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A Survey on OR and Mathematical Methods Applied on Gene-Environment Networks

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Abstract In this paper we survey the recent advances and mathematical foundations of gene-environment networks. We explain their interdisciplinary implications with special regard to human and life sciences as well as financial sciences. Special attention is paid to applications in Operational Research and environmental protection. Originally developed in the context of modeling and prediction of gene-expression patterns, gene-environment networks have proved to provide a conceptual framework for the modeling of dynamical systems with respect to errors and uncertainty as well as the influence of certain environmental items. Given the noise-prone measurement data we extract nonlinear differential equations to describe and investigate the interactions and regulating effects between the data items of interest and the environmental items. In particular, these equations reflect data uncertainty by the use of interval arithmetics and comprise unknown parameters resulting in a wide variety of the model. For an identification of these parameters Chebychev approximation and generalized semi-infinite optimization are applied. In addition, the time-discrete counterparts of the nonlinear equations are introduced and their parametrical stability is investigated by a combinatorial algorithm which detects the region of parameter stability. Finally, we analyze the topological landscape of the gene-environment networks in terms of structural stability and we conclude by a discussion of the structural frontiers, challenges and an outlook.

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1 Introduction

In this paper we survey recent advances on *gene-environment networks*, a new and pioneering research area of Operational Research in the fields of life and human sciences. Gene-environment networks, originally introduced in the context of modeling and prediction of gene-expression patterns, provide a conceptual framework for the mathematical analysis of highly interconnected systems. In the last decade, the development of high-throughput technologies resulted in an accelerated generation of massive quantities of technical, financial, environmental and biological data. The availability of large data sets now allows to gain deeper insights in the dynamic behaviour of complex systems and opens promising avenues for further scientific progress in medicine, health care, technology and life sciences. We will demonstrate this on the important issue of environmental protection and CO_2-emission control in Section 8 where we study the *Technology-Emissions-Means model* of *S. Pickl* [55], developed for a mathematical analysis of Joint Implementation Programs in the framework of the Kyoto protocol.

Achieving such a deep understanding of real-world problems necessitates the development of advanced mathematical and computational methods that allow to reveal the dynamics of the system under consideration. Such complex systems for example arise in computational biology in the context of the prediction of gene-expression patterns based on microarray measurements. At early stages of modeling so-called *genetic networks* have been used for an investigation of the dynamic relationships between the genes. Then, it turned out that a reasonable modeling could not be done without a consideration of the environment. Therefore, we and our colleagues further enhanced and mathematically improved the genetic networks and developed the concept of *gene-environment networks*. Recently, it has been shown that this approach offers a conceptual framework for a wide range of OR applications and that led to the development of the *socio-econo-environment networks*.

To give the reader an impression of how this approach works we will shortly recall genetic networks and gene-environment networks, always bearing in mind, that we will put this in a general framework for modeling of phenomena in OR.

Genetic networks in the classical sense are defined by weighted directed graphs composed of nodes representing genes, and of arcs with functional weights standing for the influences between the genes; moreover, each node can be equipped with a (level) function of the other genes' combined effects on it. For each gene we wish to predict how it influences the other genes. Various analytic and numerical tools have been developed for the construction and understanding of such networks [1, 13, 15, 25, 22–24, 27, 34, 52, 54, 66, 68, 76, 84–87, 89, 90].

In [76,77,84–87], we firstly extended genetic networks to *gene-environment networks*. Here, the new nodes are environmental items, such as toxins and radiation, that often exercise effects in mutually catalyzing or multiplicative ways. When we turn to modeling and prediction of gene-expression patterns, two quantities have to be coupled: the *states* (concentration levels) of gene-expressions, and their *dynamics* (rates of change). In addition, environmental effects have to be observed resulting in to a certain kind of duality and bilevel problems [84,86]. Indeed, we are concerned with two classes. One class of variables contains parameters under perturbation that lead to a response by the variables of the remaining second class.

Although gene expression data on a genomic scale is nowadays available in a standardized form according to the *Minimum Information About a Microarray Experiment* (MIAME) [11], it is nevertheless affected by imprecision. Therefore, we have to include noise-prone data into our model and have to be aware of measurement and reliability problems. As introduced in [77,84,87], we represent various kinds of errors by *intervals* and *error terms* [43].

To specify the (nonlinear) dynamics of our gene-environment networks we use a matrix representation of the relevant systems under uncertainty. This constitutes the basis for both a testing of the *goodness of data fitting* and *prediction* base. The concerted effect of our matrices, each of them standing for a linear transformation, can be expressed in terms of equilibrium, expansion, contraction, cyclicity or mixed asymptotic properties; these behaviours contribute to *stability* or *instability*. Differently from the stepwise or time-discrete dynamics which can be called a *forward* problem, the problem of parameter estimation is an *inverse* one. Those discrete "forward" orbits are yielded by the matrix multiplication, iteratively performed; we can analyze them by the combinatorial procedure of Brayton and Tong [10,76]. This algorithm generates and observes a sequence of compact neighbourhoods of the origin. Choosing these neighbourhoods as polytopes allows a translation into the combinatorial language of their vertices; on them the construction principle step by step executes a finite number of matrix multiplications. We note that *stability* classically has a positive interpretation in terms of a local order, a coming to a rest (recovering) or as the robustness of a system against small perturbations [29]. But there is also a negative meaning: any biosystem which is unable to adapt to a changing environment, is in a serious danger caused by bacteria, viruses, radiation and other attacks. A stability analysis can also serve for the acceptance or rejection of a mathematical model, i.e., to a testing of the goodness of data fitting and, if needed, for a model improvement. In fact, if any state dimension of the model behaves unbounded under slight parametric variations, then this contradicts the natural-technical limitation of the genetic and environmental levels by bounded intervals.

Complexity is a central property of gene-environment networks and of any approach to investigate them. Hence, we impose upper bounds into the parameter estimation problem and, by this, force the number of edges to diminish and make the parameter estimation become a *mixed continuous-discrete programming problem*. Because of the modeling deficiencies of that problem and for algorithmical reasons, we relax the inequality constraints to become continuous and depend-

ing on the environmental items, maybe also on time and, very importantly, on errors and uncertainties located in intervals, the problem becomes one from *semi-infinite programming* (*SIP*). In addition, by allowing dependence of the domain of combined external effects on the unknown environmental parameters, we obtain a *generalized semi-infinite programming* (*GSIP*) problem. Herewith, we permit regulation of the network's edge density in a more refined and soft way, and we can more confidently guarantee existence and tractability of genetic and metabolic processes. In [77, 84–87] we connected the discrete mathematics of networks with GSIP, by this introducing a new and pioneering scientific approach into computational biology. GSIP is an advancing wide problem class with many motivations, results, future challenges and practical applications [65, 62, 81].

2 Gene-Expression and Environmental Data, Modeling and Dynamics

2.1 Modeling by Intervals

Gene-environment networks and their inherent information were primarily modeled by time-continuous systems in form of autonomous ordinary differential equations (ODEs):

$$\dot{\mathbb{X}} = \mathbb{F}(\mathbb{X}).$$

Here, the d-vector $\mathbb{X} = (\mathbb{X}_1, \mathbb{X}_2, \ldots, \mathbb{X}_d)^T$ comprises the positive concentration levels of proteins (or mRNAs, or small components) and certain levels of the environmental factors, whereas $\dot{\mathbb{X}} \left(= \frac{d\mathbb{X}}{dt}\right)$ represents a continuous change in the gene-expression data, and $\mathbb{F} : \mathbb{X}^d \to \mathbb{X}^d$ is composed of nonlinear coordinate functions $\mathbb{F}_i : \mathbb{X}^d \to \mathbb{X}$ $(i = 1, 2, \ldots, d)$ (cf. [13, 33, 63, 76] for different dimensions). As the nonlinear function $\mathbb{F}$ is determined by primarily unknown parameters we have to deal with identification based on noise-prone data vectors $\bar{\mathbb{X}}$ obtained from microarray and environmental measurements. For this we have [77]

$$\mathbb{X}_i = \bar{\mathbb{X}}_i \pm \text{Err}_i \quad (i = 1, 2, \ldots, d),$$

where $\text{Err}_i > 0$ denotes the maximal error to be made at the measurements of the gene- or environmental expression level $\mathbb{X}_i$. This measurement error leads us to assume that the state $\mathbb{X}$ has to lie in the interval $[\bar{\mathbb{X}}_i - \text{Err}_i, \bar{\mathbb{X}}_i + \text{Err}_i]$ and, hence, the state vector $\mathbb{X} = (\mathbb{X}_1, \mathbb{X}_2, \ldots, \mathbb{X}_d)^T$ has to be in the parallelpipe

$$\prod_{i=1}^{d} [\bar{\mathbb{X}}_i - \text{Err}_i, \bar{\mathbb{X}}_i + \text{Err}_i].$$

Here, we can speak of confidence intervals and a confidence parallelpipe. Those parallelpipes and intervals usually come from a perspective where functional dependencies among any two of the errors made in the measurements of the gene-expression environmental levels $\mathbb{X}_i$ are not taken into account explicitly [8]. Moreover, they are usually smaller than the ellipsoides and their orthogonal projections into the 2-dimensional Cartesian planes, respectively [8]. Indeed, those confidence

ellipsoids are obtained with respect to stochastic dependencies of the error variables. Those dependencies are the case in reality, e.g., in microarray experiments and in environmental studies as well. In reverse, any ellipsoid can be inscribed into a sufficiently large parallelpipe which, in addition, could be suitably located and directed in space around its eigenaxes. According to his/her experience and wish for confidence (trust region), the modeler can enforce a certain size of the parallelpipe by additional constraints on the interval limits, which are the variables in our parameter estimation. We underline that a direct modeling with ellipsoides and corresponding parameters is possible, too. Our work is a pioneering one, demonstrating a basic approach with the help of intervals. The size of the intervals and, by this, the amount of error in real networks, is an outcome of our parameter estimation which we do by optimization theory based on real data given. The following subsections provide closer explanations and motivations about intervals. The reader may skip them on first reading and directly turn to Subsection 2.2.

2.1.1 Interval Analysis and Arithmetic

As we are interested in modeling measurement errors and uncertainty by intervals we will now have a closer look on interval analysis. Let us refer to any intervals $\mathcal{I},\ \mathcal{J} \subseteq \mathbb{X}$ recalling that also points (and thus exact data) may be considered as intervals, and let some $a \in \mathbb{X}$ be given; we define [77]:

- $\mathcal{I} + \mathcal{J} := \{x + y |\, x \in \mathcal{I}, y \in \mathcal{J}\}$,
- $\mathcal{I} - \mathcal{J} := \{x - y |\, x \in \mathcal{I}, y \in \mathcal{J}\}$,
- $\mathcal{I} \cdot \mathcal{J} := \{xy |\, x \in \mathcal{I}, y \in \mathcal{J}\}$,
- $\mathcal{I}/\mathcal{J} := \{x/y |\, x \in \mathcal{I}, y \in \mathcal{J}\}$, if $0 \notin \mathcal{J}$,
- $a + \mathcal{J} := \{a + x |\, x \in \mathcal{I}\}$,
- $a \cdot \mathcal{J} := \{ax |\, x \in \mathcal{I}\}$,
- If K is a scalar- or vector-valued function on $\mathbb{X}$ (or $\mathbb{X}^d$), then, the set-valued mapping $\tilde{\mathcal{I}} \mapsto K(\tilde{\mathcal{I}})$ of intervals (or $\tilde{\mathcal{P}} \mapsto K(\tilde{\mathcal{P}})$ of parallelpipes from $\mathbb{X}^d$) is defined by $K(\tilde{\mathcal{I}}) := \left\{ K(x) |\, x \in \tilde{\mathcal{I}} \right\}$ (and $K(\tilde{\mathcal{P}})$ likewise).

If $\mathcal{I}, \mathcal{J}, \mathcal{K}$ are intervals, then the following holds by [45]:

- commutativity: $\mathcal{I} + \mathcal{J} = \mathcal{J} + \mathcal{I}$ and $\mathcal{I} \cdot \mathcal{J} = \mathcal{J} \cdot \mathcal{I}$,
- associativity: $(\mathcal{I} + \mathcal{J}) + \mathcal{K} = \mathcal{I} + (\mathcal{J} + \mathcal{K})$ and $(\mathcal{I} \cdot \mathcal{J}) \cdot \mathcal{K} = \mathcal{I} \cdot (\mathcal{J} \cdot \mathcal{K})$,
- subdistributivity: $\mathcal{I} \cdot (\mathcal{J} + \mathcal{K}) \subseteq \mathcal{I} \cdot \mathcal{J} + \mathcal{I} \cdot \mathcal{K}$ and $\alpha \cdot (\mathcal{I} + \mathcal{J}) = \alpha \cdot \mathcal{I} + \alpha \cdot \mathcal{J}$, where $\alpha \in \mathbb{X}$ (the distributive law does *not* always hold).

In addition, we briefly describe the comparison of "orders" (*"placements"*) of intervals in the real line [14,19,77]. For this, let $\mathcal{I} = [u_-, u^-](u_- \leq u^-)$ and $\mathcal{J} = [v_-, v^-]\ (v_- \leq v^-)$ be closed intervals in $\mathbb{X}$. Then, we say that

- $\mathcal{I} < \mathcal{J}$ (or equivalently, $\mathcal{J} > \mathcal{I}$), if $u^- < v_-$,
- $\mathcal{I} = \mathcal{J}$, if $\mathcal{I} \subseteq \mathcal{J}$ and $\mathcal{I} \supseteq \mathcal{J}$,
- $\mathcal{I} \leq \mathcal{J}$ (or equivalently, $\mathcal{J} \geq \mathcal{I}$), if for all $x \in \mathcal{I} \setminus \mathcal{J}$ we have $x < \mathcal{J}$ (or, equivalently, $\mathcal{I} \cap \mathcal{J} \neq \emptyset$ and for all $y \in \mathcal{J} \setminus \mathcal{I}$ we have $y > \mathcal{I}$).

We can restate our interval arithmetics by turning to *interval numbers* and *interval matrices*. Here, we define an *interval number* as an ordered pair of real numbers $[u, v]$, where $u \leq v$. Two interval numbers $[u_-, u^-]$ and $[v_-, v^-]$ are *equal*, $[u_-, u^-] = [v_-, v^-]$, if and only if $u_- = v_-$ and $u^- = v^-$. If $[u_-, u^-] = [v_-, v^-]$, then $u^- \geq v_-$ and $u_- \leq v^-$.

Referring to any basic operation $\circ \in \{+, -, \cdot, /\}$, the arithmetic operations on intervals can be represented by

$$[u, v] \circ [w, t] = \{x \circ y \mid u \leq x \leq v, w \leq y \leq t\}\,.$$

Now, we can state:

- addition: $[u, v] + [w, t] = [u + w, v + t]$;
- subtraction: $[u, v] - [w, t] = [u - t, v - w]$;
- multiplication: $[u, v] \cdot [w, t] = [\min\{uw, ut, vw, vt\}, \max\{uw, ut, vw, vt\}]$;
- division: $[u, v]/[w, t] = [u, v] \cdot [1/t, 1/w]$, where $0 \notin [w, t]$.

We additionally note that in the presence of uncertainty *interval matrices* become important. The entries of the respective matrix are closed intervals and the matrix can be represented in the form

$$\begin{pmatrix} [\underline{a_{11}}, \overline{a_{11}}] & \dots & [\underline{a_{1m}}, \overline{a_{1m}}] \\ [\underline{a_{21}}, \overline{a_{21}}] & \dots & [\underline{a_{2m}}, \overline{a_{2m}}] \\ \vdots & \dots & \vdots \\ [\underline{a_{n1}}, \overline{a_{n1}}] & \dots & [\underline{a_{nm}}, \overline{a_{nm}}] \end{pmatrix}.$$

For more notions and details of interval algebra and comparison, including binary fuzzy operator and membership values, we refer to [14,9,19,31,45,46,61].

2.1.2 A Note on Linear Programming

In most of the optimization problems when a model is built, it is assumed that certain data are used. The values obtained are exact, but in the real world this is seldomly true. The data known and the values obtained are in some certain ranges, because there the assumptions are approximately true. For that reason, in *LP program* models, data uncertainty is unavoidable. We note that in an LP program with *interval coefficients* the solutions can be found by using simplex method [64,61].

2.2 Continuous Differential Equations on Gene-Environment-Expressions

Let us now return to our gene-environment networks and assume that the gene-environmental patterns may be represented by continuous differential equations. With respect to different stages of modeling we will distinguish two situations:

(I) Networks with n genes (by neglecting the environmental items)
(II) Networks with n genes as well as $d-n$ environmental items.

For this, we divide the vector $\mathbb{X}$ of concentration levels into two parts and obtain

$$\mathbb{X} = (\mathbb{X}_1, \ldots, \mathbb{X}_n, \mathbb{X}_{n+1}, \ldots, \mathbb{X}_d)^T,$$

where $\mathbb{X}_1, \ldots, \mathbb{X}_n$ refer to the n genes and $\mathbb{X}_{n+1}, \ldots, \mathbb{X}_d$ to the $d-n$ environmental items, respectively. When we are concerned with models of type (I), X_i denotes the expression level of gene i and X stands for the first n coordinates of the d-vector $\mathbb{X}$. Prepared by this notation and the interval arithmetics of the previous sections we can now introduce the continuous models.

2.2.1 Gene-Networks

A dynamical system of n genes (without any environmental items) can be given by the continuous differential equation

$$(\mathcal{CE})_{\text{gene}} \quad \dot{X} = A(X)X,$$

where the (interval) matrix A may depend on X (cf. [77,86]). From this equation we may obtain the following discrete-time equation and dynamics:

$$(\mathcal{DE})_{\text{gene}} \quad X^{(k+1)} = A^{(k)}X^{(k)} \ \ (k \in \mathbb{N}_0).$$

Here, $A^{(k)}$ can be taken as interval matrices and the stability can be investigated by Brayton and Tong's algorithm [4,86].

2.2.2 Example for a Gene-Network

For an example in dimension n, we mention the following system of differential equations [26,27,87]:

$$\dot{X}_i = -\delta_i X_i + \sum_{\alpha=1}^{\alpha_i} (\text{reg}\, f^+)_\alpha + \sum_{\beta=1}^{\beta_i} (\text{reg}\, f^-)_\beta + c_i \quad (i = 1, 2, \ldots, n).$$

In this system, real- or interval-valued synthesis or degradation of gene i is represented by $c_i \geq 0$ and $\delta_i \geq 0$, whereas activation and inhibition are determined by the sums. We note that the activation and inhibition functions reg f^+ and reg f^- have been shown to possess a sigmoid shape [88]. The resulting $(n \times n)$-matrix $A(E)$ has the entries

$$a_{ii}(X) = \frac{c_i}{X_i} - \delta_i + k_{ii} \frac{X_i^{a_{ii}-1}}{X_i^{a_{ii}} + \theta_{ii}^{a_{ii}}} \quad (i = 1, 2, \ldots, n),$$

$$a_{ij}(X) = k_{ij} \frac{X_j^{a_{ij}-1}}{X_j^{a_{ij}} + \theta_{ij}^{a_{ij}}} \quad (i, j = 1, 2, \ldots, n;\ i \neq j)$$

with k_{ij} and $\theta_{ij}, a_{ij}(X)$ being any nonnegative reals or intervals, respectively. Then, all or some of the parameters can be estimated with the help of the data from DNA-microarray experiments.

2.2.3 Gene-Environment Networks

In order to incorporate environmental items into our continuous model under the presence of noise and uncertainty we extended in [76,77,86] the model from [23,27] and provided the continuous equation

$$(\mathcal{CE}) \qquad \dot{\mathbb{X}} = \mathbb{A}(\mathbb{X})\mathbb{X}, \quad \mathbb{X}(t_0) = \mathbb{X}^{(0)}.$$

The associated system matrix $\mathbb{A}(\mathbb{X})$ is a $(d \times d)$-matrix whose entries are intervals, defined by a family of functions which include unknown parameters. Now, intervals represent uncertainty with respect to the interactions between the genes, to the effects between the environment and the genes, or between environmental items. The initial value $\mathbb{X}^{(0)} = (\mathbb{X}_1^{(0)}, \mathbb{X}_2^{(0)}, \ldots, \mathbb{X}_d^{(0)})^T$ consists of the interval-valued levels obtained by the first measurement $\bar{\mathbb{X}}(t_0) = \bar{\mathbb{X}}^{(0)}$. As this may result in a large and highly interconnected network we will later on restrict on an approximate model and network. For this we will improve our model by imposing bounds on the admissible number of regulating effects exercised per gene and also on the effects of the environment onto the genes.

2.2.4 Example for a Gene-Environment Network

To provide a simple example for a gene-environment network under uncertainty we introduce an interval-valued 2-vector $\mathbb{X} = (\mathbb{X}_1, \mathbb{X}_2)^T$ denoting the data. The interval-valued system matrix $\mathbb{A}(\mathbb{X})$ may be influenced by nine unknown real parameters $a_1, a_2, \ldots, a_9$ [84]:

$$\mathbb{A}_{\substack{a_1,a_2,a_3,a_4,a_5,\\ a_6,a_7,a_8,a_9}}(\mathbb{X}) := \begin{pmatrix} [a_1,a_2]\mathbb{X}_1 & [a_3\mathbb{X}_2^2, a_4\mathbb{X}_1\mathbb{X}_2] + a_5 \\ a_6\cos(\mathbb{X}_2) + [a_1,a_8]\sin(\mathbb{X}_1) & [a_7,a_8]\exp(a_9\mathbb{X}_1^2) \end{pmatrix}.$$

Here, polynomial, trigonometric, exponential but otherwise logarithmic, hyperbolic, spline, etc., entries represent any kind of *a priori* information, observation or assumption in terms of growth, cyclicity, piecewise behaviour, etc. [22]. In [70, 71], we studied the case of approximation by splines.

2.2.5 Identification and Stability

With regard to the parametrized entries of the model $(\mathcal{CE})$ we have to examine the respective *optimization* and must provide a *stability analysis*. Both issues will lead to *bilevel problems* [25,23,38,65,77,81,86]. In case of optimization we have to deal with the problem $\min_y \sum_{\kappa=0}^{l-1} \left\| \mathbb{A}_y\big(\bar{\mathbb{X}}^{(\kappa)}\big)\bar{\mathbb{X}}^{(\kappa)} - \dot{\bar{\mathbb{X}}}^{(\kappa)} \right\|_\infty^2$ and by this with approximation based on squared errors. The vector y comprises a subset of all the parameters and the vector $\dot{\bar{\mathbb{X}}}^{(\kappa)}$ consists of interval-valued *difference quotients* raised on the κth experimental data $\bar{\mathbb{X}}^{(\kappa)}$ and on step lengths $\bar{h}_\kappa := \bar{t}_{\kappa+1} - \bar{t}_\kappa$ between neighbouring samplings times [22,27,77]. As we make use of intervals we inserted *Chebychev* or *maximum norm* $\|\cdot\|_\infty$ generating the topology of uniform convergence (cf. Section 5). Until now we have only referred to a certain class of parameters, but, as we have mentioned earlier, our problems bears some "duality". Indeed, the remaining parameters not comprised in the vector y permit a *stability analysis*. For this, we can capitalize on the structure of $(\mathcal{CE})$ that allows a time-discretization represented by a sequence of matrix multiplications. A combinatorial algorithm on polyhedra sequences can then be applied to detect the regions of stability. In Section 4 we will see that this recursion admits a stability analysis of combinatorial and geometrical type with polytope series [23].

2.2.6 The Influence of the Environment

The interaction between the genes and the environment is frequently characterized as *epigenetic*. This refers to stable changes of gene expression patterns in response to environmental factors without any mutations in the DNA sequence [83]. *DNA methylation* is one of the most common epigenetic factors, but also *acetylation*, *ethylation* and *phosphorylation* provide important epigenetic regulations. Studies on identical twins showed that although they have the same genomic sequences and genes, but no epigenetic difference during the early stages of life, adult twins possessed very different epigenetic patterns affecting their genetic portrait [21]. Moreover, nutritional conditions of grandparents can have phenotypic

consequences in their grandchildren [18,40]. Lifestyle, nutritional supplementation, and environmental conditions can have a very important impact on inheritance by changing the DNA sequence with mutations and also by affecting epigenetic pattern of DNA through methylation, ethylation, etc., without changing the DNA sequence. Hence, for a better explanation of the complexity of nature, genetic networks cannot be studied solely without taking into consideration the environmental factors which affect epigenetic patterns and, thus, gene expression patterns [86].

3 Extended Dynamics of Gene-Expression and Environmental Patterns

As we have mentioned above, the continuous model $(\mathcal{CE})$ provides a convenient multiplicative structure. We note, that the gene-model $(\mathcal{CE})_{\text{gene}}$ exhibits the same structure, that provides the basis of the recursive iteration idea [23]. In [89,90] a model extension has been proposed that emphasized nonlinear interactions and introduced affine linear shift terms which provide a more accurate data fitting. In order to maintain the multiplicative recursion property of $(\mathcal{CE})_{\text{gene}}$, we shall reconstruct the form of $(\mathcal{CE})_{\text{gene}}$ by a dimensional model extension. This will even allow to represent our following *affine* continuous equation which includes a variable shift vector [66–68,76,86]:

$$(\mathcal{ACE})_{\text{gene}} \qquad \dot{X} \;=\; A(X)X + C(X).$$

We call this decomposition a *normal form*, an *unfolding* [7,12,30,38] or a *(generalized) additive model* [30,70–72]. Here, the vector $C(X)$ represents environmental perturbations and contributions and may be, e.g., exponential, logarithmic, trigonometric or piecewise polynomial (splines). In addition, it displays special effects on each gene emanated from any environmental item itself or cumulatively by all or several items working together or catalyzing each other. This cumulative effect might not be further divisible or quantifiable by the single effects.

With $(\mathcal{ACE})_{\text{gene}}$ we included the disturbances and genetic changes caused by the environment, in long and in short term, but we lost the convenient recursive idea of matrix multiplication first of all. This drawback can be overcome by increasing the dimension of the state space to $d := m + 2n$ such that we reconstruct that product structure. This reconstruction was originally presented in [86] and has been modified by interval-valued entries in [77]. By splitting the shift vector $C(X)$ of $(\mathcal{ACE})_{\text{gene}}$ into the sum $\mathrm{W}(X)\check{X} + \mathrm{V}(X)$ we obtain the decomposition

$$(\mathcal{ACE}) \quad \dot{X} \;=\; A(X)X + \mathrm{W}(X)\check{X} + \mathrm{V}(X).$$

Here, the m-vector (of intervals)

$$\check{X}(t) = \left(\check{X}_1(t), \check{X}_2(t), \ldots, \check{X}_m(t)\right)^T$$

comprises the levels of the m environmental factors that can affect the gene-expression levels and their variation.

The *single effects* of the factors $\check{X}_\ell$ on the gene-expression data X_i can be incorporated by the weight matrix $\mathrm{W} = (\mathrm{w}_{i\ell})_{\substack{i=1,\dots,n \\ \ell=1,\dots,m}}$ into the system, and by this the n genes and the m environmental factors are individually matched. In addition, the column vector $\mathrm{V}(X) = (\mathrm{v}_i)_{i=1,\dots,n}$ gene-wisely comprises all the cumulative effects of all (or several) environmental items influencing the genes together. We represent this *cumulation effect* by a new, $(m+1)$st environmental item, taken into account for each gene.

We note that the *total effect* of the environment on the expression level X_i of gene i is given by

$$\sum_{\ell=1}^{m} \mathrm{w}_{i\ell}(X)\check{X}_\ell \ + \mathrm{v}_i.$$

Now, we overcome the more additive form of the affine-continuous model $(\mathcal{ACE})$ by an idea worked out and improved in [66–68, 76, 77, 86]. For this, we define the *gene-environment* matrix

$$\check{A}(X) \ := \ \big(\,\mathrm{W}(X)\,|\,\mathrm{diag}(\mathrm{V}(X))\,\big),$$

where the second block represents $\mathrm{V}(X)$ as a diagonal matrix with intervals on the diagonal. In addition, we set

$$\check{X}^{\vee} := \big(\check{X}^T, \mathrm{e}^T\big)^T$$

with the n-vector $\mathrm{e} := (1, 1, \dots, 1)^T$ and with

$$\mathrm{W}(X)\check{X} + \mathrm{V}(X) \ = \check{A}(X)\check{X}^{\vee},$$

we obtain the following representation of $(\mathcal{ACE})$:

$$\dot{X} \ = \ A(X)X + \check{A}(X)\check{X}^{\vee}.$$

Finally, by introducing the $(d = m + 2n)$-vector

$$\mathbb{X} := \begin{pmatrix} X \\ \check{X}^{\vee} \end{pmatrix},$$

and the $(d \times d)$-matrix

$$\mathbb{A}(\mathbb{X}) = \begin{pmatrix} A(X) & \check{A}(X) \\ 0_{(m+n)\times n} & 0_{(m+n)\times(m+n)} \end{pmatrix} = \left(\begin{array}{c|cc} A(X) & \mathrm{W}(X) & \mathrm{diag}(\mathrm{V}(X)) \\ \hline 0_{m\times n} & 0_{m\times m} & 0_{m\times n} \\ 0_{n\times n} & 0_{n\times m} & 0_{n\times n} \end{array}\right),$$

we arrive at the extended (mutliplicative) system $(\mathcal{CE})$ together with an extended initial value as follows:

$$(\mathcal{CE}) \qquad \dot{\mathbb{X}} = \mathbb{A}(\mathbb{X})\mathbb{X}, \qquad \mathbb{X}^{(0)} = \mathbb{X}(t_0) = \begin{pmatrix} X^{(0)} \\ \check{X}^{\vee,0} \end{pmatrix}.$$

We note that $(\mathcal{CE})$ and the corresponding initial value problem for $(\mathcal{ACE})$ can be considered as *equivalent* [77]. From microarray experiments we obtain the initial expression values $\bar{X}^{(0)}$, whereas the initial state of the special or cumulative environmental factors $\bar{\check{X}}^{\vee,0}$ come from environmental observations.

The ℓth environmental factor $\check{X}_\ell$ permits "gene-switching", i.e., if the ℓth specific environmental factor $\check{X}_\ell$ is regarded as affecting any gene-expression level, then, initially, the ℓth component of $\bar{\bar{X}}^{(0)}$ is considered to be 1, otherwise 0. Here, 1 (0) in $\bar{\bar{X}}_\ell^{(0)}$ means that the ℓth environmental factor is "switched on" (or "off", respectively). In contrast, the cumulative environmental effect is considered to be "switched on" always.

In case of $(\mathcal{CE})$, equipped with the initial value $\check{X}^\vee(t_0) = \bar{\bar{X}}^{(0)}$, the time-dependent variable $\check{X}^\vee(t)$ is constant: $\check{X}^\vee \equiv \bar{\bar{X}}^{\vee,0}$. Indeed, we have not included any environmental dynamics, but our modeling framework allows us to do this. In fact, by turning the 0 matrices in the second and the third (block) columns of $\mathbb{A}(\mathbb{X})$ to matrices which are different from 0, we can permit variable and interacting factors of the environment. Allowing also the 0 matrices in the first column to have nonzero entries, then this would express that the genes influence various items of the environment. In addition, the vector $\mathrm{V}(X)$ and the weight matrix $\mathrm{W}(X)$ could also depend on the variable $\check{X}$ or even $\check{X}^\vee$. This higher generality of $(\mathcal{CE})$ could also be implied into the parameter estimation from Section 5.

4 The Time-Discretized Model and Stability Analysis

4.1 Time-Discretization

With regard to a numerical analysis of our time-continuous modeling of gene-expression patterns we introduced *Runge-Kutta methods* (*RK*) in [17]. Later on, a different RK method called *Heun's method* was applied in some extended model space in [66–68]. This method constitutes a modification of Euler's method; it is a more illustrative, explicit and the simplest RK approach [16, 17, 66–68]. When we apply Heun's method on the extended system $(\mathcal{CE})$ we obtain the following time-discrete equation:

$$\begin{aligned}
&\mathbb{X}^{(k+1)}\\
&= \mathbb{X}^{(k)} + \frac{h_k}{2}\mathbb{A}\big(\mathbb{X}^{(k)}\big)\mathbb{X}^{(k)} + \frac{h_k}{2}\mathbb{A}\big(\mathbb{X}^{(k)} + h_k\mathbb{A}\big(\mathbb{X}^{(k)}\big)\mathbb{X}^{(k)}\big)\\
&\quad \times \Big(\mathbb{X}^{(k)} + h_k\mathbb{A}\big(\mathbb{X}^{(k)}\big)\mathbb{X}^{(k)}\Big)\\
&= \left[I + \frac{h_k}{2}\mathbb{A}\big(\mathbb{X}^{(k)}\big) + \frac{h_k}{2}\mathbb{A}\big(\mathbb{X}^{(k)} + h_k\mathbb{A}\big(\mathbb{X}^{(k)}\big)\mathbb{X}^{(k)}\big)\big(I + h_k\mathbb{A}\big(\mathbb{X}^{(k)}\big)\big)\right]\mathbb{X}^{(k)}\\
&= \mathbb{A}^{(k)}\mathbb{X}^{(k)} \quad (k \in \mathbb{N}_0).
\end{aligned}$$

For this equation, but also in the Eulerian case and some other methods [17, 23], we can find a representation "multiplication-form":

$$(\mathcal{DE}) \quad \mathbb{X}^{(k+1)} = \mathbb{A}^{(k)}\mathbb{X}^{(k)}.$$

With this model we can now calculate predictions of future expression values. For this we introduce the data vector

$$\bar{\mathbb{X}}^{(\kappa)} := \left((\bar{X}^{(\kappa)})^T, (\check{X}^{\vee,\kappa})^T \right)^T \ (\kappa = 0, 1, \ldots, l-1),$$

which comprises the results from DNA microarray experiments and environmental measurements. The approximations (*predictions*) are denoted by $\widehat{\mathbb{X}}^{(\kappa)}$ and we set

$$\widehat{\mathbb{X}}^{(0)} = \mathbb{X}^{(0)}.$$

The kth approximation (prediction) is then calculated by

$$\widehat{\mathbb{X}}^{(k)} \ (:= \mathbb{X}^{(k)}) \ = \mathbb{A}^{(k-1)}(\mathbb{A}^{(k-2)} \cdots (\mathbb{A}^{(1)}(\mathbb{A}^{(0)}\mathbb{X}^{(0)})) \cdots) \ \ (k \in \mathbb{N}_0).$$

We note that the quality of prediction, both theoretically and by numerical examples, was investigated in [66–68, 89, 90].

4.2 Discrete and Continuous Gene-Environment Networks

Equipped with the discrete model $(\mathcal{DE})$ and the continuous model $(\mathcal{CE})$, we can introduce our *gene-environment networks* as an extension and improvement of the *genetic networks*.

In the case of the time-discrete dynamics of $(\mathcal{DE})$, we can define the *(discrete) gene-environment network* in the following way: The *vertices* of this network represent the genes and environmental items, whereas the *weighted edges* display their interactions.

When we look at the time-continuous dynamics, represented by $(\mathcal{CE})$, we can introduce the *(continuous) gene-environment networks* in a similar way. Here, the vertices stand again for the genes and environmental items, whereas the edges are now weighted with functional values.

Since the problems related with these gene-environment subnetworks are *large-scale* ones, they are very costly to solve. Even in case where the problem is solvable in polynomial time, the huge data set lets the solution become very expensive. We acknowledge this problem by simplifying the regarded gene-environment network and, herewith, all its substructures, in a selective and robust way. This network *rarefaction* will be introduced in Section 5 and continued in Section 6.

4.3 Matrix Arithmetics

We briefly recall some elements of the interval-valued version [77] of our matrix algebra and, in particular, multiplication [67, 68]. Let us refer to the *canonical* form of matrix partitioning presented for the time-continuous model in Section 3. The product of two canonical matrices $\mathbb{A}^{(k)}$, which are the foundation of our networks,

is a canonically formed matrix again. After some reorganization and notation we get

$$\mathbb{A}^{(k)} = \mathbb{I} + \frac{h_k}{2}\begin{pmatrix} A(X^{(k)}) & \check{A}(X^{(k)}) & P & \widetilde{P} \\ 0 & 0 & 0 & 0 \end{pmatrix} + \frac{h_k^2}{2}\begin{pmatrix} Q & \widetilde{Q} \\ 0 & 0 \end{pmatrix},$$

with

$$\begin{aligned} P &= A\left(X^{(k)} + h_k\left(A(X^{(k)})X^{(k)} + \check{A}(X^{(k)})\check{X}^{\vee,k}\right)\right), \\ \widetilde{P} &= \check{A}\left(X^{(k)} + h_k\left(A(X^{(k)})X^{(k)} + \check{A}(X^{(k)})\check{X}^{\vee,k}\right)\right), \\ Q &= A\left(X^{(k)} + h_k\left(A(X^{(k)})X^{(k)} + \check{A}(X^{(k)})\check{X}^{\vee,k}\right)\right)A(X^{(k)}), \\ \widetilde{Q} &= A\left(X^{(k)} + h_k\left(A(X^{(k)})X^{(k)} + \check{A}(X^{(k)})\check{X}^{\vee,k}\right)\right)\check{A}(X^{(k)}), \end{aligned}$$

such that $\mathbb{A}^{(k)}$ has its final *canonical* block form, too:

$$\begin{pmatrix} \widehat{A(X^{(k)})} & \widehat{\check{A}(X^{(k)})} \\ 0 & I_d \end{pmatrix}.$$

About the form of two or more multiplications of such matrices $\mathbb{A}^{(k)}$ and the spectral theory which is important for our stability theory we refer to [84, 86, 87].

4.4 Stability Analysis

In this subsection we will turn to a stability analysis. For this the finite set $\mathcal{A} := \{\mathbb{A}_0, \mathbb{A}_1, \ldots, \mathbb{A}_{\ell-1}\}$ of matrices with interval-entries be obtained from the time-continuous model $(\mathcal{CE})$ with a sufficiently fine discretization of A, W and V and entry-wise optimization [66–68, 77] (without any confusion with the previous meaning of $\mathbb{A}^{(k)}$ as kth iterate). In addition, the matrix set of all the finite matrix multiplications of elements from $\mathcal{A}$ be denoted by $\mathcal{A}'$. Now we can state the following definition of stability that was first given in [10] and has been extended by us dimensionally and by interval-valuedness in [87].

Definition 1 ([77]) *The matrix set $\mathcal{A}$ (herewith, $(\mathcal{DE})$), is called* stable *if for every neighbourhood in $\mathbb{C}^d$ (or relative neighbourhood in $\mathbb{C}^n \times \{0'_{n+m}\}$), $\mathcal{U}$, of the origin 0_d (or affine origin $0'_d$, given from 0_d by shifting to 1 some of the middle m coordinates and all of the last n coordinates), there exists a (relative) neighbourhood $\mathcal{V}$ of the origin 0_d (or $0'_d$) such that for each $\mathbb{A} \in \mathcal{A}'$ it holds: $\mathbb{A}\mathcal{V} \subseteq \mathcal{U}$.*

In case of constant time shifts, i.e., $h_t \equiv h\,(t \in \mathbb{R}_0^+)$, there is a continuous orbit piecewisely defined along all the intervals $[kh, (k+1)h)$ for the time-continuous system $(\mathcal{CE})$. If, in addition, the initial section $E(t),\ t \in [0, h)$ is a constant parallelpipe, then the dynamics is piecewise constant. By this, we can define a *stability* condition analogously as in the previous definition. For that case and when we concentrate on Euler discretization, having turned from the scalar- to our interval-valued model framework, if the function $\mathbb{A}$ of the right-hand side of $(\mathcal{CE})$ is Lipschitzian, we learn the following theorem from [84, 87]. It extends the real-valued case where it even holds for some Runge-Kutta discretizations presented [86].

Theorem 1 ([87]) *Let the map $x \mapsto \mathbb{A}(x)$ $(x \in \mathbb{X}^d)$ be Lipschitzian. If the Eulerian time-discrete system $\mathbb{X}^{k+1} = \mathbb{A}^k\mathbb{X}^k$ $(k \in \mathbb{N}_0)$, $\mathbb{X}^0 \in \mathbb{X}^d$, as in $(\mathcal{DE})$, some appropriate $h_{max} > 0$ being given, is stable for all values $h_k \in [0, h_{max}]$, then the time-continuous dynamics defined by the system $\dot{\mathbb{X}} = \mathbb{A}(\mathbb{X})\mathbb{X}$ (with $h > 0$ sufficiently small) is also stable.*

After some dilatation, the parallelpipes $\mathbb{X}$ can be embedded into neighbourhoods of 0_d. Multiplying our matrices and vectors (over intervals) and observing the resulting discrete orbits can be characterized by the scalar-valued case that was introduced and investigated in, e.g., [10,23,86]. Indeed, each member in an orbit of our set-valued products is representable as the convex hull of the corresponding common matrix products that we obtain by focusing on all of the finitely many combinations of the involved interval endpoints. By referring to these endpoint combinations, we actually reduced the stability condition to the classical one for the scalar-valued case [77,84,86]. Herewith, we have carried over the stability theory and algorithmic methods of our and our colleagues' former investigations, e.g., the previous condition of parametric stability can be characterized analytically, spectrally and by Lyapunov functions.

4.5 Modeling Metabolic Gene Networks

With this subsection we very briefly introduce into another area of networks in computational biology where our mathematical methods can be applied. In the paper [84] gene-environment networks and metabolic networks become treated by a unified approach given by our matrix-valued concept and calculus. Those genetic networks which are called *metabolic* can also be modeled via its pathways by a dynamical modeling as studied in [53,54]. If there are N reactions, if $v_i(E)$ is the rate of the ith gene in the reaction network $(i = 1, 2, \ldots, N)$ and S is the matrix whose elements are the coefficients (weights) of the genes in the network, then the dynamical model can be viewed as

$$(\mathcal{CE})_{\text{metabolic}} \quad \dot{G} = SV(G).$$

Here, G denotes the vector consisting of (metabolic) concentrations of the genes, and $V(G)$ is the vector which comprises the rates v_i. The matrix S is defined as follows [54]:

$$\begin{aligned} +a_{ij},&\ \text{if the reaction } i \to j \text{ "produces" gene } i,\\ -a_{ij},&\ \text{if the reaction } i \to j \text{ "consumes" metabolite } i,\\ 0,&\ \text{if the reaction } i \to j \text{ neither produces nor consumes gene } i, \end{aligned}$$

with i, j being the genes where the reaction emanates or terminates, respectively, and a_{ij} are coefficients (or weights) of the genes in the metabolic reaction scheme.

Let us look at a small example of a network with 3 genes, 3 reactions and with the concentrations of the metabolites G_i $(i = 1, 2, 3)$. Here, the reactions may be encoded be the following stoichiometric matrix:

$$\begin{aligned} &3G_1 \stackrel{V_1}{\rightarrow} G_2, \\ &G_2 \stackrel{V_2}{\leftrightarrow} 2G_3, \\ &G_1 + 2G2 \stackrel{V_3}{\rightarrow} G_3. \end{aligned}$$

Then, the dynamical model of the above system can be written as

$$\begin{bmatrix} \dot{G}_1 \\ \dot{G}_2 \\ \dot{G}_3 \end{bmatrix} = \begin{bmatrix} -3 & +1 & 0 \\ 0 & -1 & +2 \\ -1 & -2 & +1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix}.$$

By including the external effects of the environment, the system $(\mathcal{CE})_{\text{metabolic}}$ of ODEs becomes more realistically fitting to our general biological situation and data. This leads us to the metabolic model

$$(\mathcal{ACE})_{\text{metabolic}} \qquad \dot{G} \;=\; SV(G) + C(G).$$

Here, $C(G)$ comprises all the external effects, e.g.,

$$C(G) = \mathrm{W}(G)\breve{G} + \mathrm{V}(G)$$

and one special case is given by the form $V(G) = M(G)G$.

As the system $(\mathcal{ACE})_{\text{metabolic}}$ can be extended into an interval-valued setting again we can speak of *metabolism-environment networks*. Therefore, time-discretizations, matrix algebra and stability can be studied as well as parameter estimation by optimization made, likewise we are going to present it now for gene-environment networks.

5 Extracting and Optimizing Gene-Environment Networks in the Presence of Intervals

5.1 Our Hybrid Model

Many technical, financial and biological systems exhibit switching behaviour. In the context of genetic networks a *hybrid approach* has been presented in [27] which offers a complete dynamical description of the expression levels of n genes. This approach has been modified in [77, 86] by additionally matching the n genes with m special items and the cumulative item of the environment. In addition, this

contributions turned to the interval-valued (noise-prone) setting, and introduced the following *hybrid model*:

$$(\mathcal{HE})\qquad \begin{aligned} \dot{X}(t) &= A_{s(t)}X(t) + \mathrm{W}_{s(t)}\check{X}(t) + \mathrm{V}_{s(t)},\\ \text{where } s(t) &:= S(Q(X(t))) \text{ with}\\ Q(X(t)) &= (Q_1(X(t)), Q_2(X(t)), \ldots, Q_n(X(t))), \quad \text{where}\\ Q_i(X(t)) &:= \begin{cases} 0,\ X_i(t) < \theta_{i,1}\\ 1,\ \theta_{i,1} \le X_i(t) < \theta_{i,2}\\ \vdots\\ d_i,\ \theta_{i,d_i} \le X_i(t)\ \ (i = 1, 2, \ldots, n). \end{cases} \end{aligned}$$

In $(\mathcal{HE})$ *thresholds of the expression levels* are given by

$$\theta_{i,1} < \theta_{i,2} < \ldots < \theta_{i,d_i}.$$

At these thresholds instantaneous changes of the parameter constellation can occur such that we have to choose a local model by the special selection of the $(n \times n)$-matrix $A_{s(t)}$, the $(n \times m)$-matrix $\mathrm{W}_{s(t)}$ and the n-vector $\mathrm{V}_{s(t)}$ (all three ones over intervals). The function $Q : \mathbb{R}^n \to \mathbb{N}_0^n$ implies the threshold constellation, and $S(Q(X))$ indicates where in the state space the system is placed at X, and which matrices and vectors A, W, V have to be chosen to specify the system such that the given data are approximated best. The function $S : \mathbb{N}_0^n \to \mathbb{N}_0$ must be injective, such that a different triplet (A,W,V) is used whenever a threshold is traversed. This *piecewise linear* approach provides an approximation of the global nonlinearity of the systems under consideration.

The system $(\mathcal{HE})$ can indeed be generalized such that the matrices and vectors depend on X; then, the involved parameters are affected, governed and instantaneously changed via $s(t)$.

The gene-expression levels are compact intervals such that the vectors X are parallelpipes, all of them lying in a sufficiently large parallelpipe $\mathcal{P}$. Via canonical projections, the thresholds define a partition of $\mathcal{P}$ into subparallelpipes (regimes) $\mathcal{P}^{*,\rho} \subset \mathcal{P}$ $(\rho \in \{1, 2, \ldots, \ell\})$, where $\ell := \Pi_{i=1}^{n}(d_i + 1)$. Let $\ell^{\#} > \ell$ be an integer such that the difference $\ell^{\#} - \ell$ is the number of combinations where one or more thresholds are included in the possible intervals of expression. Each such a combination can be identified with another parallelpipe $\mathcal{P}^{*,\rho} \subset \mathcal{P}$ $(\rho \in \{\ell + 1, 2, \ldots, \ell^{\#}\})$ which partially (i.e., in one or several coordinates) consists of intervals between *non*neighbouring threshold values or are placed at the boundary $\partial\mathcal{P}$. We can reduce the number $\ell^{\#}$ by supposing that all the intervals $X_i(t)$ are shorter than the differences between any two nonneighbouring thresholds [84, 87].

Our understanding of $(\mathcal{HE})$ is in the sense of the placement in the set of intervals (cf. Section 2) and of an extension of Q when one or more thresholds are included in the intervals $X_i(t)$. In such a case, this extension can be made by the arithmetic mean of the corresponding Q values associated with those intervals

between and besides the thresholds which intersect with $X_i(t)$; this averaging is then followed by a rounding to an integer. Based on this definition of $s(t)$, we find $A_{s(t)}$, $\mathrm{W}_{s(t)}$ and $\mathrm{V}_{s(t)}$ (we could also directly use the averaging technique for these parameters [77]).

The *parameter estimation* for the time-continuous model and for the time-discrete system works along the following steps [27,77,86]:

1. estimation of the *thresholds* $\theta_{i,j}$,
2. calculation of the *matrices* and *vectors*, $A_{s(t)}$, $\mathrm{W}_{s(t)}$ and $\mathrm{V}_{s(t)}$, describing the system in between the thresholds.

The thresholds can be defined by *Akaike's Information Criterion* [30] as in the original hybrid model presented in [27] and in the model extensions in [3,5,25,27, 51]. We assume that all the thresholds are known as we are concentrating on the tasks in continuous optimization.

Now, for any given subparallelpipe $\mathcal{P}^* := \mathcal{P}^{*,\rho}$ we have to extract the parametric unknowns $A_{s(t)}$, $\mathrm{W}_{s(t)}$ and $\mathrm{V}_{s(t)}$ from given data. In the subparallelpipe $\mathcal{P}^*$, the hybrid system ($\mathcal{HE}$) reduces to a system of ordinary linear differential equations and we can find analytical solutions for the corresponding parts of the state space. We may assume that for the special environmental factors the times of sampling are just the genetic sampling times, and the same index sets of samplings. The environmental data $\tilde{\tilde{X}}^{(\kappa)}$ $(\kappa = 0, 1, \ldots, l-1)$ are considered to be binary and constant, but they could also be variable in a more refined modeling.

5.2 The Hybrid Model with Delayed Interactions

The hybrid model of the previous section can be further extended with regard to possible delays in the interaction of variables. Such history dependent problems have been investigated in [41] and the delays are included in the state transitions (*threshold crossing*):

$$
(\mathcal{HDE}) \qquad
\begin{aligned}
\dot{X}(t) &= A_{s(t)}X(t) + \mathrm{W}_{s(t)}\check{X}(t) + \mathrm{V}_{s(t)}, \\
&\text{where } s(t) := S(Q(X(t))) \text{ with} \\
Q(X(t)) &= (Q_1(X(t-\tau_1)), \ldots, Q_n(X(t-\tau_n))), \quad \text{where} \\
Q_i(X(t)) &:= \begin{cases} 0, \ X_i(t) < \theta_{i,1} \\ 1, \ \theta_{i,1} \le X_i(t) < \theta_{i,2} \\ \vdots \\ d_i, \ \theta_{i,d_i} \le X_i(t) \ \ (i = 1, 2, \ldots, n). \end{cases}
\end{aligned}
$$

For further details on time-delay hybrid models and a stability analysis we refer to [41].

5.3 Mixed-Integer Parameter Estimation

For an estimation of parameters we have to minimize the quadratic error between the difference quotients $\dot{\bar{X}}^{(\kappa_\alpha)}$ and the right-hand side of the differential equations evaluated at the finitely many measurement intervals $\bar{X}^{(\kappa_\alpha)} \in \mathcal{P}^*$ $(\alpha = 0, 1, \ldots, l^* - 1)$ which are lying in the regarded regime $\mathcal{P}^*$ takes the following form:

$$(\mathcal{HLS}) \qquad \min_{(a^*_{ij}),(\mathrm{W}^*_{i\ell}),(\mathrm{V}^*_i)} \sum_{\alpha=0}^{l^*-1} \left\| A^* \bar{X}^{(\kappa_\alpha)} + \mathrm{W}^* \bar{\bar{X}}^{(\kappa_\alpha)} + \mathrm{V}^* - \dot{\bar{X}}^{(\kappa_\alpha)} \right\|^2_\infty .$$

As discussed above, parallelpipe expression vectors can affect several neighbouring subparallelpipes $\mathcal{P}^*$, such that we get corresponding problems $(\mathcal{HLS})$. Criteria on which of them to put special emphasis consist in where the data vectors as parallelpipes are lying, and on further empirical evidence. In $(\mathcal{HLS})$, $\|\cdot\|_\infty$ stands for the *Chebychev norm* of the set inserted, i.e., it is the maximum norm with respect to the vector-valued functions defined by (independent) parametrization which we get from the interval-valued entries of M^*, W^* and V^* as well as the ones of the vectors $\bar{X}^{(\kappa_\alpha)}$, $\bar{\bar{X}}^{(\kappa_\alpha)}$ and $\dot{\bar{X}}^{(\kappa_\alpha)}$, respectively. For length measurement we use the Euclidean norm, such that our squared Chebychev norm is indeed a maximum over sums of squares, but we could also use the maximum or the sum (l_1) vector norm instead of the Euclidean (l_2) one. This reconsideration turns our least-squares or Gaussian approximation problem of earlier studies (cf., e.g., [86]) to some generalized Chebychev approximation problem.

The classical "scalar" version of $(\mathcal{HLS})$, i.e., Gaussian approximation, can be canonically treated by building the partial derivatives with respect to the unknowns and equating them to 0. Then, one has to solve the resulting *normal equations*, which are linear in the unknown parameters a^*_{ij}, $\mathrm{w}^*_{i\ell}$ and v^*_i, e.g., by Gaussian elimination method algorithm. But $(\mathcal{HLS})$ is a generalized Chebychev approximation problem; since it can equivalently be written as a semi-infinite optimization problem (cf. [87]), we get access to the applicable methodology of SIP.

As nowadays high-throughput technologies are available, gene-environment networks are very large. Therefore, for practical reasons we have to rarefy them by diminishing the number of arcs [77,86]. Here, upper bounds on the outdegrees of nodes are introduced firstly; then, these constraints are further weakened by a continuous way of model improvement. In this section and in Section 6, we shortly recall this process in our interval-valued generalized Chebychevian way [84]. Firstly, we define the Boolean matrices and vectors,

$$\chi = (\chi_{ij})_{i,j=1,\ldots,n}, \quad \Xi = (\xi_{i\ell})_{\substack{i=1,\ldots,n \\ \ell=1,\ldots,m}}, \quad \text{and} \quad Z = (\zeta_i)_{i=1,\ldots,n},$$

by

$$\chi_{ij} := \begin{cases} 1, & \text{provided gene } j \text{ regulates gene } i \\ 0, & \text{if gene } j \text{ does } \textit{not} \text{ regulate gene } i, \end{cases}$$

$$\xi_{i\ell} := \begin{cases} 1, & \text{provided environmental item } \ell \text{ regulates gene } i \\ 0, & \text{if environmental item } \ell \text{ does } \textit{not} \text{ regulate gene } i, \end{cases}$$

and

$$\zeta_i := \begin{cases} 1, & \text{provided the environment cumulatively regulates gene } i \\ 0, & \text{if the environment does } \textit{not} \text{ cumulatively regulate gene } i. \end{cases}$$

The *outdegrees*

$$\sum_{i=1}^{n} \chi_{ij}, \quad \sum_{i=1}^{n} \xi_{i\ell} \quad \text{and} \quad \sum_{i=1}^{n} \zeta_i$$

count the numbers of genes regulated by gene j, by environmental item ℓ or by the cumulative environment, respectively. Our network rarefaction by bounding the outdegrees obeys the principles of least-squares. We also imply any helpful *a priori* knowledge into the problem, especially, about degradation rates, and what is empirically known about the connectedness structure. Often, a lower bound $\delta_{i,\min}$ on the degradation of gene i is known or there are requests given about the feasibility of special genetic or metabolic processes [27,86]. Herewith, our parameter estimation task becomes a (generalized) *mixed-integer Chebychev approximation problem*

$$\min_{(a_{ij}^*),(\mathbf{W}_{i\ell}^*),(\mathbf{V}_i^*),(\chi_{ij}),(\xi_{i\ell}),(\zeta_i)} \sum_{\alpha=0}^{l^*-1} \left\| A^* \bar{X}^{(\kappa_\alpha)} + \mathrm{W}^* \bar{\bar{X}}^{(\kappa_\alpha)} + \mathrm{V}^* - \dot{\bar{X}}^{(\kappa_\alpha)} \right\|_\infty^2$$

$(\mathcal{MICP})$

$$\text{subject to } \begin{cases} \sum_{i=1}^{n} \chi_{ij} \le \alpha_j & (j = 1, 2, \ldots, n) \\ \sum_{i=1}^{n} \xi_{i\ell} \le \beta_\ell & (\ell = 1, 2, \ldots, m) \\ \sum_{i=1}^{n} \zeta_i \le \gamma & \\ a_{ii} \ge \delta_{i,\min} & (i = 1, 2, \ldots, n). \end{cases}$$

The connectivity of the network could be strongly restricted by the loss of the edges emanating at a few genes which are considered to play a very important role in regulation, i.e., to have very high outdegrees. This can the result of perturbations caused by the environment and affecting the problem $(\mathcal{MICP})$ with its rigid (exclusive) binary constraints. We therefore replace them by continuous constraints in Section 6.

5.4 On Spline Regression

For a good exposition of a dynamics with strong local and less global or asymptotic features of the data, piecewise polynomial or *spline* [16] functions may be used based on observed data $\bar{\mathbb{X}}$. For the sake of simplicity the following explanation on spline regression will concentrate on the *scalar*-valued framework. However, the entire modeling and optimization can be generalized into the interval-valued case, especially, with interval-valued integrals.

Splines may be described as linear combinations of basis functions; deterministic or statistical spline estimation approximates the gene expression data $\dot{\bar{\mathbb{X}}}$ by a smooth curve. However, the main difficulty when working with splines lies in the selection of the number and position of the knots and in the choice of the basis functions for a given data set. We use the data of DNA microarray experiments and environmental observations $(\bar{t}_\kappa, \dot{\bar{X}}^{(\kappa)})$ as our spline knots. In time sense, the knots can be given or selected equidistantly, but also very irregularly. Then, in $(\mathcal{ACE})_{\text{gene}}$ we can use spline functions $f_\alpha(X_\alpha)$ inside $A(E)$, $\mathrm{W}(X)$ and $\mathrm{V}(X)$, respectively. Taking into account separation of variables (gene expression levels), the entries of the matrices $A(X)$, $\mathrm{W}(X)$ and $\mathrm{V}(X)$ are represented by spline functions; e.g.,

$$\begin{aligned} a_{ij}(x) &= \beta_0^{1,i,j} + \sum_{\alpha=1}^{n} f_\alpha^{1,i,j}(X_\alpha) \\ &= \beta_0^{1,i,j} + \sum_{\alpha=1}^{n} \sum_{\gamma=1}^{p_{ij}} \theta_{\alpha,\gamma}^{1,i,j} h_{\alpha,\gamma}^{1,i,j}(X_\alpha) \quad (i,j = 1,2,\ldots,n). \end{aligned}$$

Here, $h_{\alpha,\gamma}^{1,i,j}(E_\alpha)$ are base splines evaluated at the expression levels of the αth gene. By the parameters $\beta_0^{1,i,j}$ we denote partial intercepts depending of the output data $\dot{X}^{(\kappa)}$ $(\kappa = 0,1,\ldots,l-1)$ (percentages of their averaged data). By this an additive separation of the variables is realized. However, this linear kind of interaction is not always given but can be imaginated as an approximation. Instead, below, we will come to a different interpretation of our *additive* functional structure by a clustering of the input data. This additivity may be regarded as a model richness which is intermediate in-between both affine linearity and a nonlinearity that takes into account more complex interactions and correlations between the variables or data clusters, respectively. Firstly, we choose splines degrees individually for each entry $a_{ij}(X)$. Likewise, we represent the entries of $\mathrm{W}(X)$ and $\mathrm{V}(X)$ by splines. The entries $\mathrm{w}_{il}(X)$ and $\mathrm{v}_i(X)$ can be written as

$$\begin{aligned} \mathrm{w}_{il}(X) &= \beta_0^{2,i,l} + \sum_{\alpha=1}^{n} f_\alpha^{2,i,l}(X_\alpha) = \beta_0^{2,i,l} + \sum_{\alpha=1}^{n} \sum_{\varphi=1}^{q_{il}} \theta_{\alpha,\varphi}^{2,i,l} h_{\alpha,\varphi}^{2,i,l}(X_\alpha), \\ \mathrm{v}_i(X) &= \beta_0^{3,i} + \sum_{\alpha=1}^{n} f_\alpha^{3,i}(X_\alpha) = \beta_0^{3,i} + \sum_{\alpha=1}^{n} \sum_{\nu=1}^{r_i} \theta_{\alpha,\nu}^{3,i} h_{\alpha,\nu}^{3,i}(X_\alpha) \end{aligned}$$

with $i = 1,\ldots,n;\ l = 1,\ldots,m$, where for all $i,j,l : q_{il},\ r_i \leq p_{ij}$, or $: \leq \max_j p_{ij}$. Indeed, when using spline functions for the entries $\mathrm{w}_{il}(X)$ and $\mathrm{v}_i(E)$ we must be careful since they are environmental effects influencing the gene expression levels and their approximation. Since we consider these effects to be very small, they have a restricted effect represented by the selected spline degrees for $\mathrm{w}_{il}(X)$ and $\mathrm{v}_i(X)$ not larger than those of $a_{ij}(X)$. Otherwise, the approximated gene expression levels can become affected and this may imply instability in the parameter estimation [71].

To quantify that possible instability, we refer to the second order derivatives (curvature) of the model functions. Then, looking at the equation $(\mathcal{ACE})_{\text{gene}}$, our model becomes fitted by minimizing the criterion *penalized sum of squares* [30]:

$$
\begin{aligned}
&\mathrm{PRSS}(A,\mathrm{W},\mathrm{V}) \\
&= \sum_{\kappa=0}^{l-1} \left\| \dot{\bar{X}}^{(\kappa)} - A(\bar{x}^{(\kappa)})\bar{X}^{(\kappa)} - \mathrm{W}(\bar{X}^{(\kappa)})\breve{\bar{X}}^{(\kappa)} - \mathrm{V}(\bar{X}^{(\kappa)}) \right\|_2^2 \\
&+ \text{Penalty Term} \\
&= \sum_{\kappa=0}^{l-1} \sum_{i=1}^{n} \left(\dot{\bar{X}}_i^{(\kappa)} - \sum_{j=1}^{n} a_{ij}(\bar{X}^{\kappa})\bar{X}_j^{(\kappa)} - \sum_{l=1}^{m} \mathrm{w}_{il}(\bar{X}^{(\kappa)})\breve{\bar{X}}_l^{(\kappa)} - \mathrm{v}_i(\bar{X}^{(\kappa)}) \right)^2 \\
&+ \text{Penalty Term.}
\end{aligned}
$$

Here, $\|\cdot\|_2^2$ stands for the Euclidean norm. If we use our additive model approximations for $a_{ij}(X)$, $\mathrm{w}_{il}(X)$ and $\mathrm{v}_i(X)$, then PRSS has the following form where $(\cdot)''_{X_\alpha}$ denotes differentiation with respect to X_α:

$$
\begin{aligned}
\text{Penalty Term} = &\sum_{i=1}^{n}\sum_{j=1}^{n}\sum_{\alpha=1}^{n} \left[\lambda_\alpha^{1,i,j} \int_{X_\alpha^L}^{X_\alpha^U} \left(f_\alpha^{1,i,j}(X_\alpha)X_j \right)''^2_{X_\alpha} dX_\alpha \right]^2 \\
&+ \sum_{i=1}^{n}\sum_{l=1}^{m}\sum_{\alpha=1}^{n} \left[\mu_\alpha^{2,i,l} \int_{X_\alpha^L}^{X_\alpha^U} \left(f_\alpha^{2,i,l}(X_\alpha)\breve{X}_l \right)''^2_{X_\alpha} dX_\alpha \right]^2 \\
&+ \sum_{i=1}^{n}\sum_{\alpha=1}^{n} \left[\varsigma_\alpha^{3,i} \int_{X_\alpha^L}^{X_\alpha^U} \left(f_\alpha^{3,i}(X_\alpha) \right)''^2_{X_\alpha} dX_\alpha \right]^2,
\end{aligned}
$$

where $\lambda_\alpha^{1,i,j}$, $\mu_\alpha^{2,i,\ell}$, $\varsigma_\alpha^{3,i} \geq 0$ are penalty parameters, and X_α^L, X_α^U are lower and upper bounds with levels X_α. Here, $\breve{X}_l$ are the constant environmental factors and not depending on the gene expression levels of X_α; we may uniformly replace them by the averaged data $\breve{X}_\ell := \frac{1}{l}\sum_{\kappa=0}^{l-1} \breve{\bar{X}}_l^{(\kappa)}$.

Then, denoting $\phi_{\alpha}^{2,i,l} := \mu_{\alpha}^{2,i,l}\breve{X}_l^2$, the penalty term can be written as

$$\begin{aligned}\text{Penalty Term} = &\sum_{i=1}^{n}\sum_{j=1}^{n}\sum_{\alpha=1}^{n}\left[\lambda_{\alpha}^{1,i,j}\int_{X_{\alpha}^{L}}^{X_{\alpha}^{U}}\left(f_{\alpha}^{1,i,j}(X_{\alpha})X_j\right)_{E_{\alpha}}^{''2}dX_{\alpha}\right]^2\\ &+\sum_{i=1}^{n}\sum_{\ell=1}^{m}\sum_{\alpha=1}^{n}\left[\phi_{\alpha}^{2,i,l}\int_{X_{\alpha}^{L}}^{X_{\alpha}^{U}}\left(f_{\alpha}^{2,i,\ell}(X_{\alpha})\right)_{X_{\alpha}}^{''2}dX_{\alpha}\right]^2\\ &+\sum_{i=1}^{n}\sum_{\alpha=1}^{n}\left[\varsigma_{\alpha}^{3,i}\int_{X_{\alpha}^{L}}^{X_{\alpha}^{U}}\left(f_{\alpha}^{3,i}(X_{\alpha})\right)_{X_{\alpha}}^{''2}dX_{\alpha}\right]^2\end{aligned}$$

and further evaluated. Using spline functions inside PRSS, putting

$$\begin{aligned}&G(M,\mathrm{W},\mathrm{V})\\ &:=\sum_{\kappa=0}^{l-1}\sum_{i=1}^{n}\left(\dot{\bar{X}}_i^{(\kappa)}-\sum_{j=1}^{n}a_{ij}(\bar{X}^{(\kappa)})\bar{E}_j^{(\kappa)}-\sum_{l=1}^{m}\mathrm{w}_{il}(\bar{X}^{(\kappa)})\bar{\breve{X}}_l^{(\kappa)}-\mathrm{v}_i(\bar{X}^{(\kappa)})\right)^2\\ &=:\left\|U(\theta^1,\theta^2,\theta^3)\right\|_2^2\end{aligned}$$

and using the discretized form [71] for all members in the integral terms, then we can write each of them as $\left\|V_{ij}(\theta^1)\right\|_2^2$, $\left\|W_{i\ell}(\theta^2)\right\|_2^2$ and $\left\|Z_i(\theta^3)\right\|_2^2$. Now, turning to a constrained rather than a penalized program, PRSS can be interpreted as an optimization problem of the following form:

$$\min_{t,\theta^1,\theta^2,\theta^3}\ t,$$

where

$$\begin{aligned}\left\|U(\theta^1,\theta^2,\theta^3)\right\|_2^2 &\le t^2\\ \left\|V_{ij}(\theta^1)\right\|_2^2 &\le \mathrm{A}_{ij}\quad (i,j=1,2,\ldots,n)\\ \left\|W_{il}(\theta^2)\right\|_2^2 &\le \mathrm{N}_{il}\quad (i=1,2,\ldots,n;l=1,2,\ldots,m)\\ \left\|Z_i(\theta^3)\right\|_2^2 &\le \mathrm{R}_i\qquad (i=1,2,\ldots,n)\\ t &\ge 0.\end{aligned}$$

Such an optimization program is a typical *conic quadratic programming* (*CQP*) problem, which can be solved by *interior points method* (*IPM*) [48–50, 71]. Except for very large-scale problems with dense matrices, these problems have a moderate complexity. As learned in [71], CQP and IPM are much more convenient than penalty methods connected with backfitting algorithm [30]. Conic programming is also helpful in clustering theory, especially, in computational biology [6]. We point out our work [73] on "nonsmooth" spline regression called MARS [30].

The preceding outline on spline regression focussed on the *scalar*-valued framework, but it can also be extended to our *interval*-valued model. While this can be widely done straightforward, there is one single difficulty: spline interpolation in a multivalued setting. This obstacle and how we overcome it in a meaningful way will be explained in a future paper.

6 Improved Modeling by GSIP Extension

6.1 The GSIP Extension

The *mixed-integer Chebychev approximation problem* $(\mathcal{MICP})$ includes rigid binary constraints. To alleviate the effects of these constraints we replace the binary variables χ_{ij}, $\xi_{i\ell}$ and ζ_i by real variables $p_{ij}, q_{i\ell}, r_i \in [0,1]$ which linearly depend on the elements of a_{ij}, $\mathrm{w}_{i\ell}$ and v_i (also interpretable as probabilities) and assume some reasonable box constraints. By this, the values $\sum_{j=1}^{n} p_{ij}(a_{ij}^*)$, $\sum_{i=1}^{m} q_{i\ell}(\mathrm{w}_{i\ell}^*)$ and $\sum_{i=1}^{m} r_i(\mathrm{v}_i^*)$ have become interval-valued approximations of the numbers of genes regulated by gene j, environmental item ℓ and cumulative environment, respectively. All this leads us to a *continuous optimization problem* [77, 84, 86, 87]. Having solved the continuous optimization problem, we could return the binary variables and, hence, network rarefaction, by rounding or staying below some small prescribed values $\varepsilon_{ij}, \varepsilon_{i\ell}, \varepsilon_i \in [0,1)$, respectively [86].

The environment can affect the connectedness between the genes or destroy some of the connecting paths but also cycles among the genes ("knockout"; [24]) and an external stimulus can activate a higher regulation among the genes. For those reasons, the papers [77, 86] implied all the possible convex combinations of the environmental effects into the inequalities about the bounded outdegrees. The *set of combined environmental effects* is defined as the convex hull of all the vectors $\mathrm{w}_{i\ell}^* e_{a(i-1)+\ell}$ and $\mathrm{v}_i^* e_{mn+i}$:

$$
\begin{aligned}
Y(\mathrm{V}^*, \mathrm{W}^*) := \mathrm{conv}\Big(& \left\{ \mathrm{w}_{i\ell}^* e_{m(i-1)+\ell} \,\middle|\, i = 1,2,\ldots,n;\ \ell = 1,2,\ldots,m \right\} \\
& \cup \left\{ \mathrm{v}_i^* \sigma_{i,m+1} e_{mn+i} \,\middle|\, i = 1,2,\ldots,n \right\} \Big) \\
= \Bigg\{ & \sum_{\substack{i=1,\ldots,n,\\ \ell=1,\ldots,m}} \sigma_{i\ell} \mathrm{w}_{i\ell}^* e_{m(i-1)+\ell} + \sum_{i=1,\ldots,n} \sigma_{i,m+1} \mathrm{v}_i^* e_{mn+i} \,\Bigg| \\
& \sigma_{i\tau} \geq 0 \ (i = 1,2,\ldots,n;\ \tau = 1,2,\ldots,m+1), \\
& \sum_{\substack{i=1,\ldots,n\\ \tau=1,\ldots,m+1}} \sigma_{i\tau} = 1 \Bigg\},
\end{aligned}
$$

with e_η denoting the ηth $((m+1)n)$-dimensional unit vector $(0,\ldots,1,\ldots,0)^T$. Formally, we can write $Y(\mathrm{V}^*, \mathrm{W}^*)$ as a parallelpipe [83]

$$
Y(\mathrm{V}^*, \mathrm{W}^*) = \prod_{\substack{i=1,\ldots,n\\ \ell=1,\ldots,m}} [0, \mathrm{w}_{i\ell}^*] \ \times \prod_{i=1,\ldots,n} [0, \mathrm{v}_i^*].
$$

The wealth of how the environment is implied bases on and applies any given *a priori* knowledge about the genes that helps scientists, practitioners and decision makers when determining and elaborating the rarefied network. Now, we get our (generalized) *relaxed Chebychev approximation problem*:

$$(\mathcal{RCP}) \quad \min_{(a_{ij}^*),(\mathbf{W}_{i\ell}^*),(\mathbf{V}_i^*)} \sum_{\alpha=0}^{l^*-1} \left\| A^* \bar{X}^{(\kappa_\alpha)} + \mathbf{W}^* \bar{\bar{X}}^{(\kappa_\alpha)} + \mathbf{V}^* - \dot{\bar{X}}^{(\kappa_\alpha)} \right\|_\infty^2,$$

subject to

$$\begin{array}{rll}
\sum_{i=1}^n p_{ij}(a_{ij}^*, y) \le \alpha_j(y) & & (y \in Y(\mathrm{V}^*, \mathrm{W}^*)), \\
\sum_{i=1}^m q_{i\ell}(\mathrm{w}_{i\ell}^*, y) \le \beta_\ell(y) & & (y \in Y(\mathrm{V}^*, \mathrm{W}^*)), \\
\sum_{i=1}^m r_i(\mathrm{v}_i^*, y) \le \gamma(y) & & (y \in Y(\mathrm{V}^*, \mathrm{W}^*)), \\
\delta_{i,\min} \le a_{ii}^* & & (i = 1, 2, \ldots, n), \\
\underline{a}_{ij}^* \le a_{ij}^* & \le \overline{a}_{ij}^* & (i, j = 1, 2, \ldots, n), \\
\underline{\mathrm{w}}_{i\ell}^* \le \mathrm{w}_{i\ell}^* & \le \overline{\mathrm{w}}_{i\ell}^* & (i = 1, 2, \ldots, n;\ \ell = 1, 2, \ldots, m), \\
\underline{\mathrm{v}}_i^* \le \mathrm{v}_i^* & \le \overline{\mathrm{v}}_i^* & (i = 1, 2, \ldots, n).
\end{array}$$

Now we compare $\underline{a}_{ii}^*$ and $\delta_{i,\min}$ and choose the largest of the two values as a single lower bound instead ($\delta_{i,\min} < \overline{a}_{ii}^*$ provided). As given in the objective function by generalized Chebychev approximation, this uniform interpretation of the "$\le$" conditions amounts to the SIP character of $(\mathcal{RCP})$. By the additional coupling of our inequality constraint set $Y(\mathrm{V}^*, \mathrm{W}^*)$ with the states $(\mathrm{V}^*, \mathrm{W}^*)$, $(\mathcal{RCP})$ even becomes a GSIP problem. In the objective function, the terms with the κth Chebychev norm $\|\cdot\|_\infty$ are nonsmooth max-type functions ($\kappa = 0, 1, \ldots, l^* - 1$). By the following standard technique, $(\mathcal{RCP})$ becomes smoothly modeled. For each max-type function, we introduce a new coordinate τ_κ (in addition to the unknowns of $(\mathcal{RCP})$), considered as a new coordinate and as a uniform bound for the squared Euclidean norms of the elements inside the Chebychev norms. Herewith, we minimize the sum of the bounds. As new inequalities we just introduce these bounding conditions; we write them so that the Euclidean norms of all the elements inside the Chebychev norms have uniformly to stay below the corresponding bounds.

6.2 GSIP for Gene-Environment Networks

When we apply GSIP for our gene-environment network problem $(\mathcal{RCP})$ we obtain the general program form

$$\mathcal{P}_{\mathcal{GSI}}(f, h, g, u, v) \qquad \left\{ \begin{array}{l} \text{minimize } f(x) \text{ on } M_{\mathcal{GSI}}[h, g], \text{ where} \\ M_{\mathcal{GSI}}[h, g] := \{\, x \in \mathbb{R}^d \,|\, h_i(x) = 0\ (i \in I), \\ \qquad\qquad g^j(x, y) \ge 0\ (y \in Y^j(x),\ j \in J) \,\}, \end{array} \right\} \quad (\mathcal{A}_1)$$

with $|I|, |J| < \infty$, and with sets $Y^j = Y^j(x)$ defined as *finitely constrained* ($\mathcal{F}$) feasible sets [65,62,81]. For each $x \in \mathbb{X}^d$, we have a representation

$$\left. \begin{array}{rl} Y^j(x) \;=\; & M_{\mathcal{F}}[u^j(x, \cdot), v^j(x, \cdot)] \\ := & \{\, y \in \mathbb{R}^q \,|\, u_k(x, y) = 0\ (k \in K^j),\ v_\ell(x, y) \ge 0\ (\ell \in L^j) \,\}, \end{array} \right\} \quad (\mathcal{A}_2)$$

with finite sets K^j and L^j. The model ($\mathcal{A}_1$)-($\mathcal{A}_2$) allows equality constraints on both the upper (x-) level and lower (y-) level representing, e.g., further metabolic

restrictions, reactions or balance equations [77,84,86]. The outdegree constraints in $(\mathcal{RCP})$ may be assumed to be of class C^2, too. The bounds guarantee that the feasible set $M_{\mathcal{GSI}}[h,g]$ is compact in the projective sense of the original $2(n^2 + mn + n)$ unknowns (with intervals encoded by tuples of endpoints), but not in the "height" dimensions of the new coordinates τ_κ. This noncompactness can be overcome as shown in [78,81]. Here, the sets $Y^j(x)$ are compact and fulfill the *Linear Independence Constraint Qualification* (*LICQ*), an appropriate choice of the overall box constraints provided. The works [65,77,81,86,87] provide more detailed discussions and generalizations of GSIP.

6.3 Structural Stability for Gene-Environment Networks

In this subsection we state the main theorem on *structural stability* of our gene-environment networks. *Perturbations* of the form $(f,h,g,u,v) \mapsto (\tilde{f},\tilde{h},\tilde{g},\tilde{u},\tilde{v})$ may be caused, e.g., as follows [77,86]:

(I) *Outliers of parallelpipes*: We can face such outliers by multiplying some (dampening) factor on the corresponding squared error.

(II) *"Perturbed" problems and networks*: The data gives rise to one optimization problem and network so that the data of a subsequent measurement can be viewed as a problem and network under variation.

(III) *Errors, imprecision and uncertainty*: They have been included in our modeling by the use of intervals.

The strong Whitney topology C^2_S [32,36] serves as a "measure" of perturbations so that asymptotic aspects are taken into account. For a classification of uncertainty by *five types* of errors, we refer to [20]. The "genetic (and environmental) fingerprint" of $(\mathcal{RCP})$ is given by all the lower level sets of its objective function. If the perturbed and the arbitrarily slightly unperturbed lower level sets are homeomorphic to each other, under some correspondence between the levels, we call $(\mathcal{RCP})$ *structurally stable* [36,39,78,81]. Now, we can carry over and state the *Characterization Theorem on Structural Stability for Gene-Environment Networks* from [77, 86] for $(\mathcal{RCP})$ (for details cf. [37,79–81]). Our main theorem basically states that structural stability can just be *characterized* by two well-known regularity conditions and a more technical one:

Characterization Theorem on Structural Stability for Gene-Environment Networks. [84,87]
The optimization problem $\mathcal{P}_{\mathcal{GSI}}(f,h,g,u,v)$ on gene-environment networks is structurally stable, if and only if the following triplet of conditions $\mathcal{C}_{1,2,3}$ is satisfied:

C_1. EMFCQ holds for $M_{\mathcal{GSI}}[h,g]$.
C_2. All the $\mathcal{G}$-$\mathcal{O}$ Kuhn-Tucker points $\overline{x}$ of $\mathcal{P}_{\mathcal{GSI}}(f,h,g,u,v)$ are $(\mathcal{G}$-$\mathcal{O})$ strongly stable.
C_3. For each two different $\mathcal{G}$-$\mathcal{O}$ Kuhn-Tucker points $\overline{x}^1 \neq \overline{x}^2$ of $\mathcal{P}_{\mathcal{GSI}}(f,h,g,u,v)$ the corresponding critical values are different (separate), too: $f(\overline{x}^1) \neq f(\overline{x}^2)$.

This characterization theorem helps for a well understanding of the topological "landscape" of gene-environment networks, for their perturbational behaviour and for the development of numerical procedures. For example, we can consider "mountain paths" (saddle points) between any two candidate networks being given by local minimizers of $(\mathcal{RCP})$. All the points around candidate solutions can be regarded as potential networks which may be obtained after perturbations, e.g., inward shifts from a genetic or environmental boundary to an interior position [37, 79–81]. They may be outcomes of underlying constellations in the experimental design which may have to be reconstructed, which is an inverse problem [8].

In terms of testing the *goodness of data fitting*, the lower level sets can be interpreted as confidence regions around the parameters estimated. The size of these regions is basically governed by the steepness of the function around the solution. In cases where a local or global minimizer is very steep, we can associate this with stability, whereas flatness is more likely related with instability [87]. For a better analytical understanding of $(\mathcal{RCP})$ and its solution, we identify possible pathologies in terms of one or more of the conditions $\mathcal{C}_{1,\,2,\,3}$ violated.

We point out a relation to *conic programming* (CP) [48], however, in a GSIP sense. If in $(\mathcal{RCP})$ all the functions defining the constraints are linear and the squares on the Chebychev norms deleted, then we obtain such a CP problem. If we square both the linear constraint functions and the bounds, we arrive at the special case of CP called *conic quadratic programming* (*CQP*) [48, 71]. In CP problems, *interior point methods* can be introduced and efficiently applied.

7 Modeling by Stochastic Differential Equations

A further interesting approach to our modeling is based on *stochastic differential equations* (SDE). Such an equation is typically given by

$$\begin{aligned} \dot{X}(t) &= a(X,t) + b(X,t)\delta_t \quad (t \in [0,\infty)) \\ X(0) &= x_0, \end{aligned}$$

where a is the deterministic part, $b\delta_t$ is the stochastic part, and δ_t denotes a generalized stochastic process [42]. An example for a generalized stochastic process is white noise. Suppose that W_t is a generalized version of a Wiener process, i.e., a time-continuous process with the property $W_t \sim N(0,t)$ $(0 \leq t \leq T)$. To obtain our approximate and a smoothed model, we treat W_t as differentiable. Then, white noise δ_t is defined as $\delta_t = \dot{W}_t = dW_t/dt$ and a Wiener process can be obtained by smoothing the white noise. If we replace $\delta_t dt$ by dW_t in our SDE, we obtain

$$dX_t = a(X_t,t)dt + b(X_t,t)dW_t,$$

where $a(X_t,t)$ and $b(X_t,t)$ are drift and diffusion terms, respectively, and X_t is a solution which we try to find based on the experimental data. Since we do not know

the distribution of X_t, we want to simulate its values. For this reason, we simulate a discretized version of SDE. We consider the *Milstein scheme* and obtain the

$$X_{k+1} = X_k + a(X_k,t)(t_{k+1}-t_k) + b(X_k,t)(W_{k+1}-W_k) + \frac{1}{2}(b'b)(X_j,t)\Big(\big(W_{k+1}-W_k\big)^2 - \big(t_{k+1}-t_k\big)\Big)$$

as an approximation for X_t (here, we understand X_k in the sense of our estimation $\widehat{X}^{(k)}$; cf. Subsection 4.1). When we refer to the finitely many sample points $\big(\overline{X}_j, \bar{t}_j\big)$, we get the discrete approximation

$$\dot{\overline{X}}_\kappa = a\big(\overline{X}_\kappa, \bar{t}_\kappa\big) + b\big(\overline{X}_\kappa, \bar{t}_\kappa\big)\,\frac{\Delta W_\kappa}{\overline{h}_\kappa} + \frac{1}{2}(b'b)\big(\overline{X}_\kappa, \bar{t}_\kappa\big)\left(\frac{(\Delta W_\kappa)^2}{\overline{h}_\kappa} - 1\right)$$

for $\kappa = 0, 1, \ldots, N$. Here, the vector $\dot{\overline{X}}_\kappa$ represents difference quotients based on the κth experimental data and on step lengths $\overline{h}_\kappa := \bar{t}_{\kappa+1} - \bar{t}_\kappa = \Delta\bar{t}_\kappa$ between neighbouring sampling times. This relation cannot hold in an exact sense since we consider real data, but it is satisfied best in the *approximate* sense of least squares of errors. The increments ΔW_t are independent on non-overlapping intervals and we have $\mathrm{Var}\big(\Delta\overline{W}_t\big) = \Delta\bar{t}_\kappa$. Hence, the increments having a normal distribution can be simulated by normal distributed random numbers $\overline{Z}_\kappa$ and we obtain a discrete model:

$$\Delta\overline{W}_t = \overline{Z}_\kappa\sqrt{\Delta\bar{t}_\kappa},\ \overline{Z}_\kappa \sim N(0,1).$$

If we use this in our discretized equation, we obtain

$$\dot{\overline{X}}_\kappa = a\big(\overline{X}_\kappa, \bar{t}_\kappa\big) + b\big(\overline{X}_\kappa, \bar{t}_\kappa\big)\,\frac{\overline{Z}_\kappa}{\sqrt{\overline{h}_\kappa}} + \frac{1}{2}(b'b)\big(\overline{X}_\kappa, \bar{t}_\kappa\big)\big(\overline{Z}_\kappa^2 - 1\big).$$

We can rewrite this as

$$\dot{\overline{X}}_\kappa = \overline{G}_\kappa + \overline{H}_\kappa\overline{c}_\kappa + \big(\overline{H}'_\kappa\overline{H}_\kappa\big)\,\overline{d}_\kappa,$$

where

$$\overline{c}_\kappa := \frac{\overline{Z}_\kappa}{\sqrt{\overline{h}_\kappa}},\ \overline{d}_\kappa := \frac{1}{2}\big(\overline{Z}_\kappa^2 - 1\big),\ \overline{G}_\kappa := a\big(\overline{X}_\kappa, \bar{t}_\kappa\big),\ \overline{H}_\kappa := b\big(\overline{X}_\kappa, \bar{t}_\kappa\big).$$

The unknowns $\overline{G}_\kappa$ and $\overline{H}_\kappa$ can be determined by the optimization problem

$$\min_y \ \sum_{\kappa=1}^{l-1}\left\|\dot{\overline{X}}_\kappa - \big(\overline{G}_\kappa + \overline{H}_\kappa\overline{c} + \big(\overline{H}'_\kappa\overline{H}_\kappa\big)\,\overline{d}\big)\right\|_2^2,$$

where the vector y comprises all the parameters in the Milstein model. As the data may have a high variation we must use a parameter estimation method which will give a smoother approximation to the data. In [69] *splines* were used to avoid large oscillations observed for high degree polynomial approximation. In addition, a *penalized residual sum of squares* for SDE and a related *Tikhonov regularization problem* (that could be solved with MATLAB Regularization Toolbox) have been proposed. Alternatively to the concept of Tikhonov regularization we can apply *conic quadratic programming* and we refer to [35, 69] for further details.

8 Socio-Econo-Environment Networks

Beside the application in medicine and life sciences our modeling and analysis provides a conceptual framework for various problems in Operational Research. We illustrate this with an important example from environmental protection and CO_2-Emissions-Control. By this, our gene-environment networks are extended to so-called *socio-econo-environment networks*.

We now refer to the so-called *Technology-Emissions-Means Model* (in short: *TEM model*), developed by *Stefan W. Pickl* [55] for the mathematical analysis of international collaborations and joint implementation programs (JI) in the framework of the Kyoto Protocol. The TEM model integrates the simulation of the technical and financial parameters and describes the economical interactions between several actors (countries, companies) which intend to minimize their emissions by means of cooperative game theory [74, 75]. The players are linked by technical cooperations and the market, which expresses itself in the nonlinear time discrete dynamics of the TEM model [44, 56–58]. We denote by E_i the emissions caused by technologies T_i using financial means E_i, where the index i stands for the ith player $(i = 1, 2, \ldots, N)$. The relationship between financial means and reduced emission in a JI program is given by

$$\begin{aligned} \Delta\mathsf{E}_i(k) &= \sum_{j=1}^{N} \mathsf{em}_{ij}(k)\mathsf{M}_j(k), \\ \Delta\mathsf{M}_i(k) &= -\lambda_i \mathsf{M}_i(k)(\overline{\mathsf{M}}_i - \mathsf{M}_i(k))(\mathsf{E}_i(k) + \varphi_i \Delta\mathsf{E}_i(k)). \end{aligned}$$

with

$$\Delta\mathsf{E}_i(k) := \mathsf{E}_i(k+1) - \mathsf{E}_i(k) \quad \text{and} \quad \Delta\mathsf{M}_i(k) := \mathsf{M}_i(k+1) - \mathsf{M}_i(k),$$

where the discrete times t_k are renamed by k. Furthermore, $\overline{\mathsf{M}}_i$ stands for the upper bounds for the financial investigations. The first equation describes the time-dependent behaviour of the emissions reduced so far by each player [2]. These levels E_i are influenced by financial investigations M_j which are restricted by the second equation. We understand E_i as the reduced emissions of actor i in $\%$ and M_i as the financial means of actor i. The parameters φ_i are called *memory parameters*. Thus, the multiplication of $\Delta\mathsf{E}_i$ with φ_i can be regarded as a *memory effect*; this expression stands for the influence of earlier investments. The first part of the second equation resembles a logistic difference equation, where the proportional factor λ_i can be seen as a *growth parameter*. Each coefficient em_{ij} describes the effect on the emissions of the ith actor if the jth actor invests one unit of money for his technologies, e.g., devices of filters in energy production of consumption. This also shows how effective technology cooperations are, what is the kernel of the JI program. The parameters em_{ij} have to be determined empirically.

The numerical examinations which show that chaotic behaviour can occur, underline the necessity of a control theoretic approach which is implied by an additional control term in the second equation of the TEM model:

$$\mathsf{E}_i(k+1) = \mathsf{E}_i(k) + \sum_{j=1}^{N} \mathsf{em}_{ij}(k)\mathsf{M}_j(k),$$

$$\mathsf{M}_i(k+1) = \mathsf{M}_i(k) - \lambda_i \mathsf{M}_i(k)(\overline{\mathsf{M}}_i - \mathsf{M}_i(k))\,(\mathsf{E}_i(k) + \varphi_i \Delta \mathsf{E}_i(k)) + u_i(k),$$

We note that the TEM model relies on exact data, but this approach aims to model real-world processes, imprecisions and errors have to be considered. For this, in [82] an interval-valued reformulation within the framework of our gene-environment networks has been proposed. For this the TEM model has been structured in this way:

$$(\mathsf{E}^T, \mathsf{M}^T)^{T\,(k+1)} = M^{(k)}((\mathsf{E}^T, \mathsf{M}^T)^{T\,(k)})(\mathsf{E}^T, \mathsf{M}^T)^{T\,(k)}.$$

Having added the control parameter, we obtain the time-discrete dynamics

$$\begin{pmatrix} \mathsf{E} \\ \mathsf{M} \end{pmatrix}^{(k+1)} = M^{(k)}\left(\begin{pmatrix} \mathsf{E} \\ \mathsf{M} \end{pmatrix}^{(k)}\right)\begin{pmatrix} \mathsf{E} \\ \mathsf{M} \end{pmatrix}^{(k)} + \begin{pmatrix} 0 \\ u^{(k)} \end{pmatrix},$$

which we can represented by

$$(\mathcal{DE}) \quad \mathbb{X}^{(k+1)} = \mathbb{A}^{(k)}\mathbb{X}^{(k)}.$$

Here, the matrices $\mathbb{A}^{(k)}$ incorporate the control variables. In this extended space notation, the variable $\mathbb{X}$ and entire dynamics $(\mathcal{DE})$ could be enriched by further environmental and, in particular, genetical items and relations. The shift vector $(0^T, (u^{(k)})^T)^T$ can be regarded as parametric and as a realization of $\mathrm{V}(X, \check{X}^\vee)$ in the sense of Section 3; then, our stability theory could be employed. According to how those matrices are adjusted, we arrive at different behaviours of stability or instability of $(\mathcal{DE})$, in the sense of dynamical systems (Section 4) or of parameter estimation (Section 6.2). As a dual alternative to that feedback-like realization by the vector $\mathrm{V}(X, \check{X}^\vee)$ which becomes incorporated into the matrix $\mathbb{A}^{(k)}$, the control vectors $u^{(k)}$ could also become integrated into $\mathbb{X}^{(k)}$. The time-dependent parameters $\mathsf{em}_{ij}^{(k)}$ can be treated in similar ways as the controls.

9 Conclusion

In this paper, we surveyed the recent advances in mathematical modeling and prediction for industrial, economical, financial and medical applications within the conceptual framework of gene-environment networks. Uncertainties and measurement errors in DNA microarray experiments have been incorporated in our parameter-dependent model and a matrix algebra based on interval arithmetics has been provided. This led us to approximation problems of a generalized Chebychevian kind and we investigated them by generalized semi-infinite optimization.

We stated a characterization result on structural stability and contributed by this to a better understanding of the topological landscape of gene-environment networks. In addition, we pointed out to the relations to conic quadratic programming and spline regression. Furthermore, some related future research directions in metabolic engineering were established.

All this demonstrated in a dynamical modeling context the importance of discrete and continuous optimization in a modern interdisciplinary approach. We note that this approach provides a wide framework for various problems affected with noise and imprecision as they appear in modern industrial, economical and medical applications. In the future, more emphasis has to be given to an extension of our model to further important real-world applications as the recently introduced metabolic networks and the socio-econo-environment networks [28, 59, 60, 82, 83, 86].

This paper is mainly addressed to colleagues from OR, especially, from optimization theory and mathematical modeling, but also computational statistics. Besides further theoretical improvements within these methods and communities, other research challenges consist in advances concerning comparability and dimensions, aspects of data quality included, probabilistic aspects of modeling refined and in further implementation and comparisons with other methods.

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References

1. Ahuja RK, Magnanti TL, Orlin JB (1993) Network flow: theory, algorithms and applications. Prentice Hall, N.J.
2. Ahn H, Moore M, Chen YQ (2004) Stability analysis of iterative learning control system with interval uncertainty. College of Engineering, Utah State University
3. Akçay D (2005) Inference of switching networks by using a piecewise linear formulation. Institute of Applied Mathematics, METU, MSc thesis
4. Akhmet MU, Gebert J, Lätsch M, Pickl SW, Weber GW, Wünschiers R (2004) Algorithmic computational biology: stability analysis of gene-expression patterns, in: part 1 of common special issue of Journal of Computational Technologies 9 (2004) and of The Bulletin of Kazakh National University 42, 3 (Mathematics, Mechanics and Informatics Issue; 2004) 10-17, at the occasion of International Conference *Computational Technologies and Mathematical Models for Research, Engineering and Education* in Almaty, Kazakhstan, October 2004
5. Akhmet MU, Gebert J, Öktem H, Pickl SW, Weber GW (2005) An improved algorithm for analytical modeling and anticipation of gene expression patterns. Journal of Computational Technologies 10, 4: 3-20
6. Akteke-Öztürk B, Weber GW, Kropat E (2008) Continuous optimization approaches for clustering via minimum sum of squares, submitted to the ISI Proceedings of 20th Mini-EURO Conference *Continuous Optimization and Knowledge-Based Technologies*, May 20-23, 2008, Neringa, Lithuania

7. Amann H (1983) Gewöhnliche Differentialgleichungen. Walter de Gruyter, Berlin, New York
8. Aster A, Borchers B, Thurber C (2004) Parameter estimation and inverse problems. Academic Press
9. Branzei R, Dimitrov D, Tijs S (2003) Shapley-like values for interval bankcruptcy games. Economics Bulletin 3: 1-7, http://economicsbulletin.vanderbilt.edu/2003/volume3/, EB-03C70012A.pdf
10. Brayton RK, Tong CH (1979) Stability of dynamical systems: a constructive approach. IEEE Transactions on Circuits and Systems 26, 4: 224-234
11. Brazma A, Hingamp P, Quackenbush J, Sherlock G, Spellman P, Stoeckert C, Aach J, Ansorge W, Ball CA, Causton HC, Gaasterland T, Glenisson P, Holstege FCP, Kim IF, Markowitz V, Matese JC, Parkinson H, Robinson A, Sarkans U, Schulze-Kremer S, Stewart J, Taylor R, Vilo J, Vingron (2001) Minimum information about a microarray experiment (MIAME) toward standards for microarray data. Nature Genetics, 29, pp 365-371
12. Bröcker T, Lander L (1975) Differentiable germs and catastrophes. London Mathematical Society Lecture Note Series 17, Cambridge University Press
13. Chen T, He HL, Church GM (1999) Modeling gene expression with differential equations. In: Proc. Pacific Symposium on Biocomputing, pp 29-40
14. Collins WD, Hu C, Fuzzily determined interval matrix games, http://www-bisc.cs.berkeley.edu/BISCSE2005/Abstracts_Proceeding/Friday/FM3/Chenyi_Hu.pdf
15. DeRisi J, Iyer V, Brown P (1997) Exploring the metabolic and genetic control of gene expression on a genomic scale. Science 278: 680-686
16. Dubois DM, Kalisz E (2004) Precision and stability of Euler, Runga-Kutta and incursive algorithm for the harmonic oscillator. International Journal of Computing Anticipatory Systems 14: 21-36
17. Ergenç T, Weber GW (2004) Modeling and prediction of gene-expression patterns reconsidered with Runge-Kutta discretization. Special issue at the occasion of seventieth birthday of Prof. Dr. Karl Roesner, TU Darmstadt, Journal of Computational Technologies 9, 6: 40-48
18. Feil R (2006) Environmental and nutritional effects on the epigenetic regulation of genes, Mutation Research 600, 1-2, pp 46-57
19. Fiedler M, Nedoma J, Ramik J, Rohn J, Zimmermann K (2006) Linear optimization problems with inexact data. Springer Verlag, Berlin
20. Filar JA (2002) Mathematical models. In: Knowledge for sustainable development - an insight into the encyclopedia of life support systems, UNESCO/EOLSS, released at the world summit on sustainable development, Johannesburg, South Africa, ISBN: 0 9542989-0-X, Vol. I: 339-354
21. Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, Heine-Suner D, Cigudosa JC, Urioste M, Benitez J, Boix-Chornet M, Sanchez-Aguilera A, Ling C, Carlsson E, Poulsen P, Vaag A, Stephan Z, Spector TD, Wu YZ, Plass C, Esteller M (2005) Epigenetic differences arise during the lifetime of monozygotic twins, PNAS 102, pp 10604-10609.
22. Gebert J, Lätsch M, Pickl SW, Weber GW, Wünschiers R (2004) Genetic networks and anticipation of gene expression patterns. In: Computing Anticipatory Systems: CASYS(92)03 – Sixth International Conference, AIP Conference Proceedings 718: 474-485
23. Gebert J, Lätsch M, Pickl SW, Weber GW, Wünschiers R (2006) An algorithm to analyze stability of gene-expression pattern. In: Anthony M, Boros E, Hammer PL, Kogan

A (guest eds.) Special issue *Discrete Mathematics and Data Mining II* of Discrete Applied Mathematics 154, 7: 1140-1156
24. Gebert J, Lätsch M, Quek EMP, Weber GW (2004) Analyzing and optimizing genetic network structure via path-finding, Journal of Computational Technologies 9, 3, pp. 3-12
25. Gebert J, Öktem H, Pickl SW, Radde N, Weber GW, Yılmaz FB (2004) Inference of gene expression patterns by using a hybrid system formulation – an algorithmic approach to local state transition matrices. In: Lasker GE, Dubois DM (eds.) Anticipative and predictive models in systems science I, IIAS (International Institute for Advanced Studies) in Windsor, Ontario, pp 63-66
26. Gebert J, Radde N (2006) A network approach for modeling procaryotic biochemical networks with differential equations. In: Computing Anticipatory Systems, CASYS'05, Seventh International Conference on Computing Anticipatory Systems, Liege, Belgium, August, 2005, pp 526-533
27. Gebert J, Radde N, Weber GW (2006) Modelling gene regulatory networks with piecewise linear differential equations, to appear in the special issue (feature cluster) *Challenges of Continuous Optimization in Theory and Applications* of European Journal of Operational Research
28. Gökmen A, Kayaligil S, Weber GW, Gökmen I, Ecevit M, Sürmeli A, Bali T, Ecevit Y, Gökmen H, DeTombe DJ (2004) Balaban Valley Project: Improving the quality of life in rural area in Turkey, International Scientific Journal of Methods and Models of Complexity 7, 1, `http://www.fss.uu.nl/ms/cvd/isj/index7-1.htm`
29. Guckenheimer J, Holmes P (1997) Nonlinear oscillations, dynamical systems, and bifurcations of vector fields. Springer
30. Hastie T, Tibshirani R, Freedman J (2001) The elements of statistical learning – data mining, inference and prediction, Springer Series in Statistics
31. Hayes B (2003) A lucid interval. American Scientist 91, 6: 484-488
32. Hirsch MW (1976) Differential Topology. Springer
33. Hoon MD, Imoto S, Kobayashi K, Ogasawara N, Miyano S (2003) Inferring gene regulatory networks from time-ordered gene expression data of Bacillus subtilis using differential equations. In: Proc. Pacific Symposium on Biocomputing, pp 17-28
34. Huang S (1999) Gene expression profiling, genetic networks and cellular states: an integrating concept for tumorigenesis and drug discovery. Journal of Molecular Medicine 77, 6: 469-480
35. Işcanoğlu A, Weber GW, Taylan P (2007) Predicting Default Probabilities with Generalized Additive Models for Emerging Markets, Invited Lecture, Graduate Summer School on New Advances in Statistics, METU, August 11-24, 2007
36. Jongen HT, Jonker P, Twilt F (2000) Nonlinear optimization in finite dimensions – morse theory, chebyshev approximation, transversality, flows, parametric aspects. Nonconvex optimization and its applications 47, Kluwer Academic Publishers, Boston
37. Jongen HT, Rückmann JJ, Stein O (1998) Generalized semi-infinite optimization: a first order optimality condition and examples. Mathematical Programming 83: 145-158
38. Jongen HT, Weber GW (1990) On parametric nonlinear programming. Annals of Operations Research 27: 253-284
39. Jongen HT, Weber GW (1991) Nonlinear optimization: characterization of structural stability. Journal of Global Optimization 1: 47-64
40. Kaati G, Bygren L, Edvinsson S (2002) Cardiovascular and diabetes mortality determined by nutrition during parents and grandparents slow growth period, European Journal of Human Genetics 10, pp 682-688
41. Kahraman M, Öktem H, Weber GW, Akhmet M (2008) Using piecewise linear systems with delay to grab the functional dynamics in biological systems, preprint at Institute

of Applied Mathematics, METU, submitted to the proceedings of International Symposium on Health Informatics and Bioinformatics, Turkey08, May 18-20, 2008, Istanbul, Turkey
42. Kloeden PE, Platen E, Schurz H (1994) Numerical Solution of SDE Through Computer Experiments, Springer Verlag, New York
43. Li YF, Venkatesh S, Li D (2004) Modeling global emissions and residues of pesticided, Environmental Modeling and Assessment 9, pp 237-243
44. Lozovanu D, Pickl SW, Weber GW (2004) Optimization, monotonicity and the determination of Nash equilibria - an algorithmic analysis, invited paper, Computing Anticipatory Systems: CASYS'03 - Sixth International Conference, AIP Conference Proceedings 718: 351-361
45. Moore RE (1966) Interval analysis. Prentice-Hall, Inc.
46. Moore RE (1979) Methods and applications of interval analysis. SIAM, Philadelphia
47. Nash SG, Sofer A (1996) Linear and nonlinear programming. McGraw-Hill
48. Nemirovski A (2002) Five lectures on modern convex optimization. C.O.R.E. Summer School on Modern Convex Optimization, August 26-30, 2002, `http://iew3.technion.ac.il/Labs/Opt/opt/LN/Final.pdf`
49. Nemirovski A (2002) Lectures on modern convex optimization, Israel Institute of Technology, `http://iew3.technion.ac.il/Labs/Opt/opt/LN/Final.pdf`
50. Nesterov YE, Nemirovskii AS (1993) Interior point methods in convex programming, SIAM
51. Öktem H (2005) A survey on piecewise-linear models of regulatory dynamical systems, Nonlinear Analysis 63: 336-349
52. Özcan S, Yıldırım V, Kaya L, Becher D, Hecker M, Özcengiz G, Phanerochaete chrysoporium proteome and a large scale study of heavy metal response. In: HIBIT – Proceedings of International Symposium on Health Informatics and Bioinformatics, Turkey'05, Antalya, Turkey, November (2005) 108-114
53. Özöğür S (2005) Mathematical Modelling of Enzymatic Reactions, Simulation and Parameter Estimation, MSc. thesis at Institute of Applied Mathematics, METU, Ankara
54. Özöğür S, Sağdıçoğlu Celep AG, Karasözen B, Yıldırım N, Weber GW (2005) Dynamical modelling of enzymatic reactions, simulation and parameter estimation with genetic algorithms. In: HIBIT – Proceedings of International Symposium on Health Informatics and Bioinformatics, Turkey'05, Antalya, Turkey (November 2005) 78-84
55. Pickl S (1998) Der τ-value als Kontrollparameter - Modellierung und Analyse eines Joint-Implementation Programmes mithilfe der dynamischen kooperativen Spieltheorie und der diskreten Optimierung. Doctoral thesis, Darmstadt University of Technology, Department of Mathematics
56. Pickl S (2001) Convex games and feasible sets in control theory. Mathematical Methods of Operations Research 53, 1: 51-66
57. Pickl S (2002) An iterative solution to the nonlinear time-discrete TEM model - the occurence of chaos and a control theoretic algorithmic approach. AIP Conference Proceedings 627, 1: 196-205
58. Pickl S, An algorithmic solution for an optimal decision making process within emission trading markets, Annales du Lamsade No.3, Laboratoire d'Analyse et Modélisation de Systmes pour l'Aide a la Décision, Proceedings of the DIMACS-LAMSADE Workshop on Computer Science and Decision Theory
59. Pickl S, Weber GW (2001) Optimization of a time-discrete nonlinear dynamical system from a problem of ecology - an analytical and numerical approach. Journal of Computational Technologies 6, 1: 43-52

60. Pickl S, Weber GW (2002) Optimal control of heating processes – with special emphasis on earth warming. In: Chamoni P, Leisten R, Martin A, Minnemann J, Stadler H (eds.) Operations Research Proceedings 2001, pp 247-254
61. Ramadan K (1996) Linear programming with interval coefficients. Carleton University, Ottawa, Ontario
62. Rückmann JJ, Gómez JA (2006) On generalized semi-infinite programming. Top 14, 1: 1-59
63. Sakamoto E, Iba H (2001) Inferring a system of differential equations for a gene regulatory network by using genetic programming. In: Proc. Congress on Evolutionary Computation, pp 720-726
64. Shaocheng T (1994) Interval number and fuzzy number linear programmings, Fuzzy Sets and Systems 66, pp 301-306
65. Stein O (2003) Bi-level strategies in semi-infinite programming. Kluwer Academic Publishers, Boston
66. Taştan M (2005) Analysis and prediction of gene expression patterns by dynamical systems, and by a combinatorial algorithm. Institute of Applied Mathematics, METU, MSc Thesis
67. Taştan M, Ergenç T, Pickl SW, Weber GW (2005) Stability analysis of gene expression patterns by dynamical systems and a combinatorial algorithm. In: HIBIT – Proceedings of International Symposium on Health Informatics and Bioinformatics, Turkey '05, Antalya, Turkey (November 2005) 67-75
68. Taştan M, Pickl SW, Weber GW (2005) Mathematical modeling and stability analysis of gene-expression patterns in an extended space and with Runge-Kutta discretization. In: Proceedings of Operations Research 2005, Bremen, September 2005, Springer, pp 443-450
69. Taylan P, Weber GW (2007) Approximation of stochastic differential equations by additive models using splines and conic programming, to appear in the proceedings of CASYS07, Eighth International Conference on Computing Anticipatory Systems, Liege, Belgium, August 6-11, 2007, D.M. Dubois (ed.)
70. Taylan P, Weber GW (2007) New approaches to regression in financial mathematics by additive models. Journal of Computational Technologies 12, 2: 3-22
71. Taylan P, Weber GW, Beck A, New approaches to regression by generalized additive models and continuous optimization for modern applications in finance, science and techology. To appear in the special issue of Optimization in honour of Prof. Dr. Alexander Rubinov
72. Taylan P, Weber GW, Urgan NN, On the parameter estimation for generalized partial linear models with B-Splines and continuous optimization, preprint at Institute of Applied Mathematics, submitted to TOP
73. Taylan P, Weber GW, Yerlikaya F (2008) Continuous optimization applied in MARS for modern applications in finance, science and technology, to appear in the ISI Proceedings of 20th Mini-EURO Conference Continuous Optimization and Knowledge-Based Technologies, May 20-23, Neringa, Lithuania
74. Tijs S (2003) Introduction to game theory. Hindustan Book Agency, India
75. Tijs SH, Branzei R (2004) Cost sharing in a joint project. In: Carraro C, Fragnelli V (eds.) Game practice and the environment. Fondazione Eni Enrico Mattei, pp 113-124
76. Uğur Ö, Pickl SW, Weber GW, Wünschiers R, Operational research meets biology: An algorithmic approach to analyze genetic networks and biological energy production, preprint no. 50, Institute of Applied Mathematics, METU, 2006, submitted for the special issue of Optimization at the occasion of the 5th Ballarat Workshop on Global and Non-Smooth Optimization: Theory, Methods, and Applications, November 28-30, 2006.

77. Uğur Ö, Weber GW (2007) Optimization and dynamics of gene-environment networks with intervals. In the special issue at the occasion of the 5th Ballarat Workshop on Global and Non-Smooth Optimization: Theory, Methods and Applications, November 28-30, 2006, of Journal of Industrial Management and Optimization 3, 2 (May 2007) 357-379
78. Weber GW (1992) Charakterisierung struktureller Stabilität in der nichtlinearen Optimierung. In: Bock HH, Jongen HT, Plesken W (eds.) Aachener Beiträge zur Mathematik 5, Augustinus publishing house (now: Mainz publishing house) Aachen
79. Weber GW (1998) Generalized semi-infinite optimization: on iteration procedures and topological aspects. In: Kröplin B, Rudolph S, Brückner S (eds.) Similarity Methods. International Workshop, Institute for Statics and Dynamics of Aerospace Structures, Stuttgart, pp 281-309
80. Weber GW (1999) Generalized semi-infinite optimization: on some foundations. Journal of Computational Technologies 4, 3: 41-61
81. Weber GW (2003) Generalized Semi-Infinite Optimization and Related Topics. Heldermann Publishing House, Research and Exposition in Mathematics 29, Lemgo, Hofmannn KH, Wille R (eds.)
82. Weber GW, Alparslan-Gök SZ, Dikmen N, Environmental and life sciences: gene-environment networks - optimization, games and control - a survey on recent achievements, preprint at Institute of Applied Mathematics, invited paper, to appear in the special issue of Journal of Organisational Transformation and Social Change, guest editor: D. DeTombe
83. Weber GW, Alparslan-Gök SZ, Söyler B (2007) A new mathematical approach in environmental and life sciences: gene-environment networks and their dynamics. To appear in Environmental Modeling & Assessment, DOI number: 10.1007/s10666-007-9137-z.
84. Weber GW, Taylan P, Alparslan-Gök Z, Özöğür S, Akteke-Öztürk B (2006) Optimization of gene-environment networks in the presence of errors and uncertainty with Chebychev approximation. Preprint, Institute of Applied Mathematics, METU, submitted to TOP
85. Weber GW, Tezel A (2007) On generalized semi-infinite optimization of genetic networks. TOP 15, 1: 65-77
86. Weber GW, Tezel A, Taylan P, Soyler A, Çetin M (2008) Mathematical contributions to dynamics and optimization of gene-environment networks, to appear in Special Issue: *In Celebration of Prof. Dr. Dr. Hubertus Th. Jongen's 60th Birthday*, guest editors: Pallaschke D, Stein O, of Optimization 57, 2
87. Weber GW, Uğur Ö, Taylan P, Tezel A, On optimization, dynamics and uncertainty: a tutorial for gene-environment networks. To appear in the special issue *Networks in Computational Biology* of Discrete Applied Mathematics
88. Yagil G, Kreinovich V (1971) On the relation between effector concentration and the rate of induced enzyme synthesis. Biophysical Journal 11: 11-27
89. Yılmaz FB (2004) A mathematical modeling and approximation of gene expression patterns by linear and quadratic regulatory relations and analysis of gene networks. Institute of Applied Mathematics, METU, MSc Thesis
90. Yılmaz FB, Öktem H, Weber GW (2005) Mathematical modeling and approximation of gene expression patterns and gene networks. In: Fleuren F, den Hertog D, Kort P (eds.) Operations Research Proceedings, pp 280-287