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

Milias Argeitis, Andreas; Kurdyaeva, Tamara

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Notation and definitions

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

- *Moment* μ_α of order α is defined as

$$\mu_\alpha = \mathbb{E}_{p(\boldsymbol{x})}\left[\boldsymbol{X}^\alpha\right] = \int_{\mathbb{R}_+^N} \boldsymbol{x}^\alpha p(\boldsymbol{x}) d\boldsymbol{x}, \tag{1}$$

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

- The joint *moment-generating function (MGF)* $M_{\boldsymbol{X}}(\boldsymbol{\theta})$ is

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

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

  for $\boldsymbol{\theta} \in \mathbb{R}^N$ 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:

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

Moment generating function

$$M_A(\theta) = 1 + \mu_1 \theta + \frac{\mu_2}{2!}\theta^2 + ...$$
$$\frac{\partial M_A(\theta)}{\partial \theta} = \mu_1 + \mu_2 \theta + \mu_3 \frac{\theta^2}{2!} ...$$
$$\frac{\partial^k M_A(\theta)}{\partial \theta^k} = \mu_k + \mu_{k+1}\theta + \mu_{k+2}\frac{\theta^2}{2!} ... = \sum_{n=k}^{\infty} \frac{\theta^{n-k}}{(n-k)!}\mu_n$$

Formula to derive moment equations using MGF

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

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

Left-hand side integral in (4):

$$\frac{d}{dt}\int_{-\infty}^{\infty} Q^2(A)\exp(\theta A)p(A,t)dA = \frac{d}{dt}\int_{-\infty}^{\infty}\left(16+8A^2+A^4\right)\exp(\theta A)p(A,t)dA \overset{(2)}{=}$$

$$= \frac{d}{dt}\left[16\sum_{n=0}^{\infty}\frac{\theta^n}{n!}\mu_n + 8\sum_{n=2}^{\infty}\frac{\theta^{n-2}}{(n-2)!}\mu_n + \sum_{n=4}^{\infty}\frac{\theta^{n-4}}{(n-4)!}\mu_n\right] =$$

$$= 16\sum_{n=1}^{\infty}\frac{\theta^n}{n!}\frac{d\mu_n}{dt} + 8\sum_{n=2}^{\infty}\frac{\theta^{n-2}}{(n-2)!}\frac{d\mu_n}{dt} + \sum_{n=4}^{\infty}\frac{\theta^{n-4}}{(n-4)!}\frac{d\mu_n}{dt} \tag{5}$$

Right-hand side integral in (4):

$$\int_{-\infty}^{\infty}\left(2\frac{dQ(A)}{dA}P(A) + \theta P(A)Q(A)\right)\exp(\theta A)p(A,t)dA =$$

$$= \int_{-\infty}^{\infty}\Big(16A - 0.16A^2 - 0.04A^4 +$$

$$+16\theta - 0.16\theta A + 4\theta A^2 - 0.08\theta A^3 - 0.01\theta A^5\Big)\exp(\theta A)p(A,t)dA \overset{(2)}{=}$$

$$= 16\sum_{n=1}^{\infty}\frac{\theta^{n-1}}{(n-1)!}\mu_n - 0.16\sum_{n=2}^{\infty}\frac{\theta^{n-2}}{(n-2)!}\mu_n - 0.04\sum_{n=4}^{\infty}\frac{\theta^{n-4}}{(n-4)!}\mu_n + \tag{6}$$

$$+ 16\sum_{n=0}^{\infty}\frac{\theta^{n+1}}{n!}\mu_n - 0.16\sum_{n=1}^{\infty}\frac{\theta^n}{(n-1)!}\mu_n + 4\sum_{n=2}^{\infty}\frac{\theta^{n-1}}{(n-2)!}\mu_n - 0.08\sum_{n=3}^{\infty}\frac{\theta^{n-2}}{(n-3)!}\mu_n - 0.01\sum_{n=5}^{\infty}\frac{\theta^{n-4}}{(n-5)!}\mu_n$$

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 $\theta^0, \theta^1, \theta^2$:

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

Then we collect the corresponding terms:

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

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:

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

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:

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

Moment generating function

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

$$\begin{aligned}\frac{\partial M_{A,g}(\theta_1,\theta_2)}{\partial\theta_1} &= \mu_{(1,0)} + \mu_{(2,0)}\theta_1 + \mu_{(1,1)}\theta_2 + ... \\ \frac{\partial M_{A,g}(\theta_1,\theta_2)}{\partial\theta_2} &= \mu_{(0,1)} + \mu_{(0,2)}\theta_2 + \mu_{(1,1)}\theta_1 + ... \\ \frac{\partial^{p+q} M_{A,g}(\theta_1,\theta_2,t)}{\partial\theta_1^p\partial\theta_2^q} &= \sum_{n=p}^{\infty}\sum_{m=q}^{\infty}\frac{\theta_1^{n-p}\theta_2^{m-q}}{(n-p)!(m-q)!}\mu_{(n-p,m-q)}\end{aligned}$$

Formula to derive moment equations using MGF

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

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

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

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

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

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:

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