Inverse Problems in Complex Multi-Modal Regulatory Networks Based on Uncertain Clustered Data

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Abstract Complex regulatory networks effected by noise and data uncertainty occur in many OR applications. The complexity is compounded by the unknown interactions between the system variables that have to be revealed from unprecise measurement data. The concept of target-environment networks provides a generic framework for the analysis of complex regulatory systems under uncertainty. Data mining methods like clustering and classification can be applied for an identification of functionally related groups of targets and environmental factors. The effects of the intricate connections between target and environmental clusters on single entities are determined by a parameterized time-discrete model. A crisp regression

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problem is introduced for parameter estimation and in case of uncertain data, ellipsoids are used to describe the clusters and error sets what refers to particular robust counterpart programs.

1 Introduction

The modeling and prediction of *regulatory networks* is of considerable importance in many disciplines such as finance, biology, medicine and life sciences. The identification of the underlying network topology and the regulating effects allows to gain deeper insights in the hidden relationships between the entities under consideration. This is even more promising as the technical developments of the last decades have produced a huge amount of data that is still waiting for a deeper analysis. Although many theoretical contributions from various disciplines have focussed on the analysis of such systems, the identification of regulatory networks from real-world data is still challenging mathematics. In particular, the presence of noise and data uncertainty raises serious problems to be dealt with on both the theoretical and computational side. There are many sources of uncertainty in the real world. We refer here to technological and market uncertainty, noise in observation and experimental design, incomplete information and vagueness in decision making. Beside this, the regulatory system has often to be further extended and improved with regard to the unknown effects of additional parameters and factors which may exert a disturbing influence on the key variables (target variables) under consideration. All these dynamical networks and multi-modal systems are affected

- by uncertainty in the data, both in their input and their output parts, or, in other words,
- by uncertainty in the scenarios and by random fluctuation,
- by the necessity to reduce the model complexity, i.e., to regularize, rarefy and stabilize.

In this regard, we are on the way between complete determinism in processes and the rich randomness as it can be investigated by stochastic calculus and, especially, Lévy processes. In 2002, we started our modelling of processes related with *genetic networks* in the deterministic case where, then, in the following years, we included the role of additional environmental factors which yielded us our multi-modal systems such as *gene-environment* and *eco-finance networks*. Since in these kinds of dynamics, the impact of the environmental items became implied as additive "shift" terms which can also be called as *perturbations*, we arrived at our first implication of noise. Having once entered the domain of uncertainty, we went on working it out, firstly, by *interval uncertainty* where, however, the dependencies and correlations between the various items from biology, medicine, these sectors of ecology, education and finance were not taken into account yet [55, 58]. We treated those modelling tasks by the help of *Chebychev approximation* and *Generalized Semi-Infinite Optimization* [46, 47, 48, 49, 51, 52, 59, 60]. By turning to the case of *ellipsoidal uncertainty* [25, 26, 27] and, as far as splines were used for approximation, by applying *Multivariate Adaptive Regression Spline* instead of *Generalized Additive Models* [43, 44, 45], we could overcome that drawback and we included stochastic dependencies and interactions into our model. Here, the dimensions of the ellipsoids are motivated by additional information related to the model items and their similarities, i.e., on how much they are close to each other and how the distribution of such clusters expresses itself geometrically in ellipsoidal forms. In game theoretical contexts, we called these clusters *(sub) coalitions*. In this way, we arrived at a family or, in particular, sequence of ellipsoids which can be regarded as the bodies which contain our target or environmental variables at the corresponding times, i.e., the processes studied, by confidence levels of, e.g., 95%.

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 [29], 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 regulatory systems where environmental effects are strongly involved. Among them are, e.g., *metabolic networks* [9, 35, 55], *immunological networks* [18], *social-* and *ecological networks* [17]. We refer to [1, 13, 12, 15, 16, 19, 20, 21, 40, 41, 42, 32, 54, 61, 62] for applications, practical examples and numerical calculations.

Whenever we want to particularly address items to the financial sector among the target variables or the environmental variables which, in fact, maybe be regarded in a dual relationship mutually, then we arrive at *eco-finance networks* [24, 53]. This interpretation and variety of our studies also represents that the identification of dynamics related with the Kyoto Protocol, where financial expenditures and emissions reduced interact in time (TEM model) [20, 23, 28, 36, 37, 38, 39]. Financial negotiation processes, represented in the way of collaborative game theory [50, 51], and the identification and dynamics of financial processes given by stochastic differential equations and their time-discretized versions [56, 57], are an important part our research. Incorporating uncertainty in cooperative game theory is motivated by the need to handle uncertain outcomes in collaborative situations. Interval uncertainty is a natural instance of uncertainty which influences cooperation. A broader overview on recent developments on interval solutions and their applications can be found in [2, 11]. Cooperative games are the games whose characteristic functions are interval valued, i.e., the worth of a coalition is not a real number, but a compact interval of real numbers. This means that one observes a lower and an upper bound of the considered coalitions. This is very important from computational and algorithmic viewpoint. We notice that the approach is general, since the characteristic function interval-values may result from solving general optimization problems. Cooperative interval games and interval solution concepts are useful tools for modeling various economic and Operations Research situations where payoffs are affected by interval uncertainty. The interval Baker-Thompson rule for solving the aircraft fee problem of an airport with one runway when there is uncertainty regarding the costs of the pieces of the runway is presented and identified in [5] and an axiomatic characterization of the interval Baker-Thompson rule is given in [3]. Further, one-machine sequencing situations with interval data are considered in [4] for which they present different possible scenarios and extend to the interval setting classical results regarding well known rules and sequencing games. Two classical bankruptcy rules, namely the proportional rule and the rights-egalitarian rule, are extended in [10] using a cooperative interval game approach. They show that interval allocations generated by such rules belong to the interval core of related cooperative interval games. Finally, [30] deal with cost allocation problems arising from connection situations where edge costs are closed intervals of real numbers, and to solve such problems, they extend classical solutions from the theory of minimum cost spanning tree games.

Recent studies on target-environment and gene-environment networks focussed on systems with functionally related groups of target and environmental factors. These groups are identified in a preprocessing step of clustering and classification and the corresponding uncertain multivariate states are represented by ellipsoids [25, 26, 27]. The interaction of clusters is determined by affine-linear equations based on ellipsoidal calculus. Various regression problems are introduced for an identification of unknown system parameters from (ellipsoidal) measurement data. In addition, problems of network rarefication and the corresponding mixed-integer regression problems as well as a further relaxation by means of continuous optimization have been addressed in [27]. For further details on the underlying set-theoretic regression theory and the solvability by semi-definite programming we refer to [25, 26, 27].

In this paper, we further extend this approach and offer a new perspective where potentially overlapping clusters of targets and groups of environmental factors take influence on the states and values of *single targets* and *single environmental variables*.

The comparison of measurements and predictions of the model leads to a regression model for parameter estimation. Since clusters can be affected by noise and errors, the uncertain multivariate states are represented by ellipsoids what refers to the concept of *robustness* for mathematical programming problems. This approach complements and further extends the framework developed in [25, 26, 27] for multimodal systems under ellipsoidal uncertainty.

The chapter is organized as follows: In Section 2 some basic facts and notation about target and environmental variables as well as the partitioning of data in possibly overlapping clusters are provided. Then, in Section 3, a time-discrete linear model is introduced that relates the single variables and the multivariate states of groups of target and environmental factors. The corresponding regression model for parameter estimation is addressed in Section 4. In a further step, data uncertainty becomes included into our modelling in Section 5 and Section 6, where the multivariate states of clusters are represented in terms of ellipsoids. Hereby, the corresponding regression models can be reformulated in terms of robust counterpart programs.

2 Target-Environment Networks

The time-discrete *target-environment regulatory systems* under consideration consist of n targets and m environmental factors and, thus, constitutes a *two-modal system*. The expression values of the target variables are given by the vector $\mathbb{X} = \left[\mathbb{X}_1, \ldots, \mathbb{X}_n\right]'$ and the vector $\mathbb{E} = \left[\mathbb{E}_1, \ldots, \mathbb{E}_m\right]'$ denotes the states of the environmental variables, where $[\cdot]'$ stands for the transposition of a matrix or vector. Data mining methods like clustering and classification as well as statistical data analysis can be used for an identification of functionally related groups of targets and environmental factors. These groups can show a direct interaction, but they can also have a regulating effect on single targets or environmental factors. In this paper, we focus on the interactions between clusters and single targets or environmental factors. For a deeper analysis of inter-cluster regulatory networks under ellipsoidal uncertainty we refer to [25, 26, 27].

When a cluster partition is established, the set of targets can be divided in R clusters $C_r \subset \{1, \ldots, n\}$, $r = 1, \ldots, R$. Similarly, the set of all environmental items is divided in S clusters $D_s \subset \{1, \ldots, m\}$, $s = 1, \ldots, S$. Depending on the data structure and the data mining method used, the clusters might be disjoint or overlapping [22]. We note that in case of a strict sub-division of variables, 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. However, in many applications a single entity might be involved in more than one regulating cycle and for this reason we do not explicitly impose such restrictions and refer to the more general situation of *overlapping clusters*. According to the cluster structure, we introduce the sub-vector $X_r \in \mathbb{R}^{|C_r|}$ of $\mathbb{X}$ as the restriction of $\mathbb{X}$ given by elements of C_r. In the same way, the sub-vector $E_s \in \mathbb{R}^{|D_s|}$ is defined as the restriction of $\mathbb{E}$ given by elements of D_s.

3 The Time-Discrete Model

In this section, we introduce a time-discrete model for the states of the targets $\mathbb{X}_j$, $j = 1, \ldots, n$, and environmental factors $\mathbb{E}_i$, $i = 1, \ldots, m$. Four types of interactions and regulating effects are involved:

(TT) target cluster $\to$ target variable,
(ET) environmental cluster $\to$ target variable,
(TE) target cluster $\to$ environment variable,
(EE) environmental cluster $\to$ environment variable.

When we refer to cluster partitions with potentially overlapping clusters, single entities can refer to more than one group of data items. In such a situation, the *target-environment regulatory model* can be formulated as follows:

$$\left.\begin{aligned} \mathbb{X}_j^{(\kappa+1)} &= \zeta_{j0}^T + \sum_{r=1}^{R} \left[X_r^{(\kappa)}\right]' \Theta_{jr}^{TT} + \sum_{s=1}^{S} \left[E_s^{(\kappa)}\right]' \Theta_{js}^{ET}, \\ \mathbb{E}_i^{(\kappa+1)} &= \zeta_{i0}^E + \sum_{r=1}^{R} \left[X_r^{(\kappa)}\right]' \Theta_{ir}^{TE} + \sum_{s=1}^{S} \left[E_s^{(\kappa)}\right]' \Theta_{is}^{EE} \end{aligned}\right\} \qquad \text{(CM)}$$

with $\kappa \geq 0$, where (CM) stands for *cluster model*. The initial values $\mathbb{X}^{(0)}$ and $\mathbb{E}^{(0)}$ can be given by the first measurements of targets and environmental factors, i.e., $\mathbb{X}^{(0)} := \overline{\mathbb{X}}^{(0)}$ and $\mathbb{E}^{(0)} := \overline{\mathbb{E}}^{(0)}$. The vectors Θ_{jr}^{TT} and Θ_{ir}^{TE} are $|C_r|$-subvectors of the parameter vectors $\Theta_j^{TT} \in \mathbb{R}^n$ and $\Theta_i^{TE} \in \mathbb{R}^n$, respectively. These subvectors are given by the indices of cluster C_r. Similarly, the vectors Θ_{js}^{ET} and Θ_{is}^{EE} are $|D_s|$-subvectors of the parameter vectors $\Theta_j^{ET} \in \mathbb{R}^m$ and $\Theta_i^{EE} \in \mathbb{R}^m$. The additional parameters $\zeta_{j0}^T, \zeta_{i0}^E \in \mathbb{R}$ are intercepts. We note that if all clusters are disjoint, the aforementioned subvectors correspond to distinct parts of the parameter vectors, but we do not make this restriction here.

4 The Regression Problem

We now turn to an estimation of parameters of the cluster model (CM). For a regression analysis, the predictions of (CM) have to be compared with the states of targets $\overline{\mathbb{X}}^{(\kappa)} = \left[\overline{\mathbb{X}}_1^{(\kappa)}, \ldots, \overline{\mathbb{X}}_n^{(\kappa)}\right]' \in \mathbb{R}^n$ and environmental observations $\overline{\mathbb{E}}^{(\kappa)} = \left[\overline{\mathbb{E}}_1^{(\kappa)}, \ldots, \overline{\mathbb{E}}_m^{(\kappa)}\right]' \in \mathbb{R}^m$, $\kappa = 0, 1, \ldots, T$, which are obtained from measurements taken at sampling times $t_0 < t_1 < \ldots < t_T$. By inserting these *measurements* in model (CM) we obtain the following *predictions*:

$$\begin{aligned} \widehat{\mathbb{X}}_j^{(\kappa+1)} &= \zeta_{j0}^T + \sum_{r=1}^{R} \left[\overline{X}_r^{(\kappa)}\right]' \Theta_{jr}^{TT} + \sum_{s=1}^{S} \left[\overline{E}_s^{(\kappa)}\right]' \Theta_{js}^{ET}, \\ \widehat{\mathbb{E}}_i^{(\kappa+1)} &= \zeta_{i0}^E + \sum_{r=1}^{R} \left[\overline{X}_r^{(\kappa)}\right]' \Theta_{ir}^{TE} + \sum_{s=1}^{S} \left[\overline{E}_s^{(\kappa)}\right]' \Theta_{is}^{EE}, \end{aligned}$$

where $\kappa = 0, 1, \ldots, T-1$. We use the initial values $\widehat{\mathbb{X}}_j^{(0)} := \overline{\mathbb{X}}_j^{(0)}$, $\widehat{\mathbb{E}}_i^{(0)} := \overline{\mathbb{E}}_i^{(0)}$ and define the vectors $\widehat{\mathbb{X}}^{(\kappa)} = \left[\widehat{\mathbb{X}}_1^{(\kappa)}, \ldots, \widehat{\mathbb{X}}_n^{(\kappa)}\right]'$ and $\widehat{\mathbb{E}}^{(\kappa)} = \left[\widehat{\mathbb{E}}_1^{(\kappa)}, \ldots, \widehat{\mathbb{E}}_m^{(\kappa)}\right]'$, where $\kappa = 0, 1, \ldots, T$; $i = 1, \ldots, n$; $j = 1, \ldots, m$.

When we compare measurements and predictions, we obtain the following regression problem:

$$\text{Minimize} \quad \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} \left| \widehat{\mathbb{X}}_j^{(\kappa)} - \overline{\mathbb{X}}_j^{(\kappa)} \right| + \sum_{i=1}^{m} \left| \widehat{\mathbb{E}}_i^{(\kappa)} - \overline{\mathbb{E}}_i^{(\kappa)} \right| \right\}. \qquad \text{(RP)}$$

5 Ellipsoidal Uncertainty

Ben-Tal and Nemirovski introduced the concept of robustness for programming problems where data is subject to ellipsoidal uncertainty [6, 8]. In general, 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 (or shape) matrix* $\Sigma \in \mathbb{R}^{p\times p}$ as

$$\mathscr{E}(c,\Sigma) = \{\Sigma u + c \,|\, \|u\|_2 \leq 1\}.$$

In order to include data uncertainty into our model, we now assume that the states of the clusters of target variables and environmental factors are subject to ellipsoidal uncertainty. That means, our regression analysis will be based on set-valued data

$$\begin{aligned} X_r^{(\kappa)} &\in \mathscr{E}\big(\overline{X}_r^{(\kappa)}, \overline{\Sigma}_r^{(\kappa)}\big) \subset \mathbb{R}^{|C_r|}, \\ E_s^{(\kappa)} &\in \mathscr{E}\big(\overline{E}_s^{(\kappa)}, \overline{\Pi}_s^{(\kappa)}\big) \subset \mathbb{R}^{|D_s|}, \end{aligned}$$

with $\kappa = 0, 1, \ldots, T$. The measurements $\overline{X}_r^{(\kappa)}$ and $\overline{E}_s^{(\kappa)}$ determine the centers of the ellipsoids and the corresponding symmetric shape matrices $\overline{\Sigma}_r^{(\kappa)}$ and $\overline{\Pi}_s^{(\kappa)}$ are given by the variance-covariance matrices of cluster data what also refers to partial correlations and partial variances of cluster elements.

6 Robust Regression under Ellipsoidal Uncertainty

Measurements and observations of targets and environmental factors are usually affected by uncertainty. The regression problem (RP) depends on crisp (numerical) measurements and does not reflect the disturbing influence of unprecise data. For this reason, we now turn to robust regression models with regard to data sets with (overlapping) cluster partition. There are several ways to describe data uncertainty from a set-theoretic perspective. When an individual error can be assigned to each target and environmental factor, the corresponding states of variables are given by intervals, whereas the states of clusters are represented by hyperrectangles. When errors of clusters elements are correlated, non-paraxial sets have to be considered and the polyhedral uncertainty sets can be replaced by error ellipsoids.

In order to include data uncertainty in the regression problem (RP) it is convenient to reformulate this model as follows:

$$\text{Minimize } \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)} \right\}$$

$$\text{such that } \left| \widehat{\mathbb{X}}_j^{(\kappa)} - \overline{\mathbb{X}}_j^{(\kappa)} \right| \le p_j^{(\kappa)} \ \ (\kappa = 1,\dots,T;\ j = 1,\dots,n),$$

$$\left| \widehat{\mathbb{E}}_i^{(\kappa)} - \overline{\mathbb{E}}_i^{(\kappa)} \right| \le q_i^{(\kappa)} \ \ (\kappa = 1,\dots,T;\ i = 1,\dots,m).$$

This problem can be equivalently written as

$$\text{Minimize } \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)} \right\}$$

$$\text{such that } \left| \zeta_{j0}^{T} + \sum_{r=1}^{R} \left[\overline{X}_r^{(\kappa-1)} \right]' \Theta_{jr}^{TT} + \sum_{s=1}^{S} \left[\overline{E}_s^{(\kappa-1)} \right]' \Theta_{js}^{ET} - \overline{\mathbb{X}}_j^{(\kappa)} \right| \le p_j^{(\kappa)},$$

$$\left| \zeta_{i0}^{E} + \sum_{r=1}^{R} \left[\overline{X}_r^{(\kappa-1)} \right]' \Theta_{ir}^{TE} + \sum_{s=1}^{S} \left[\overline{E}_s^{(\kappa-1)} \right]' \Theta_{is}^{EE} - \overline{\mathbb{E}}_i^{(\kappa)} \right| \le q_i^{(\kappa)}$$

$$(\kappa = 1,\dots,T;\ j = 1,\dots,n;\ i = 1,\dots,m).$$

We assume that the constraints are satisfied for all realizations of the states $X_r^{(\kappa)} \in \mathscr{E}\left(\overline{X}_r^{(\kappa)}, \overline{\Sigma}_r^{(\kappa)}\right)$ and $E_s^{(\kappa)} \in \mathscr{E}\left(\overline{E}_s^{(\kappa)}, \overline{\Pi}_s^{(\kappa)}\right)$ and in this way we obtain the following robust regression problem with uncertain ellipsoidal states:

$$\text{Minimize } \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)} \right\}$$

$$\text{such that } \left| \zeta_{j0}^{T} + \sum_{r=1}^{R} \left[X_r^{(\kappa-1)} \right]' \Theta_{jr}^{TT} + \sum_{s=1}^{S} \left[E_s^{(\kappa-1)} \right]' \Theta_{js}^{ET} - \overline{\mathbb{X}}_j^{(\kappa)} \right| \le p_j^{(\kappa)},$$

$$\left| \zeta_{i0}^{E} + \sum_{r=1}^{R} \left[X_r^{(\kappa-1)} \right]' \Theta_{ir}^{TE} + \sum_{s=1}^{S} \left[E_s^{(\kappa-1)} \right]' \Theta_{is}^{EE} - \overline{\mathbb{E}}_i^{(\kappa)} \right| \le q_i^{(\kappa)}$$

$$(\kappa = 1,\dots,T;\ j = 1,\dots,n;\ i = 1,\dots,m)$$

$$\forall X_r^{(\kappa)} \in \mathscr{E}\left(\overline{X}_r^{(\kappa)}, \overline{\Sigma}_r^{(\kappa)}\right) \ \ (\kappa = 0,\dots,T-1;\ r = 1,\dots,R),$$

$$\forall E_s^{(\kappa)} \in \mathscr{E}\left(\overline{E}_s^{(\kappa)}, \overline{\Pi}_s^{(\kappa)}\right) \ \ (\kappa = 0,\dots,T-1;\ s = 1,\dots,S).$$

The above problem can be rewritten:

$$
\begin{aligned}
\text{Minimize } & \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)} \right\} \\
\text{such that } \quad & \zeta_{j0}^{T} + \sum_{r=1}^{R} \big[X_r^{(\kappa-1)}\big]' \Theta_{jr}^{TT} + \sum_{s=1}^{S} \big[E_s^{(\kappa-1)}\big]' \Theta_{js}^{ET} - \overline{\mathbb{X}}_j^{(\kappa)} \le p_j^{(\kappa)}, \\
& -\zeta_{j0}^{T} - \sum_{r=1}^{R} \big[X_r^{(\kappa-1)}\big]' \Theta_{jr}^{TT} - \sum_{s=1}^{S} \big[E_s^{(\kappa-1)}\big]' \Theta_{js}^{ET} + \overline{\mathbb{X}}_j^{(\kappa)} \le p_j^{(\kappa)}, \\
& \zeta_{i0}^{E} + \sum_{r=1}^{R} \big[X_r^{(\kappa-1)}\big]' \Theta_{ir}^{TE} + \sum_{s=1}^{S} \big[E_s^{(\kappa-1)}\big]' \Theta_{is}^{EE} - \overline{\mathbb{E}}_i^{(\kappa)} \le q_i^{(\kappa)}, \\
& -\zeta_{i0}^{E} - \sum_{r=1}^{R} \big[X_r^{(\kappa-1)}\big]' \Theta_{ir}^{TE} - \sum_{s=1}^{S} \big[E_s^{(\kappa-1)}\big]' \Theta_{is}^{EE} + \overline{\mathbb{E}}_i^{(\kappa)} \le q_i^{(\kappa)} \\
& (\kappa = 1, \ldots, T;\ j = 1, \ldots, n;\ i = 1, \ldots, m) \\
& \forall X_r^{(\kappa)} \in \mathscr{E}\big(\overline{X}_r^{(\kappa)}, \overline{\Sigma}_r^{(\kappa)}\big) \ \ (\kappa = 0, \ldots, T-1;\ r = 1, \ldots, R), \\
& \forall E_s^{(\kappa)} \in \mathscr{E}\big(\overline{E}_s^{(\kappa)}, \overline{\Pi}_s^{(\kappa)}\big) \ \ (\kappa = 0, \ldots, T-1;\ s = 1, \ldots, S).
\end{aligned}
$$

This problem has an infinite number of constraints as it depends on all possible realizations of ellipsoidal states of targets and environmental factors. Another reformulation of this problem can be obtained when the ellipsoids are represented as follows:

$$
\begin{aligned}
\mathscr{E}\big(\overline{X}_r^{(\kappa)}, \overline{\Sigma}_r^{(\kappa)}\big) &= \left\{ \overline{X}_r^{(\kappa)} + \overline{\Sigma}_r^{(\kappa)} u_r \,\middle|\, \|u_r\|_2 \le 1 \right\}, \\
\mathscr{E}\big(\overline{E}_s^{(\kappa)}, \overline{\Pi}_s^{(\kappa)}\big) &= \left\{ \overline{E}_s^{(\kappa)} + \overline{\Pi}_s^{(\kappa)} v_s \,\middle|\, \|v_s\|_2 \le 1 \right\}.
\end{aligned}
$$

With

$$
\begin{aligned}
U_r &:= \left\{ u_r \in \mathbb{R}^{|C_r|} \,\middle|\, \|u_r\|_2 \le 1 \right\},\ r = 1, \ldots, R, \\
V_s &:= \left\{ v_s \in \mathbb{R}^{|D_s|} \,\middle|\, \|v_s\|_2 \le 1 \right\},\ s = 1, \ldots, S
\end{aligned}
$$

we then obtain the equivalent problem

$$\text{Minimize} \sum_{\kappa=1}^{T} \left\{ \sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)} \right\}$$

$$\begin{aligned}
\text{such that} \quad & \zeta_{j0}^{T} + \sum_{r=1}^{R} [\overline{X}_r^{(\kappa-1)}]' \Theta_{jr}^{TT} + \sum_{r=1}^{R} \max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa-1)} \Theta_{jr}^{TT} \} \\
& + \sum_{s=1}^{S} [\overline{E}_s^{(\kappa-1)}]' \Theta_{js}^{ET} + \sum_{s=1}^{S} \max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa-1)} \Theta_{js}^{ET} \} \\
& - \overline{\mathbb{X}}_j^{(\kappa)} \le p_j^{(\kappa)} \ \ (\kappa = 1, \ldots, T;\ j = 1, \ldots, n),
\end{aligned}$$

$$\begin{aligned}
& -\zeta_{j0}^{T} - \sum_{r=1}^{R} [\overline{X}_r^{(\kappa-1)}]' \Theta_{jr}^{TT} - \sum_{r=1}^{R} \max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa-1)} \Theta_{jr}^{TT} \} \\
& - \sum_{s=1}^{S} [\overline{E}_s^{(\kappa-1)}]' \Theta_{js}^{ET} - \sum_{s=1}^{S} \max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa-1)} \Theta_{js}^{ET} \} \\
& + \overline{\mathbb{X}}_j^{(\kappa)} \le p_j^{(\kappa)} \ \ (\kappa = 1, \ldots, T;\ j = 1, \ldots, n),
\end{aligned}$$

$$\begin{aligned}
& \zeta_{i0}^{E} + \sum_{r=1}^{R} [\overline{X}_r^{(\kappa-1)}]' \Theta_{ir}^{TE} + \sum_{r=1}^{R} \max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa-1)} \Theta_{ir}^{TE} \} \\
& + \sum_{s=1}^{S} [\overline{E}_s^{(\kappa-1)}]' \Theta_{is}^{EE} + \sum_{s=1}^{S} \max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa-1)} \Theta_{is}^{EE} \} \\
& - \overline{\mathbb{E}}_i^{(\kappa)} \le q_i^{(\kappa)} \ \ (\kappa = 1, \ldots, T;\ i = 1, \ldots, m),
\end{aligned}$$

$$\begin{aligned}
& -\zeta_{i0}^{E} - \sum_{r=1}^{R} [\overline{X}_r^{(\kappa-1)}]' \Theta_{ir}^{TE} - \sum_{r=1}^{R} \max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa-1)} \Theta_{ir}^{TE} \} \\
& - \sum_{s=1}^{S} [\overline{E}_s^{(\kappa-1)}]' \Theta_{is}^{EE} - \sum_{s=1}^{S} \max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa-1)} \Theta_{is}^{EE} \} \\
& + \overline{\mathbb{E}}_i^{(\kappa)} \le q_i^{(\kappa)} \ \ (\kappa = 1, \ldots, T;\ i = 1, \ldots, m).
\end{aligned}$$

The equations

$$\begin{aligned}
\max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa)} \Theta_{jr}^{TT} \} &= \max_{u_r \in U_r} \{ -u_r' \overline{\Sigma}_r^{(\kappa)} \Theta_{jr}^{TT} \} = \left\| \overline{\Sigma}_r^{(\kappa)} \Theta_{jr}^{TT} \right\|_2, \\
\max_{u_r \in U_r} \{ u_r' \overline{\Sigma}_r^{(\kappa)} \Theta_{ir}^{TE} \} &= \max_{u_r \in U_r} \{ -u_r' \overline{\Sigma}_r^{(\kappa)} \Theta_{ir}^{TE} \} = \left\| \overline{\Sigma}_r^{(\kappa)} \Theta_{ir}^{TE} \right\|_2, \\
\max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{ET} \} &= \max_{v_s \in V_s} \{ -v_s' \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{ET} \} = \left\| \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{ET} \right\|_2, \\
\max_{v_s \in V_s} \{ v_s' \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{EE} \} &= \max_{v_s \in V_s} \{ -v_s' \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{EE} \} = \left\| \overline{\Pi}_s^{(\kappa)} \Theta_{is}^{EE} \right\|_2
\end{aligned}$$

lead to a further description of the regression problem:

$$\text{Minimize } \sum_{\kappa=1}^{T}\left\{\sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)}\right\}$$

$$\text{such that } \left|\zeta_{j0}^{T} + \sum_{r=1}^{R}\left[\overline{X}_r^{(\kappa-1)}\right]'\Theta_{jr}^{TT} + \sum_{s=1}^{S}\left[\overline{E}_s^{(\kappa-1)}\right]'\Theta_{js}^{ET} - \overline{\mathbb{X}}_j^{(\kappa)}\right|$$

$$+ \sum_{r=1}^{R}\left\|\overline{\Sigma}_r^{(\kappa-1)}\Theta_{jr}^{ET}\right\|_2 + \sum_{s=1}^{S}\left\|\overline{\Pi}_s^{(\kappa-1)}\Theta_{js}^{ET}\right\|_2 \le p_j^{(\kappa)},$$

$$\left|\zeta_{i0}^{E} + \sum_{r=1}^{R}\left[\overline{X}_r^{(\kappa-1)}\right]'\Theta_{ir}^{TE} + \sum_{s=1}^{S}\left[\overline{E}_s^{(\kappa-1)}\right]'\Theta_{is}^{EE} - \overline{\mathbb{E}}_i^{(\kappa)}\right|$$

$$+ \sum_{r=1}^{R}\left\|\overline{\Sigma}_r^{(\kappa-1)}\Theta_{ir}^{TE}\right\|_2 + \sum_{s=1}^{S}\left\|\overline{\Pi}_s^{(\kappa-1)}\Theta_{is}^{EE}\right\|_2 \le q_i^{(\kappa)}$$

$$(\kappa = 1,\ldots,T;\ j = 1,\ldots,n;\ i = 1,\ldots,m).$$

Finally, with the vectors

$$\begin{aligned}
\Theta_j^T &= \left[\zeta_{j0}^T, \Theta_{j1}^{TT}, \ldots, \Theta_{jR}^{TT}, \Theta_{j1}^{ET}, \ldots, \Theta_{jS}^{ET}\right]^T, \\
\Theta_i^E &= \left[\zeta_{i0}^E, \Theta_{i1}^{TE}, \ldots, \Theta_{iR}^{TE}, \Theta_{i1}^{EE}, \ldots, \Theta_{iS}^{EE}\right]^T, \\
c^{(\kappa)} &= \left[1, \overline{X}_1^{(\kappa)}, \ldots, \overline{X}_R^{(\kappa)}, \overline{E}_1^{(\kappa)}, \ldots, \overline{E}_S^{(\kappa)}\right]^T
\end{aligned}$$

we obtain the following program for an estimation of the parameters of the cluster model (CM) based on ellipsoidal uncertainty:

$$\text{Minimize } \sum_{\kappa=1}^{T}\left\{\sum_{j=1}^{n} p_j^{(\kappa)} + \sum_{i=1}^{m} q_i^{(\kappa)}\right\}$$

$$\text{such that } \left|\left[c^{(\kappa-1)}\right]'\Theta_j^T - \overline{\mathbb{X}}_j^{(\kappa)}\right| + \sum_{r=1}^{R}\left\|\overline{\Sigma}_r^{(\kappa-1)}\Theta_{jr}^{TT}\right\|_2 + \sum_{s=1}^{S}\left\|\overline{\Pi}_s^{(\kappa-1)}\Theta_{js}^{ET}\right\|_2 \le p_j^{(\kappa)},$$

$$\left|\left[c^{(\kappa-1)}\right]'\Theta_i^E - \overline{\mathbb{E}}_i^{(\kappa)}\right| + \sum_{r=1}^{R}\left\|\overline{\Sigma}_r^{(\kappa-1)}\Theta_{ir}^{TE}\right\|_2 + \sum_{s=1}^{S}\left\|\overline{\Pi}_s^{(\kappa-1)}\Theta_{is}^{EE}\right\|_2 \le q_i^{(\kappa)}$$

$$(\kappa = 1,\ldots,T;\ j = 1,\ldots,n;\ i = 1,\ldots,m). \qquad \text{(RCPE)}$$

To be able to solve the problems like RCPE, stochastic programming, dynamic programming and robust optimization methods are principle methods which cope with uncertainty. Although it seems that the areas of them overlap, they are developed freely of one another. Stochastic programming methods present the uncertain data by scenarios which are created in advance while dynamic programming methods handle stochastic uncertain systems over multiple stages. As an alternative to stochastic and dynamic programming methods, robust optimization methods deal with uncertainty as deterministic, but do not limit parameter values to point estimates [14]. The purpose of robust optimization is to find an optimal or near optimal solution which is feasible for any values of the uncertain parameters in prespecified uncertainty sets that have special shape such as polyhedral and ellipsoidal. For further details on robust optimization and the numerical treatment of the corresponding uncertainty-affected programming problems with polyhedral and ellipsoidal uncertainty we refer to [7, 31, 33, 34].

7 Conclusion

In this chapter, we analyzed inverse problems for target-environment networks under ellipsoidal uncertainty. This theoretical framework is particularly suited for parameter identification of gene-environment networks in system genetics and computational biology as well as eco-finance networks of OR-applications. This approach constitutes a further extension of our analysis of target-environment networks in OR that are based on interval arithmetics where Chebychev approximation and generalized semi-infinite optimization are considered. In this paper, we focused on time-discrete two-modal models that determine the response of single target variables and environmental factors to the actual states of potentially overlapping clusters or coalitions of system variables. This complements our recently introduced concept of target-environment networks for an analysis of the intrinsic interactions and synergetic connections between clusters. The underlying regression models are based on ellipsoidal calculus and in future work, combinations of both approaches have to considered such that clusters may take influence on target and environmental clusters as well as single genes and single environmental factors simultaneously.

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