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Derivation of moment equations for a nonlinear gene expression model with initial condition and parameter uncertainty

Notation and definitions

Given a multivariate random variable $X \in \mathbb{R}^N$ with probability density function $p(x)$:

- *Moment* μ_α of order α is defined as

$$\mu_\alpha = \mathbb{E}_{p(x)} [X^\alpha] = \int_{\mathbb{R}_+^N} \mathbf{x}^\alpha p(x) dx, \quad (1)$$

where the multi-index $\alpha = (\alpha_1, \alpha_2, \dots, \alpha_N)$ and $\mathbf{x}^\alpha = x_1^{\alpha_1} x_2^{\alpha_2} \dots x_N^{\alpha_N}$.

- The joint *moment-generating function (MGF)* $M_X(\theta)$ is

$$M_X(\theta) = \mathbb{E}_{p(x)} [\exp(\theta^T X)] = \sum_{|\alpha| \geq 0} \frac{\theta^\alpha}{\alpha!} \mu_\alpha, \quad (2)$$

$$|\alpha| = \alpha_1 + \alpha_2 + \dots + \alpha_N,$$

$$\alpha! = \alpha_1! \alpha_2! \dots \alpha_N!$$

for $\theta \in \mathbb{R}^N$ belonging to a open rectangle that contains the origin, and for which the above expectation is finite.

ODE model of an autoinhibitory gene circuit dynamics for 1-dimensional case

We assume that in this case only the protein concentration A is uncertain where the dynamics of A is governed by the following ODE:

$$\frac{dA}{dt} = F(A) = \frac{P(A)}{Q(A)} = \frac{1}{1 + A^2/4} - 0.01A = \frac{4 - 4 \cdot 0.01A - 0.01A^3}{4 + A^2} \quad (3)$$

Moment generating function

$$M_A(\theta) = 1 + \mu_1 \theta + \frac{\mu_2}{2!} \theta^2 + \dots$$

$$\frac{\partial M_A(\theta)}{\partial \theta} = \mu_1 + \mu_2 \theta + \mu_3 \frac{\theta^2}{2!} \dots$$

$$\frac{\partial^k M_A(\theta)}{\partial \theta^k} = \mu_k + \mu_{k+1} \theta + \mu_{k+2} \frac{\theta^2}{2!} \dots = \sum_{n=k}^{\infty} \frac{\theta^{n-k}}{(n-k)!} \mu_n$$

Formula to derive moment equations using MGF

$$\frac{d}{dt} \int Q^2(A) \exp(\theta A) p(A, t) dx = \int \left(2 \frac{dQ(A)}{dA} P(A) + \theta P(A) Q(A) \right) \exp(\theta A) p(A, t) dA \quad (4)$$

- $Q^2(A) = 16 + 8A^2 + A^4$
- $2 \frac{dQ(A)}{dA} P(A) = 2 \cdot 2A (4 - 4 \cdot 0.01A - 0.01A^3) = 16A - 0.16A^2 - 0.04A^4$
- $\theta P(A) Q(A) = 16\theta - 0.16 \cdot \theta A + 4 \cdot \theta A^2 - 0.08 \cdot \theta A^3 - 0.01 \cdot \theta A^5$

Left-hand side integral in (4):

$$\begin{aligned}
\frac{d}{dt} \int_{-\infty}^{\infty} Q^2(A) \exp(\theta A) p(A, t) dA &= \frac{d}{dt} \int_{-\infty}^{\infty} (16 + 8A^2 + A^4) \exp(\theta A) p(A, t) dA \stackrel{(2)}{=} \\
&= \frac{d}{dt} \left[16 \sum_{n=0}^{\infty} \frac{\theta^n}{n!} \mu_n + 8 \sum_{n=2}^{\infty} \frac{\theta^{n-2}}{(n-2)!} \mu_n + \sum_{n=4}^{\infty} \frac{\theta^{n-4}}{(n-4)!} \mu_n \right] = \\
&= 16 \sum_{n=1}^{\infty} \frac{\theta^n}{n!} \frac{d\mu_n}{dt} + 8 \sum_{n=2}^{\infty} \frac{\theta^{n-2}}{(n-2)!} \frac{d\mu_n}{dt} + \sum_{n=4}^{\infty} \frac{\theta^{n-4}}{(n-4)!} \frac{d\mu_n}{dt} \tag{5}
\end{aligned}$$

Right-hand side integral in (4):

$$\begin{aligned}
&\int_{-\infty}^{\infty} \left(2 \frac{dQ(A)}{dA} P(A) + \theta P(A) Q(A) \right) \exp(\theta A) p(A, t) dA = \\
&= \int_{-\infty}^{\infty} (16A - 0.16A^2 - 0.04A^4 + \\
&+ 16\theta - 0.16\theta A + 4\theta A^2 - 0.08\theta A^3 - 0.01\theta A^5) \exp(\theta A) p(A, t) dA \stackrel{(2)}{=} \\
&= 16 \sum_{n=1}^{\infty} \frac{\theta^{n-1}}{(n-1)!} \mu_n - 0.16 \sum_{n=2}^{\infty} \frac{\theta^{n-2}}{(n-2)!} \mu_n - 0.04 \sum_{n=4}^{\infty} \frac{\theta^{n-4}}{(n-4)!} \mu_n + \\
&+ 16 \sum_{n=0}^{\infty} \frac{\theta^{n+1}}{n!} \mu_n - 0.16 \sum_{n=1}^{\infty} \frac{\theta^n}{(n-1)!} \mu_n + 4 \sum_{n=2}^{\infty} \frac{\theta^{n-1}}{(n-2)!} \mu_n - 0.08 \sum_{n=3}^{\infty} \frac{\theta^{n-2}}{(n-3)!} \mu_n - 0.01 \sum_{n=5}^{\infty} \frac{\theta^{n-4}}{(n-5)!} \mu_n \tag{6}
\end{aligned}$$

We substitute the results from (5) and (6) in the main relation in (2) and expand the power series by writing down the terms associated with $\theta^0, \theta^1, \theta^2$:

$$\begin{aligned}
&16 \frac{d\mu_1}{dt} \theta + 8 \frac{d\mu_2}{dt} \theta^2 + \dots + 8 \frac{d\mu_2}{dt} + 8 \frac{d\mu_3}{dt} \theta + 4 \frac{d\mu_4}{dt} \theta^2 + \dots + \frac{d\mu_4}{dt} + \frac{d\mu_5}{dt} \theta + 0.5 \frac{d\mu_6}{dt} \theta^2 = \\
&= 16\mu_1 + 16\mu_2\theta + 8\mu_3\theta^2 + \dots \\
&- 0.16\mu_2 - 0.16\mu_3\theta - 0.08\mu_4\theta^2 - \dots \\
&- 0.04\mu_4 - 0.04\mu_5\theta - 0.02\mu_6\theta^2 - \dots \\
&+ 16\theta + 16\mu_1\theta^2 + \dots \\
&- 0.16\mu_1\theta - 0.16\mu_2\theta^2 - \dots \\
&+ 4\mu_2\theta + 4\mu_3\theta^2 + \dots \\
&- 0.08\mu_3\theta - 0.08\mu_4\theta - \dots \\
&- 0.01\mu_5\theta - 0.01\mu_6\theta^2 - \dots
\end{aligned}$$

Then we collect the corresponding terms:

$$\begin{aligned}
\theta^0 : 8 \frac{d\mu_2}{dt} + \frac{d\mu_4}{dt} - 16\mu_1 + 0.16\mu_2 + 0.04\mu_4 &= 0 \\
\theta^1 : 16 \frac{d\mu_1}{dt} + 8 \frac{d\mu_3}{dt} + \frac{d\mu_5}{dt} - 16 + 0.16\mu_1 - 20\mu_2 + 0.24\mu_3 + 0.05\mu_5 &= 0
\end{aligned}$$

Finally, we arrive to the equations for the first and the second moments of A for 1-dimensional case:

Moment equations for 1-dimensional case:

$$\begin{aligned} \theta^1 : \frac{d\mu_1}{dt} &= -0.5 \frac{d\mu_3}{dt} - 0.0625 \frac{d\mu_5}{dt} + 1 - 0.01\mu_1 + 1.25\mu_2 - 0.015\mu_3 - 0.003125\mu_5 \\ \theta^0 : \frac{d\mu_2}{dt} &= -0.125 \frac{d\mu_4}{dt} + 2\mu_1 - 0.02\mu_2 - 0.005\mu_4 \end{aligned} \quad (7)$$

ODE model of an autoinhibitory gene circuit dynamics for 2-dimensional case

In this example we consider both the protein concentration A and the parameter g of the maximal rate of expression to be uncertain, Since the parameter g is constant in time, the original ODE model (3) is expanded to the following system:

$$\begin{aligned} \frac{dA}{dt} &= \frac{P(A, g)}{Q(A, g)} = \frac{g}{1 + A^2/4} - 0.01A = \frac{4g - 4 \cdot 0.01A - 0.01A^3}{4 + A^2} \\ \frac{dg}{dt} &= 0 \end{aligned} \quad (8)$$

Moment generating function

$$\begin{aligned} M_{A,g}(\theta_1, \theta_2) &= \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \exp(\theta_1 A + \theta_2 g) p(A, g, t) dA dg \\ &= \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \left(1 + \theta_1 A + \frac{\theta_1^2}{2} A^2 + \dots\right) \left(1 + \theta_2 g + \frac{\theta_2^2}{2} g^2 + \dots\right) p(A, g, t) dA dg \\ &= \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \left(1 + \theta_1 A + \theta_2 g + \frac{\theta_1^2}{2} A^2 + \frac{\theta_2^2}{2} g^2 + \theta_1 \theta_2 A g + \dots\right) p(A, g, t) dA dg \\ &= 1 + \mu_{(1,0)} \theta_1 + \mu_{(0,1)} \theta_2 + \frac{\mu_{(2,0)}}{2} \theta_1^2 + \frac{\mu_{(0,2)}}{2} \theta_2^2 + \mu_{(1,1)} \theta_1 \theta_2 + \dots = \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} \frac{\theta_1^n \theta_2^m}{n! m!} \mu_{(n,m)} \end{aligned}$$

$$\frac{\partial M_{A,g}(\theta_1, \theta_2)}{\partial \theta_1} = \mu_{(1,0)} + \mu_{(2,0)} \theta_1 + \mu_{(1,1)} \theta_2 + \dots$$

$$\frac{\partial M_{A,g}(\theta_1, \theta_2)}{\partial \theta_2} = \mu_{(0,1)} + \mu_{(0,2)} \theta_2 + \mu_{(1,1)} \theta_1 + \dots$$

$$\frac{\partial^{p+q} M_{A,g}(\theta_1, \theta_2, t)}{\partial \theta_1^p \partial \theta_2^q} = \sum_{n=p}^{\infty} \sum_{m=q}^{\infty} \frac{\theta_1^{n-p} \theta_2^{m-q}}{(n-p)! (m-q)!} \mu_{(n-p, m-q)}$$

Formula to derive moment equations using MGF

$$\begin{aligned} \frac{d}{dt} \int \int Q^2(A, g) \exp(\theta_1 A + \theta_2 g) p(A, g, t) dA dg &= \\ = \int \int \left(2 \frac{dQ(A, g)}{dA} P(A, g) + \theta P(A, g) Q(A, g) \right) \exp(\theta_1 A + \theta_2 g) p(A, g, t) dA dg \end{aligned} \quad (9)$$

- $Q^2(A, g) = 16 + 8A^2 + A^4$
- $2 \frac{dQ(A, g)}{dA} P(A, g) = 2 \cdot 2A (4g - 4 \cdot 0.01A - 0.01A^3) = 16Ag - 0.16A^2 - 0.04A^4$

- $\theta P(A, g)Q(A, g) = 16\theta g - 0.16 \cdot \theta A + 4 \cdot \theta g A^2 - 0.08 \cdot \theta A^3 - 0.01 \cdot \theta A^5$

Similar to derivation (5) and (6) in 1-dimensional case, we derive the following relations between the power series of θ_1, θ_2 :

$$\begin{aligned}
& 16 \frac{d\mu_{(1,0)}}{dt} \theta_1 + 8 \frac{d\mu_{(2,0)}}{dt} \theta_1^2 + 16 \frac{d\mu_{(1,1)}}{dt} \theta_1 \theta_2 + \dots \\
& + 8 \frac{d\mu_{(2,0)}}{dt} + 8 \frac{d\mu_{(3,0)}}{dt} \theta_1 + 8 \frac{d\mu_{(2,1)}}{dt} \theta_2 + 4 \frac{d\mu_{(4,0)}}{dt} \theta_1^2 + 4 \frac{d\mu_{(2,2)}}{dt} \theta_2^2 + 8 \frac{d\mu_{(3,1)}}{dt} \theta_1 \theta_2 + \dots \\
& + \frac{d\mu_{(4,0)}}{dt} + \frac{d\mu_{(5,0)}}{dt} \theta_1 + \frac{d\mu_{(4,1)}}{dt} \theta_2 + 0.5 \frac{d\mu_{(6,0)}}{dt} \theta_1^2 + 0.5 \frac{d\mu_{(4,2)}}{dt} \theta_2^2 + \frac{d\mu_{(5,1)}}{dt} \theta_1 \theta_2 + \dots \\
& - 16\mu_{(0,1)}\theta_1 - 16\mu_{(1,1)}\theta_1^2 - 16\mu_{(0,2)}\theta_1\theta_2 + \dots \\
& + 0.16\mu_{(1,0)}\theta_1 + 0.16\mu_{(2,0)}\theta_1^2 + 0.16\mu_{(1,1)}\theta_1\theta_2 + \dots \\
& - 16\mu_{(1,1)} - 16\mu_{(2,1)}\theta_1 - 16\mu_{(1,2)}\theta_2 - 8\mu_{(3,1)}\theta_1^2 - 8\mu_{(1,3)}\theta_2^2 - 16\mu_{(2,2)}\theta_1\theta_2 + \dots \\
& - 4\mu_{(2,1)}\theta_1 - 4\mu_{(3,1)}\theta_1^2 - 4\mu_{(2,2)}\theta_1\theta_2 + \dots \\
& + 0.16\mu_{(2,0)} + 0.16\mu_{(3,0)}\theta_1 + 0.16\mu_{(2,1)}\theta_2 + 0.08\mu_{(4,0)}\theta_1^2 + 0.08\mu_{(2,2)}\theta_2^2 + 0.16\mu_{(3,1)}\theta_1\theta_2 + \dots \\
& + 0.08\mu_{(3,0)}\theta_1 + 0.08\mu_{(4,0)}\theta_1^2 + 0.08\mu_{(3,1)}\theta_1\theta_2 + \dots \\
& + 0.04\mu_{(4,0)} + 0.04\mu_{(5,0)}\theta_1 + 0.04\mu_{(4,1)}\theta_2 + 0.02\mu_{(6,0)}\theta_1^2 + 0.02\mu_{(4,2)}\theta_2^2 + 0.04\mu_{(5,1)}\theta_1\theta_2 + \dots \\
& + 0.01\mu_{(5,0)}\theta_1 + 0.01\mu_{(6,0)}\theta_1^2 + 0.01\mu_{(5,1)}\theta_1\theta_2 + \dots = 0
\end{aligned}$$

Then we collect the corresponding terms:

$$\begin{aligned}
\theta_1^0 \theta_2^0 &: 8 \frac{d\mu_{(2,0)}}{dt} + \frac{d\mu_{(4,0)}}{dt} - 16\mu_{(1,1)} + 0.16\mu_{(2,0)} + 0.04\mu_{(4,0)} = 0 \\
\theta_1^1 &: 16 \frac{d\mu_{(1,0)}}{dt} + 8 \frac{d\mu_{(3,0)}}{dt} + \frac{d\mu_{(5,0)}}{dt} - 16\mu_{(0,1)} + 0.16\mu_{(1,0)} - 20\mu_{(2,1)} + 0.24\mu_{(3,0)} + 0.05\mu_{(5,0)} = 0 \\
\theta_2^1 &: 8 \frac{d\mu_{(2,1)}}{dt} + \frac{d\mu_{(4,1)}}{dt} - 16\mu_{(1,2)} + 0.16\mu_{(2,1)} + 0.04\mu_{(4,1)} = 0 \\
\theta_1^2 &: 8 \frac{d\mu_{(2,0)}}{dt} + 4 \frac{d\mu_{(4,0)}}{dt} + 0.5 \frac{d\mu_{(6,0)}}{dt} - 16\mu_{(1,1)} + 0.16\mu_{(2,0)} - 12\mu_{(3,1)} + 0.16\mu_{(4,0)} + 0.03\mu_{(6,0)} = 0 \\
\theta_2^2 &: 4 \frac{d\mu_{(2,2)}}{dt} + 0.5 \frac{d\mu_{(4,2)}}{dt} - 8\mu_{(1,3)} + 0.08\mu_{(2,2)} + 0.02\mu_{(4,2)} = 0 \\
\theta_1 \theta_2 &: 16 \frac{d\mu_{(1,1)}}{dt} + 8 \frac{d\mu_{(3,1)}}{dt} + \frac{d\mu_{(5,1)}}{dt} - 16\mu_{(0,2)} + 0.16\mu_{(1,1)} - 20\mu_{(2,2)} + 0.24\mu_{(3,1)} + 0.05\mu_{(5,1)} = 0
\end{aligned}$$

Finally, we get the equations for the first and the second moments of A for 2-dimensional case.

Moment equations for 2-dimensional case:

$$\begin{aligned}
\theta_1^1 &: \frac{d\mu_{(1,0)}}{dt} = -0.5 \frac{d\mu_{(3,0)}}{dt} - 0.0625 \frac{d\mu_{(5,0)}}{dt} + \\
& \quad + \mu_{(0,1)} - 0.01\mu_{(1,0)} + 1.25\mu_{(2,1)} - 0.015\mu_{(3,0)} - 0.003125\mu_{(5,0)} \\
\theta_1^0 \theta_2^0 &: \frac{d\mu_{(2,0)}}{dt} = -0.125 \frac{d\mu_{(4,0)}}{dt} + 2\mu_{(1,1)} - 0.02\mu_{(2,0)} - 0.005\mu_{(4,0)}
\end{aligned} \tag{10}$$