

Dynamical Systems in Biological Engineering:

Slides for parts of chapter on stochastic models

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Example: mRNA production and degradation



could alternatively model as “ $G \rightarrow G + M$ ” instead of “ $0 \rightarrow M$ ”
where G would indicate the activity level of the gene G

The stoichiometry matrix and propensities are:

$$\Gamma = \begin{pmatrix} 1 & -1 \end{pmatrix}, \quad \rho_1(k) = \alpha, \quad \rho_2(k) = \beta k$$

so that

$$f(k) = \alpha - \beta k$$

The CME (flow-into minus flow-out-of state k) becomes:

$$\frac{dp_k}{dt} = \alpha p_{k-1} + (k+1)\beta p_{k+1} - \alpha p_k - k\beta p_k$$

(w/ convention is that a term is zero if the subscript is negative)

here $k \in K = \mathbb{Z}_{\geq 0}$ is just a non-negative integer

let π be the steady-state probability distribution, setting $\frac{dp}{dt} = 0$
(under technical conditions, unique and $\pi_k = \lim_{t \rightarrow \infty} p_k(t)$)

interpret as the probability distribution of $X(\infty)$

Steady state

$$\alpha\pi_{k-1} + (k+1)\beta\pi_{k+1} - \alpha\pi_k - k\beta\pi_k = 0, \quad k = 0, 1, 2, \dots$$

(first term is not there if $k = 0$) which solving gives Poisson distribution:

$$\pi_k = e^{-\lambda} \frac{\lambda^k}{k!}$$

where $\lambda = \frac{\alpha}{\beta}$

Bursts of mRNA production

if mRNA is produced in “bursts” of $r > 1$ transcripts:



with stoichiometry matrix and propensities:

$$\Gamma = (r \quad -1), \quad \rho_1(k) = \alpha, \quad \rho_2(k) = \beta k$$

so

$$f(k) = r\alpha - \beta k$$

same as in the non-bursting case! (with rate α redefined as $r\alpha$)
so deterministic chemical equation representation same as before!
mean of stochastic process will also be same (up to redefining α)
but we will see that variance depends on r

A simple dimerization example

Suppose that a molecule of A can be produced at constant rate α and degrades when dimerized:



leads to

$$\Gamma = \begin{pmatrix} 1 & -2 \end{pmatrix}, \quad \rho_1(k) = \alpha, \quad \rho_2(k) = \frac{\beta k(k-1)}{2}$$

$$f(k) = \alpha - \beta k(k-1) = \alpha + \beta k - \beta k^2$$

Transcription and translation

$$\begin{aligned} 0 &\xrightarrow{\alpha} M \xrightarrow{\beta} 0 \\ M &\xrightarrow{\theta} M + P, \quad P \xrightarrow{\delta} 0 \\ \Gamma &= \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix} \end{aligned}$$

$$\rho_1(k) = \alpha, \rho_2(k) = \beta k_1, \rho_3(k) = \theta k_1, \rho_4(k) = \delta k_2$$

vector $k = (k_1, k_2)$ counts mRNA and protein numbers respectively and (writing “ (M, P) ” instead of $k = (k_1, k_2)$):

$$f(M, P) = \begin{pmatrix} \alpha - \beta M \\ \theta M - \delta P \end{pmatrix}$$

P does not affect M , so behavior of M same as transcription model in particular the steady-state distribution of M is Poisson
however, P depends on M , making problem much more interesting

Mean and Variance

intuitively if noise was “external” and mean zero:

$$dx/dt = f(x) + w$$

then $d\mathbb{E}[x]/dt = \mathbb{E}[dX/dt] = \mathbb{E}[f(x) + w] = \mathbb{E}[f(x)]$
for “internal” noise,

$$d\mathbb{E}[x]/dt = \mathbb{E}[f(x)]$$

also true, but slightly harder to prove (see notes)
(also there’s a formula for variance, a bit more complicated)

warning for means: not the same as $f(\mathbb{E}[x])$
so not same as deterministic equation for means!

Variance

intuition (still for extrinsic noise, not intrinsic)

suppose $f(x) = ax - bx^2$, as in logistic equation

$$d\mathbb{E}[x]/dt = \mathbb{E}[ax - bx^2] = \mathbb{E}[ax] - b\mathbb{E}[x^2]$$

and $\sigma^2(X) = \mathbb{E}[x^2] - \mathbb{E}[x]^2 \Rightarrow \mathbb{E}[x^2] = \sigma^2(X) + \mathbb{E}[x]^2$ so

$$d\mathbb{E}[x]/dt = \mathbb{E}[ax] - b(\mathbb{E}[x]^2 + \sigma^2(x)) = f(\mathbb{E}[x]) - b\sigma^2(x)$$

i.e. $d\mu/dt = f(\mu) - b\sigma^2$; additional term compared to deterministic

same true, but harder to prove, for intrinsic

from now on **assume reactions of order zero or one only**

very restrictive case - but ideas can be generalized and used in approximation and truncation algorithms

Case when f is an affine function

For mass-action kinetics and all reactions of order zero or one

i.e. $f(x) = Ax + b$ (matrix, vector)

the mean $\mu(t) = \mathbb{E}[X(t)]$ and covariance matrix $\Sigma(t) = \mathbb{V}\text{ar}[X(t)]$ are solutions of the coupled system of differential equations:

$$\begin{aligned}\dot{\mu} &= A\mu + b \\ \dot{\Sigma} &= \Sigma A' + A\Sigma + B(\mu)\end{aligned}$$

where

$$B(\mu) = \Gamma \begin{pmatrix} \rho_1(\mu) & 0 & \dots & 0 \\ 0 & \rho_2(\mu) & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \rho_{n_r}(\mu) \end{pmatrix} \Gamma'$$

(prime is transpose)

similar to “Lyapunov” equation in control theory

called “fluctuation-dissipation” equation:

first two terms for Σ describe a “dissipation” of initial uncertainty

last represents “fluctuation” due to future randomness

Example: mRNA model

$0 \xrightarrow{\alpha} M \xrightarrow{\beta} 0$, $G = (1, -1)$, $\rho_1(k) = \alpha$, $\rho_2(k) = \beta k$, $f(k) = \alpha - \beta k$

reactions are of order 0 and 1

$$\dot{\mu} = f(\mu), \quad \dot{\Sigma} = \Sigma A' + A \Sigma + B(\mu)$$

(both μ and Σ are scalar variables)

$$A = -\beta, \quad B(\mu) = \sum_{j=1}^2 \rho_j(\mu) \gamma_{1j} \gamma_{1j} = \alpha 1^2 + \beta \mu (-1)^2 = \alpha + \beta \mu$$

so:

$$\begin{aligned}\dot{\mu} &= \alpha - \beta \mu \\ \dot{\Sigma} &= -2\beta \Sigma + \alpha + \beta \mu\end{aligned}$$

unique steady state: $\mu = \alpha/\beta = \lambda$ and

$$\Sigma = \frac{\alpha + \beta \mu}{2\beta} = \frac{\alpha}{\beta} = \lambda$$

(consistent with variance = mean for Poisson)

coefficient of variation:

$$\mathbf{cv}[X] := \frac{\sigma[X]}{\mathbb{E}[X]}$$

(only defined if $\mathbb{E}[X] \neq 0$)

represents a “relative noise” and is “dimensionless”

(“Fano factor” $\frac{\sigma^2(X)}{\mathbb{E}[X]}$ not dimensionless)

for a Poisson random variable X with parameter λ ,

$\mathbb{E}[X] = \lambda$ and $\sigma[X] = \sqrt{\lambda}$, so $\mathbf{cv}[X] = 1/\sqrt{\lambda}$

Example: mRNA bursting model



$$G = (r, -1), \rho_1(k) = \alpha, \rho_2(k) = \beta k, f(k) = r\alpha - \beta k$$

here $A = -\beta$ and $B(\mu) = \alpha r^2 + \beta\mu$ so

$$\dot{\mu} = f(\mu) = \alpha r - \beta\mu$$

$$\dot{\Sigma} = -2\beta\Sigma + B(\mu) = -2\beta\Sigma + \alpha r^2 + \beta\mu$$

in particular, at steady state we have (with $\lambda = \frac{\alpha}{\beta}$):

$$\mu = \frac{\alpha r}{\beta} = \lambda r$$

$$\Sigma = \frac{\alpha r^2 + \beta \frac{\alpha r}{\beta}}{2\beta} = \frac{\alpha r^2 + \alpha r}{2\beta} = \lambda \frac{r(r+1)}{2}$$

$$\text{cv}[M]^2 = \lambda \frac{r(r+1)}{2} \bigg/ \lambda^2 r^2 = \frac{r+1}{2r} \frac{1}{\lambda}$$

which specializes to $1/\lambda$ in the Poisson case (no bursting, $r = 1$)
CV lower as r higher, but never lower than $1/2$ of Poisson rate

Compare to deterministically equivalent non-bursting



$$\text{cv}[M]^2 = \frac{r+1}{2r} \frac{\beta}{\alpha}$$



$$\text{cv}[M]^2 = \frac{\beta}{r\alpha} = \frac{1}{r} \frac{\beta}{\alpha}$$

comparing:

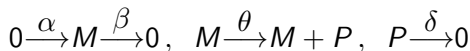
$$\frac{r+1}{2r} \frac{\beta}{\alpha} > \frac{1}{r} \frac{\beta}{\alpha}$$

happens if

$$r > 1$$

i.e. bursty transcription is more noisy

Transcription/translation model



$$\Gamma = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$$

$$\rho_1(k) = \alpha, \quad \rho_2(k) = \beta k_1, \quad \rho_3(k) = \theta k_1, \quad \rho_4(k) = \delta k_2$$

and (writing “ (M, P) ” instead of $k = (k_1, k_2)$):

$$f(M, P) = \begin{pmatrix} \alpha - \beta M \\ \theta M - \delta P \end{pmatrix}$$

there are 5 differential equations:

2 for means and 3 (omitting one by symmetry) for the covariances

Continued:

for means we have:

$$\dot{\mu}_M = \alpha - \beta\mu_M$$

$$\dot{\mu}_P = \theta\mu_M - \delta\mu_P$$

$$\begin{aligned} B(\mu) &= \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix} \begin{pmatrix} \alpha \\ \beta\mu_M \\ \theta\mu_M \\ \delta\mu_P \end{pmatrix} \begin{pmatrix} 1 & 0 \\ -1 & 0 \\ 0 & 1 \\ 0 & -1 \end{pmatrix} \\ &= \begin{pmatrix} \alpha + \beta\mu_M & 0 \\ 0 & \theta\mu_M + \delta\mu_P \end{pmatrix} \end{aligned}$$

$$A = \text{Jacobian of } \begin{pmatrix} \alpha - \beta M \\ \theta M - \delta P \end{pmatrix} = \begin{pmatrix} -\beta & 0 \\ \theta & -\delta \end{pmatrix}$$

Continued:

it follows that the variance part of the FD equation

$$\dot{\Sigma} = \Sigma A' + A \Sigma + B$$

is (omitting the symmetric equation for Σ_{PM}):

$$\begin{aligned}\dot{\Sigma}_{MM} &= -2\beta \Sigma_{MM} + \alpha + \beta \mu_M \\ \dot{\Sigma}_{PP} &= -2\delta \Sigma_{PP} + 2\theta \Sigma_{MP} + \theta \mu_M + \delta \mu_P \\ \dot{\Sigma}_{MP} &= \theta \Sigma_{MM} - (\beta + \delta) \Sigma_{MP}\end{aligned}$$

in particular, at steady state we have the following mean number of proteins:

$$\mu_P = \frac{\alpha \theta}{\beta \delta}$$

and the following squared coefficient of variation for protein numbers:

$$\mathbf{cv}[P]^2 = \frac{\Sigma_{PP}}{\mu_P^2} = \frac{(\theta + \beta + \delta)\beta\delta}{\alpha\theta(\beta + \delta)} = \frac{1}{\mu_P} + \frac{1}{\mu_M} \frac{\delta}{\beta + \delta}$$

Continued:

first term: “*intrinsic noise*” of transcription

what the cv would be, if M was constant (so P Poisson)

second: “*extrinsic noise*” of transcription, due to mRNA variability

total noise is bounded below by the intrinsic noise,

and above by the sum of intrinsic noise and mRNA noise:

$$\frac{1}{\mu_P} \leq \mathbf{cv}[P]^2 \leq \frac{1}{\mu_P} + \frac{1}{\mu_M}$$

(second inequality because $\frac{\delta}{\beta+\delta} < 1$)

even if the mean protein number $\mu_P \gg 1$,

term $\frac{1}{\mu_M} \frac{\delta}{\beta+\delta}$, may be large,

so that extrinsic noise may dominate even in “large” systems

moreover, even accounting for much faster mRNA than protein

degradation: $\beta \gg \delta$, which implies $\frac{\delta}{\beta+\delta} \ll 1$,

this term may well be large if $\mu_M \ll 1$

Continued:

another way to rewrite the total protein noise:

$$\mathbf{cv}[P]^2 = \frac{1}{\mu_P} \left[1 + \frac{b}{1 + \eta} \right]$$

where $\eta = \frac{\theta}{\beta}$ is the ratio of mRNA to protein lifetimes, and $b = \theta/\beta$ is the *burst factor* of the translation/transcription process number η is typically very small, so

$$\mathbf{cv}[P]^2 \approx \frac{1 + b}{\mu_P}$$

as b is typically much larger than one, this means that the noise in P is much larger than would be expected for Poisson
e.g.: typical values for b are 40 for lacZ and 5 for lacI