Asymptotic convergence study of a Partial Integro-Differential Equation (PIDE) used to model gene regulatory networks.

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Consejo Superior de Investigaciones Científicas

Index

Index

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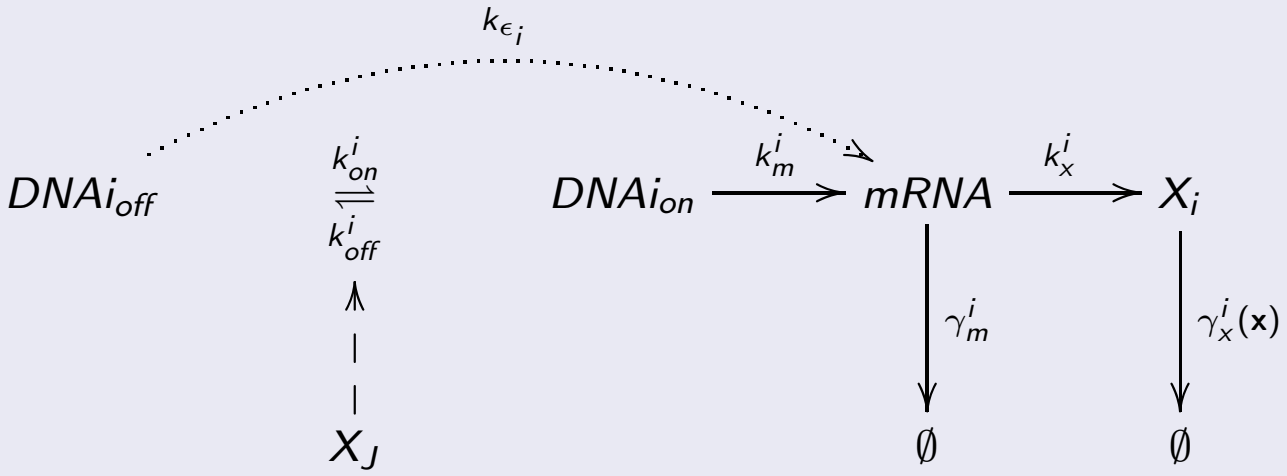
Friedman, N., Cai, L., and Xie, X. S. (2006).
Linking stochastic dynamics to population distribution: An analytical framework of gene expression.
Phys. Rev. Lett., 97(16), 168302.

- Study of self regulated gene expression networks usually involve low copy numbers. Stochastic processes. Chemical Master Equation (CME), its solution is not available in the most cases.
- We derive the partial integral differential (PIDE) model, proposed by Friedman et al., as the continuous counterpart of one master equation with jump processes.
- Using entropy methods we study the convergence to equilibrium, we prove (1D PIDE) or find numerical evidences (nD PIDE) of exponential stability.

Index

Gene Regulatory Network



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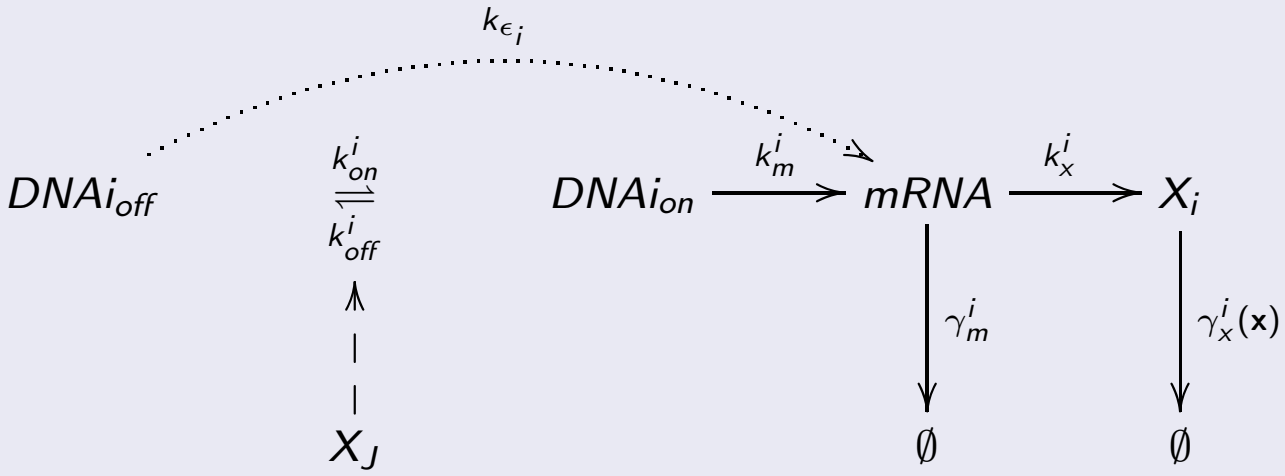

Reaction Steps

1. $\emptyset \xrightarrow{k^i_m c_i(\mathbf{x})} mRNA_i$
2. $mRNA_i \xrightarrow{k^i_x} mRNA_i + X_i$
3. $mRNA_i \xrightarrow{\gamma^i_m} \emptyset$
4. $X_i \xrightarrow{\gamma^i_x(\mathbf{x})} \emptyset$

- Self regulation mechanism: $c(x) = [1 - \rho(x)] + \rho(x)\varepsilon$, with $\varepsilon = \frac{k_\varepsilon}{k_m} \in (0,\, 1)$ the transcriptional leakage constant and $\rho(x) = \frac{x^H}{x^H + K^H}$ the Hill type function, where $K = \frac{k_{off}}{k_{on}}$ is an equilibrium constant and H the Hill coefficient.

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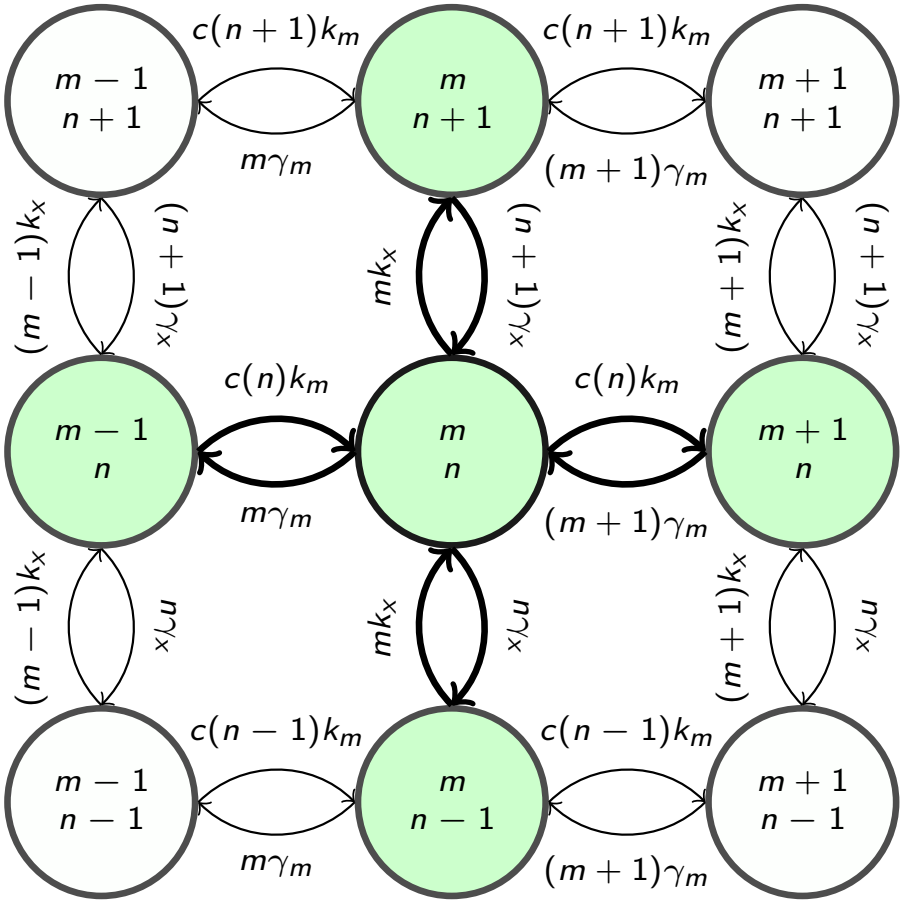
- Protein production in bursts: $\omega(x - y) = \dfrac{1}{b} \exp\left[\dfrac{-(x-y)}{b}\right]$ the conditional probability for protein level to jump from a state y to x.

Index

Chemical Master Equation (CME)

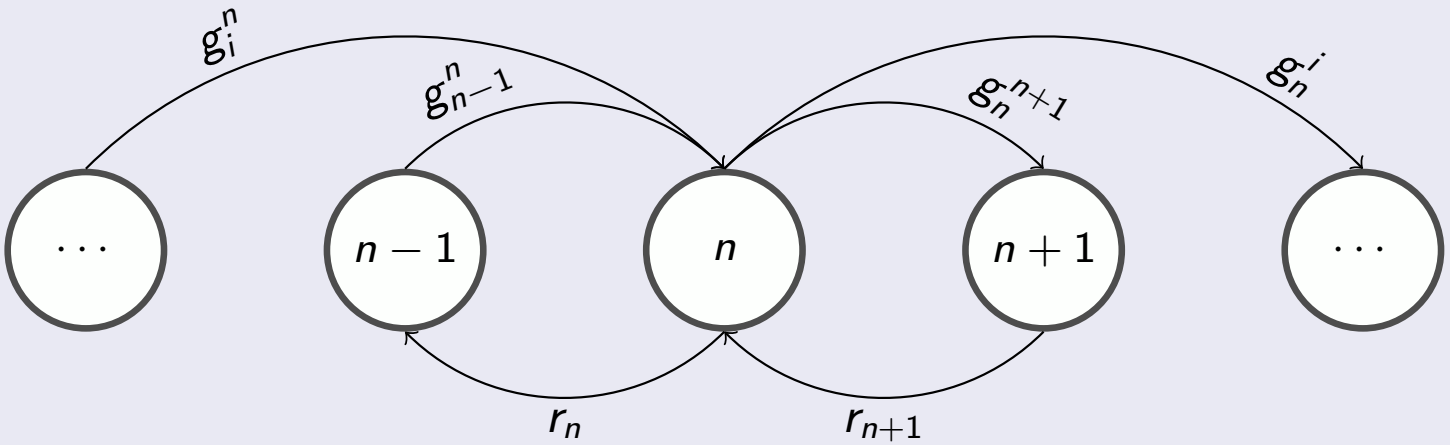


$$\frac{\partial p_{mn}}{\partial t} = k_m c(n)(\mathbb{E}_m^{-1} - 1)p_{mn} + \gamma_m(\mathbb{E}_m^1 - 1)mp_{mn} + k_x m(\mathbb{E}_n^{-1} - 1)p_{mn} + \gamma_x(\mathbb{E}_n^1 - 1)np_{mn}$$

with $\mathbb{E}_m$ and $\mathbb{E}_n$ being step operators such that:

$$\mathbb{E}_m^{-1} p_{mn} = p_{m-1n}$$
$$\mathbb{E}_m^1 mp_{mn} = (m+1)p_{m+1n}$$
$$\mathbb{E}_n^{-1} p_{mn} = p_{mn-1}$$
$$\mathbb{E}_n^1 np_{mn} = (n+1)p_{mn+1}$$

Master equation deduction

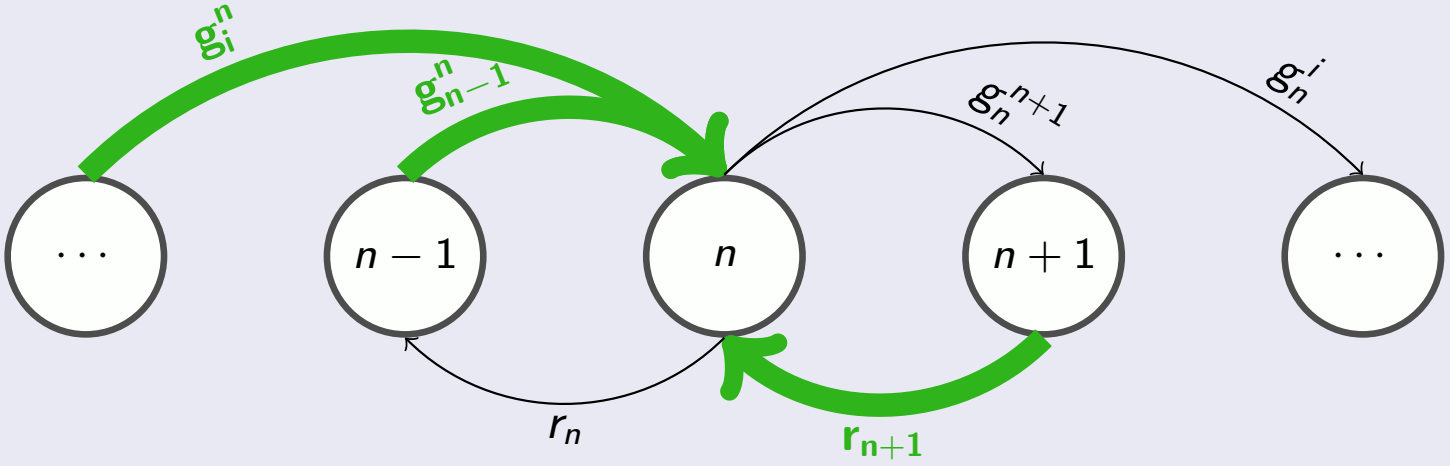


Transition probabilities

- $g_i^n := k_m c(i)\omega(n-i)$
- $r_n := \gamma_x n$

$$P(t+\Delta t, n) = \tag{1}$$

Master equation deduction



Transition probabilities

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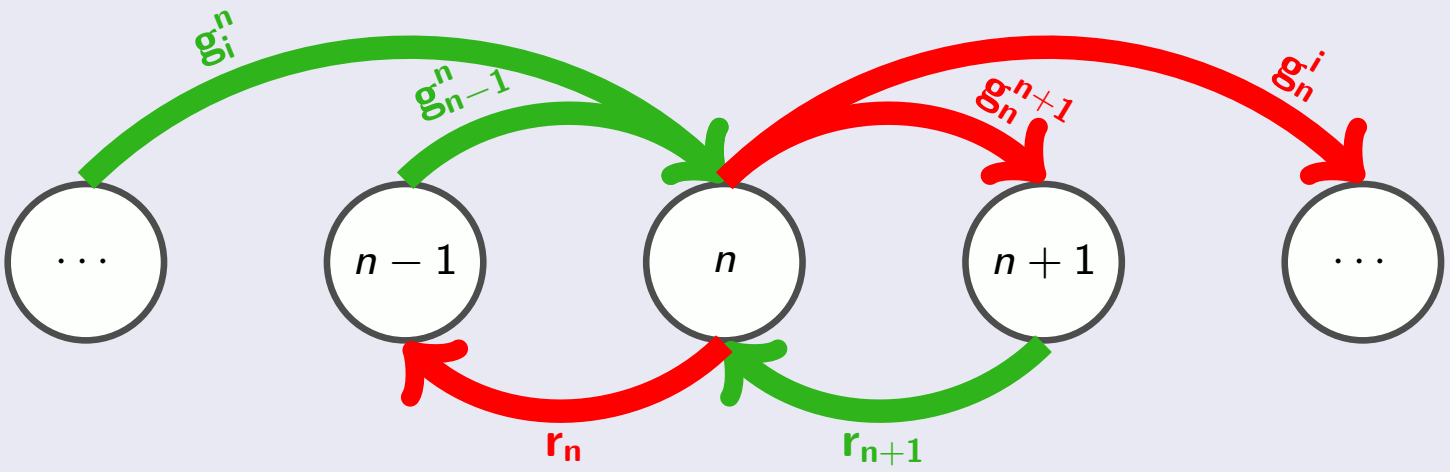
$$P(t+\Delta t, n) = \sum_{i=0}^{n-1} g_i^n P(t,i)\Delta t + r_{n+1} P(t, n+1)\Delta t \tag{1}$$

Master equation deduction



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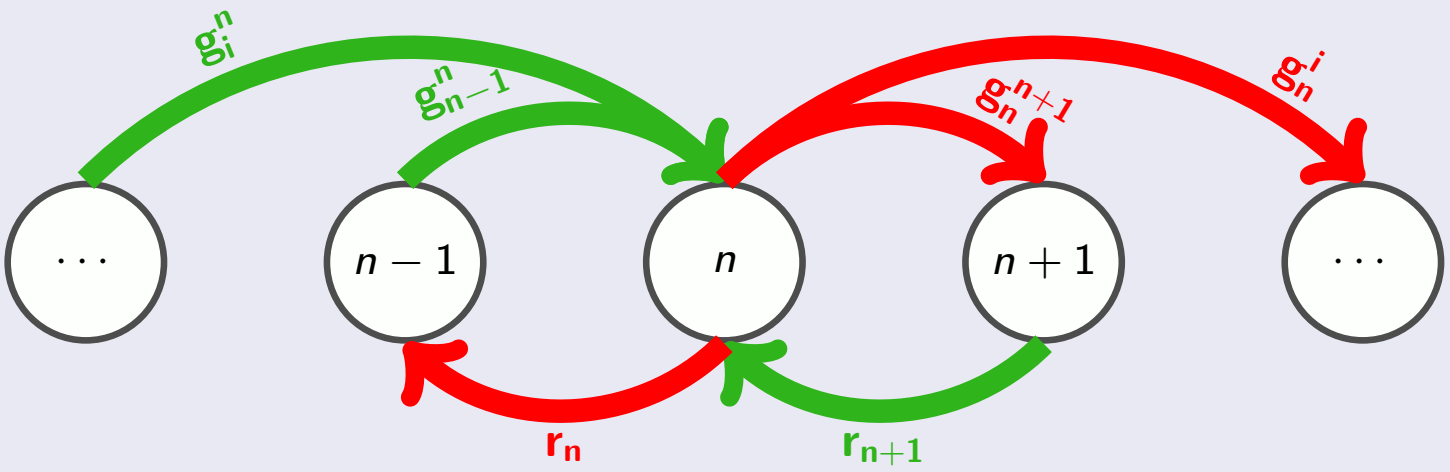
Master equation deduction



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Master equation with jump processes

$$\frac{\partial P(t,n)}{\partial t} = \sum_{i=0}^{n-1} g_i^n P(t,i) - \sum_{i=n+1}^{\infty} g_n^i P(t,n) + r_{n+1}P(t,n+1) - r_n P(t,n) \quad (2)$$

Continuous formulation (PIDE)

Master equation with jump processes

$$\frac{\partial P(t,n)}{\partial t} = \sum_{i=0}^{n} g_i^n P(t,i) - \sum_{i=n}^{\infty} g_n^i P(t,n) + r_{n+1} P(t,n+1) - r_n P(t,n) \tag{3}$$

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Master equation with jump processes

$$\frac{\partial P(t,n)}{\partial t} = \underbrace{\sum_{i=0}^{n} g_i^n P(t,i)}_{\wr\wr \; k_m \int_0^x \omega(x-y)c(y)P(t,y)\mathrm{d}\,y} - \sum_{i=n}^{\infty} g_n^i P(t,n) + r_{n+1}P(t,n+1) - r_n P(t,n) \tag{3}$$

The integer indexes n and i are substituted by real x and y respectively:

- $\sum_{i=0}^{n} g_i^n P(t,i) \approx \int_0^x g_y^x p(t,y)\,\mathrm{d}y = k_m \int_0^x \omega(x-y)c(y)P(t,y)\mathrm{d}\,y$

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$$\frac{\partial P(t,n)}{\partial t} = \sum_{i=0}^{n} g_i^n P(t,i) - \sum_{i=n}^{\infty} g_n^i P(t,n) + \underbrace{r_{n+1}P(t,n+1) - r_n P(t,n)}_{\approx \frac{\partial}{\partial x}\left[\gamma_x\, x\, P(t,x)\right]} \tag{3}$$

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- $r_{x+1}p(t,x+1) \approx r_x p(t,x) + \dfrac{\partial\left[r_x p(t,x)\right]}{\partial x}$ (Taylor theorem)

Continuous formulation (PIDE)

Master equation with jump processes

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Partial Integral Differential Equation (PIDE)

$$\frac{\partial p(\tau,x)}{\partial \tau} = \frac{\partial\left[x p(\tau,x)\right]}{\partial x} - a c(x) p(\tau,x) + a\int_0^x \omega(x-y)c(y)p(\tau,y)\,\mathrm{d}y \tag{4}$$

with dimensionless time, $\tau = \gamma_x t$ and $a = k_m/\gamma_x$.

Generalized PIDE

Generalized Partial Integral Differential Equation

$$\frac{\partial p(t,\mathbf{x})}{\partial t} = \sum_{i=1}^{n} \left(\frac{\partial}{\partial x_i} \left[\gamma_x^i(\mathbf{x}) x_i p(t,\mathbf{x}) \right] - k_m^i c_i(\mathbf{x}) p(t,\mathbf{x}) + k_m^i \int_0^{x_i} \omega_i(x_i - y_i) c_i(\mathbf{y}_i) p(t,\mathbf{y}_i)\, \mathrm{d}y_i \right)$$

$\mathbf{y}_i$ represents the vector state $\mathbf{x}$, whose i position is changed for y_i, ($(\mathbf{y}_i)_j = x_j$ if $j \neq i$ and $(\mathbf{y}_i)_j = y_i$ if $j = i$), $\gamma_x^i(\mathbf{x})$ is the degradation rate function of each protein and

$$\omega_i(x_i - y_i) = \frac{1}{b_i} \exp(-\frac{x_i - y_i}{b_i})$$

is the conditional probability for protein jumping from a state y_i to x_i after a burst. The function $c_i(\mathbf{x})$ ($c_i : \mathbb{R}_+^n \to [\varepsilon_i,\ 1]$) is the input function which models the regulation mechanism.

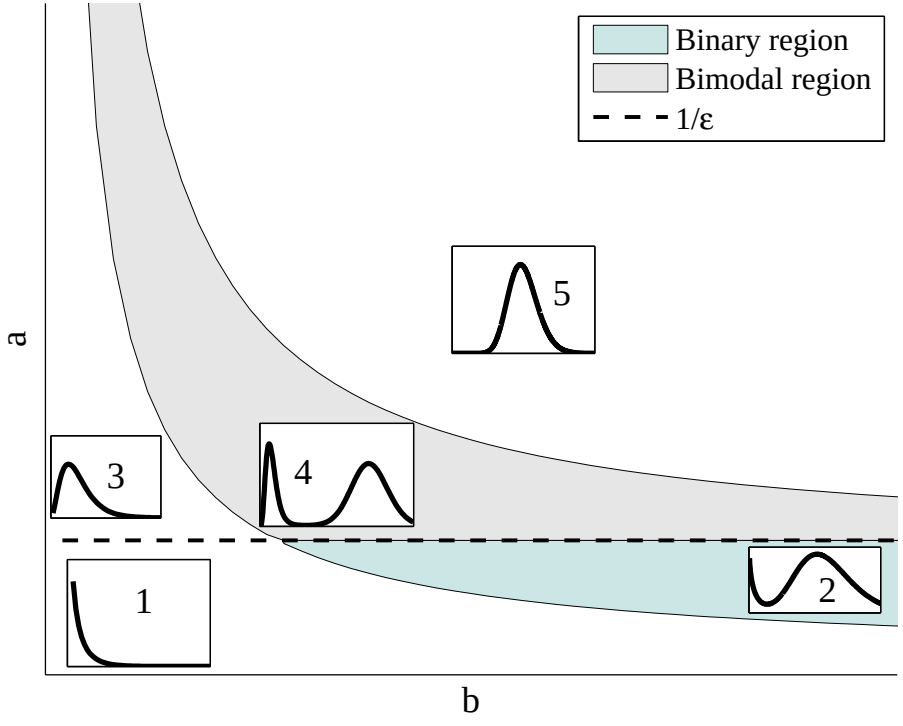
Pájaro, M., Alonso, A. A., Otero-Muras, I., and Vázquez, C. (2017).
Stochastic Modeling and Numerical Simulation of Gene Regulatory Networks with Protein Bursting.
J. Theor. Biol., 421, 51-70.

Steady state solution PIDE (1D)

Analytic steady state solution for the 1D PIDE

$$P_\infty(x) := Z\,[\rho(x)]^{\frac{a(1-\varepsilon)}{H}}\; x^{-(1-a\varepsilon)}\, e^{\frac{-x}{b}}$$
$$= Z\left[x^H + K^H\right]^{\frac{a(\varepsilon-1)}{H}}\; x^{a-1}\, e^{\frac{-x}{b}},$$

with $\rho(x) = \frac{x^H}{x^H+K^H}$ and Z being a normalizing constant such that $\int_0^\infty P_\infty(x) = 1$.



Pájaro, M., Alonso, A. A., and Vázquez, C. (2015).
Shaping protein distributions in stochastic self-regulated gene expression networks.
Phys. Rev. E, 92(3), 032712.

Index

Entropy inequality (I)

General entropy functional

$$\mathcal{G}_H(u) := \int_0^\infty H(u(x))P_\infty(x)\mathrm{d}x, \tag{5}$$

with $H(u)$ being any convex function of $u(x)$ and $u(x) := \frac{p}{P_\infty}(x)$.

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Proposition 1

Let $\mathcal{G}_H(u)$ be the general entropy functional, then the following equality is verified

$$\frac{\mathrm{d}\mathcal{G}_H(u)}{\mathrm{d}\tau} = \mathcal{D}_H(u), \tag{6}$$

$$\mathcal{D}_H(u) = a\int_0^\infty \int_y^\infty \omega(x-y)\left[H(u(x)) - H(u(y)) + H'(u(x))\left(u(y)-u(x)\right)\right] c(y)P_\infty(y)\mathrm{d}x\mathrm{d}y.$$

Michel, P., Mischler, S., and Perthame, B. (2005).
General relative entropy inequality: An illustration on growth models.
J. Math. Pures Appl., 84(9), 1235–1260.

Entropy inequality (II)

Entropy functional

We consider $H(u) = (u-1)^2$ with $u(x) := \frac{p}{P_\infty}(x)$,

$$\mathcal{G}_2(u) := \int_0^\infty \left(\frac{p}{P_\infty}(x) - 1\right)^2 P_\infty(x)\mathrm{d}x = \int_0^\infty u(x)^2 P_\infty(x)\mathrm{d}x - 1 \tag{7}$$

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Proposition 1

Let $\mathcal{G}_2(u)$ be the entropy functional, then the following equality is verified

$$\frac{\mathrm{d}\mathcal{G}_2(u)}{\mathrm{d}\tau} = -\mathcal{D}_2(u), \tag{8}$$

with $\mathcal{D}_2(u) = a\int_0^\infty \int_y^\infty \omega(x-y)\,(u(x)-u(y))^2\, c(y)P_\infty(y)\mathrm{d}x\mathrm{d}y.$

Numerical evidence of exponential stability

Purpose

To prove that: $\mathcal{G}_2(u) \leq \frac{1}{2\beta}\mathcal{D}_2(u)$

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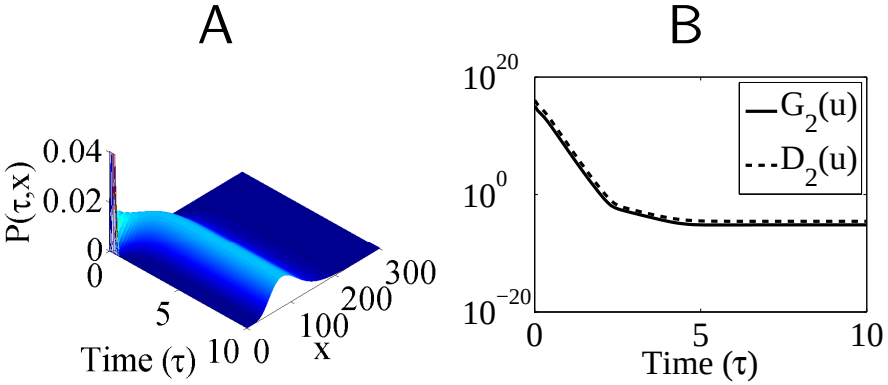

Figure: The temporal evolution of (4) is represented in plot A for parameters $a = 10$, $b = 20$, $H = 1$, $K = 70$ and $\varepsilon = 0.05$. The dashed and continuous lines in plot B represent $\mathcal{G}_2(u)$ and $\mathcal{D}_2(u)$ respectively.

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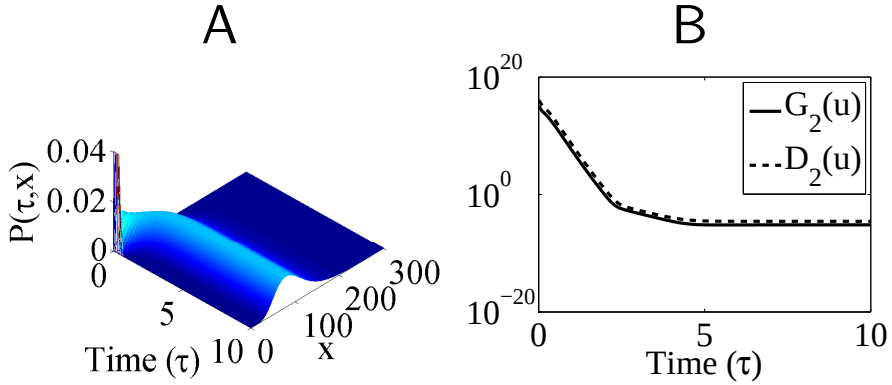

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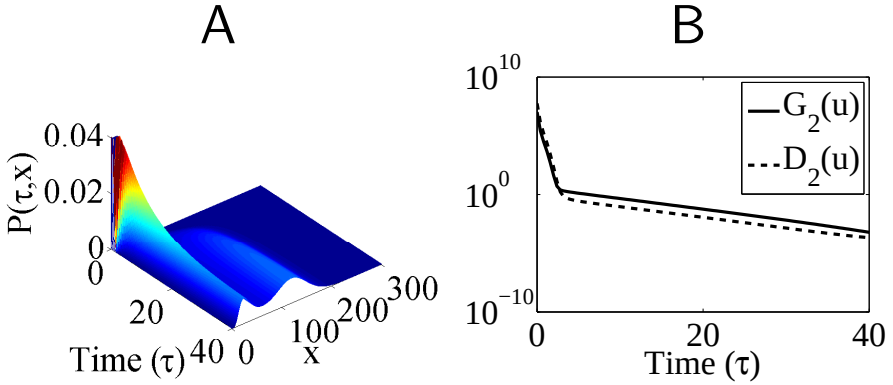

Figure: The temporal evolution of (4) is represented in plot A for parameters $a = 27$, $b = 5$, $H = -4$, $K = 70$ and $\varepsilon = 0.2$. The dashed and continuous lines in plot B represent $\mathcal{G}_2(u)$ and $\mathcal{D}_2(u)$ respectively.

Index

Preliminary results (I)

Lemma 1

Let $P_\infty : (0,\ \infty) \to \mathbb{R}_+$ *be the steady state solution of the 1D PIDE model such that* $\int_0^\infty P_\infty(x)\mathrm{d}x = 1$. *Defining*

$$\mathcal{H}_2(u) := \int_0^\infty \int_y^\infty P_\infty(x)P_\infty(y)\left(u(x) - u(y)\right)^2 \mathrm{d}x\mathrm{d}y, \tag{9}$$

with $u(x) = \frac{p(x)}{P_\infty(x)}$, *there holds:*

$$\mathcal{G}_2(u) = \mathcal{H}_2(u). \tag{10}$$

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Preliminary results (II)

Lemma 2 (P_∞ bounds)

For $\delta > 0$ we define the intervals of length $\frac{1}{2}$:

$$I_{k,\delta} := \left(\delta + \frac{k}{2},\ \delta + \frac{k+1}{2}\right], \qquad k \geq 0 \ \ \textit{integer}, \tag{11}$$

and

$$p_k := Z\left[\left(\delta + \frac{k}{2}\right)^H + K^H\right]^{\frac{a(\varepsilon-1)}{H}} \left(\delta + \frac{k}{2}\right)^{a-1} e^{\frac{-(\delta+\frac{k}{2})}{b}} = P_\infty(\delta + \frac{k}{2}). \tag{12}$$

Then, the following inequality holds:

$$A(\delta) \leq \frac{P_\infty(x)}{p_k} \leq B(\delta), \qquad \forall x \in I_{k,\delta} \ \ \textit{and} \ \ \forall k, \tag{13}$$

with $P_\infty(x) = Z\left[x^H + K^H\right]^{\frac{a(\varepsilon-1)}{H}} x^{a-1} e^{\frac{-x}{b}}$ and Z being a normalizing constant such that $\int_0^\infty P_\infty(x) = 1$.

Preliminary results (II)

Proof of Lemma 2 (P_∞ bounds)

$$A(\delta,k) := \begin{cases} \left(\dfrac{(\delta+\frac{k+1}{2})^H + K^H}{(\delta+\frac{k}{2})^H + K^H}\right)^{\frac{a(\varepsilon-1)}{H}} e^{\frac{-1}{2b}} & \text{if } \ a \geq 1 \\[2ex] \left(\dfrac{(\delta+\frac{k+1}{2})^H + K^H}{(\delta+\frac{k}{2})^H + K^H}\right)^{\frac{a(\varepsilon-1)}{H}} e^{\frac{-1}{2b}} \left(\dfrac{2\delta+k+1}{2\delta+k}\right)^{a-1} & \text{if } \ a < 1 \end{cases}$$

and

$$B(\delta,k) := \begin{cases} \left(\dfrac{2\delta+k+1}{2\delta+k}\right)^{a-1} & \text{if } \ a > 1 \\[2ex] 1 & \text{if } \ a \leq 1 \end{cases}$$

Notice that,

$$\lim_{k\to\infty} A(\delta,k) = e^{-\frac{1}{2b}}, \qquad \lim_{k\to\infty} B(\delta,k) = 1$$

and they are $A(\delta) := \min_{k\geq 0}(A(\delta,k))$ and $B(\delta) := \max_{k\geq 0}(B(\delta,k))$

Preliminary results (III)

Lemma 3

We define the term M_j as:

$$M_j := \sum_{k=1}^{j-1} \frac{1}{m_k} \tag{14}$$

with $\{m_k\}_{k\geq 1}$ a positive sequence given by $m_k = p_k e^{\frac{\delta+\frac{k}{2}}{2b}}$. Then, the following inequality is verified:

$$m_k \sum_{j=k+1}^{\infty} M_j p_j \leq C p_k, \tag{15}$$

for some constant $C > 0$.

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$$p_k = P_\infty(\delta + \frac{k}{2}) = Z\left[\left(\delta + \frac{k}{2}\right)^H + K^H\right]^{\frac{a(\varepsilon-1)}{H}} \left(\delta + \frac{k}{2}\right)^{a-1} e^{\frac{-(\delta+\frac{k}{2})}{b}} = P_\infty(\delta + \frac{k}{2}).$$

Preliminary results (III)

Lemma 3

Defining $\{a_j\}_{j\geq 1}$ with $a_j = \frac{1}{m_j}$ we have that

$$\lim_{j\to\infty} \frac{a_{j+1} - a_j}{M_{j+1} - M_j} = e^{\frac{1}{4b}} - 1$$

Since this limit exist and $\{M_j\}_{j\geq 1}$ is a strictly increasing and divergent sequence, we can use the Stolz-Cesàro theorem to obtain that $M_j \leq C_0 a_j$, with $C_0 > 0$ constant. Then,

$$m_k \sum_{j=k+1}^{\infty} M_j p_j \leq C_0 m_k \sum_{j=k+1}^{\infty} a_j p_j, \quad \text{with} \quad \sum_{j=k+1}^{\infty} a_j p_j = \sum_{j=k+1}^{\infty} e^{-\frac{2\delta+j}{4b}} = \frac{e^{-\frac{2b-1}{4b}}}{e-1} e^{-\frac{2\delta+k}{4b}}$$

So that,

$$m_k \sum_{j=k+1}^{\infty} M_j p_j \leq C m_k e^{-\frac{2\delta+k}{4b}} = C p_k, \quad \text{with} \quad C = C_0 \frac{e^{-\frac{2b-1}{4b}}}{e-1}$$

Main results (I)

Purpose

To prove that: $\mathcal{G}_2(u) = \mathcal{H}_2(u) \leq \frac{1}{2\beta}\mathcal{D}_2(u)$

$$\text{with} \quad \mathcal{D}_2(u) = a\int_0^\infty \int_y^\infty \omega(x-y)\left(u(x)-u(y)\right)^2 c(y)P_\infty(y)\mathrm{d}x\mathrm{d}y$$

$$\text{and} \quad \mathcal{H}_2(u) = \int_0^\infty \int_y^\infty P_\infty(x)P_\infty(y)\left(u(x)-u(y)\right)^2 \mathrm{d}x\mathrm{d}y$$

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Proposition 2

The following inequality is verified:

$$\lambda\mathcal{H}_2(u) \leq \int_0^\infty \int_y^{y+1} P_\infty(y)\left(u(x)-u(y)\right)^2 \mathrm{d}x\mathrm{d}y := D(u), \tag{16}$$

for some constant $\lambda > 0$.

Main results (II)

Proposition 2

The following inequality is verified:

$$\lambda \mathcal{H}_2(u) \leq \int_0^\infty \int_y^{y+1} P_\infty(y)\,(u(x)-u(y))^2\,\mathrm{d}x\mathrm{d}y, \quad \textit{for some constant } \lambda > 0.$$

Proposition 3

The following inequality is verified:

$$\alpha \int_0^\infty \int_y^{y+1} P_\infty(y)\,(u(x)-u(y))^2\,\mathrm{d}x\mathrm{d}y \leq \mathcal{D}_2(u) \tag{17}$$

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$$\mathcal{D}_2(u) = a \int_0^\infty \int_y^\infty \omega(x-y)\,(u(x)-u(y))^2\,c(y)P_\infty(y)\mathrm{d}x\mathrm{d}y$$

Main results (Proof) (I)

Proof of Proposition 2

We take $0 < \delta < 1$ and split $\mathcal{H}_2(u)$ in two parts:

$$\mathcal{H}_2(u) = \int_\delta^\infty \int_y^\infty P_\infty(x)P_\infty(y)\,(u(x)-u(y))^2\,\mathrm{d}x\mathrm{d}y$$
$$+ \int_0^\delta \int_y^\infty P_\infty(x)P_\infty(y)\,(u(x)-u(y))^2\,\mathrm{d}x\mathrm{d}y := \mathcal{H}_{21}(u) + \mathcal{H}_{22}(u)$$

For $i, j \geq 0$ integers we define:

$$A_{i,j} := \int_{I_{i,\delta}} \int_{I_{j,\delta}} (u(x)-u(y))^2\,\mathrm{d}y\mathrm{d}x = \int_{I_{i,\delta}} \int_{I_{j,\delta}} (u(x)-u(y))^2\,\mathrm{d}x\mathrm{d}y.$$

We can estimate both the left and the right hand side of (16) by using the quantities $A_{i,j}$.

Main results (Proof) (II)

Proof of Proposition 2

$$\mathcal{H}_{21}(u) \leq B(\delta)^2 \sum_{i=0}^{\infty} \sum_{j=0}^{i} p_i p_j A_{i,j} \tag{18}$$

$$\sum_{i=0}^{\infty} p_i^2 A_{i,i} \leq \frac{P_M}{A(\delta)^2} D(u) \tag{19}$$

Using that $A_{i,j} \leq M_j \sum_{k=i}^{j-1} m_k A_{k,k+1}$ for all $j > i$, we have

$$\begin{aligned} \sum_{i=0}^{\infty} \sum_{j=i+1}^{\infty} p_i p_j A_{i,j} &\leq \sum_{i=0}^{\infty} \sum_{j=i+1}^{\infty} p_i p_j M_j \sum_{k=i}^{j-1} m_k A_{k,k+1} = \sum_{k=0}^{\infty} m_k A_{k,k+1} \sum_{j=k+1}^{\infty} p_j M_j \sum_{i=0}^{k} p_i \\ &\leq C_\delta^1 \sum_{k=0}^{\infty} A_{k,k+1} m_k \sum_{j=k+1}^{\infty} M_j p_j \leq C \sum_{k=0}^{\infty} A_{k,k+1} p_k \leq \frac{C}{A(\delta)} D(u) \end{aligned} \tag{20}$$

$$\lambda_1 \mathcal{H}_{21}(u) \leq D(u) \tag{21}$$

Index

Entropy inequality nD (I)

General entropy functional

$$\mathcal{G}_H^n(u) = \int_{\mathbb{R}_+^n} H(u(\mathbf{x}))P_\infty(\mathbf{x})\mathrm{d}\mathbf{x}, \tag{22}$$

with $H(u)$ being any convex function of $u(\mathbf{x})$ and $u(\mathbf{x}) := \frac{p}{P_\infty}(\mathbf{x})$.

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Proposition 4

Let $\mathcal{G}_H^n(u)$ be the general entropy functional, then the following equality is verified

$$\frac{\mathrm{d}\mathcal{G}_H(u)}{\mathrm{d}\tau} = \mathcal{D}_H^n(u), \tag{23}$$

$$\mathcal{D}_H^n(u) = \sum_{i=1}^{n} k_m^i \int_{\mathbb{R}_+^n} \int_{y_i}^{\infty} \omega_i(x_i - y_i)\left[H(u(\mathbf{x})) - H(u(\mathbf{y}_i)) + H'(u(\mathbf{x}))(u(\mathbf{y}_i) - u(\mathbf{x}))\right]$$

$$\times c_i(\mathbf{y}_i)P_\infty(\mathbf{y}_i)\mathrm{d}x_i\mathrm{d}\mathbf{y}_i$$

where $\mathbf{y}_i$ represents the vector state $\mathbf{x}$, whose i component is replaced by y_i.

Entropy inequality nD (II)

Entropy functional

We consider $H(u) = (u-1)^2$ with $u(\mathbf{x}) := \frac{p}{P_\infty}(\mathbf{x})$,

$$\mathcal{G}_2^n(u) := \int_{\mathbb{R}_+^n} \left(\frac{p}{P_\infty} - 1\right)^2 P_\infty \mathrm{d}\mathbf{x} = \int_{\mathbb{R}_+^n} u^2 P_\infty \mathrm{d}\mathbf{x} - 1 \tag{24}$$

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Proposition 1

Let $\mathcal{G}_2^n(u)$ be the entropy functional, then the following equality is verified

$$\frac{\mathrm{d}\mathcal{G}_2^n(u)}{\mathrm{d}\tau} = -\mathcal{D}_2^n(u), \tag{25}$$

with $\mathcal{D}_2^n(u) = \sum_{i=1}^{n} -k_m^i \int_{\mathbb{R}_+^n} \int_{y_i}^{\infty} \omega_i(x_i - y_i)\left[u(\mathbf{x}) - u(\mathbf{y}_i)\right]^2 c_i(\mathbf{y}_i) P_\infty(\mathbf{y}_i) \mathrm{d}x_i \mathrm{d}\mathbf{y}_i$

Numerical evidence of exponential stability 2D

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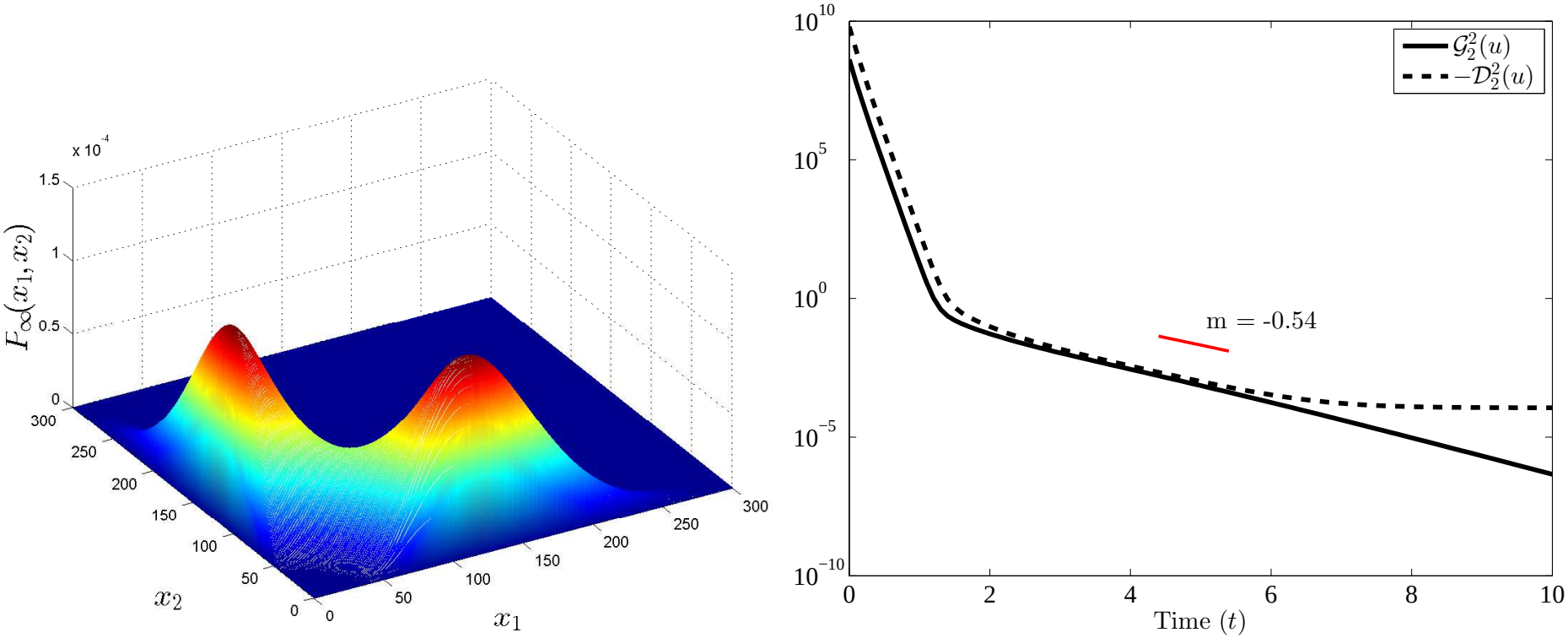

Figure: Steady state distribution of a mutual repression example and time evolution of $\mathcal{G}_2^n(u)$ and $-\mathcal{D}_2^n(u)$.

Index

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Index

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