Fundamental Limitations between Noise and Back-action in Bio-molecular Networks

by

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Submitted to the Department of Electrical Engineering and Computer Science in partial fulfillment of the requirements for the degree of Master of Science in Electrical Engineering and Computer Science at the MASSACHUSETTS INSTITUTE OF TECHNOLOGY

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Abstract

In an interconnection of two components in a bio-molecular network, noise in the downstream component can be reduced by increasing the magnitude of the downstream signal. However, this method of reducing noise increases the back-effect to the upstream system, called ‘retroactivity’, thereby increasing the perturbation to the upstream system. In this thesis, we seek to quantify the total error in the system caused by the perturbations due to retroactivity and noise, and to analyze the trade-off between the two errors. We model the system as a set of non-linear chemical Langevin equations and quantify the trade-off for two different approximations of this non-linear model. First we consider a system linearized about a fixed point and quantify the trade-off using transfer functions. Next we use a linear approximation of the propensity functions in the Langevin equation and quantify the error by calculating upper bounds using contraction theory for deterministic and stochastic systems. Future research directions in improving the upper bounds are discussed.

Thesis Supervisor: Domitilla Del Vecchio
Title: Associate Professor
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Average of 400 simulations.
Chapter 1

Introduction

The activity inside a cell can be thought of as a network of information flow between a set of nodes, with the nodes representing different molecules such as proteins, DNA, metabolites etc.[1] Viewing the cellular functions as a network has facilitated the comparison of biological systems with engineering. Hartwell et al.[9] identified the notion of modularity within networks as a key feature linking biology and engineering. R. Milo et al.[16] defined network motifs, a recurring pattern of interconnections, to be the simple building blocks of complex networks. While these studies have been carried out in cell and systems biology to understand existing network pathways in biology, comparison of biology to engineering systems further promote the emerging field, synthetic biology. Being an interdisciplinary study, synthetic biology employs a bottom-up approach to design and build well-characterized biological parts that can be interconnected to form networks that perform complex tasks. Engineering new biological devices has a large scope of potential applications including bio-sensing, disease fighting, production of pharmaceuticals, biofuels etc. Several biological parts have already been produced such as switches [21], oscillators [5, 6], and logic circuits [24].

However, a major problem that has been identified in synthetic biology is the inability of the modules to maintain their pre-characterized behavior upon interconnection. This is due to the back-actions between modules that appear at interconnections, similar to loading effects that takes place in electrical circuits. Del Vecchio
et al. [22] quantified this effect and termed it 'retroactivity', which has been shown to increase with high demand from the load. The effect of retroactivity has also been shown experimentally, in particular for a gene transcriptional module in [10] and a signal transduction network in [12].

Another property to be considered in designing biological networks is the stochastic nature of the cellular environment. Noise is inherently present in gene networks due to randomness in chemical reactions and low copy numbers of molecules [17, 4]. It has been shown both theoretically and experimentally that increasing the species concentration can reduce that intrinsic noise in the species [4, 19, 3]. In particular, Swain et al. [19] shows that in gene expression, increasing the gene copy number reduces the amount of intrinsic noise in the protein.

As it has been shown that the retroactivity increases with high gene copy numbers, the trade-off between noise and retroactivity has to be analyzed when interconnecting components. Studies have been carried out to analyze the impact of attenuating retroactivity on the noise in interconnected components [11]. However a trade-off between suppressing noise using the gene copy numbers leading to increased retroactivity has not been formally quantified.

In this work, we consider an interconnection of two transcriptional components in biology and quantify the above trade-off for two different system models. This thesis is organized as follows.

In Chapter 2 the mathematical model for the system is derived and the mathematical problem formulation is presented. The system is modeled as a set of non-linear chemical Langevin equations [8] and model order reduction is also performed using singular perturbation tools enabling the analysis to be carried out using a reduced order model.

Chapter 3 gives an account of the quantification of the trade-off for a system linearized about a fixed point. Tools from linear systems theory such as Laplace transforms are used to carry out this analysis. This section illustrates quantitatively that the percentage error due to retroactivity and the error due to noise vary inversely as the gene copy number is changed, highlighting the need for an optimized design in
interconnecting two components.

Chapter 4 extends the analysis to a system where the non-linear system has been approximated to a system that has linear propensity functions. The main tools used for analysis in this section will be the non-linear contraction theory and linear filtering theory. Non-linear contraction theory, first defined for deterministic systems [15], provides a set of tools to analyze the incremental stability properties of non-linear systems. Recently these results have been extended for the analysis of singularly perturbed systems [23]. Furthermore, contraction theory principles have also been extended to stochastic systems [18] to investigate the incremental stability properties of Itô stochastic dynamical systems. Describing the system as a set of ordinary differential equations allow the application of deterministic contraction theory to provide an upper bound for the deterministic error in the system. The chemical Langevin equation [8] can be used to derive the Itô stochastic differential equations, which can then be used with the stochastic contraction theory to provide a bound for the stochastic error in the system. The error due to the stochasticity in the upstream system will be upper bounded using theories in linear filtering. Minkowski Inequality, a generalized triangular rule giving the bound for the sum of the errors, will be used to assess the total error in the measurement. The error will be analyzed relative to the nominal protein concentration to minimize the relative perturbation in the measurement.

Chapter 5 discusses future work to be carried out. In particular, we discuss the approach for quantifying this trade-off for the original non-linear system introduced in Chapter 2. The main tools used in this approach will be the deterministic and stochastic contraction theory applied to a 2-dimensional system which causes some limitations in the design. We also discuss the limitations in the model order reduction technique that we have used and propose a singular perturbation approximation for stochastic differential equations that will provide a better approximated reduced model.
Chapter 2

System Model and Problem Statement

This section first provides a description of the system considered and then the mathematical model is derived using chemical Langevin equations [8]. Using a two-time scale property in bio-molecular reactions, a model order reduction is performed employing singular perturbation tools [14]. Finally the mathematical problem statement is given specifying the objectives of the work.

2.1 System Model

Measuring the amount of protein concentration through a reporter gene is an example of interconnecting two biological components as shown in Figure 2-1. The protein to be measured, produced by the ‘upstream component’, acts as an activator for the ‘downstream component’ which produces the reporter protein, that has easily measurable characteristics such as fluorescence.
The chemical reactions for the system in Figure 2-1 are as follows.

\[ X + p_0 \xrightarrow{\alpha_1} C_0 \]  
\[ C_0 \xrightarrow{\beta_1} Y + C_0 \]  
\[ Y \xrightarrow{\delta_1} \phi \]

Reaction (2.1) gives the binding/unbinding reaction between the input protein X and the promoter \( p_0 \) where \( \alpha_1 \) and \( \alpha_2 \) are association and dissociation rates, respectively. Reaction (2.2) describes the production of protein Y, lumping both transcription and translation where \( \beta_1 \) is the total production rate. Reaction (2.3) describes the decay of protein Y where \( \delta_1 \) is the decay rate accounting for degradation and dilution.

A similar set of reactions can be written for the downstream component where,

\[ Y + p \xrightarrow{\alpha_3} C \]  
\[ C \xrightarrow{\beta_2} G + C \]  
\[ G \xrightarrow{\delta_2} \phi \]

Reaction (2.4) gives the binding and unbinding reaction with \( \alpha_3 \) and \( \alpha_4 \) being the association and dissociation rates, respectively. The reaction (2.5) describes the transcription and translation of G with \( \beta_2 \) as the total production rate. Reaction (2.6)
gives the decay of $G$ with a decay rate of $\delta_2$.

Let the total concentrations of promoters in the upstream and downstream components be $p_{t0}$ and $p_t$, respectively. Since the total concentration of promoter is conserved, we can write the conservation laws,

$$p_{t0} = p_0 + C_0$$
$$p_t = p + C$$

The chemical Langevin Equations for the above system is given below where $\Gamma_i$ for $i = \{1, 8\}$ are independent gaussian white noise processes:

$$\frac{dC_0}{dt} = \alpha_1 X(p_{t0} - C_0) - \alpha_2 C_0 + \sqrt{\alpha_1 X(p_{t0} - C_0)} \Gamma_1 - \sqrt{\alpha_2 C_0} \Gamma_2 \tag{2.7}$$
$$\frac{dY}{dt} = \beta_1 C_0 - \delta_1 Y + \sqrt{\beta_1 C_0} \Gamma_3 - \sqrt{\delta_1 Y} \Gamma_4 \left[-\alpha_3 Y(p_t - C) + \alpha_4 C \right]$$
$$\frac{dC}{dt} = \alpha_3 Y(p_t - C) - \alpha_4 C + \sqrt{\alpha_3 Y(p_t - C)} \Gamma_5 - \sqrt{\alpha_4 C} \Gamma_6 \tag{2.8}$$
$$\frac{dG}{dt} = \beta_2 C - \delta_2 G + \sqrt{\beta_2 C} \Gamma_7 - \sqrt{\delta_2 G} \Gamma_8 \tag{2.9}$$

The terms multiplied by $\Gamma_i$ represent the intrinsic noise in the system and the boxed term represent the retroactivity in the system. We define this system (2.7) - (2.10) as the ‘perturbed system’ due to the presence of the perturbations given by the noise and retroactivity. We also define a ‘nominal system’ that gives the ideal system behavior in the absence of these perturbations. Figure 2-2 illustrates the nominal and perturbed behavior of signal $G$ for a low amount of downstream component. It can be seen that the noise in the signal is very high but the perturbed signal closely follows the nominal signal. Figure 2-3 illustrates how increasing the downstream components ($p_t$) reduces the noise in the signal but the signal is highly attenuated. This attenuation is due to the retroactivity and increasing the number of downstream components leads to an
increased error due to retroactivity. Therefore the total error in the system is given by both noise and retroactivity where the quantities vary inversely with $p_t$. In this work we want to quantify the limitation in changing the parameter $p_t$ to minimize the total error in the system.

Figure 2-2: Low amount of downstream components

Figure 2-3: High amount of downstream components
2.2 Model Reduction

Consider a system of the form,

\[
\dot{x} = f(x, t, z, \epsilon) \quad (2.11)
\]
\[
\epsilon \dot{z} = g(x, t, z, \epsilon) \quad (2.12)
\]

For this form of systems, where \(x\) is defined as a slow variable and \(z\) is defined as a fast variable, Tikhonov's theorem[14] provides a model reduction technique based on the small parameter \(\epsilon\).

Separation of timescales is a common feature in bio-molecular systems and we use this property to separate the slow and fast variables in the system in (2.7) - (2.10) and perform model order reduction using the Tikhonov's theorem.

Binding/unbinding reactions are much faster than protein production/decay and therefore we can write \(\alpha_2 \gg \delta_1\). Let \(k_{d1} = \frac{\alpha_2}{\alpha_1}\), \(k_{d2} = \frac{\alpha_4}{\alpha_3}\) be the dissociation constants.

To take the system into standard singular perturbation form given in (2.11) - (2.12), write \(\epsilon = \frac{\delta_1}{\alpha_2}\) where \(\epsilon \ll 1\) and \(\alpha_4 = a\alpha_2\). Then \(\alpha_2 = \frac{\delta_1}{\epsilon}, \alpha_1 = \frac{\delta_1}{\epsilon k_{d1}}, \alpha_3 = \frac{\delta_1}{\epsilon k_{d2}}, \alpha_4 = \frac{\delta_1}{\epsilon}\).

With the definitions the above system becomes

\[
\frac{dC_0}{dt} = \frac{\delta_1}{\epsilon k_{d1}} X(p_0 - C_0) - \frac{\delta_1}{\epsilon} C_0 + \sqrt{\frac{\delta_1}{\epsilon k_{d1}}} X(p_0 - C_0) \Gamma_1 - \sqrt{\frac{\delta_1}{\epsilon} C_0 \Gamma_2}
\]
\[
\frac{dY}{dt} = \beta_1 C_0 - \delta_1 Y + \sqrt{\beta_1 C_0 \Gamma_3} - \sqrt{\delta_1 Y \Gamma_4} - \frac{a\delta_1}{\epsilon k_{d2}} Y(p_t - C) - \frac{a\delta_1}{\epsilon} C
\]
\[
+ \sqrt{\frac{a\delta_1}{\epsilon k_{d2}}} Y(p_t - C) \Gamma_5 - \sqrt{\frac{a\delta_1}{\epsilon} C \Gamma_6}
\]
\[
\frac{dC}{dt} = \frac{a\delta_1}{\epsilon k_{d2}} Y(p_t - C) - \frac{a\delta_1}{\epsilon} C + \sqrt{\frac{a\delta_1}{\epsilon k_{d2}}} Y(p_t - C) \Gamma_5 - \sqrt{\frac{a\delta_1}{\epsilon} C \Gamma_6}
\]
\[
\frac{dG}{dt} = \beta_2 C - \delta_2 G + \sqrt{\beta_2 C \Gamma_7} - \sqrt{\delta_2 G \Gamma_8}
\]

Although the singular perturbation parameter \(\epsilon\) appears in the equations, the system is still not in the standard singular perturbation form. Therefore we introduce the
change of variable $Y_T = Y + C$, which takes the system to the standard singular perturbation form where $Y_T$ and $G$ are the slow variables of the system.

\[
\begin{align*}
\epsilon \frac{dC_0}{dt} &= \frac{\delta_1}{k_{d1}} X (p_{t0} - C_0) - \delta_1 C_0 + \sqrt{\frac{\epsilon \delta_1}{k_{d1}}} X (p_{t0} - C_0) \Gamma_1 - \sqrt{\epsilon \delta_1 C_0} \Gamma_2 \\
\frac{dY_T}{dt} &= \beta_1 C_0 - \delta_1 (Y_T - C) + \sqrt{\beta_1 C_0} \Gamma_3 - \sqrt{\delta_1 (Y_T - C)} \Gamma_4 \\
\epsilon \frac{dC}{dt} &= \frac{a \delta_1}{k_{d2}} (Y_T - C)(p_t - C) - a \delta_1 C + \sqrt{\frac{a \epsilon \delta_1}{k_{d2}}} (Y_T - C)(p_t - C) \Gamma_5 - \sqrt{a \epsilon \delta_1 C} \Gamma_6 \\
\frac{dG}{dt} &= \beta_2 C - \delta_2 G + \sqrt{\beta_2 C} \Gamma_7 - \sqrt{\delta_2 G} \Gamma_8
\end{align*}
\]

Then, we apply Theorem 11.1 in [14] where we obtain the slow manifolds $C_0$ and $\tilde{C}$ after a fast transient by setting $\epsilon = 0$, with $|C_0(t, \epsilon) - \tilde{C}_0(t)| = O(\epsilon)$ and $|C(t, \epsilon) - \tilde{C}(t)| = O(\epsilon)$:

\[
\begin{align*}
\tilde{C}_0 &= \frac{p_{t0} X}{X + k_{d1}} \\
\tilde{C} &= \frac{p_t \tilde{Y}}{\tilde{Y} + k_{d2}}
\end{align*}
\]

Then, we define $\tilde{Y}$ the value of $Y$ when $\epsilon = 0$, where $|Y(t, \epsilon) - \tilde{Y}(t)| = O(\epsilon)$,

\[
\begin{align*}
\frac{d\tilde{Y}}{dt} &= \frac{dY_T}{dt} - \frac{d\tilde{C}}{dt} \\
\frac{d\tilde{Y}}{dt} &= \frac{dY_T}{dt} - \frac{d\tilde{C}}{dt} \\
\frac{d\tilde{Y}}{dt} &= \frac{dY_T}{dt} - \frac{d\tilde{C}}{dt} \\
\frac{d\tilde{Y}}{dt} &= \frac{dY_T}{dt} - \frac{d\tilde{C}}{dt} \\
\end{align*}
\]
Let \( \frac{d\bar{C}}{d\bar{Y}} = R_1(\bar{Y}) = \frac{p_t k_{d2}}{(Y + k_{d2})^2} \). Then the dynamics of \( Y \) can be approximated as (omitting the bar to simplify notation and taking \( Y \approx \bar{Y} \)),

\[
\frac{dY}{dt} = \left( \frac{\beta_1 p_{t0} X}{X + k_{d1}} - \delta_1 Y + \sqrt{\frac{\beta_1 p_{t0} X}{X + k_{d1}}} \Gamma_3 - \sqrt{\delta_1 Y \Gamma_4} \right) \frac{1}{1 + R_1(Y)}
\]

Therefore, the dynamics of \( Y \) can be obtained as,

\[
\frac{dY}{dt} = (1 - R(Y)) \left( \frac{\beta_1 p_{t0} X}{X + k_{d1}} - \delta_1 Y + \sqrt{\frac{\beta_1 p_{t0} X}{X + k_{d1}}} \Gamma_3 - \sqrt{\delta_1 Y \Gamma_4} \right) \text{ with } R(Y) = \frac{1}{1 + \frac{(Y + k_{d2})^2}{p_t k_{d2}}}
\]

Similarly, the reduced order dynamics for \( G \) are given by

\[
\frac{dG}{dt} = \frac{\beta_2 p_t Y}{Y + k_{d2}} - \delta_2 G + \sqrt{\frac{\beta_2 p_t Y}{Y + k_{d2}}} \Gamma_7 - \sqrt{\delta_2 G \Gamma_8}
\]

As \( \Gamma_i \) are independent identical Gaussian white noise processes, we can further simplify the system by writing \( \sigma_1 \Gamma_3 - \sigma_2 \Gamma_4 = \sqrt{\sigma_1^2 + \sigma_2^2} \Gamma_Y \) and \( \sigma_1 \Gamma_3 - \sigma_2 \Gamma_4 = \sqrt{\sigma_3^2 + \sigma_4^2} \Gamma_G \), where \( \Gamma_Y \) and \( \Gamma_G \) are also independent identical Gaussian white noises. Therefore,

\[
\frac{dY}{dt} = (1 - R(Y)) \left( \frac{\beta_1 p_{t0} X}{X + k_{d1}} - \delta_1 Y + \sqrt{\frac{\beta_1 p_{t0} X}{X + k_{d1}}} \Gamma_Y \right) \quad (2.13)
\]

\[
\frac{dG}{dt} = \frac{\beta_2 p_t Y}{Y + k_{d2}} - \delta_2 G + \sqrt{\frac{\beta_2 p_t Y}{Y + k_{d2}}} \Gamma_G \quad (2.14)
\]

We call the system (2.13) - (2.14) as the reduced perturbed system and we also introduce a reduced nominal system given by

\[
\frac{dY_N}{dt} = \frac{\beta_1 p_{t0} X}{X + k_{d1}} - \delta_1 Y_N \quad (2.15)
\]

\[
\frac{dG_N}{dt} = \frac{\beta_2 p_t Y_N}{Y_N + k_{d2}} - \delta_2 G_N \quad (2.16)
\]
Using these systems we want to quantify the total error $|G - G_N|$ in the output signal $G$ caused by both retroactivity and noise. In particular, using $p_t$ as a design parameter, we seek to quantify the trends of the errors due to retroactivity and noise.
Chapter 3

Linearized System

3.1 Introduction

In this section, as an initial step in analyzing the trade-off, we consider a system linearized about a fixed point. As we consider inputs with small amplitudes a linear system about a fixed point gives a good approximation of the non-linear system in a small region of interest. We then employ transfer functions to quantify the trade-off.

3.2 Linear System

Considering the input signal of small amplitude $\tilde{X}$ the system of equations (2.13) and (2.14) are linearized around the constant inputs $X = X_e, \Gamma_Y = \Gamma_G = 0$ and the corresponding equilibrium points $Y_e = \frac{\beta_1 X_e P_0}{\delta_1 (X_e + k_{d1})}, G_e = \frac{\beta_2 Y_e P_2}{\delta_2 (Y_e + k_{d2})}$ to give,

\[
\frac{d\tilde{Y}}{dt} = (1 - R(Y_e)) \left( \frac{\beta_1 k_{d1} P_0 \tilde{X}}{(X_e + k_{d1})^2} - \delta_1 \tilde{Y} + \sqrt{\frac{2\beta_1 P_0 X_e}{X_e + k_{d1}}} \tilde{\Gamma}_Y \right)
\]  

\[
R(Y_e) = \frac{1}{1 + \frac{(Y_e + k_{d2})^2}{p_t k_{d2}}}
\]  

\[
\frac{d\tilde{G}}{dt} = \frac{\beta_2 k_{d2} P_t \tilde{Y}}{(Y_e + k_{d2})^2} - \delta_2 \tilde{G} + \sqrt{\frac{2\beta_2 P_t Y_e}{Y_e + k_{d2}}} \tilde{\Gamma}_G
\]  

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where $\tilde{Y}$, $\tilde{G}$, $\tilde{\Gamma}_Y$, $\tilde{\Gamma}_G$ are small perturbation about the equilibrium point equal to $\tilde{Y} = Y - Y_e$, $\tilde{G} = G - G_e$, $\tilde{\Gamma}_Y = \Gamma_Y$ and $\tilde{\Gamma}_G = \Gamma_G$.

### 3.3 Transfer Functions

Figure 3-1 gives a block diagram representation of the system.

![Block diagram of the system](image)

Figure 3-1: Block diagram of the system

The upstream component in this system has the inputs $\tilde{X}$ and $\tilde{\Gamma}_Y$ and the downstream component has the inputs $\tilde{Y}$, $\tilde{\Gamma}_G$. As the system is linear, to analyze the effect of retroactivity and noise on the output $\tilde{G}$, we can take the Laplace transforms of equations (3.1) and (3.2) which leads to

\[
\begin{align*}
    s\tilde{Y}(s) &= (1 - R(Y_e)) \left( \frac{\beta_1 k_{d1} p_{00} \tilde{X}(s)}{(X_e + k_{d1})^2} - \delta_1 \tilde{Y}(s) + \sqrt{\frac{2\beta_1 p_{00} X_e}{X_e + k_{d1}}} \tilde{\Gamma}_Y(s) \right) \\
    \tilde{Y}(s) &= (1 - R(Y_e)) \left( \frac{\beta_1 k_{d1} p_{00} \tilde{X}(s)}{(X_e + k_{d1})^2} + \frac{\sqrt{2\beta_1 p_{00} X_e}}{s + (1 - R(Y_e))\delta_1} \tilde{\Gamma}_Y(s) \right) \\
    s\tilde{G}(s) &= \frac{\beta_2 k_{d2} p_{22} \tilde{Y}(s)}{(Y_e + k_{d2})^2} - \delta_2 \tilde{G}(s) + \sqrt{\frac{2\beta_2 p_{22} Y_e}{Y_e + k_{d2}}} \tilde{\Gamma}_G(s) \\
    \tilde{G}(s) &= \frac{\beta_2 k_{d2} p_{22} \tilde{Y}(s)}{s + \delta_2} + \sqrt{\frac{2\beta_2 p_{22} Y_e}{s + \delta_2}} \tilde{\Gamma}_G(s)
\end{align*}
\]

(3.3)

Substituting (3.3) in (3.4) we obtain
\[
\tilde{G}(s) = \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(Y_e + k_{d2})^2} \left( \frac{\beta_1 k_{d1} p_{d0} \tilde{X}(s)}{(X_e + k_{d1})^2} + \frac{\sqrt{2 \beta_1 p_{d0} X_e}}{X_e + k_{d1}} \tilde{Y}_{G}(s) \right) \bigg{)} \bigg{)} + \frac{\sqrt{2 \beta_1 p_{d0} X_e}}{Y_e + k_{d2}} \tilde{Y}_{G}(s) \\
\end{align*}
\[
\tilde{G}(s) = \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} \left( \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} + \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} \right) \tilde{G}(s)
\]
\[
\tilde{G}(s) = \frac{\beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0} \tilde{X}(s)}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} \left( R(Y_e) \beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0} \tilde{X}(s) \right) \bigg{)} \bigg{)} + \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} + \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} \tilde{G}(s)
\]

Let \( \tilde{G}(s) = T_N(s) \tilde{X}(s) + T_R(s) \tilde{Y}(s) + T_S(s) \tilde{G}(s) \) where

\[
T_N(s) = \frac{\beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0}}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} 
\]

is the nominal transfer function from \( \tilde{X}(s) \) to \( \tilde{G}(s) \).

\[
T_R(s) = \frac{-R(Y_e) \beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0}}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} 
\]

in which \( \tilde{Y}_{Y} \) and \( \tilde{Y}_{G} \) are independent white noise processes. Therefore their Laplace transforms are equivalent and can be denoted by \( \tilde{Y}(s) \). As a consequence, we have

\[
\tilde{G}(s) = \frac{\beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0} (1 - R(Y_e)) \tilde{X}(s)}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} + \left( \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} + \frac{\beta_2 k_{d2} p_{e} (1 - R(Y_e))}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2} \right) \tilde{G}(s)
\]

Let \( \tilde{G}(s) = T_N(s) \tilde{X}(s) + T_R(s) \tilde{Y}(s) + T_S(s) \tilde{G}(s) \) where

\[
T_N(s) = \frac{\beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0}}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} 
\]

is the nominal transfer function from \( \tilde{X}(s) \) to \( \tilde{G}(s) \).

\[
T_R(s) = \frac{-R(Y_e) \beta_2 k_{d2} p_{e} \beta_1 k_{d1} p_{d0}}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_{d2})^2(X_e + k_{d1})^2} 
\]
is the transfer function from $\tilde{X}(s)$ to $\tilde{G}(s)$ due to retroactivity, and

$$T_S(s) = \frac{\beta_2 k_d p_2 p_1 (1 - R(Y_e)) \sqrt{\frac{2\beta_1 p_1 p_0 X_e}{X_e + k_d}}}{(s + \delta_2)(s + (1 - R(Y_e))\delta_1)(Y_e + k_d) + \sqrt{\frac{2\beta_2 p_1 Y_e}{Y_e + k_d}} + \frac{s + \delta_2}{s + \delta_2}}$$ (3.7)

is the transfer function from $\tilde{\Gamma}(s)$ to $\tilde{G}(s)$.

We then analyze the frequency response corresponding to $T_N$, $T_R$ and $T_S$. Then $|T_N(jw)\tilde{X}(jw)|$ is the magnitude of the output signal $G$ in the nominal system. $|T_R(jw)\tilde{X}(jw)|$ is the contribution of retroactivity to the magnitude of the perturbed system, and $|T_S(jw)\tilde{\Gamma}(jw)|$ is the contribution of noise to the magnitude of the perturbed system.

### 3.4 Performance Criteria

We want to analyze the error in the system caused by the perturbations due to retroactivity and noise, and therefore as a measure of the error, we look at the relative change in the magnitude of the signal due to each of the errors, with respect to its nominal value. For retroactivity, this can be quantified by $\frac{|T_R(jw)|^2}{|T_N(jw)|^2}$ which is the ratio of the transfer function due to retroactivity to the nominal transfer function. Let this be $E_1$ the error due to retroactivity. Then,

$$E_1^2 = \frac{|T_R(jw)|^2}{|T_N(jw)|^2}$$

Using the equations (3.5) and (3.6) we obtain

$$E_1^2 = \left( \frac{-R(Y_e)\beta_2 k_d p_2 p_1 k_d p_0}{(jw+\delta_2)(jw+(1-R(Y_e))\delta_1)(Y_e+k_d)^2(X_e+k_d)^2} \frac{-R(Y_e)\beta_2 k_d p_2 p_1 k_d p_0}{(jw+\delta_2)(jw+(1-R(Y_e))\delta_1)(Y_e+k_d)^2(X_e+k_d)^2} \right)$$

$$\frac{\beta_2 k_d p_2 p_1 k_d p_0}{(jw+\delta_2)(jw+(1-R(Y_e))\delta_1)(Y_e+k_d)^2(X_e+k_d)^2} \frac{\beta_2 k_d p_2 p_1 k_d p_0}{(jw+\delta_2)(jw+(1-R(Y_e))\delta_1)(Y_e+k_d)^2(X_e+k_d)^2}$$

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This expression simplifies to \( E_1^2 = R(Y_e)^2 \). Therefore,

\[
E_1 = R(Y_e) = \frac{1}{1 + \frac{(Y_e + k_{d2})^2}{p_t k_{d2}}}
\]  

(3.8)

\[
E_2 = \frac{|T_S(j\omega)|^2}{|T_N(j\omega)|^2}
\]

(3.9)

It can be seen that the error \( E_1 \) increases with \( p_t \) with a maximum value of 1, at which point the percentage change in the signal is 100\% and therefore the signal is completely attenuated (as illustrated in Figure 3-2).

![Percentage error due to retroactivity](image)

Figure 3-2: Percentage error due to retroactivity. The parameter values are \( X_e = 5, Y_e = 9.901, \beta_1 = \beta_2 = 0.1, \delta_1 = \delta_2 = 0.1, p_{t0} = 100, k_{d1} = k_{d2} = 50 \).

The error due to noise can be quantified by \( \frac{|T_S(j\omega)|}{|T_N(j\omega)|} \) which is the ratio of the transfer function from noise, to the nominal transfer function. Let this be \( E_2 \). Then,

\[
E_2^2 = \frac{|T_S(j\omega)|^2}{|T_N(j\omega)|^2}
\]
Using (3.5) and (3.7) we obtain

\[
E_2^2 = \left[ \frac{\beta_3 k_{d2} p_t (1-R(Y_e))}{(jw+\delta_2)(jw+(1-R(Y_e))\delta_1)(Y_e+k_{d2})^2} \right]^2 + \left[ \frac{\beta_2 k_{d2} p_t (1-R(Y_e))}{Y_e+k_{d2}} \right]^2 + \left[ \frac{\beta_2 k_{d2} p_t (1-R(Y_e))}{(-jw+\delta_2)(-jw+(1-R(Y_e))\delta_1)(Y_e+k_{d2})^2} \right]^2
\]

\[
E_2^2 = \frac{2(1-R)^2 X_e (X_e + k_{d1})^3 (Y_e + k_{d2})}{p_t \beta_2 \beta_1 p_t k_{d1}^2} + \frac{4((1-R)^2) \delta_1 (Y_e + k_{d2})^{3/2}}{(p_t \beta_2)^{3/2} (\beta_1 p_t o k_{d1})^{3/2} k_{d2}^2} \sqrt{X_e Y_e}
\]

\[
+ \frac{2Y_c (w^2 + ((1-R)\delta_1)^2) (Y_e + k_{d2})^3 (X_e + k_{d1})^4}{p_t (\beta_1 k_{d1} p_t o)^2 \beta_2 k_{d2}^2}
\]

(3.10)

It can be seen from expression (3.10) that \( E_2 = O(\frac{(1-R)^2}{p_t} + \frac{(1-R)^2}{p_t} + \frac{(1-R)^2}{p_t} \). \( (1-R) \) decreases as \( p_t \) increases and therefore it can be seen that in contrast to \( E_1 \), the error \( E_2 \) decreases with \( p_t \), with its minimum value tending to zero given at very high values of \( p_t \) as shown in Figure 3-3.
Furthermore, from (3.8) we obtain the expression,

\[ \frac{1}{p_t} = \frac{k_{d2}(1 - E_1)}{E_1(Y_e + k_{d2})^2} \]  \hfill (3.11)

Using (3.10) and (3.11) we obtain

\[ E_2^2 = \frac{2(1 - E_1)^3 X_e(X_e + k_{d1})^3}{E_1 \beta_2 \beta_1 p_{t0} k_{d1}^2} + \frac{4(1 - E_1)^{1/2} \delta_1(Y_e + k_{d2})^{3/2}(X_e + k_{d1})^{1/2} \sqrt{X_e Y_e}}{E_1 \beta_2^2 (\beta_1 p_{t0} k_{d2})^{3/2} k_{d1}^2} \]

\[ + \frac{2(1 - E_1) Y_e w^2(Y_e + k_{d2})(X_e + k_{d1})^4}{E_1(\beta_1 k_{d1} p_{t0})^{3/2} \beta_2 k_{d2}} + \frac{2(1 - E_1)^3 Y_e \delta_1^{3/2}(Y_e + k_{d2})(X_e + k_{d1})^4}{E_1(\beta_1 k_{d1} p_{t0})^{3/2} \beta_2 k_{d2}} \]  \hfill (3.12)

\[ = \frac{2(1 - E_1)^3 c_1}{E_1} + \frac{4(1 - E_1)^{1/2} c_2}{E_1^{1/2}} + \frac{2(1 - E_1) c_3}{E_1} + \frac{2(1 - E_1)^3 c_4}{E_1} \]  \hfill (3.13)

where \( c_1 = \frac{X_e(X_e + k_{d1})^3}{\beta_2 \beta_1 p_{t0} k_{d1}^2} \), \( c_2 = \frac{\delta_1(Y_e + k_{d2})^{3/2}(X_e + k_{d1})^{1/2} \sqrt{X_e Y_e}}{\beta_2^2 (\beta_1 p_{t0} k_{d2})^{3/2} k_{d1}^2} \), \( c_3 = \frac{Y_e w^2(Y_e + k_{d2})(X_e + k_{d1})^4}{(\beta_1 k_{d1} p_{t0})^{3/2} \beta_2 k_{d2}} \) and \( c_4 = \frac{Y_e \delta_1(Y_e + k_{d2})(X_e + k_{d1})^4}{(\beta_1 k_{d1} p_{t0})^{3/2} \beta_2 k_{d2}} \).

The expression in (3.13) quantifies the trade-off between attenuating retroactivity and noise amplification in bio-molecular circuits. The limiting values of this expression are,

\[ \lim_{E_1 \to 0} E_2 = \infty \]

\[ \lim_{E_2 \to 0} E_1 = 1 \]

This can be seen clearly in Figure 3-4 where reducing the error due to retroactivity causes an increase in the error due to noise. As the error due to noise is minimized to zero the error due to retroactivity is at its maximum at 100% and as the error due to retroactivity is minimized the error due to noise increases tends to its limiting value. It can be seen that as the frequency increases above the cutoff frequency of
the nominal system, there is a higher increase in noise.

![Trade-off between retroactivity and noise](image)

Figure 3-4: Trade-off between $E_1$ and $E_2$ as a percentage, for different frequency values. The parameter values are $X_e = 5, Y_e = 9.901, \beta_1 = \beta_2 = 0.1, \delta_1 = \delta_2 = 0.1, p_{t0} = 100, k_{d1} = k_{d2} = 50$.

### 3.5 Discussion

In this section we mathematically quantified the magnitude errors in the system due to retroactivity and noise, which clearly illustrates a trade-off between the two quantities. Therefore it is important to consider this trade-off when interconnecting components to minimize the total error in the output signal. Next, we consider another approximation to the non-linear system where we upper bound the magnitude of the errors which allows us to find the optimum $p_t$ concentration that can be used when designing interconnections.
Chapter 4

System with Linearized Propensity Functions

4.1 Introduction

In this section another approximation to the non-linear system is considered where we use the assumption that the signals $X$ and $Y$ are much less than the dissociation constants $k_{d1}$ and $k_{d2}$. This is a reasonable assumption to be made in bio-molecular systems, especially for binding reactions where the affinity is low. With this assumption we can assume that $p_{t0} \gg C_0$ and $p_t \gg C$ in the system model in (2.7)-(2.10) giving us an approximated system with linear propensity functions in the Langevin equations. For this system, we use tools from linear and non-linear control theory to compute upper bounds for the errors due to retroactivity and noise and use these upper bounds to analyze the trade-off in reducing each of the errors with the design parameter $p_t$. We first introduce the tools used in this chapter and then proceed to the analysis by starting with an outline of the solution approach.
4.2 Mathematical Tools

4.2.1 Deterministic Contraction Theory

Theorem 1

(Contraction) Adapted from [3]. Consider the m-dimensional deterministic system
\[ \dot{x} = f(x, t) \]
where \( f \) is a smooth nonlinear function. The system is said to be contracting if any two trajectories, starting from different initial conditions, converge exponentially to each other. A sufficient condition for a system to be contracting is the existence of some matrix measure, \( \mu \), such that \( \exists \lambda \geq 0, \forall x, \forall t \geq 0, \mu \left( \frac{\partial f(x,t)}{\partial x} \right) \leq -\lambda \). The scalar \( \lambda \) defines the contraction rate of the system.

In this work the vector norm \(|.|\) used will be the \( l_2 \) norm defined as the \( |x|_2 = (\sum_{j=1}^{m} |x_j|^2)^{\frac{1}{2}} \) and the matrix measure used will be \( \mu_2(A) = \max \left( \frac{A + A^T}{2} \right) \).

Lemma 1

(Robustness) Adapted from [3]. Assume that the system \( \dot{x} = f(x, t) \) is contracting, with the contraction rate \( \lambda \), and consider the perturbed system \( \dot{x}_p = f(x_p, t) + d(x_p, t) \) where \( d(x_p, t) \) is bounded, that is, \( \exists d \geq 0, \forall x_p, \forall t \geq 0, |d(x_p, t)| \leq d \). Then, any trajectory of the perturbed system satisfies
\[ |x_p(t) - x(t)| \leq \chi e^{-\lambda t} |x_p(0) - x(0)| + \frac{d}{\lambda} \]

4.2.2 Stochastic Differential Equations and Contraction

Itô Differential Equations

An Itô differential equation takes the form
\[ dx = f(x, t)dt + \sigma(x, t)dW \]

(4.1)
where \( W \) is a standard Wiener process, which is a real function continuous in time \( t \), and is Gaussian. A standard Wiener process has zero mean, variance \( t \), and independent increments which are also Gaussian processes. i.e. \( \text{Var}[dW] = E [|dW|^2] = dt \), where \( dW(t) = W(t + dt) - W(t) \). The chemical Langevin equation [8] and Itô differential equations are closely related and we can derive one from the other in the following way.

A standard-form Langevin equation is of the form [5]

\[
X_i(t + dt) = X_i(t) + \sum_{j=1}^{M} v_{ji}a_j(X(t))dt + \sum_{j=1}^{M} v_{ji}a_j^{(1/2)}(X(t))N_j(t)(dt)^{(1/2)}
\]

\[(i = 1...N)\] (4.2)

Using linearity of normal random variables \( N_j(t)(dt)^{(1/2)} = N(0, dt) \ i.e \ a \ normal \ random \ variable \ with \ zero \ mean \ and \ variance \ equal \ to \ dt \). Since an increment \( dW \) is a normal random variable with zero mean and variance equal to \( dt \), the expression in (4.2) can be used to represent an Itô differential equation giving,

\[
X_i(t + dt) - X_i(t) = \sum_{j=1}^{M} v_{ji}a_j(X(t))dt + \sum_{j=1}^{M} v_{ji}a_j^{(1/2)}(X(t))N_j(t)(dt)^{(1/2)}
\]

\[dX_i = \sum_{j=1}^{M} v_{ji}a_j(X(t))dt + \sum_{j=1}^{M} v_{ji}a_j^{(1/2)}(X(t))dW\]

\[(i = 1...N)\]

**Stochastic Contraction Theory**

This theorem is adapted from [18]. (Proof given in the Appendix)

Consider the following augmented system

\[
dx = \begin{pmatrix} f(a, t) \\ f(b, t) \end{pmatrix} dt + \begin{pmatrix} 0 & 0 \\ 0 & \sigma(b, t) \end{pmatrix} dW
\]

\[= \dot{f}(x, t)dt + \sigma(x, t)dW\]
Assume the system verifies the following hypotheses H1 and H2 with $M=I$.

(H1) There exists a state-independent, uniformly positive definite metric $M(t) = \Theta(t)^T\Theta(t)$, with the lower-bound $\beta > 0$ (i.e. $\forall x, t \ x^T M(t) x \geq \beta \|x^2\|$) and $f$ is contracting in that metric, with contraction rate $\lambda$;

(H2) $E[tr(\sigma(a, t)^T M(t) \sigma(a, t))]$ is uniformly upper bounded by a constant $C$

Let $a(t)$ be a noise-free trajectory starting at $a_0$ and $b(t)$ a noisy trajectory whose initial condition is independent of the noise and given by a probability distribution $p(\varepsilon_2)$. Then,

$$E[|a(t) - b(t)|^2] \leq \frac{C}{2\lambda} + E[|a_0 - \varepsilon_2|^2]e^{-2\lambda t} \quad \forall t \geq 0$$

**Stochastic Input through a linear system**

Consider a linear system with input $x$, output $y$ and impulse response $h(a)$. (Figure 4-1).

![Figure 4-1: Linear System](image)

The input auto-correlation is defined as $R_{xx}(\tau) = E[x(t)x(t+\tau)]$ where $R_{xx}(\tau) \leq R_{xx}(0)$. Then the cross-correlation of the signal is given by

$$R_{xy}(\tau) = \int_{-\infty}^{+\infty} R_{yy}(\tau - a)h(a)da$$

The output auto-correlation $R_{yy}(\tau) = E[y(t)y(t+\tau)]$ is given by

$$R_{yy}(\tau) = \int_{-\infty}^{+\infty} R_{xy}(\tau - a)h(a)da$$
4.2.3 Differential Inequalities

Theorem 9.5 in [20]. Assume the right hand side of the equation \( \frac{dy}{dt} = \sigma(t, y) \) to be continuous in an open region \( D \). Let \((t_0, y_0) \in D\) and denote by \( w^+(t) \) the maximum solution through \((t_0, y_0)\), reaching the boundary of \( D \) by its right-hand extremity, and defined in the interval \( \Delta_+ = [t_0, \alpha_0) \). Let \( y = \phi(t) \) be a continuous curve for \( t \in \Delta_+ = [t_0, \alpha_0) \), contained in \( D \) and satisfying the initial inequality

\[
\phi(t_0) \leq y_0
\]

and the differential inequality

\[
D\phi(t_0) \leq \sigma(t, \phi(t))
\]

Under these assumptions we have

\[
\phi(t) \leq w^+(t)
\]

4.2.4 Minkowski Inequality

Let \( p \) be a real number with \( 1 \leq p \leq \infty, \varepsilon \) and \( \eta \) random variable with \( E[|\varepsilon|^2] < \infty \) and \( E[|\eta|^2] < \infty \). Then we have

\[
\sqrt{E[|\varepsilon + \eta|^2]} \leq \sqrt{E[|\varepsilon|^2]} + \sqrt{E[|\eta|^2]} \tag{4.3}
\]

4.3 System Equations

Using the assumption \( X \ll kd_1 \) and \( Y \ll kd_2 \) to the system in (2.13) - (2.14) we obtain the dynamics of the approximated system as,

\[
\frac{dY}{dt} = \left(1 - \frac{1}{1 + \frac{k\eta}{N}} \right) \left( \frac{1}{k_{d1}} - \delta Y + \sqrt{\frac{\beta_1 p_0 X}{k_{d1}}} + \delta Y \right) \tag{4.4}
\]
\[
\frac{dG}{dt} = \frac{\beta_2 p_1 Y}{k_d} - \delta_2 G + \sqrt{\frac{\beta_2 p_1 Y}{k_d}} + \delta_2 G \Gamma G
\]  
(4.5)

We define the nominal system (4.6) - (4.7) which we use to quantify and analyze the total error in the system:

\[
\begin{align*}
\frac{dY_N}{dt} &= \frac{\beta_1 p_0 X}{k_d} - \delta_1 Y_N \\
\frac{dG_N}{dt} &= \frac{\beta_2 p_1 Y}{k_d} - \delta_2 G_N
\end{align*}
\]  
(4.6) \hspace{2cm} (4.7)

### 4.4 Solution Approach

We use a set of intermediate systems as outlined below to find the total error between the nominal signals in (4.6) - (4.7) and perturbed signals in (4.4) - (4.5).

Let \( Y_R \) and \( G_R \) be the upstream and downstream output signals when the system is perturbed with retroactivity. The reduced dynamics of this system is given by

\[
\begin{align*}
\frac{dY_R}{dt} &= \left(1 - \frac{1}{1 + \frac{k_d}{p_1}}\right) \left(\frac{\beta_1 p_0 X}{k_d} - \delta_1 Y_R\right) \\
\frac{dG_R}{dt} &= \frac{\beta_2 p_1 Y_R}{k_d} - \delta_2 G_R
\end{align*}
\]  
(4.8) \hspace{2cm} (4.9)

There is an error between \( Y_R \) and \( Y_N \) in the upstream system, which propagates to the downstream system causing the error between \( G_R \) and \( G_N \). An upper bound for this error can be found using the non-linear contraction theory giving \(|G_R - G_N|\). Define this as the deterministic error.

Next consider the signal \( Y_S \) where the upstream system has been perturbed with both retroactivity and noise. There is no noise perturbation in the downstream component. The reduced dynamics of this system is given by

\[
\begin{align*}
\frac{dY_S}{dt} &= \left(1 - \frac{1}{1 + \frac{k_d}{p_1}}\right) \left(\frac{\beta_1 p_0 X}{k_d} - \delta_1 Y_S + \sqrt{\frac{\beta_1 p_0 X}{k_d}} + \delta_1 Y_S \Gamma Y\right) \\
\frac{dG_S}{dt} &= \frac{\beta_2 p_1 Y_S}{k_d} - \delta_2 G_S
\end{align*}
\]  
(4.10) \hspace{2cm} (4.11)
There is an error in magnitude between the two signals $Y_S$ and $Y_R$ which propagates to the downstream component causing an error between $G_S$ and $G_R$. As the error in $Y_S$ is caused by noise, the output signal $G_S$ is stochastic. Therefore stochastic contraction theory and linear filtering theory can be used to find an upper bound for the expected value of the error in the output signal. Define this error $E[|G_S - G_R|^2]$ as the input stochastic error.

Next consider the signal $G_P$, where the downstream component takes as input $Y_S$, but is also is perturbed with another noise input. The dynamics of this system is given by

$$\frac{dY_S}{dt} = \left(1 - \frac{1}{1 + \frac{k_{d1}}{p_t}}\right) \left(\frac{\beta_1 p_t X}{k_{d1}} - \delta_1 Y_S + \sqrt{\frac{\beta_1 p_t X}{k_{d1}}} + \delta_1 Y_S \Gamma_Y\right)$$  \hspace{1cm} (4.12)

$$\frac{dG_P}{dt} = \frac{\beta_2 p_t Y_S}{k_{d2}} - \delta_2 G_P + \sqrt{\frac{\beta_2 p_t Y_S}{k_{d2}}} + \delta_2 G_P \Gamma_G$$  \hspace{1cm} (4.13)

Again stochastic contraction theory can be used to find the error $E[|G_P - G_S|^2]$. Define this error as the output stochastic error. Finally the total error in the system can be found using the Minkowski Inequality as

$$\sqrt{E[|G_P - G_N|^2]} \leq \sqrt{E[|G_P - G_S|^2]} + \sqrt{E[|G_S - G_R|^2]} + \sqrt{E[|G_R - G_N|^2]}$$

As we are analyzing the total error relative to the nominal signal we take the ratio of the error to the steady state of the nominal signal $G_e = \frac{\delta_2 p_t Y_S}{\delta_1 k_{d2}}$ defining the total relative error as,

$$\frac{\sqrt{E[|G_P - G_N|^2]}}{G_e} \leq \frac{\sqrt{E[|G_P - G_S|^2]}}{G_e} + \frac{\sqrt{E[|G_S - G_R|^2]}}{G_e} + \frac{\sqrt{E[|G_R - G_N|^2]}}{G_e}$$

4.5 Deterministic Error

In this section we consider the error between the nominal signal $G_N$ and $G_R$ where the signal has been perturbed due to retroactivity. The dynamics of these signals are
given by

\[
\frac{dG_N}{dt} = \frac{\beta_2 p t Y_N}{k_d} - \delta_2 G_N \tag{4.14}
\]

\[
\frac{dG_R}{dt} = \frac{\beta_2 p t Y_R}{k_d} - \delta_2 G_R \tag{4.15}
\]

The error between \( G_N \) and \( G_R \) can be found by using Lemma 1 in deterministic contraction theory. Defining the nominal and perturbed dynamics of \( G \) as

\[
\frac{dG_N}{dt} = f(G_N, Y_N) \tag{4.16}
\]

\[
\frac{dG_R}{dt} = f(G_R, Y_N + \Delta Y) = f(G_R, Y_N) + f(G_R, Y_N + \Delta Y) - f(G_R, Y_N) \tag{4.17}
\]

takes the system in to the form, \( \frac{dG_R}{dt} = f(G_R, Y_N) + d(G_R, Y_R) \) where Lemma 1 can be applied with \( d(G_R, Y_R) = f(G_R, Y_N + \Delta Y) - f(G_R, Y_N) \).

To find an upper bound for \( |d(G_R, Y_R)| \), consider that

\[
d(G_R, Y_R) = f(G_R, Y_N + \Delta Y) - f(G_R, Y_N) = \frac{\beta_2 p t(Y_N + \Delta Y)}{k_d} - \delta_2 G_R - \frac{\beta_2 p t Y_N}{k_d} + \delta_2 G_R = \frac{\beta_2 p t(Y_N + \Delta Y)}{k_d} - \frac{\beta_2 p t Y_N}{k_d} = \frac{\beta_2 p t(\Delta Y)}{k_d}
\]

Let \( \Delta Y_{\text{max}} \) be the maximum value of \( |\Delta Y| \). Then an upper bound for \( |d(G_R, Y_R)| \) is given when \( |\Delta Y| \leq \Delta Y_{\text{max}} \)

\[
|d(G_R, Y_R)| \leq \frac{\beta_2 p t \Delta Y_{\text{max}}}{k_d}
\]

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Therefore the error due to retroactivity is given by

\[
|G_R - G_N| \leq e^{-\lambda G_R t} |G_R(0) - G_N(0)| + \frac{\beta_2 P_t \Delta Y_{\text{max}}}{k_{d2} \lambda_{G_N}} \tag{4.18}
\]

where \(\lambda_{G_N}\) is the contraction rate of the nominal system in (4.16).

The contraction rate is given by,

\[
\mu \left( \frac{\partial f(G_N, Y_N)}{\partial G_N} \right) \leq -\lambda_{G_N} = -\delta_2
\]

To evaluate the expression (4.18), an upper bound on \(\Delta Y\) is needed. Applying Lemma 1 to the dynamics of \(Y\) would enable us to find this upper bound. Consider the system,

\[
\begin{align*}
\frac{dY_N}{dt} &= \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_N \\ 
\frac{dY_R}{dt} &= (1 - R_a) \left( \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_R \right) \\
&= \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_R - R_a \left( \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_R \right) \tag{4.19, 4.20}
\end{align*}
\]

where \(R_a = \frac{1}{1 + \frac{k_{d2}}{P_t}}\).

Lemma 1 can be applied with \(d_y(Y_R, X) = -R_a \left( \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_R \right)\). To bound the disturbance \(|d_y(Y_R, X)|\), consider that

\[
|d_y(Y_R, X)| = \left| -R_a \left( \frac{\beta_1 p_{i0} X}{k_{d1}} - \delta_1 Y_R \right) \right|
\]

With \(R_a \leq \frac{P_t}{P_t + k_{d2}}\), \(Y_R \leq Y_{R\text{max}}\) and \(X_{\text{min}} \leq X \leq X_{\text{max}}\), we have that

\[
|d_y(Y_R, X)| \leq \frac{P_t}{P_t + k_{d2}} \max \left\{ \left| \frac{\beta_1 p_{i0} X_{\text{max}}}{X_{\text{max}} + k_{d1}} \right|, \left| \frac{\beta_1 p_{i0} X_{\text{min}}}{X_{\text{min}} + k_{d1}} - \delta_1 Y_{R\text{max}} \right| \right\}
\]
To find $Y_{R_{\text{max}}}$, we apply Theorem 9.5 in [20] for the system 4.8. Then,

\[
\dot{Y}_R \leq (1 - R_d) \left( \frac{\beta_1 p_{t0} X_{\text{max}}}{k_{d1}} - \delta_1 Y_R \right) \tag{4.21}
\]

\[
Y_{R_{\text{max}}} = \frac{\beta_1 p_{t0} X_{\text{max}}}{\delta_1 k_{d1}} + Y_R(0) \tag{4.22}
\]

Therefore, the maximum error in $Y$ is given by,

\[
\Delta Y = |Y_R - Y_N| \leq e^{-\lambda_{Y_N} t} |Y_R(0) - Y_N(0)| + \frac{P_t}{P_t + k_{d2}} \max \left\{ \left| \frac{\beta_1 p_{t0} X_{\text{max}}}{X_{\text{max}} + k_{d1}} \right|, \left| \frac{\beta_1 p_{t0} X_{\text{min}}}{X_{\text{min}} + k_{d1}} - \delta_1 Y_{R_{\text{max}}_ADDRESS_1} \right| \right\} \lambda_{Y_N}
\]

where $\lambda_{Y_N}$ is the contraction rate of the nominal system in (4.19).

The contraction rate is given by,

\[
\mu \left( \frac{\partial f(Y_N, X)}{\partial Y_N} \right) \leq -\lambda_{Y_N} = -\delta_1
\]

The final deterministic error for identical initial conditions of the nominal and perturbed systems is given by

\[
|G_R - G_N| \leq \beta_2 P_t \max \left\{ \left| \frac{\beta_1 p_{t0} X_{\text{max}}}{X_{\text{max}} + k_{d1}} \right|, \left| \frac{\beta_1 p_{t0} X_{\text{min}}}{X_{\text{min}} + k_{d1}} - \delta_1 Y_{R_{\text{max}}_ADDRESS_1} \right| \right\} \frac{1}{k_{d2} \delta_1 \delta_2}
\]

We find the relative error by taking the ratio with the steady state of the nominal
signal \( G_e = \frac{\beta_2P_t Y_e}{\delta_2 k_{d2}} \), so that

\[
\frac{|G_R - G_N|}{G_e} \leq \frac{P_t}{P_t + k_{d2}} \max \left\{ \frac{\beta_1 p_0 X_{\text{max}}}{X_{\text{max}} + k_{d1}}, \frac{\beta_1 p_0 X_{\text{min}}}{X_{\text{min}} + k_{d1}} - \delta_1 Y_{R\text{max}} \right\}
\]

As the design parameter \( p_t \) changes the upper bound for the relative deterministic error changes according to the expression \( \frac{P_t}{P_t + k_{d2}} \). Therefore as expected the error due to retroactivity increases as the amount of downstream components \( p_t \) increases. Figure 4-2 shows the upper bound and the simulated error for the given choice of parameters.

![Figure 4-2: Error due to retroactivity. The parameter values are \( \beta_1 = 0.001, \beta_2 = 0.3, \delta_1 = \delta_2 = 0.01, p_0 = 100, k_{d1} = 0.1, k_{d2} = 10, w = 0.005, x = 0.01(1 + \sin(wt)) \), Average of 400 simulations.](image)

As it can be seen the simulated error lies below the upper bound although there is about a 50% change between the upper bound and the simulated error. A cause for this could be that the bound given by the contraction theory is too conservative. One
way of improving this could be to use a better metric transformation in using the contraction theory for calculating the upper bound.

4.6 Input Stochastic Error

In this section we consider the error between $G_R$ and $G_S$ which arise due to the noise in the upstream component. The dynamics of these signals are given by

$$
\frac{dG_R}{dt} = \frac{\beta_2 p_{t} Y_R}{k_d} - \delta_2 G_R \tag{4.23}
$$

$$
\frac{dG_S}{dt} = \frac{\beta_2 p_{t} Y_S}{k_d} - \delta_2 G_S \tag{4.24}
$$

Defining the error between $Y_S$ and $Y_R$ due to the noise perturbation as $\Delta Y_S$, we can write $Y_S = Y_R + \Delta Y_S$. Define $\Delta G_S$ as the error between $G_S$ and $G_R$ caused by the input error $\Delta Y_S$. Then due to the linearity of the system,

$$
\frac{d\Delta G_S}{dt} = \frac{\beta_2 p_{t} \Delta Y_S}{k_d} - \delta_2 \Delta G_S \tag{4.25}
$$

The autocorrelation of $\Delta Y_S$ is given by $R_{yy}(\tau) = E[\Delta Y_S(t)\Delta Y_S(t + \tau)]$ with

$$
R_{yy}(\tau) \leq R_{yy}(0)
$$

$$
R_{yy}(0) = E[\Delta Y_S(t)^2] = E[|Y_S - Y_R|^2]
$$

Let the impulse response of the system (4.25) be $h(a)$, so that

$$
h(a) = \frac{\beta_2 p_{t}}{k_d} e^{-\delta_2 a} u(a)
$$

where $u(a)$ is the unit step.

Then the cross-correlation between the input signal $\Delta Y_S$ and the output signal $\Delta G_S$ is given by

$$
R_{ye}(\tau) = \int_{-\infty}^{+\infty} R_{yy}(\tau - a) h(a) da
$$
\[ R_{ye}(\tau) \leq \int_{-\infty}^{+\infty} E[|Y_S - Y_R|^2] h(a) da \]

\[ R_{ye}(\tau) \leq E[|Y_S - Y_R|^2] \int_{-\infty}^{+\infty} \frac{\beta_2 P_t}{\delta_2 k d_2} e^{-\frac{\delta_2 u(a)}{k d_2}} da \]

\[ R_{ye}(\tau) \leq E[|Y_S - Y_R|^2] \frac{\beta_2 P_t}{\delta_2 k d_2} \left[ \frac{e^{-\delta_2 \gamma}}{-\delta_2} \right]_0^{+\infty} \]

\[ R_{ye}(\tau) \leq E[|Y_S - Y_R|^2] \frac{\beta_2 P_t}{\delta_2 k d_2} \]

The output auto-correlation \( R_{ee}(\tau) = E[\Delta G_S(t)\Delta G_S(t + \tau)] \) is given by

\[ R_{ee}(\tau) = \int_{-\infty}^{+\infty} R_{ye}(\tau - a) h(a) da \]

\[ R_{ee}(\tau) \leq \int_{-\infty}^{+\infty} R_{ye}(0) h(a) da \]

\[ R_{ee}(\tau) \leq E[|Y_S - Y_R|^2] \frac{\beta_2 P_t}{\delta_2 k d_2} \int_{-\infty}^{+\infty} \frac{\beta_2 P_t}{\delta_2 k d_2} e^{-\frac{\delta_2 u(a)}{k d_2}} da \]

\[ R_{ee}(\tau) \leq E[|Y_S - Y_R|^2] \frac{1}{\delta_2} \left( \frac{\beta_2 P_t}{\delta_2 k d_2} \right)^2 \left[ \frac{e^{-\delta_2 \gamma}}{-\delta_2} \right]_0^{+\infty} \]

\[ R_{ee}(\tau) \leq E[|Y_S - Y_R|^2] \left( \frac{\beta_2 P_t}{\delta_2 k d_2} \right)^2 \]

Using \( R_{ee}(\tau) \leq R_{ee}(0) \), we obtain

\[ R_{ee}(0) \leq E[|Y_S - Y_R|^2] \left( \frac{\beta_2 P_t}{\delta_2 k d_2} \right)^2 \]

\[ R_{ee}(0) = E[|\Delta G_S|^2] = E[|G_S - G_R|^2] \]

\[ E[|G_S - G_R|^2] \leq E[|Y_S - Y_R|^2] \left( \frac{\beta_2 P_t}{\delta_2 k d_2} \right)^2 \]

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$E[|Y_S - Y_R|^2]$ can be found by applying stochastic contraction theory to the system

\[
\begin{align*}
\frac{dY_R}{dt} &= \left(1 - \frac{1}{1 + \frac{k_d}{p_t}}\right) \left(\frac{\beta_1 p_0 X}{k_d} - \delta_1 Y_R\right) \\
\frac{dY_S}{dt} &= \left(1 - \frac{1}{1 + \frac{k_d}{p_t}}\right) \left(\frac{\beta_1 p_0 X}{k_d} - \delta_1 Y_S + \sqrt{\frac{\beta_1 p_0 X}{k_d} + \delta_1 Y_S \Gamma_Y}\right)
\end{align*}
\] (4.26) (4.27)

This system can be written in the following form as a set of Itô differential equations,

\[
dY = \begin{pmatrix} f(Y_R, X) \\ f(Y_S, X) \end{pmatrix} dt + \begin{pmatrix} 0 & 0 \\ 0 & \sigma(Y_S, X) \end{pmatrix} dW
\]

where stochastic contraction theory can be applied. H1 can be verified by finding the contraction rate of $f(Y_R, X)$

\[
\mu \left(\frac{\partial f(Y_R, X)}{\partial Y_R}\right) \leq -\lambda_{Y_R}
\]

\[
\lambda_{Y_R} = \left(1 - \frac{1}{1 + \frac{k_d}{p_t}}\right)
\]

\[
\lambda_{Y_R} = \left(\frac{k_d}{p_t + k_d}\right)
\]

The condition $\lambda_{Y_R} > 0$ can be ensured with the constraint that $p_t < \infty$.

To verify H2, let $E[\text{tr}(\sigma(Y_S, X)\sigma(Y_S, X))] \leq C_y$. In this system $\sigma(Y_S, X) = \left(1 - \frac{1}{1 + \frac{k_d}{p_t}}\right) \sqrt{\frac{\beta_1 p_0 X}{k_d} + \delta_1 Y_S}$.

Taking $M = I$ and $E[|Y_S|] \leq Y_{R_{max}}$, we have

\[
C_y = \left(\frac{k_d}{p_t + k_d}\right)^2 \left[\frac{\beta_1 p_0 X_{max}}{k_d} + \delta_1 Y_{R_{max}}\right]
\]

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Then using stochastic contraction theory, for identical initial conditions of the nominal and perturbed signals, the mean square error between $Y_S$ and $Y_R$ is given by

$$E[|Y_R - Y_S|^2] \leq \frac{C_y}{2\lambda_{Y_R}}$$

With $C_y$ calculated above, we have

$$E[|Y_R - Y_S|^2] \leq \left( \frac{k_{d2}}{p_t + k_{d2}} \right)^2 \left[ \frac{\beta_1 p_{t0} X_{\text{max}}}{k_{d1}} + \delta_1 Y_{R\text{max}} \right]$$

$$E[|Y_R - Y_S|^2] \leq \frac{2 \left( \frac{k_{d2}}{p_t + k_{d2}} \right) \delta_1}{\beta_1 p_{t0} X_{\text{max}} / k_{d1} + \delta_1 Y_{R\text{max}}}$$

$Y_{R\text{max}}$ was calculated using differential inequalities in (4.22) giving,

$$Y_{R\text{max}} = \frac{\beta_1 p_{t0} X_{\text{max}}}{\delta_1 k_{d1}} + Y_R(0)$$

Then,

$$E[|G_S - G_R|^2] \leq \left( \frac{\beta_2 p_t}{\delta_2 k_{d2}} \right)^2 \left[ \frac{k_{d2}}{p_t + k_{d2}} \right] \left[ \frac{2\beta_1 p_{t0} X_{\text{max}}}{k_{d1}} + \delta_1 Y_R(0) \right]$$
Then the relative mean square error is given by

\[
\frac{\sqrt{E[|G_S - G_R|^2]}}{G_e} \leq \sqrt{\left(\frac{k_{d2}}{p_t + k_{d2}}\right) \left[\frac{2\beta_1 p_{t0} X_{max}}{k_{d1}} + \delta_1 Y_R(0)\right]} \left/ \sqrt{2\delta_1 Y_e}\right. 
\]

It can be seen that the input stochastic error bound changes according to the expression \(\sqrt{\frac{k_{d2}}{p_t + k_{d2}}}\) and therefore as \(p_t\) increases the error due to input noise decreases as seen in Figure 4-3.

Figure 4-3: Error due to input noise. The parameter values are \(\beta_1 = 0.001, \beta_2 = 0.3, \delta_1 = \delta_2 = 0.01, p_{t0} = 100, k_{d1} = 0.1, k_{d2} = 10, w = 0.005, x = 0.01(1 + \sin(wt)),\) Average of 400 simulations.

It can be seen that the bound correctly predicts the behavior of the simulated error but it is still about 55% higher in magnitude. The conservativeness of this bound lies mainly in the upper bounding of the autocorrelation of the signal. Therefore one way of tightening this upper bound would be to look at different methods of upper
bounding the autocorrelation.

4.7 Output Stochastic Error

In this section we consider the error between the signals $G_S$ and $G_P$, where $G_P$ is perturbed due to noise in the downstream component. The dynamics of these signals are given by

\[
\frac{dG_S}{dt} = \frac{\beta_2 p_t Y_s}{k_d} - \delta_2 G_S \\
\frac{dG_P}{dt} = \frac{\beta_2 p_t Y_s}{k_d} - \delta_2 G_P + \sqrt{\frac{\beta_2 p_t Y_s}{k_d}} + \delta_2 G_P \Gamma_G
\]

This system can be written as a set of Itô differential equations in the form,

\[
dG = \begin{pmatrix} f(G_S, Y_s) \\ f(G_P, Y_s) \end{pmatrix} dt + \begin{pmatrix} 0 & 0 \\ 0 & \sigma(G_P, Y_s) \end{pmatrix} dW
\]

where stochastic contraction theory can be applied. H1 can be verified by finding the contraction rate of $f(G_S, Y_S)$

\[
\mu \left( \frac{\partial f(G_S, Y_S)}{\partial G_S} \right) \leq -\lambda_{G_N} = -\delta_2
\]

To verify H2, let $E[tr(\sigma(G_P, Y_S)^T M \sigma(G_P, Y_S))] \leq C$. In this system $\sigma(G_P, Y_S) = \sqrt{\frac{\beta_2 p_t Y_s}{k_d} + \delta_2 G_P}$.
Taking $M = I$, we have

$$E \left[ \text{tr}(\sigma(G_P, Y_S)^T M \sigma(G_P, Y_S)) \right] = E \left[ \frac{\beta_2 p_t Y_S}{k_{d2}} + \delta_2 G_P \right]$$

$$= \frac{\beta_2 p_t E[Y_S]}{k_{d2}} + \delta_2 E[G_P] \tag{4.28}$$

To bound the expression (4.28) an upper bound on $E[Y_S]$, $E[G_P]$ is needed. To find an upper bound on the dynamics of $E[Y_S]$ consider the dynamics of $Y_S$ given by

$$Y_S = \frac{\beta_1 p_{t0} X}{k_{d1}} - \delta_2 Y_S + \sqrt{\frac{\beta_1 p_{t0} X}{k_{d1}}} + \delta_2 Y_S$$

Taking the expected value of this expression results in

$$\frac{dE[Y_S]}{dt} = E \left[ \frac{\beta_1 p_{t0} X}{k_{d1}} \right] - \delta_2 E[Y_S] \tag{4.29}$$

$$\tag{4.30}$$

Using $X \leq X_{max}$, we can apply Theorem 9.5 in [20] to the differential equation in (4.29) we have

$$\frac{dE[Y_S]}{dt} \leq E \left[ \frac{\beta_1 p_{t0} X_{max}}{k_{d1}} \right] - \delta_2 E[Y_S]$$

Then,

$$E[Y_S] \leq \frac{\beta_1 p_{t0} X_{max}}{k_{d1} \delta_1} + E[Y_S(0)]$$

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Following a similar procedure to bound the $E[G_S]$, we take

$$
G_S = \frac{\beta_2 p t Y_S}{k_{d_1}} - \delta_2 G_S + \sqrt{\frac{\beta_2 p t G_S}{k_{d_2}}} + \delta_2 G_S
$$

$$
\frac{dE[G_S]}{dt} = E\left[\frac{\beta_2 p t G_S}{k_{d_1}} \right] - \delta_2 E[G_S]
$$

Denote the maximum value of $E[Y_S]$ by $E[Y_S]_{\text{max}}$. Then, applying Theorem 9.5 in [20] to the differential equation in (5.1) we have

$$
E[G_S] \leq \frac{\beta_2 p t E[Y_S]_{\text{max}}}{\delta_2 k_{d_2}} + E[G_S(0)]
$$

Then verifying (H2),

$$
C = \frac{2\beta_2 p t \left[\frac{\beta_1 p t_0 X_{\text{max}}}{k_{d_1} \delta_1} + E[Y_S(0)]\right]}{k_{d_2} \delta_1} + \delta_2 E[G_P(0)]
$$

Then using stochastic contraction theory, for identical initial conditions of the nominal and perturbed signals, the mean square error between $G_S$ and $G_P$ is given by

$$
E[|G_S - G_P|^2] \leq \frac{C}{2\delta_2}
$$

With $C$ calculated above, we have

$$
E[|G_S - G_P|^2] \leq \frac{2\beta_2 p t \left[\frac{\beta_1 p t_0 X_{\text{max}}}{k_{d_1} \delta_1} + E[Y_S(0)]\right] + k_{d_2} \delta_2 E[G_P(0)]}{2\delta_2 k_{d_2}}
$$
Normalizing this error by the steady state $G_e = \frac{\beta_2 p_t Y_e}{\delta_2 k_{d2}}$ gives

$$\sqrt{E[|G_S - G_P|^2]} \leq \frac{\sqrt{2 \beta_2 p_t \left( \frac{\beta_1 p_t X_{max}}{k_{d1}} + E[Y_S(0)] \right) + k_{d2} \delta_2 E[G_P(0)]}}{2 \beta_2 p_t Y_e} \frac{\delta_1 k_{d2}}{2}$$

It can be seen that the output stochastic error is of the $O(\sqrt{p_t})$ and therefore as $p_t$ increases the error due to noise decreases. Figure 4-4 illustrates this with a simulation. It can be see that the bound correctly predicts the behavior of this error with only a 10% change in the magnitude.

Figure 4-4: Error due to output noise. The parameter values are $\beta_1 = 0.001, \beta_2 = 0.3, \delta_1 = \delta_2 = 0.01, p_{t0} = 100, k_{d1} = 0.1, k_{d2} = 10, w = 0.005, x = 0.01(1 + \sin(wt))$, Average of 400 simulations.
4.8 Total Error

The total error in the system is given by

$$\sqrt{E[(G_P - G_N)^2]} \leq \frac{P_t}{P_t + k_{d2}} \max \left\{ \left| \frac{\beta_1 P_{00} X_{max}}{X_{max} + k_{d1}} \right|, \left| \frac{\beta_1 P_{00} X_{min}}{X_{min} + k_{d1}} - \delta_1 Y_{R_{max}} \right| \right\} \frac{\delta_1 Y_e}{G_e}$$

$$+ \sqrt{\left( \frac{k_{d2}}{P_t + k_{d2}} \right) \left[ \frac{2\beta_1 P_{00} X_{max}}{k_{d1}} + \delta_1 Y_{R(0)} \right]} \frac{\sqrt{2\delta_1 Y_e}}{\sqrt{2\delta_1 Y_e}}$$

$$+ \frac{\sqrt{2\beta_2 P_t} \left[ \frac{\beta_1 P_{00} X_{max}}{k_{d1} \delta_1} + E[Y_S(0)] \right] + k_{d2} \delta_2 E[G_P(0)]}{2\beta_2 P_t Y_e} \frac{\delta_1 k_{d2}}{2}$$

This upper bound is illustrated in Figure 4-5 for the given set of parameters. It can be seen that the bound predicts a minimum error for an intermediate value of \( p_t \), indicating the trade-off between noise error and retroactivity error. However, in comparison with the simulated error there is about a 50% difference in the predicted optimal value of \( p_t \). Therefore improvement is needed in making the bounds tighter, mainly in input noise and the deterministic error bounds.

4.9 Discussion

In this section we considered an approximation to the non-linear system to quantify the total error in the system by calculating upper bounds for each of the different errors in the system. It was seen that the bounds correctly illustrate the different behaviors of the different errors as the design parameter \( p_t \) is changed and therefore illustrate the need for an optimal value of \( p_t \) to minimize the error in interconnecting two components. However, some of the upper bounds calculated in this section are shown to be too conservative in comparison to the simulated error and therefore improvement is to be made in those sections to obtain a much tighter bound that correctly predicts the value of the optimal \( p_t \).
Figure 4.5: Total Error: The parameter values are $\beta_1 = 0.001$, $\beta_2 = 0.3$, $\delta_1 = \delta_2 = 0.01$, $p_0 = 100$, $k_{d1} = 0.1$, $k_{d2} = 10$, $w = 0.005$, $x = 0.01(1 + \sin(wt))$, Average of 400 simulations.
Chapter 5

Future Work and Conclusion

5.1 Introduction

The previous chapters considered different approximations to the non-linear system in (2.13) - (2.14) to quantify the trade-off between the perturbation due to retroactivity and noise. In this chapter, we discuss the proposed approach for quantifying the trade-off for the non-linear system using non-linear contraction theory and limitations of the design that arise due to this approach. Next we discuss a singular perturbation approach for stochastic systems that give a better approximation to the system than using the singular perturbation tools defined for deterministic systems.

5.2 Non-linear System

As described in Chapter 2 we want to quantify the error between the two systems, perturbed:

\[
\frac{dY_T}{dt} = (1 - R(Y_T)) \left( \frac{\beta_1 p_0 X}{X + k_{d1}} - \delta_1 Y_T + \sqrt{\frac{\beta_1 p_0 X}{X + k_{d1}}} + \delta_1 Y_T \Gamma_Y \right) \tag{5.1}
\]

\[
\frac{dG_T}{dt} = \frac{\beta_2 p_t Y_T}{Y_T + k_{d2}} - \delta_2 G_T + \sqrt{\frac{\beta_2 p_t Y_T}{Y_T + k_{d2}}} + \delta_2 G_T \Gamma_G \tag{5.2}
\]
and nominal:

\[
\frac{dY_0}{dt} = \frac{\beta_1 p_{10} X}{X + k_{d1}} - \delta_1 Y_0 \tag{5.3}
\]

\[
\frac{dG_0}{dt} = \frac{\beta_2 p_{11} Y_N}{Y_N + k_{d2}} - \delta_2 G_0 \tag{5.4}
\]

We define the intermediate system that is only perturbed due to retroactivity as follows.

\[
\frac{dY_I}{dt} = (1 - R(Y_I)) \left( \frac{\beta_1 p_{10} X}{X + k_{d1}} - \delta_1 Y_I \right) = f_1(Y_I, X) \tag{5.5}
\]

\[
\frac{dG_I}{dt} = \frac{\beta_2 p_{11} Y}{Y + k_{d2}} - \delta_2 G_I = f_2(G_I, Y_I) \tag{5.6}
\]

Then the deterministic error in the system \(|G_I - G_0|\) can be found using Lemma 1 in contraction theory, similar to the procedure in Chapter 4. Next to find the stochastic error in the system we consider the 2-dimensional systems (5.1) - (5.2) and (5.5) - (5.6) with \(L_i = [Y_i, G_i]\). Then the stochastic contraction theory can be used to find an upper bound for the error \(E[|L_T - L_I|^2]\). This quantity upper bounds the error \(E[|G_T - G_I|^2]\) which gives a measure of the error due to noise in the system.

### 5.2.1 Limitations

The main limitation in this approach is the necessity of contraction of the 2-dimensional system (5.5) - (5.6). The contraction rate for this system is given by \(\lambda_I > 0\)

\[
\lambda_{\text{max}} \left( \begin{array}{cc} \frac{df_1}{dY_I} & \frac{df_1}{dG_I} \\ \frac{df_2}{dY_I} & \frac{df_2}{dG_I} \end{array} \right) \preceq -\lambda_I
\]

where \(\lambda_{\text{max}}\) denotes the maximum eigenvalue of the matrix.
Computing this results in,

\[ \lambda_{\text{max}} = \delta_2 - \max \left( \frac{df_1}{dY_1} \right) - \sqrt{\delta_2 + \max \left( \frac{df_1}{dY_1} \right)^2 + \left( \frac{\beta_2 p_t}{k_{d2}} \right)^2} \]

\[ \max \left( \frac{df_1}{dY_1} \right) = \frac{3\sqrt{3}}{8} \sqrt{\frac{1}{k_{d2} p_t} X + k_{d1}} - \delta_1 \left( \frac{k_{d2}}{p_t + k_{d2}} \right) \]

with the following parameter constraints to ensure the negativity of the eigenvalues.

\[ \beta_1 \leq \frac{8\delta_1 k_{d3} \sqrt{k_{d2} p_t}}{3\sqrt{3}(k_{d2} + p_t)} \]

\[ \beta_2 \leq \sqrt{4\delta_2 \frac{\delta_1 k_{d2}}{(k_{d2} + p_t)}} - \sqrt{\frac{1}{k_{d2} p_t} X + k_{d1}} \frac{k_{d2}}{p_t} \]

It can be seen that as \( p_t \) increases the contraction rate tends to 0, restricting the amount of \( p_t \) that can be used. This imposes a constraint our design parameter preventing its use to its full capacity.

### 5.3 Stochastic Singular Perturbation Approach

In Chapter 2 we carried out model order reduction by applying singular perturbation techniques defined for a deterministic system. It was seen that as \( \epsilon \to 0 \) the solution converges to a deterministic slow manifold and stays within a neighborhood of \( O(\epsilon) \). However this does not capture correctly the effect of the noise perturbation on the convergence to the slow manifold and the probability of being around a neighborhood of this slow manifold due to the stochasticity of the system. There have been several studies on singular perturbation of different stochastic systems such as the generalized Langevin equation [8], and recently the chemical master equation [7]. There have been more recent studies on time scale separation of stochastic systems notably [13].
which provides a stochastic version of the Tikhonov’s theory for a system of the type
\[ \epsilon \dot{z} = F(x, t, z) + \sigma(\epsilon)G(x, t, z) \] where \( \sigma = O\left(\frac{1}{\ln \epsilon}\right) \). They mention another class of systems \( \sigma = O(\sqrt{\epsilon}) \) (the class of systems that we consider) which is in general studied with Bogoliubov average principle. In this type of systems the fast variable ‘z’ may be oscillatory and will not converge in probability. There has been another study carried out by Berglund and Gentz in [2] for the above type of systems with \( \sigma \) as a function of \( \epsilon \). They use a sample-path approach to find the probability of the solution being concentrated around a neighborhood of the slow manifold. However their analysis does not capture correctly the probability when \( \sigma = O(\sqrt{\epsilon}) \) which indicates that the probability of being inside the neighborhood of \( \epsilon \) decreases as \( \epsilon \) decreases. This does not agree with the simulations we have performed which illustrate that the solution is more concentrated around the slow manifold as \( \epsilon \) decreases. Therefore for the class of systems with \( \sigma = O(\sqrt{\epsilon}) \) there have not been studies that correctly quantify the convergence of the system solution to a neighborhood around the slow manifold.

We propose the following framework to capture this behavior.

Consider the system,

\[ \dot{x} = f(x, t, z, \epsilon) + \sigma_x(x, t, z)\Gamma_x \quad (5.7) \]

\[ \epsilon \dot{z} = g(x, t, z, \epsilon) + \sqrt(\epsilon)\sigma_z(x, t, z)\Gamma_z \quad (5.8) \]

Define the slow manifold \( \gamma(x(t)) \) as \( \epsilon \to 0 \),

\[ g(x, t, z, 0) = 0 \quad (5.9) \]

\[ z = \gamma(x(t)) \quad (5.10) \]

Let \( z_d \) be the solution to the equation (5.8). We want to quantify \( |z_d - \gamma(x(t))| \), the error between the slow manifold and the system solution after a fast transient.

Define the system \( \epsilon \dot{z} = g(x, t, z, \epsilon) \) where the stochastic perturbation is absent. Let \( z_d \) be the solution to this system. Then using deterministic contraction theory we can find \( |z_d - \gamma(x(t))| \), where \( \gamma(x(t)) \) as defined above is the solution to the equation.
\( g(x, t, z, \epsilon) = 0 \) as \( \epsilon \to 0 \). Using stochastic contraction theory we can find \( E[|z_s - z_d|^2] \) the mean error between the stochastic and deterministic systems. Finally the Minkowski Inequality gives us the expression \( \sqrt{E[|z_s - \gamma(x(t))|^2]} \leq \sqrt{E[|z_s - z_d|^2]} + \sqrt{E[|z_d - \gamma(x(t))|^2]} \) which gives an upper bound to the mean error between the slow manifold and the system solution. We expect this error to be in \( O(\epsilon) \), as we have observed in simulation.

5.4 Conclusion

In this work we analyzed the trade-off between retroactivity and noise in an interconnection of two components in a bio-molecular network. We modeled the system as a set of non-linear chemical Langevin equations and analyzed the trade-off for two different approximations of this non-linear model. First we studied a system linearized about a fixed point and quantified the trade-off between retroactivity and noise using transfer functions. Next we used a linear approximation of the propensity functions in the Langevin equation and quantified the trade-off by calculating upper bounds for the errors. The limitations of the upper bounds and improvements to be carried out were discussed. Finally we discussed the future work to be carried out in quantifying the error for the original non-linear system and also outlined a proposed framework for singular perturbation techniques in stochastic differential equations.
Appendix A

Proof of Stochastic Contraction Theory

The alterations made to the proof in [18] is given below. The hypothesis (H1) in [18] is unchanged. We alter the hypothesis (H2) to give $E[tr(\sigma(a, t)^T M(t)\sigma(a, t))]$ is uniformly upper-bounded by a constant $C$.

Lemma 2: Under (H1) and (H2), one has

$$LV(x, t) \leq -2\lambda V(x, t) + h(x, t)$$

where

$$h(x, t) = tr(\sigma(a, t)^T M(t)\sigma(a, t)) + tr(\sigma(b, t)^T M(t)\sigma(b, t))$$

Proof Let us compute first $LV$

$$LV(x, t) = \frac{\partial dV}{dt} + \frac{\partial dV}{dx} f(x, t) + \frac{1}{2} tr(\sigma(a, t)^T \frac{\partial dV^2}{dx^2} \sigma(a, t))$$

$$= (a - b)^T \left( \frac{d}{dt} M(t) \right) (a - b)$$

$$+ 2(a - b)^T M(t)(f(a, t) - f(b, t))$$

$$+ tr(\sigma(a, t)^T M(t)\sigma(a, t)) + tr(\sigma(b, t)^T M(t)\sigma(b, t))$$
Now following the same procedure in [18] we can apply the Gronwall-type lemma 1 to obtain

\[
E(||a(t) - b(t)||^2) \leq \frac{1}{\beta} \left( \frac{C}{\lambda} + E(\xi_1 - \xi_2)^T M(0)(\xi_1 - \xi_2)e^{-2\lambda t} \right)
\]
Bibliography


