Final report

Project title: **Analysis and Control of Nonlinear Polynomial Systems Using Optimization Methods**
Project identifier: OTKA/NKFIH NF104706
Duration: September 1, 2012 – November 30, 2016

1 Aims of the research

The fundamental problem of the planned research was how to efficiently utilize the special algebraic and structural properties of dynamical models given in the form of polynomial ordinary differential equations for the analysis, identification and control of nonlinear dynamical systems. Our approach was based on the working hypothesis that the fulfillment of the studied or required system properties can be traced back to the solution of computation problems, where optimization plays a key role [45]. We have put special emphasis on the class of nonnegative systems, where the dynamics preserves the nonnegativity of the state variables [43]. Moreover, the detailed study of the generally non-unique directed graph structure corresponding to polynomial models was also targeted, motivated by the known and still continuously improving useful results on the relations between network structure and system behaviour [46, 39, 47]. Finally, the developed theoretical results and computational methods were expected to support the deeper integration of the studied system classes into nonlinear systems and control theory, mainly by defining appropriate control system structures and by designing stabilizing controllers.

2 Institutional and personal background

The research work started at the Institute of Computer Science and Control (MTA SZTAKI) in September, 2012. In 2013, Gábor Szederkényi obtained a full professor status at the Faculty of Information Technology and Bionics, Pázmány Péter Catholic University (PPKE). Therefore, the transfer of the grant to PPKE was initiated, and finally authorized in July 2013 by the OTKA Commission and PPKE according to the corresponding regulations. In January 2014, Dr. Balázs Boros joined the project for one year as a senior researcher. After defending their PhDs, János Rudan and Zoltán A. Tuza left PPKE for the University of Boston and the University of Stuttgart, respectively. At the same time, new PhD students joined the group: Bernadett Ács and Péter Polcz started their PhD studies under the supervision of Gábor Szederkényi in 2014 and 2016, respectively.

3 Summary of scientific results

During the entire supported period, we achieved the following scientific results within the framework of the research project. The results are grouped according to the work-packages of the original research plan. The five most important publications and the corresponding main results are typed in boldface.

3.1 Solving fundamental problems in the analysis and synthesis of polynomial systems

We proposed a mixed-integer linear programming algorithm capable of determining the minimal deficiency weakly reversible reaction network which admits a mass-action system that is linearly conjugate to a given reaction network [14]. Using this method, it is possible to compute the lower bound for the deficiency of the kinetic representation of a nonnegative polynomial system with a given complex (i.e. monomial) set.

The solution of an important inverse problem was published in [17], where an optimization-based computational method was given to compute deficiency zero realizations of kinetic systems given in the form of ordinary differential equations. Through establishing an equivalent condition for zero deficiency, the problem was traced back to the solution of an appropriately constructed mixed integer linear programming problem. Furthermore, it was shown that weakly reversible deficiency zero realizations can be determined in polynomial time using standard linear programming.

Effective algorithms based on linear programming were proposed in [24] to compute possible structures (realizations) for kinetic systems that enable us to handle realistic, large networks consisting even several thousand complexes. In [25], we presented two new algorithms having polynomial time-complexity to find dynamically equivalent weakly reversible realizations of a given kinetic model. An algorithm for the computation of mass conservative dynamically equivalent chemical reaction network structures was proposed in [23].

In [34], we studied the variety of kinetic representations for systems with complex (chaotic) dynamics. For this, all possible sparse chemical reaction network structures of a classical three-dimensional Lorenz system were computed assuming a given chemical complex set. The resulting structures were briefly analyzed and compared from a structural point of view. The obtained degree of structural non-uniqueness was unexpected, since we found a large number (i.e. several thousands) of mathematically feasible and structurally different sparse kinetic realizations for the same low-dimensional chaotic dynamics.

In [38] we gave an algorithm to determine all possible structurally different linearly conjugate realizations of a given kinetic polynomial system. To the best of our knowledge, this is the first solution in the literature for the exhaustive enumeration of all possible reaction graph structures realizing a given kinetic dynamics. The correctness of the method was proved and it was shown that polynomial time is elapsed between displaying any two consecutive graph structures. A different solution for the same problem was given in [36] generally requiring less optimization steps.

A mixed integer linear programming based computational method was proposed in [30] for the computation of dense and sparse reaction network structures for kinetic polynomial models with uncertain parameters represented as intervals. In [16], a new procedure was given for computing weakly reversible structures of interval-based models. The handled class of uncertainty has been extended to a more general (polytopic) type in [50] and [51].

The set of equilibrium solutions of weakly reversible kinetic models was explored in [1] through a novel factorization of the kernel of the system equations. Using this approach, we proposed a canonical representation of feasible representation, and gave an alternative proof for the well-known Deficiency One Theorem [41].

Two classes of positive polynomial systems, quasi-polynomial (QP) systems and reaction kinetic networks with mass action law (MAL-CRN), are considered in [12]. Using appropriate mathematical transformations, it is possible to establish sufficient structural stability conditions based on the underlying reaction graph properties for a certain subset of QP system models that enable such a construction. In-

spired by previous work on the entropy-functionals for Markov chains [42], and using our previous results on CRN and QP-systems theory, in [10] we characterized MAL-CRNs and QP systems that enable both types of entropy-like Lyapunov functions.

In [8] we considered the problem of verification of large dynamic models of biological systems by presenting syntactical criteria based on biochemical kinetics to ensure the plausibility of a model and the positivity of its solution.

3.2 Identification (and identifiability analysis) of polynomial system models

The structural identifiability analysis was performed on a nonlinear blood glucose dynamics model in [15]. Using the analysis results, we proposed an iterative parameter estimation procedure which improved the model fit compared to earlier literature results.

In the framework of a Fulbright Fellowship, Zoltán A. Tuza actively took part in the laboratory work related to a cell-free transcription/translation process at the Department of Control and Dynamical Systems, California Institute of Technology. The mathematical model of the system suitable for identification was developed and analyzed in [26] and [33], based on the laboratory measurements. The identification process using both both transcriptional and translational data was supported by structural identifiability analysis in [32].

In [37], a graph theory based algorithm was given for computing dense weakly reversible linearly conjugate realizations of kinetic systems on a fixed set of complexes. To prove the correctness of the method, it was shown that weakly reversible linearly conjugate CRN realizations containing the maximal number of directed edges form a unique super-structure among all linearly conjugate weakly reversible realizations. Basically, this result allowed the correctness proof of the algorithm in [38] mentioned above.

In [7], the previously constructed computational framework for analyzing directed graph structures of polynomial kinetic systems was extended to nonnegative models containing rational terms. An algorithm was given to compute a possible (canonical) reaction graph from the kinetic differential equations. It was shown that under some technical assumptions, the so-called dense realization containing the maximal number of reactions, forms a super-structure among all possible reaction-graphs in this case, too. Moreover, optimization based methods were given to find dynamically equivalent realizations with preferred properties. The concept of linear conjugacy [44] was extended to rational kinetic models in [9]. With the extensions in [7] and [9], the problem of structural non-uniqueness becomes computationally tractable for a significantly larger class of dynamic models often used in biochemistry and systems biology.

As we mentioned above, we have initial results on the characterization and distinguishability analysis of polynomial models with uncertainties, that are closely related to practical parameter estimation. The results in [50, 51] can be used in the case when the monomial coefficients are estimated from measurement data, and their uncertainty is characterized e.g. by the corresponding covariance matrix.

An optimization-based method was proposed in [13] for the complexity reduction of kinetic models. With a given detailed kinetic mechanism and measured data of the key species over a finite time horizon, the complexity reduction is formulated in the form of a mixed-integer quadratic optimization problem where the objective function is derived from the parametric sensitivity matrix.

3.3 Controller synthesis for nonnegative polynomial systems

We gave a computational solution to the feedback equivalence problem for kinetic systems in [20]. The task was to construct nonlinear feedback controllers for the stabilization of polynomial systems with linear input structure around a positive equilibrium point. The controller gain matrix and the appropriate graph structure corresponding to the closed loop system are computed in one optimization (linear programming) step. We showed that the robust version of the problem, when a convex set of polynomial systems is given over which a stabilizing controller is searched for, is also solvable with an LP solver. It was also shown that involving new monomials (complexes) into the feedback does not improve the solvability of the problems. Special cases of the controller design were published in [29, 19, 18]. The approach can be considered as 'bio-inspired feedback design' in the sense that the controlled system behaves like a stable biochemical system, even if the original open-loop model is not a biochemical one. The possible recent proof of the Global Attractor Conjecture in [40] probably strengthens the significance of our results as well, since it implies the global stability of complex balanced closed loop systems with a known Lyapunov function.

In [11] we proposed a hierarchically structured model for process systems that gives rise to a distributed controller structure that is in agreement with the traditional hierarchical process control system structure where local controllers are used for mass inventory control and coordinating controllers are used for shaping the system dynamics. The stability of the closed loop system is proved using the theory of linear time varying systems and compartmental models.

In [21] and [22] the stabilizing controller design problem of QP systems is considered with different approaches that in general require the solution of linear or bilinear matrix inequalities.

3.4 Applications and case studies

The algorithms that have been developed in recent years for the computation of kinetic structures with given properties, were published in a freely downloadable software toolbox for the Matlab environment [28], which is regularly updated.

We proposed a linearization-based controller in [35] for a biologically motivated robotic mechanism containing flexor and extensor actuators thus significantly reducing backlash.

The following results offer computational methods for the analysis of complex technological systems exploiting the underlying network structure. The effect of cooperativity in the operation of traffic networks was studied in [6] using the tools of game theory and optimization. It was shown that cooperation may imply both negative and positive externalities in the defined game. Optimization methods were used in [2] for the analysis and economic operation planning of power transmission networks. It was studied, how false information from power generators influences the overall system's behaviour. The same system was theoretically analyzed from the point of view of safety in [4]. The local routing protocol on scale-free networks embedded in a plane was studied in [5]. It was shown that the proposed cooperation model enhances the network performance in the sense of reduced passage time and jamming. A cooperative game-theoretic framework is introduced in [3] to study the behavior of cooperating and competing electrical-energy providers in the wholesale market considering price-preference rational consumers. The constructed model is able to demonstrate some interesting benefits of cooperation as well as the effect of market regulations and asymmetric information on the resulting profits and total social cost.

4 Publication summary

The data of publications already published or accepted in final form and related to the project are summarized in the following table:

Type	*Number*
Journal papers with impact factor	24
Q1 papers[1] (not including D1 papers below)	10
D1 papers[1]	5
Refereed journal papers without impact factor	5
Defended PhD dissertations	2
Conference papers	25
Conference lectures with abstract	3
Book chapters	2
Book	1
Total number of publications	62
Sum of impact factors	54.25

[1]According to MTMT, the official database of Hungarian scientific publications

5 Additional information

In 2013, Gábor Szederkényi obtained the 'Doctor of the Hungarian Academy' scientific title in Engineering Science for his research work closely related to the project. Additionally, the following PhD theses were successfully defended with the support of the project:

- János Rudan (co-supervised). *Optimization-based analysis and control of complex networks with nonlinear dynamics.* Roska Tamás Doctoral School of Science and Engineering, PPKE, 2014 (summa cum laude result)
- Zoltán A. Tuza. *Structural Analysis of Kinetic Systems with Application to Cell-free Expression Systems.* Roska Tamás Doctoral School of Science and Engineering, PPKE, 2015 (summa cum laude result)

Bernadett Ács and György Lipták are expected to submit their PhD theses in 2017. Both of them already have the necessary publications to start the PhD procedure.

Four works related to the project were prepared in the framework of the Scientific Students' Associations (TDK). All of them were recommended to be presented at the National Conference of Scientific Students' Associations (OTDK).

A contract was signed with Elsevier in 2015 for preparing a book [49] to be published in the first half of 2017, where the support of the project will be indicated.

The full texts of the publications supported by the project are available at:
http://daedalus.itk.ppke.hu/wp-content/uploads/2015/05/NF104706_publ_all.html

Selected publications related to the project

[1] **A. A. Alonso and G. Szederkényi. Uniqueness of feasible equilibria for mass action law (MAL) kinetic systems. *Journal of Process Control*, 48:41–71, 2016.**

[2] D. Csercsik. Lying generators: manipulability of centralized payoff mechanisms in electrical energy trade. *Central European Journal of Operations Research*, 24:923–937, 2016.

[3] D. Csercsik. Competition and cooperation in a bidding model of electrical energy trade. *Networks and Spatial Economics*, available in electronic form:1–31, DOI: 10.1007/s11067–015–9310–x, 2016.

[4] D. Csercsik and H. Habis. Cooperation with externalities and uncertainty. *Networks and Spatial Economics*, 15:1–16, 2015.

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