Sensitivity analysis for the Chemical Master Equation

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ANR project OPT-MC
(OPTimal control of Markov Chains & OPTogenetics control of Microbial Communities)
between DISCO[1] team and LIFEWARE[2] team

Outline

- The Chemical Master Equation (CME)
- A toy example of optimal control problem for the CME
- Sensitivity analysis for the CME

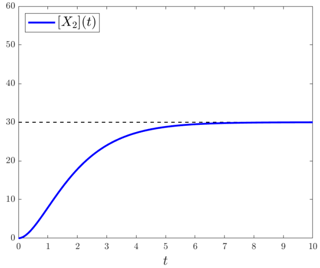
Introduction

Simplified protein-production model (X_1 = mRNA & X_2 = protein)

$$\varnothing \xrightarrow{\lambda_1} X_1, \qquad X_1 \xrightarrow{\lambda_2 [X_1]} X_1 + X_2, \qquad X_1 \xrightarrow{\mu_1 [X_1]} \varnothing, \qquad X_2 \xrightarrow{\mu_2 [X_2]} \varnothing.$$

Chemical kinetic equation (deterministic point of view)

$$\frac{\mathrm{d}}{\mathrm{d}t}[X_1] = \lambda_1 - \mu_1 [X_1], \qquad \frac{\mathrm{d}}{\mathrm{d}t}[X_2] = \lambda_2 [X_1] - \mu_2 [X_2].$$



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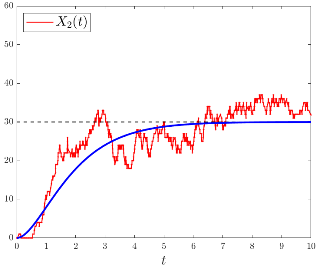
Chemical Master Equation (stochastic point of view)

- ▷ We denote by $X(t) = (X_1(t), X_2(t))$ the state of the system at time t.
- ▷ We assume that the instants at which reactions occur are random, so that $X(t)$ is a continuous-time Markov chain on $\mathbb{N}^2$.
- ▷ Each reaction R_r is defined by its propensity $a_r(x)$ and its stoichiometric vector ν_r.

⇝ If the system is in state x, the probability that R_r fires in time Δt is equal to $a_r(x)\Delta t$.

Ex: For the 2nd reaction, we have $a_2(x) = \lambda_2 x_1$ and $\nu_2 = (0, 1)$.



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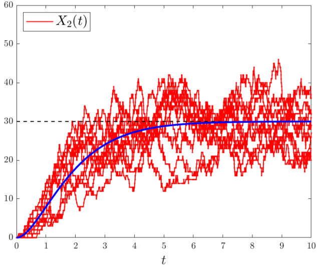

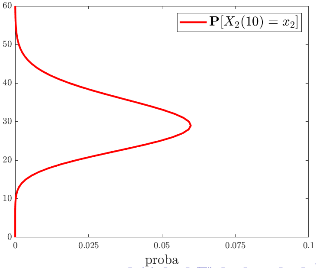

Chemical Master Equation

▷ The law of $X(t)$ satisfies a Kolmogorov equation, called the Chemical Master Equation (CME) in this context,

$$\frac{\mathrm{d}}{\mathrm{d}t}\mathbb{P}[X(t)=x] = \sum_{r=1}^{4}\Big(a_r(x-\nu_r)\mathbb{P}[X(t)=x-\nu_r] - a_r(x)\mathbb{P}[X(t)=x]\Big), \quad x \in \mathbb{N}^2.$$

⇝ Thus, the CME is a countable collection of coupled ODEs indexed by $\Omega = \mathbb{N}^2$.

General CME

For a set of R reactions involving d species, we set $\Omega = \mathbb{N}^d$ and $p(t,x) = \mathbb{P}[X(t)=x]$, then

$$\dot{p}(t,x) = \sum_{r=1}^{R}\Big(a_r(x-\nu_r)p(t,x-\nu_r) - a_r(x)p(t,x)\Big), \quad x \in \Omega.$$

In what follows, the rewrite the CME in matrix form as

$$\dot{p}(t) = p(t)\mathbf{Q} \qquad \text{and} \qquad p(0) = p_0,$$

with $p(t)$ the vector of the probabilities $p(t,x)$ and $\mathbf{Q}$ the matrix of the propensities $a_r(x)$.

Optimal control problem

Simplified protein-production model (X_1 = mRNA & X_2 = protein)

$$\varnothing \xrightarrow{(1-u)\lambda_1} X_1, \qquad X_1 \xrightarrow{u\lambda_2 x_1} X_1 + X_2, \qquad X_1 \xrightarrow{\mu_1 x_1} \varnothing, \qquad X_2 \xrightarrow{\mu_2 x_2} \varnothing.$$

▷ The control u (e.g. a light stimulus) acts globally on the system to:

– inhibit the growth of mRNAs X_1. – strengthen the production of proteins X_2.

▷ We may want to maximize the expected number of proteins X_2 at time T, i.e. solve

$$\max_u \varphi(u), \quad \text{with} \quad \varphi(u) = \sum_{x \in \Omega} x_2\, p_u(T, x),$$

and where p_u is solution of the controlled CME

$$\dot{p}(t) = p(t)\mathbf{Q}_u \qquad \text{and} \qquad p(0) = p_0.$$

⇝ To derive the optimality conditions for this problem,
we need to perform a sensitivity analysis of the CME w.r.t. the matrix $\mathbf{Q}$.

CME with source term

CME with source term

In what follows, we denote by $\mathsf{P}[\mathbf{Q}, p_0, f]$ the solution of the CME

$$\dot{p}(t) = p(t)\mathbf{Q} + f(t) \qquad \text{and} \qquad p(0) = p_0.$$

Existence and uniqueness

▷ Depending on the growth of $a_r(x)$ as $\langle x \rangle \to +\infty$, $\mathsf{P}[\mathbf{Q}, p_0, f]$ might not be unique.

⇝ If $a_r(x)$ grows at most linearly as $\langle x \rangle \to +\infty$, then $\mathsf{P}[\mathbf{Q}, p_0, f]$ is unique.

▷ In any case, we can work with the so-called minimal solution.

⇝ The constructive definition of the minimal solution can be used to get energy estimates.

Minimal solution

▷ Let $(\omega_n)_{n\in\mathbb{N}}$ be any sequence of finite subsets of Ω s.t. $\omega_n \uparrow \Omega$ as $n \to +\infty$.

▷ Then, the minimal solution $\mathsf{P}[\mathbf{Q}, p_0, f]$ is defined by

$$\mathsf{P}[\mathbf{Q}, p_0, f] = \lim_{n\to+\infty}\uparrow \mathsf{P}_n[\mathbf{Q}, p_0, f],$$

where $\mathsf{P}_n[\mathbf{Q}, p_0, f]$ is the solution of the restricted CME

$$\dot{p}(t) = p(t)\mathbf{Q}_{|\omega_n} + f(t)_{|\omega_n} \qquad \text{and} \qquad p(0) = p_{0|\omega_n}.$$

Energy estimates

Functional setting

- Since the solution of the CME is a probability mass function, it naturally belongs to the space ℓ^1 of vectors $p \in \mathbb{R}^\Omega$ s.t. $\sum_{x\in\Omega} p(x) < +\infty$.
- Moreover, we set:
  - ℓ^1_1 the subspace of $p \in \ell^1$ with finite expected value, i.e. s.t. $\sum_{x\in\Omega} x_i p(x) < +\infty$;
  - ℓ^1_2 the subspace of $p \in \ell^1$ with finite variance, i.e. s.t. $\sum_{x\in\Omega} x_i^2 p(x) < +\infty$;
  - etc...

Energy estimates

Let $\mathsf{P}[\mathbf{Q}, p_0, f]$ be the minimal solution of the CME

$$\dot{p}(t) = p(t)\mathbf{Q} + f(t) \qquad \text{and} \qquad p(0) = p_0.$$

For $m \in \mathbb{N}$, there exists $\mathsf{C}_m \geq 0$ s.t.

$$\left\|\mathsf{P}[\mathbf{Q}, p_0, f](t)\right\|_{\ell^1_m} \leq \mathsf{C}_m\left(\|p_0\|_{\ell^1_m} + \|f\|_{L^1(\ell^1_m)}\right), \quad t \in [0, T].$$

Sensitivity w.r.t. $\mathbf{Q}$

▷ Let $\mathbf{Q}$, $\overline{\mathbf{Q}}$ be CME matrices and $p_0 \in \ell^1_1$.

▷ We denote $p = \mathsf{P}[\mathbf{Q}, p_0, 0]$ and $\overline{p} = \mathsf{P}[\overline{\mathbf{Q}}, p_0, 0]$. We then have

$$\boxed{p - \overline{p} = \mathsf{P}\left[\overline{\mathbf{Q}}, 0, p(\mathbf{Q} - \overline{\mathbf{Q}})\right]}$$

and there exists $\mathsf{C} \geq 0$ s.t.

$$\boxed{\|p(t) - \overline{p}(t)\|_{\ell^1} \leq \mathsf{C}\|p_0\|_{\ell^1_1} \left\|\mathbf{Q} - \overline{\mathbf{Q}}\right\|_{\ell^1_1, \ell^1}, \quad t \in [0, T].}$$

⚠ Since the propensities $a_r(x)$ can grow linearly as $\langle x \rangle \to +\infty$, $\mathbf{Q}$ and $\overline{\mathbf{Q}}$ are only bounded from ℓ^1_1 to ℓ^1.

Sensitivity w.r.t. u

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▷ Here, the CME matrix is of the form $\mathbf{Q}_u = \mathbf{Q}_0 + u\,\delta\mathbf{Q}$, where $\delta\mathbf{Q} = \mathbf{Q}_1 - \mathbf{Q}_0$.

Sensitivity w.r.t. u

▷ Let $u, \overline{u} \in L^\infty(0,T;[0,1])$ and $p_0 \in \ell^1_2$.

▷ We denote $p_u = \mathsf{P}[\mathbf{Q}_u, p_0, 0]$ and $p_{\overline{u}} = \mathsf{P}[\mathbf{Q}_{\overline{u}}, p_0, 0]$. We then have

$$p_u - p_{\overline{u}} = \mathsf{P}\Big[\mathbf{Q}_{\overline{u}}, 0, (u-\overline{u})p_{\overline{u}}\delta\mathbf{Q}\Big] + \mathsf{P}\Big[\mathbf{Q}_{\overline{u}}, 0, (u-\overline{u})(p_u - p_{\overline{u}})\delta\mathbf{Q}\Big].$$

▷ The 1st-order term $\mathsf{P}\Big[\mathbf{Q}_{\overline{u}}, 0, (u-\overline{u})p_{\overline{u}}\delta\mathbf{Q}\Big]$ is linear w.r.t. $u - \overline{u}$.

▷ For the 2nd-order term, there exists $C' \geq 0$ s.t.

$$\Big\|\mathsf{P}\Big[\mathbf{Q}_{\overline{u}}, 0, (u-\overline{u})(p_u - p_{\overline{u}})\delta\mathbf{Q}\Big](t)\Big\|_{\ell^1} \leq C'\|p_0\|_{\ell^1_2}\|u-\overline{u}\|^2_{L^\infty}, \quad t \in [0,T].$$

⇝ For the cost $\varphi(u) = \sum_{x\in\Omega} x_2\, p_u(T,x)$, we thus have

$$\varphi(u) - \varphi(\overline{u}) = \sum_{x\in\Omega} x_2\, \mathsf{P}\Big[\mathbf{Q}_{\overline{u}}, 0, (u-\overline{u})p_{\overline{u}}\delta\mathbf{Q}\Big](T,x) + o\big(\|u-\overline{u}\|_{L^\infty}\big).$$

▷ **Summary:**

- We consider a toy example of optimal control problem for the CME.
- We use the notion of minimal solution to perform a sensitivity analysis for the CME.
- This analysis leads to a Taylor expansion of the cost w.r.t. the control and ultimately to optimality conditions.

▷ **Perspectives:**

- Study relevant simple biological models.

$\rightsquigarrow$ grower/producer model, bursty protein production, ...

- Solve these optimal control problems numerically.

Thank you for your attention