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The Use of Interval Methods in Signal Processing and Control for Systems Biology

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Abstract— **The development of approaches for understanding the complex dynamics of biological systems is a growing research area in electrical engineering, particularly in the fields of signal processing and controls. The focus of our research is the exploitation of the parallels between engineering and biology through the development of optimization and identification methods. Specifically, this research consists of developing methods for the estimation of unmeasured states, the identification of parameters of kinetic models and the validation of biochemical models. This work falls under the general research topic of systems biology.**

We explore the use of interval analysis in developing numerical algorithms for optimization and validation of systems biology problems. A major attribute of this method is that convergence to global minima is guaranteed. This paper includes a development of an adaptive interval optimization method based on the branch-and-bound method known as Smooth Interval Branch-and-Bound.

One potential impact of this research is the development of more accurate models of biological systems. This will aid in the design of drugs for cancer and disease treatment and aid in the study of how they propagate.

I. Introduction

Systems biology is an emerging research field that focuses on acquiring a system-level understanding of biological processes through multifaceted approaches based on analytical, computational, and experimental techniques. The idea of acquiring a system-level understand of biological processes is not a new concept. This idea has a long history and goes back to the days of Wiener [1] and Bertalanffy [2]. The renewed interest in this area is partly due to the tremendous strides that have been accomplished over the last decades in molecular biology, specifically in the areas of genomics and proteomics. These advancements in molecular biology and computer technology have equipped the research community with knowledge of molecular level biological components that describes biological systems corresponding to gene regulation, protein creation, cellular signaling, and metabolite production and consumption. An understanding of the individual components, however, is not adequate for interpreting the underlying system-level characteristics of a given biological process.

The advancements of quantitative experimental approaches has also aided in acquiring knowledge about these biological systems. These advancements have yielded high throughput experimental techniques that are capable of generating large amounts of biological, genomic, proteomic, and metabolomic data [3] [4] [5]. These techniques allow the collection of comprehensive data sets that are representative of the overall system performance of the biological process [6]. This increase in data is responsible for the increased interest in the areas of bioinformatics and computational biology. However, a systems level understanding of biological systems will require a multifaceted approach to analyzing this data that goes beyond the traditional heuristic and statistical approaches used in computational biology and bioinformatics today. One approach would be to integrate methodologies from systems and control theory along with computationally intelligent approaches in order to acquire accurate analytical representations that would aid in the analysis and control of these biological systems.

Two important steps that are needed in order to gain this systems-level understanding of biological systems are: (1) the identification of the system structure and associated components of the system and (2) identification and validation of the dynamics of the system [7]. Identification of the system structure is in itself a difficult task. Current knowl-

edge that has been acquired from advancements made in the fields of molecular and computational biology has aided tremendously in the generation and verification of valid network topologies for biological systems. Network topologies have been derived from varying amounts of information, which include sequence analysis [8], in-depth study of molecular interactions, and gene expression analysis [9] [10]. The identification of analytical models that are capable of replicating the true dynamics of these systems seems to be a more elusive objective. This is still an open research area where computationally intelligent approaches, particularly those based on interval arithmetic [11][12][13], can be used to help solve various aspects of this problem.

Due to the complex nature of biological systems, traditional analytical approaches to analyzing these processes often fail. Thus, there is a a need to integrate computationally intelligent approaches into these analysis schemes. Interval analysis [13] [14] represent a class of computationally intelligent approaches that can be readily integrated into analysis schemes such as state estimation, parameter identification, and model validation for biological systems. Several attractive attributes of interval analysis include their ability to locate all solutions set for nonlinear equations and their ability to provide reliable bounds on these solution sets [12]. In our previous work, we have developed an algorithm for adaptive filtering that can be extended to address these systems biology problems [15].

The outline of this paper is as follows: Section II discusses the background material of interval analysis and adaptive filters. A description of the development of an adaptive global optimization method, using an adaptive filtering formulation, for parameter identification is discussed in Section III. Section IV outlines areas in systems biology where interval approaches can be used. A synopsis of this work will be provided in the conclusion, Section V.

II. Background

A. Interval Analysis

Interval Arithmetic [11], the primary tool for performing interval analysis, was developed as a way of bounding the errors due to rounding and quantization that accrue during numerical computations, and is based on the manipulation of intervals, or sets, of real numbers, instead of individual real numbers. An interval X is defined as $X = [a, b]$ such that $X = \{x \in \mathbb{R} : a \leq x \leq b\}$. A real number x is defined as a *degenerate* interval if $X = [x, x]$. The basic arithmetic operations of addition, subtraction, multiplication and division are generally defined for intervals as:.

$$X \star Y = \{x \star y : x \in X, y \in Y\} \qquad (1)$$

where $\star$ denote one of the interval arithmetic operations. An important aspect of interval computations is that outward rounding is used to guarantee that the infinite precision result is within the bounded interval. To illustrate, consider a function $f(\mathbf{x})$ over a region $\mathcal{D}$ such that $f_L \leq f(\mathbf{x}) \leq f_U, \ \forall \mathbf{x} \in \mathcal{D}$. Note that f_L and f_U may not be exactly representable in a floating-point or fixed-point number system. The result of computing the range of f over $\mathcal{D}$ using interval arithmetic will be an interval $\mathbb{F} = [\underline{f}, \bar{f}]$ where $\underline{f}$ is the largest machine representable number smaller than or equal to f_L, and $\bar{f}$ is the smallest machine representable number that is larger than or equal to f_U. By rounding f_L to $\underline{f}$ and f_U to $\bar{f}$, a process called *outward rounding*, $\overline{\mathbb{F}}$ is guaranteed to contain the true range, $[f_L, f_U]$.

Interval functions are typically used to provide sharp bounds on the range of real functions over an interval. This is done by using the principle of *monotonicity*. An interval function, F, is said to be *inclusion monotonic* if $X_i \subset Y_i \ (i = 1, 2, \ldots, n)$ implies that $F(X_1, X_2, \ldots, X_n) \subset F(Y_1, Y_2, \ldots, Y_n)$. Consider the following theorem:

***Theorem** 1:* [12] Let $F(X_1, \ldots, X_n)$ be a rational interval function. Assume F is evaluated using a fixed form with a fixed sequence of operations involving only interval addition, subtraction, multiplication, and division. Then F is inclusion monotonic.

The above theorem leads to the following *Fundamental Theorem of Interval Analysis* [12]. One of the far-reaching consequences of this theorem is that it allows for the solution of global optimization problems.

***Theorem** 2:* [12] Let $F(X_1, \ldots, X_n)$ be an inclusion monotonic interval extension of a real function $f(x_1, \ldots, x_n)$. Then $F(X_1, \ldots, X_n)$ contains the

range of values of $f(x_1, \ldots, x_n)$ for all $x_i \in X_i$ $(i = 1, \ldots, n)$

Interval functions can be implemented in multiple forms. The standard form, called the *Natural Interval Extension* directly translates arithmetic operations into their interval equivalent. Other forms include the Centered Form [16][17] which incorporates interval gradient information and the Taylor Form [18] which uses both gradient and Hessian information.

B. Adaptive Signal Processing

Adaptive Infinite Impulse Response (IIR) filters [19][20] represent a particular class of filters whose output is formed as a linear combination of past and present inputs and past outputs. They are particularly attractive solutions for applications where power and memory resources are limited. Consider the general adaptive filtering setup shown in Fig. 1, where $d(n)$ is a stochastic, discrete-time sequence called the desired signal, $y(n)$ is the filter output and $e(n)$ is the output error. The input, $x(n)$, is a stochastic, discrete-time sequence whose statistical characteristics are assumed to be known (at least partially). The linear difference equation governing the output of the adaptive filter is:

$$y(n) = \sum_{i=0}^{N-1} b_i(n)x(n-i) + \sum_{j=1}^{M} a_j(n)y(n-j) \quad (2)$$

where the b_i's and a_j's are referred to as the feedforward and feedback filter coefficients respectively. N is the length of the feedforward section of the filter and M is the length of the feedback section. The error signal, $e(n)$, is given by:

$$e(n) \;=\; d(n) - y(n). \quad (3)$$

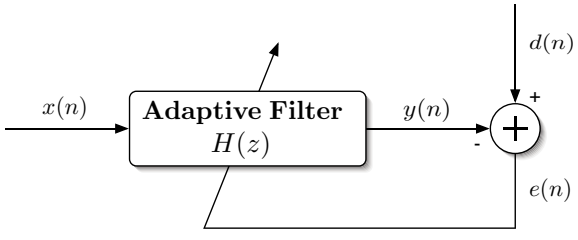

Fig. 1. Basic Adaptive IIR Filtering Setup

One of the most fundamental properties of adaptive filters is their self-adjusting nature. Filters adjust their coefficients in such a way that performance objectives are met when a given cost or performance function, ξ, is minimized. Although there are several cost functions to choose from, the most widely used one, primarily because of its simplicity, is the Mean Square Error (MSE) function given by

$$\xi(n) = \mathrm{E}\left[e^2(n)\right], \quad (4)$$

where $\mathrm{E}(\cdot)$ is the expectation operator. It represents the optimum criterion when distribution of the input data is Gaussian.

Stearns [21] showed that in general, the MSE cost function of an adaptive IIR filter is multimodal and so minimization of ξ in order to meet performance objectives requires the use of global optimization algorithms. Several stochastic global optimization algorithms including the computational intelligent methods of Simulated Annealing [22] and Genetic Algorithms (GA) [23] have been used to minimize ξ. However, as expected, they only converge to global minima with probabillity one. Since convergence to local minima yields suboptimal solutions, these algorithms are not suitable for use in practice.

We have focused part of our research efforts on the development of an adaptive IIR filtering algorithm that addresses the issue of convergence to local minima. This effort has resulted in the development of an adaptive Branch-and-Bound global optimization method for signal processing called the Smoothed Interval Branch-and-Bound (SIBB) [15]. This algorithm is discussed further in Section III.

III. Adaptive Systems

One method being investigated for parameter identification is the Smoothed Interval Branch-and-Bound (SIBB) algorithm [15]. This adaptive method is designed to minimize the MSE cost function of adaptive IIR filters despite its multimodal nature of ξ, as defined in (4). The SIBB algorithm is based on the global optimization technique of Branch-and-Bound [24][25][12], which has a theoretical guarantee of convergence to global minima. Branch-and-bound techniques locate the global minima of functions by splitting up the search space into sub-regions, determining the range of the function over each region (a process called *bounding*) and

discarding those regions that are guaranteed *not* to contain global minimum point(s).

The process of bounding the cost function is a critical one for two reasons. First, computations have to be performed in such a way that the bounds obtained are guaranteed to contain the infinite precision range of ξ despite rounding errors which occur naturally on digital computers [12]. Secondly, the computation of bounds is complicated by the fact that ξ is a stochastic function of $e(n)$. We addressed the first issue by employing interval arithmetic for performing computations as discussed in Section II-A, and resolved the second issue by developing an exponential weighting scheme which is presented in detail next.

A. Exponential Weighting Scheme

The MSE cost function, ξ, is a function of the output error, $e(n)$, which is a random process. In practice, only one realization of $e(n)$ is available and so, ensemble averages cannot be computed. However, if $e(n)$ is assumed to be ergodic, ξ can be estimated using time averages. Based on this, we developed an exponential weighting (*smoothing*) scheme for estimating ξ at time n as follows:

$$\bar{\hat{\xi}}(n) = \frac{1}{K} \sum_{i=n-K+1}^{n} \lambda^{n-i} e^2(i) \qquad (5)$$

for $n = K,\ 2K,\ 3K,\ \ldots$ The parameter λ is called the forgetting factor and K is the size of the window over which the cost function is averaged. The forgetting factor, λ, controls the amount of memory in the estimation process and takes on values such that $0 < \lambda \leq 1$.

B. Smoothed Interval Branch-and-Bound Algorithm

The use of the exponential weighting scheme described in Section III-A, together with interval arithmetic, results in the SIBB algorithm [15]. It is an iterative algorithm designed to process discrete-time data and does not make use of gradient information. The feasible region, **S**, represents a large enough region within which global minima are believed to lie. The smoothing step, where averaging of ξ takes place according to (5), is the most computationally intensive step. The algorithm spends K time steps at this stage every time through before moving on to update the filter coefficients. Thus, SIBB processes blocks of K data samples at a time and updates filter coefficients once every K time steps.

Memory is required to track boxes in the system that require further processing, and the total amount of memory needed is linked to the branching strategy employed in the splitting step. This is because it is a function of the number of boxes produced after splitting a single box, which is exponentially related to the number of dimensions that are split, k. Specifically, each box produces q^k new boxes, where q represents the number of times each dimension is split. This phenomenon of exponential growth is called the *curse of dimensionality*. Although several methods have been proposed for splitting boxes [24], no particular strategy has been found to be the best. For instance, while Hansen [12] suggests splitting boxes along the two largest dimensions (each dimension being split in two), Markót *et. al.* [26] note that splitting along one dimension is sometimes a better strategy. In our implementations, $k = 2$ and $q = 1$.

At termination, SIBB not only provides the coordinates of the global minimum point(s), but also returns bounds on the minimum value of the ξ.

IV. Systems Biology

A. State Estimation

Accurate mathematical models that are capable of capturing the dynamic characteristics of biological systems have been an attractive objective in the field of systems biology. Many system identification approaches require measurements of all time-varying components of the system in order to be effective. The fact remains that even though there have been great advancements in the development of high throughput experimental techniques, it can be very time consuming, expensive, or sometimes just impossible for these techniques to measure all time-varying components in the systems. Thus, most system identification approaches remain underutilized in this field of research. One means of addressing this bottleneck in biological systems modeling is to develop techniques that are able to estimate the unmeasured components of the system using the measurements that can be acquired from current experimental techniques [27] [28] [29] [9].

Biochemical networks are often represented in a nonlinear state-space form. The discrete forms of

these representations can often be expressed as

$$\mathbf{x}_{k+1} = \mathbf{A}\mathbf{x}_k + \mathbf{B}\mathbf{v}_k(\mathbf{x}_k, \mathbf{p}) \tag{6}$$

where $\mathbf{x}$ represents the components or states of the system, $\mathbf{v}$ represents the state-dependent nonlinearity that drives the dynamics of the system, $\mathbf{A}$ describes the linear degradation/production of the states, and $\mathbf{p}$ is the vector of kinetic parameters. The matrix $\mathbf{B}$ is known as the stoichiometric matrix and is derived completely from the network topology.

State estimation methods, similar to those outlined by Mahadevan et al. and Gadkar et al., are based on the premise that biological systems operate according to some internal optimal objective. Equation (6) is used in combination with the optimal objective to form a constrained optimization problem for calculating the estimates of the unknown dynamics of the system. Local search algorithms present an attractive means of implementing this constrained optimization due to their low complexity and are often used in these types of estimation procedures [29] [9]. Local search algorithms, however, have several drawbacks and, except for the most simplest of optimization problems, often produce suboptimal results. Global search algorithms are more robust and often produce results that are better than local search methods. Williams et al. demonstrated that a constrained global search algorithm based on Real-Coded Genetic Algorithms (RCGA) was able to produce estimates of the unmeasured states that more closely matched the true dynamics of the biological system [30] as compared with standard nonlinear programming methods. RCGA, however, is still a stochastic global search algorithm and is not guaranteed to yield the most optimal solution for any given optimization problem.

Guaranteed estimation of the states for a nonlinear system can be achieved using interval methods, as describe in [13]. These interval based solutions take into account the uncertainties without applying local linearization. Guaranteed estimation is achieved by either bounding the appropriate variables or through constraint satisfaction.

B. Parameter Identification

The vector $\mathbf{p}$ in (6) represents a collection of kinetic parameters that are often very difficult to estimate experimentally. Parameter identification, or system identification, is often used as a means of estimating these parameters given that we have adequate knowledge about the system. This includes having knowledge about the true functional form of the state-dependent nonlinearity in (6) as well as full state information over the time interval of interest. Estimation procedures, like the one described above, can be employed if the complete state of the system cannot be measured. The parameters $\mathbf{p}$ are then varied in order to minimize the error between the states from the analytical model and the measurements of the states. This process is illustrated in Figure 2.

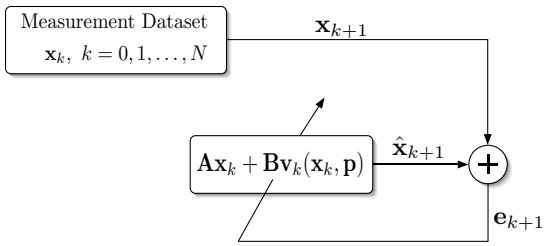

Fig. 2. Parameter Identification Procedure

The number of kinetic parameters for biological systems are often large, resulting in a high dimensional optimization problem. Due to the curse of dimensionality, high dimensions on the parameter vector can often have adverse affects on the optimization algorithm, leading to a low confidence in the estimates that are produced. In these situations, interval methods for parameter estimation can be used to obtain not only the estimates, but also a measure of the level of confidence. This measure of confidence is determined by the width of the interval estimates. In addition, inherent to interval analysis is that appropriately setting the bounds on the initial estimates also bounds the search space [13].

C. Validation of Biochemical Models

The model described in (6) is often used as a first step in analyzing the system aspects of biological system. The fact is that most biological system have some level of uncertainty associated with them. A system with uncertainty is represented as

$$\mathbf{x}_{k+1} = \mathbf{A}\mathbf{x}_k + \mathbf{B}\mathbf{v}_k(\mathbf{x}_k, \mathbf{p}) + \beta_k. \tag{7}$$

The added term β_k describes any uncertainty associated with the system. This uncertainty may be due to noise in the system, unknown or un-modeled dynamics of the system, uncertainty in the initial condition, or uncertainty in the kinetic parameters. The problem now is to determine whether the measurement data set obtained from experimental procedures is consistent with the given uncertainty model. In other words, we wish to establish whether the observed data could have been produced by the model given some bounded uncertainty within the system [31]. This is called the model validation problem. Model validation serves as a precursor to many aspects of system analysis. The use of interval methods for performing model validation represents a recent research topic within systems biology, see [32] and the upcoming NATO Symposium on Computational Uncertainty [33]. Furthermore, model validation for systems biology becomes a major factor in insuring that system models developed mimic the actual biological system very closely. This will insure that the medical community has confidence in the work of system biologist and there results.

D. Application of SIBB to System Biology

The solution of parameter identification and state estimation problems found in Systems Biology, as well as the validation of the dynamical models used requires computationally intelligent schemes just as adaptive filtering does. As a result, with some modifications, algorithms such as SIBB can be used to solve these problems. For instance, in determining the kinetic parameters, $\mathbf{p}$, of the nonlinear, state-space model given in (6), the problem can be placed in the adaptive filtering framework where the filter output represents estimates of the state vector, denoted by $\hat{\mathbf{x}}_k$. The error, $\mathbf{e}_k$, will then be the difference between the measured data, $\mathbf{x}_k$, and $\hat{\mathbf{x}}_k$:

$$\mathbf{e}_k = \mathbf{x}_k - \hat{\mathbf{x}}_k \tag{8}$$

The goal here will be to minimize the error in the mean-square sense. The advantage of using SIBB is that although it was designed for adaptive linear systems, it can be easily extended for use with nonlinear systems similar to that in (6). One extension that has to made to SIBB is to give it the capability of handling linear constraints.

V. CONCLUSION

We have discussed in this paper our research thrust in the field of systems biology. In general, the research consist of the estimation of unmeasured states, the identification of kinetic model parameters, and the validation of dynamical chemical models. We use the reliable computational and numerical method of interval analysis to solve the above problems. These methods are important for optimization because convergence to the global minima is guaranteed. Also, computational and measurement uncertainty can be incorporated into the estimation and identification procedures. One such method is the Smoothed Interval Branch-and-Bound (SIBB) algorithm. Though the SIBB algorithm was developed for solving the adaptive IIR filtering problem, it can be used to solve the similar problem in system biology of parameter identification.

Accurate models of biological systems will enable researchers to observe and predict the behavior due to internal and/or external perturbations of the system. This knowledge can have a direct impact on the design of drugs with fewer side effects as well as the treatment of cancer and diseases for which, presently, there is no cure.

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