Sinusoidal-Input Describing Function of a Simple Biomolecular Signaling System

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Abstract. Understanding biomolecular systems is important both for the analysis of naturally occurring systems as well as for the design of new ones. However, mathematical tools for analysis of such complex systems are generally lacking. Here, we present an application of the method of sinusoidal-input describing function for the analysis of such a system. Using this technique, we approximate the input-output response of a simple biomolecular signaling system both computationally and analytically. We systematically investigate the dependence of this approximation on system parameters. Finally, we estimate the error involved in this approximation. These results can help in establishing a framework for analysis of biomolecular systems through the use of simplified models.

1 Introduction

Design of systems made out of biomolecular substrates is a key challenge with potential applications in agriculture and medicine [4]. Complementarily, analyzing how interactions between biomolecules combine to determine cellular behavior is a fundamental problem in biology [2]. Developing useful mathematical models can facilitate the achievement of both these goals. For example, in a design problem, such models provide a way to test if the proposed design will achieve desired behavior before actual implementation as well as to compare alternative design solutions. Similarly, in an analysis problem, mathematical models provide a succinct representation to capture observed behavior and obtain insight into the interactions underlying it. The
mathematical models used in these instances can be complex, being high-dimensional as well as nonlinear. Indeed, analysis of such models is challenging from a mathematical point of view. Therefore, developing new mathematical tools as well as adapting existing ones for the study of these problems is an essential requirement.

A typical mathematical model representation of a biomolecular system is through ordinary differential equations. In this representation, the variables are the concentrations of various biomolecular components, which change depending on the interactions between them. These interaction terms can be determined from mass action kinetics and are a frequent source of nonlinearities. One approach to analyze these equations is computer simulations. Indeed, exhaustive simulations can be useful in charting out system behavior, for example in [3]. These are especially insightful when coupled with simple analytical treatments. Another approach is theoretical, which seeks to use the structure of nonlinearities to infer general aspects of system behavior. An example of this approach is the theory of monotone systems [5]. An intermediary approach is also possible, such as that provided by the method of describing functions [1]. In control engineering, this method has been used to estimate the onset of limit cycle oscillations as well as in replacing the input-output map of a nonlinear system with a corresponding linear approximation for different classes of inputs including sinusoidal and random. In fact, the former of these applications has been successfully used in the context of biomolecular oscillators [6]. It is likely that approximating input-output maps in biomolecular systems using this technique will also be of use.

As an example of a biomolecular system (Fig. 1), consider a biomolecular species (A) that can interconvert between two forms (A₀ and A₁) at certain forward and reverse rates (k₊ and k₋). Such a two-state model presents a good representative example for two main reasons. One, because it recurs in a wide range of biological contexts. This includes biomolecular signal transduction, where an input such as temperature or pheromones is mapped to an output representing transcriptional or other biomolecular activity inside the cell. In the two-state model, the input can be modeled as modulating the rate k₊ and the output as the concentration of A₁, the active form of the protein A. Two, because it represents a relatively simple
example of the kind of nonlinearities that are present in biomolecular systems. A mathematical model for in the context of biomolecular signal transduction can be obtained using mass action kinetics,

\[ \frac{dA_1}{dt} = k_+ (A_T - A_1) + k_- A_1. \]  

Here, the total concentration of the protein is denoted by \( A_T = A_0 + A_1 \). Due to the presence of the term \( k_+ A_1 \), where the input term and the output multiply each other, this is a nonlinear equation. The form of the approximation of the input-output map using the describing function technique and its dependence on system parameters is unclear.

Here, we aim to approximate the input-output map of such a biomolecular system using the describing function technique. Specifically, we use the sinusoidal-input describing function technique that allows the approximation of input-output maps for the class of sinusoidal inputs. We compute the system approximation both computationally and analytically. Next, we investigate the dependence of this approximation on system parameters. Finally, we compute the error between the system response and its approximation. These results should help in developing a framework for approximations of biomolecular signaling systems with potential applications in analysis and design.

2 Results

2.1 Calculation of the Approximation

In this section, we use the technique of sinusoidal-input describing functions to calculate the approximation of the input-output map in Eq. 1 from \( k_+ \) to \( A_1 \). To do this, we set the input to be a sinusoidal function, \( k_+ = k_{+0} + b \sin(\omega t) \). Here, \( b \) is the forcing amplitude, \( \omega \) is the forcing frequency, and \( k_{+0} \) is the input bias. As variables in biomolecular systems are positive, we constrain our analysis in the limit \( b < k_{+0} \). Our goal is to calculate the resulting first harmonic of the output. The ratio of this harmonic and the forcing amplitude is the describing function approximation. We calculate this approximation both computationally and analytically.

To compute this approximation, we numerically simulate the ordinary differential equations in Eq. 1 with the input set to be \( k_+ = k_{+0} + b \sin(\omega t) \). The initial condition is chosen as \( A_T k_{+0}/(k_{+0} + k_-) \), which is equal to the steady-state for \( b = 0 \). To obtain the output \( A_1(t) \), the simulation is continued as long as the \( A_1(t) \) in a cycle is close to that in the previous cycle. These simulations are performed in MATLAB.
using the solver ode23s with default options. The describing function approximation, $G(j\omega, b, k_{+0})$ is given by the formulas

$$
\begin{align*}
Re(G(j\omega, b, k_{+0})) &= \frac{\omega}{\pi b} \int_0^{2\pi} A_1(t) \sin(\omega t) dt, \\
Im(G(j\omega, b, k_{+0})) &= \frac{\omega}{\pi b} \int_0^{2\pi} A_1(t) \cos(\omega t) dt.
\end{align*}
$$

The results of this computation are shown in Fig. 2 (blue line).

To obtain an analytical approximation, we use a mathematical trick. For this, we use a first harmonic approximation to search for solutions of Eq. 1 of the form $A_1 = A_{10} + A_{1b} \sin(\omega t + \theta)$. Substituting the sinusoidal input and output expressions in Eq. 1 yields,

$$
\omega A_{1b} \cos(\omega t + \theta) = k_{+0} A_T + b A_T \sin \omega t - (k_{+0} + k_-) A_{10} - (k_{+0} + k_-) A_{1b} \sin(\omega t + \theta) - A_{1b} b \sin \omega t \sin(\omega t + \theta).
$$

Expressions for $A_{10}$, $A_{1b}$, and $\theta$ need to be determined here. In this equation, we neglect higher harmonics such as $\sin(2\omega t)$ and $\cos(2\omega t)$,

$$
\omega A_{1b} \cos(\omega t + \theta) = k_{+0} A_T + b A_T \sin \omega t - (k_{+0} + k_-) A_{10} - (k_{+0} + k_-) A_{1b} \sin(\omega t + \theta) - A_{1b} b \frac{1}{2} \cos \theta.
$$

After neglecting this higher harmonics, we equate separately the constant terms, and the terms multiplying $\sin(\omega t)$ and $\cos(\omega t)$,

$$
\begin{align*}
0 &= k_{+0} A_T - (k_{+0} + k_-) A_{10} - \frac{1}{2} A_{1b} b \cos \theta, \\
\omega A_{1b} \cos \theta &= -(k_{+0} + k_-) A_{1b} \sin \theta, \\
-\omega A_{1b} \sin \theta &= b (A_T - A_{10}) - (k_{+0} + k_-) A_{1b} \cos \theta.
\end{align*}
$$

These equations can be used to obtain expressions for the desired quantities,

$$
\begin{align*}
A_{10} &= A_T \frac{k_{+0} - \alpha}{k_- + k_{+0} - \alpha}, \quad \alpha = \frac{1}{2} b^2 \frac{k_{+0} + k_-}{\omega^2 + (k_{+0} + k_-)^2}, \\
A_{1b} &= (A_T - A_{10}) \frac{b}{\sqrt{\omega^2 + (k_{+0} + k_-)^2}}, \\
\theta &= -\tan^{-1} \left( \frac{\omega}{k_{+0} + k_-} \right).
\end{align*}
$$

(2)
Figure 2: Calculation of the approximation. Magnitude and phase of the approximation are plotted as a function of forcing frequency. Blue solid lines in each plot are obtained computationally. Red dashed lines are obtained analytically as shown in Eq. 2. Parameters used in these plots are $A_T = 100nM$, $k_- = 100/hr$, $k_{+0} = k_-$, $b = k_{+0}/2$. $\omega/2\pi$ is varied logarithmically in the range $0.1/hr–10^4/hr$. 

\begin{align*}
|A_{1b}/b| & \quad \text{Magnitude (nM/hr)} \\
\angle A_{1b}/b & \quad \text{Angle (rad)} \\
\end{align*}

\begin{align*}
\omega/2\pi & \quad \text{Frequency (/hr, log scale)} \\
\end{align*}
From this, we note that $A_{1b}/b$ and $\theta$ represent respectively the magnitude and phase of the describing function approximation,
\[ G(j\omega, b, k_{+0}) = \frac{A_{1b}}{b} e^{j(\omega t + \theta)}. \]
This is a function of the operating bias ($k_{+0}$), the forcing amplitude ($b$), the forcing frequency ($\omega$) as well as the system parameters $A_T$ and $k_-$. These results are superimposed on the computational results in Fig. [2] (red dashed line).

We find that the analytical and computational results for the describing function approximation match well. Further, we note that these results converge to the linearized frequency response in the limit $b \to 0$,
\[ \lim_{b \to 0} G(j\omega, b, k_{+0}) = \frac{A_T k_-/(k_- + k_{+0})}{\sqrt{\omega^2 + (k_{+0} + k_-)^2}} e^{j(\omega t + \theta)} \]
where the linearization is about the operating point ($k_+ = k_{+0}$, $A_1 = A_T k_+/(k_+ + k_-)$). This shows that the describing function approximation captures the effect of the nonlinearity at large forcing amplitudes that is not present in the linearization.

The computational method is likely to be of more use than analytical methods as the systems get more complex. Even in this example, the computed solution helps to verify the analytical solution. However, the ability to obtain analytical solutions for simple examples and compare with computational results can yield insight into how these sorts of nonlinearities can be approximated.

### 2.2 Parametric Dependence of Approximation

Having computed the describing function approximation to the system response, we next investigated how this approximation depends on the parameters of the biomolecular signaling system. In particular, we are interested in determining how the magnitude and phase of the approximation depends on parameters of the input and of the system.

We find that the phase of the approximation is independent of the forcing amplitude $b$. In fact, the phase behavior of the approximation coincides with the phase behavior associated with the linearization. The crossover frequency is $\omega_0 = k_{+0} + k_-$. At frequencies lower than this ($\omega << \omega_0$), the output is in phase with the input. At frequencies higher than this ($\omega >> \omega_0$), the output lags the input by $\pi/2$.

As far as the magnitude is concerned, an examination of Eq. [2] shows that it increases as the forcing amplitude $b$ increases. This contrasts with the effect of the forcing amplitude on the phase suggesting that the nonlinearity is such that it has an
effect on the magnitude of the approximation. This is also a counterintuitive result for the following reason. The steady-state solution of Eq. [1] for a constant input $k_+$ is,

$$A_1 = A_T \frac{k_+}{k_+ + k_-}.$$  

This is an increasing function of $k_+$ which saturates when $k_+ \sim k_-$ or higher. This suggests that a sinusoidal input of amplitude $b$ around an input bias point $k_+ = k_{+0}$ will have a lower gain if the region of saturation is encountered. Consequently, the magnitude of the output corresponding to this sinusoidal component should decrease. Contrastingly, our results suggest that the opposite is true. The resolution of this paradox is that in the describing function approximation, the sinusoidal term in the output is relative to the mean output level $A_{10}$, which itself decreases as the forcing amplitude $b$ increases. Therefore, consideration of the describing function approximation provides a clarification on the gain corresponding to a sinusoidal input.

As expected from a simple linearization, the magnitude of the approximation decreases as the frequency $\omega$ is increased. In addition to the frequency dependent decrease that occurs in the magnitude, there is an additional effect, this time nonlinear, which causes a decrease in amplitude as frequency is increased. This can be seen through how the magnitude of the approximation depends on the frequency through the term $\alpha$ in Eq. [2].

The main source of effect of the input bias point $k_{+0}$ as well as the reverse rate in the system $k_-$ is through the crossover frequency $\omega_0$. Increasing either $k_{+0}$ or $k_-$ increases the crossover frequency and makes the phase of the output more in phase with that of the input. Additionally, $k_-$ appears in the numerator of the equation for the magnitude. To investigate these effects further, we consider the following two limits,

$$\omega_0 \ll \omega \implies \frac{A_{1b}}{b} = A_T \frac{k_-}{\omega_0 \omega},$$

$$\omega_0 \gg \omega \implies \frac{A_{1b}}{b} = A_T \frac{k_-}{\omega_0^2 - b^2/2}.$$

In both these limits, the magnitude is a decreasing function of $k_{+0}$. Contrastingly, $k_-$ has different effects in the two limits. In the high frequency limit, the magnitude is an increasing function of $k_-$. In the low frequency limit, the magnitude first increases and then decreases as $k_-$ is increased.

Finally, changing the total protein level $A_T$ scales the magnitude of the response and does not affect its phase. This can be seen through an examination of Eq. [2].
Together, these results present a systematic mapping of the dependence of the describing function approximation on the parameters of the input and of the system.

2.3 Approximation Error

An important qualifier for an approximation is an estimate of the approximation error. In the present case, how does the error depend on the forcing frequency? To address this, we computed the error as the difference between the actual system response and the one given by the describing function-based approximation. Specifically, we expressed this difference as magnitude of the mean square error between the two responses over one cycle relative to the magnitude of the first harmonic,

\[ e = \frac{1}{A_{1b}} \sqrt{\frac{1}{T} \int_{0}^{T} (y(t) - \tilde{y}(t))^2 dt} \] (3)

We obtained \( y(t) \) by numerically simulating Eq. 1 with sinusoidal forcing, as described above. For \( \tilde{y}(t) \), we used the expression,

\[ \tilde{y}(t) = A_{10} + A_{1b} \sin(\omega t + \theta) \]

We numerically computed the error for different values of the forcing frequency for a fixed value of other parameters. In these simulations, the error first decreases and then increases as frequency is increased. This computation also shows that the maximum magnitude of error for low frequencies (\( \omega \ll \omega_0 \)) is \( \approx 10\% \). These results present an estimate of error incurred through the use of this approximation.

3 Discussion

The technique of describing functions provides an elegant way to approximate the input-output response of a nonlinear system with an equivalent linearization. Here, we apply this technique on a computational model of a simple yet widely occurring biomolecular signaling system. First, we calculate the describing function approximation both analytically and computationally. Second, we systematically map the dependence of this approximation on the system parameters. Third, we computationally estimate the error in this approximation through the difference between the actual system and the describing function approximation. Together, these results should help to develop a framework for approximating biomolecular signaling systems using linear representations and corresponding error estimates.
Figure 3: Approximation Error. Solid line shows the computation of approximation error (Eq. 3) as forcing frequency is increased. Parameters are as in Fig. 2.

Describing function approximations of the sort presented here are often given the interesting interpretation of replacing a nonlinearity with a proportional-plus-derivative element [1]. In this interpretation, the coefficients of the proportional and derivative elements are functions of the forcing frequency and amplitude. In the example presented here, this interpretation takes the form,

\[ A_1(t) \approx A_{10} + \left[ \frac{A_{1b}}{b} \cos \theta + \frac{A_{1b}}{b} \sin \theta \frac{1}{\omega} \frac{d}{dt} \right] b \sin \omega t. \]

A natural task for future work is to catalog describing function approximations for different biomolecular systems. Examples that can be considered include signaling systems more complex than the present one as well as those that are capable of generating hysteric input-output maps. Consideration of these examples may suggest a classification of different behaviors that are dominant in biomolecular systems. The process of obtaining such simplified approximations may also offer ways to further develop the describing function method.

Developing approximate models is useful for multiple reasons, including for simplified representations of large-scale complex systems as well as highlighting key aspects that govern system behavior in all scales of systems. Both the reduced model as well as obtaining figure of merit for its goodness are important aspects of this goal. In this study, we have presented an example of this using the tool of describing functions to approximate the input-output response of a simple, yet widely occurring, biomolecular signaling system. Such examples should aid in developing a framework for analysis and design of large scale complex biomolecular systems.
References


