Fourier solution for mRNA metabolism

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Model

We model the dynamics of mRNA metabolism by expressing the steps involved—transcription, splicing, degradation—as a system of coupled ordinary differential equations.

$$\frac{\mathrm{d}u(t)}{\mathrm{d}t} = \alpha(t) - \beta u(t) \tag{1}$$

$$\frac{\mathrm{d}s(t)}{\mathrm{d}t} = \beta u(t) - \gamma(t)s(t) \tag{2}$$

α: synthesis rate
β: splicing rate
γ: degradation rate

Unspliced solution

We assume that $u(t)$ and $\alpha(t)$ are periodic functions. Thus, we can express $u(t)$ and $\alpha(t)$ as sums of Fourier series.

$$u(t) = \sum_{n=-\infty}^{+\infty} u_n e^{\frac{i2\pi nt}{P}} \tag{3}$$

$$\alpha(t) = \sum_{n=-\infty}^{+\infty} \alpha_n e^{\frac{i2\pi nt}{P}}, \tag{4}$$

wehre P : the period of oscillation. Let $\theta = \frac{2\pi t}{P}$, such that $\theta \in (0, 1)$

Thus, we have

$$\begin{aligned}
u(\theta) &= \sum_{n=-\infty}^{+\infty} u_n e^{in\theta} \\
\frac{\mathrm{d}u(\theta)}{\mathrm{d}t} &= \sum_{n=-\infty}^{+\infty} inu_n e^{in\theta} \\
\alpha(\theta) &= \sum_{n=-\infty}^{+\infty} \alpha_n e^{in\theta}
\end{aligned}$$

Using these in equation (1), we get,

$$\begin{aligned}
&\sum_{n=-\infty}^{+\infty} inu_n e^{in\theta} = \sum_{n=-\infty}^{+\infty} \alpha_n e^{in\theta} - \beta \sum_{n=-\infty}^{+\infty} u_n e^{in\theta} \\
&\sum_{n=-\infty}^{+\infty} \left(iu_n n - \alpha_n + \beta u_n\right) e^{in\theta} = 0 \\
&iu_n n - \alpha_n + \beta u_n = 0 \\
&u_n = \frac{\alpha_n}{\beta + in}
\end{aligned}$$

The Fourier approximation for $u(\theta)$

$$u(\theta) = \sum_{n=-\infty}^{+\infty} \left(\frac{\alpha_n}{\beta + in}\right) e^{in\theta} \tag{5}$$

When performing numerical optimization, it is convenient to have real-valued parameters, *i.e.* Fourier coefficients for $\alpha(\theta)$ and $\gamma(\theta)$. Fourier series for α with real-values co-efficients can be written as

$$\alpha(\theta) = \alpha_0 + \sum_{n=1}^{N} \alpha_n^A + \cos(n\theta) + \alpha_n^B \sin(n\theta)$$

We can recover the complex co-efficients

$$\begin{aligned} \alpha_n &= \frac{\alpha_n^A + i\alpha_n^B}{2} && \text{(for } n < 0) \\ \alpha_n &= \frac{\alpha_n^A - i\alpha_n^B}{2} && \text{(for } n > 0) \end{aligned}$$

Spliced solution

Akin to $u(\theta)$ and $\alpha(\theta)$, we expect $s(\theta)$ and $\gamma(\theta)$ also to be periodic functions. The Fourier series expansion of s and γ (as a function of θ) is,

$$\begin{aligned} s(\theta) &= \sum_{n=-N}^{N} s_n e^{in\theta} \\ \gamma(\theta) &= \sum_{n=-N}^{N} \gamma_n e^{in\theta} \end{aligned}$$

Using these expressions in (2),

$$\sum_{n=-N}^{N} ins_n e^{in\theta} = \beta \sum_{n=-N}^{N} u_n e^{in\theta} - \sum_{n=-N}^{N} \sum_{m=-N}^{N} s_n \gamma_m e^{i(m+n)\theta} \tag{6}$$

In the last term in the above equation, let $k = m + n$

$$\begin{aligned} \sum_{n=-N}^{N} \sum_{m=-N}^{N} s_n \gamma_m e^{i(m+n)\theta} &= \sum_{n=-N}^{N} \sum_{m=-N}^{N} s_n \gamma_m e^{ik\theta} \\ &= \sum_{n=-N}^{N} \sum_{m=-N}^{N} \sum_{k=-N}^{N} s_n \gamma_m \delta_{n+m,k} e^{ik\theta} \\ &= \sum_{k=-N}^{N} \sum_{m=-N}^{N} \sum_{n=-N}^{N} s_k \gamma_m \delta_{k+m,n} e^{in\theta} \\ &= \sum_{n=-N}^{N} \sum_{m=-N}^{N} \sum_{k=-N}^{N} s_k \gamma_m \delta_{k+m,n} e^{in\theta} \end{aligned}$$

Using this in (6)

$$\sum_{n=-N}^{N} ins_n e^{in\theta} = \beta \sum_{n=-N}^{N} u_n e^{in\theta} - \sum_{n=-N}^{N} \sum_{m=-N}^{N} \sum_{k=-N}^{N} s_k \gamma_m \delta_{k+m,n} e^{in\theta}$$

$$ins_n = \beta u_n - \sum_{m=-N}^{N} \sum_{k=-N}^{N} s_k \gamma_m \delta_{k+m,n}$$

$$\sum_{k=-N}^{N} \left[\delta_{k,n} in + \sum_{m=-N}^{N} \gamma_m \delta_{k+m,n} \right] s_k = \beta u_n$$

$$\sum_{k=-N}^{N} G_{nk} s_k = \beta u_n$$

We can express this as a matrix equation

$$\mathbf{s} = \beta \mathbf{G}^{-1} \mathbf{u} \tag{7}$$

where $\mathbf{G}$ is a $(2N+1) \times (2N+1)$ matrix:

$$\begin{pmatrix} \gamma_0 - Ni & \gamma_{-1} & \cdots & \gamma_{-N} & 0 & \cdots & 0 & 0 \\ \gamma_1 & \gamma_0 - (N-1)i & \cdots & \gamma_{-(N-1)} & \gamma_{-N} & \cdots & 0 & 0 \\ \gamma_2 & \gamma_1 & \cdots & \gamma_{-(N-2)} & \gamma_{-(N-1)} & \cdots & 0 & 0 \\ \vdots & \vdots & \cdots & \vdots & \vdots & \cdots & \vdots & \vdots \\ 0 & 0 & \cdots & \gamma_{N-2} & \gamma_{N-3} & \cdots & \gamma_{-1} & \gamma_{-2} \\ 0 & 0 & \cdots & \gamma_{N-1} & \gamma_{N-2} & \cdots & \gamma_0 + (N-1)i & \gamma_{-1} \\ 0 & 0 & \cdots & \gamma_N & \gamma_{N-1} & \cdots & \gamma_1 & \gamma_0 + Ni \end{pmatrix} \tag{8}$$

Model fitting

The optimization was performed using `scipy.optimize.minimize`, we used the following loss function for the optmization,

$$\text{Loss} = \lambda_1 \frac{N}{2} \left[\log \sum_{i=1}^{N} (u_i^{\text{data}} - u_i^{\text{model}})^2 + \log \sum_{i=1}^{N} (s_i^{\text{data}} - s_i^{\text{model}})^2 \right] + \lambda_2 \left[\sum_{i=1}^{N} \Theta(-\alpha) \cdot \alpha^2 + \sum_{i=1}^{N} \Theta(-\gamma) \cdot \gamma^2 \right]$$
$$+ \lambda_3 \left[\sum_{i=1}^{N} \Delta\theta_i \sqrt{1 + \left(\frac{\mathrm{d}\alpha}{\mathrm{d}\theta}\right)_i^2} + \sum_{i=1}^{N} \Delta\theta_i \sqrt{1 + \left(\frac{\mathrm{d}\gamma}{\mathrm{d}\theta}\right)_i^2} \right]$$