Linear gene networks

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1   Definitions

Consider a set of stochastic linear differential equations which govern the concentration of RNA x_i and protein y_i associated with a particular gene:

$$\dot{x}_i = \sum_j m_{ij} y_j - \alpha_i x_i + \sigma_x \eta_i^x$$

$$\dot{y}_i = r_i x_i - \beta_i y_i + \sigma_y \eta_i^y$$

where m_{ij} is the linear effect of a transcription factor j on gene i and therefore represents the rate of transcription. Similarly, r_i represents the rate of translation from RNA to protein. The constants α_i and β_i are the RNA degradation and protein degradation rates, respectively. Since these equations are stochastic, the gold-standard is to find a probability density $P_\theta(\boldsymbol{x}, \boldsymbol{y}; t)$. In higher dimensions, this is a very difficult problem and we may need to settle for finding the stationary distribution $P_\theta^0(\boldsymbol{x}, \boldsymbol{y})$, if it exists and finding its solution is tractable. To do this for the set of equations above, a fundamental assumption is that the rate of translation and protein degradation approximately balance and the timescale of of changes in protein concentration is very long. Intuitively, if y_j's are constant, growth or decay of the first term will eventually balance with the $-\alpha_i x_i$ term and the system will approach a fixed point.

If indeed changes in protein concentration are negligible over the course of evolution of the system i.e., $\dot{y}_i \approx 0$ we have that

$$y_i = \frac{r_i x_i - \sigma_x \eta_i^y}{\beta_i}$$

This assumption allows us to rewrite the system above as a single equation per gene

$$\dot{x}_i = \sum_j m_{ij} \frac{r_j x_j - \sigma_x \eta_j^y}{\beta_j} - \alpha_i x_i + \sigma_x \eta_i^x$$

$$= \sum_j \left(\gamma_{ij} x_j - \theta_{ij} \eta_j^y \right) - \alpha_i x_i + \sigma_x \eta_i^x$$

If we additionally assume that $\sigma_x << r_i x_i$

$$\dot{x}_i = \sum_j \gamma_{ij} x_j - \alpha_i x_i + \sigma_x \eta_i^x$$

which is the multivariate Ornstein-Uhlenbeck process. This can then be written as an Ito stochastic differential equation

$$dx = -\Gamma x \, dt + \Sigma dW$$

For example, when $N = 3$ we have the following matrix Γ

$$\Gamma = \begin{bmatrix} \gamma_{11} - \alpha_1 & \gamma_{21} & \gamma_{31} \\ \gamma_{12} & \gamma_{22} - \alpha_2 & \gamma_{32} \\ \gamma_{13} & \gamma_{23} & \gamma_{33} - \alpha_3 \end{bmatrix}$$

2 The multivariate Fokker-Planck equation

The SDE given above corresponds to the Kramers-Moyal expansion (KME) of a transition density $T(x', t'|x, t)$ see (Risken 1989) for a full derivation.

$$\frac{\partial P}{\partial t} = \sum_{n=1}^{\infty} \frac{1}{n!} \left(-\frac{\partial}{\partial x} \right)^n [M_n(x, t) P(x, t)] \tag{1}$$

where M_n is the nth moment of the transition density. In the diffusion approximation, the KME becomes the Fokker-Planck equation (FPE) (Risken 1989). For the sake of demonstration, consider the univariate case with random variable x and the form of $T(x', t'|x, t)$ is a Gaussian with mean $\mu(t)$ and variance $\sigma^2(t)$. In this scenario, the FPE applies because $M_n = 0$ for all $n > 2$. Given that $M_1(x, t) = \mu(t)$ (drift) and $M_2(x, t) = \sigma^2(t)$ (diffusion), the FPE reads

$$\frac{\partial P(x,t)}{\partial t} = \left(-\frac{\partial}{\partial x}\mu(t) + \frac{\sigma^2(t)}{2}\frac{\partial^2}{\partial x^2}\right)P(x,t) \qquad (2)$$

It is common to additionally define the probability current $J(x,t)$ as

$$J(x,t) = \left(-\mu(t) + \frac{\sigma^2(t)}{2}\frac{\partial}{\partial x}\right)P(x,t) \qquad (3)$$

which allows us to write the FPE as a continuity equation

$$\frac{\partial P(x,t)}{\partial t} = \frac{\partial J(x,t)}{\partial x} \qquad (4)$$

If we now generalize the above equation to a case where we are faced with many variables $\boldsymbol{x} = (x_1, x_2, ..., x_n)$. The continuity equation becomes

$$\frac{\partial P(x,t)}{\partial t} = \nabla_{\boldsymbol{x}} \cdot J(\boldsymbol{x},t) \qquad (5)$$

where the multivariate probability current is given as

$$J(\boldsymbol{x},t) = \left(-\boldsymbol{\mu}(t) + \boldsymbol{D}\nabla_{\boldsymbol{x}}\right)P(\boldsymbol{x},t) \qquad (6)$$

with $D = \frac{\Sigma\Sigma^T}{2}$. but the transition density remains Gaussian. Here, $M_1(\boldsymbol{x},t) = \boldsymbol{\mu}(t)$ and $M_2(\boldsymbol{x},t) = \boldsymbol{\Sigma}(t)$

$$\frac{\partial P(\boldsymbol{x},t)}{\partial t} = \nabla_{\boldsymbol{x}} \cdot J(\boldsymbol{x},t) \qquad (7)$$

$$= -\sum_{i=1}^{N}\boldsymbol{\mu}_i\frac{\partial P(\boldsymbol{x},t)}{\partial x_i} + \sum_{i,j}^{N}D_{ij}\frac{\partial^2 P(\boldsymbol{x},t)}{\partial x_i\partial x_j} \qquad (8)$$

It proves quite useful in this form because we can see that $\partial P/\partial t$ is nothing but an operator acting on the current distribution $P(x,t)$

$$\mathcal{L}_{FP} = -\sum_{i=1}^{N}\frac{\partial}{\partial x_i}S_i + \sum_{i,j=1}^{N}D_{ij}\frac{\partial^2}{\partial x_i\partial x_j} \qquad (9)$$

S_i is the drift vector and D_{ij} the diffusion matrix. The second term is the diffusion term which is volatile over time. Incorporating the quantities $S = \Gamma x$ and $2D = \Sigma\Sigma^T$ into this form for the OU process,

$$\frac{\partial P}{\partial t} = \left(-\sum_{i=1}^{N} \frac{\partial}{\partial x_i} \Gamma x + \frac{1}{2} \sum_{i,j=1}^{N} (\Sigma\Sigma^T)_{ij} \frac{\partial^2}{\partial x_i \partial x_j} \right) P \tag{10}$$

$$\tag{11}$$

A distribution π is the stationary distribution (equilibrium distribution) of P if $\mathcal{L}_{FP}\pi = 0$. Such a system is said to obey *detailed balance*, in which the Fokker-Planck operator leaves the distribution invariant. Qualitatively, this means that, at equilibrium, the probability current out of an infinitesimal volume dV in the state space Ω is balanced by an equal and opposite current into dV.

$$\frac{\partial P}{\partial t} = \left(-\sum_{i=1}^{N} \frac{\partial}{\partial x_i} \Gamma x + \frac{1}{2} \sum_{i,j=1}^{N} (\Sigma\Sigma^T)_{ij} \frac{\partial^2}{\partial x_i \partial x_j} \right) P \tag{12}$$

$$\tag{13}$$

3   Fourier Transform of the FPE

Fourier transformation is a general method used in the solution of differential equations. It is particularly useful for second order equations like the FPE. You may have seen its use in the heat equation, which is the Fokker-Planck equation for Brownian motion.