

The transcription regulation part of the integrated network is considered as a system where transcription factors (TFs) regulate target genes and the dynamic model of gene x is described by a stochastic equation as follows:

$$x_g[t] = B_g + (1 - \lambda_g)x_g[t-1] + \sum_{i=1}^N R_{ig} z_i[t-1] + \varepsilon_g[t-1] \quad (1)$$

where $x_g[t]$ is the mRNA expression level of gene g at time t . It is modeled as a function of the basal level B_g , the expression level at the prior time point $x_g[t-1]$, the regulation level $z_i[t-1]$ of TF i , and stochastic noise ε_g . R_{ig} represents the regulatory parameter of transcription factor i to target gene g , which indicates activation if positive and repression otherwise. λ_g denotes the degradation effects. The regulation level z_i is defined as the sigmoid function $f_i(y_i[t])$ of the protein activity y_i , which is described below to model signaling regulatory pathway.

For the protein-protein interactions, the dynamic model of the activity $y_n[t]$ for a target protein n is described by the following equation

$$y_n[t] = B'_n + (1 - \lambda'_n)y_n[t-1] + \sum_{j=1}^N I_{nj} y_n[t-1] y_j[t-1] + T_n x_n[t-1] + \varepsilon'_n[t-1] \quad (2)$$

where B'_n is the basal activity level of protein n , λ'_n indicates the degradation effect of the protein, and I_{nj} denotes the interaction parameter of protein n and j . In addition, the protein activity level is also affected by the expression level of the corresponding gene $x_n[t-1]$ and T_n represents translation effect from mRNA to protein. ε'_n denotes the stochastic noise.

Note that the two networks interact in two ways - in equation (1), the protein activities of TFs regulate their target genes and in equation (2), genes affect the activities of their corresponding proteins through translation effect. Regulatory parameters R and interaction parameters I are computed, based on gene expression data collected at multiple time points, by solving the constrained least square parameter estimation problem. Given the regulatory parameters, significant interactions and regulations in the integrated network are identified via Akaike Information Criterion (AIC, measure of goodness of fit of a statistical model) and the Student's t -test.