Biomathematics and Interval Analysis: A Prosperous Marriage

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Abstract. In this survey paper we focus our attention on dynamical bio-systems involving uncertainties and the use of interval methods for the modelling study of such systems. The kind of envisioned uncertain systems are those described by a dynamical model with parameters bounded in intervals. We point out to a fruitful symbiosis between dynamical modelling in biology and computational methods of interval analysis. Both fields are presently in the stage of rapid development and can benefit from each other. We point out on recent studies in the field of interval arithmetic from a new perspective — the midpoint-radius arithmetic which explores the properties of error bounds and approximate numbers. The midpoint-radius approach provides a bridge between interval methods and the "uncertain but bounded" approach used for model estimation and identification. We briefly discuss certain recently obtained algebraic properties of errors and approximate numbers.

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INTRODUCTION

In this survey paper we focus our attention on biological dynamical systems involving uncertainties. Such systems are a subject of investigation at present by a number of researchers. We quote [12]:

"*Uncertain* means here that some part of the model is not precisely known, or there may be some noise. Given some outputs (the measurements), one tries to estimate (or *identify*) the unknown variables or parameters. ... Traditional approaches used in biological sciences are often based on regression methods (for instance least-squares methods) by minimization of the deviation between the data and the model, or more elaborated criterions [38]. These approaches are powerful and easy to implement, but, in the case of uncertain models, might present drawbacks:

— In the presence of uncertainties (or noises) on the model, the asymptotic convergence of the average estimates is guaranteed under some statistical hypotheses (mean values and covariances of the noises need usually to be known). An important issue for the biologist is then to decide if these hypotheses are fulfilled on the data. Very often, these hypotheses are difficult or impossible to check.

— Because of uncertainties, a static estimation of the initial values of the state variables is in general not adapted to the estimation of current values of these variables, there is a need for an adaptive dynamic method.

— Let us suppose that we want to estimate a parameter; if this parameter is in fact a forcing term slowly varying with time, it is interesting to reconstruct these variations with the help of a dynamic method."

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One of the simplest mathematical tools that can be applied for the treatment of uncertainties is interval analysis based on interval arithmetic. Interval arithmetic and interval analysis are rapidly developed fields of applied mathematics.

In Section 2 we present a simple example illustrating the complexity of bio-process modeling and the need for a relevant treatment of uncertainties. In Section 3 we focus attention on recent studies in the field of interval arithmetic from a new perspective — the midpoint-radius arithmetic which explores the properties of errors and approximate numbers.

BIOMATHEMATICAL MODELLING

Biomathematics is a rapidly developed scientific field[1].We focus our attention on biological dynamical systems involving uncertainties. Such systems arise typically every time when proteins[2] are involved, or when (micro-)organisms are involved, as then again proteins play an active role. Typical complex biological system arise in the field of protein dynamics[3], in particular enzyme kinetics[4], metabolic networks[5] and signal pathways[6]. In biology, proteins bear various names depending on their physiological functions (enzymes, receptors, ion channels, hormones, structural proteins, etc.), however from an abstract mathematical point of view their dynamics is similar. As a typical case we next focus on the dynamics of the enzyme proteins, familiar as enzyme kinetics. Enzymes are proteins partaking in metabolic processes.

Case study: enzyme kinetics

Modelling in enzyme kinetics is based on mass action law. Recall the mass action law in its dynamic form. In the simplest case when two substances A, B interact to produce a third substance N, $A+B \to N$, according to mass action law we have

$$\frac{dn}{dt} = kab, \tag{1}$$

wherein $a = a(t)$, $b = b(t)$, $n = n(t)$ are resp. the concentrations of substances A, B, N. Denoting a_0, b_0 the initial concentrations of A, B, and taking into account that $a = a_0 - n$, $b = b_0 - n$, the latter equation becomes

$$\frac{dn}{dt} = k(a_0 - n)(b_0 - n), \;\; n(0) = 0.$$

This simple IVP for ODE can be integrated analytically:

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[1] http://en.wikipedia.org/wiki/Mathematical_and_theoretical_biology
[2] http://en.wikipedia.org/wiki/Proteins
[3] http://en.wikipedia.org/wiki/Protein-protein_interaction
[4] http://en.wikipedia.org/wiki/Enzyme_kinetics
[5] http://en.wikipedia.org/wiki/Metabolic_network
[6] http://en.wikipedia.org/wiki/Signal_transduction

$$n(t) = \begin{cases} a_0 \dfrac{e^{kt(a_0-b_0)}-1}{(a_0/b_0)\,e^{kt(a_0-b_0)}-1} & \text{if } a_0 \neq b_0 \\ \dfrac{a_0^2 kt}{a_0 kt+1} & \text{if } a_0 = b_0. \end{cases}$$

The graph of the solution is presented on Figure 1 for three different sets of values of the parameters a_0, b_0.

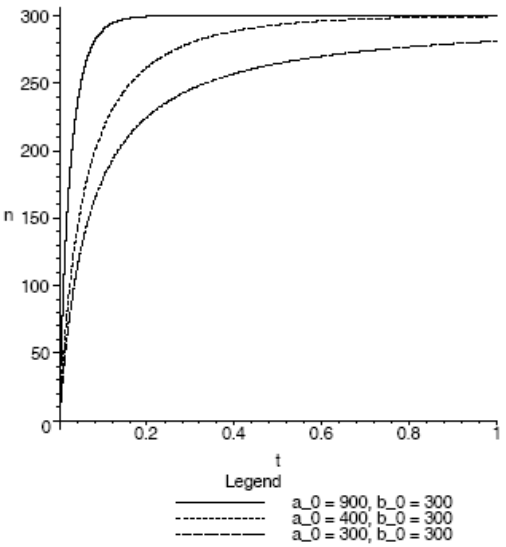

FIGURE 1. Simplest mass-action dynamics

Chemical reactions are modeled using mass action law usually in the form (1). However, in contrast to the simple dynamics of chemical processes based on mass action law, the dynamics of interactions involving proteins is much more complex. This is quite intriguing if we note that the only difference consists in that proteins do not interact instantaneously but for a certain period of time they "do some work" making "complexes" with some other substances or proteins. During that period proteins are engaged (bound) and are inactive. The simplest enzyme kinetics process [29] involves a substrate S, an enzyme E and a product P

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} SE \overset{k_2}{\to} P + E, \tag{2}$$

where SE is the bounded enzyme. Process (2) is easily modelled applying several times the mass action law [29]. Before presenting the corresponding model — equations (4) below — let us present the approximate ODE for the concentration s of the substrate S is

$$\frac{ds}{dt} = -\frac{Qs}{K_m + s}, \quad s(0) = s_0 \tag{3}$$

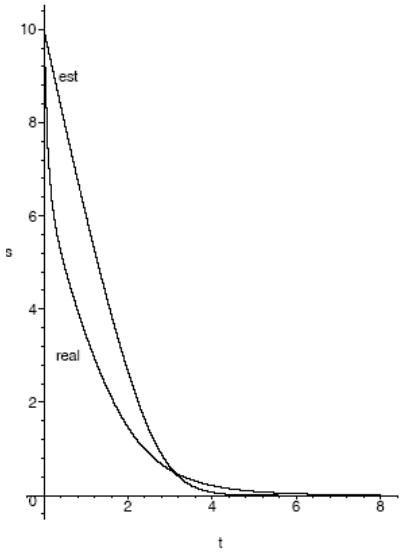

FIGURE 2. Dynamics of substrate uptake

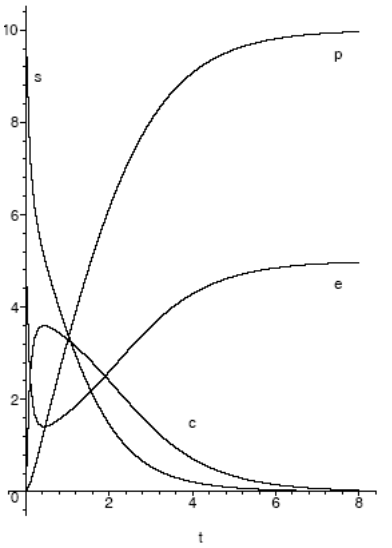

FIGURE 3. Dynamics of simplest enzyme process

Equation (3) is usually known as Michaelis-Menten equation; it gives the dynamics of the substrate concentration s. Figure 2 presents the substrate uptake in two versions: one (graph denoted "est") according to (3) and another (graph denoted "real") computed according to the realistic system (4) to be explained below. The comparison shows how inaccurate can be the use of model (3) usually applied by biologist [13] for the computation of the Michaelis-Menten constant K_m which characterizes the activity of the protein. Already here we notice that the constant K_m computed on the base of (3) will contain some error as the realistic uptake curve differs form the one computed by means of the approximate model (3).

The realistic enzyme kinetics model based on the mass action law according to scheme (2) involves the concentration c of the bounded enzyme SE [29]:

$$\begin{aligned} \frac{ds}{dt} &= -k_1 es + k_{-1} c, & \frac{de}{dt} &= -k_1 es + (k_{-1} + k_2) c, \\ \frac{dc}{dt} &= k_1 es - (k_{-1} + k_2) c, & \frac{dp}{dt} &= k_2 c, \\ & s(0) = s_0,\ e(0) = e_0,\ c(0) = 0,\ p(0) = 0, \end{aligned} \tag{4}$$

wherein e, c are the concentrations of E, SE, resp., and p is the concentration of the product P. Figure 3 presents the dynamics of model (4). The four state variables are presented. One sees clearly the boundary layer w. r. t. the "stiff" variables for the enzyme concentrations e, c. Note that the graph of the substrate concentration s is the same as the one shown on Figure 2. (marked as "real"). The difference between the two graphs is small when the ratio $e(0)/s(0)$ is small (say, of order 10^{-7}), however in many real situations this ratio may not be small [29], [34].

One can see already in this first steps of the introduction to simplest enzyme kinetics models elements of the holistic[7] biology[8]: the simple behavior of the dynamics of the mass action law transforms into the rather complicated behavior of the Michaelis-Menten dynamics where some variables change extremely rapidly relative to others. Marxsists[9] may find here a confirmation of Hegel's law[10] that quantity is transformed into quality (quantitative changes become qualitative ones).

We see that modeling of the dynamics of the concentration of even a single protein (with just one site) leads to complex and sensitive mathematical problems. Imagine how complex things become when several interacting proteins are involved, as is the case of modeling metabolic processes, signaling pathways, etc. Similar is the situation in problems related to bio-reactors, waste water treatment etc., where microbial populations are involved. In fact the interactive parts in microbial species dynamics are again proteins, which explains why related mathematical problems usually involve Michaelis-Menten type kinetics.

Bio-modeling and interval methods

Biological dynamic systems typically involve: i) uncertain (interval) data; ii) numerical or/and inherent sensitivity; iii) structural uncertainties that imply the need of model validation. Several contemporary mathematical tools are used for the treatment of problems involving uncertainties. Amongst these tools are fuzzy-set analysis, set-valued analysis, interval analysis and control theory under uncertainties.

Interval analysis is a rapidly developed field of applied mathematics, providing practically useful mathematical tools for reliable computation. A number of researchers and research groups worldwide are presently using interval analysis tools while modeling bio-processes. Important work within these lines has been done by French researchers who focus attention to so-called observable variables (like biomass concentration) which cannot be measured in real time during biotechnological processes. For such variables one can construct interval bounds on the bases of feedback relations depending only on measurable (in real time) variables, so-called interval observers, see, e.g., [10], [11], [12], [15]. Several American researchers investigate bifurcations related to dynamical bio-processes pointing attention to cases when the type of the equilibrium points of sensitive dynamical processes may change with the uncertainties of the input coefficients [8], [9], [14]. Other American researchers apply interval and fuzzy methods to various application areas related to biology and medicine [18], [19]. Important related work has been done by German [36], [37], and Spanish researchers [31], [32].

Some work in the above mentioned directions is also done in the Department Biomathematics of the Institute of Mathematics and Informatics at the Bulgarian Academy of Sciences[11] [1]–[6], [21], [24].

In what follows we focus our attention to interval analysis and interval arithmetic.

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[7] http://en.wikipedia.org/wiki/Holism

[8] http://en.wikipedia.org/wiki/Systems_biology

[9] http://www.marxists.org/reference/archive/cooper/hegel-marx/ch01.htm

[10] http://www.marxists.org/reference/archive/hegel/index.htm

[11] http://www.math.bas.bg/index.html/

INTERVAL ANALYSIS AND INTERVAL ARITHMETIC

Intervals are usually conceived as compact sets of real numbers. Interval arithmetic defines operations and relations over intervals in a similar way as done in the arithmetic for real numbers. Two such operations are addition and multiplication by scalars (multiplication of intervals is also defined but for simplicity we shall not consider this operation here); another important relation is familiar inclusion.

Interval arithmetic as algebraic structure has already more than half century of scientific development after the fundamental work of T. Sunaga [26], [35]. During this development many efforts have been invested in studying interval arithmetic leading to axiomatic definitions of interval spaces, cf. [16], [17], [33].

It has been observed that abstract interval spaces, so-called "quasi-linear spaces" [22], [23] are direct sums of two spaces: i) the familiar vector space, and ii) so-called symmetric quasi-vector space. The first space corresponds to the set of degenerate (point) intervals, whereas the second one — to the space of symmetric intervals. Thus every interval is a sum of a real number and a symmetric interval. In other words, the natural presentation of an interval (from the point of view of abstract theory) is by means of a pair $(a';a'')$ of two coordinates, where the first one a' is the midpoint of the interval, and the second one a'' is the radius of the interval.

Although both forms — the end-point form (also known as "inf-sup" form) and the mid-rad form — represent same the objects, they induce two different aspects: the inf-sup form corresponds to the "interval-as-set" aspect, whereas the mid-rad form induces the "approximate-number" aspect. The "interval-set" aspect is usually related to our perception of "wide" intervals that commonly appear as input data for problems with "significant" uncertainties, whereas the "approximate-number" aspect relates to "narrow" ("tiny") intervals that correspond to relatively small uncertainties in the input data and/or appear during computations due to round-off and truncation errors. In this second "narrow" case we consider the midpoint as a "main value" of an "approximate number" and the radius — as an error bound, briefly: "error". Instead of "error" some authors prefer to use the more technical term "noise."

Main idea of interval analysis

Traditional use of computer systems produce floating point results for the solutions of mathematical problems, such as $s = 3.47492599546923$. Such a result does not tell us anything about its accuracy, in other words we do not know how many digits are true (in fact, in some cases it may happen that there are no true digits at all). An alternative approach, used in interval analysis, is when we want to obtain a result in the form: $s \in [3.47492598, 3.47492600]$. A similar form is $s = 3.47492599 \pm 10^{-8}$.

When using the "interval" approach our aim is to obtain a mathematical statement saying: "the result is bounded within the interval ...", or: "the upper bound of the error in the computed result is ...". The idea of interval analysis is namely to obtain results in such form. The aim is to organize numerical algorithms in such a way that they produce true mathematical statements saying where computed results actually lie. A fundamental tool of interval analysis is interval arithmetic. The following examples gives an idea of interval arithmetic and interval analysis.

Assume we wish to compute the function $f(x) = \pi + 2x$ at the point $1/3$, that is $f(1/3) = \pi + 2(1/3)$, knowing intervals for π and $1/3$:

$$\pi \in [3.14159265, 3.14159266] = \Pi, \quad 1/3 \in [0.33333333, 0.33333334] = \Delta.$$

Then it is natural to write $f(1/3) \in \Pi + 2 * \Delta$ wherein:

$\Pi + 2 * \Delta = [3.14159265, 3.14159266] + [0.33333333, 0.33333334] = [3.80825931, 3.80825933]$.

Writing this we actually define the operations addition and multiplication by scalars of intervals. More formally, denote $\mathbb{R}$ the set of reals, $\mathbb{IR}$, $\mathbb{IR}^n$ the sets of intervals, resp. interval vectors. For a given real function $f(\alpha, \beta, ...), \alpha, \beta \in \mathbb{R}$, and intervals $a, b.... \in \mathbb{IR}$ we write for the range of f: $f(a, b, ...) = \{f(\alpha, \beta, ...) \mid \alpha \in a, \beta \in b, ...\}$. In particular we define for $a, b, ... \in \mathbb{IR}^n$, $\gamma \in \mathbb{R}$, $\alpha \in \mathbb{R}^n$:

$a + b = \{\alpha + \beta \mid \alpha \in a, \beta \in b\}$ addition;

$\gamma * b = \{\gamma \cdot \beta \mid \beta \in b\}$ multiplication by scalars;

$a \subseteq b \Longleftrightarrow \alpha \in a \Longrightarrow \alpha \in b$ inclusion.

The interval operations addition and multiplication by scalars are inclusion isotone in the sense that i) $a \subseteq c \Longrightarrow a + b \subseteq c + b$; ii) $a \subseteq c \Longrightarrow \gamma * a \subseteq \gamma * c$. Due to inclusion isotonicity of interval operations the following property holds true.

Inclusion monotonicity property. If $a_i \subseteq b_i$, $a_i, b_i \in \mathbb{IR}$, $i = 1, ..., n$, then $\sum \gamma_i * a_i \subseteq \sum \gamma_i * b_i$.

The interval operations and relations can be easily written in terms of end-points (inf-sup format) or midpoint-radius coordinates (mid-rad format). Whenever implemented in a software environments interval operations are rounded outwards, in accordance with the inclusion monotonicity property. So computer results always contain the true ones, independently of round-off errors. Besides, truncation errors can (and should) be controlled by suitable modifications in the interval numerical algorithm.

Computation of functional ranges

We illustrate the application of interval analysis to computation of functional ranges. For $a_i \in \mathbb{IR}$, $i = 1, ..., n$, using interval addition and multiplication by scalars, we have

$$\{\sum_{i=1}^{n} \gamma_i \cdot \alpha_i \mid \alpha_i \in a_i\} = \sum_{i=1}^{n} \gamma_i * a_i = \gamma_1 * a_1 + \gamma_2 * a_2 + ... + \gamma_n * a_n. \tag{5}$$

Note that in (5) we have just substituted (re-defined, over-loaded) the numeric operations by interval ones.

As an example consider a Lagrange polynomial[12] $\sum l_i(\xi_1, ..., \xi_n; \tau) \cdot \eta_i$ through n given points (ξ_j, η_j), $j = 1, ..., n$, in the plane Oxy. Let the y-values η_i be "uncertain but bounded" in given intervals y_i, that is $\eta_i \in y_i \in \mathbb{IR}$. Then using (5) we have for any fixed τ:

$$\{\sum l_i(\xi_1, ..., \xi_n; \tau) \cdot \eta_i \mid \eta_i \in y_i\} = \sum l_i(\xi_1, ..., \xi_n; \tau) * y_i. \tag{6}$$

The right-hand side of (6) is an interval function (interval Lagrange polynomial) in the sense that it takes interval values. Such function can be effectively computed within a software environment allowing interval arithmetic. Moreover, such an environment may account easily for computational (round-off) errors using directed roundings (available in IEEE 754 standard) on the basis of the inclusion monotonicity property.

[12] http://en.wikipedia.org/wiki/Lagrange_polynomial

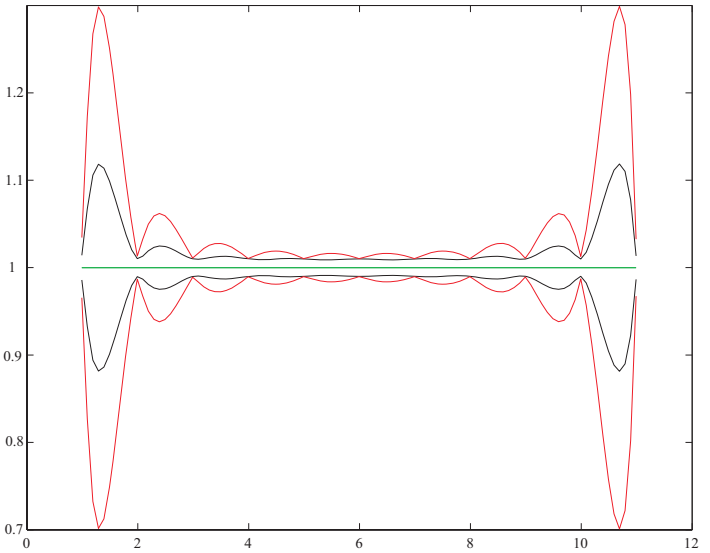

FIGURE 4. Interval Lagrange polynomial interpolating the points $(j,0),\ j=1,...,11$, whenever the zero values contain noise

Figure 4 presents a Lagrange polynomial for ten points $(\xi_j = j, \eta_j = 0), \quad j = 1,...,11$, which is zero if $\eta_j = 0$ exactly. The outer envelope represents the same polynomial with "noise intervals" $\eta_j \in y_j = [-\varepsilon, \varepsilon]$, wherein $\varepsilon = 0.05$, and the inner envelope with slightly smaller "noise intervals" $\eta_j \in [-0.02, 0.02]$. As we can see from the graphics the interval Lagrange polynomial presents a clear visualization of the distribution of the noise/error over the interpolating intervals (extrapolation part has not been shown as there the error becomes too large).

Interval arithmetic

Apart of the inclusion isotonicity property interval arithmetic operations possess interesting properties. Thus intervals are elements of a quasi-linear space that is axiomatically defined as follows.

Quasi-linear space. An algebraic structure[13] $(\mathbb{Q},+,\mathbb{R},*)$ is a *quasi-linear space (of monoid structure) over* $\mathbb{R}$, if for all $A,B,C \in \mathbb{Q},\ \alpha,\beta,\gamma \in \mathbb{R}$:

$$(A+B)+C = A+(B+C), \tag{7}$$

$$\exists\, 0 \in \mathbb{Q} : A+0 = A, \tag{8}$$

[13] http://en.wikipedia.org/wiki/Algebraic_structure

$$A+B = B+A, \tag{9}$$
$$A+C=B+C \implies A=B, \tag{10}$$
$$\alpha*(\beta*C) = (\alpha\beta)*C, \tag{11}$$
$$1*A = A, \tag{12}$$
$$\gamma*(A+B) = \gamma*A+\gamma*B, \tag{13}$$
$$(\alpha+\beta)*C = \alpha*C+\beta*C, \quad \text{if } \alpha\beta \geq 0. \tag{14}$$

Note that if we omit condition $\alpha\beta \geq 0$ in the last axiom (14), then we obtain a definition of a linear (vector) space! Note also that the algebraic structure $(\mathbb{Q},+)$ as defined by axioms (7)–(10) is a commutative (abelian) cancellative monoid which is embedable in a group. When embedding $(\mathbb{Q},+)$ in a group and isomorphically extending multiplication by scalars we obtain a quasi-linear space of group structure [22], [23]. The latter is a direct sum of a vector space and a symmetric quasi-linear space [22]. (Symmetric here means: $(-1)*A=A$.) We thus obtain that the algebraically natural presentation of intervals is the mid-rad one, midpoints belonging to the linear space and errors (radii, noises) belonging to a (symmetric) quasi-linear space. As linear spaces are well-known what remains is to study quasi-linear (error) spaces. Note that both errors and intervals are elements of quasi-linear spaces, while errors are elements of symmetric quasi-linear spaces (as errors are identified with symmetric intervals).

Extended interval arithmetic

As already mentioned, an error space is a special case of a quasi-linear space with the additional axiom for symmetry: $(-1)*A=A$. As addition is not invertable, computation in such a space is rather limited. To extend computing possibilities with errors (which can be identified with nonnegative numbers, resp. with vectors of nonnegative numbers), one can introduce the operation

$$A+^{-}B = \begin{cases} Y|_{B+Y=A} & \text{if } B \leq A; \\ X|_{A+X=B} & \text{if } A \leq B. \end{cases} \tag{15}$$

In words, $A+^{-}B$ is either the solution Y of $B+Y=A$ or is the solution X of $A+X=B$ depending on which one exists; note that if both solutions X,Y exist (which only happens when $A=B$), then they coincide $X=Y=0$.

Remark. In familiar terms operation (15) is written as $A+^{-}B=|A-B|$. However, strictly speaking we have no right to write $|A-B|$ in $\mathbb{R}^{+}$, resp in $\mathbb{R}^{+n}$ as we cannot define operation subtraction $A-B$ in $(\mathbb{R}^{+},+)$, resp in $(\mathbb{R}^{+n},+)$.

The extended quasi-linear space $(\mathbb{Q},+,+^{-},\mathbb{R},*)$ can be defined abstractly axiomatically, or can be introduced specifically for interval vectors. This space has a rich algebraic structure suitable for computation. A detailed study of the algebraic properties of this system is undertaken in [27], [28]. Extended interval arithmetic enriches interval analysis with more possibility to tight or exact presentation of functional ranges [2], [20].

CONCLUSIONS

Dynamical bio-systems are usually highly sensitive and involve uncertainties. Therefore such systems need to be carefully studied with respect to various type of errors. One of the most

developed tool for error analysis is interval analysis. Recent developments both in the theory and the practical application of interval arithmetic make interval analysis is a suitable tool for the mathematical modelling of bio-systems.

The midpoint-radius approach provides a bridge between the interval methodology and the "uncertain but bounded" approach used for model estimation and identification [25], [30], [31], [32], [38].

Recently a standardization process of interval arithmetic started under the auspices of IEEE [7]. The process[14] is analogous to the standardization of floating-point computation leading to the IEEE 754 standard that has been rapidly adopted in existing arithmetic processors. The standardization of interval arithmetic will make interval computations available in arithmetic processors of future computers. This will greatly facilitate the usage of guaranteed interval numerical algorithms.

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