Appendix 5: Transcriptional Regulation Model

Transcription factors regulate promoter activity through binding to the promoter region. One can approximate the promoter activity by using the Hill equation

$$V_{promoter,i}(t) = \frac{\lambda_i \prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}}{1 + \prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}} \qquad \textbf{[E1]}$$

The mRNA level in the cell is a balance between rate of mRNA synthesis (promoter activity) and the rate of mRNA degradation, which is assumed to follow the first-order kinetics

$$V_{degradation,i}(t) = k_{d,i} mRNA_i(t) \qquad \textbf{[E2]}$$

Thus,

$$\frac{d\left(mRNA_i(t)\right)}{dt} = V_{promoter,i}(t) - V_{degradation,i}(t)$$

$$= \frac{\lambda_i \prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}}{1 + \prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}} - k_{degradation,i} mRNA_i(t) \qquad [E3]$$

On time scales >10 min[4], the mRNA levels reach a quasi-steady state, and the above equation can be set to zero. Thus, we have

$$mRNA_i(t) = \frac{\dfrac{\lambda_i}{k_{degradation,i}} \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}}{1 + \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}} \qquad \textbf{[E4]}$$

Microarray data are commonly expressed in terms of expression ratios, which are

$$\frac{mRNA_i(t)}{mRNA_i(0)} = \prod_{j=1}^{L} \left(\frac{TFA_j(t)}{TFA_j(0)} \right)^{h_{i,j}} \frac{1 + \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(0)}{k_{i,j}} \right)^{h_{i,j}}}{1 + \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}} \qquad \textbf{[E5]}$$

Taking the logarithm of the above equation, we obtain

$$\log_{10}\left(Er_i(t)\right) = \sum_{j=1}^{L} h_{i,j} \log_{10}\left(TFAr_j(t)\right) + \log_{10}\left(\frac{1 + \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(0)}{k_{i,j}} \right)^{h_{i,j}}}{1 + \displaystyle\prod_{j=1}^{L} \left(\frac{TFA_j(t)}{k_{i,j}} \right)^{h_{i,j}}} \right) \qquad \textbf{[E6]}$$

where Er_i is the expression ratio of $mRNA_i$ and $TFAr$ is the ratio of TFA. When $TFA_j(t)$ is in the neighborhood of $TFA_j(0)$, the second term on the right can be neglected, achieving linearization in the logarithmic space. Therefore, Eq. **8** in the text can be regarded as a log-linearized form of the Hill equation.