REGULATORY NETWORKS UNDER ELLIPSOIDAL UNCERTAINTY - OPTIMIZATION THEORY AND DYNAMICAL SYSTEMS

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Abstract. In this paper, we introduce and analyze time-discrete target-environment regulatory systems (TE-systems) under ellipsoidal uncertainty. The uncertain states of clusters of target and environmental items of the regulatory system are represented in terms of ellipsoids and the interactions between the various clusters are defined by affine-linear coupling rules. The parameters of the coupling rules and the time-dependent states of clusters define the regulatory network. Explicit representations of the uncertain multivariate states of the system are determined with ellipsoidal calculus. In addition, we introduce various regression models that allow us to determine the unknown system parameters from uncertain (ellipsoidal) measurement data by applying semidefinite programming and interior point methods. Finally, we turn to rarefications of the regulatory network. We present a corresponding mixed integer regression problem and achieve a further relaxation by means of continuous optimization. We analyze the structure of the optimization problems obtained, especially, in view of their solvability, we discuss the structural frontiers and research challenges, and we conclude with an outlook.

Key words. regulatory Systems, continuous optimization, mixed integer programming, mathematical modeling, uncertainty, networks, operations research, parameter estimation, dynamical systems, gene-environment networks, eco-finance networks

AMS subject classifications. 90C22, 90C25, 90C30, 91B28, 93A30

1. Introduction.

Regulatory networks are often characterized by the presence of a large number of variables and parameters resulting in a complexity which is beyond man's everyday perception. The development of high throughput technologies led to a generation of massive quantities of data and this technological progress has been accompanied by the development of new mathematical methods for the analysis of highly interconnected systems that allows to gain deeper insights in the dynamic behaviour and the topological aspects of complex regulatory systems in biology, finance and engineering sciences.

In this paper, we address the special class of so-called *TE-regulatory systems* (Target-Environment regulatory systems). These systems are composed of two distinct groups of data, exhibiting a completely different behaviour, although they are strongly related. The first group consists of the *targets*; these are the most important variables of the system and they depend on an additional group of so-called *environmental items*. This specific type of regulatory systems occurs in many applications. For example, in modeling and prediction of gene-expression and environmental patterns, so-called *gene-environment networks* are investigated in order to determine the complex interactions between genes and other components of cells and tissues. Here, the target variables are the expression values of the genes while the environmental items are given by toxins, transcription factors, radiation, etc. [1, 17, 20, 21, 22, 23, 24, 25, 31, 33, 49, 51, 60, 61, 62, 69, 70, 76, 77, 82, 83, 84, 85, 88, 89].

In Operational Research, *eco-finance networks* were introduced in [38] and applied to an extension of the Technology-Emissions-Means Model (in short: TEM-model), which allows a simulation of the cooperative economic behaviour of countries/enterprises with the aim of a reduction of greenhouse gas emissions. Here, the target variables are the emissions that

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the actors wish to reduce and the required financial means act as additional environmental items [32, 34, 35, 36, 41, 53, 54, 55, 56].

As it is clearly understood today, environmental factors constitute an essential group of regulating components and by including these additional variables the models performance can be significantly improved. The advantage of such an refinement has been demonstrated for example in [42], where it is shown that prediction and classification performances of supervised learning methods for the most complex genome-wide human disease classification can be greatly improved by considering environmental aspects. Many other examples from biology and life sciences refer to TE-regulatory systems where environmental effects are strongly involved. Among them are, e.g., *metabolic networks* [15, 52, 82], *immunological networks* [28], *social-* and *ecological networks* [26]. We refer to [23, 32, 60, 61, 62, 88, 89] for applications, practical examples and numerical calculations.

TE-models are usually based on measurements which are always effected by random noise and uncertainty. In order to include errors and uncertainty in TE-regulatory systems various regression models based on interval arithmetics but also on spline regression and stochastic differential equations have been developed. In particular, *generalized additive models* and models based on *multivariate adaptive regression splines* (MARS) have been introduced and the related *Tikhonov regularization problem* was treated by methods from *conic quadratic programming* [63, 64, 65, 66, 67, 68, 86, 87]. In general, for data corrupted by random noise the probability function is usually assumed to be Gaussian. This assumption has computational advantages but this approach is not sufficient as in case of real world data one has to include non-Gaussian or nonwhite noise. To overcome these difficulties, set theoretic approaches can be used where bounds on the uncertain variable are imposed. Here, we focus on *ellipsoids* which have proved to be suitable for data corrupted by noise. Ellipsoids are very flexible with respect to correlations of the data, while intervals and parallelpipes usually come from a perspective where stochastic dependencies among any two of the errors made in the measurements of the expression values of targets and environmental levels are not taken into account explicitly [7]. Moreover, these sets are usually smaller than the ellipsoids and their orthogonal projections into the 2-dimensional Cartesian planes, respectively [7]. 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.

There is a rich list of roles and performances delivered which are associated and assigned to ellipsoids. They include: *(i)* encompassing of objects, *(ii)* inner or outer approximation of shapes and bodies, of discrete or continuous kinds of sets, *(iii)* support for classification of objects and discrimination of different objects, *(iv)* defining critical points or contours which mark tails of higher dimensional and connected versions of tails that describe neighbourhoods of infinity, usually with small values of small probabilities assigned, *(v)* set-valued generalizations of numbers, and generalizations of balls with a reduced wealth of symmetries but still highly symmetrical, *(vi)* geometrical representation of linear mappings which execute certain expansions and contractions (herewith, deformation; e.g., applied to a ball) and rotations, with respect to axes in an orthogonal system of coordinates, *(vi)* geometrical representation of some symmetry breakings, compared with balls, *(vii)* geometrical representation of dependencies, especially, of variances and correlations, *(viii)* easy measurability and support for an approximate measuring of other sets and subsets.

Clustering and *classification* provides an insight in the structure of the data and allows to identify groups of data items jointly acting on other clusters of target and environmen-

tal items. The uncertain states of these clusters are represented by ellipsoids and ellipsoidal calculus is applied to model the dynamics of the TE-regulatory system. *Affine-linear transformations* define the coupling rules which describe the multiple interactions between the clusters and lead to a propagation of ellipsoidal states. The unknown parameters of the time-discrete TE-model are also arranged in clusters and have to be adapted according to uncertain (ellipsoidal) measurement data. Various *regression models* will be introduced which compare measurements and predictions. For parameter estimation we have to measure the size of certain ellipsoids which will be expressed by nonnegative criteria functions associated with the configuration matrix of the ellipsoid. The trace, the trace of square, the determinant or the volume are examples of such measures and they lead to different regression models for parameter estimation of the TE-model. In particular, *semidefinite programming* as well as *conic programming* and *interior point methods* can be applied to solve the various regression models.

Complex regulatory systems usually consist of a large number of interconnected components and the TE-regulatory network is highly structured with multiple interactions between many different clusters. For practical reasons, it may be necessary to reduce the number of branches of the TE-regulatory network. In this situation, bounds on the indegrees of the nodes (clusters) can reduce the complexity of the model. Binary constraints can be used to decide whether or not there is a connection between pairs of clusters. Adding these additional constraints to the objective function of the regression problem, we obtain a *mixed integer optimization problem* which corresponds to our network rarefication. However, binary constraints are very strict and in some situations they can even destroy the connectivity of the regulatory network. In order to avoid these difficulties, the binary constraints can be replaced by more flexible continuous constraints leading to a further *relaxation* in terms of *continuous optimization*.

The paper is organized as follows: In Section 2, we state some basic facts about ellipsoids and introduce basic operations of ellipsoidal calculus. In Section 3, we introduce the time-discrete TE-model under ellipsoidal uncertainty. Explicit representations of the predictions of this model are given in Section 3.2. In Section 4, we turn to an estimation of parameters of the TE-model and introduce various regression models. We discuss their solvability by semidefinite programming and interior point methods. Reduction of complexity will be addressed in Section 5, where an associated mixed integer approximation problem and a further relaxation based on continuous optimization are introduced.

2. Ellipsoidal Calculus. The states of target and environmental variables of our TE-model will be represented in terms of ellipsoids. In this section, we introduce the basic operations needed to deal with ellipsoidal uncertainty such as *sums*, *intersections (fusions)* and *affine-linear transformations* of ellipsoids. The family of ellipsoids in $\mathbb{R}^p$ is closed with respect to affine-linear transformations but neither the sum nor the intersection is generally ellipsoidal, so both must be approximated by ellipsoidal sets.

2.1. Ellipsoidal Descriptions. An *ellipsoid* in $\mathbb{R}^p$ will be parameterized in terms of its center $c \in \mathbb{R}^p$ and a symmetric non-negative definite *configuration matrix* $\Sigma \in \mathbb{R}^{p\times p}$ as

$$\mathcal{E}(c,\Sigma) = \{\Sigma^{1/2}u + c \,|\, \|u\| \leq 1\},$$

where $\Sigma^{1/2}$ is any matrix square root satisfying $\Sigma^{1/2}(\Sigma^{1/2})^T = \Sigma$. When Σ is of full rank, the non-degenerate ellipsoid $\mathcal{E}(c,\Sigma)$ may be expressed as

$$\mathcal{E}(c,\Sigma) = \{x \in \mathbb{R}^p \,|\, (x-c)^T\Sigma^{-1}(x-c) \leq 1\}.$$

The eigenvectors of Σ point in the directions of principal semiaxes of $\mathcal{E}$. The lengths of the semiaxes of the ellipsoid $\mathcal{E}(c,\Sigma)$ are given by $\sqrt{\lambda_i}$, where λ_i are the eigenvalues of Σ for

$i = 1, \ldots, p$. The volume of the ellipsoid $\mathcal{E}(c, \Sigma)$ is given by $\operatorname{vol}\mathcal{E}(c, \Sigma) = V_p\sqrt{\det(\Sigma)}$, where V_p is the volume of the unit ball in $\mathbb{R}^p$, i.e.,

$$V_p = \begin{cases} \dfrac{\pi^{p/2}}{(p/2)!} & \text{, for even } p \\ \dfrac{2^p\pi^{(p-1)/2}((p-1)/2)!}{p!} & \text{, for odd } p. \end{cases}$$

2.2. Affine Transformations. The family of ellipsoids is closed with respect to *affine transformations*. Given an ellipsoid $\mathcal{E}(c, \Sigma) \subset \mathbb{R}^p$, matrix $A \in \mathbb{R}^{m\times p}$ and vector $b \in \mathbb{R}^m$ we get $A\mathcal{E}(c, \Sigma) + b = \mathcal{E}(Ac + b, A\Sigma A^T)$. Thus, ellipsoids are preserved under affine transformation. If the rows of A are linearly independent (which implies $m \leq p$), and $b = 0$, the affine transformation is called *projection* [40].

2.3. Sums of two Ellipsoids. Given two non-degenerate ellipsoids $\mathcal{E}_1 = \mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}_2 = \mathcal{E}(c_2, \Sigma_2)$, their *geometric (Minkowksi) sum* $\mathcal{E}_1 + \mathcal{E}_1 = \{z_1 + z_2 \,|\, z_1 \in \mathcal{E}_1,\ z_2 \in \mathcal{E}_2\}$ is not generally an ellipsoid. However, it can be tightly approximated by parameterized families of external ellipsoids. The range of values of $\mathcal{E}_1 + \mathcal{E}_1$ is contained in the ellipsoid

$$\mathcal{E}_1 \oplus \mathcal{E}_1 := \mathcal{E}(c_1 + c_2, \Sigma(s))$$

for all $s > 0$, where

$$\Sigma(s) = (1 + s^{-1})\Sigma_1 + (1 + s)\Sigma_2.$$

For a *minimal* and *unique* external ellipsoidal approximation an additional condition has to be fulfilled. The value of s is commonly chosen to minimize either the trace or the determinant of $\Sigma(s)$. If we select

$$s = \frac{(\operatorname{Tr}\Sigma_1)^{1/2}}{(\operatorname{Tr}\Sigma_2)^{1/2}},$$

then this value defines the ellipsoid containing the sum that has minimal trace, or, sum of squares of semiaxes. We note that the minimum trace calculation can be used in case of degenerate ellipsoids [19, 39, 40].

2.4. Sums of K Ellipsoids. Given K bounded ellipsoids of $\mathbb{R}^p$, $\mathcal{E}_k = \mathcal{E}(c_k, \Sigma_k)$, $k = 1, \ldots, K$. We adapt the notion of the minimal trace ellipsoid from [18] and introduce the outer ellipsoidal approximation $\mathcal{E}(\sigma, P) = \oplus_{k=1}^K \mathcal{E}_k$ containing the sum $\mathcal{S} = \sum_{k=1}^K \mathcal{E}_k$ of ellipsoids which is defined by

$$\sigma = \sum_{k=1}^K c_k$$

and

$$P = \left(\sum_{k=1}^K \sqrt{\operatorname{Tr}\Sigma_k}\right)\left(\sum_{k=1}^K \frac{\Sigma_k}{\sqrt{\operatorname{Tr}\Sigma_k}}\right).$$

2.5. Intersection of Ellipsoids. As the intersection of two ellipsoids is generally not an ellipsoid we replace this set by the outer ellipsoidal approximation of minimal volume. We adapt the notion of *fusion* of ellipsoids from [58]. Given two non-degenerate ellipsoids $\mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}(c_2, \Sigma_2)$ in $\mathbb{R}^p$ with $\mathcal{E}(c_1, \Sigma_1) \cap \mathcal{E}(c_2, \Sigma_2) \neq \emptyset$ we define an ellipsoid

$$\mathcal{E}_\lambda(c_0, \Sigma_0) := \{x \in \mathbb{R}^p \mid \lambda(x - c_1)^T \Sigma_1^{-1}(x - c_1) + (1 - \lambda)(x - c_2)^T \Sigma_2^{-1}(x - c_2) \leq 1\},$$

where $\lambda \in [0, 1]$.

The ellipsoid $\mathcal{E}_\lambda(c_0, \Sigma_0)$ coincides with $\mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}(c_2, \Sigma_2)$ for $\lambda = 1$ and $\lambda = 0$, respectively. In order to determine a tight external ellipsoidal approximation $\mathcal{E}_\lambda(c_0, \Sigma_0)$ of the intersection of $\mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}(c_2, \Sigma_2)$, we introduce

$$\mathcal{X} := \lambda\Sigma_1^{-1} + (1 - \lambda)\Sigma_2^{-1}$$

and

$$\tau := 1 - \lambda(1 - \lambda)(c_2 - c_1)^T \Sigma_2^{-1} \mathcal{X}^{-1} \Sigma_1^{-1}(c_2 - c_1).$$

The ellipsoid $\mathcal{E}_\lambda(c_0, \Sigma_0)$ is given by the center

$$c_0 = \mathcal{X}^{-1}(\lambda\Sigma_1^{-1}c_1 + (1 - \lambda)\Sigma_2^{-1}c_2)$$

and configuration matrix

$$\Sigma_0 = \tau\mathcal{X}^{-1}.$$

The *fusion* of $\mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}(c_2, \Sigma_2)$, whose intersection is a nonempty bounded region, is defined as the ellipsoid $\mathcal{E}_\lambda(c_0, \Sigma_0)$ for the value $\lambda \in [0, 1]$ that minimizes its volume [58]. The fusion of $\mathcal{E}(c_1, \Sigma_1)$ and $\mathcal{E}(c_2, \Sigma_2)$ is $\mathcal{E}(c_1, \Sigma_1)$, if $\mathcal{E}(c_1, \Sigma_1) \subset \mathcal{E}(c_2, \Sigma_2)$; or $\mathcal{E}(c_2, \Sigma_2)$, if $\mathcal{E}(c_2, \Sigma_2) \subset \mathcal{E}(c_1, \Sigma_1)$; otherwise, it is $\mathcal{E}_\lambda(c_0, \Sigma_0)$ defined as above where λ is the only root in $(0, 1)$ of the following polynomial of degree $2p - 1$:

$$\tau(\det \mathcal{X}) \operatorname{Tr}(\operatorname{co}(\mathcal{X})(\Sigma_1^{-1} - \Sigma_2^{-1})) - p(\det \mathcal{X})^2 \times (2c_0^T\Sigma_1^{-1}c_1 - 2c_0^T\Sigma_2^{-1}c_2 + c_0^T(\Sigma_2^{-1} - \Sigma_1^{-1})c_0 - c_1^T\Sigma_1^{-1}c_1 + c_2^T\Sigma_2^{-1}c_2) = 0.$$

Here, $\operatorname{co}(\mathcal{X})$ denotes the matrix of cofactors of $\mathcal{X}$. Since $\mathcal{X}^{-1} = \operatorname{co}(\mathcal{X})/\det \mathcal{X}$, we represent this polynomial as

$$\tau(\det \mathcal{X})^2 \operatorname{Tr}(\mathcal{X}^{-1}(\Sigma_1^{-1} - \Sigma_2^{-1})) - p(\det \mathcal{X})^2 \times (2c_0^T\Sigma_1^{-1}c_1 - 2c_0^T\Sigma_2^{-1}c_2 + c_0^T(\Sigma_2^{-1} - \Sigma_1^{-1})c_0 - c_1^T\Sigma_1^{-1}c_1 + c_2^T\Sigma_2^{-1}c_2) = 0.$$

We note that it is also possible to define an inner ellipsoidal approximation. The method of finding the internal ellipsoidal approximation of the intersection of two ellipsoids is described in [71].

3. Target-Environment Regulatory Systems under Ellipsoidal Uncertainty. In this section, we introduce a time-discrete model for TE-regulatory systems under ellipsoidal uncertainty. This approach is based on clustering of the sets of targets and environmental items what refers to combinations of variables commonly exerting influence on other groups of system variables. The uncertain states of these clusters are represented in terms of ellipsoids which provide a more detailed description of uncertainty that reflects the correlation of data items. The dynamic behaviour of the clusters and their interactions are determined by clusters of unknown parameters which directly depend on the structure of the system variables. This approach further extends the time-discrete models developed for an analysis of gene-environment networks and eco-finance networks where errors and uncertainty are represented by intervals [38, 78, 79, 81].

3.1. The Time-Discrete Model. In our time-discrete TE-regulatory system, the n-vector $X = (X_1, \ldots, X_n)^T$ denotes the expression values of the n target variables and the m-vector $E = (E_1, \ldots, E_m)^T$ represents the values of the m environmental items. By a preprocessing step of clustering the set of targets can be divided in R disjoint or overlapping clusters $C_r \subset \{1, \ldots, n\},\ r = 1, \ldots, R$. Similarly, the set of all environmental items can be divided in S (disjoint or overlapping) clusters $D_s \subset \{1, \ldots, m\},\ s = 1, \ldots, S$. In case of disjoint clusters the relations $C_{r_1} \cap C_{r_2} = \emptyset$ for all $r_1 \neq r_2$ and $D_{s_1} \cap D_{s_2} = \emptyset$ for all $s_1 \neq s_2$ are fulfilled. The papers [2, 10, 11, 50, 72] introduce into clustering theory as a central element of unsupervised learning and data mining, and they discuss the questions of how to determine the number of clusters and of the stability of the clustering. In addition, *nearest neighbor methods* can be applied [30], in particular, in combination with the *discriminant adaptive nearest-neighbor metric* (DANN) which uses local discriminant information to estimate an effective metric for classification and identification of ellipsoidal neighborhoods [29]. For clustering techniques based on *nonsmooth optimization* we refer to [8, 9]. With each cluster of targets we assign a $|C_r|$-subvector X_r of X that is given by the indices of C_r. In reverse, the n-vector $\widetilde{X}_r$ is obtained from X_r by expanding X_r to a n-vector, where the missing components are equal to zero. Similarly, E_s is a $|D_s|$-subvector of E given by the indices of D_s and $\widetilde{E}_s$ is its expansion to a m-vector with zero-entries at the missing components.

In the following, we will assign an ellipsoid to each cluster. That means, the vectors X_r represent ellipsoidal states of the targets given by the ellipsoid $\mathcal{E}(\mu_r, \Sigma_r) \subset \mathbb{R}^{|C_r|}$ and E_s represent the ellipsoidal states of the environmental items given by the ellipsoids $\mathcal{E}(\rho_s, \Pi_s) \subset \mathbb{R}^{|D_s|}$. These ellipsoids can be expanded to (flat) ellipsoids $\widetilde{X}_r \equiv \mathcal{E}(\widetilde{\mu}_r, \widetilde{\Sigma}_r) \subset \mathbb{R}^n$ and $\widetilde{E}_s \equiv \mathcal{E}(\widetilde{\rho}_s, \widetilde{\Pi}_s) \subset \mathbb{R}^m$. We note that ellipsoids can be identified with intervals if clusters are singletons. In addition, flat ellipsoids $\mathcal{E}(\mu_r, \Sigma_r)$ and $\mathcal{E}(\rho_s, \Pi_s)$ would refer to data sets where at least one of the variables is exactly known, but, if necessary in the approximating sense, we can avoid this by an artificial extension in the corresponding coordinate directions of length $\varepsilon > 0$. In other words, one can impose lower bounds on the semiaxes lengths. Similarly, one can control the extension by imposing sufficiently large upper bounds and, thus, avoid needle-shaped or degenerate ellipsoids.

The dynamic behaviour of the time-discrete TE-regulatory system is governed by affine-linear coupling rules which describe the interactions between the various clusters. These affine-linear relations have to reflect the mutual dependence of pairs of clusters but also overlaps of clusters have to be taken into account.

The *regulatory system of the target items* is defined by

(1) the interactions between the clusters of target items
(represented by an $n \times n$-*interaction matrix* A^{TT} and an n-*intercept vector* V^{TT}),
(2) the effects of the clusters of environmental items on the target clusters
(represented by an $n \times m$ *interaction-matrix* A^{TE} and an n-*intercept vector* V^{TE}).

The entries of the interaction matrices A^{TT}, A^{TE} and the intercept vectors V^{TT}, V^{TE} comprise the unknown parameters of the regulatory system. Clusters of parameters, given by specific sub-matrices and sub-vectors of A^{TT}, A^{TE} and V^{TT}, V^{TE}, define the affine-linear coupling rules. In order to describe the interactions between the clusters of target items we assign a sub-matrix $\Gamma_{jr}^{TT} \in \mathbb{R}^{|C_j| \times |C_r|}$ of A^{TT} to each pair C_j and C_r (the elements of C_j and C_r determine the indices of rows and columns). This sub-matrix can in turn be considered as a *connectivity matrix* between the clusters C_j and C_r that represents the (uncertain) degree of connectivity between the elements of the two clusters of targets. Later we will add an additional shift (intercept) by the sub-vector $\Phi_j^{TT} \in \mathbb{R}^{|C_j|}$ of V^{TT}. We note that the sub-matrices Γ_{jr}^{TT} and sub-vectors Φ_j^{TT} will be partly composed of the same elements in case of overlapping clusters.

In an analogous manner we can describe the effects of the clusters of environmental items on the target clusters. For each pair of target clusters C_j and environmental clusters D_s we define a sub-matrix $\Gamma_{js}^{TE} \in \mathbb{R}^{|C_j| \times |D_s|}$ (the elements of C_j and D_s determine the indices of rows and columns) and a sub-vector $\Phi_j^{TE} \in \mathbb{R}^{|C_j|}$ of V^{TE}. The sub-matrix Γ_{js}^{TE} acts as a *connectivity matrix* between the clusters C_j and D_s and Φ_j^{TE} acts as a shift.

Beside the regulatory system of target variables, there can be an additional *environmental regulatory system* which is defined by

(3) the interactions between the clusters of environmental items
(represented by an $m \times m$ interaction-matrix A^{EE} and an m-intercept vector V^{EE}),
(4) the effects of the target clusters on the environmental clusters
(represented by an $m \times n$ interaction-matrix A^{ET} and an m-intercept vector V^{ET}).

The degree of connectivity between pairs of environmental clusters D_i and D_s or a pair of environmental and target clusters, D_i and C_r, is given by the sub-matrices $\Gamma_{is}^{EE} \in \mathbb{R}^{|D_i| \times |D_s|}$ of A^{EE} and $\Gamma_{ir}^{ET} \in \mathbb{R}^{|D_i| \times |C_r|}$ of A^{ET} as well as the sub-vectors Φ_i^{EE} of V^{EE} and Φ_i^{ET} of V^{ET}.

Now we introduce our time-discrete model that allows us to calculate predictions $X_r^{(k)}$ and $E_s^{(k)}$ of the ellipsoidal states targets and environmental variables.

TE-Model

For $k = 0, 1, 2, \ldots$

For $j = 1, 2, \ldots, R$:

(1) **Interactions between the clusters of targets**

(A) Effect of cluster C_r on cluster C_j

$$G_{jr}^{(k)} = \Gamma_{jr}^{TT} \cdot X_r^{(k)} + \Phi_j^{TT},\ r = 1, 2, \ldots, R$$

(B) Sum of the effects of all clusters of targets on cluster C_j

$$G_j^{(k)} = \bigoplus_{r=1}^{R} G_{jr}^{(k)}$$

(2) **Effects of the environmental clusters on the clusters of targets**

(A) Effect of environmental cluster D_s on target cluster C_j

$$H_{js}^{(k)} = \Gamma_{js}^{TE} \cdot E_s^{(k)} + \Phi_j^{TE},\ s = 1, 2, \ldots, S$$

(B) Sum of the effects of all environmental clusters on cluster C_j

$$H_j^{(k)} = \bigoplus_{s=1}^{S} H_{js}^{(k)}$$

(3) **Sum of effects on the target clusters**

$$\boldsymbol{X_j^{(k+1)} = G_j^{(k)} \oplus H_j^{(k)}}$$

For $i = 1, 2, \ldots, S$:

(1) **Interactions between the clusters of environmental items**

(A) Effect of cluster D_s on cluster D_i

$$M_{is}^{(k)} = \Gamma_{is}^{EE} \cdot E_s^{(k)} + \Phi_i^{EE},\ s = 1, 2, \ldots, S$$

(B) Sum of the effects of all environmental clusters on cluster D_i

$$M_i^{(k)} = \bigoplus_{s=1}^{S} M_{is}^{(k)}$$

(2) **Effects of the target clusters on the clusters of environmental items**

(A) Effect of target cluster C_r on environmental cluster D_i

$$N_{ir}^{(k)} = \Gamma_{ir}^{ET} \cdot X_r^{(k)} + \Phi_i^{ET},\ r = 1, 2, \ldots, R$$

(B) Sum of the effects of all target clusters on environmental cluster D_i

$$N_i^{(k)} = \bigoplus_{r=1}^{R} N_{ir}^{(k)}$$

(3) **Sum of effects on clusters of environmental items**

$$\boldsymbol{E_i^{(k+1)} = M_i^{(k)} \oplus N_i^{(k)}}$$

Since $\Gamma_{jr}^{TT} \cdot X_r^{(k)} + \Phi_j^{TT}$, $\Gamma_{js}^{TE} \cdot E_s^{(k)} + \Phi_j^{TE}$, $\Gamma_{is}^{EE} \cdot E_s^{(k)} + \Phi_i^{EE}$ and $\Gamma_{ir}^{ET} \cdot X_r^{(k)} + \Phi_i^{ET}$ are affine-linear transformations, the sets $G_{jr}^{(k)}$, $H_{js}^{(k)}$, $M_{is}^{(k)}$ and $N_{ir}^{(k)}$ are ellipsoids. In addition, $G_j^{(k)}$, $H_j^{(k)}$, $M_i^{(k)}$ and $N_i^{(k)}$ are defined as sums of ellipsoids and, therefore, constitute ellipsoids themselves. Therefore, the above algorithm allows us to calculate predictions

$$\big(X_1^{(k+1)}, \ldots, X_R^{(k+1)},\, E_1^{(k+1)}, \ldots, E_S^{(k+1)}\big)$$

of the ellipsoidal states of targets and environmental items. In the next subsection, we investigate the structure of the ellipsoids and determine the corresponding centers and configuration matrices.

REMARK The relations and interconnections between the various clusters of target and environmental items of the regulatory system can be represented in terms of a highly interconnected *TE-regulatory network* (Target-Environment regulatory network). The nodes of this network are given by the clusters and the branches are weighted by the matrices and vectors that determine the affine linear coupling rules of the TE-model. Additional weights can be assigned to the nodes of the network. This can be, e.g., the ellipsoids (or some measures of the size of the ellipsoids) associated with the clusters. Although the weights of the branches are static, the evolution of ellipsoids leads to a time-dependent *TE-regulatory network*. Hereby, discrete mathematics and its network algorithms in both versions, statically and dynamically, becomes applicable on subjects such as connectedness, components, clusters, cycles, shortest paths or further subnetworks. Beside these discrete-combinatorial aspects, combinatorial relations between graphs and (nonlinear) optimization problems as well as topological properties of regulatory networks can be analyzed [37]. When we regard the matrices of interactions as a map, then we can "navigate" between the different entries [76, 77]. This can be considered as a focus and control about the dynamics of, e.g., medical, environmental or financial items and their change rates. This kind of navigation is represented by discrete homotopies within the matrices and by continuous homotopies between the underlying ellipsoids. This very much depends on the structures of overlapping or (projective) intersections of these ellipsoidal sets, which are of a polynomial definition [12, 14, 27]. Via such intersections and, covering the paths of navigation, unions of ellipsoids, we in fact arrive at real semialgebraic sets. Then, these classes represent the uncertainty which we study in this paper and take the place of σ-algebras that we would employ from an alternative stochastic viewpoint. We note that the study of our paths of navigation can be analyzed by homotopy theory [27]. The paper [57] gives example how conic, especially, semidefinite programming comes into play via introducing semialgebraic sets, and we remark that the normal forms (sums of squares of polynomials) relate with regression theory where also conic quadratic programming serves for [12, 14, 27]. In forthcoming papers, we shall work out these various new aspects.

3.2. Algorithm. With the TE-Model we can calculate predictions of the ellipsoidal states $X_r^{(k)}$ and $E_s^{(k)}$ of targets and environmental items in terms of subsets of $\mathbb{R}^{|C_r|}$ and $\mathbb{R}^{|D_s|}$, respectively. Now, we introduce an algorithm that allows us to determine centers and configuration matrices of the predictions obtained from the TE-model. At time step $k \in \mathbb{N}_0$ these predictions are given by the ellipsoids $X_r^{(k)} = \mathcal{E}\big(\mu_r^{(k)}, \Sigma_r^{(k)}\big)$ and $E_s^{(k)} = \mathcal{E}\big(\rho_s^{(k)}, \Pi_s^{(k)}\big)$. Applying the ellipsoidal calculus from Section 2, we obtain the following algorithm:

TE-Model: Centers and Configuration Matrices

For $k = 0, 1, 2, \ldots$

For $j = 1, 2, \ldots, R$:

(1) **Interactions between the clusters of targets**

(A) Effect of cluster C_r on cluster C_j

$$g_{jr}^{(k)} = \Gamma_{jr}^{TT} \mu_r^{(k)} + \Phi_j^{TT} \ , \ r = 1, 2, \ldots, R$$
$$\mathcal{G}_{jr}^{(k)} = \Gamma_{jr}^{TT} \Sigma_r^{(k)} (\Gamma_{jr}^{TT})^T \ , \ r = 1, 2, \ldots, R$$
$$G_{jr}^{(k)} = \mathcal{E}\big(g_{jr}^{(k)}, \mathcal{G}_{jr}^{(k)}\big) \quad , \ r = 1, 2, \ldots, R$$

(B) Sum of the effects of all clusters of targets on cluster C_j

$$g_j^{(k)} = \sum_{r=1}^{R} g_{jr}^{(k)}$$
$$\mathcal{G}_j^{(k)} = \left(\sum_{r=1}^{R} \sqrt{\operatorname{Tr} \mathcal{G}_{jr}^{(k)}}\right) \cdot \left(\sum_{r=1}^{R} \frac{\mathcal{G}_{jr}^{(k)}}{\sqrt{\operatorname{Tr} \mathcal{G}_{jr}^{(k)}}}\right)$$
$$G_j^{(k)} = \mathcal{E}\big(g_j^{(k)}, \mathcal{G}_j^{(k)}\big)$$

(2) **Effects of the environmental clusters on the clusters of targets**

(A) Effect of environmental cluster D_s on target cluster C_j

$$h_{js}^{(k)} = \Gamma_{js}^{TE} \rho_s^{(k)} + \Phi_j^{TE} \ , \ s = 1, 2, \ldots, S$$
$$\mathcal{H}_{js}^{(k)} = \Gamma_{js}^{TE} \Pi_s^{(k)} (\Gamma_{js}^{TE})^T, \ s = 1, 2, \ldots, S$$
$$H_{js}^{(k)} = \mathcal{E}\big(h_{js}^{(k)}, \mathcal{H}_{js}^{(k)}\big) \quad , \ s = 1, 2, \ldots, S$$

(B) Sum of the effects of all environmental clusters on cluster C_j

$$h_j^{(k)} = \sum_{s=1}^{S} h_{js}^{(k)}$$
$$\mathcal{H}_j^{(k)} = \left(\sum_{s=1}^{S} \sqrt{\operatorname{Tr} \mathcal{H}_{js}^{(k)}}\right) \cdot \left(\sum_{s=1}^{S} \frac{\mathcal{H}_{js}^{(k)}}{\sqrt{\operatorname{Tr} \mathcal{H}_{js}^{(k)}}}\right)$$
$$H_j^{(k)} = \mathcal{E}\big(h_j^{(k)}, \mathcal{H}_j^{(k)}\big)$$

(3) **Sum of effects on the target clusters**

$$\mu_j^{(k+1)} = g_j^{(k)} + h_j^{(k)}$$
$$\Sigma_j^{(k+1)} = \left(\sqrt{\operatorname{Tr} \mathcal{G}_j^{(k)}} + \sqrt{\operatorname{Tr} \mathcal{H}_j^{(k)}}\right) \cdot \left(\frac{\mathcal{G}_j^{(k)}}{\sqrt{\operatorname{Tr} \mathcal{G}_j^{(k)}}} + \frac{\mathcal{H}_j^{(k)}}{\sqrt{\operatorname{Tr} \mathcal{H}_j^{(k)}}}\right)$$
$$X_j^{(k+1)} = \mathcal{E}\big(\mu_j^{(k+1)}, \Sigma_j^{(k+1)}\big)$$

TE-Model: Centers and Configuration Matrices (continued)

For $i = 1, 2, \ldots, S$:

(1) **Interactions between the clusters of environmental items**

(A) Effect of cluster D_s on cluster D_i

$$\begin{aligned} m_{is}^{(k)} &= \Gamma_{is}^{EE}\rho_s^{(k)} + \Phi_i^{EE} \ , \ s = 1, 2, \ldots, S \\ \mathcal{M}_{is}^{(k)} &= \Gamma_{is}^{EE}\Pi_s^{(k)}(\Gamma_{is}^{EE})^T, \ s = 1, 2, \ldots, S \\ M_{is}^{(k)} &= \mathcal{E}\big(m_{is}^{(k)}, \mathcal{M}_{is}^{(k)}\big) \ \ , \ s = 1, 2, \ldots, S \end{aligned}$$

(B) Sum of the effects of all environmental clusters on cluster D_i

$$\begin{aligned} m_i^{(k)} &= \sum_{s=1}^{S} m_{is}^{(k)} \\ \mathcal{M}_i^{(k)} &= \left(\sum_{s=1}^{S} \sqrt{\mathrm{Tr}\,\mathcal{M}_{is}^{(k)}}\right) \cdot \left(\sum_{s=1}^{S} \frac{\mathcal{M}_{is}^{(k)}}{\sqrt{\mathrm{Tr}\,\mathcal{M}_{is}^{(k)}}}\right) \\ M_i^{(k)} &= \mathcal{E}\big(m_i^{(k)}, \mathcal{M}_i^{(k)}\big) \end{aligned}$$

(2) **Effects of the target clusters on the clusters of environmental items**

(A) Effect of target cluster C_r on environmental cluster D_i

$$\begin{aligned} n_{ir}^{(k)} &= \Gamma_{ir}^{ET}\mu_r^{(k)} + \Phi_i^{ET} \ , \ r = 1, 2, \ldots, R \\ \mathcal{N}_{ir}^{(k)} &= \Gamma_{ir}^{ET}\Sigma_r^{(k)}(\Gamma_{ir}^{ET})^T \ , \ r = 1, 2, \ldots, R \\ N_{ir}^{(k)} &= \mathcal{E}\big(n_{ir}^{(k)}, \mathcal{N}_{ir}^{(k)}\big) \ \ , \ r = 1, 2, \ldots, R \end{aligned}$$

(B) Sum of the effects of all target clusters on environmental cluster D_i

$$\begin{aligned} n_i^{(k)} &= \sum_{r=1}^{R} n_{ir}^{(k)} \\ \mathcal{N}_i^{(k)} &= \left(\sum_{r=1}^{R} \sqrt{\mathrm{Tr}\,\mathcal{N}_{ir}^{(k)}}\right) \cdot \left(\sum_{r=1}^{R} \frac{\mathcal{N}_{ir}^{(k)}}{\sqrt{\mathrm{Tr}\,\mathcal{N}_{ir}^{(k)}}}\right) \\ N_i^{(k)} &= \mathcal{E}\big(n_i^{(k)}, \mathcal{N}_i^{(k)}\big) \end{aligned}$$

(3) **Sum of effects on clusters of environmental items**

$$\begin{aligned} \rho_i^{(k+1)} &= m_i^{(k)} + n_i^{(k)} \\ \Pi_i^{(k+1)} &= \left(\sqrt{\mathrm{Tr}\,\mathcal{M}_i^{(k)}} + \sqrt{\mathrm{Tr}\,\mathcal{N}_i^{(k)}}\right) \cdot \left(\frac{\mathcal{M}_i^{(k)}}{\sqrt{\mathrm{Tr}\,\mathcal{M}_i^{(k)}}} + \frac{\mathcal{N}_i^{(k)}}{\sqrt{\mathrm{Tr}\,\mathcal{N}_i^{(k)}}}\right) \\ \boldsymbol{E_i^{(k+1)}} &= \boldsymbol{\mathcal{E}\big(\rho_i^{(k+1)}, \Pi_i^{(k+1)}\big)} \end{aligned}$$

4. The Regression Problem. We now turn to an estimation of parameters of the time-discrete TE-model with ellipsoidal states. As mentioned before, the states of predictions of targets and environmental items depend on the unknown entries of the interaction matrices A^{TT}, A^{TE}, A^{EE}, A^{ET} and vectors V_j^{TT}, V_j^{TE}, V_i^{EE} and V_i^{ET}. For an estimation of parameters we compare the predictions

$$\widehat{X}_r^{(\kappa)} = \mathcal{E}\big(\widehat{\mu}_r^{(\kappa)},\, \widehat{\Sigma}_r^{(\kappa)}\big), \quad \widehat{E}_s^{(\kappa)} = \mathcal{E}\big(\widehat{\rho}_s^{(\kappa)},\, \widehat{\Pi}_s^{(\kappa)}\big)$$

calculated with the algorithm from Subsection 3.2 with the data

$$\overline{X}_r^{(\kappa)} = \mathcal{E}\big(\overline{\mu}_r^{(\kappa)},\, \overline{\Sigma}_r^{(\kappa)}\big), \quad \overline{E}_s^{(\kappa)} = \mathcal{E}\big(\overline{\rho}_s^{(\kappa)},\, \overline{\Pi}_s^{(\kappa)}\big),$$

obtained from measurements of target and environmental items at sampling times $t_0 < t_1 < \ldots < t_T$. The initial values of the algorithm may be given by $\widehat{X}_r^{(0)} := \overline{X}_r^{(0)}$ and $\widehat{E}_s^{(0)} := \overline{E}_s^{(0)}$ (here, $r = 1, \ldots, R$, $s = 1, \ldots, S$, $\kappa = 0, 1, \ldots, T$).

As the predictions and measurement values (both ellipsoids) should overlap as much as possible, we introduce the ellipsoids

$$\Delta X_r^{(\kappa)} := \widehat{X}_r^{(\kappa)} \cap \overline{X}_r^{(\kappa)} \quad \text{and} \quad \Delta E_s^{(\kappa)} := \widehat{E}_s^{(\kappa)} \cap \overline{E}_s^{(\kappa)}$$

and state the **regression problem**

$$(R) \quad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \Big\{ \sum_{r=1}^{R} \Big\| \Delta X_r^{(\kappa)} \Big\|_* + \sum_{s=1}^{S} \Big\| \Delta E_s^{(\kappa)} \Big\|_* \Big\}.$$

Here, $\|\cdot\|_*$ denotes a measure that reflects the geometrical size of the intersections (fusions) and we assume that $\|\Delta X_r^{(\kappa)}\|_* = 0$, if $\Delta X_r^{(\kappa)} = \emptyset$ and $\|\Delta E_s^{(\kappa)}\|_* = 0$, if $\Delta E_s^{(\kappa)} = \emptyset$. There exist various measures that are related to the shape of the intersections, e.g., the *volume* (which corresponds to the ellipsoid matrix determinant), the *sum of squares of semiaxes* (which corresponds to the trace of the configuration matrix), the *length of the largest semiaxes* (which corresponds to the eigenvalues of the configuration matrix). All these examples lead to specific formulations of the regression problem (R) and they depend on the configuration matrices of the fusions $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$.

The fusion $\Delta X_r^{(\kappa)} = \widehat{X}_r^{(\kappa)} \cap \overline{X}_{C_r}^{(\kappa)}$ is an ellipsoid $\mathcal{E}\big(\Delta\mu_r^{(\kappa)},\, \Delta\Sigma_r^{(\kappa)}\big)$ with center

$$\Delta\mu_r^{(\kappa)} = \big[\mathcal{X}_r^{(\kappa)}\big]^{-1}\big(\lambda\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}\widehat{\mu}_r^{(\kappa)} + (1-\lambda)\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}\overline{\mu}_r^{(\kappa)}\big)$$

and configuration matrix

$$\Delta\Sigma_r^{(\kappa)} = \xi_r^{(\kappa)}\,\big[\mathcal{X}_r^{(\kappa)}\big]^{-1},$$

where

$$\mathcal{X}_r^{(\kappa)} := \lambda\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1} + (1-\lambda)\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}$$

and

$$\xi_r^{(\kappa)} := 1 - \lambda(1-\lambda)\big(\overline{\mu}_r^{(\kappa)} - \widehat{\mu}_r^{(\kappa)}\big)^T\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}\big[\mathcal{X}_r^{(\kappa)}\big]^{-1}\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}\big(\overline{\mu}_r^{(\kappa)} - \widehat{\mu}_r^{(\kappa)}\big).$$

The parameter λ is the only root in $(0,1)$ of the following polynomial of degree $2|C_r|-1$:

$$\begin{aligned}&\xi_r^{(\kappa)}\big(\det\mathcal{X}_r^{(\kappa)}\big)^2\operatorname{Tr}\Big(\big[\mathcal{X}_r^{(\kappa)}\big]^{-1}\Big(\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}-\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}\Big)\Big)-|C_r|\big(\det\mathcal{X}_r^{(\kappa)}\big)^2\\&\times\Big(2\big[\Delta\mu_r^{(\kappa)}\big]^T\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}\widehat{\mu}_r^{(\kappa)}-2\big[\Delta\mu_r^{(\kappa)}\big]^T\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}\overline{\mu}_r^{(\kappa)}\\&+\big[\Delta\mu_r^{(\kappa)}\big]^T\Big(\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}-\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}\Big)\Delta\mu_r^{(\kappa)}-\big[\widehat{\mu}_r^{(\kappa)}\big]^T\big[\widehat{\Sigma}_r^{(\kappa)}\big]^{-1}\widehat{\mu}_r^{(\kappa)}\\&+\big[\overline{\mu}_r^{(\kappa)}\big]^T\big[\overline{\Sigma}_r^{(\kappa)}\big]^{-1}\overline{\mu}_r^{(\kappa)}\Big)=0.\end{aligned}$$

Similarly, the fusion $\Delta E_s^{(\kappa)}=\widehat{E}_s^{(\kappa)}\cap\overline{E}_s^{(\kappa)}$ is an ellipsoid $\mathcal{E}\big(\Delta\rho_s^{(\kappa)},\,\Delta\Pi_s^{(\kappa)}\big)$ with center

$$\Delta\rho_s^{(\kappa)}=\big[\mathcal{Y}_s^{(\kappa)}\big]^{-1}\big(\lambda\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}\widehat{\rho}_s^{(\kappa)}+(1-\lambda)\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}\overline{\rho}_s^{(\kappa)}\big)$$

and configuration matrix

$$\Delta\Pi_s^{(\kappa)}=\eta_s^{(\kappa)}\,\big[\mathcal{Y}_s^{(\kappa)}\big]^{-1},$$

where

$$\mathcal{Y}_s^{(\kappa)}:=\lambda\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}+(1-\lambda)\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}$$

and

$$\eta_s^{(\kappa)}:=1-\lambda(1-\lambda)\big(\overline{\rho}_s^{(\kappa)}-\widehat{\rho}_s^{(\kappa)}\big)^T\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}\big[\mathcal{Y}_s^{(\kappa)}\big]^{-1}\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}\big(\overline{\rho}_s^{(\kappa)}-\widehat{\rho}_s^{(\kappa)}\big).$$

The parameter λ is the only root in $(0,1)$ of the following polynomial of degree $2|D_s|-1$:

$$\begin{aligned}&\eta_s^{(\kappa)}\big(\det\mathcal{Y}_s^{(\kappa)}\big)^2\operatorname{Tr}\Big(\big[\mathcal{Y}_s^{(\kappa)}\big]^{-1}\Big(\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}-\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}\Big)\Big)-|D_s|\big(\det\mathcal{Y}_s^{(\kappa)}\big)^2\\&\times\Big(2\big[\Delta\rho_s^{(\kappa)}\big]^T\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}\widehat{\rho}_s^{(\kappa)}-2\big[\Delta\rho_s^{(\kappa)}\big]^T\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}\overline{\rho}_s^{(\kappa)}\\&+\big[\Delta\rho_s^{(\kappa)}\big]^T\Big(\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}-\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}\Big)\Delta\rho_s^{(\kappa)}-\big[\widehat{\rho}_s^{(\kappa)}\big]^T\big[\widehat{\Pi}_s^{(\kappa)}\big]^{-1}\widehat{\rho}_s^{(\kappa)}\\&+\big[\overline{\rho}_s^{(\kappa)}\big]^T\big[\overline{\Pi}_s^{(\kappa)}\big]^{-1}\overline{\rho}_s^{(\kappa)}\Big)=0.\end{aligned}$$

As a measure for the size of a p-dimensional ellipsoid $\mathcal{E}(0,Q)$ (here, the size of the fusion) we use nonnegative-valued criteria functions $\psi(\mathcal{E}(0,Q))$ defined on the set of all nondegenerate ellipsoids and which are monotonous by increasing with respect to inclusion, i.e., $\psi(\mathcal{E}_1)\le\psi(\mathcal{E}_2)$ if $\mathcal{E}_1\subseteq\mathcal{E}_2$. Such measures are, e.g.,

(a) *the trace of* Q,

$$\psi_T(\mathcal{E}(0,Q)):=\operatorname{Tr}Q=\lambda_1+\ldots+\lambda_p,$$

where λ_i are the eigenvalues of Q (i.e., $\operatorname{Tr}Q$ is equal to the sum of the squares of the semiaxes),

(b) *the trace of square of* Q,

$$\psi_{TS}(\mathcal{E}(0,Q)):=\operatorname{Tr}Q^2,$$

(c) *the determinant of* Q,

$$\psi_{Det}(\mathcal{E}(0,Q)) := \det Q = \lambda_1 \cdot \ldots \cdot \lambda_p,$$

which is equal to the product of eigenvalues and proportional to the volume

$$\operatorname{vol}\mathcal{E}(0,Q) = \pi^{\frac{p}{2}} (\det Q)^{\frac{1}{2}} \left(\Gamma\left(\tfrac{p}{2}+1\right)\right)^{-1}$$

of the ellipsoid, where Γ stands for the Gamma-function,

(d) *the diameter*,

$$\psi_{Dia}(\mathcal{E}(0,Q)) := \operatorname{diam}(\mathcal{E}(0,Q)) := d,$$

where

$$\max\{\lambda_i \in \mathbb{R} \,|\, i = 1,\ldots,p\} = \left(\frac{d}{2}\right)^2,$$

so that $d/2$ is the radius of the smallest p-dimensional ball that includes $\mathcal{E}(0,Q)$.
For further details on criteria functions we refer to [39], p. 101. The measures stated above lead to different representations of the regression problem (R) and we study them now in more detail.

4.1. The Trace Criterion. The first regression problem is based on the traces of the configuration matrices of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$:

$$(R_{Tr}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \operatorname{Tr}\left(\Delta\Sigma_r^{(\kappa)}\right) + \sum_{s=1}^{S} \operatorname{Tr}\left(\Delta\Pi_s^{(\kappa)}\right) \right\}.$$

As the trace of the configuration matrix is equal to the sum of the squares of the semiaxes, the regression problem takes the form

$$(R'_{Tr}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \sum_{j=1}^{|C_r|} \lambda_{r,j}^{(\kappa)} + \sum_{s=1}^{S} \sum_{i=1}^{|D_s|} \Lambda_{s,i}^{(\kappa)} \right\},$$

where $\lambda_{r,j}^{(\kappa)}$ and $\Lambda_{s,i}^{(\kappa)}$ are the eigenvalues of $\Delta\Sigma_r^{(\kappa)}$ and $\Delta\Pi_s^{(\kappa)}$, respectively.

4.2. The Trace of the Square Criterion. Another variant of our regression problem can be obtained with the traces of the squares of the configuration matrices of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$:

$$(R_{TS}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \operatorname{Tr}\left(\Delta\Sigma_r^{(\kappa)}\right)^2 + \sum_{s=1}^{S} \operatorname{Tr}\left(\Delta\Pi_s^{(\kappa)}\right)^2 \right\}.$$

4.3. The Determinant Criterion. Referring to the determinants of the configuration matrices of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$, we obtain the following model:

$$(R_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \det\left(\Delta\Sigma_r^{(\kappa)}\right) + \sum_{s=1}^{S} \det\left(\Delta\Pi_s^{(\kappa)}\right) \right\}.$$

Equivalent formulations of (R_{Det}) can be given in terms of the eigenvalues of the configuration matrices

$$(R'_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \prod_{j=1}^{|C_r|} \lambda_{r,j}^{(\kappa)} + \sum_{s=1}^{S} \prod_{i=1}^{|D_s|} \Lambda_{s,i}^{(\kappa)} \right\}$$

and the volumes of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$

$$(R''_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \left[\pi^{\frac{2}{|C_r|}} \, \Gamma\left(\frac{|C_r|}{2} + 1 \right) \text{vol}\left(\Delta X_r^{(\kappa)} \right) \right]^2 + \sum_{s=1}^{S} \left[\pi^{\frac{2}{|D_s|}} \, \Gamma\left(\frac{|D_s|}{2} + 1 \right) \text{vol}\left(\Delta E_s^{(\kappa)} \right) \right]^2 \right\}.$$

4.4. The Diameter Criterion. The diameter of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$ can be used to introduce the following regression model:

$$(R_{Dia}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \text{diam}\big(\mathcal{E}\big(0, \Sigma_r^{(\kappa)}\big)\big) + \sum_{s=1}^{S} \text{diam}\big(\mathcal{E}\big(0, \Pi_s^{(\kappa)}\big)\big) \right\}.$$

An equivalent formulation of (R_{Dia}) can be given in terms of the eigenvalues of $\Sigma_r^{(\kappa)}$ and $\Pi_s^{(\kappa)}$:

$$(R'_{Dia}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} 2 \cdot \sqrt{\lambda_r^{(\kappa)}} + \sum_{s=1}^{S} 2 \cdot \sqrt{\Lambda_s^{(\kappa)}} \right\}$$

with $\lambda_r^{(\kappa)} := \max\{\lambda_{r,j}^{(\kappa)} \,|\, j = 1, \ldots, |C_r|\}$ and $\Lambda_s^{(\kappa)} := \max\{\Lambda_{s,i}^{(\kappa)} \,|\, i = 1, \ldots, |D_s|\}$. As the objective function of (R'_{Dia}) is nonsmooth with well-understood max-type functions [73, 74, 75] but not Lipschitz-continuous, we also introduce the additional regression problem

$$(R''_{Dia}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \lambda_r^{(\kappa)} + \sum_{s=1}^{S} \Lambda_s^{(\kappa)} \right\}$$

as an alternative proposal.

4.5. Optimization Methods. The regression models of the previous subsections depend on the configuration matrices $\Sigma_r^{(\kappa)}$ and $\Pi_s^{(\kappa)}$ of the ellipsoids $\Delta X_r^{(\kappa)}$ and $\Delta E_s^{(\kappa)}$. Semidefinite programming [16] can be applied, because the objective functions of these volume-related programming problems depend on, e.g., the determinant or eigenvalues of symmetric positive semidefinite matrices. However, in order to obtain positive semidefinite representable objective functions [13], some regression models have to be slightly modified. For example, the objective function of the regression model (R_{Det}) depends directly on the determinant of the configuration matrices. Unfortunately, $\det(M)$ considered as a function of symmetric positive semidefinite $n \times n$-matrices M (short: $M \succcurlyeq 0$) is neither a convex nor a concave function of M (if $n \geq 2$). However, if p is a rational number with $0 \leq p \leq \frac{1}{n}$, then

$$f(M) = \begin{cases} -\det^p(M) & , M \succcurlyeq 0 \\ \infty & , \text{otherwise} \end{cases}$$

is positive semidefinite representable ([13], p. 81). Therefore, we introduce the regression model

$$(\widetilde{R}_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T}\left\{-\sum_{r=1}^{R}\det{}^{p}\left(\Delta\Sigma_r^{(\kappa)}\right)-\sum_{s=1}^{S}\det{}^{q}\left(\Delta\Pi_s^{(\kappa)}\right)\right\},$$

where the rational numbers p, q fulfill the conditions $0 \leq p \leq \frac{1}{|C_r|}$ and $0 \leq q \leq \frac{1}{|D_s|}$. As $\det(M) = \prod_{i=1}^{n}\lambda_i(M)$, where $\lambda_i(M)$ are the eigenvalues of M, we can replace (R'_{Det}) by

$$(\widetilde{R}'_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T}\left\{-\sum_{r=1}^{R}\left(\prod_{j=1}^{|C_r|}\lambda_{r,j}^{(\kappa)}\right)^{p}-\sum_{s=1}^{S}\left(\prod_{i=1}^{|D_s|}\Lambda_{s,i}^{(\kappa)}\right)^{q}\right\}$$

and instead of (R''_{Det}) we suggest

$$(\widetilde{R}''_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T}\left\{\sum_{r=1}^{R}\left[\pi^{\frac{2}{|C_r|}}\,\Gamma\left(\frac{|C_r|}{2}+1\right)\text{vol}\left(\Delta X_r^{(\kappa)}\right)\right]^{2p} + \sum_{s=1}^{S}\left[\pi^{\frac{2}{|D_s|}}\,\Gamma\left(\frac{|D_s|}{2}+1\right)\text{vol}\left(\Delta E_s^{(\kappa)}\right)\right]^{2q}\right\}.$$

In case of positive definite configuration matrices $\Delta\Sigma_r^{(\kappa)}$ and $\Delta\Pi_s^{(\kappa)}$ negative powers of the determinant can be used. If p is a positive rational, the function

$$f(M) = \begin{cases}\det{}^{-p}(M) & , M \succ 0\\ \infty & , \text{otherwise}\end{cases}$$

of the symmetric $n \times n$-matrix M is positive semidefinite representable ([13], p. 83). Here, $M \succ 0$ means that M is positive semidefinite. Now, with two positive rationals p, q we obtain the additional regression model

$$(R'''_{Det}) \qquad \text{Maximize} \qquad \sum_{\kappa=1}^{T}\left\{\sum_{r=1}^{R}\det{}^{-p}\left(\Delta\Sigma_r^{(\kappa)}\right)+\sum_{s=1}^{S}\det{}^{-q}\left(\Delta\Pi_s^{(\kappa)}\right)\right\}.$$

The regression model (R''_{Dia}) directly depends on the largest eigenvalues of the configuration matrices $\Delta\Sigma_r^{(\kappa)}$ and $\Delta\Pi_s^{(\kappa)}$ and, thus, on positive semidefinite representable functions ([13], p. 78). In (R'_{Tr}), sums of all eigenvalues of the configuration matrices $\Delta\Sigma_r^{(\kappa)}$ and $\Delta\Pi_s^{(\kappa)}$ are considered, which can also be regarded as positive semidefinite representable functions ([13], p. 80). In general, *interior point methods* can applied which have a moderate complexity [44, 45, 46, 48]. Alternatively, for regression problems with sums of eigenvalues or maximal eigenvalues in the objective function, asscociated *bilevel problems* can be considered which could be solved by *gradient methods*. In fact, in [47] structural frontiers of conic programming are discussed with other optimization methods compared, and future applications in machine learning and data mining prepared.

5. Mixed Integer Regression Problem. As nowadays high-throughput technologies are available, regulatory networks are huge and for practical reasons we have to rarefy them by diminishing the number of branches. Here, upper bounds on the indegrees of nodes are introduced firstly. That means, the number of clusters regulating a specific target or environmental cluster in our network has to be bounded. We use *binary constraints* to decide whether or not there is a connection between two clusters of data and by this we obtain a *mixed-integer optimization problem*. As these constraints are very strict and as they can even destroy our regulatory network, we pass to continuous constraints and introduce a further relaxation in terms of a *continuous optimization problem*.

Given two clusters A, B we use the notation $A \sim B$ if cluster A is regulated by cluster B and $A \not\sim B$ if cluster A is not regulated by cluster B. Now, we define the Boolean matrices

$$\chi_{jr}^{TT} = \begin{cases} 1 & \text{, if } C_j \sim C_r \\ 0 & \text{, if } C_j \not\sim C_r, \end{cases} \qquad \chi_{js}^{TE} = \begin{cases} 1 & \text{, if } C_j \sim D_s \\ 0 & \text{, if } C_j \not\sim D_s, \end{cases}$$

$$\chi_{is}^{EE} = \begin{cases} 1 & \text{, if } D_i \sim D_s \\ 0 & \text{, if } D_i \not\sim D_s, \end{cases} \qquad \chi_{ir}^{ET} = \begin{cases} 1 & \text{, if } D_i \sim C_r \\ 0 & \text{, if } D_i \not\sim C_r, \end{cases}$$

indicating whether or not pairs of clusters in our regulatory network are directly related. If two clusters are not related, the corresponding parts of the matrices A^{TT}, A^{TE}, A^{EE}, A^{ET} and vectors V^{TT}, V^{TE}, V^{EE}, V^{ET} have zero entries.

For $j \in \{1, \ldots, R\}$ we define the *indegree* of cluster C_j in our regulatory network with respect to the target clusters and environmental clusters by

$$\deg(C_j)^{TT} := \sum_{r=1}^{R} \chi_{jr}^{TT} \quad \text{and} \quad \deg(C_j)^{TE} := \sum_{s=1}^{S} \chi_{js}^{TE},$$

respectively. That means, the indegrees $\deg(C_j)^{TT}$ and $\deg(C_j)^{TE}$ count the number of target and environmental clusters which regulate cluster C_j. Similarly, for $i \in \{1, \ldots, S\}$ the *indegree* of cluster D_i with respect to the environmental clusters and the target clusters is given by

$$\deg(D_i)^{EE} := \sum_{s=1}^{S} \chi_{is}^{EE} \quad \text{and} \quad \deg(D_i)^{ET} := \sum_{r=1}^{R} \chi_{ir}^{ET}.$$

Now, the indegrees $\deg(D_i)^{EE}$ and $\deg(D_i)^{ET}$ count the number of environmental and target clusters which regulate cluster D_i.

For network rarefication we introduce upper bounds on the indegrees. The values of these bounds depend on any a priori information available and they have to be given by the practitioner. Including these additional constraints, we obtain the following *mixed integer optimization problem*:

$$(RMI) \quad \begin{cases} \text{Maximize} & \displaystyle\sum_{\kappa=1}^{T} \left\{ \sum_{r=1}^{R} \left\| \Delta X_r^{(\kappa)} \right\|_* + \sum_{s=1}^{S} \left\| \Delta E_s^{(\kappa)} \right\|_* \right\} \\ \text{subject to} & \deg(C_j)^{TT} \leq \alpha_j^{TT},\ j = 1, \ldots, R \\ & \deg(C_j)^{TE} \leq \alpha_j^{TE},\ j = 1, \ldots, R \\ & \deg(D_i)^{EE} \leq \alpha_i^{EE},\ i = 1, \ldots, S \\ & \deg(D_i)^{ET} \leq \alpha_i^{ET},\ i = 1, \ldots, S. \end{cases}$$

We note that our network rarefication can also be achieved by bounding the outdegrees of the nodes. Such an approach was utilized in [76, 77, 78] in order to obtain a more flexible representation of gene-environment networks with respect to uncertain states in terms of intervals and parallelpipes.

The binary constraints of (RMI) are very strict and if the constraints are not appropriate, important branches of the regulatory network could be deleted. For this reason, we use continuous optimization for a relaxation of (RMI) by replacing the binary variables χ_{jr}^{TT}, χ_{js}^{TE}, χ_{is}^{EE} and χ_{ir}^{ET} with real variables $P_{jr}^{TT}, P_{js}^{TE}, P_{is}^{EE}, P_{ir}^{ET} \in [0,1]$, which is also interpretable as probabilities (we refer to [59] for optimization models with probabilistic constraints). These variables should linearly depend on the corresponding elements of $\Gamma_{jr}^{TT}, \Gamma_{js}^{TE}, \Gamma_{is}^{EE}, \Gamma_{ir}^{ET}$ and $\Phi_{j}^{TT}, \Phi_{j}^{TE}, \Phi_{i}^{EE}, \Phi_{i}^{ET}$.

The real-valued *indegree* of cluster C_j in our regulatory network with respect to the target clusters and environmental clusters are now defined by

$$\deg(C_j)^{TT} := \sum_{r=1}^{R} P_{jr}^{TT}\big(\Gamma_{jr}^{TT}, \Phi_{j}^{TT}\big) \quad \text{and} \quad \deg(C_j)^{TE} := \sum_{s=1}^{S} P_{js}^{TE}\big(\Gamma_{js}^{TE}, \Phi_{j}^{TE}\big),$$

respectively. Similarly, the real-valued *indegree* of cluster D_i with respect to the environmental clusters and the target clusters is given by

$$\deg(D_i)^{EE} := \sum_{s=1}^{S} P_{is}^{EE}\big(\Gamma_{is}^{EE}, \Phi_{i}^{EE}\big) \quad \text{and} \quad \deg(D_i)^{ET} := \sum_{r=1}^{R} P_{ir}^{ET}\big(\Gamma_{ir}^{ET}, \Phi_{i}^{ET}\big).$$

Now, we replace the binary constraints of (RMI) with continuous constraints and obtain the following optimization problem:

$$(RC) \quad \begin{cases} \text{Maximize} & \displaystyle\sum_{\kappa=1}^{T}\Big\{\sum_{r=1}^{R}\Big\|\Delta X_r^{(\kappa)}\Big\|_* + \sum_{s=1}^{S}\Big\|\Delta E_s^{(\kappa)}\Big\|_*\Big\} \\ \text{subject to} & \displaystyle\sum_{r=1}^{R} P_{jr}^{TT}\big(\Gamma_{jr}^{TT}, \Phi_{j}^{TT}\big) \le \alpha_j^{TT},\ j = 1,\dots,R \\ & \displaystyle\sum_{s=1}^{S} P_{js}^{TE}\big(\Gamma_{js}^{TE}, \Phi_{j}^{TE}\big) \le \alpha_j^{TE},\ j = 1,\dots,R \\ & \displaystyle\sum_{s=1}^{S} P_{is}^{EE}\big(\Gamma_{is}^{EE}, \Phi_{i}^{EE}\big) \le \alpha_i^{EE},\ i = 1,\dots,S \\ & \displaystyle\sum_{r=1}^{R} P_{ir}^{ET}\big(\Gamma_{ir}^{ET}, \Phi_{i}^{ET}\big) \le \alpha_i^{ET},\ i = 1,\dots,S. \end{cases}$$

REMARK We point out that the methods introduced are particularly applicable in the financial sector, e.g., in the modeling of stochastic differential equations and, as a very new contribution, the optimization of the statistical ROC curve for an improved classification and prediction of credit default [80]. Here, we point out a new view onto credits given by the study of our paper. All the interaction among the items that we investigate can be regarded as a "credit" taken or given, as a measurement which asks for an appropriate response, such as an equivalent effect (maybe, plus a gain) in future. There are consumptions of various kinds, medical treatments, expenditures in education, science and the improvements in environmental protection. The realization of their purposes has to be priced, discounted and

compared, the degrees of these achievements can be enforced by penalty terms in our models of optimization and dynamics. This new view is subject of our future studies.

6. Conclusion. In this paper, we analyzed a time-discrete model of target-environment networks under ellipsoidal uncertainty. We introduced the power of modern optimization by means of semidefinite programming and the efficiency of interior point methods for the modeling of our regression problem and nonsmooth optimization that we use a priori for clustering our items. This pioneering approach offers a new view on parameter estimation and optimization of TE-regulatory systems depending on various kinds of errors, where the dynamics of clusters of targets and environmental items and their mutual effects are determined by corresponding clusters of parameters. Our research includes clustering theory which we support by statistical investigations about the number of clusters and their stability and by means of statistical learning we find the clusters with the help of nonsmooth optimization. The representation of the dynamic states in terms of ellipsoids was motivated by our and our colleagues' studies on gene-environment networks and eco-finance networks, where errors and uncertainty are modeled by intervals [86, 88, 89]. Here, we extended the interval model by a representation of errors in terms of ellipsoids what refers to stochastic dependencies between the various target and environmental items. These uncertainty sets are directly related to covariance matrices and they provide good approximations of convex sets. In particular, models based on Gaussian random noise refer to the ellipsoidal approach. However, Gaussian random distributions are often used as simplifications and in many applications non-Gaussian probability distributions have to be applied. Therefore, we will further extend our models based on ellipsoidal calculus and, by this, in future works we will turn to a more set-theoretic representation of errors and uncertainty based on semi-algebraic sets. We will combine this new perception with refined optimization methods and by this we will offer a further avenue for the analysis of TE-regulatory systems, particularly with regard to applications and real-world data. Furthermore, we propose that collaborative game theory under uncertainty which was recently modeled with the help of intervals [3, 4, 5, 6] could become refined by our ellipsoidal calculus, herewith allowing a great wealth of dependencies and subcoalitions preassigned.

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REFERENCES

[1] M. U. AKHMET, J. GEBERT, H. ÖKTEM, S. W. PICKL, AND G.-W. WEBER, *An improved algorithm for analytical modeling and anticipation of gene expression patterns*, Journal of Computational Technologies 10, 4 (2005), pp. 3–20.

[2] D. AKUME, G.-W. WEBER, *Cluster algorithms: theory and methods*, Journal of Computational Technologies, 7, 1 (2002), pp. 15–27.

[3] S. Z. ALPARSLAN GÖK, *Cooperative interval games*, PhD Thesis at Institute of Applied Mathematics of METU, Ankara, (2009).

[4] S. Z. ALPARSLAN GÖK, R. BRANZEI, AND S. TIJS, *Convex interval games*, preprint no. 100, Institute of Applied Mathematics, METU and Tilburg University, Center for Economic Research, The Netherlands, CentER DP 37 (2008).

[5] S. Z. ALPARSLAN GÖK, R. BRANZEI, AND S. TIJS, *Airport interval games and their Shapley value*, to appear in Operations Research and Decisions, 1 (2009).

[6] S. Z. ALPARSLAN GÖK, S. MIQUEL, AND S. TIJS, *Cooperation under interval uncertainty*, Math. Methods Oper. Res., 69 (2009), pp. 99–109.

[7] A. ASTER, B. BORCHERS, AND C. THURBER, *Parameter estimation and inverse problems*, Academic Press, 2004.

[8] A. M. BAGIROV AND J. UGON, *Piecewise partially separable functions and a derivative-free algorithm for large scale nonsmooth optimization*, J. Global Optim., 35 (2006), pp. 163–195.

[9] A. M. BAGIROV AND J. YEARWOOD, *A new nonsmooth optimization algorithm for minimum sum-of-squares clustering problems*, European J. Oper. Res., 170, 2 (2006), pp. 578–596.
[10] Z. BARZILY, Z. V. VOLKOVICH, B. AKTEKE-ÖZTÜRK, AND G.-W. WEBER, *Cluster stability using minimal spanning trees*, ISI Proceedings of 20th Mini-EURO Conference *Continuous Optimization and Knowledge-Based Technologies* (Neringa, Lithuania, May 20-23, 2008) (2008), pp. 248–252.
[11] Z. BARZILY, Z. V. VOLKOVICH, B. AKTEKE-ÖZTÜRK, AND G.-W. WEBER, *On a minimal spanning tree approach in the cluster validation problem*, to appear in the special issue of INFORMATICA at the occasion of 20th Mini-EURO Conference *Continuous Optimization and Knowledge Based Technologies* (Neringa, Lithuania, May 20-23, 2008), G. Dzemyda, K. Miettinen, and L. Sakalauskas, guest eds., (2008).
[12] R. BENEDETTI, *Real algebraic and semi-algebraic sets*, Hermann, Ed. des Sciences et des Arts, Paris (1990).
[13] A. BEN-TAL, *Conic and robust optimization*, Lecture notes (2002)
Available at http://iew3.technion.ac.il/Home/Users/morbt.phtml.
[14] J. BOCHNAK, M. COSTE, AND M.-F. ROY, *Real algebraic geometry*, Springer (1998).
[15] E. BORENSTEIN, AND M. W. FELDMAN, *Topological signatures of species interactions in metabolic networks*, J. Comput. Biol., 16, 2, (2009), pp. 191–200, DOI: 10.1089/cmb.2008.06TT.
[16] S. BOYD, AND L. VANDENBERGHE, *Convex Optimization*, Cambridge University Press (2004).
[17] T. CHEN, H. L. HE, AND G. M. CHURCH, *Modeling gene expression with differential equations*, Proc. Pacific Symposium on Biocomputing (1999), pp. 29–40.
[18] P. DURIEU, É. WALTER, AND B. POLYAK, *Multi-input multi-output ellipsoidal state bounding*, J. Optim. Theory Appl., 111, 2 (2001), pp. 273–303.
[19] I. ELISHAKOFF, *Whys and Hows in Uncertainty Modelling: Probability, Fuzziness and Anti-Optimization*, Springer (1999).
[20] T. ERGENÇ AND G.-W. WEBER, *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 (2004), pp. 40–48.
[21] J. GEBERT, M. LÄTSCH, S. W. PICKL, N. RADDE, G.-W. WEBER, AND R. WÜNSCHIERS, *Genetic networks and anticipation of gene expression patterns*, Computing Anticipatory Systems: CASYS(92)03 – Sixth International Conference, AIP Conference Proceedings, 718 (2004), pp. 474–485.
[22] J. GEBERT, M. LÄTSCH, S. W. PICKL, G.-W. WEBER, AND R. WÜNSCHIERS, *An algorithm to analyze stability of gene-expression pattern*, in M. Anthony, E. Boros, P. L. Hammer, and A. Kogan, guest eds., special issue *Discrete Mathematics and Data Mining II* of Discrete Appl. Math., 154, 7 (2006), pp. 1140–1156.
[23] J. GEBERT, M. LÄTSCH, E. M. P. QUEK, AND G.-W. WEBER, *Analyzing and optimizing genetic network structure via path-finding*, Journal of Computational Technologies, 9, 3 (2004), pp. 3–12.
[24] J. GEBERT, H. ÖKTEM, S. W. PICKL, N. RADDE, G.-W. WEBER, AND F. B. YILMAZ, *Inference of gene expression patterns by using a hybrid system formulation – an algorithmic approach to local state transition matrices*, in G. E. Lasker and D. M. Dubois, eds., Anticipative and predictive models in systems science I, IIAS (International Institute for Advanced Studies) in Windsor, Ontario, 2004, pp. 63–66.
[25] J. GEBERT, N. RADDE, AND G.-W. WEBER, *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 J. Oper. Res. (2006).
[26] A. GÖKMEN, S. KAYALGIL, G.-W. WEBER, I. GÖKMEN, M. ECEVIT, A. SÜRMELI, T. BALI, Y. ECEVIT, H. GÖKMEN, AND D. J. DETOMBE, *Balaban Valley Project: Improving the Quality of Life in Rural Area in Turkey*, International Scientific Journal of Methods and Models of Complexity, 7, 1 (2004).
[27] R. M. HARDT, P. LAMBRECHTS, V. TURCHIN, AND I. VOLIĆ, *Real homotopy theory of semi-algebraic sets*, eprint arXiv:0806.0476 (2008).
[28] J. R. HARRIS, W. NYSTAD, AND P. MAGNUS, *Using genes and environments to define asthma and related phenotypes: applications to multivariate data*, Clinical and Experimental Allergy, 28, 1 (1998), pp. 43–45.
[29] T. HASTIE AND R. TIBSHIRANI, *Discriminant adaptive nearest neighbor classification*, IEEE Transactions on Pattern Analysis and Machine Intelligence, 18, 6 (1996), pp. 607–616.
[30] T. HASTIE, R. TIBSHIRANI, AND J. FRIEDMAN, *The elements of statistical learning*, Springer (2001).
[31] M. D. HOON, S. IMOTO, K. KOBAYASHI, N. OGASAWARA, AND S. MIYANO, *Inferring gene regulatory networks from time-ordered gene expression data of Bacillus subtilis using differential equations*, Proc. Pacific Symposium on Biocomputing (2003), pp. 17–28.
[32] A. IŞCANOĞLU, G.-W. WEBER, AND P. TAYLAN, *Predicting default probabilities with generalized additive models for emerging markets*, invited lecture, Graduate Summer School on New Advances in Statistics, METU (2007).
[33] H. D. JONG, *Modeling and simulation of genetic regulatory systems: a literature review*, J. Comput. Biol., 9 (2002), pp. 103–129.
[34] W. KRABS, *Mathematical modelling*, Teubner, Stuttgart (1997).

[35] W. KRABS, *Dynamische Systeme: Steuerbarkeit und chaotisches Verhalten*, Teubner, Stuttgart (1998).
[36] W. KRABS AND S. PICKL, *A game-theoretic treatment of a time-discrete emission reduction model*, Int. Game Theory Rev., 6, 1 (2004), pp. 21–34.
[37] E. KROPAT, S. PICKL, A. RÖSSLER, AND G.-W. WEBER, *On theoretical and practical relations between discrete optimization and nonlinear optimization*, in special issue Colloquy Optimization Structure and Stability of Dynamical Systems (at the occasion of the colloquy with the same name, Cologne, October 2000) of Journal of Computational Technologies, 7, Special Issue, (2002), pp. 27–62.
[38] E. KROPAT, G.-W. WEBER, AND B. AKTEKE-ÖZTÜRK, *Eco-Finance networks under uncertainty*, in J. Herskovits, A. Canelas, H. Cortes, and M. Aroztegui, eds., Proceedings of the International Conference on Engineering Optimization (ISBN 978857650156-5, CD), EngOpt 2008, Rio de Janeiro, Brazil (2008).
[39] A. B. KURZHANSKI, AND I. VÁLYI, *Ellipsoidal calculus for estimation and control*, Birkhäuser, 1997.
[40] A. A. KURZHANSKI, AND P. VARAIYA, *Ellipsoidal toolbox manual*, EECS Department, University of California, Berkeley, 2008.
[41] Y. F. LI, S. VENKATESH, AND D. LI, *Modeling global emissions and residues of pesticided*, Environmental Modeling and Assessment, 9, (2004), pp. 237–243.
[42] Q. LIU, J. YANG, Z. CHEN, M. Q. YANG, A. H. SUNG, AND X. HUANG, *Supervised learning-based tagSNP selection for genome-wide disease classifications*, BMC Genomics, 9, 1 (2007).
[43] R. LORENZ AND S. BOYD, *An ellipsoidal approximation to the Hadamard product of ellipsoids*, Proceedings IEEE Conference on Acoustics, Speech, and Signal Processing (ICASSP), (2002), pp. 1193–1196.
[44] A. NEMIROVSKI, *Five lectures on modern convex optimization*, C.O.R.E. Summer School on Modern Convex Optimization (2002)
Available at `http://iew3.technion.ac.il/Labs/Opt/opt/LN/Final.pdf`.
[45] A. NEMIROVSKI, *Lectures on modern convex optimization*, Israel Institute of Technology (2002), available at `http://iew3.technion.ac.il/Labs/Opt/opt/LN/Final.pdf`.
[46] A. NEMIROVSKI, *Interior point polynomial time algorithms in convex programming*, lecture Notes (2004), available at https://itweb.isye.gatech.edu.
[47] A. NEMIROVSKI, *Modern convex optimization*, PASCAL Workshop, Thurnau, March 16-18 (2005).
[48] Y. E. NESTEROV AND A. S. NEMIROVSKII, *Interior point polynomial algorithms in convex programming*, SIAM, 1994.
[49] S. ÖZÖĞÜR, *Mathematical modelling of enzymatic reactions, simulation and parameter estimation*, MSc. thesis at Institute of Applied Mathematics, METU, Ankara (2005).
[50] S. ÖZÖGÜR-AKYÜZ, B. AKTEKE-ÖZTÜRK, T. TCHEMISOVA, AND G.-W. WEBER, *New optimization methods in data mining*, to appear in the proceedings of International Conference Operations Research (OR 2008; Augsburg, Germany, September 3-5, 2008), Springer Verlag, 2008.
[51] S. ÖZÖĞÜR, A. G. SAĞDIÇOĞLU CELEP, B. KARASÖZEN, N. YILDIRIM, AND G.-W. WEBER, *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 (2005), pp. 78–84.
[52] M. PARTNER, N. KASHTAN, AND U. ALON, *Environmental variability and modularity of bacterial metabolic networks*, BMC Evolutionary Biology, 7 (2007), 169doi:10.1186/1471-2148-7-169.
[53] S. PICKL, *Der τ-value als Kontrollparameter - Modellierung und Analyse eines Joint-Implementation Programmes mithilfe der dynamischen kooperativen Spieltheorie und der diskreten Optimierung*, thesis, Darmstadt University of Technology, Department of Mathematics (1998).
[54] S. PICKL, *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 (2002), pp. 196–205.
[55] S. PICKL, *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.
[56] S. PICKL AND G.-W. WEBER, *Optimization of a time-discrete nonlinear dynamical system from a problem of ecology - an analytical and numerical approach*, Journal of Computational Technologies, 6, 1 (2001), pp. 43–52.
[57] C. RIENER AND T. THEOBALD, *Positive Polynome und semidefinite Optimierung*, Jahresbericht der DMV - JB 100. Band, Heft 2 (2008), pp. 57–76.
[58] L. ROS, A. SABATER, AND F. THOMAS, *An ellipsoidal calculus based on propagation and fusion*, IEEE Transactions on Systems, Man and Cybernetics, Part B: Cybernetics, 32, 4 (2002), pp. 430–442.
[59] A. SHAPIRO, D. DENTCHEVA, AND A. RUSZCZYŃSKI, *Lectures on stochastic programming: modeling and theory*, to be published by SIAM, Philadelphia (2009).
[60] M. TAŞTAN, *Analysis and prediction of gene expression patterns by dynamical systems, and by a combinatorial algorithm*, Institute of Applied Mathematics, METU, MSc Thesis (2005).
[61] M. TAŞTAN, T. ERGENÇ, S. W. PICKL, AND G.-W. WEBER, *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 (2005), pp. 67–75.

[62] M. TAŞTAN, S. W. PICKL, AND G.-W. WEBER, *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.

[63] P. TAYLAN AND G.-W. WEBER, *New approaches to regression in financial mathematics by additive models*, Journal of Computational Technologies 12, 2 (2007), pp. 3–22.

[64] P. TAYLAN, G.-W. WEBER, AND A. BECK, *New approaches to regression by generalized additive models and continuous optimization for modern applications in finance, science and techology*, in the special issue in honour of Prof. Dr. Alexander Rubinov, Burachik, B., Yang, X. (guest eds.) Optimization, 56, 5-6 (2007), pp. 1–24, DOI number: http://dx.doi.org/doi:10.1080/02331930701618740.

[65] P. TAYLAN, G.-W. WEBER, AND E. KROPAT, *Approximation of stochastic differential equations by additive models using splines and conic programming*, to appear in International Journal of Computing Anticipatory Systems 20-21-22, ISSN 1373-5411 (at the occasion of CASYS07, Eighth International Conference on Computing Anticipatory Systems, Liege, Belgium, August 6-11, 2007) D. M. Dubois, ed. (2008).

[66] P. TAYLAN, G.-W. WEBER, AND N. N. URGAN, *On the parameter estimation for generalized partial linear models with B-Splines and continuous optimization*, preprint at Institute of Applied Mathematics, submitted to TOP.

[67] P. TAYLAN, G.-W. WEBER, AND F. YERLIKAYA, *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 (2008).

[68] P. TAYLAN, G.-W. WEBER, AND F. YERLIKAYA, *A new approach to multivariate adaptive regression spline by using Tikhonov regularization and continuous optimization*, to appear in TOP (the Operational Research journal of SEIO (Spanish Statistics and Operations Research Society), selected papers at the Occasion of 20th EURO Mini Conference Continuous Optimization and Knowledge-Based Technologies (Neringa, Lithuania, May 20-23, 2008) (2008).

[69] Ö. UĞUR, S. W. PICKL, G.-W. WEBER, AND R. WÜNSCHIERS, *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 (2006).

[70] Ö. UĞUR AND G.-W. WEBER, *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 J. Ind. Manag. Optim., 3, 2 (2007) pp. 357–379.

[71] A. Y. VAZHENTSEV, *On Internal ellipsoidal approximations for problems of control synthesis with bounded coordinates*, J. Comput. System Sci. Int., 39, 3, (2000), 399.

[72] Z. VOLKOVICH, Z. BARZILY, G.-W. WEBER, AND D. TOLEDANO-KITAI, *Cluster stability estimation based on a minimal spanning trees approach*, to appear in the proceedings of PCO 2009, Global Conference on Power Control and Optimization, Bali, Indonesia (2009).

[73] G.-W. WEBER, *Charakterisierung struktureller Stabilität in der nichtlinearen Optimierung*, in Aachener Beiträge zur Mathematik 5, H. H. Bock, H. T. Jongen, and W. Plesken, eds., Augustinus publishing house (now: Mainz publishing house) Aachen (1992).

[74] G.-W. WEBER, *Minimization of a max-type function: Characterization of structural stability*, in: Parametric Optimization and Related Topics III, J. Guddat, J., H. Th. Jongen, and B. Kummer, and F. Nožička, eds., Peter Lang publishing house, Frankfurt a.M., Bern, New York (1993), pp. 519–538.

[75] G.-W. WEBER, *Generalized semi-infinite optimization and related topics*, Heldermann Publishing House, Research and Exposition in Mathematics 29, Lemgo, K. H. Hofmannn and R. Wille, R., eds. (2003).

[76] G.-W. WEBER, S. Z. ALPARSLAN-GÖK, AND N. DIKMEN, *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, 5, 3, 197-233 (2008).

[77] G.-W. WEBER, S. Z. ALPARSLAN-GÖK, AND B. SÖYLER, *A new mathematical approach in environmental and life sciences: gene-environment networks and their dynamics*, to appear in Environmental Modeling & Assessment (2007), DOI number: 10.1007/s10666-007-9137-z.

[78] G.-W. WEBER, E. KROPAT, B. AKTEKE-ÖZTÜRK, AND Z.-K. GÖRGÜLÜ, *A survey on OR and mathematical methods applied on gene-environment networks*, to appear in the special issue on "Innovative Approaches for Decision Analysis in Energy, Health, and Life Sciences" of Cent. Eur. J. Oper. Res. (CEJOR) at the occasion of EURO XXII 2007 (Prague, Czech Republic, July 8-11, 2007), issue 3 or 4 (2009).

[79] G.-W. WEBER, E. KROPAT, A. TEZEL, AND S. BELEN, *Optimization applied on regulatory and eco-finance networks - survey and new developments*, to appear in Pac. J. Optim., 6, 3, special issue in memory of Professor Alexander Rubinov, M. Fukushima, M., et al., guest eds. (2010).

[80] G.-W. WEBER, E. KÜRÜM, AND K. YILDIRAK, *A classification problem of credit risk rating investigated and solved by optimization of the ROC curve*, presentation at occasion of the Workshop on Recent Developments in Applied Probability and Statistics Dedicated to the Memory of Professor Jürgen Lehn, Middle East Technical University, Ankara, Turkey (2009).

[81] G.-W. WEBER, S. ÖZÖGÜR-AKYÜZ, AND E. KROPAT, *A review on data mining and continuous optimization applications in computational biology and medicine*, invited paper, to appear in Embryo Today, Birth Defects Research Part C (2009).

[82] G.-W. WEBER, P. TAYLAN, S.-Z. ALPARSLAN-GÖK, S. ÖZÖĞÜR, AND B. AKTEKE-ÖZTÜRK, *Optimization of gene-environment networks in the presence of errors and uncertainty with Chebychev approximation*, to appear in TOP, the Operational Research journal of SEIO (Spanish Statistics and Operations Research Society) , DOI number: 10.1007/s11750-008-0052-5.

[83] G.-W. WEBER AND A. TEZEL, *On generalized semi-infinite optimization of genetic networks*, TOP, 15, 1, (2007), pp. 65–77.

[84] G.-W. WEBER, A. TEZEL, P. TAYLAN, A. SOYLER, AND M. ÇETIN, *Mathematical contributions to dynamics and optimization of gene-environment networks*, in D. Pallaschke, O. Stein (guest eds.) special issue *In Celebration of Prof. Dr. Dr. Hubertus Th. Jongen's 60th Birthday*, Optimization, 57, 2 (2008).

[85] G.-W. WEBER, Ö. UĞUR, P. TAYLAN, AND A. TEZEL, *On optimization, dynamics and uncertainty: a tutorial for gene-environment networks*, to appear in the special issue *Networks in Computational Biology* of Discrete Appl. Math., DOI number: doi:10.1016/j.dam.2008.06.030.

[86] F. YERLIKAYA, *A new contribution to nonlinear robust regression and classification with mars and its applications to data mining for quality control in manufacturing*, thesis, Middle East Technical University, Ankara, Turkey, 2008.

[87] F. YERLIKAYA, G.-W. WEBER, I. BATMAS, G. KÖKSAL, AND P. TAYLAN, *MARS Algoritmasında Tikhonov düzenlemesi ve çok amaçli optimizasyon kullanimi*, in the Proceedings of Operational Research and Industrial Engineering Annual Conference (YA/EM08), Galatasaray University, Istanbul, Turkey, 2008.

[88] F. B. YILMAZ, *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, 2004.

[89] F. B. YILMAZ, H. ÖKTEM, AND G.-W. WEBER, *Mathematical modeling and approximation of gene expression patterns and gene networks*, in Operations Research Proceedings, F. Fleuren, D. den Hertog, and P. Kort, eds., 2005, pp. 280–287.