

On the Incremental Stability of PIDE-based Stochastic Gene Regulatory Networks under Switching Inducer Profiles

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Abstract—The design of robust control strategies for stochastic Gene Regulatory Networks (GRNs) requires modeling frameworks that effectively balance accuracy with computational efficiency. Partial Integro-Differential Equations (PIDEs) offer a compelling solution, providing a continuous approximation of the Chemical Master Equation (CME) suitable for real-time control applications. In this paper, we focus on the incremental stability of these PIDE models when subjected to time-varying switching profiles of chemical inducers. We show that the PIDE operator is inherently non-expansive in the L^1 norm for identical switching inputs, providing a theoretical guarantee that the distance between any two trajectories of the same system does not increase over time. Beyond this property, our numerical results suggest a strong practical contractivity: regardless of the initial cell population distribution, the system trajectories converge toward a unique solution determined by the sequence of inducers. These findings confirm that the PIDE framework is a reliable basis for cybergenetics, ensuring that a given inducer profile produces consistent and predictable outcomes.

I. INTRODUCTION

A central aim of cybergenetics is to achieve automated control over living cells [1], a goal challenged by the inherent stochasticity of biochemical reaction networks governing cell regulation [2]. To achieve predictable behaviors in such noisy environments, models are needed that are computationally tractable for control synthesis while remaining mathematically rigorous [3]. While the Chemical Master Equation (CME) provides a rigorous description of these processes, its high dimensionality often limits its use in real-time control. Partial Integro-Differential Equation (PIDE) models have emerged as a scalable and efficient alternative, capturing population dynamics while significantly reducing the computational burden compared to traditional stochastic simulations [4], [5]. Recent works have demonstrated the effectiveness of the PIDE framework for the control of gene regulatory circuits [6]. Notably, recent proofs of strong contractivity for nonautonomous master equations [7] motivate a stability analysis of our PIDE framework, since its compartmental discretization [8] shares the same

underlying mathematical structure. In the broader nonlinear-systems literature, Lyapunov-based arguments are a classical reference point for stability [9]; here, however, we formulate the analysis directly in the space of probability densities, using an L^1 operator perspective that is naturally aligned with the PIDE setting.

In GRN control, stimuli are frequently applied through the switching of chemical inducers [10]. For these strategies to be robust and reproducible, the system must exhibit incremental stability; that is, the influence of the initial population state should vanish over time, with all trajectories converging to a common path defined by the input signal [11]. This property, often framed within contraction analysis [12], [13], ensures that biological experiments are consistent even when the starting conditions of the cell population are uncertain or heterogeneous.

This paper analyzes the incremental stability of PIDE-based GRNs under switching inducer profiles. We first present a theoretical derivation showing that the PIDE operator is non-expansive in the L^1 space, building upon the operator theory of strongly continuous semigroups [14], [15]. We then provide numerical evidence suggesting convergence of the trajectories for biologically relevant parameters, indicating that the influence of the initial state becomes progressively attenuated over time. This practical contractivity suggests that a prescribed sequence of inducers will drive the population towards a consistent target distribution, regardless of the initial configuration.

The paper is organized as follows: Section II introduces the PIDE framework; Section III details the stability and non-expansivity analysis; Section IV presents numerical case studies including a 1D self-regulated gene and a 2D genetic toggle switch; and Section V offers concluding remarks.

II. MATHEMATICAL MODELING

A. PIDE Model Framework

We consider a gene regulatory network consisting of n genes ($DNA_1, \dots, DNA_n$) that are transcribed into n messenger RNAs, which are subsequently translated into n proteins ($X_1, \dots, X_n$). The dynamics are governed by transcription rates k_m^i , translation rates k_x^i , and degradation rates γ_m^i and γ_x^i for mRNA and protein, respectively, for each $i \in \{1, \dots, n\}$. A fundamental assumption in this framework is that mRNA degradation is significantly faster than that of its corresponding protein ($\gamma_m^i \gg \gamma_x^i$). Under this bursting assumption, the dynamics of the protein concentrations $\mathbf{x} \in \mathbb{R}_+^n$ are described by a multidimensional Partial Integro-Differential Equation (PIDE) [4]:

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$$\begin{aligned} \frac{\partial p(t, \mathbf{x})}{\partial t} &= \sum_{i=1}^n \frac{\partial}{\partial x_i} [\gamma_i^j x_i p(t, \mathbf{x})] \\ &+ \sum_{i=1}^n k_m^i \left(\int_0^{x_i} [\omega_i(x_i - y_i) - \delta(x_i - y_i)] c_{i,\mathbf{u}}(\mathbf{y}_i) p(t, \mathbf{y}_i) dy_i \right), \end{aligned} \quad (1)$$

where $p : \mathbb{R}_+ \times \mathbb{R}_+^n \rightarrow \mathbb{R}_+$ denotes the probability density function of protein concentrations. The first term on the right-hand side represents protein degradation (drift) with rates γ_i^j . The second term captures the production of proteins in bursts, where the regulatory function $c_{i,\mathbf{u}}(\mathbf{y}_i)$ —parameterized by the inducer profile $\mathbf{u}$ —modulates the burst frequency. The kernel ω_i defines the jump size distribution as:

$$\omega_i(x_i - y_i) = \frac{1}{b_i} \exp \left[-\frac{(x_i - y_i)}{b_i} \right], \quad (2)$$

with $b_i = k_m^i / \gamma_m^i$ being the mean burst size and δ represents the Dirac delta function. To simplify the notation in the integral, $\mathbf{y}_i$ denotes the vector $\mathbf{x}$ where only the i -th coordinate has been replaced by the integration variable y_i , i.e., $\mathbf{y}_i = (x_1, \dots, y_i, \dots, x_n)$.

B. Regulation and Switching Control

The regulatory architecture is captured by the functions $c_{i,\mathbf{u}}(\mathbf{x})$, representing the probability of gene i being active. This probability is determined by a combination G of Hill-type regulatory terms $\rho_{ij,\mathbf{u}}$, which depend on the protein concentrations and the external control:

$$c_{i,\mathbf{u}}(\mathbf{x}) = G(\rho_{i1,\mathbf{u}}(x_1), \dots, \rho_{in,\mathbf{u}}(x_n)). \quad (3)$$

Control is exerted via external inducers $\mathbf{u}(t) = [I_1(t), \dots, I_n(t)]$. The effect of an inducer I_k on a repressive interaction is modeled by a modulatory function $F_k(I_k)$, which scales the repression threshold:

$$F_k(I_k) = \frac{1}{1 + \left(\frac{I_k}{\theta_{I_k}} \right)^{\mu_k}}, \quad (4)$$

where θ_{I_k} and μ_k are the half-saturation constant and Hill coefficient of the inducer, respectively. The protein-to-protein regulatory terms are thus parameterized by the control signal:

$$\rho_{ij,\mathbf{u}}(x_j) = \frac{K_{ij}^{H_{ij}}}{K_{ij}^{H_{ij}} + x_j^{H_{ij}} F_k(I_k)}, \quad (5)$$

where K_{ij} and H_{ij} define the sensitivity and cooperativity of the regulation.

We consider a switching control mechanism where the input $\mathbf{u}(t)$ is piecewise constant, switching between a finite set of N_u configurations:

$$\mathbf{u}(t) \in \mathcal{U} = \{\mathbf{u}^{(1)}, \mathbf{u}^{(2)}, \dots, \mathbf{u}^{(N_u)}\}. \quad (6)$$

The switching is defined by a signal $\sigma(t) : [0, \infty) \rightarrow \{1, \dots, N_u\}$, such that $\mathbf{u}(t) = \mathbf{u}^{(\sigma(t))}$. This implies that the functions $c_{i,\mathbf{u}}(\mathbf{x})$ change abruptly at specific time instants, effectively modifying the landscape of the probability distribution. A critical question for the reliability of such

strategies—and the core of this paper—is whether the resulting trajectories are stable and independent of the initial population state $p(0, \mathbf{x})$ under a given switching sequence $\sigma(t)$.

Numerical solutions for this model are obtained using the semi-Lagrangian approach implemented in the SELANSI software [5], which efficiently handles the multidimensional nature of the PIDE while preserving the positivity and mass of the probability density function.

III. INCREMENTAL STABILITY ANALYSIS

A central theoretical property of the PIDE models used in this framework is their *non-expansivity in the L^1 space*. Intuitively, the forward evolution of probability densities under a fixed inducer profile cannot amplify their differences: two distinct initial distributions of the same system subject to the same switching control signal do not diverge over time. This non-expansivity establishes the baseline for geometric contractivity, where differences between solutions decay exponentially. These properties justify the robustness of the switching control strategy: once a control sequence is fixed, long-term outcomes depend predominantly on the control profile and not on the particular choice of the initial condition for a given network realization.

Below we provide the full mathematical statements and their proofs, relying on standard results from semigroup theory [14], [16] and Markov-process ergodic theory [17].

A. Notation and Standing Hypotheses

Let $\mathbf{x} = (x_1, \dots, x_n) \in \mathbb{R}_+^n$. For a fixed inducer profile $\mathbf{u}$, we denote by $c_{i,\mathbf{u}}(\mathbf{x})$ the corresponding input functions and by $U_{\mathbf{u}}(t, \sigma)$ the propagator mapping a density at time σ to the density at time $t \geq \sigma$. We assume the following hypotheses:

- (H1) Constant positive degradation rates $\gamma^i > 0$ for $i = 1, \dots, n$; set $\gamma_{\min} := \min_i \gamma^i > 0$.
- (H2) Burst kernels $\omega_i \geq 0$ with $\int_0^\infty \omega_i(s) ds = 1$ and finite mean $b_i := \int_0^\infty s \omega_i(s) ds < \infty$.
- (H3) Synthesis rates $k_m^i > 0$, and $k_{\max} := \sum_{i=1}^n k_m^i$.
- (H4) $0 \leq c_{i,\mathbf{u}}(\mathbf{x}) \leq 1$ for all $\mathbf{x} \in \mathbb{R}_+^n$ and any inducer $\mathbf{u}$.
- (H5) Weak solution regularity: we consider non-negative, mass-preserving weak solutions $p \in C([0, \infty); L^1(\mathbb{R}_+^n))$.

B. Infinitesimal Generator and Adjoint Derivation

Let L denote the infinitesimal generator of the Markov process on observables. For smooth test functions $\varphi \in C_c^\infty(\mathbb{R}_+^n)$ (infinitely differentiable with compact support), the operator is decomposed as $L\varphi(\mathbf{x}) = A\varphi(\mathbf{x}) + B\varphi(\mathbf{x})$, with the transport term

$$A\varphi(\mathbf{x}) := - \sum_{i=1}^n \gamma^i x_i \partial_{x_i} \varphi(\mathbf{x}), \quad (7)$$

and the jump term

$$B\varphi(\mathbf{x}) := \sum_{i=1}^n k_m^i c_{i,\mathbf{u}}(\mathbf{x}) \int_0^\infty (\varphi(\mathbf{x} + s\mathbf{e}_i) - \varphi(\mathbf{x})) \omega_i(s) ds. \quad (8)$$

The forward evolution of the probability density is governed by the adjoint operator $L^\dagger$, defined through the duality relation

$$\int_{\mathbb{R}_+^n} (L\varphi)(\mathbf{x}) p(\mathbf{x}) d\mathbf{x} = \int_{\mathbb{R}_+^n} \varphi(\mathbf{x}) (L^\dagger p)(\mathbf{x}) d\mathbf{x}. \quad (9)$$

The resulting adjoint operator, which describes the generalized Fokker-Planck form for this system, is given by:

$$\begin{aligned} L^\dagger p(\mathbf{x}) &= \sum_{i=1}^n \partial_{x_i} (\gamma^i x_i p(\mathbf{x})) \\ &+ \sum_{i=1}^n k_m^i \left((\omega_i * (c_{i,\mathbf{u}} p))(\mathbf{x}) - c_{i,\mathbf{u}}(\mathbf{x}) p(\mathbf{x}) \right). \end{aligned} \quad (10)$$

To derive this explicit form, we analyze the transport and jump parts separately. For the transport part $A^\dagger$, integrating by parts in the i -th coordinate yields:

$$\begin{aligned} \int_{\mathbb{R}_+^n} -\gamma^i x_i [\partial_{x_i} \varphi(\mathbf{x})] p(\mathbf{x}) d\mathbf{x} &= \\ \int_{\mathbb{R}_+^{n-1}} \left[-\gamma^i x_i \varphi(\mathbf{x}) p(\mathbf{x}) \right]_0^\infty d\mathbf{x}_{i'} &+ \int_{\mathbb{R}_+^n} \varphi(\mathbf{x}) \partial_{x_i} [\gamma^i x_i p(\mathbf{x})] d\mathbf{x}, \end{aligned} \quad (11)$$

where $d\mathbf{x}_{i'}$ denotes integration over all variables except x_i . The boundary term vanishes since φ has compact support and the factor x_i is zero at the origin. Summing over i , we obtain the transport adjoint

$$A^\dagger p(\mathbf{x}) = \sum_{i=1}^n \partial_{x_i} [\gamma^i x_i p(\mathbf{x})]. \quad (12)$$

The derivation of the jump adjoint $B^\dagger$ requires more care. Integrating $B\varphi$ against p and exchanging the order of integration, we separate the gain and loss terms:

$$\begin{aligned} \int_{\mathbb{R}_+^n} B\varphi(\mathbf{x}) p(\mathbf{x}) d\mathbf{x} &= \sum_{i=1}^n k_m^i \left(\int_{\mathbb{R}_+^n} \int_0^\infty c_{i,\mathbf{u}}(\mathbf{x}) \varphi(\mathbf{x} + s\mathbf{e}_i) \right. \\ &\times \omega_i(s) p(\mathbf{x}) ds d\mathbf{x} - \left. \int_{\mathbb{R}_+^n} c_{i,\mathbf{u}}(\mathbf{x}) \varphi(\mathbf{x}) p(\mathbf{x}) d\mathbf{x} \right). \end{aligned} \quad (13)$$

To find the explicit form of the gain term $\mathcal{J}_i$, we apply the change of variables $\mathbf{y} = \mathbf{x} + s\mathbf{e}_i$. For each fixed jump size s , this is a translation with unit Jacobian ($d\mathbf{y} = d\mathbf{x}$). The constraint $x_i = y_i - s > 0$ restricts the jump sizes to $s \in (0, y_i)$. Applying Fubini's Theorem to exchange the order of integration, we obtain:

$$\mathcal{J}_i = \int_{\mathbb{R}_+^n} \varphi(\mathbf{y}) \left(\int_0^{y_i} \omega_i(s) c_{i,\mathbf{u}}(\mathbf{y} - s\mathbf{e}_i) p(\mathbf{y} - s\mathbf{e}_i) ds \right) d\mathbf{y}. \quad (14)$$

By collecting terms and using the notation $\mathbf{y}_i = (x_1, \dots, y_i, \dots, x_n)$, the convolution in the i -th coordinate is defined as:

$$(\omega_i * (c_{i,\mathbf{u}} p))(\mathbf{x}) := \int_0^{x_i} \omega_i(x_i - y_i) c_{i,\mathbf{u}}(\mathbf{y}_i) p(\mathbf{y}_i) dy_i. \quad (15)$$

Substituting this into the integral of the gain term, the jump adjoint operator $B^\dagger$ is expressed compactly as:

$$B^\dagger p(\mathbf{x}) = \sum_{i=1}^n k_m^i \left((\omega_i * (c_{i,\mathbf{u}} p))(\mathbf{x}) - c_{i,\mathbf{u}}(\mathbf{x}) p(\mathbf{x}) \right). \quad (16)$$

This identification allows us to recover the full adjoint operator $L^\dagger p = A^\dagger p + B^\dagger p$ as stated in (10).

C. Non-expansivity

In the implementation of a switching control strategy, we consider a temporal partition $t_0 < t_1 < \dots < t_M$. On each interval $(t_m, t_{m+1}]$, the controller applies a constant mode $\mathbf{u}_m$. The total propagator $U_{\mathbf{u}}(t_M, t_0)$ is the composition of the evolution operators for each interval.

Proposition: Under the standing hypotheses, for every fixed mode $\mathbf{u}_m$ the operator norm inequality

$$\|U_{\mathbf{u}_m}(t_{m+1}, t_m) f\|_{L^1} \leq \|f\|_{L^1}, \quad \forall f \in L^1(\mathbb{R}_+^n), \quad (17)$$

holds. Consequently, for any switching realization $\mathbf{u}$ and any pair of initial densities p_0, q_0 ,

$$\|U_{\mathbf{u}}(t_M, t_0) p_0 - U_{\mathbf{u}}(t_M, t_0) q_0\|_{L^1} \leq \|p_0 - q_0\|_{L^1}. \quad (18)$$

Proof: We first analyze the transport semigroup $S(t)$ generated by $A^\dagger$. The characteristic flow is given by

$$\Phi_t(\mathbf{x}) = (e^{-\gamma^1 t} x_1, \dots, e^{-\gamma^n t} x_n). \quad (19)$$

For any initial density $p_0 \in L^1$, the push-forward is defined as

$$(S(t)p_0)(\mathbf{x}) := p_0(\Phi_{-t}(\mathbf{x})) |\det D\Phi_{-t}(\mathbf{x})|. \quad (20)$$

The determinant of the Jacobian is $e^{(\sum_i \gamma^i)t}$, which compensates for the change of variables $\mathbf{y} = \Phi_{-t}(\mathbf{x})$, ensuring that

$$\int_{\mathbb{R}_+^n} (S(t)p_0)(\mathbf{y}) d\mathbf{y} = \|p_0\|_{L^1} \quad (21)$$

for $p_0 \geq 0$. Since $S(t)$ preserves positivity and mass, it is a contraction in L^1 , i.e., $\|S(t)p_0\|_{L^1} \leq \|p_0\|_{L^1}$. Standard semigroup theory asserts that $A^\dagger$ generates this strongly continuous semigroup on a suitable domain [14].

To establish that $B^\dagger$ is a well-behaved operator on $L^1(\mathbb{R}_+^n)$, we first analyze the gain term. For any $p \geq 0$, applying Tonelli's theorem to exchange the order of integration yields:

$$\begin{aligned} \|\omega_i * (c_{i,\mathbf{u}} p)\|_{L^1} &= \int_{\mathbb{R}_+^n} \int_0^{x_i} \omega_i(x_i - y_i) c_{i,\mathbf{u}}(\mathbf{y}) p(\mathbf{y}) dy_i d\mathbf{x} \\ &\leq \int_{\mathbb{R}_+^n} c_{i,\mathbf{u}}(\mathbf{y}) p(\mathbf{y}) \left(\int_{y_i}^\infty \omega_i(x_i - y_i) dx_i \right) d\mathbf{y}. \end{aligned} \quad (22)$$

Since $\int_0^\infty \omega_i(s) ds = 1$, the inner integral equals unity. Given that $0 \leq c_{i,\mathbf{u}} \leq 1$, we conclude that $\|\omega_i * (c_{i,\mathbf{u}} p)\|_{L^1} \leq \|p\|_{L^1}$. By linearity and the triangle inequality, the full jump operator is bounded:

$$\|B^\dagger p\|_{L^1} \leq \sum_{i=1}^n k_m^i (\|\omega_i * (c_{i,\mathbf{u}} p)\|_{L^1} + \|c_{i,\mathbf{u}} p\|_{L^1}) \leq 2k_{\max} \|p\|_{L^1}, \quad (23)$$

confirming that $B^\dagger$ is a bounded linear operator on L^1 , denoted by $B^\dagger \in \mathcal{B}(L^1(\mathbb{R}_+^n))$.

Furthermore, $B^\dagger$ is mass-preserving. To verify this, we integrate the operator over the entire domain:

$$\int_{\mathbb{R}_+^n} (B^\dagger p)(\mathbf{x}) d\mathbf{x} = \sum_{i=1}^n k_m^i \left(\int_{\mathbb{R}_+^n} (\omega_i * (c_{i,\mathbf{u}} p))(\mathbf{x}) d\mathbf{x} - \int_{\mathbb{R}_+^n} c_{i,\mathbf{u}}(\mathbf{x}) p(\mathbf{x}) d\mathbf{x} \right). \quad (24)$$

By applying Fubini's theorem to rearrange the nested integrals and noting that $\int_0^\infty \omega_i(s) ds = 1$, we find:

$$\int_{\mathbb{R}_+^n} (\omega_i * (c_{i,\mathbf{u}} p))(\mathbf{x}) d\mathbf{x} = \int_{\mathbb{R}_+^n} c_{i,\mathbf{u}}(\mathbf{y}) p(\mathbf{y}) d\mathbf{y}. \quad (25)$$

This shows that the gain and loss integrals for each coordinate i are identical, leading to:

$$\int_{\mathbb{R}_+^n} B^\dagger p(\mathbf{x}) d\mathbf{x} = \sum_{i=1}^n k_m^i \left(\int_{\mathbb{R}_+^n} c_{i,\mathbf{u}} p d\mathbf{y} - \int_{\mathbb{R}_+^n} c_{i,\mathbf{u}} p d\mathbf{x} \right) = 0. \quad (26)$$

Thus, the jump operator reshapes the distribution without altering its total mass.

We combine these results to construct the full semigroup $T(t)$ generated by $L^\dagger = A^\dagger + B^\dagger$ on $L^1(\mathbb{R}_+^n)$. From previous results, $A^\dagger$ generates a positive contraction semigroup $S(t)$ preserving total mass and $B^\dagger$ is a bounded operator that satisfies a Miyadera–Voigt estimate, namely

$$\int_0^{\hat{t}_0} \|B^\dagger S(s)p\|_{L^1} ds \leq q \|p\|_{L^1}, \quad q < 1,$$

which follows directly from the bound $\|B^\dagger\| \leq 2k_{\max}$ and the isometry property of $S(t)$.

Therefore, by the Miyadera–Voigt perturbation theorem, the closure of $L^\dagger$ generates a positive C_0 -semigroup $T(t)$ represented by the Dyson–Phillips series [14], [16], [18]. Since $S(t)$ preserves mass and $\int_{\mathbb{R}_+^n} (B^\dagger q)(\mathbf{x}) d\mathbf{x} = 0$ for all $q \in L^1$, each Dyson–Phillips term has zero integral, and thus $T(t)$ preserves total mass.

For general $f \in L^1$, we use the Jordan decomposition $f = f_+ - f_-$. By linearity and the preservation of the norm for non-negative functions, we have:

$$\begin{aligned} \|T(t)f\|_{L^1} &\leq \|T(t)f_+\|_{L^1} + \|T(t)f_-\|_{L^1} \\ &= \|f_+\|_{L^1} + \|f_-\|_{L^1} = \|f\|_{L^1}. \end{aligned} \quad (27)$$

Thus, for any fixed mode $\mathbf{u}_m$, the propagator $T_{\mathbf{u}_m}(t)$ is contractive.

Finally, the total evolution $U_{\mathbf{u}}(t_M, t_0)$ under a switching profile is the composition of these contractive operators:

$$U_{\mathbf{u}}(t_M, t_0) = T_{\mathbf{u}_{M-1}}(\Delta t_{M-1}) \circ \cdots \circ T_{\mathbf{u}_0}(\Delta t_0). \quad (28)$$

Since the composition of non-expansive mappings is itself non-expansive, the trajectory form of the inequality holds:

$$\|U_{\mathbf{u}}(t_M, t_0)(p_0 - q_0)\|_{L^1} \leq \|p_0 - q_0\|_{L^1}. \quad (29)$$

This confirms that the L^1 distance between two solutions evolving under the same switching sequence cannot increase over time. $\square$

IV. NUMERICAL RESULTS

In this section, we present numerical evidence to illustrate the incremental stability properties of the PIDE framework under switching control inputs. Specifically, we investigate whether the system dynamics, beyond being theoretically non-expansive in the L^1 norm, also exhibit contractive behavior in practice. This suggests that trajectories starting from disparate initial probability distributions tend to coalesce toward a unique solution determined by the applied inducer sequence, effectively reducing the influence of the initial condition over time.

To explore this behavior, we conducted a series of experiments where the same pre-computed switching control signal $\mathbf{u}(t)$ was applied to the system starting from three radically different initial conditions (ICs). We monitored the evolution of the pairwise L^1 distances between the resulting probability densities. While the non-increase in these distances is a direct consequence of the theoretical non-expansivity, the observed rapid decay in the L^1 metric provides numerical evidence of practical contractivity under the studied switching regimes.

A. Case Study I: 1D Self-Regulated Gene

The first case study considers a single gene with negative auto-regulation. The control objective is to steer the population to a unimodal distribution centered at a protein copy number of $x \approx 50$. We apply a switching input sequence over a time horizon $T = 20$ and observe the evolution of three distinct initial distributions:

- (IC1) **Uncontrolled Steady-State (Low):** The natural stationary distribution of the system, whose mode lies significantly below the target.
- (IC2) **Target-Centered Gaussian:** A Gaussian distribution initialized exactly at the target mean ($x = 50$).
- (IC3) **High-Mean Gaussian:** A distribution initialized with a high mean ($x = 100$), representing an “overshoot” scenario.

Figure 1 illustrates the results. As shown in the pairwise L^1 norm evolution (Fig. 1.Top), the distance between any pair of trajectories decreases monotonically immediately after the control is applied. Notably, the convergence is rapid; despite the significant initial spatial separation between the “Low” and “High” distributions, the L^1 error vanishes, driving all densities to indistinguishable states. The snapshots in Fig. 1 (middle-bottom) visually confirm this coalescence: regardless of whether the system starts from a low-expression state or an overexpression state, the switching profile effectively reshapes the density into the desired profile.

B. Case Study II: 2D Genetic Toggle Switch

To evaluate the **non-expansive nature** of the system in a higher-dimensional setting characterized by inherent bimodality, we consider the genetic toggle switch. This system naturally settles into a distribution where two proteins mutually inhibit each other. The control goal is to steer the population and concentrate the probability mass into the mode where Protein 1 is dominant ($x_1 \gg x_2$), effectively

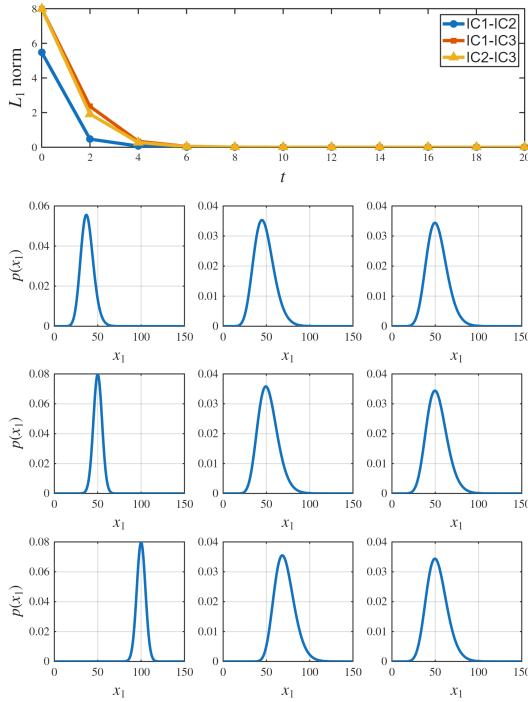


Fig. 1: Numerical validation of contractivity for the 1D self-regulated gene system. The plot at the top displays the temporal evolution of the pairwise L^1 distances between the three test cases, where the monotonic decay confirms the non-expansive nature of the PIDE dynamics and the rapid convergence illustrates practical geometric contractivity. The three panels below show the temporal snapshots of the probability density functions starting from different initial conditions: the uncontrolled steady state (top-middle), a Gaussian at the target mean (bottom-middle), and an over-expressed Gaussian (bottom). Regardless of the starting point, the switching profile effectively drives all populations toward the same identical distribution at $x \approx 50$ by the end of the simulation.

overcoming the autonomous bimodal landscape. The three initial conditions tested are:

- (IC1) **Bimodal Reference:** The uncontrolled steady-state distribution, representing a heterogeneous population with cells in both basins of attraction.
- (IC2) **P1-Dominant Gaussian (Target):** A distribution already initialized within the basin of attraction of the target mode.
- (IC3) **P2-Dominant Gaussian (Opposite):** A distribution initialized in the opposing basin of attraction (x_2 dominant), representing the "worst-case" scenario for control.

The results, presented in Figure 2, provide a demonstration of global contractivity. The pairwise L^1 distances (Fig. 2.Top) exhibit a sharp exponential decay. Crucially, this includes the distance between the P1-dominant and P2-dominant initializations. This result is significant because it implies that the applied switching signal is sufficiently

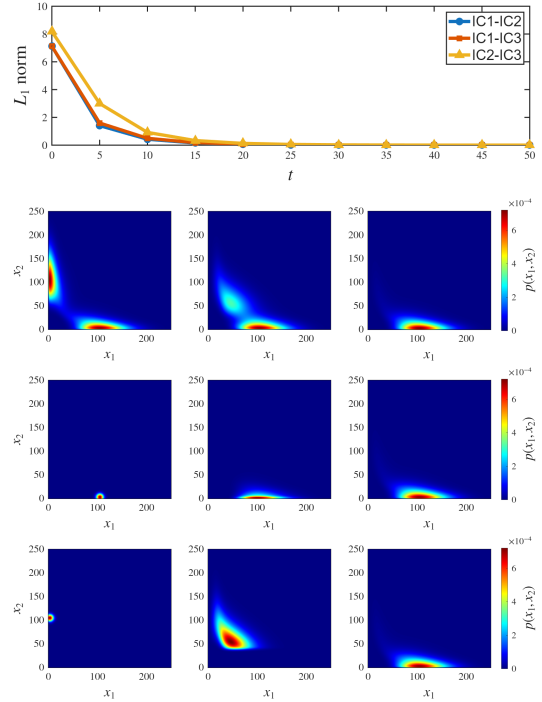


Fig. 2: Contractivity analysis and initial condition independence in the 2D genetic toggle switch. The top plot shows the pairwise L^1 norm distances between trajectories starting from disparate regions of the state space, exhibiting a sharp exponential decay that proves the system erases the memory of its initial state. The subsequent three rows illustrate the joint probability distributions evolving from: the symmetric bimodal steady state (top-middle), a P1-dominant Gaussian (bottom-middle), and an opposing P2-dominant Gaussian (bottom). Despite the markedly different initial probability landscapes, all trajectories evolve toward similar final distributions under the same switching profile, illustrating the ability of the control signal to progressively reshape and align the population dynamics.

authoritative to reshape the underlying probability landscape, effectively overcoming the system's inherent bimodality. Consequently, the probability mass initially concentrated in disjoint regions of the state space is driven to coalesce and align with the target trajectory. The distributional snapshots (Fig. 2.middle-bottom) corroborate this: by the end of the simulation window, the final densities for all cases become indistinguishable, suggesting that the memory of the initial bimodal distribution is effectively erased under the action of the control signal.

C. Discussion: Efficiency and Practical Implications

The numerical results above extend the theoretical guarantee of non-expansivity to a practical demonstration of geometric contractivity. The monotonic and often exponential decay of the L^1 distance between trajectories suggests that the PIDE model under switching control is an incrementally stable system.

This property has profound practical implications for the control of gene regulatory networks. It establishes that a single control sequence—computed for a nominal reference case—is robust to initialization errors. In a laboratory setting, this means that the exact initial state of the cell population need not be perfectly known or measured. As long as the control signal is applied, the contractive nature of the dynamics ensures that any initial discrepancy will dissipate, and the population will reliably converge to the desired biological phenotype. This independence from the initial condition highlights the efficiency of the proposed approach, allowing for reliable open-loop implementation of complex distributional shaping tasks.

V. CONCLUSIONS

This work establishes a rigorous theoretical foundation for the use of Partial Integro-Differential Equation (PIDE) models in the control of stochastic gene regulatory networks. By leveraging the theory of strongly continuous semigroups and perturbation methods, we have formally proven that the PIDE operator governing gene expression is non-expansive in the L^1 space. This result validates the PIDE framework not merely as an efficient computational approximation of the Chemical Master Equation, but as a robust mathematical object suitable for control synthesis.

From a cybergenetic perspective, our analysis shows that switching control strategies based on inducer modulation provide a robust framework for population steering. The results indicate that the system consistently overcomes its initial state, with trajectories converging toward a unique profile dictated by the input sequence. This property is crucial for experimental reproducibility, ensuring that identical control protocols yield consistent phenotypic outcomes regardless of biological variability or initialization errors.

These findings reinforce the reliability of PIDE-based architectures for the systematic design of robust control laws in synthetic biology. By providing a theoretical guarantee of stability, this work facilitates the development of automated strategies where consistent performance is required despite inherent biological noise. Future research will explore the implications of this non-expansive nature in alternative models of transcriptional regulation [19], its integration into generalized feedback control frameworks, and the experimental validation of the initial-state independence predicted under switching control strategies in real biological platforms.

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