Exercise 05 - Solutions

The transcriptional machinery in eukaryotes

(a) The states to be considered in this case are:

1. Promoter empty.
2. Promoter bound by X.
3. Promoter bound by X and X bound by Y.

For simplicity we will identify x and y with the statistical weights corresponding to having X and Y bound, respectively. For example, we have

$$x = \frac{[\mathrm{X}]}{c_0} e^{-\beta \Delta \varepsilon_{xd}}. \tag{1}$$

The probability of finding the X-Y complex bound to the promoter is

$$p_{bound} = \frac{xy}{1 + x + xy} = \left(1 + \frac{1}{y} + \frac{1}{xy}\right)^{-1}. \tag{2}$$

This is clearly not the same functional form that we get for the bacterial case.

This probability can be reduced to a one molecule problem in certain limits. For example, if the binding of X to the DNA is much more likely than the binding of Y to X (that is $x \gg y$) the probability of finding the complex bound to the promoter reduces to

$$p_{bound} \simeq \left(1 + \frac{1}{y}\right)^{-1}. \tag{3}$$

This corresponds to a case where X is always bound so that the problem becomes the binding of Y to the X-promoter complex.

On the other hand, we can take the limit $y \gg x$. As one would expect, in this case, X and Y will be always associated. The corresponding p_{bound} will be that of the X-Y species binding to the promoter:

$$p_{bound} = \left(1 + \frac{1}{xy}\right)^{-1}. \tag{4}$$

However, this doesn't necessarily tell us about transcriptional regulation. For example, does the expression for the fold change in gene expression for the case of repression look the same for both the eukaryotic and prokaryotic cases? We explore that in the next part of the problem.

(b) We now add a repressor that can bind to a site overlapping the X binding site. Its statistical weight is r and the resulting p_{bound} is

$$p_{bound} = \frac{xy}{1 + x + xy + r}. \tag{5}$$

The fold change in gene expression is given by

$$\text{fold change} = \frac{1 + x + xy}{x + xy + (1 + r)}. \tag{6}$$

By weak promoter we understand that the probability of finding the transcriptional machinery assembled on the promoter is low. We assume that this means that the statistical weights corresponding to X and Y are small, namely $x, y \ll 1$. If this is the case the fold change reduces to the familiar

$$\text{fold change} = (1 + r)^{-1}. \tag{7}$$

For an activator interacting with Y the probability of finding the X-Y complex bound to the promoter is

$$p_{bound} = \frac{xy + xy\,af}{1 + x + yx + a + ax + xy\,af}. \tag{8}$$

Here we have defined a as the statistical weight corresponding to the activator being bound to its site on DNA. f is the weight of the interaction between the activator and Y. This is the equivalent to $e^{-\beta\varepsilon_{ap}}$ in the case of bacterial activation. After some algebra we see that this probability can also be written in the following way

$$p_{bound} = \left(1 + \frac{1 + x + a(1 + x)}{xy(1 + af)}\right)^{-1}. \tag{9}$$

The fold change in gene expression is given by

$$\text{fold change} = \frac{1 + x + xy}{xy + \frac{1+x+a(1+x)}{1+af}}. \tag{10}$$

We now make use of the weak promoter approximation, namely that $x, y \ll 1$

$$\text{fold change} \approx \left(xy + \frac{1 + a}{1 + af}\right)^{-1} = \left(xy + F_{reg}^{-1}\right)^{-1}. \tag{11}$$

In this last expression we used $F_{reg} = (1 + af)/(a + 1)$, which is the regulation factor for activation derived from the bacterial case. What we end up getting is something very similar to the prokaryotic case. The promoter doesn't just have to be weak, it has to be weaker than F_{reg}^{-1} (with F_{reg} being bigger than one for activation). If this is the case then $F_{reg}^{-1} \gg x, y$ and the fold change in gene expression due to activation is F_{reg} like in the bacterial case.

(c) We again define x and y as the statistical weights corresponding to having the species X and Y bound to DNA respectively. Now, however, when both of them are bound we'll add an extra weight g representing their interaction. The probability of finding the X-Y complex bound to the promoter is

$$p_{bound} = \frac{xyg}{1 + x + y + xyg}. \tag{12}$$

We can think of the complex as one effective species if the interaction between them is very strong, namely if $g \gg x + y$. In that case we get

$$p_{bound} = \frac{xyg}{1 + xyg}. \tag{13}$$

Now we switch gears and address the regulation of the binding of the X-Y complex to the DNA. First, we assume that a repressor can bind to the Y site impeding Y from binding to the DNA without affecting the binding of X. The probability of finding X-Y bound to the promoter is

$$p_{bound} = \frac{xyg}{1 + x + y + xyg + r + rx}. \tag{14}$$

The corresponding fold change in gene expression results in

$$\text{fold change} = \frac{1 + x + y + xyg}{1 + x + y + xyg + r + rx}. \tag{15}$$

Just as we did in part (b) we will assume that the promoter is weak. This means that $x, y, g \ll 1$, which results in

$$\text{fold change} \approx \frac{1}{1 + r} = F_{reg}, \tag{16}$$

a regulation factor for repression equivalent to the prokaryotic one.

Finally, we model activation of the X-Y complex through an activator that can contact Y. The statistical weight for the activator being bound to DNA is a and the interaction term between the activator and Y is given by f. In this case p_{bound} is

$$p_{bound} = \frac{xyg + af\,xyg}{1 + \text{x} + \text{y} + \text{xyg} + a + a\,x + af\,y + af\,xyg}. \tag{17}$$

The fold change in gene expression is

$$\text{fold change} = \frac{(1+af)(1+x+y+xyg)}{1+x+y+xyg+a(1+x+f\,y+f\,xy\mathbf{g})}. \tag{18}$$

Once more we use the weak promoter approximation $x, y, g \ll 1$ leading to

$$\text{fold change} \approx= \frac{1+af}{1+a+af\,y+af\,xyg}. \tag{19}$$

To make progress we look at the denominator. If we can say that $1+a(1+f\,y+f\,xyg) \approx 1+a$ then the fold change in gene expression would adopt the familiar form known from the bacterial case. We then invoke the following constraint

$$f\,y + f\,xyg \ll 1 \tag{20}$$

$$f \ll \frac{1}{y+xyg}. \tag{21}$$

Similarly to what happened in part (b), for the activation to have an fold change analogous to the bacterial case we do not only need a weak promoter. We also need that the promoter is weaker than the activation itself.