

Table S3. Mathematical models used for linear noise approximation of five simple network motifs in the form $\frac{d\bar{y}}{dt} = \mathbf{R}$. For species m_i , $i = 1$ in the coupled form and 2 in the uncoupled form.

Model	\bar{y}^*	\mathbf{R}
Gene expression	$\begin{bmatrix} \langle m_1 \rangle \\ \langle A \rangle \\ \langle m_2 \rangle \\ \langle B \rangle \end{bmatrix}$	$\begin{bmatrix} k_m - k_{mdeg} \langle m_1 \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle A \rangle \\ k_m - k_{mdeg} \langle m_2 \rangle \\ k_{tsn} \langle m_2 \rangle - k_{deg} \langle B \rangle \end{bmatrix}$
Linear metabolic pathway	$\begin{bmatrix} \langle A \rangle \\ \langle B \rangle \\ \langle I \rangle \\ \langle P \rangle \end{bmatrix}$	$\begin{bmatrix} k_{tsn} \langle m_1 \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle B \rangle \\ v_1 \langle A \rangle - v_2 \frac{\langle I \rangle \langle B \rangle}{K_m + \langle I \rangle} - k_{deg} \langle I \rangle \\ v_2 \frac{\langle I \rangle \langle B \rangle}{K_m + \langle I \rangle} - k_u \langle P \rangle \end{bmatrix}$
Redundant metabolic step	$\begin{bmatrix} \langle A \rangle \\ \langle B \rangle \\ \langle P \rangle \end{bmatrix}$	$\begin{bmatrix} k_{tsn} \langle m_1 \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle B \rangle \\ v_1 \langle A \rangle + v_2 \langle B \rangle - k_u \langle P \rangle \end{bmatrix}$
Metabolic branch point	$\begin{bmatrix} \langle S \rangle \\ \langle A \rangle \\ \langle B \rangle \end{bmatrix}$	$\begin{bmatrix} k_{in} - k_1 \frac{\langle S \rangle \langle A \rangle}{K_m + \langle A \rangle} - k_2 \frac{\langle S \rangle \langle B \rangle}{K_m + \langle B \rangle} - k_{deg} \langle S \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle B \rangle \end{bmatrix}$
Covalent modification	$\begin{bmatrix} \langle A \rangle \\ \langle B \rangle \\ \langle AB \rangle \\ \langle A^* \rangle \end{bmatrix}$	$\begin{bmatrix} k_{tsn} \langle m_1 \rangle - k_b \langle A \rangle \langle B \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_b \langle A \rangle \langle B \rangle + k_p \langle AB \rangle - k_{deg} \langle B \rangle \\ k_b \langle A \rangle \langle B \rangle - k_p \langle AB \rangle - k_{deg} \langle AB \rangle \\ k_p \langle AB \rangle - k_{deg} \langle A^* \rangle \end{bmatrix}$
Multiple gene regulators	$\begin{bmatrix} \langle A \rangle \\ \langle B \rangle \\ \langle m_p \rangle \\ \langle P \rangle \end{bmatrix}$	$\begin{bmatrix} k_{tsn} \langle m_1 \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_{deg} \langle B \rangle \\ k_{mpb} + k_{mp} \frac{\langle A \rangle + \langle B \rangle}{K_m + \langle A \rangle + \langle B \rangle} - k_{mdeg} \langle m_p \rangle \\ k_{tsnp} \langle m_p \rangle - k_{deg} \langle P \rangle \end{bmatrix}$
Stoichiometric interaction	$\begin{bmatrix} \langle A \rangle \\ \langle B \rangle \\ \langle AB \rangle \end{bmatrix}$	$\begin{bmatrix} k_{tsn} \langle m_1 \rangle - k_b \langle A \rangle \langle B \rangle + k_d \langle AB \rangle - k_{deg} \langle A \rangle \\ k_{tsn} \langle m_1 \rangle - k_b \langle A \rangle \langle B \rangle + k_d \langle AB \rangle - k_{deg} \langle B \rangle \\ k_b \langle A \rangle \langle B \rangle - k_d \langle AB \rangle - k_{deg} \langle AB \rangle \end{bmatrix}$

Variable definitions: m_1, m_2, m_p : mRNA. A, B : expressed proteins. AB : protein complex. A^ : Modified form of A . S, I : metabolic substrate and intermediates. P : metabolic product, or protein gene product in the Multiple Gene Regulator model.