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Gene activation model and implementation of ssLNA

The full model of the gene activation model is listed in equation (SM1) below:

$$\begin{aligned}
\frac{d[T]}{dt} &= -2\left(k_1[T]^2 - k_2[T2]\right)\\
\frac{d[T_2]}{dt} &= k_1[T]^2 - k_2[T_2] - k_3[T_2][G] + k_4[GT_2]\\
\frac{d[G]}{dt} &= -k_3[T_2][G] + k_4[GT_2]\\
\frac{d[GT_2]}{dt} &= k_3[T_2][G] + k_4[GT_2]\\
\frac{d[M]}{dt} &= k_{ms}[GT_2] - k_{md}[M]\\
\frac{d[P]}{dt} &= k_{ps}[M] - k_{pd}[p]
\end{aligned} \qquad \text{(SM1)}$$

The mRNA (M), and protein (P) are the slow species, while the transcription factor (T) and its dimer (T_2), the DNA promoter (G), and the transcription factor dimer-DNA promoter complex, GT_2, are the fast species regulated by fast binding/unbinding reactions [1].

In addition, conservation laws lead to equation (SM2) below, where G_T is the total number of DNA, and T_T is the total number of bound plus unbound transcription factor monomers. As a result, the reduced gene activation model only needs the ODEs of two variables, M and P.

$$\begin{cases} G_T = [G] + [GT_2] \\ T_T = [T] + 2([T_2] + [GT_2]) \end{cases} \qquad \text{(SM2)}$$

The stoichiometric matrix, $\boldsymbol{S}$, and the vector of macroscopic rate functions, $\vec{f}$, for the gene activation model are listed in equation (SM3) below. Note that $\vec{f}$ includes the rates of the eight elementary reactions as listed in equations (1)-(6) of the main text, while $\boldsymbol{S}$ shows the molecular change of species M, P, T_2, and GT_2 in the corresponding elementary reactions. The dotted line in $\boldsymbol{S}$ indicates the partitioning of $\boldsymbol{S}$ into $\boldsymbol{S}_s$ and $\boldsymbol{S}_f$ as demonstrated in equation (13) in the main text.

$$\boldsymbol{S} = \left[\begin{array}{cccccccc}
0 & 0 & 0 & 0 & +1 & 0 & -1 & 0 \\
0 & 0 & 0 & 0 & 0 & +1 & 0 & -1 \\
\hdashline
+1 & -1 & -1 & +1 & 0 & 0 & 0 & 0 \\
0 & 0 & +1 & -1 & 0 & 0 & 0 & 0
\end{array}\right] \begin{array}{c} M \\ P \\ \\ T_2 \\ GT_2 \end{array} \qquad \vec{f} = \begin{bmatrix} k_1(T_T - 2(T_2 + [GT_2]))^2 \\ k_2[T_2] \\ k_3(G_T - [GT_2])[T_2] \\ k_4[GT_2] \\ k_{ms}[GT_2] \\ k_{ps}[M] \\ k_{md}[M] \\ k_{pd}[P] \end{bmatrix} \qquad \text{(SM3)}$$

Due to QSSA, X_f is assumed to reach steady state and thus we have

$$\begin{cases} -2\left(k_1[T]^2 - k_2[T_2]\right) & = 0 \\ k_1[T]^2 - k_2[T_2] - k_3[T_2][G] + k_4[GT_2] & = 0 \\ k_3[T_2][G] + k_4[GT_2] & = 0 \\ k_3[T_2][G] - k_4[GT_2] & = 0 \end{cases} \quad \text{(SM4)}$$

Using (SM4) we can calculate the amount of GT_2 at quasi-steady state:

$$[GT_2] = \frac{k_1 k_3}{k_2 k_4}[G][T]^2 \quad \text{(SM5).}$$

Combining (SM5) and the first equation of (SM2), we can then arrive at the transcription rate given by equation (7) of the main text. Substituting this transcription rate, we have the following reduced slow-scale model (SM6):

$$\frac{d[M]}{dt} = k_{ms}\frac{[T]^2}{[T]^2 + k_d^2} - k_{md}[M]$$

$$\frac{d[P]}{dt} = k_{ps}[M] - k_{pd}[P] \quad \text{(SM6)}$$

where [T] is the steady-state solution of (SM2) and (SM5). Following the recipe for the ssLNA, one can write the Jacobian of the full system (SM1), and partition it according to the slow and fast species as equation (SM7) below. Note that J_s is exactly the same as J_h, the Jacobian of the reduced model (SM6).

$$\boldsymbol{J}_F = \frac{\partial(\boldsymbol{S}\vec{f})}{\partial \vec{X}_F} = \left[\begin{array}{c|c} \boldsymbol{J}_s & \boldsymbol{J}_{sf} \\ \hline \boldsymbol{J}_{fs} & \boldsymbol{J}_f \end{array}\right] = \quad \text{(SM7)}$$

$$= \left[\begin{array}{cc|cc} -k_{md} & 0 & 0 & k_{ms} \\ k_{ps} & -k_{pd} & 0 & 0 \\ \hline 0 & 0 & k_3([GT_2] - G_T) - k_2 + k_1(8[GT_2] + 8[T_2] - 4T_T) & k_4 + k_3[T_2] + k_1(8[GT_2] + 8[T_2] - 4T_T) \\ 0 & 0 & -k_3([GT_2] - G_T) & -k_4 - k_3[T_2] \end{array}\right]$$

After calculating D_{ss} using formula (15) of the main text, and substituting D_{ss} and J_s into the differential equation (14) of the main text, one calculates the correlation matrix H_{ss}. Finally the CV of M and P are obtained as the square root of the variances in the diagonal of H_{ss} divided by the means. Note that the variances in ssLNA framework are dependent on terms in D_{ss} that are functions of the fast variables, while the hLNA method only takes into account of slow variables. Thus the ssLNA method acquires higher noise precision.

Implementation of heuristic SSA and LNA (hSSA & hLNA) for the gene activation model

Both hSSA and hLNA are based entirely on the reduced slow-scale model (SM6). Specifically, for hSSA, the propensity function for the mRNA synthesis is now the Hill rate given by equation (7) of the main text. For hLNA, the stoichiometry matrix S_h and rate

functions $\vec{f}_h$ are obtained for the reduced model (SM6) as follows.

$$\boldsymbol{S}_h = \begin{bmatrix} +1 & 0 & -1 & 0 \\ 0 & +1 & 0 & -1 \end{bmatrix} \begin{matrix} M \\ P \end{matrix} \qquad \vec{\boldsymbol{f}}_{\boldsymbol{h}} = \begin{bmatrix} k_{ms} G_T \frac{[T]^2}{[T]^2 + k_d^2} \\ k_{ps}[M] \\ k_{md}[M] \\ k_{pd}[P] \end{bmatrix} \quad \text{(SM8)}$$

The Jacobian $\boldsymbol{J}_h$ is given by equation (SM9):

$$J_h = \frac{\partial\left(S_h \vec{f}_h\right)}{\partial \vec{X}_h} = \begin{bmatrix} -k_{md} & 0 \\ k_{ps} & -k_{pd} \end{bmatrix} \quad \text{(SM9)}$$

Notice that, in the heuristic cases, D_h below is not influenced by the fast species:

$$D_h = S_h diag\left(\vec{f}_h\right) S_h^T \quad \text{(SM10).}$$

Gene inhibition model and implementation of ssLNA

The complete list of ODEs that describes the gene inhibition model is listed in equation (SM11) with the red term highlighting the only difference from the gene activation model:

$$\begin{aligned}
\frac{d[T]}{dt} &= -2\left(k_1[T]^2 - k_2[T2]\right) \\
\frac{d[T_2]}{dt} &= k_1[T]^2 - k_2[T_2] - k_3[T_2][G] + k_4[GT_2] \\
\frac{d[G]}{dt} &= -k_3[T_2][G] + k_4[GT_2] \\
\frac{d[GT_2]}{dt} &= k_3[T_2][G] + k_4[GT_2] \\
\frac{d[M]}{dt} &= k_{ms}[G] - k_{md}[M] \\
\frac{d[P]}{dt} &= k_{ps}[M] - k_{pd}[p]
\end{aligned} \quad \text{(SM11)}$$

The model is under the same conservation laws as described by equation (SM2). Its stoichiometric matrix, S, and the vector of macroscopic rate functions, $\vec{f}$, are listed in equation (SM12) below. Again, M and protein P are the slow species, while T, T_2, G and GT_2 are the fast species.

$$\boldsymbol{S} = \left[\begin{array}{cccccccc} 0 & 0 & 0 & 0 & +1 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & +1 & 0 & -1 \\ \hline +1 & -1 & -1 & +1 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & +1 & 0 & 0 & 0 & 0 \end{array}\right] \begin{array}{c} M \\ P \\ \\ T_2 \\ G \end{array} \qquad \vec{f} = \begin{bmatrix} k_1(T_T - 2([T_2] + (G_T - [G])))^2 \\ k_2[T_2] \\ k_3[G][T_2] \\ k_4(G_T - [G]) \\ k_{ms}[G] \\ k_{ps}[M] \\ k_{md}[M] \\ k_{pd}[P] \end{bmatrix} \tag{SM12}$$

For the ssLNA, the partitioning of the Jacobian of the full system is given by equation (SM13) below. Again, J_s is exactly the same as J_h, the Jacobian of the reduced system under QSSA.

$$\boldsymbol{J}_F = \frac{\partial(\boldsymbol{S}\vec{f})}{\partial \vec{X}_F} = \left[\begin{array}{c|c} \boldsymbol{J}_s & \boldsymbol{J}_{sf} \\ \hline \boldsymbol{J}_{fs} & \boldsymbol{J}_f \end{array}\right] = \tag{SM13}$$

$$= \left[\begin{array}{cc|cc} -k_{md} & 0 & 0 & k_{ms} \\ k_{ps} & -k_{pd} & 0 & 0 \\ \hline 0 & 0 & k_3([GT_2] - G_T) - k_2 + k_1(8[GT_2] + 8[T_2] - 4T_T) & k_4 + k_3[T_2] + k_1(8[GT_2] + 8[T_2] - 4T_T) \\ 0 & 0 & -k_3([GT_2] - G_T) & -k_4 - k_3[T_2] \end{array}\right]$$

The rest computation of the covariance matrix $\boldsymbol{H}_{ss}$ follows the same procedure as that for the gene activation model.

Implementation of heuristic SSA and LNA (hSSA & hLNA) for the gene inhibition model

For hSSA computation of the gene inhibition model, the propensity function for the mRNA synthesis is given by the Hill function in equation (9) of the main text. For the hLNA method, the stoichiometry matrix,same as that for the gene activation model, and the rate functions are given in equation (SM14) below.

$$\boldsymbol{S}_h = \left[\begin{array}{cccc} +1 & 0 & -1 & 0 \\ 0 & +1 & 0 & -1 \end{array}\right] \begin{array}{c} M \\ P \end{array} \qquad \vec{f_h} = \begin{bmatrix} k_{ms} G_T \frac{k_d^2}{[T]^2 + k_d^2} \\ k_{ps}[M] \\ k_{md}[M] \\ k_{pd}[P] \end{bmatrix} \tag{SM14}$$

The Jacobian matrix as well as the rest of the computation is the same as that for the activation model.

References

1. Thomas, P., Straube, A.V., and Grima, R. (2012). The slow-scale linear noise approximation: an accurate, reduced stochastic description of biochemical networks under timescale separation conditions. BMC Syst Biol 6, 39.