Environmental and Life Sciences: Gene-Environment Networks - Optimation, Games and Control - A Survey on Recent Achievements

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Abstract

A centrally important research area of computational biology, biotechnology - and life sciences at all - is devoted to modeling, prediction and dynamics of gene-expression patterns. However, this enterprise cannot be investigated in a satisfying way without the role of the environment, including the societies, members of the international community of nations. For a representation of past, present and predicted future states, we also acknowledge the existence of uncertainties in modern technology and decision making, and the negotions in solving societal problems and in international collaboration. We survey and closer explain recent advances in understanding the mathematical foundations and interdisciplinary implications of the newly introduced gene-environment networks; the main basis of our paper is [104]. We integrate the important theme of environmental protection by joint international projects into the our context of networks and their dynamics. As an example of environmental protection, we study CO_2 emissions, their implications for global warming by greenhouse effect, the reduction of both and the joint implementation requested for this purpose by Kyoto protocol. Given data from DNA microarray experiments and environmental records, we extract nonlinear ordinary differential equations which contain parameters that have to be determined. This is done by modern approximation and optimization. After this, time-discretized dynamical systems are studied by a combinatorial algorithm which detects the region of parametric stability. Finally, we analyze the "landscape" of gene-environment networks. Its structure and stability have a very important meaning for the understanding of life and social system and of the conductability of common enterprises, e.g., in the environmental sector. To represent the interactions between the project participants, we imply modern *collaborative game theory* where the players may be individuals or companies or, in particular, nations.

This pioneering work is practically motivated and theoretically elaborated; it is devoted to support improvements in the living conditions of people all over the

world, especially, in health care, medicine, education, environmental protection and public awareness. The authors invite the interested readers to future research.

Key words: Living Conditions, Environment, Computational Biology, Medicine, Uncertainty, Modeling, Collaboration, Games, Joint Project, CO_2 emissions, Global Warming, Dynamics, Matrix, Structure, Complexity, Stability, Optimization

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1 Introduction

"*Can mathematics or Operations Research model the complexity of nature and environment under the limitations of modern technology and in the presence of various societal problems?*" We answer: "yes", but in the margins of our developing understanding only, in this sense: approximately, dynamically and, newly, as being in a game. Any new improvement of the model gives a chance for a deeper insight into the nature and a hope for a continuous service to the people, an overcoming of most challenging problems, on the microscopical, the local and on the global stage as well. The complexity of the environment also includes psychological, societal and political phenomena; tackling its modern challenges as far as it concerns the relations to nature and the life of humankind is not an easy task. However, we present another extension of our previous research it this direction, a first one in our research tradition which more systematically employs game theory. This contribution is established on three of directions of of consideration: *(i)* contemporary progress in modeling and prediction of gene-expression patterns, *(ii)* recent inclusions of the interactions between biological life and the environment (cf. [104] which is an basis of this paper), and of *(iii)* errors in modern technology, e.g., DNA microarrays, of environmental data recording and processing, and in the uncertainties of various kinds of dependencies, decisions and negotiations. Our special emphasis will be on a use of cooperative game theory to represent the international collaboration of *joint projects* [92].

We aim at a contribution to scientific progress and, eventually, to services in medicine, health, food production, industry, politics, education and environmental protection. This work benefits from the recent paper [104] which firstly introduced CO_2 emission control by joint projects (joint implementation of Kyoto Protocol) into our modeling of biosystems.

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For modeling and prediction of gene-expression or environmental levels, two quantities are coupled: the concentrations or *states* and their *dynamics* (rates of change); both of them are of a "primal" importance. For the environmental effects, a "dual" role is reserved; indeed, we can speak of some "duality", the two sides of one coin [94,106] which jointly characterize our learning problem. In terms of optimization and decision, this is called a bilevel problem [106,107]. Here, one class of variables contains parameters under perturbation that lead to a response by the variables of the remaining second class. In this context, a perturbation means some slight impact or stimulus on a parameter, especially, by the environment. For a deep understanding about the states and the variation of genetic and environmental patterns we employ the tableworks of *matrices*, received via least-squares estimation, we employ a matrix algebra and a game theoretical interpretation. Matrices encode our gene-environment networks and they specify their concrete dynamics. 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 characterized by various dynamical phenomena and comprised by *stability* or *instability*. Those discrete "forward" orbits are generated by matrix multiplication, iteratively performed; we can analyze them by the combinatorial procedure of Brayton and Tong [12,93].

Stability classically, e.g., in physics, mechanics, technology, population dynamics and medicine, has a positive interpretation in terms of some local order, a coming to a rest (recovering) or as the robustness of a system against small perturbations such as infections or attacks [40]. In contrast, there is also a negative meaning: an organism, a living being, a biosystem, which is inflexible by being unable to adapt to a changing environment; then it is in a serious danger caused by bacteria, viruses, radiation and other kinds of attacks. Furthermore, 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 parametric variations, then this contradicts the natural-technical limitation of the genetic and environmental levels by bounded intervals.

Genetic networks mean a weighted directed graph composed of nodes representing genes, and of arcs with functional weights standing for the influences between the genes; but also 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 [1,20,23,31–34,36,48,68,101,84,86,93,105–108,112,113]. A simple additive shift included on the right-hand side of differential equations served to appropriately extend the model space; then, we interpreted the shift by the relevant environmental factors. In [93,94,105–108], we firstly extended ge-

netic networks to *gene-environment networks*. Now, the new nodes are environmental items such as poison in soil, groundwater, in air or food, emissions, radiation, but also the welfare and living conditions, temperature (e.g., global warming), but also education, campaigns for a healthy lifestyle and joint projects in ecology.

Errors, uncertainties and measurement ambiguities belong to the characteristic features of technology, even to high tech. In particular, for a large number of genes the expression levels can easily be monitored by *DNA-microarray experiments* [17], but despite the fast technological advances, it is nevertheless affected with imprecision, ambivalence and uncertainty [29,94,107,108]. Therefore, we included these errors into our model. We represent various kinds of errors by *intervals* [94,104,107,108].

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 deficiences of that problem and for algorithmical reasons, we relax the inequality constraints to become continuous and depending on the environmental items, maybe also on time and, very importantly, on errors and uncertainties located in intervals, the problem becomes a 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. GSIP is an advancing wide problem class with many motivations, results, future challenges and many practical applications even today [79,83,102].

Environmental items themselves and how they exercise effects - often in mutually catalyzing or multiplicative ways, are becoming very important, the more so as we are living in a time of globalization, of rapid information exchange, of mobility and multicausalities in all kinds of biosystems, communities and societies. This paper acknowledges this situation and offers a mathematical contribution to its challenges.

Control of carbon dioxide emission is an central issue in environmental protection [56–58,71–73]. We will embed CO_2 emissions reduced as well as finanical means of the countries into the gene-environment network, and look at this topic from the viewpoint of modeling and stability of a time-discrete dynamical system. By this we provide an important example and *module* which will in future become closer integrated into the entire wide spectrum of biological and environmental items. Before we return to this in Section 8, let us sketch

the situation briefly.

2 CO_2 Emission Increase and Global Warming: Problem and First Approaches

2.1 Introduction

Carbon dioxide (CO_2) is a naturally occuring gas. Plants need it to live and grow. But over billions of years, plants have used and trapped a large portion of the CO_2 in the earth's atmosphere. As the plants turned into oil and coal, CO_2 was trapped underground. Carbon dioxide is an invisible gas that is harmless to humans. Both CO_2 and carbon monoxide are produced by burning fossil fuels (gas, coal and oil). The initial CO_2 in the atmosphere of the young earth was produced by volcanic activity, this was essential for a warm and stable climate conducive to life. Volcanic activity now releases about 145 million to 255 million short tons of carbon dioxide each year. Volcanic releases are about 1 % of the amount which is released by human activities. There has been a rise of the CO_2 concentration in the earth's atmosphere of around 40 % since the beginning of global industrial revolution (see Figure 1). It is present in the earth's atmosphere at a low concentration of approximately 0.038 % and is an important greenhouse gas. The rise in concentration is directly related to the rate of CO_2 emissions. Anything one can do to reduce CO_2 emissions will directly effect the concentration of this gas, albeit in a small way. Despite its small concentration, CO_2 is a very important component of earth's atmosphere, because it absorbs infrared radiation and enhances the greenhouse effect. First humans lived in an environment with reduced CO_2 concentration. Modern use of oil, coal, natural gas, etc. is releasing trapped CO_2 back into the atmosphere very quickly. Figure 2 illustrates the CO_2 variations, its cycles and the rapid change which happens in these decades. The main effect of CO_2 in the atmosphere is that it acts as a *greenhouse gas*, trapping the heat of the sun inside the atmosphere and making the earth warm up. Warmer temperatures will mean that the icecaps and glaciers of the south pole and other areas will melt, raising the sea level.

2.1.1 The Kyoto Protocol

The Kyoto Protocol is an agreement made under the *United Nations Framework Convention on Climate Change* (*UNFCCC*). Countries that ratify this protocol commit to reduce their emissions of carbon dioxide and some other greenhouse gases, or engage in emissions trading if they maintain or increase emissions of these gases (see Figure 3). The objective is "*the stabilization of*

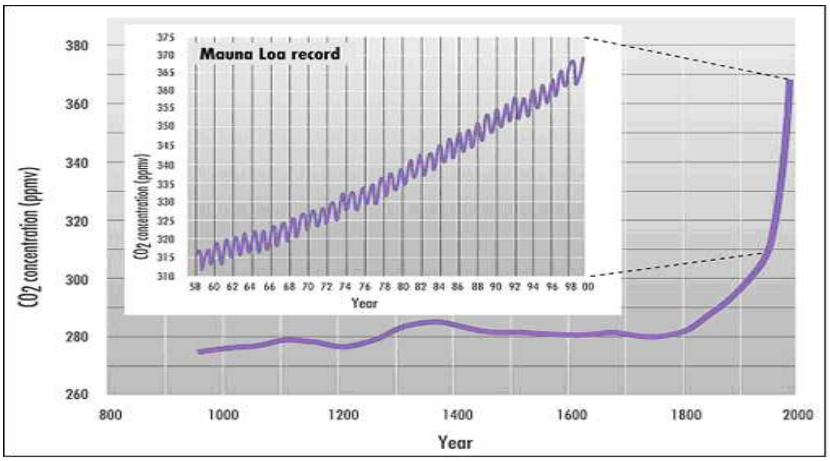

Fig. 1. The change in the atmospheric concentration of CO_2 over the last 1000 years, based on ice core analysis and, since 1958, on direct measurements. Inset is the monthly average concentration of CO_2 (in parts per million by volume) since 1958 at Mauna Loa, Hawaii [11].

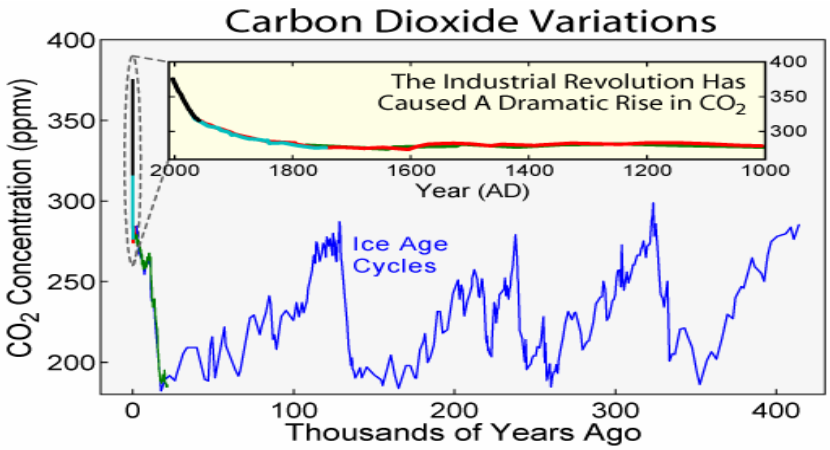

Fig. 2. Variations in concentration of CO_2 in the atmosphere during the last 400 thousand years [56–58].

greenhouse gas concentrations in the atmosphere at a level that would prevent dangerous anthropogenic interference with the climate system". The treaty was negotiated in Kyoto, Japan, in December 1997, opened for signature on March 16, 1998, and closed on March 15, 1999. The agreement came into force on February 16, 2005, following the ratification by Russia on November 18, 2004. As of April 2006, a total of 163 countries have ratified the agreement. The Kyoto protocol now includes more than 163 countries globally and over 55 % of global greenhouse gas emissions (cf. Figure 4). The protocol also reaffirms the principle that developed countries have to pay, and supply technology to other countries for climate-related studies and projects. This was originally agreed in the UNFCCC. Economists have been trying to investigate the overall net benefit of Kyoto Protocol through a cost-benefit analysis. Just as in the case of climatology, there is disagreement due to large uncertainties in economic

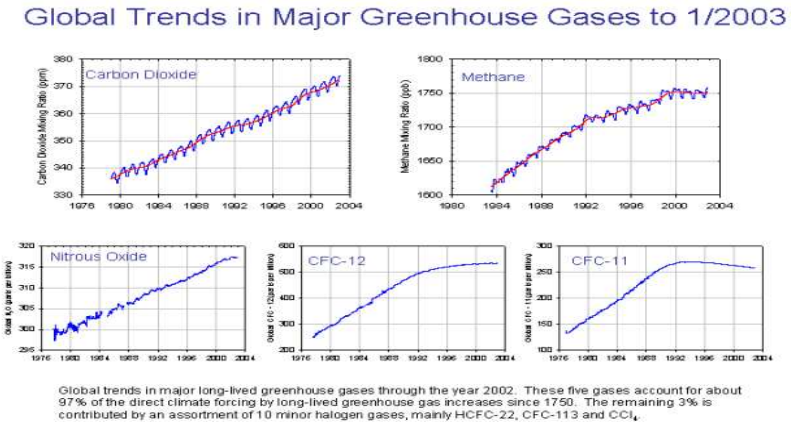

Fig. 3. *Global trends in major long-lived greenhouse gases through the year* 2002. *Five gases account for about* 97 % *of the direct climate forcing by long-lived greenhouse gas increases since* 1750 *[57].*

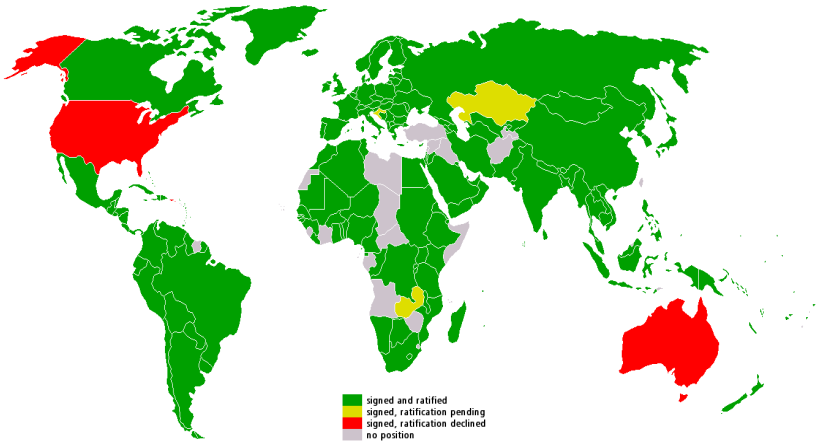

Fig. 4. *Participation in the Kyoto Protocol, where dark green indicates countries that have signed and ratified the treaty and yellow indicates states that have signed and hope to ratify the treaty. Australia and the United States have signed but, currently, decline to ratify it [57].*

variables. Still, the estimates so far generally indicate either that observing the Kyoto Protocol is more expensive than the not observing the Kyoto Protocol or that the Kyoto Protocol has a marginal net benefit which exceeds the cost of simply adjusting to global warming. The Copenhagen consensus project found that the Kyoto Protocol would slow down the process of global warming, but has a superficial overall benefit [57].

The *Convention on Climate Change* sets an overall framework for intergovernmental efforts to tackle the challenge posed by climate change. It recognizes that the climate system is a shared resource whose stability can be affected by industrial and other emissions of carbon dioxide and other greenhouse gases. This convention enjoys near universal membership, with 189 countries having

ratified. Under the convention, governments [56] *(I)* gather and share information on greenhouse gas emissions, national policies and best practices, *(II)* launch national strategies for addressing greenhouse gas emissions and adapting to expected impacts, including the provision of financial and technological support to developing countries, and *(III)* cooperate in preparing for adaptation to the impacts of climate change.

2.1.2 Climate Change

The climate change refers to the variation in the earth's global climate or regional climates over time. It describes changes in the variability or average state of the atmosphere - or average weather - over time scales ranging from decades to millions of years. These changes may come from internal processes, be driven by external forces or, most recently, be caused by human activities [57]. Greenhouse gases, primarily CO_2, methane and water vapour contribute to global warming [58]. In recent usage, especially in the context of environmental policy, the term *climate change* is often used to refer only to the continuous changes in today's climate, including the average rise in surface temperature known as global warming. How large are CO_2 emissions from human fossil-fuel energy consumption? The annual increase in measured CO_2 amounts in air is approximately 60% of the amount that is added annually from these sources. It is estimated that the remainder is absorbed into oceans [21].

Each greenhouse gas - such as carbon dioxide, methane and water vapour - has a different capacity to cause global warming, or the *global warming potential* (GWP), defined as the warming influence over a set time period of a gas relative to that of carbon dioxide. A 100-year time horizon is used in the Kyoto Protocol. It is thought that CO_2 will be responsible for about two thirds of the expected future warming. By the middle of the next century, it may be warmer than it has been since before the last ice age. Small island states and countries close to sea level - such as Bangladesh, with extensive low-lying coastal areas - are especially vulnerable to sea-level rise. Many high-mountain regions could experience significant changes in ecosystems and water resources [96]. On the other hand, a warmer climate may seem welcome. But it could bring disruption of crops in the world's main food-producing regions, famine, economic instability, civil unrest and even war.

In Section 8, we will return to this problem field and present our model, control and game.

3 Gene-Expression and Environmental Data, Modeling and Dynamics

3.1 Introduction

3.1.1 Modeling by Intervals

At first and preliminary stages of modeling, time-continuous models of the following form of time-autonomous ordinary differential equations (ODEs) tried to imply gene-environment networks and their information:

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

Here, $\mathbb{E} = (\mathbb{E}_1, \mathbb{E}_2, \ldots, \mathbb{E}_d)^T$ is the d-vector of both positive concentration levels of proteins (or mRNAs, or small components) and certain levels of the environmental factors, while $\dot{\mathbb{E}}\,(= \frac{d\mathbb{E}}{dt})$ represents a continuous change in the gene-expression data, and $\mathbb{F}_i : \mathbb{R}^d \to \mathbb{R}$ are nonlinear coordinate functions of $\mathbb{F}$ (cf. [20,47,80,93] for different dimensions). In this paper, we present a parameter estimation of unknowns implied into the definition of $\mathbb{F}$, established on experimental data vectors $\overline{\mathbb{E}}$ of those levels. Since these vectors $\overline{\mathbb{E}}$, obtained from microarray and environmental measurements, are merely approximating the actual states $\mathbb{E}$ at the sample times of the experiments, we have the following relations at these times [94] $\mathbb{E}_i = \overline{\mathbb{E}}_i \pm \mathrm{err}_i \quad (i = 1, 2, \ldots, d)$. Here, $\mathrm{err}_i \geq 0$ is an error likely to be made at the experimental measurements of the gene- or environmental expression level $\mathbb{E}_i$. For a closed representation of all cases, we use intervals $[A_i, B_i]$ determined by some maximal measurement error $\mathrm{Err}_i > 0$ which leads us to consider the state $\mathbb{E}_i$ just to be the interval $[A_i, B_i] := [\overline{\mathbb{E}}_i - \mathrm{Err}_i, \overline{\mathbb{E}}_i + \mathrm{Err}_i]$ and, hence, $\mathbb{E} = (\mathbb{E}_1, \mathbb{E}_2, \ldots, \mathbb{E}_d)^T$ to be in the d-dimensional parallelpipe $\bigtimes_{i=1}^{n}[A_i, B_i] = [A_1, B_1] \times [A_2, B_2] \times \cdots \times [A_d, B_d]$.

For closer information about this approach recently repared and introduced for gene-environment networks, we refer to [94,107,108].

3.1.2 Basic Connections with Intervals Dynamics and Optimization

When a model is built by mathematics, certain precise data are assumed; however, in the real world, this is seldom fulfilled. Indeed, the data known and the values obtained are in some certain ranges, where assumptions hold true approximately. Therefore, in *linear programming* (*LP*) programs, data uncertainty is unavoidable. Let $\sum_{i=1}^{n}[u_i, v_i]x_i$ be the objective function of an optimization problem which is subject to $x_i \geq 0$ $(i = 1, 2, \ldots, n)$. Then, the relation $\sum_{i=1}^{n} u_i x_i \geq \sum_{i=1}^{n} v_i x_i$ is valid for all nonnegative vectors $x =$

$(x_1, x_2, \ldots, x_n)^T \geq 0$ [78]. If we have an LP program with *interval coefficients*, then, the solutions can be found by using simplex method [12,78].

In the presence of uncertainty, interval matrices M play an important role; their entries are closed intervals:

$$\begin{pmatrix} \left[\underline{m_{11}}, \overline{m_{11}}\right] & \ldots & \left[\underline{m_{1n}}, \overline{m_{1n}}\right] \\ \left[\underline{m_{21}}, \overline{m_{21}}\right] & \ldots & \left[\underline{m_{2n}}, \overline{m_{2n}}\right] \\ \vdots & \ldots & \vdots \\ \left[\underline{m_{n1}}, \overline{m_{n1}}\right] & \ldots & \left[\underline{m_{mn}}, \overline{m_{mn}}\right] \end{pmatrix},$$

and a concept about *block* matrices whose entries are interval matrices themselves, can also be developed. Let us consider a dynamical system of continuous differential equations on gene-expressions as follows:

$$(\mathcal{CE})_{\text{gene}} \quad \dot{E} = M(E)E.$$

From $(\mathcal{CE})_{\text{gene}}$ we get the following time-discrete equation:

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

Here, the interval matrices $M^{(k)}$ are taken from $M(E)$, and their stability can be investigated by Brayton and Tong's algorithm [4,12,34,106,107]. For more notions, details and application of interval algebra and comparison, we refer to Section 5 and [13,22,28,42,61,62,78,107].

This entire wide framework allows us to approximately address the nature of biological and environmental phenomena, and technical phenomena of measurement and modeling as well; it extends the one from [34,36] such that the continuous equation looks as follows [93,94,106]:

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

Here, $\mathbb{M}(\mathbb{E})$ is a $(d \times d)$-matrix whose entries are intervals and 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. By this, they will constitute a dynamics. The point $\mathbb{E}^{(0)} = (\mathbb{E}_1^{(0)}, \mathbb{E}_2^{(0)}, \ldots, \mathbb{E}_d^{(0)})^T$ consists of the interval-valued initial levels, available, e.g., by the first experimental data point $\overline{\mathbb{E}}(t_0) = \overline{\mathbb{E}}^{(0)}$. For finding an approximate model and network, the least-squares or Chebychevian optimization problem will finally be restricted by bounds imposed on the number of regulating effects exercised per gene and depending on the effects of the environment onto the genes.

Example 3.1 *An easy 2-vector* $\mathbb{E} = (\mathbb{E}_1, \mathbb{E}_2)^T$ *is given by the matrix* $\mathbb{M}(\mathbb{E})$

with nine unknown real parameters $a_1, a_2, \ldots, a_9$ [107]:

$$\mathcal{M}^{a_1,a_2,a_3,a_4,a_5,}_{a_6,a_7,a_8,a_9}(\mathbb{E}) := \begin{pmatrix} [a_1,a_2]\mathbb{E}_1 & [a_3E_2^2, a_4\mathbb{E}_1\mathbb{E}_2] + a_5 \\ a_6\cos(\mathbb{E}_2) + [a_1,a_8]\sin(\mathbb{E}_1) & [a_7,a_8]\exp(a_9\mathbb{E}_1^2) \end{pmatrix},$$

where each entry is an interval. 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. [31]. In [87,88], we studied the case of approximation by splines.

3.1.3 Two Levels of the Parametric Task

Referring to the parametrized entries, a *bilevel problem* [33,34,52,83,94,102,106] of two different problem stages can be distinguished, namely, optimization and stability analysis:

(I) The *optimization (approximation) problem* of squared errors bases on the form $\min_y \sum_{\kappa=0}^{l-1} \left\| \mathbb{M}_y(\overline{\mathbb{E}}^{(\kappa)})\overline{\mathbb{E}}^{(\kappa)} - \dot{\overline{\mathbb{E}}}^{(\kappa)} \right\|_\infty^2$, where the vector y is comprises a first subset of all the parameters. The vector $\dot{\overline{\mathbb{E}}}^{(\kappa)}$ consists of interval-valued *difference quotients* raised on the κth experimental data $\overline{\mathbb{E}}^{(\kappa)}$ and on step lengths $\overline{h}_\kappa := \overline{t}_{\kappa+1} - \overline{t}_\kappa$ between neighbouring samplings times [31,36,94]. Since we turned to an interval-valued setting, we inserted the *Chebychev* or *maximum norm* $\|\cdot\|_\infty$ generating the topology of uniform convergence (cf. Section 6). Thus, we turned from *discrete* (Gaussian or least-squares) approximation and nonlinear optimization [10,31,36,41,50,63,93] to *uniform* (Chebychev) approximation and semi-infinite optimization [94,107,108] (cf. Section 7). (II) *Stability of the dynamics* is investigated with respect to the remaining parameters. For this a combinatorial algorithm on polyhedra sequences observed is used to detect the regions of stability. Indeed, the key advantage of ($\mathcal{CE}$) lies in its structure that allows a time-discretization represented by a sequence of matrix multiplications. Based on this recursion, a stability analysis of combinatorial and geometrical type with polytope series is permitted [34] (cf. Section 5).

3.1.4 The Influence of the Environment

Gene-environment interaction is frequently characterized as *epigenetic*, which refers to stable changes of gene expression patterns in response to environmental factors without any mutations in the DNA sequence [104]. Besides *DNA methylation* being one of the most common epigenetic factors, there are also others, such as *acetylation*, *ethylation* and *phosphorylation*, providing

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 gene-expression portrait [30]. Moreover, nutritional conditions of grandparents can have phenotypic consequences in their grandchildren [27,55]. 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 [106]. As an important example, we will study carbon dioxide emissions and global warming.

3.1.5 Example for a Gene-Network

Let us from now on for a while focus on the n genes and their interactions and, then, step by step, return to our general model in dimension $d > n$; actually, $d = m+2n$ as we will see, with m being the number of environmental items. In Section 4, we shall return to the d dimensional (extended) model and mainly add the influence of the environment on the gene.

Example 3.2 *In dimension n, we look at the following system of differential equations [35,36,108]:*

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

where $c_i \geq 0$ and $\delta_i \geq 0$ represent real- or interval-valued rates of basic synthesis and basic degradation, and the sums correspond to activation or inhibition by other network components, respectively. The activation and inhibition functions $reg\, f^+$ and $reg\, f^-$ have been shown to possess a sigmoid shape [110]. The resulting $(n \times n)$-matrix $M(E)$, where $E = (E_1, E_2, \ldots, E_n)^T$ consists of the first n components of $\mathbb{E}$, has the entries

$$m_{ii}(E) = \frac{c_i}{E_i} - \delta_i + k_{ii} \frac{E_i^{m_{ii}-1}}{E_i^{m_{ii}} + \theta_{ii}^{m_{ii}}} \quad (i = 1, 2, \ldots, n),$$

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

with k_{ij} and $\theta_{ij}, m_{ij}(E)$ being any or nonnegative reals (or intervals), respectively. Now, some or all of the parameters can be estimated based on data from DNA-microarray experiments.

4 From the Special to the Extended Dynamics of Gene-Expression and Environmental Patterns

When especially referring to the n genes and their interaction alone, the dynamics looks as follows: $(\mathcal{CE})_{\text{gene}}$ $\dot{E} = M(E)E$, sharing with $(\mathcal{CE})$ the same multiplicative structure, which is the basis of the recursive iteration idea [34]. Not to lose this recursion property by the shifts proposed in the model extension of $(\mathcal{CE})_{\text{gene}}$ by introducing constant affine linear shifts terms in [112,113], 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 [84–86,93,106]:

$$(\mathcal{ACE})_{\text{gene}} \qquad \dot{E} \;=\; M(E)E + C(E),$$

where the additional column $C(E)$ provides a more accurate data fitting and may represent a vector of environmental perturbations or contributions. Differently from $M(E)E$ which exhibits E as a factor explicitly, the shift $C(E)$ does not need to imply E as a factor. This shift may be, e.g., exponential, logarithmic, trigonometric, but also piecewise polynomial (splines). If the interval entries of $M(E)$ and $C(E)$ are given in a closed or piecewise form by polynomials, then the vector $C(E)$ of various environmental effects should reveal degrees less than the ones in the vector $M(E)E$. We can call an additive decomposition as given by $(\mathcal{ACE})_{\text{gene}}$ a *normal form*, an *unfolding* [9,16,41,52] or a *(generalized) additive model* [41,87–89]. In fact, emissions, poison in water or food, dangerous drugs, social stress, changes in the lifestyle, (quantifiable) educational measurements, and other environmental effects are displayed to form the right-hand side of the system $(\mathcal{ACE})_{\text{gene}}$. In this sense, we distinguish and display special effects on each gene examinated by any environmental item itself or cumulatively by all or several items working together or catalyzing each other. This cumulative effect might not be further splittable 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 presented in [106] but now modified by interval-valued entries [94], works as follows. We split $C(E)$ of $(\mathcal{ACE})_{\text{gene}}$ into the sum $\mathrm{W}(E)\check{E} + \mathrm{V}(E)$, which gives

$$(\mathcal{ACE}) \qquad \dot{E} \;=\; M(E)E + \mathrm{W}(E)\check{E} + \mathrm{V}(E)$$

with $\check{E}(t) = \left(\check{E}_1(t), \check{E}_2(t), \ldots, \check{E}_m(t)\right)^T$ being a specific m-vector (of intervals) which comprises the levels of the m environmental factors that can affect the gene-expression levels and their variation. While some of the coordinates

(factors) $\check{E}_\ell$ affect in a short term, the others may affect in a long term. We may think of $\check{E}$ as constant, but also piecewise constant or, generally, time-dependent. In the case of a constant component $\check{E}_j$, we can easily normalize it to unity: $\check{E}_j \equiv 1$.

By the weight matrix $\mathrm{W} = (\mathrm{w}_{i\ell})_{\substack{i=1,\ldots,n \\ \ell=1,\ldots,m}}$, the effects of the factors $\check{E}_\ell$ on the gene-expression data E_i become incorporated into the system, and the n genes and the m environmental factors are individually matched. Differently and complementary to this, the column vector $\mathrm{V}(E) = (\mathrm{v}_i)_{i=1,\ldots,n}$ gene-wisely comprises all the cumulative effects of all (or several) environmental items influencing the genes together. This cumulation effect could also be represented by a new, $(m+1)$st environmental item, taken into account for each gene. In the time-continuous (instantaneous) system $(\mathcal{ACE})$, the interval value $\sum_{\ell=1}^{m} \mathrm{w}_{i\ell}(E)\check{E}_\ell \ + \mathrm{v}_i$ is interpreted as the total effect of the environment on the expression level E_i of gene i. Now, we overcome the more complex form of $(\mathcal{ACE})$ by an idea worked out and improved in [84–86,93,94,106]:

$$\mathrm{W}(E)\check{E} + \mathrm{V}(E) \ = \check{M}(E)\check{E}^{\vee},$$

where the *gene-environment* matrix $\check{M}(E) := \Big(\mathrm{W}(E) \,|\, \mathrm{diag}(\mathrm{V}(E))\Big)$ consists of $n \cdot (m+n)$ intervals. Its second block represents $\mathrm{V}(E)$ as a diagonal matrix with intervals on the diagonal. Now, putting $\check{E}^{\vee} := (\check{E}^T, \mathrm{e}^T)^T$ with the n-vector $\mathrm{e} := (1, 1, \ldots, 1)^T$ of ones only, we get the following compact form for $(\mathcal{ACE})$:

$$\dot{E} \ = \ M(E)E + \check{M}(E)\check{E}^{\vee}.$$

Introducing the $d = m + 2n$-vector

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

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

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

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

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

We understand that there is an *equivalence* between this initial value problem and the corresponding initial value problem for $(\mathcal{ACE})$ [94]. In general, $E^{(0)}$ and $\check{E}^{\vee,0}$ are chosen as the first experimental data vectors $\overline{E}^{(0)}$ and $\overline{\check{E}}^{\vee,0}$ coming from microarray experiments, followed by the environmental observations. Here, $\overline{\check{E}}^{\vee,0}$ is the initial state of the special or cumulative environmental factors having an impact on E and being expressed in a physical, chemical, financial or social dimension. If the ℓth specific environmental factor $\check{E}_\ell$ is regarded as affecting any gene-expression level, then, initially, the ℓth component of $\overline{\check{E}}^{(0)}$ is considered to be 1, otherwise 0. Here, 1 (0) in $\overline{\check{E}}_\ell^{(0)}$ 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 $(\mathcal{CE})$, equipped with the initial value $\check{E}^{\vee}(t_0) = \overline{\check{E}}^{(0)}$, the time-dependent variable $\check{E}^{\vee}(t)$ is constant: $\check{E}^{\vee} \equiv \overline{\check{E}}^{\vee,0}$. Indeed, we have not included any environmental dynamics, but our modeling framework allows us to do this!

5 The Time-Discretized Model and Stability Analysis

5.1 Time-Discretization

Heun's method is a prominent example of the famous Runge-Kutta methods on an approximative time-discrete modeling of our gene-environmental patterns [24,26,84–86]. applied on $(\mathcal{CE})$, Heun's method looks as follows:

$$\begin{aligned}\mathbb{E}^{(k+1)} &= \mathbb{E}^{(k)} + \frac{h_k}{2}\mathbb{M}(\mathbb{E}^{(k)})\mathbb{E}^{(k)} + \frac{h_k}{2}\mathbb{M}(\mathbb{E}^{(k)} + h_k\mathbb{M}(\mathbb{E}^{(k)})\mathbb{E}^{(k)}) \\ &\quad \times \left(\mathbb{E}^{(k)} + h_k\mathbb{M}(\mathbb{E}^{(k)})\mathbb{E}^{(k)}\right) \\ &= \left[I + \frac{h_k}{2}\mathbb{M}(\mathbb{E}^{(k)}) + \frac{h_k}{2}\mathbb{M}(\mathbb{E}^{(k)} + h_k\mathbb{M}(\mathbb{E}^{(k)})\mathbb{E}^{(k)})(I + h_k\mathbb{M}(\mathbb{E}^{(k)}))\right]\mathbb{E}^{(k)} \\ &= \mathbb{M}^{(k)}\mathbb{E}^{(k)}.\end{aligned}$$

Here, but also in the Eulerian case and some other methods [26,34], we can comprise the discrete "pulse" compactly by matrix-multiplication:

$$(\mathcal{DE}) \qquad \mathbb{E}^{(k+1)} = \mathbb{M}^{(k)}\mathbb{E}^{(k)}.$$

Let the given data from DNA microarray experiments and environmental measurements be comprised by $\overline{\mathbb{E}}^{(\kappa)} := \left((\overline{E}^{(\kappa)})^T, (\check{E}^{\vee,\kappa})^T\right)^T$ $(\kappa = 0, 1, \ldots, l-1)$.

By $\widehat{\mathbb{E}}^{(\kappa)}$ $(\kappa = 0, 1, \ldots, l-1)$ we denote the approximations in the sense of $(\mathcal{DE})$, and we put $\widehat{\mathbb{E}}^{(0)} = \mathbb{E}^{(0)}$. Now, the kth approximation or prediction, $\widehat{\mathbb{E}}^{(k)}$, is calculated by

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

Referring to earlier stages of modeling, in [84–86,112,113], we compared the first l predicted expression vectors with the l data vectors and, by this, investigated the quality of prediction, both theoretically and by numerical examples.

Via $(\mathcal{DE})$ we obtain our *gene-environment networks* by the time-discrete dynamics (while our investigation permits a time-continuous approach to the networks via $(\mathcal{CE})$, too). Indeed, the genes and environmental items are represented by the nodes (vertices) of our network; the interactions between them turn to edges weighted with effects (in the time-continuous case: with functional values). Actually, the significant entries of $\mathbb{M}^{(k)}$, say, $m_{ij}^{(k)}$, $m_{i,n+\ell}^{(k)}$ or $m_{i,n+m+i}^{(k)}$, are the effects multiplied by $\mathbb{E}_j^{(k)}$, $\mathbb{E}_\ell^{(k)}$ or 1. Thus, at the discrete time step $k \mapsto k+1$ the expression level of the ith gene becomes changed by the one of the jth gene (or ℓth environmental item or the cumulative environmental, respectively).

5.2 Matrix Arithmetics Applied

We briefly recall some elements of the interval-valued version [94] of our matrix algebra and, in particular, multiplication [85,86]. Let us refer to the *canonical* form of matrix partitioning presented for the time-continuous model in Section 4. The product of two canonical matrices $\mathbb{M}^{(k)}$, which are the foundation of our networks, is a canonically formed matrix again. After some reorganization and notation we get

$$\mathbb{M}^{(k)} = \mathbb{I} + \frac{h_k}{2}\begin{pmatrix} M(E^{(k)}) & \check{M}(E^{(k)}) & A & \widetilde{A} \\ 0 & 0 & 0 & 0 \end{pmatrix} + \frac{h_k^2}{2}\begin{pmatrix} B & \widetilde{B} \\ 0 & 0 \end{pmatrix}, \quad \text{with}$$

$$\begin{aligned}
A &= M\left(E^{(k)} + h_k\left(M(E^{(k)})E^{(k)} + \check{M}(E^{(k)})\check{E}^{\vee,k}\right)\right), \\
\widetilde{A} &= \check{M}\left(E^{(k)} + h_k\left(M(E^{(k)})E^{(k)} + \check{M}(E^{(k)})\check{E}^{\vee,k}\right)\right), \\
B &= M\left(E^{(k)} + h_k\left(M(E^{(k)})E^{(k)} + \check{M}(E^{(k)})\check{E}^{\vee,k}\right)\right) M(E^{(k)}), \\
\widetilde{B} &= M\left(E^{(k)} + h_k\left(M(E^{(k)})E^{(k)} + \check{M}(E^{(k)})\check{E}^{\vee,k}\right)\right) \check{M}(E^{(k)}),
\end{aligned}$$

such that $\mathbb{M}^{(k)}$ has its final *canonical* block form, too: $\begin{pmatrix} \widehat{M(E^{(k)})} & \widehat{\check{M}(E^{(k)})} \\ 0 & I_d \end{pmatrix}$.

About the form of two or more multiplications of such matrices $\mathbb{M}^{(k)}$ and the spectral theory which is important for our stability theory we refer to [106–108].

5.3 Stability Analysis

Let $\mathcal{M} := \{\mathbb{M}_0, \mathbb{M}_1, \ldots, \mathbb{M}_{\ell-1}\}$ as a set of finitely many matrices over the intervals (as entries) be yielded by $(\mathcal{CE})$ with a sufficiently fine discretization of M, W and V and entry-wise optimization [84–86,94] (without any confusion with the previous meaning of $\mathbb{M}^{(k)}$ as kth iterate). Furthermore, let $\mathcal{M}'$ be the matrix set of all the finite matrix multiplications of elements from $\mathcal{M}$. The following definition originates in [12], but has been extended by us dimensionally and by interval-valuedness [108].

Definition. [94] The matrix set $\mathcal{M}$ (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 $\mathbb{M} \in \mathcal{M}'$ it holds: $\mathbb{M}\mathcal{V} \subseteq \mathcal{U}$.

For the time-continuous system $(\mathcal{CE})$, 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 $[kh, (k+1)h)$. (If, in addition, the initial section $E(t)$, $t \in [0, h)$ is a constant parallelpipe, then the dynamics is piecewise constant.) Herewith, a *stability* condition can be defined 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 $\mathbb{M}$ of the right-hand side of $(\mathcal{CE})$ is Lipschitzian, we learn the following theorem from [107,108]. It extends the real-valued case where it even holds for some Runge-Kutta discretizations presented [106].

Theorem. [108] Let the map $x \mapsto \mathbb{M}(x)$ $(x \in \mathbb{R}^d)$ be Lipschitzian. If the *Eulerian* time-discrete system $\mathbb{E}^{k+1} = \mathbb{M}^k\mathbb{E}^k$ $(k \in \mathbb{N}_0)$, $\mathbb{E}^0 \in \mathbb{R}^d$, 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 $\dot{\mathbb{E}} = \mathbb{M}(\mathbb{E})\mathbb{E}$ (with $h > 0$ sufficiently small) is also stable.

After some dilatation, the parallelpipes $\mathbb{E}$ can be embedded into neighbourhoods of 0_d. Multiplying our matrices and vectors (over intervals) and ob-

serving the resulting discrete orbits can be characterized by the scalar-valued case that was introduced and investigated in, e.g., [12,34,106]. 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 [94,106,107]. 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.

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

6.1 Introduction into the Model and Its Estimation

6.1.1 Our Hybrid Model

In the paper [36], a hybrid approach has been presented which offers a complete dynamical description of the expression levels of n genes. Then, the contributions [94,106] modified it by additionally matching the n genes with m special items and the cumulative item of the environmental, and by turning to the interval-valued setting:

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

In $(\mathcal{HE})$, $\theta_{i,1} < \theta_{i,2} < \ldots < \theta_{i,d_i}$ are thresholds of the expression levels where instantaneous changes of the parameter constellation can occur; $M_{s(t)}$, $\mathrm{W}_{s(t)}$ are matrices of the type $n \times n$ and $n \times m$, respectively, and $\mathrm{V}_{s(t)}$ is an n-vector (all three ones over intervals). The function $Q : \mathbb{R}^n \to \mathbb{N}_0^n$ implies the threshold constellation, and $S(Q(E))$ indicates where in the state space the system is placed at E, and which matrices and vectors M, 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 (M,W,V) is used whenever a threshold is traversed. This *piecewise linear* approach provides an approximation of the global nonlinearity of nature.

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

The gene-expression levels are compact intervals such that the vectors E 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 $E_i(t)$ are shorter than the differences between any two nonneighbouring thresholds [107,108].

Our understanding of ($\mathcal{HE}$) is in the sense of the placement in the set of intervals (cf. Section 3) and of an extension of Q when one or more thresholds are included in the intervals $E_i(t)$. 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 $E_i(t)$; this averaging is then followed by a rounding to an integer. Based on this definition of $s(t)$, we find $M_{s(t)}$, $\mathrm{W}_{s(t)}$ and $\mathrm{V}_{s(t)}$ (we could also directly use the averaging technique for these parameters [94]).

For our time-continuous (or -discrete) system, the parameter estimation works along the following steps [36,94,106]:

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

In [36], those thresholds are defined by, e.g., *Akaike's Information Criterion* [41] (cf. also [3,4,33,36,67]. Since we are concentrating on the tasks in continuous optimization, we assume that we already know all the thresholds.

For any given subparallelpipe $\mathcal{P}^* := \mathcal{P}^{*,\rho}$ we have to extract the parametric unknowns $M_{s(t)}$, $\mathrm{W}_{s(t)}$ and $\mathrm{V}_{s(t)}$ from given data. In $\mathcal{P}^*$, the hybrid system ($\mathcal{HE}$) reduces to a system of ordinary linear differential equations. Hence, 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 $\overline{\breve{E}}^{(\kappa)}$ ($\kappa = 0, 1, \ldots, l-1$) are considered to be binary and constant, but they could also be variable in a more refined modeling.

6.1.2 Mixed-Integer Parameter Estimation

Minimization of the quadratic error between the difference quotients $\overline{\dot{E}}^{(\kappa_\alpha)}$ and the right-hand side of the differential equations evaluated at the finitely many measurement intervals $\overline{E}^{(\kappa_\alpha)} \in \mathcal{P}^*$ ($\alpha = 0, 1, \ldots, l^* - 1$) which are lying in the regarded regime $\mathcal{P}^*$ takes the following form:

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

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 $\overline{E}^{(\kappa_\alpha)}$, $\overline{\breve{E}}^{(\kappa_\alpha)}$ and $\overline{\dot{E}}^{(\kappa_\alpha)}$, 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., [106]) 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 m_{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. [108]), we get access to the applicable methodology of SIP.

Real-world gene-environment networks are huge, such that for practical reasons we have to rarefy them by diminishing the number of arcs [94,106]. Here, upper bounds on the outdegrees of nodes are introduced firstly; later on, these constraints are undergoing a softening by a continuous way of model improvement. In this section and in Section 7, we shortly recall this process in our interval-valued generalized Chebychevian way [107]. Firstly, we define

the Boolean matrices and vectors, $X = (\chi_{ij})_{i,j=1,\dots,n}$, $\Xi = (\xi_{i\ell})_{\substack{i=1,\dots,n \\ \ell=1,\dots,m}}$ and $Z = (\zeta_i)_{i=1,\dots,n}$, representing by the values 1 and 0 whether or not gene j regulates gene i, environmental item ℓ regulates gene i and the environment cumulatively regulates gene i.

Hence, the so-called *outdegrees* $\sum_{i=1}^{n} \chi_{ij}$, $\sum_{i=1}^{n} \xi_{i\ell}$ and $\sum_{i=1}^{n} \zeta_i$ 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 [36,106]. Herewith, our parameter estimation task becomes a (generalized) *mixed-integer Chebychev approximation problem*:

$$(\mathcal{MICP}) \qquad \min_{(m_{ij}^*),(\mathrm{W}_{i\ell}^*),(\mathrm{V}_i^*),(\chi_{ij}),(\xi_{i\ell}),(\zeta_i)} \sum_{\alpha=0}^{l^*-1} \left\| M^* \overline{E}^{(\kappa_\alpha)} + \mathrm{W}^* \overline{\breve{E}}^{(\kappa_\alpha)} + \mathrm{V}^* - \overline{\dot{E}}^{(\kappa_\alpha)} \right\|_\infty^2,$$

subject to

$$\begin{aligned} \textstyle\sum_{i=0}^{n} \chi_{ij} &\le \alpha_j \qquad (j = 1, 2, \dots, n), \\ \textstyle\sum_{i=0}^{n} \xi_{i\ell} &\le \beta_\ell \qquad (\ell = 1, 2, \dots, m), \\ \textstyle\sum_{i=1}^{n} \zeta_i &\le \gamma, \\ m_{ii}^* &\ge \delta_{i,\min} \ (i = 1, 2, \dots, n). \end{aligned}$$

The loss of the edges amenating at a few genes which are considered to play a very important role in regulation, i.e., to have very high outdegrees, could strongly restrict the connectivity of the network. Such a loss can be the result of perturbations caused by the environment and affecting the problem ($\mathcal{MICP}$) with its rigid (exclusive) binary constraints. We therefore make them "softer" (continuous) in the next Section 7.

7 Improved Modeling by GSIP Extension

7.1 The GSIP Extension

Prepared by [94,106–108], we use continuous optimization for a "softening" of ($\mathcal{MICP}$) by replacing the binary variables χ_{ij}, $\xi_{i\ell}$ and ζ_i with real variables $p_{ij}, q_{i\ell}, r_i \in [0, 1]$ which linearly depend on the elements of m_{ij}, $\mathrm{w}_{i\ell}$ and v_i (also interpretable as probabilities). For the latter ones we assume some reasonable box constraints. Herewith, the values $\sum_{j=1}^{n} p_{ij}(m_{ij}^*)$, $\sum_{i=1}^{m} q_{i\ell}(\mathrm{w}_{i\ell}^*)$

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. 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 [106].

On the one hand, the environment can affect the connectedness between the genes or destroy some of the connecting paths but also cycles among the genes ("knockout"; [32]). On the other hand, an external stimulus may activate a higher regulation among the genes. For those reasons, the papers [94,106] 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 $\mathrm{w}_{i\ell}^* e_{m(i-1)+\ell}$ and $\mathrm{v}_i^* e_{mn+i}$:

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

e_η standing for 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 [104]. The richness of how the environment is implied by and employs 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*:

$$
(\mathcal{RCP}) \quad \min_{(m_{ij}^*),(\mathrm{W}_{i\ell}^*),(\mathrm{V}_i^*)} \sum_{\alpha=0}^{l^*-1} \left\| M^* \overline{E}^{(\kappa_\alpha)} + \mathrm{W}^* \overline{\breve{E}}^{(\kappa_\alpha)} + \mathrm{V}^* - \dot{\overline{E}}^{(\kappa_\alpha)} \right\|_\infty^2,
$$

subject to

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

Firstly, we compare $\underline{m}_{ii}^*$ and $\delta_{i,\min}$, then, take the largest of the two values as a single lower bound instead ($\delta_{i,\min} < \overline{m}_{ii}^*$ 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.

7.2 On GSIP and Structural Stability for Gene-Environment Networks

7.2.1 Introduction

GSIP revisited and applied for our gene-environment network problem $(\mathcal{RCP})$, reveals the following general program form [79,83,102]:

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

with finite cardinalities of $|I|$ and $|J|$, and with sets $Y^j = Y^j(x)$ defined as *finitely constrained* ($\mathcal{F}$) feasible sets. For each $x \in \mathbb{R}^d$, we have a representation

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

with finite sets K^j and L^j. What is more, 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 [94,106,107]. 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 [98,102]. Here, the sets $Y^j(x)$ are compact indeed, moreover, they fulfill the *Linear Independence Constraint Qualification* (*LICQ*), an appropriate choice of the overall box constraints provided. The works [83,94,102,106,108] provide more detailed discussions and generalizations of GSIP.

7.2.2 Stability Theory

Perturbations of our gene-environment networks, $(f,h,g,u,v) \mapsto (\tilde{f},\tilde{h},\tilde{g},\tilde{u},\tilde{v})$, are generated or caused, e.g., as follows [94,106]: (I) Some data may be outliers as parallelpipes, in size or position. We can face them by multiplying some (dampening) factor on the corresponding squared error (e.g., 0.9). (II) There can be regularly repeated measurement series, where the data of, e.g., a week, a month, etc., give rise to one optimization problem and network, such that the data of the following week, month, etc., can be viewed as a "perturbed" problem and network. Let us also mention perturbations of data into other subparallelpipes $\mathcal{P}^*$ [108]. Finally, our entire interval-valued modeling has been representing perturbations of the form of (III) errors, imprecision and uncertainty. The so-called strong Whitney topology C^2_S [46,51] 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 [29].

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* [51,53,98,102]. Now, we can carry over and state the *Characterization Theorem on Structural Stability for Gene-Environment Networks* from [94,106] for ($\mathcal{RCP}$) (for details cf. [54,99,100,102]). 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. [107,108]
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 theorem helps for a well understanding of the "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 [54,99,100,102]. They may be outcomes of underlying constellations in the experimental design which may have to be reconstructed, which is an inverse problem [10].

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 [108]. 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) [64], 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*) [64,88]. In CP problems, *interior point methods* can be introduced and efficiently applied.

In the remainder of this paper, we return to the example for our method which we introduced in Section 2, located in the environmental part module of our networks. We shall focus on three environmental items: CO_2 emissions and their reduction, financial means and technological levels. Those emissions have a strong impact on living conditions, health and biological states, especially, by global warming caused. In fact, the extension of our example to further

items of the environment and to genetical information, too, can be provided and is proposed to the readers.

8 Modeling, Prediction, Control and Games in CO_2 Emission Reduction

8.0.3 Interpretation

The conferences of *Rio de Janerio* (1992) and *Kyoto* (1997) demand for new and important economic instruments which have a focus on environmental protection in the macro and micro economy. An important economic tool being part of Kyoto treaty in that area is a *Joint Implementation* (*JI*) *program*, explicitly mentioned in Kyoto Protocol. This is an international program which intends to strengthen international cooperations between enterprises in order to reduce CO_2 and further greenhouse gas emissions.

The United Nations, by a headline and just as a first definition, define *sustainable development* as [95,104]: "*Development that meets the needs of the present without compromising the ability of future generations to meet their own needs*". In order to support a sustainable development by specific instruments, it is adviced that they are embedded into an (if possible) *optimal energy management*. According to JI this means that it must work on the micro level with minimal costs and it should be protected against misuse on the macro level. For that reason, the *Technology-Emissions-Means model*, in short: *TEM model*, was developed by *Stefan W. Pickl* [70], giving the possibility to simulate such an extraordinary market situation and behaviour. The case of a cooperative economic behaviour including co-funding in joint international projects is considered (cf. Subsection 8.4), and the mathematical analysis of several trend scenarios as well. This leads to new results in the area of cooperative time-discrete dynamic games using discrete optimization techniques and exploiting the underlying combinatorial structure (cf. Subsection 5.3). The realization of JI is subject to technical and financial constraints. Specifically, the concept of JI involves a bilateral or multilateral deal in which countries are facing a high pollution abatement in countries with lower costs, and receive credit for the resulting reduction in greenhouse gas emissions.

The reductions in emissions resulting from technical cooperations are recorded at the *Clearing House* whose establishment is also a demand of Kyoto Protocol. The TEM model was developed to capture these constraints in an emprically practicable way. The kernel of the TEM model represents an underlying cost game. It can be used to determine feasible sets. This model bases only on empirical parameters; we can compare them with real-world phenomena. The associated cost reductions should then be allocated in an optimal way. This

approach is well integrated into the TEM model as the possibility to regard the influence of several cost allocations on the feasible set of control parameters. In the played cost game, a special solution called the τ value which stands for a rational allocation process is examined [15,91]; it was introduced into CO_2 emission control in [70]. The main question is: In which situations can the τ value be equivalent to the control parameters needed to reach the regions mentioned in Kyoto Protocol? The results in the area of cooperative dynamical games can lead to new insights in JI and can support an improvement of such an important economical management tool [56,57,60,71–73].

The *Framework Convention on Climate Change* (*FCCC*) of Kyoto Protocol demands for reductions in greenhouse gas emissions by the industrialized countries. On the other hand, developing countries are expanding their energy consumption, which leads to increased levels of greenhouse gas emissions. The preparation of an optimal management tool in that field requires the possibility to identify, assess and compare several technological options. For that reason, the mathematical TEM model presented was elaborated. According to FCCC, control parameters were incorporated which have to be determined iteratively, according to the negotiation process. It is a model which integrates economical and technical investments in a coupled time-discrete nonlinear (quadratic) system of equations. The iterative solution of the TEM model with time-discrete control variables implied is an approach to successfully overcome the occurrence of chaos in the TEM model and, by this, to help decision makers for a better predictable, more secure future and for a sustainable development [71].

Environmental problems belong to the main challenging problems of the 21st century. There is a lack of new allocation principles for investments. Several approaches from game theory concerning this topic may be found. Additionally to these approaches, the improvement of technical effectivity through cooperation JI is the center of interest. Therefore, the TEM model was developed giving the possibility to combine both intentions [60].

8.1 Technology-Emissions-Means Model and Games

The TEM model integrates both the simulation of the technical and financial parameters. It is treated as a time-discrete control problem [60]. It describes the economical interactions between several actors (countries, or companies, etc., in general: players in a *game*) which intend to minimize their emissions, E_i, caused by technologies, T_i, using financial means, E_i, respectively. The index i stands for the ith player ($i = 1, 2, \ldots, N$). The players are linked by technical cooperations and the market, which expresses itself in the nonlinear time discrete dynamics of the TEM model [60,71,72]. For a transparent representation of the relationship between financial means and reduced emissions

in a JI program, not mixing the indices, we rename the discrete times t_k by k and write them as arguments rather than as indices:

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

Here, $\Delta \mathsf{E}_i(k) := \mathsf{E}_i(k+1) - \mathsf{E}_i(k)$ and $\Delta \mathsf{M}_i(k) := \mathsf{M}_i(k+1) - \mathsf{M}_i(k)$. Both differences can be interpreted as difference quotients $\dot{\mathsf{E}}_i^{(k)}$ and $\dot{\mathsf{M}}_i^{(k)}$, referring to a constant steplength $h_k \equiv 1$. 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. These levels E_i $(i = 1, 2, \ldots, N)$ are influenced by financial investigations M_j $(j = 1, 2, \ldots, N)$ 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.

In the first equation, the level of the reduced emissions at the kth discrete time point depends upon the last value plus a market effect. This effect expresses itself in the additive terms which might be negative or positive [2,3]. In general, $\mathsf{E}_i > 0$ implies that the actors have reached yet the demanded value $\mathsf{E}_i = 0$ (normalized *Kyoto-Level*). A value $\mathsf{E}_i < 0$ means that the emissions are less than the requirements of the treaty. The second equation reveals that for such a situation the financial means increase, whereas $\mathsf{E}_i > 0$ leads to a reduction [60,72]: $\mathsf{M}_i(k+1) = \mathsf{M}_i(k) - \lambda_i \mathsf{M}_i(k)(\overline{\mathsf{M}}_i - \mathsf{M}_i(k))(\mathsf{E}_i(k) + \varphi_i \Delta \mathsf{E}_i(k))$. The TEM model is a mathematical model which supports the development of a management tool in the creation of a JI program, which intends to strengthen technical cooperations in order to fulfill Kyoto Protocol. The different parameters em_{ij} stands for the technical relationships between the actors. Their economical interpretation can lead to case studies, in which the range of relevant data can be gained. These data sets might be a good basis for the iterative solution and game theoretic approach [71].

8.2 Control Theory

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:

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

u_i $(i = 1, 2, \ldots, N)$ being the *control variables*. The TEM model is time-discrete, we start with a special parameter set and observe the resulting discrete orbits. Usually, the actors start with a negative value, i.e., they lie under the baseline mentioned in Kyoto Protocol. They try to reach a positive value of E_i. By adding control parameters, we enforce this development using an additive financial term. Therefore, the control parameters are added into the second equation. The aim is to reach a state mentioned in the treaty of Kyoto by choosing the control parameters such that the emissions of each player become minimized. The focus lies in the realization of the necessary optimal control parameters via a played cost game, determined by the way of cooperation between the actors [60]. According to Kyoto Protocol, this approach means that each actor invests additional financial means. There are several possibilities to solve the problem of controllability. Concentrating on the feasible sets and their properties in the area of convex games, we just refer to one numerical result showing that it is possible to steer the system into the fixed points [72].

8.3 Interval-Valued Model Reformulation

The TEM model and its controlled version are time-discrete systems. Aiming at the time-discrete dynamics discussed in Section 5, it can firstly be structured in the 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:

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

which we compactly write as

$$(\mathcal{DE}) \qquad \mathbb{E}^{(k+1)} = \mathbb{M}^{(k)}\mathbb{E}^{(k)},$$

such that, now, the matrices $\mathbb{M}^{(k)}$ incorporate the control variables. In this extended space notation, the variable $\mathbb{E}$ 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 $\mathrm{V}(E, \check{E}^\vee)$ in the sense of Section 4; 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 or of parameter estimation. As a dual alternative to that feedback-like realization by the vector $\mathrm{V}(E, \check{E}^\vee)$ which becomes incorporated into the matrix $\mathbb{M}^{(k)}$, the control vectors $u^{(k)}$ could also become integrated into $\mathbb{E}^{(k)}$. The time-dependent parameters $\mathsf{em}_{ij}^{(k)}$ can be treated in similar ways as the controls.

In our paper, each $\mathbb{M}^{(k)}$ is assumed to be an element of a finite set of interval matrices and the optimized outcome of a time-discretization. With the remaining set of parameters which are not already estimated by GSIP, we represent and study different managerial and decision scenarios. The aim of the TEM model is to reduce the CO_2 emission of the countries according to the Kyoto Protocol. This refers to real-world processes with all their uncertainties; however, until now research with the TEM model has been done with exact data [60,71–73] only. Hence, the corresponding model and results have been a bit far from reality with its imprecions, errors, etc.. For example, the budgets $\overline{\mathsf{M}}_i$ of the countries were regarded as the same for a 10 or 20 years period, while in reality they vary. Moreover, the two parameters λ (*growth*) and φ (*memory*), and the entire *effectivity matrix* em are hard to quantify by a specific constant value, and it is uncertain whether the emission levels will be the same as predicted. For reasons like these, we reconsider the parameters as intervals and, what is more, the entire TEM model with its variables can be remodelled with *intervals*. In this course, also the controls become interval-valued. Then, the model reflects the reality more widely, and the stability and prediction results obtained can be expected to be more confidential.

8.4 Further Elements of Games

As observed in [104], firstly, our game theoretical interpretation firstly was a bit close to the Lotka-Volterra predator-prey equations and Richardson arms race model, both underlying the uncontrolled TEM model. After insertion of control variables into the TEM model and optimization of the dynamics by an object function which represents minimization of a payoff function or coming closest possible to the goals of Kyoto Protocol, or both, chaotic system behaviour and elements of noncooperation or competition turn to the orchestrated behaviour of cooperation. For such a cooperative behaviour of Joint Implementation, the core and the τ value by Stef H. Tijs stand in our

research [13,15,91]. We also mention the related research on cost sharing in a joint project [92], the P-value for cost sharing in minimum cost spanning tree situations [14], and our future investigations on an cooperative game theory generalized in an interval-valued way [104].

9 Conclusion

In this paper, we surveyed the work done by us with our colleages (especially, [104]) in modeling, optimization, dynamical representation and game theory about the patterns of genetic and environmental information have been presented. A special emphasis was was put on the challenge of CO_2 emission control, for which we related our model with a one called TEM. Measurement errors and uncertainties in DNA microarray experiments and environmental observations were taken into account and incorporated. We arrived at approximation problems of a generalized Chebychevian kind and investigated them by GSIP. For a deep understanding of the topological landscape of gene-environment networks determined by that optimization, we state a characterization result on structural stability, and we informed about the related conic quadratic programming. Complementary to our optimization theory, we gave a stability theory on dynamical systems which supports the prediction of genetic and environmental levels and the testing of the goodness of data fitting. We point out that among the important application areas of GSIP there are heating and cooling problems [75,101,102] indeed, complex ones of those studied in this paper.

As we learned, environmental data from, e.g., CO_2 emission but also global warming, can be included, aspects of lifestyle and awareness, the sustainable development of our societies [38], and educational measurements as well. *Socio-econo - environment* networks can become an expression of such an extension, which might be called "soft" today but can be in the range and service of applied mathematics tomorrow. Recent collections of selected contributions to "*OR for Better Management of Sustaiable Development*" are given in [59,76]. The authors tried to give a more theoretical but helpful contribution to a better understanding of nature and for improvements in health care, medicine, living conditions, environmental protection and decision making about the future.

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