Submitted, 2012 American Control Conference (ACC)
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Delay-Based Approximations of Biological Systems for Analysis and Design

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Abstract— **In this paper we explore the use of time-delayed differential equation as a means of obtaining a simplified description of very high order dynamics.This paper finds results for a particular type of system, a single-input single-output (SISO) linear system with a nonlinear feedback. We begin with a high dimensional system in state space and reduce the dimension by finding a delay based approximation which could be a smaller set of integro-differential equations or DDEs. We argue that approximations of high order linear subsystems whose distribution functions have relatively smaller variance such as delta functions, give a conservative approximation of a system's stable parameter space. Through examples inspired by biology, we show how these approximations can be used to verify stability. We analyze the system's stability and robustness dependence on statistical properties, mainly relative variance and expectation for a symmetric distribution function.**

I. Introduction

Distributed delays have been used to model biological systems, an example being the use of integro-differential equations to model single population dynamics in which the delays model the time required for maturity [1]. The use of integro-differential equations allows one to incorporate complex dynamics without introducing new states into the system. For detailed genetic regulatory networks (GRNs), there can be distributed delays in the variation of the finite time required for transcription and translation. GRN models are often highly dimensional because of the detail required to express complex dynamics in non-delayed differential equations. The dimension of these systems can be reduced by delay-based approximations if we can correctly identify the location and magnitude of effective delays. This paper illustrates an example of how delay based approximation can be used for analysis and system design.

In biological systems there are often a series of kinetic reactions, removing these by finding their equivalent convolution model reduces the number of states. Although the use of integro-differential equations reduces the number of states they are not useful for analysis if the impulse function is complicated. We can find an approximation of the impulse function, for which the approximation has a relatively simple laplace transform allowing us to apply analysis tools from control theory. Although finite delays correspond to infinite dimensional state space systems, for the purpose of this paper they will be not be considered complex. There are tools for analysis of DDEs when working in the Laplace domain. If the number of states are reduced sufficiently we can easily implement current tools in control theory for analysis.

This work was not supported by any organization

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This may be useful in biology where there are a large number of states and parameters. General analysis of system dynamics is difficult. With the emergence of synthetic biology one would like to predict behavior of GRNs by properly encapsulating the essence of the dynamics of a system with minimal parameters and states. Some may be tempted to ignore dynamics on fast time scales such as those associated with transcription and translation but these seemingly negligible dynamics are critical for the robust stability of many biological systems. Later we will show the stabilizing effects of such distributed delays which serve as controllers to create robustly stable systems.

Prior work has considered the use of delay-based modeling of physical and biological systems. In [2] an oscillating GRN is modeled with four DDEs which is unusual but advantageous, considering it took 25 first order differential equations in [3] to model a similar system. Unfortunately, there are not many formal methods to find delay-based models of systems and it is usually done ad hoc. However, in [4] a formal method is presented. A high order controller is approximated by simple finite delays and integrators by fitting either a finite sum of Heaviside step functions or piecewise linear curves to the corresponding impulse function. The dimension of the system is reduced as the number of required integrals in the approximation is less than the original dimension of the system.

The contributions of this paper are mainly analysis as to the effects of delays in robustness and stability and a potential method of using delay-based model reduction to approximate the stable parameter space of the original system. These results only extend to the system analyzed in the paper. Stability analysis for other distributed delay systems have been investigated in [5] and [6]. The results in this paper coincide with results from other work. For example, the work in [7] suggests that delays may lead to robust oscillations. In [8] the authors analyze three systems in which distributed delays are likely to be present. Different types of distributions are used for the three systems but each is characterized by a mean delay and standard deviation. It is shown through simulation that as the standard deviation is increased the complexity of the steady state solution is reduced or even abolished. This paper shows similar results through a more formal analysis using control theory as oppose to only looking at simulations.

II. Justification of Delay Based Approximations

The problem at hand is how to find the best approximating distributed delay model. In [4], the author describes several methods of doing exactly this.

Let $g(\tau)$ be the impulse function corresponding to a high order controller. The input into the plant is the convolution of the impulse function of the controller and the output of the system;

$$u(t) = \int_{-\infty}^{\infty} g(\tau)y(t-\tau)d\tau. \tag{1}$$

We can assume without loss of generality that $g(\tau) = 0$ for $\tau < \tau_{min}$ for some $\tau_{min} \geq 0$ and in an approximation give an upper bound to the integral τ_{max}. This bounded integral can be expressed by its Riemann integral

$$u(t) = \lim_{n\to\infty} \frac{\tau_{max} - \tau_{min}}{n} \sum_{i=1}^{n} g(\tau_i)y(t-\tau_i) \tag{2}$$

assuming $g(\tau)$ is continuous. In this form one can see that the input can be viewed as the sum of delayed output values whose weight is determined by the magnitude of the impulse function evaluated at the respective delay. The impulse function $g(t)$ can be understood as a non-normalized delay distribution function in this sense. We will exploit this concept further throughout the paper.

III. Problem Description

In this paper we will analyze the Goodwin oscillator [9] of order $p+2$,

$$\begin{aligned} \dot{x}_0 &= \frac{1}{1+x_{p+1}^2} - \alpha x_0 \\ \dot{x}_j &= -a(x_j - x_{j-1}) \quad \text{for} \quad j = 1, ..., p+1 \end{aligned} \tag{3}$$

This system may interpret a GRN, where protein x_0 is self-regulated through the promotion of a series of protein expressions for which the end product inhibits its own production. Suppose we can control the degradation rate, α, of x_0 and we want to know for what values of α, the system will have a stable equilibrium point. If the system happens to be high dimensional, such analysis can be difficult. Although, the problem can be solved numerically it is advantageous to have an analytical solution.

The purpose of this paper is to show that we can find a conservative approximation to the stable parameter space of the system by looking at a finite delay based approximation. First, we will show that the approximation is conservative. Second, we demonstrate the use of the method with an example. Last,we will discuss the implications stemming from the results of the paper.

IV. Distributed Delay Form

Not coincidentally, system (3) has an exact integro-differential form [10]. Taking the integro-differential equation

$$\frac{dx}{dt} = \frac{1}{1+\tilde{x}^2} - \alpha x, \tag{4}$$

with

$$\tilde{x} = \int_0^{\infty} h(\tau)x(t-\tau)d\tau, \tag{5}$$

we can extend the integral to

$$\tilde{x} = \int_{-\infty}^{\infty} \hat{h}(\tau)x(t-\tau)d\tau \tag{6}$$

by defining

$$\hat{h}(\tau) = \begin{cases} h(\tau) & \text{if } \tau \geq 0 \\ 0 & \text{otherwise} \end{cases}.$$

This gives us a convolution model. The Laplace transform of two convolved functions is the product of the Laplace transform of the individual functions,

$$\mathcal{L}(\tilde{x}) = \mathcal{L}(\hat{h})X(s). \tag{7}$$

Let the distribution function have the form

$$h(\tau) = \frac{a^{p+1}\tau^p}{p!}e^{-a\tau} \tag{8}$$

and take the Laplace transform in the time domain. This gives

$$\mathcal{L}(\hat{h}) = \mathcal{L}(h) = \frac{a^{p+1}}{(s+a)^{p+1}}.$$

The dimension of the equivalent non-delayed system is $p+2$. One can imagine $p+1$ equivalent transfer functions in series representing the dynamics of $p+1$ states, whose last state is in feedback to the first state x. This is in fact the transfer function from x_1 to x_{p+1} in system (3). We will refer to (8) as the delay distribution function.

V. Stability Analysis through Statistical Properties of the Delay Distribution Function

Now we will analyze the system behavior and its dependence on the statistical properties of the delay distribution function. We will show for the example shown above that stability in the delay based approximation guarantees stability in the original system, thus we have a conservative approximation.

For a general system of the form

$$\begin{aligned} \dot{x} &= h(x, \tilde{x}) \\ \tilde{x} &= \int_{-\infty}^{\infty} f(\tau)x(t-\tau)d\tau \end{aligned} \tag{9}$$

we can do a bifurcation analysis on the nonlinear integro-differential equation [5]. For system (3) the linearized system is

$$\frac{dx'}{dt} = -\alpha x' + \beta\tilde{x}' \tag{10}$$

where

$$x' = x - x*$$

and

$$\tilde{x}' = \int_{-\infty}^{\infty} f(\tau)x'(t-\tau)d\tau.$$

The subscript * refers to the equilibrium point of the system. Here f is the impulse function corresponding to the transfer

function from x_1 to x_{p+1}. We assume $f(\tau) = 0$ for $\tau < \tau_{min}$, for some $\tau_{min} \geq 0$. The parameters α and β are defined as follows

$$\alpha = \left.\frac{\partial h}{\partial x_0}\right|_{x_0=x_{0*}} \quad \text{and} \quad \beta = -\left.\frac{\partial h}{\partial x_{p+1}}\right|_{x_{p+1}=x_{p+1*}}.$$

Now we take the Laplace transform of the linearized system, which gives

$$sX'(s) = -\alpha X'(s) - \beta \hat{f}(s) X'(s).$$

$\hat{f}(s)$ is the laplace transform of the impulse function $f(\tau)$. The resulting characteristic equation is

$$s + \alpha + \beta \hat{f}(s) = 0.$$

For equation (3)

$$\hat{f}(s) = \frac{a^{p+1}}{(s+a)^{p+1}}$$

and so the form of the delay distribution function is given by equation (8).

Now we find the relative variance of the distribution function as defined in [6]

$$R = \frac{V}{E^2},$$

where E is the expected value defined by the first moment of the distribution function $f(\tau)$,

$$E = \int_0^\infty \tau f(\tau) d\tau$$

and V is the variance defined by the second moment of the distribution function around E,

$$V = \int_0^\infty (\tau - E)^2 f(\tau) d\tau.$$

The resulting relative variance and expectation are

$$R = \frac{1}{p+1}$$

and

$$E = \frac{p+1}{a}.$$

As the variance approaches zero the distribution becomes more concentrated at the expected value E.

We can show that distribution function will approach a dirac delta function centered at E in the limit. Taking the limit as R approaches zero is equivalent to taking the limit as $p+1$ approaches infinity. We will use the latter limit for the proof. We take the limit of the delay distribution function in the Laplacian domain,

$$\lim_{(p+1)\to\infty} \hat{f}(s) = \frac{a^{p+1}}{(s+a)^{p+1}}.$$

After rearranging the terms and making substitutions, taking the limit in the Laplacian domain gives

$$\lim_{(p+1)\to\infty} \frac{1}{(\frac{sE}{(p+1)} + 1)^{(p+1)}} = \frac{1}{e^{sE}} = e^{-sE}.$$

The Laplace inverse of the limit gives

$$\mathcal{L}^{-1}(e^{-sE}) = \delta(t - E).$$

Also, note that

$$\int_0^\infty f(\tau) d\tau = 1,$$

therefore, the distribution function will approach a delta function centered at E as R approaches zero.

The characteristic equation of the linearized system (10) is

$$s + \alpha + \beta \left(\frac{a}{s+a}\right)^{p+1} = 0$$

and can be re-written in terms of R and E as

$$s + \alpha + \beta \left(\frac{1}{sRE+1}\right)^{\frac{1}{R}} = 0, \quad \text{where} \quad \frac{1}{R} \in \mathbb{Z}^+. \quad (11)$$

We can determine the stability of the system for a given R and E using the Routh-Hurwitz criterion. Stability is determined by the poles of the system, which are given by the zeros of the characteristic equation. The zeros of the function lie in the complex plane and if the real part of the solutions lie in the left half of the complex plane, the linearized system has an exponentially asymptotically stable equilibrium point [11]. If a polynomial satisfies the Routh-Hurwitz criterion then we can be assured that all roots of the polynomial lie on the left hand side of the complex plane.

The system is a linearized approximation so β is a function of the equilibrium point of the system. With the given distribution function, changing R while keeping E constant does not change the equilibrium point of the system. We can analyze the effects of changing R without having to consider changes in the linearized system. We would like to know the effects of changing R on the stability and robustness of the system. We will do this using tools well known in controls.

In controls, gain and phase margins are tools used to analyze the robustness of a linear system. If we put the characteristic equation in the form

$$G(s) = -1,$$

we can determine the gain and phase margin through the Nyquist stability criterion. If the original system is stable then any encirclement of -1 in the Nyquist plot of $G(s)$ will result in instability. The gain margin is the largest interval $[\underline{\gamma}, \overline{\gamma}]$ such that for $\forall k \in [\underline{\gamma}, \overline{\gamma}]$

$$kG(s)$$

still satisfies the Nyquist stability criterion. The lower (upper) bound on the gain margin can be understood as the distance between -1 and the closest intersection of the Nyquist plot and the $-\Re$ axis to the left (right) side of the critical point -1. If there does not exist an intersection to the left (right) the corresponding bound is $-\infty$ (∞). The phase margin is the minimum angle the Nyquist plot would have to rotate to intersect -1. If no such intersection ever occurs the system has an infinite phase margin.

For the nonlinear system the gain margin loses meaning since any deviation from gain $k = 1$ will change the equilibrium point of the system, but it can still help us understand the effects of changing the relative variance of the distribution function. We apply the method above with

$$G(s) = \frac{s+\alpha}{\beta \hat{f}(s)}$$

to find the bounds on the gain margin. The upper bound is infinity and the lower bound is given in Figure 1 as a function of R. Figure 1 shows that as R increases the gain margin increases. The Nyquist plot moves away from the critical point as the relative variance increases. Whether instability is achieved as $R \to 0$ is dependent on E. Now we will

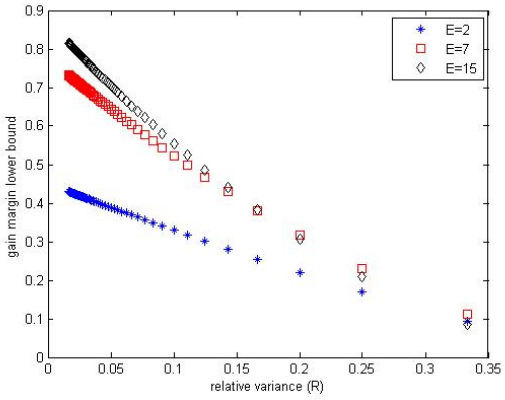

Fig. 1. Lower bound,$\underline{\gamma}$, on gain margin as a function of R for $\alpha = .5885$.

define a new gain margin that carries more meaning to the nonlinear system. We define a new system as

$$\begin{aligned} \dot{x}_0 &= \frac{1}{1+(kx_{p+1})^2} - \alpha x_0 \\ \dot{x}_j &= -a(x_j - x_{j-1}) \quad \text{for} \quad j = 1, ..., p+1\,. \end{aligned} \tag{12}$$

Now β is a function of the gain k. We find $k > 0$ closest to -1 on either side such that the linearized system becomes unstable. If $k < 1$ ($k > 1$) then $\underline{\gamma} = k$ ($\overline{\gamma} = k$). The gain margin is the largest interval including 1 such that the linearized system is stable for all values of $k \in [\underline{\gamma}, \overline{\gamma}]$.

Using this robustness measure, Figure 2 shows that the system's gain margin increases as R increases. This shows that the robustness of the system to variations in the concentration of the regulating protein. The gain margins for both plots were found numerically.

VI. Stable Parameter Space Dependence on Relative Variance

Using a delay based approximation we can find the range of parameters that guarantee stability for the system above. By stability we mean the system has an asymptotically stable equilibrium point. We do this by bifurcation analysis where the parameter α, as previously defined, is treated as the bifurcation parameter. Bifurcation occurs when the roots of

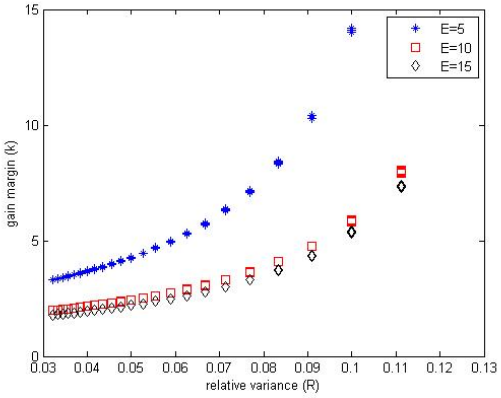

Fig. 2. Lower bound, $\underline{\gamma}$, on newly defined gain margin as a function of R for $\alpha = .5885$.

this characteristic equation cross the imaginary axis. We substitute $s = iw$ to find the boundary between unstable and stable region of the system.

Figure 3 shows the critical values of α as a function of the relative variance while maintaining E and x^* constant. We can see that as R decreases the range of values of α, for

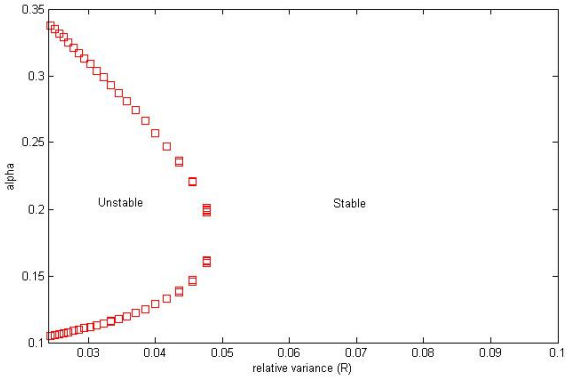

Fig. 3. Stability curve for alpha as a function of the relative variance R with E=20.

which the system becomes unstable, increases.

In Figure 3 the system is stable for all values of α up until a certain critical value of R. The decrease in relative variance can de-stabilize an otherwise stable system. A further decrease in R increases the region of instability. This suggest that analyzing a delay based approximation to this system with a relative variance smaller than that of the original system will give a conservative approximation of the stable region. We have yet to show this to be true in general.

VII. Example: Approximations with Finite Delay

As an example, take an oscillator that may arise from a system such as that in Figure 4. Such a series of kinetic reactions are common in GRNs. Suppose each of the reac-

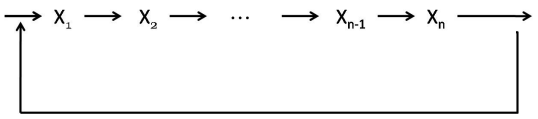

Fig. 4. A periodic metabolic system with a single feedback loop.

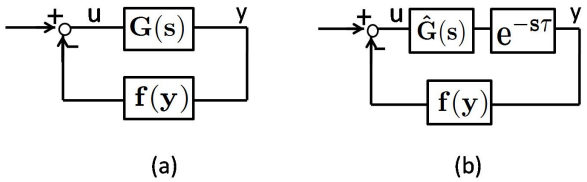

Fig. 5. (a) The Goodwin Oscillator. (b) A reduced order approximation of the Goodwin Oscillator.

tions are the the same and the feedback is nonlinear. In this example we take the dimension of the system $n = 80$. The dynamics of the system in Laplacian domain are

$$x_n(s) = \frac{1}{s}\left(\frac{.8}{s+.8}\right)^n \mathcal{L}\left[f(x_n(t))\right] \tag{13}$$

where $\mathcal{L}[f(x_n(t))]$ denotes the Laplace transform of the nonlinearity in the time domain. The nonlinear portion is a saturated amplifier.

$$f(x_n) = \begin{cases} 1 & \text{if } x_n \geq 1 \\ x_n & \text{if } -1 < x_n < 1 \\ -1 & \text{if } x_n \leq -1 \end{cases}$$

We want to find gain, k, and delay, τ, such that the following system

$$x_n(s) = \left(\frac{.8}{s+.8}\right)^N \frac{k}{s} e^{-s\tau_k} \mathcal{L}\left[f(x_n)\right] \quad \text{for} \quad N < n \tag{14}$$

provides a good approximation to system (13). The two different models are depicted in Figure 5 with

$$G(s) = \frac{1}{s}\left(\frac{.8}{s+.8}\right)^n$$

and

$$\hat{G}(s) = \frac{k}{s}\left(\frac{.8}{s+.8}\right)^N.$$

Figure 5 shows the oscillator and the approximating system to its right where the order of $\hat{G}(s)$ is much less than the order of $G(s)$.

We will solve this problem two different ways. One way using the describing function (DF) method which is useful in predicting frequency and amplitude of limit cycles in oscillatory systems. For the second method we will use information from the impulse function corresponding to the dynamics we wish to approximate with distributed delays.

For a single-input single output (SISO) LTI system with nonlinear feedback one can apply the describing function method to derive constraints for an appropriate approximating function. This method ensures the approximating system will have a limit cycle of the same amplitude and frequency of the original system. The DF method is derived from the method of harmonic balance and approximates the periodic solution with the first harmonic under the assumption that the LTI portion acts as a low pass filter and damps out higher harmonics. See [12] for a more detailed description on harmonic balancing and the DF method.

In the second method we use the impulse function. As shown previously the normalized impulse function for the omitted dynamics is

$$h(\tau) = \frac{a^{p+1}\tau^p}{p!} e^{-a\tau}.$$

The delay value to be used in the approximation is the expected value of the distribution function.

$$\tau = \frac{p+1}{a},$$

where p and a uniquely defines the delay distribution function 8 with $p + 1 = n - N$ and $a = .8$.

Tables I and II compare results obtained from the DF method and the second method. The results are comparable. Figure 6 shows the output of the approximating systems and the original system.

TABLE I

APPROXIMATING DELAY VALUES (S)

N	DF Method	Expected Delay Method
40	50.1	50.0
30	62.6	62.5
20	75.1	75.0
10	87.6	88.7

TABLE II

PERCENT ERROR IN APPROXIMATIONS

N	Error in Amp. for DF Method	Error in Amp. for Expected Delay Method
40	2.9	2.9
30	3.9	3.8
20	5.0	4.9
10	6.4	7.7

The advantage of using the second method is that it does not require the system to be oscillatory nor does it require knowledge of the original system's behavior. The describing function method was successfully used because the system was known to have a periodic solution. In addition, the frequency and the amplitude of the periodic solution was also known.

The distribution function corresponding to a finite delay is the delta function. In this example, the high order dynamics were approximated by a finite delay which is a very crude approximation. We would like to know how the accuracy of approximation changes if we instead replace the dynamics with a distributed delay.

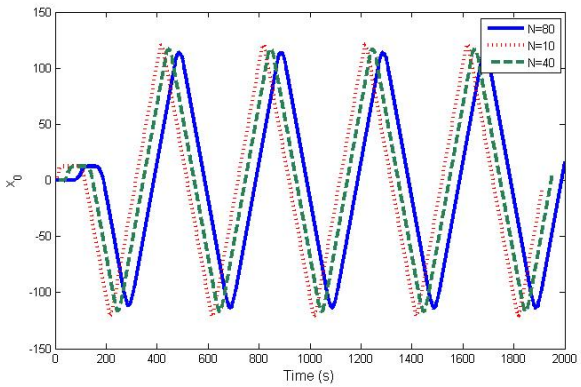

Fig. 6. Original system and approximating systems, where N is the dimension of the approximation.

VIII. Summary

We showed evidence to support the idea that the stability region of the finite delay based approximation for the given example is a conservative approximation for the stability region of the original system. In addition, we have also given evidence to support that implementing finite delays in a system may result in robust oscillatory behavior. Note that upon bifurcation this system has a stable limit cycle. Evidence suggests that as the delayed portion of the system changes from single finite delay to a distribution of delays the system becomes more stable. A finite delayed system appears to be the most unstable of all the distributed delay systems for the given example.

The qualitative information obtained in the previous section can be used for the design of synthetic networks. If robust oscillations are the desired behavior for a system of this structure, then we know we can achieve that with a low relative variance. If we want a stable non-oscillatory system then we should aim to have a larger relative variance.

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