and the fraction of copies in state n is G_n/G_T. The transcription rate for a copy of the gene with n transcription factors bound is denoted ν_n, and the total transcriptional rate is

$$\beta = \sum_{n=0}^{N} \nu_n G_n.$$

We will assume that $\nu_0 = 0$ and that increased binding gives increased transcription, which implies that the maximum possible transcription rate occurs when G_N is the only occupied state. Thus, the maximum transcription rate is $\beta_{\max} = \nu_N G_T$. The concentration of transcription factor is sufficiently large that changes in the value of unbound X need not be considered. All questions assume that binding has reached equilibrium.

Cooperativity at a particular value of X is defined as $(d/d\ln X)\ln[\beta/(\beta_{\max} - \beta)]$, usually evaluated at the value of X giving half-maximal transcription, $\beta = \beta_{\max}/2$. Note that $d/d\ln X$ is $X d/dX$ by the chain rule.

1. Fully cooperative binding. The standard model for fully cooperative binding is that only the two states G_0 and G_N exist, $G_0 + NX \rightleftharpoons G_N$, with forward rate constant k_f and backward rate constant k_b.

   (a) Show that β as a function of X is proportional to $(X/K)^N/[1+(X/K)^N]$. Provide K as a function of model parameters.

   (b) Provide $\beta/(\beta_{\max} - \beta)$.

   (c) Show that the cooperativity is N regardless of the value of X.

2. Fully independent and additive binding. Suppose each site is bound independently. Each site has two states, u (unbound) and b (bound), with $u + X \rightleftharpoons b$. The forward rate constant is k'_f, and the backward rate constant is k'_b. Because this expression in in terms of a single site, $u + b = 1$. When n sites are bound, the transcription rate is additive, $\nu_n = n\Delta\nu$.

   (a) What is the probability θ that a particular site is bound?

   (b) In terms of θ, what is the probability G_n/G_T that n of the N sites are bound for a particular copy of the gene?

(c) Show that the transcription rate is $\beta = G_T \Delta\nu \sum_{n=0}^{N} nC(N,n)\theta^n(1-\theta)^{N-n}$, where $C(N,n)$ is the combinatorial factor $N!/n!(N-n)!$.

(d) Define $\tilde{\theta}(s) = \sum_{n=0}^{N} e^{-sn}C(N,n)\theta^n(1-\theta)^{N-n}$. Show that $\tilde{\theta}(s) = (1-\theta+e^{-s}\theta)^N$. Use this result to calculate $\langle n \rangle$ as $-(d/ds)\ln\tilde{\theta}(s)$.

(e) Show that β for a particular value of X is $\beta_{\max}\theta$.

(f) What is the cooperativity for independent binding and additive transcription? How does the cooperativity depend on the transcription factor concentration?

3. Sequential binding. Here we model a system that is intermediate between independent binding and cooperative binding. In this model, the transcription factors bind in spatial order with transitions possible only between neighboring states:

$$G_n + X \rightleftharpoons G_{n+1}.$$

The forward rate constant is k_f'' and the backward rate constant is k_b''.

(a) Define $\lambda = G_1/G_0$. Provide λ in terms of model parameters k_f'', k_b'', and X.

(b) Provide the general term G_n/G_0 in terms of λ.

(c) Use the normalization $\sum_{n=0}^{\infty} G_n = G_T$ to provide G_n/G_T in terms of λ without G_0.

(d) At what value of λ are all the states equally occupied, $G_0 = G_1 = \ldots = G_N = G_T/(N+1)$?

(e) Suppose that the transcriptional activation is additive, $\nu_n = n\Delta\nu$. Show that $\beta = G_T\langle n \rangle \Delta\nu$, where

$$\langle n \rangle = \frac{\sum_{n=0}^{N} n\lambda^n}{(\lambda^{N+1}-1)/(\lambda-1)}.$$