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An Optimization-Based Method for Bounding State Functionals of Nonlinear Stochastic Systems

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Abstract— **We propose a method for bounding state functionals of a class of nonlinear stochastic differential equations. Given a class of state functionals of a stochastic system, the Feynman-Kac Lemma is a backward in time partial differential equation that describes the evolution of the state functional. We bound these state functionals based on a method which uses barrier functionals. We show that, under the assumption of polynomial data, the bounds can be obtained by using semi-definite programming. The proposed method is then applied to the case study of noise in genetic negative autoregulation to bound a functional of the second moment, which is of specific interest to experimental assays. The bound obtained is found to be in good agreement with experimental results in the literature.**

I. INTRODUCTION

The complexity of many dynamical systems in nature and engineering requires models that are described by stochastic differential equations (SDEs). For example, in biochemical interactions, where the occurrence of reactions due to thermal fluctuations is a random process, deterministic models fail to capture the dynamics properly, especially in the case of small species populations [1].

Finding explicit solutions to nonlinear SDEs is a cumbersome task in general. Hence, numerical methods, such as the Euler-Maruyama method [2], are used to approximate solutions. Yet, for significant classes of SDEs, approximating solutions is too computationally demanding, in particular, if there is uncertainty in the parameters or initial conditions. Fortunately, Lyapunov methods can be used to study stability and convergence properties of SDEs without the need to approximate solutions [3].

Rather than studying stability, in many important applications, we are merely interested in evaluating the moments or integral functionals of the moments at particular points in time. It is well known that functionals of the solutions of the stochastic models for asset prices describe the price of an option [4]. For nonlinear SDEs, finding the dynamics of the statistical moments is not trivial, because the dynamics of the lower-order moments depend on the higher-order moments: the moment closure problem. This problem has been studied extensively in the context of biological applications [5] and, in particular, biochemical reaction networks [6], [7].

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In this paper, we propose a method for bounding state functionals of a class of nonlinear SDEs. The method is based on a generalized version of the Feynman-Kac Lemma, which describes the backward dynamics of a cost functional of the moments of an SDE. The main tool is the barrier functional [8], which is a generalization of barrier certificates [9] to infinite-dimensional systems. We demonstrate that if the barrier functional satisfies two inequalities along the solutions of the backward dynamics, then we can infer bounds on the cost functional of the moments. We further show that, under the assumption of polynomial data, the proposed method can be cast as a semi-definite program (SDP). In this regard, we generalize our earlier results in [10] and in [11] to integral inequalities with time dependence. Furthermore, we formulate an S-procedure-like theorem for integral inequalities.

The proposed method is applied to the case study of negative autoregulation. This gene circuit motif implements the simplest form of biological negative feedback. As understanding of biological systems with feedback increases [12], [13], there is an ever greater need for the application of theoretical tools to the fields of systems and synthetic biology. Negative autoregulation is well studied and ubiquitous in nature [14], [15]. Though it has been shown that negative autoregulation experimentally reduces rise time, measuring the dynamics of such systems in an experimental context continues to be challenging. On the other hand, noisy data, at both culture and single cell level, is a common and reliable tool [14], [15]. This motivates the need for accurate theoretical tools to calculate and predict the concentration distributions of studied proteins across a populations of cells.

The rest of this paper is as follows. In Section II, we briefly review some background definitions and theorems. In Section III, we describe the proposed method for bounding state functionals of SDEs using barrier functionals. We then propose a computational method based on SDPs to find these bounds. Section IV considers the application of the proposed method to find bounds on a functional of the second moment of a model of negative autoregulation. Finally, Section V concludes the paper.

Notation:

The n-dimensional Euclidean space is denoted by $\mathbb{R}^n$ and the set of non-negative reals by $\mathbb{R}_{\geq 0}$. The n-dimensional set of positive integers is denoted by $\mathbb{N}^n$, and the n-dimensional space of non-negative integers is denoted by $\mathbb{N}^n_{\geq 0}$. The notation M' denotes the transpose of matrix M and $\mathrm{Tr}\{M\}$ is the trace of the square matrix M. A domain Ω is an open subset of $\mathbb{R}^n$ with $\mathcal{C}^1$ boundary $\partial\Omega$. The ring of polynomials on real variables $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ is denoted $\mathcal{R}[x, y]$. The space of k-times continuous differentiable functions defined on Ω is denoted by $\mathcal{C}^k(\Omega)$ and the space of $\mathcal{C}^k(\Omega)$ functions mapping to a set Γ is denoted $\mathcal{C}^k(\Omega; \Gamma)$. For a multivariable function $f(x, y)$, we use the notation $f(x, \cdot) \in \mathcal{C}^k[x]$ to show k-times continuous differentiability of f with respect to variable x. If $p \in \mathcal{C}^1(\Omega)$, then $\partial_x p$ denotes the derivative of p with respect to variable $x \in \Omega$. In addition, we adopt Schwartz's multi-index notation. For $u \in \mathcal{C}^k(\Omega; \mathbb{R}^n)$, $\alpha \in \mathbb{N}^n_{\geq 0}$, define

$$D^\alpha u := (u_1, \partial_x u_1, \ldots, \partial_x^{\alpha_1} u_1, \ldots, u_n, \partial_x u_n, \ldots, \partial_x^{\alpha_n} u_n) .$$

For functions $f \in \mathcal{C}^1(\Omega)$ and $g \in \mathcal{C}^2(\Omega)$, ∇f denotes the gradient vector and $\nabla^2 g$ denotes the Hessian matrix. For a random variable X, $E\{X\}$ denotes its expected value.

II. Preliminaries

Let $T > 0$ and let $(\Gamma, \mathcal{J}, \{\mathcal{J}_s\}_{s\geq 0}, \mathrm{P})$ be a complete and right-continuous filtered probability space, where Γ is a sample space, $\{\mathcal{J}_s\}_{s\geq 0}$ with $\mathcal{J}_s \subseteq \mathcal{J}$ for each s is a filteration of the σ-algebra $\mathcal{J}$, and P is the probability measure function. Consider the following SDE

$$\begin{cases} \mathrm{d}X(s) = f(s, X(s))\mathrm{d}s + g(s, X(s))\mathrm{d}W(s), & s \in [t, T], \\ X(t) = x, \end{cases} \tag{1}$$

where x is a $\mathcal{J}_t$-measurable random variable, $X(s) \in \Omega \subset \mathbb{R}^d$ denotes the states and $W(s) \in \mathbb{R}^m$ is an m-dimensional standard $\{\mathcal{J}_s\}_{s\geq 0}$-Wiener process starting at t (i.e., $W(t) = 0$). Moreover, consider the following backward in time PDE

$$\begin{aligned} -\partial_t u(t, x) &= \frac{1}{2}\mathrm{Tr}\{g(t, x)g'(t, x)\nabla^2 u(t, x)\} \\ &\quad + f'(t, x)\nabla u(t, x) + c(t, x)u(t, x) \\ &\quad + h(t, x), \qquad (t, x) \in [0, T) \times \Omega, \\ u(T, x) &= q(x). \end{aligned} \tag{2}$$

Assumption I: The maps $f : [0, T] \times \Omega \to \mathbb{R}^d$ and $g : [0, T] \times \Omega \to \mathbb{R}^{d\times m}$, $c, h : [0, T] \times \Omega \to \mathbb{R}$, and $q : \Omega \to \mathbb{R}$ are uniformly continuous, c is bounded, and there exists a constant $L > 0$ such that for $\phi = f, g, c, h$,

$$\begin{cases} |\phi(t, x) - \phi(t, \hat{x})| \leq L|x - \hat{x}|, & \forall t \in [0, T], x, \hat{x} \in \Omega \\ |\phi(t, 0)| \leq L, & \forall t \in [0, T]. \end{cases} \tag{3}$$

Remark 1: If Assumption I holds, there exists a unique $\{\mathcal{J}_s\}_{s\geq 0}$-adapted continuous process $X(s)$, $s \geq 0$ that is a unique strong solution to SDE (1) (see Definition 6.2 in [16]).

Define

$$\tau := \inf\{s \in [t, T] \mid X(s) \notin \Omega\} . \tag{4}$$

We recall the following result (Theorem 4.2, p. 374 in [16] and Theorem 7.6, p. 366 in [17]), which is a generalized version of the Feynman-Kac Lemma.

Theorem 1: Consider (2) with boundary conditions $u\,|_{\partial\Omega} = \psi(t, x)$ and SDE (1). Let Assumption I hold. Let

$$\Psi(t, x) = \begin{cases} q(x), & (t, x) \in [0, T] \times \Omega, \\ \psi(t, x), & (t, x) \in [0, T] \times \partial\Omega, \end{cases} \tag{5}$$

be a continuous function on $([0, T] \times \Omega) \cup ([0, T] \times \partial\Omega)$. Then, (2) with boundary conditions $u\,|_{\partial\Omega} = \psi(t, x)$ admits a unique viscosity solution given by

$$\begin{aligned} u(t, x) = E\bigg\{ &\int_t^\tau h(s, X(s))e^{-\int_t^s c(r, X(r))\mathrm{d}r}\mathrm{d}s \\ &+ \Psi(\tau, X(\tau))e^{-\int_t^\tau c(r, X(r))\mathrm{d}r} \mid X(t) = x\bigg\}, \\ &(t, x) \in [0, T] \times \Omega, \end{aligned} \tag{6}$$

where X is the unique strong solution of SDE (1). In addition, if (1) admits a classical solution, then (6) is a classical solution to (2).

Theorem 1 relates the solutions of the SDE (1) to the solution of the backward PDE (2) through functional (6). The functional given in (6) encompasses a rich class of state functionals of SDE (1). For instance, for $c = 0$, $h(s, X(s)) = X^3(s)$ and $q(X(T)) = X^3(T)$,

$$u(0, x) = E\bigg\{ \int_0^T X^3(s)\mathrm{d}s + X^3(T) \mid X(0) = x\bigg\},$$

represents the finite-time cost functional with a terminal value of the third moment of the solutions to SDE (1).

III. Main Results

In this section, we propose a method for bounding state functionals of SDEs based on barrier functionals, which reduces to solving an optimization problem. Moreover, we show that, in the case of polynomial data, the optimization problem can be cast as an SDP.

A. Bounding State Functionals of SDEs using Barrier Functionals

Let $\mathcal{U} \subseteq \mathcal{C}^1[t] \cap \mathcal{C}^2[x]$. We define the *Barrier Functional*

$$B(t, u) = \mathscr{B}(t)u, \tag{7}$$

where $\mathscr{B}(t) : \mathcal{U} \to \mathbb{R}$ is a possibly nonlinear operator.

Finding bounds on the moments of the nonlinear SDE (1) is not straightforward due to the moment closure problem. In addition, when (1) is nonlinear, solving the backward PDE (2) in general is cumbersome. In the following, we propose a method for bounding the solutions of PDE (2) and hence state functionals of (1).

We begin by showing that if the barrier functional (7) satisfies two inequalities along the solutions of the backward system (2), we can ensure that the solutions of (2) avoid an undesirable set.

Theorem 2: Consider the backward PDE (2). Given a set of terminal conditions

$$\mathcal{U}_T = \{u \in \mathcal{U} \mid u(T, x) = q(x)\}, \tag{8}$$

an undesirable set $\mathcal{Y}_u$ such that $\mathcal{U}_T \cap \mathcal{Y}_u = \emptyset$, and $t_0 \in [0, T]$, if there exists a barrier functional $B(t, u(t, x)) \in \mathcal{C}^1[t]$ as in (7) such that the following inequalities hold

$$B(t_0,u(t_0,x)) - B(T,u(T,x)) > 0, \quad \forall u(t_0,x) \in \mathcal{Y}_u,\ \forall u(T,x) \in \mathcal{U}_T, \tag{9a}$$

$$\frac{\mathrm{d}B(t,u(t,x))}{\mathrm{d}t} \geq 0,\ \forall t \in [0,T],\ \forall u \in \mathcal{U}, \tag{9b}$$

along the solutions of (2), then the solutions $u(t,x)$ of (2) satisfy $u(t_0,x) \notin \mathcal{Y}_u$ for $t_0 \in [0,T]$.

Proof: We prove the theorem by contradiction. Assume that at time $t_0 \in [0,T]$, there exists a solution $u(t,x)$ to (2) with $u(T,x) \in \mathcal{U}_T$ that satisfies $u(t_0,x) \in \mathcal{Y}_u$. Then, from (9a), we have

$$B(t_0,u(t_0,x)) - B(T,u(T,x)) > 0. \tag{10}$$

On the other hand, inequality (9b) implies that for all $t \in [0,T]$, it holds that $\frac{\mathrm{d}B(t,u(t,x))}{\mathrm{d}t} \geq 0$. Integrating both sides of the latter inequality, from t to T, yields

$$\int_t^T \frac{\mathrm{d}B(t,u(t,x))}{\mathrm{d}t}\ \mathrm{d}t = B(T,u(T,x)) - B(t,u(t,x)) \geq 0.$$

Since $t, t_0 \in [0,T]$, this contradicts (10). Therefore, there is no solution to (2) that satisfies $u(t_0,x) \in \mathcal{Y}_u$. ■

In the next Corollary, we show how Theorem 2 can be used for bounding state functionals of SDE (1). We use an appropriate definition for the undesirable set $\mathcal{Y}_u$ and a corresponding optimization problem.

Corollary 1: Consider PDE (2) and SDE (1). Let

$$\mathcal{Y}_u = \{u \in \mathcal{U} \mid u(t_0,x) > \gamma\}. \tag{11}$$

If there exists a barrier functional $B(t,u(t,x)) \in \mathcal{C}^1[t]$ such that inequalities (9a) and (9b) are satisfied along the solutions of (2), then we have

$$E\bigg\{ \int_{t_0}^{\tau} h(s,X(s)) e^{-\int_{t_0}^{s} c(r,X(r))\mathrm{d}r} \mathrm{d}s + \Psi(\tau,X(\tau)) e^{-\int_{t_0}^{\tau} c(r,X(r))\mathrm{d}r} \mid X(t_0)=x \bigg\} \leq \gamma. \tag{12}$$

Proof: If there exists a barrier functional $B(t,u(t,x)) \in \mathcal{C}^1[t]$ such that inequalities (9a) and (9b) are satisfied along the solutions of (2), from Theorem (2), we can infer that $u(t_0,x) \notin \mathcal{Y}_u$ with $\mathcal{Y}_u$ as described by (11). Thus, $u(t_0,x) \leq \gamma$. From Theorem 1, we have

$$u(t_0,x) = E\bigg\{ \int_{t_0}^{\tau} h(s,X(s)) e^{-\int_{t_0}^{s} c(r,X(r))\mathrm{d}r} \mathrm{d}s + \Psi(\tau,X(\tau)) e^{-\int_{t_0}^{\tau} c(r,X(r))\mathrm{d}r} \mid X(t)=x \bigg\}, \tag{13}$$

Therefore, $u(t_0,x) \leq \gamma$ implies that (12) holds. ■

In order to find the upper bound on the state functional, i.e., minimum γ in (12), we solve the following optimization problem

$$\min_{B(t,u(t,x))} \gamma \quad \textit{subject to (9a) and (9b).} \tag{14}$$

Remark 2: If the domain Ω is chosen such that for all $s \in [0,T]$, $X(s) \in \Omega$, we can replace τ with T and $\Psi(t,x) = q(x)$ in Theorem 1 and Corollary 1. Then, we have

$$u(t_0,x) = E\bigg\{ \int_{t_0}^{T} h(s,X(s)) e^{-\int_{t_0}^{s} c(r,X(r))\mathrm{d}r} \mathrm{d}s + q(X(T)) e^{-\int_{t_0}^{T} c(r,X(r))\mathrm{d}r} \mid X(t)=x \bigg\}.$$

Remark 3: In [18], an SDP-based method for bounding the moments of continuous-time Markov chains, based on the Foster-Lyapunov stability theory (see condition CD2′ in [19]), is proposed. Continuous-time Markov chains can be represented by the Chemical Master Equations (CMEs) [20], which are a set of ODEs. When the system is sufficiently large, CMEs can be approximated by a set of SDEs called Chemical Langevin Equations (CLEs) [21] to which the method studied in this paper can be applied to find bounds.

B. Computational Method Based on SDPs

This section focuses on the computation of barrier functionals satisfying the conditions of Theorem 2 and Corollary 1 using semi-definite programming under some assumptions. In this respect, we reformulate the problem of checking positivity of time-dependent integral inequalities into solving SDPs.

1) Solving Integral Inequalities in 1D: This subsection presents conditions for the verification of time-dependent integral inequalities, defined in a bounded interval. These conditions are obtained by considering a quadratic-like representation of the integrand and differential relations among the dependent variables. As a result, the positivity of the integral is checked via the positivity of a matrix function, describing the quadratic form in the integrand, over the domain of integration. The conditions and the main steps for their derivation are presented below. These steps are all automated and available as a plug-in to SOSTOOLS [22].

Let $\Omega = (a,b) \subset \mathbb{R}$. Consider the following inequality

$$\mathcal{F} = \int_a^b (D^\alpha u)' F(t,x) (D^\alpha u)\ \mathrm{d}x - \big[(D^{\alpha-1}u(t,b))' F_1(t) (D^{\alpha-1}u(t,b)) - (D^{\alpha-1}u(t,a))' F_0(t) (D^{\alpha-1}u(t,a)) \big] \geq 0. \tag{15}$$

with $F : \mathbb{R}_{\geq 0} \times (a,b) \to \mathbb{S}^{n_\alpha}$, $n_\alpha = \sum_{k=1}^n \alpha_k$, $F_i(t) : \mathbb{R}_{\geq 0} \to \mathbb{S}^{n_{\alpha-1}}$, $n_{\alpha-1} = \sum_{k=1}^n (\alpha_k - 1)$, $i = 0,1$ and the dependent variable u satisfying

$$u \in \mathcal{U}_s(Q) := \left\{ u \mid Q \begin{bmatrix} D^{\alpha-1}u(t,b) \\ D^{\alpha-1}u(t,a) \end{bmatrix} = 0 \right\}, \tag{16}$$

where $Q \in \mathbb{R}^{n\alpha \times 2n\alpha}$. In the following, we show how to account for (16) when solving (15). The lemma below establishes a relation between the values at the boundary $u(t,b)$ and $u(t,a)$ and the integrand and is a straightforward application of the Fundamental Theorem of Calculus. It will be used to introduce extra terms in the integral in (15).

Lemma 1: Consider a matrix function $H(t,x) \in \mathcal{C}^1[x]$, $H : \mathbb{R}_{\geq 0} \times (a,b) \to \mathbb{S}^{n_{\alpha-1}}$. We have

$$\begin{aligned}
&\int_a^b \frac{\mathrm{d}}{\mathrm{d}x}\left[(D^{\alpha-1}u)' H(t,x)(D^{\alpha-1}u)\right]\,\mathrm{d}x \\
&= \int_a^b (D^{\alpha-1}u)' \tfrac{\partial H(t,x)}{\partial x}(D^{\alpha-1}u) \\
&\qquad + 2(D^{\alpha-1}u)' H(t,x)(D^{\alpha}u)\,\mathrm{d}x \\
&= (D^{\alpha-1}u(t,b))' H(t,b)(D^{\alpha-1}u(t,b)) \\
&\qquad - (D^{\alpha-1}u(t,a))' H(t,a)(D^{\alpha-1}u(t,a)).
\end{aligned} \tag{17}$$

In order to write terms in (17) in a compact form, define the matrix function $\bar{H}(x) \in \mathcal{C}^1[x]$, $\bar{H} : \mathbb{R}_{\geq 0} \times (a,b) \to \mathbb{S}^{n_{\alpha}}$ to be the matrix satisfying

$$\begin{aligned}
&(D^{\alpha}u)' \bar{H}(t,x)(D^{\alpha}u) \\
&:= (D^{\alpha-1}u)' \left[\frac{\partial H(t,x)}{\partial x}(D^{\alpha-1}u) + 2H(t,x)(D^{\alpha}u)\right].
\end{aligned} \tag{18}$$

At this stage, we are ready to present conditions to verify inequality (15) for u satisfying (16). Let $T \geq 0$.

Proposition 1: Consider integral inequality (15). If there exist a matrix polynomial $H(t,x)$ and a matrix polynomial $\bar{H}(t,x)$ as defined in (18) such that

$$F(t,x) + \bar{H}(t,x) \geq 0, \ \forall t \in [0,T], \ x \in (a,b), \tag{19}$$

and

$$\begin{aligned}
&(D^{\alpha-1}u(t,b))' \left(H(t,b) + F_1(t)\right)(D^{\alpha-1}u(t,b)) \\
&- (D^{\alpha-1}u(t,a))' \left(H(t,a) + F_0(t)\right)(D^{\alpha-1}u(t,a)) \leq 0, \\
&\qquad\qquad \forall u \in \mathcal{U}_s(Q)
\end{aligned} \tag{20}$$

then $\mathcal{F} \geq 0$ for all $u \in \mathcal{U}_s(Q)$ and $t \in [0,T]$.

Proof: The proof follows the same lines as the proof of Theorem 1 in [10] and is omitted here due to lack of space. ■

2) Barrier Functionals as Integral Functionals: Note that the method described in the previous subsection requires the problem data to be polynomial. Furthermore, in Theorem 2 and Corollary 1 the only assumption on the barrier functional was $B(t,u(t,x)) \in \mathcal{C}^1[t]$, however, in order to provide a computational formulation based on SDPs, we consider the following structure for the barrier functionals

$$B(t,u(t,x)) = \int_\Omega b(t,x,u,\partial_x u, \partial_x^2 u)\,\mathrm{d}x, \tag{21}$$

with $b \in \mathcal{R}[t,x,u,\partial_x u,\partial_x^2 u]$, that is, $\mathscr{B}(t) : u \mapsto \int_\Omega b(t,x,u,\partial_x u,\partial_x^2 u)\,\mathrm{d}x$ as in (7).

Then, in order to solve the associated integral inequalities with SDPs, we assume that $f,g \in \mathcal{R}[s,X]$ as in (1), $c,h \in \mathcal{R}[t,x]$ as in (2) and $q \in \mathcal{R}[x]$ as in (2).

We consider the following undesirable set

$$\begin{aligned}
\mathcal{Y}_u = \Big\{ &u \in \mathcal{U} \mid \int_\Omega p_i(t,x,u,\partial_x u,\partial_x^2 u)\,\mathrm{d}x \leq 0, \\
&\int_\Omega \tilde{p}_j(t,x,u,\partial_x u,\partial_x^2 u)\,\mathrm{d}x = 0, \ (i,j) \in I_u \times J_u \Big\},
\end{aligned} \tag{22}$$

where $\{p_i : \mathcal{C}^1\left(\mathbb{R}_{\geq 0} \times \Omega \times \mathbb{R}^{3n}; \mathbb{R}\right)\}_{i \in I_u}$ and $\{\tilde{p}_j : \mathcal{C}^1\left(\mathbb{R}_{\geq 0} \times \Omega \times \mathbb{R}^{3n}; \mathbb{R}\right)\}_{j \in J_u}$, $I_u, J_u \subset \mathbb{N}_{\geq 0}$ are index sets.

For the set of terminal or initial conditions in the form of (8), we just need to substitute $u(T,x) = q(x)$ in the barrier functional, i.e.,

$$B(T,u(T,x)) = \int_\Omega b\left(T,x,q(x),\partial_x q(x),\partial_x^2 q(x)\right)\,\mathrm{d}x.$$

Under the above assumptions, the conditions of Theorem 2, and Corollary 1 become integral inequalities with polynomial integrands, which are required to hold in sets defined by integral inequality constraints. For example, substituting (21) in (9a) yields

$$\begin{aligned}
&\int_\Omega b\left(t_0,x,D^2u(t_0,x)\right)\,\mathrm{d}x \\
&\qquad - \int_\Omega b\left(T,x,D^2u(T,x)\right)\,\mathrm{d}x > 0, \\
&\qquad\qquad \forall u(t_0,x) \in \mathcal{Y}_u,
\end{aligned} \tag{23}$$

The following Theorem is instrumental in solving constrained inequalities similar to (23).

Theorem 3 (S-Procedure for Integral Inequalities): Consider the following integral inequality

$$\int_a^b f(t,x,D^{\psi_1}u)\,\mathrm{d}x \geq 0, \tag{24}$$

subject to

$$\begin{aligned}
u \in \mathcal{U}' = \Big\{ u \mid &\int_a^b g_1(t,x,D^{\psi_2}u)\,\mathrm{d}x \leq 0, \\
&\int_a^b g_2(t,x,D^{\psi_2}u)\,\mathrm{d}x = 0 \Big\},
\end{aligned} \tag{25}$$

where $f \in \mathcal{R}[t,x,D^{\psi_1}u]$, and $g_1, g_2 \in \mathcal{R}[t,x,D^{\psi_2}u]$. Let

$$v_i(t,x) = \int_a^x g_i(t,x,D^{\psi_2}u)\,\mathrm{d}x, \ i = 1,2, \tag{26}$$

satisfying

$$\begin{cases}
v_1(t,a) = 0, \\
v_1(t,b) \leq 0, \\
v_2(t,a) = 0, \\
v_2(t,b) = 0.
\end{cases} \tag{27}$$

If there exist $F(t,x) \in \mathcal{R}[t,x]$, and $N(t,x) \in \mathcal{R}[t,x]$ such that

$$\begin{aligned}
\int_a^b \Big(&f(t,x,D^{\psi_1}u) \\
&+ F(t,x)\left(\partial_x v_1(t,x) - g_1(t,x,D^{\psi_2}u)\right) \\
&+ N(t,x)\left(\partial_x v_2(t,x) - g_2(t,x,D^{\psi_2}u)\right)\Big)\,\mathrm{d}x \geq 0
\end{aligned} \tag{28}$$

then (24) holds subject to (25).

After applying Theorem 3, inequality (28) should be checked via the result in Proposition 1.

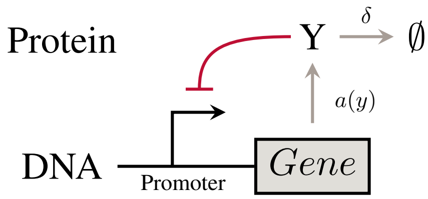

Fig. 1: Diagram of negative autoregulation, modelled in (29). The red barred line represents the repressive behaviour of the protein Y on the transcription of the gene.

TABLE I: Parameters to simulate negative autoregulation.

Param.	Val.	Param.	Val.
α	20nMs^{-1}	δ	0.025min^{-1}
K	200nM^{-2}	n	2

IV. Case Study: Negative Autoregulation

In the following, a model of negative autoregulation is developed using standard principles. Then, using the method developed in Section III, we bound a functional of the second moment.

A. The Model

This section will begin with the construction of a standard single state model of negative autoregulation [23]. The mechanisms included are: 1) the expression of a gene producing a protein, 2) the dilution and degradation of protein, and 3) the interaction between protein and DNA that accounts for the negative autoregulation.

Using standard techniques [23], the following ODE model of negative autoregulation can be constructed:

$$\frac{\mathrm{d}y}{\mathrm{d}t} = a(y) - \delta y, \tag{29}$$

where y is the concentration of expressed protein, $a(y)$ is the expression rate, which is dependent on y. Also, δ is dilution and degradation rate of the protein. It is through the expression rate $a(y)$ that the feedback occurs. The interaction between gene and protein and its effect on transcription is modelled using the classic Hill Function $a(y) = \alpha/(1 + Ky^n)$, where α is the maximal expression rate, K accounts for the affinity between the gene and the protein and n is the Hill Coefficient. This system is presented in Figure 1.

Typical parameters used to simulate the system are presented in Table I and we use these values in the following. More information on modelling gene regulatory networks is available in [23]. System (29) has a steady state at $y^* = 1.5864\text{nM}$, which was obtained in MATLAB by setting the left hand side of (29) to zero.

In order to account for the biochemical noise affecting the system, we consider a stochastic version of the system presented in (29). We follow the methodology given in [24] and, instead of introducing additive noise, we consider multiplicative noise originating from intrinsic biological fluctuations.

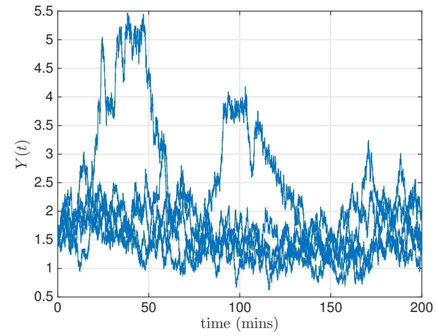

Fig. 2: Five trajectories of SDE (30) starting at $Y = y^*$.

The SDE model is described as follows

$$\mathrm{d}Y = \left(\frac{\alpha'_y}{1+KY^n} - \delta_y Y\right)\mathrm{d}s + \sqrt{\frac{\alpha'_y}{1+KY^n}}\,\mathrm{d}W_1 - \sqrt{\delta_y Y}\,\mathrm{d}W_2,\ \ s \in [t,T], \tag{30}$$

where W_1 and W_2 are two independent Wiener processes. It can be observed that, although $y^* = 1.5864\text{nM}$ is a stationary solution to the deterministic system (29), system (30) is subject to stochastic fluctuations around this stationary solution. This phenomenon tallies with experimental data [14], [15]. Fig. 2 shows five different solutions of SDE (30) starting at $Y = y^*$.

B. Bounding the Second Moment

We are interested in finding bounds on the second moment of Y, as it allows us to compare computational estimates of the noise with experimental data. To this end, we consider (2) with $c = 0$, $h = \frac{1}{2T}y^2$ and $q = \frac{y^2}{2}$. Then the corresponding backward PDE is given by

$$\begin{aligned} -\partial_t u(t,y) =& \left(\frac{\alpha'_y}{1+Ky^n} - \delta_y y\right)\partial_y^2 u(t,y) \\ &+ \left(\frac{\alpha'_y}{1+Ky^n} - \delta_y y\right)\partial_y u(t,y) + \frac{y^2}{2T}, \\ u(T,y) =& \frac{y^2}{2}, \qquad t \in [0,T],\ y \in \Omega. \end{aligned} \tag{31}$$

We assume Ω is chosen such that for all $s \in [0,T]$, $Y(s) \in \Omega$ (see Remark 2). In this case, based on 5000 Monte Carlo simulations of (30), $\Omega = [0, 10\text{nM}]$ satisfies this requirement for $T = 300\text{mins}$. From Theorem 1, we have

$$u(t,y) = \frac{1}{2}E\left\{\frac{1}{T}\int_t^T Y^2(s)\ \mathrm{d}s + Y^2(T) \mid Y(t) = y\right\}. \tag{32}$$

The boundary conditions are set to $u(t,0) = u(t,10) = 0$. Next, we find bounds on the following functional

$$u(0,y^*) = \frac{1}{2}E\left\{\frac{1}{T}\int_0^T Y^2(s)\ \mathrm{d}s + Y^2(T) \mid Y(0) = y^*\right\}, \tag{33}$$

i.e., the average plus the terminal cost of the second moment around the stationary solution. In order to find bounds

TABLE II: Obtained bounds on functional (33).

$deg(b(t,y))$	2	4	6	8
bound (nM^2)	8.7401	6.3642	4.4562	3.3791

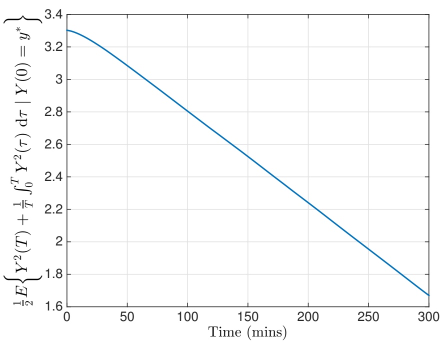

Fig. 3: The evolution of the cost functional (32) with $T = 300$ obtained from 5000 Monte Carlo simulations.

on the above functional, we consider the following barrier functional

$$B\left(t, u(t,y)\right) = \int_{\Omega} (1 + Ky^n) b(t,y) u^2(t,y) \; \mathrm{d}y. \tag{34}$$

Notice with this choice of barrier functional both inequalities (9a) and (9b) are integral inequalities with polynomial integrands. Based on Theorem 2 and solving optimisation problem (14), we obtain the bounds given in Table II, where $deg(b(t,y))$ is the degree of the certificate $b(t,y)$ in t and y. For degree 8, we found a bound of $u(0,y^*) \leq 3.3791$.

This is consistent with the result obtained from 5000 Monte Carlo simulations as illustrated in Fig. 3, where the value for $u(0,y^*)$ from Monte Carlo simulations is 3.3417.

Employing the bound on the second moment of 3.3791nM^2 and the mean steady state value of the system of $y^* = 1.5864$nM, the coefficient of variance was calculated to be $v_c = 0.5854$. Looking at [15], page 5, Fig. 4D 'TG-nf', which shows coefficient of variance data from experiments on a system equivalent to the one studied here, the values are in close agreement.

V. Conclusions

We proposed a method for bounding state functionals of a class of nonlinear stochastic systems based on barrier functionals. The method can be cast as solving SDPs in the case of polynomial data. The method was applied to a stochastic model of negative autoregulation. It was shown that the resulting bound on the second moment yielded a coefficient of variance that closely mirrored experimental data. The Gillespie algorithm [1], which is commonly used to model such processes can provide estimates of moments, but these are never bounded with certificates. Further application of such techniques to more complete and complex models of biological systems of more than one state would be a powerful tool in the study of these systems. It would allow for more accurate prediction of stochastic behaviour and yield further insight into the relative roles of the various modelling techniques employed in fields such as systems and synthetic biology.

References

[1] D. T. Gillespie, "A general method for numerically simulating the stochastic time evolution of coupled chemical reactions," *Journal of Computational Physics*, no. 4, pp. 403–434, 1976.

[2] K. Burrage, P. Burrage, and T. Mitsui, "Numerical solutions of stochastic differential equations: implementation and stability issues," *Journal of Computational and Applied Mathematics*, no. 1&2, pp. 171–182, 2000.

[3] R. Khasminskii, *Stochastic Stability of Differential Equations*, ser. Stoch. Model. Appl. Probab. New York, US: Springer, 2012, no. 66.

[4] R. C. Merton, "Theory of rational option pricing," *The Bell Journal of Economics and Management Science*, no. 1, pp. 141–183, 1973.

[5] M. Soltani, C. Vargas-Garcia, and A. Singh, "Conditional moment closure schemes for studying stochastic dynamics of genetic circuits," *Biomedical Circuits and Systems, IEEE Transactions on*, no. 4, pp. 518–526, Aug 2015.

[6] C. Gillespie, "Moment-closure approximations for mass-action models," *Systems Biology, IET*, no. 1, pp. 52–58, January 2009.

[7] A. Singh and J. Hespanha, "Approximate moment dynamics for chemically reacting systems," *Automatic Control, IEEE Transactions on*, no. 2, pp. 414–418, Feb 2011.

[8] M. Ahmadi, G. Valmorbida, and A. Papachristodoulou, "Barrier functionals for output functional estimation of PDEs," in *American Control Conference (ACC), 2015*, July 2015, pp. 2594–2599.

[9] S. Prajna, "Barrier certificates for nonlinear model validation," *Automatica*, no. 1, pp. 117 – 126, 2006.

[10] G. Valmorbida, M. Ahmadi, and A. Papachristodoulou, "Stability analysis for a class of partial differential equations via semi-definite programming," *IEEE Transactions on Automatic Control*, 2016, to Appear, DOI:10.1109/TAC.2015.2479135.

[11] M. Ahmadi, G. Valmorbida, and A. Papachristodoulou, "Dissipation inequalities for the analysis of a class of PDEs," *Automatica*, pp. 163 – 171, 2016.

[12] T. Afroz and C. L. Beisel, "Understanding and exploiting feedback in synthetic biology," *Chemical Engineering Science*, pp. 1–12, nov 2013.

[13] A. W. K. Harris, J. A. Dolan, C. L. Kelly, J. Anderson, and A. Papachristodoulou, "Designing Genetic Feedback Controllers," *IEEE Transactions on Biomedical Circuits and Systems*, no. 4, pp. 475–484, 2015.

[14] A. Becskei and L. Serrano, "Engineering stability in gene networks by autoregulation." *Nature*, no. June, pp. 590–593, 2000.

[15] Y. Dublanche, K. Michalodimitrakis, N. Kummerer, M. Foglierini, and L. Serrano, "Noise in transcription negative feedback loops: simulation and experimental analysis," *Mol.Syst.Biol.*, no. 1744-4292 (Electronic), p. 41, 2006.

[16] J. Yong and X. Y. Zhou, *Stochastic Controls: Hamiltonian Systems and HJB Equations*, ser. Applications of Mathematics. Springer, 1999, no. 43.

[17] I. Karatzas and S. E. Shreve, *Brownian Motion and Stochastic Calculus*, 2nd ed., ser. Graduate Texts in Mathematics. Springer, 1991.

[18] A. Milias-Argeitis and M. Khammash, "Optimization-based Lyapunov function construction for continuous-time Markov chains with affine transition rates," in *Decision and Control (CDC), 2014 IEEE 53rd Annual Conference on*, Dec 2014, pp. 4617–4622.

[19] S. P. Meyn and R. L. Tweedie, "Stability of Markovian Processes III: Foster-Lyapunov Criteria for Continuous-Time Processes," *Advances in Applied Probability*, no. 3, 1993.

[20] N. V. Kampen, *Stochastic Processes in Physics and Chemistry*, third edition ed. Amsterdam: Elsevier, 2007.

[21] D. Gillespie, "The chemical Langevin equation," *Journal of Chemical Physics*, no. 1, pp. 297–306, 2000.

[22] G. Valmorbida and A. Papachristodoulou, "Introducing INTSOSTOOLS: A SOSTOOLS plug-in for integral inequalities," in *Control Conference (ECC), 2015 European*, 2015, pp. 1231–1236.

[23] U. Alon, *An introduction to systems biology: design principles of biological circuits*. Boca Raton, Florida: Chapman & Hall, 2006.

[24] H. El-Samad, S. Prajna, A. Papachristodoulou, J. Doyle, and M. Khammash, "Advanced methods and algorithms for biological networks analysis," *Proceedings of the IEEE*, no. 4, pp. 832–853, April 2006.