Structural Analysis and Identifiability of Biologically Motivated Complex System Models

Theses of the Ph.D. Dissertation

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1 Introduction

It is known that several dynamical systems possess a graphical representation in which the nodes represent the individual components while edges correspond to the functional relations between components [1, 2, 3]. For example in a gene regulatory network individual genes can be written as nodes and edges represent functional connections between pairs of genes, such as activation, inhibition [6]. The dynamical model of a system may encode the network structure in terms of the parameters of the underlying differential or difference equation system. In the case of linear dynamical systems the state transition (system) matrix encodes the interaction pattern of state variables (individual components) by its non-zero off-diagonal entries [7]. In non-linear dynamical system models the differential equations may also convey information about the underlying network structure of the interacting components, e.g. in the class of kinetic systems it is proven that the model parameters and edges of the respective graph-based representation are quantitatively related to each other [4, 5]. In Figure 1 we illustrate that dynamical model and network-based representation can also be associated to the same biological process. Here it is also illustrated that the differential equation model can be used to derive the graphical representation of the same system.

This thesis is centered around the structural analysis, realizability and identification of various system models. The main motivation of this work is to provide theoretically grounded computational methods for the analysis of biologically motivated system models, but the developed methods and algorithms can also be used for studying various other systems of engineering and physical importance. We study the relationship between the network structure and dynamical behavior of different system models, such as discrete time linear dynamical systems and discrete state chemical reaction networks. We examine whether there exist structurally (topologically) different realizations of the same dynamical system. We wish to provide algorithms capable of determining structurally different realizations of a dynamical system model, assuming that the network-based representation is not unique. We also examine structural identifiability, a quantitative property ensuring parametric uniqueness, which is closely related to structural uniqueness of the underlying network representation. Structural identifiability can help us quantifying network structure related properties of dynamical system models as it is related to the parameterization of the dynamical system model. Since biologically motivated dynamical systems com-

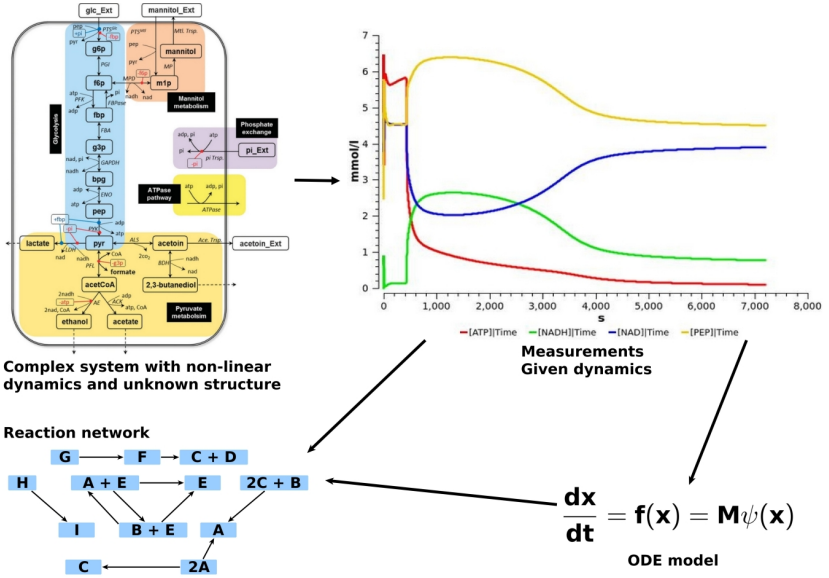

Figure 1: Illustration of different representations of a complex biological system. Based on the observed dynamical behavior of the underlying biological system one can (re)construct both a dynamical system model (ODE model) and a graphical representation (reaction network). It is also indicated by an arrow that the ODE model can be used to write out the graphical representation of the system.

monly involve time delayed terms, we consider structural identifiability of non-linear time delayed system with the assumption that time delays are constant parameters to be identified and we examine the joint identifiability of time delays and ordinary system parameters related to the underlying network structure.

2 Applied tools and methods

2.1 Structural identifiability

Let us consider a continuous single-input single-output (SISO) dynamical system model:

$$M(t, \theta, u, y, p) = 0, \tag{1}$$

where u and y are the input excitation and the respective output of the system. The signals u and y can involve arbitrary number of constant time delays, i.e.

$$\begin{aligned} u &= \left\{u(t), u(t - T_1^u), \dots \ u(t - T_{k_u}^u)\right\}, \\ y &= \left\{y(t), y(t - T_1^y), \dots \ y(t - T_{k_y}^y)\right\}, \end{aligned} \tag{2}$$

with k_u, k_y denoting the number of delayed components with respect to u and y, respectively. θ denotes the set of parameters, which includes the time delays $T_1^u, \dots T_{k_u}^u, T_1^y, \dots T_{k_y}^y \in \mathbb{R}$. θ is assumed to be independent of the initial conditions and the input signals. p denotes the differentiation operator. The system operator $M(.)$ is assumed to be analytic. The analytic assumption on $M(.)$ is not restrictive as it is satisfied by several important systems, e.g. systems of polynomial non-linearities, which are widely used to model physical, chemical and biological systems. $M(.)$ may also involve non-linearities in terms of θ.

The input-output model structure defined by Eq. (1) may be obtained from non-linear state space models by differential algebraic elimination of unobserved state variables [8, 9].

Prior to any parameter estimation procedure performed on a model of Eq. (1), it is useful to examine whether it is theoretically possible to uniquely determine the system parameters.

Definition 1. *The model of Eq. (1) is said to be structurally globally identifiable (s.g.i.), if*

$$y(\theta) = y(\hat{\theta}) \quad \textit{implies} \quad \theta = \hat{\theta} \tag{3}$$

for any measurable value of θ, where $y(\theta)$ denotes the output of the system Eq. (1) parameterized with θ.

If Eq. (3) is valid only in a bounded neighborhood $\mathcal{V}(\theta)$ of θ, then the system is said to be structurally locally identifiable (s.l.i.) around θ. If the system is not identifiable, it is called structurally unidentifiable (s.u.i.). If the identfiability definitions are restricted to a subset $\overline{\theta} \subset \theta$, then the respective parameters $\overline{\theta}$ are said to be s.g.i, s.l.i and s.u.i.

$\diamond$

By involving the time delays in the parameter set θ, we consider structural identifiability jointly for the ordinary system parameters and the time delays.

Structural identifiability is a model property depending on the underlying model structure and possibly on the initial conditions. It is independent of the amount and quality of data obtained during system operation.

2.2 Realization theory of linear time-invariant systems

A discrete time linear dynamical system (LDS) in state space representation is given by a tuple $\Theta = (A, B, C, D)$ and the associated system of difference equations (DEs) is as follows:

$$\begin{aligned} x(k+1) &= Ax(k) + Bu(k), \quad x(0) = x_0, \\ y(k) &= Cx(k) + Du(k), \end{aligned} \tag{4}$$

where $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times m}$, $C \in \mathbb{R}^{p\times n}$ and $D \in \mathbb{R}^{p\times m}$. $x(k) \in \mathbb{R}^n$ denotes the vector of state variables, $u(k) \in \mathbb{R}^m$ and $y(k) \in \mathbb{R}^p$ are the input and the associated output of the system.

Though the solution associated to a particular parametrization Θ and initial condition x_0 is unique, the parameters characterizing the underlying dynamics are not necessarily. There may exist distinct Θ, Θ' parametrizations of the same input-output behavior meaning that the system is not structurally identifiable. In case of structural non-identifiability, in order to quantitatively characterize the system, it is appealing to describe the feasible set of possible parameters. A quantitative characterization of the feasible set may help us finding realizations of favorable properties, such as sparsity.

Definition 2. *It is said that a tuple $\Theta' = (A', B', C', D')$ is a (dynamically equivalent) realization of a LDS of the form Eq. (4) parametrized by Θ, if Θ' provides the same input-output behavior, i.e. $y(k|\Theta') = y(k|\Theta)$ for any admissible input signal $u(k)$, $k \geq 0$.* $\diamond$

By recursively expanding Eq. (4) one can obtain the input-output equations – a common starting point of system identification – of the following form:

$$y(k) = CA^k x(0) + \sum_{i=0}^{k-1} Y_{k-i-1} u(i) + Du(k), \tag{5}$$

where the terms $Y_{k-i-1} = CA^{k-i-1}B$ and D are called the Markov parameters of the systems, which are unique descriptors of the input-output behavior and are invariant to any invertible state transformations. Since Markov parameters are unique regarding the input-output behavior, we can formulate sufficient and necessary condition of dynamical equivalence with respect to the Markov parameters as follows: a tuple $\Theta' = (A', B', C', D')$ is a dynamically equivalent realization of $\mathcal{Y} = \{Y_k = CA^kB\}_{k\geq 0}$, if it satisfies $Y_k = C'A'^kB'$ for $k \geq 0$ and $D' = D$.

A related problem of structural non-identifiability of LDSs is the existence of distinct, A, $A' \in \mathbb{R}^{n\times n}$ state transition matrices having different patterns in their non-zero entries, i.e. structurally different state transition matrices. Assuming that Eq. (4) describes the dynamical behavior of a network-based system, the state transition matrix A can be viewed as a weighted adjacency matrix characterizing the interactions – in terms of both the interaction pattern and the magnitudes – among the components, i.e. state variables. Such a way structural non-uniqueness of a network topology can be recast as an identification problem, namely finding structurally different n-dimensional state space realizations.

2.3 Integer feasibility problem

An Integer Linear Programming (ILP) instance can be formulated as follows:

$$ILP \begin{cases} \min_x \{a^\top x\} \\ subject\ to \\ Ax \leq b \\ x \in \mathbb{Z}^n \end{cases} \tag{6}$$

where x is the n-dimensional vector of decision variables while $a \in \mathbb{Z}^n$, $A \in \mathbb{Z}^{m\times n}$ and $b \in \mathbb{Z}^m$ are fixed coefficients. Generally, the above ILP computational problem is known to be NP-hard that may highly confine our ability to efficiently solve problems of integers in high dimension.

However, if the value of the decision vector that minimizes (or max-

imizes) the prescribed objective function is not important for us, but only the existence of a $x \in \mathbb{Z}^n$ vector satisfying the set of specified constraints, then the problem is called ILP feasibility problem:

$$FP \begin{cases} P = \{x \mid Ax \leq b,\ A \in \mathbb{Z}^{m \times n},\ b \in \mathbb{Z}^m,\ x \in \mathbb{R}^n\} \\ P \cap \mathbb{Z}^n \stackrel{?}{=} \emptyset \end{cases} \tag{7}$$

An ILP feasibility problem – as a decision problem – addresses the question of whether the polytope P contains an integer lattice point, formally $P \cap \mathbb{Z}^n \stackrel{?}{=} \emptyset$. While a FP is also known to be NP-hard, it has well-decoupled time complexity with respect to the number of variables, the number of constraints and the maximum of the absolute values of the entries of A and b. Therefore, a feasibility problem of the form (7) – assuming fixed dimension n – can be decided in polynomial time in the number of constraints m and the maximum of the absolute values of the coefficients A and b by means of the Lenstra algorithm [10, 11]. Moreover, the number of integer lattice points in P can also be enumerated in polynomial time in m and the maximum of the absolute value of the coefficients using Barvinok's integer lattice point counting algorithm [12, 13, 14, 15]. We note that for the Barvinok algorithm there exists an effective implementation called LattE [16].

We also emphasize that special form of an ILP can also provide efficient (polynomial time) relaxation methods: if A and b are of integer entries and A is totally unimodular, then running a linear program (LP) instead of the IP results in an integer solution of the decision variables x, that is the optimum is guaranteed to be integer.

2.4 Discrete state reaction networks

A discrete state Chemical Reaction Network (d-CRN) with n species, m complexes and l reactions is a triple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ so that:

$$\mathcal{S} = \{s_i \mid i = 1, \ldots, n\}$$

$$\mathcal{C} = \{y_j = \sum_{i=1}^{n} \alpha_{ji} s_i \mid s_i \in \mathcal{S},\ \alpha_{ji} \in \mathbb{Z}_{\geq 0},\ i = 1, \ldots, n,\ j = 1, \ldots, m\}$$

$$\mathcal{R} = \{r_v = y_{source(r_v)} \to y_{product(r_v)} \mid y_{source(r_v)}, y_{product(r_v)} \in \mathcal{C}, v = 1, \ldots, l\}$$

where s_i is the i'th species, y_j is the j'th complex and r_v is the v'th reaction of the network. Moreover, α_{ji} is the stoichiometric coefficient of the i'th species in the j'th complex. For a reaction $r_v = y_{source(r_v)} \to$

$y_{product(r_v)}$ of $\mathcal{R}$, $y_{source(r_v)}$ and $y_{product(r_v)}$ are the source complex and the product complex, respectively.

For each complex $y_j \in \mathcal{C},\ j \in \{1, \ldots, m\}$, the stoichiometric coefficients of the species can be represented as a vector of the form:

$$\overline{y}_j = [\alpha_{j1}\ \alpha_{j2}\ \ldots\ \alpha_{jn}]^\top \tag{8}$$

For each $r \in \mathcal{R}$, a reaction vector $r_{ij} \in \mathbb{Z}^n$ can be associated to track the net molecular count changes of the species upon firing the reaction:

$$r_{ij} = \overline{y}_j - \overline{y}_i \tag{9}$$

so that y_j and y_i are the corresponding source and product complexes of r. The notation r_i will be used for denoting both the i'th reaction of the d-CRN and the associated reaction vector, as well. We will also assume that for all the examined d-CRNs a fixed order of the reaction vectors is given, i.e. an order $r_1,\ r_2, \ldots, r_l$ is fixed and $l = |\mathcal{R}|$.

A d-CRN can also be represented by a directed graph $G = G(V, E)$ such that the vertices and edges correspond to the complexes and the reactions, respectively, i.e.:

$$V = \mathcal{C} \tag{10}$$

$$E = \mathcal{R} \tag{11}$$

The direction of the edges are determined by the reactions of $\mathcal{R}$, so that if $y_i \to y_j \in \mathcal{R}$ then there exists an edge $e \in E$ from the vertex representing y_i to the vertex of y_j. For each edge a weight corresponding to the reaction rate constant (also called intensity or propensity) corresponding to the respective reaction can also be associated.

Beyond the above representations it is also possible to describe a d-CRN in an algebraic way by means of its unique stoichiometric matrix.

Definition 3. *Let us consider a d-CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. The stoichiometric matrix $\Gamma \in \mathbb{Z}^{n \times l}$ of $\mathcal{N}$ is defined as*

$$\Gamma = [r_1\ \ldots\ r_l] \tag{12}$$

$\diamond$

The entry $[\Gamma]_{ij}$ encodes the net molecule count change on species s_i upon occuring rection r_j.

The molecular count of each species of a d-CRN at any time $t \geq 0$ is given by its state vector $X(t) \in \mathbb{Z}^n_{\geq 0}$ and the time evolution of the system is characterized by the following **discrete state equation**:

$$X(t) = X(0) + \Gamma N(t) \tag{13}$$

where $X(0)$ is the state vector belonging to the initial time instant and $N(t) = [N_1(t), N_2(t), \ ... \ N_l(t)]^\top \in \mathbb{Z}^l_{\geq 0}$ such that $N_k(t) \in \mathbb{Z}_{\geq 0}$ stores the number of occurrences of the k'th reaction up to time t. We note that $N(t)$ is typically modeled as some point process [18, 19].

The above described formal model of d-CRNs is closely related to theoretical computer science, as it is equivalent to Petri nets and Vector Addition Systems with States (VASS).

3 New scientific contributions and thesis points

Thesis I. I proposed a novel method for testing structural identifiability in time delayed non-linear dynamical system models [J1].

I applied the Volterra series representation of single input single output nonlinear dynamical systems with constant time delays to give sufficient conditions for the joint structural identifiability of system parameters and delays. Using the frequency domain representation of the Volterra kernels in the form of generalized frequency response functions (GFRFs), I showed that the unique solution of a set of appropriately constructed nonlinear algebraic equations implies the joint structural identifiability of the delayed model.

Thesis II. I proved that the set of feasible state transition matrices of a discrete time linear dynamical system (LDS) is convex, assuming that the matrices B, C and D are fixed. Making use of the convexity of feasible system matrices I obtained convex optimization based algorithm for finding different dynamically equivalent n-order realizations with theoretical guarantee [J2].

I inductively proved that the set of feasible system (state transition) matrices of a discrete time LDS is convex, assuming that the matrices B, C and D are fixed and C is invertible. I showed that the convexity of the set of system matrices can be used to determine different dynamically equivalent realizations of the system $\Theta = (A, B, C, D)$. I developed new algorithms from the theory of kinetic systems (mass action law reaction networks) to find structurally different realizations of a discrete time LDS.

Thesis III. I developed a computational method for deciding reachability and coverability problems in discrete state chemical reaction networks with novel upper bound on the length of cycle-free state transition sequences [J3].

I employed an integer programming feasibility based computational approach for deciding the reachability problem of discrete state chemical reaction networks with novel upper bound on the number of decision variables. The method relies on the Lenstra algorithm capable of deciding integer programming feasibility problems in polynomial time, assuming fixed dimension in terms of the decision variables. I gave new upper bounds for the maximal length of cycle-free state transition sequences between any pair of initial and target states in subconservative reaction network structures. Considering subconservative reaction networks of state space dimension smaller than or equal to two, I proved that the reachability property is equivalent to the non-negative integer solution of the associated reaction network state equation.

Thesis IV. I gave network topology related conditions under which the d-CRN reachability relation for any pair of initial and target states is equivalent to the existence of a non-negative integer solution of the d-CRN state equation. This way an Integer Programming feasibility problem is obtained. I proved that under the same conditions, the resulting IP feasibility problem can be relaxed to a Linear Problem with guaranteed polynomial time complexity [J4, J7].

1. It is known that a subconservative network has bounded reachable state space, while that of a superconservative one is unbounded. I gave a proof that the reachability problem of superconservative reaction networks is equivalent to the reachability problem of subconservative reaction networks. The practical importance of the relation between the sub-and superconservative reachability is that the reachability problem of a superconservative system – with state space guaranteed to be unbounded – can be traced back to that of a subconservative network having bounded state space. In the classes of sub-and superconservative reaction networks I gave conditions for network structure under which the reachability property is equivalent to the existence of a non-negative integer solution of the associated state equation characterizing the time evolution of the chemical reaction networks. The equivalence, using the Lenstra algorithm, implies an

integer programming based feasibility approach [J4].

2. I showed that the stoichiometric matrix – under the same conditions as IV/1 – is totally unimodular. It is known that an integer program with totally unimodular constraint matrix can be relaxed to a linear program. This way I obtained a linear program with guaranteed polynomial time complexity for the reachability problem [J7].

4 Application possibilities

The main motivation behind the methods and computational procedures proposed in this thesis is to study the dynamical and structural properties in biologically motivated system models. An important aspect of this work is to quantitatively examine the relationship between dynamical (differential/difference equation-based) and structural (topological, graph-based) properties of system models. The main application is the analysis of biological systems as they are commonly represented by both dynamical equations and network representations. The identifiability approach of Thesis I can be used as a prior step to any parameter estimation procedure performed on delayed biological processes. The realizability results proposed in Thesis II are also related to structural identifiability. Clearly, the existence of structurally different dynamically equivalent realizations of a discrete time LDS implies local structural unidentifiability. Furthermore, determining structurally different realizations can provide means for synthetic biology, it may possible to find the most suitable (biochemically feasible) network structure to implement a prescribed molecular functionality. The novel results obtained for d-CRNs (Thesis III, Thesis IV) can be used to computationally examine the properties of molecular circuits of low molecular multiplicity and epidemiological process of low population size. Synthetic biology is also a possible application field as the gate-implementability problem is known to be equivalent to the d-CRN reachability problem [20]. Since the formal model of d-CRNs considered in this thesis is equivalent to Petri nets and VASS, the reachability results can also be applied to solve problems in theoretical computer science and related applications, such as verification of distributed, concurrent and parallel systems.

The following research directions are listed for future work:

1. Structural identifiability of delayed systems: we used the GFRFs

to obtain sufficient conditions for joint structural identifiability analysis of ordinary model parameters and constant time delays. A possible extension is to examine whether there exists an upper bound (depending on the model structure) on the minimal number of distinct GFRFs to be computed for structural identifiability testing. Clearly, by obtaining an upper bound with theoretical guarantees would imply necessary and sufficient condition of structural identifiability in non-linear time delayed systems. We also note that there exists recursive formula for computing the GFRFs [21]. A recursive formula could provide means for examining the minimal number of GFRFs required for obtaining necessary and sufficient condition of structural identifiability.

2. Finding all structurally different realizations of discrete time LDSs: extending the proposed computational methods to find all the structurally different realizations of discrete time LDSs with theoretical guarantee. The embedding eigenvalue assignment procedure employed to reduce the number of non-zero Markov parameters is useful for determining structurally different realizations, but we have no theoretical guarantee that this way all the structurally different realizations can be computed. An interesting way for extending the proposed work is to examine whether it is possible to substitute the embedding eigenvalue assignment procedure with another method for which the obtained compressed set of Markov parameters is proven to be useful for finding all the structurally different realizations of the original LDS.

3. Extension of the reachability results to more general classes of d-CRN structures: the network structure-related conditions for the equivalence of d-CRN reachability and the existence of a non-negative integer solution of the respective d-CRN state equation is restricted to certain network structure classes. An interesting way for further research is to examine whether it is possible to extend the obtained reachability result to a wider class of d-CRN structures by means of networks structure transformations.

The Author's journal papers with impact factor

[J1] G. Szlobodnyik, G. Szederkényi, "Structural Identifiability Analysis of Non-linear Time Delayed Systems with Generalized Fre-

quency Response Functions", Kybernetika, Vol. 57(6), pp. 939-957., 2021., **Impact Factor: 0.892**

[J2] G. Szlobodnyik, G. Szederkényi, "Computing Different Realizations of Linear Dynamical Systems with Embedding Eigenvalue Assignment", Acta Cybernetica, Vol. 25(3), pp. 585-611., 2022., **Impact Factor: 0.38**

[J3] G. Szlobodnyik, G. Szederkényi, M. Johnston, "Reachability analysis of subconservative discrete chemical reaction networks", MATCH Commun. Math. Comput. Chem., Vol. 81(3), pp. 705-736., 2019., **Impact Factor: 2.126**

[J4] G. Szlobodnyik, G. Szederkenyi, "Reachability Analysis of Low-Order Discrete State Reaction Networks Obeying Conservation Laws", Complexity, Vol. 2019, Article ID 1035974, 13 pages, 2019., **Impact Factor: 2.591**

[J5] B. Ács, G. Szlobodnyik, and G. Szederkényi, "A computational approach to the structural analysis of uncertain kinetic systems," Computer Physics Communications, Vol. 228, pp. 83–95, 2018., **Impact Factor: 3.309**

[J6] G. Szlobodnyik, L. Farkas, "Data Augmentation by Guided Deep Interpolation", Applied Soft Computing, Vol. 111., 2021., **Impact Factor: 6.725**

[J7] G. Szlobodnyik, G. Szederkényi, "Polynomial Time Reachability Analysis in Discrete State Chemical Reaction Networks Obeying Conservation Laws", submitted to MATCH Commun. Math. Comput. Chem.

The Author's other refereed journal papers

[J8] G. Szederkenyi, B. Acs, G. Szlobodnyik, "Structural analysis of kinetic systems with uncertain parameters", IFAC-PapersOnLine, Vol. 49., Issue 24., 2016, pp. 24-27.

[J9] M. Vághy, G. Szlobodnyik, G. Szederkenyi, "Kinetic realization of delayed polynomial dynamical models", IFAC-PapersOnLine, Vol. 52(7), pp. 45-50., 2019.

The Author's conference publications

[C1] G. Szlobodnyik, "Extracting Activity Patterns from Altering Biological Networks: A Sparse Autoencoder Approach", IEEE 32nd International Symposium on Computer-Based Medical Systems (CBMS), 2019.

[C2] G. Szlobodnyik, G. Szederkényi, "Reachability analysis of discrete state epidemiological models", In: H., Cherifi et al. - Complex Networks 2018. The 7th International Conference on Complex Networks and Their Applications. Book of Abstracts Cambridge: University of Cambridge, pp. 119-121., 3 p., 2018.

[C3] G. Szlobodnyik, G. Szederkényi, "Reachability analysis of discrete state chemical reaction networks obeying conservation laws", Bioinspired Analysis of Dynamical Systems and Protein Network Analysis, Esztergom, 2019.

References

[1] E. D. Kolaczyk, "Statistical Analysis of Network Data. Methods and Models", Springer, New York, 2009.

[2] L. Chuang, et. al. "Computational network biology: Data, models, and applications", Physics Reports, Vol. 846., pp. 1-66., 2020.

[3] E. Sontag, A Kiyatkin, B.N. Kholodenko, "Inferring dynamic architecture of cellular networks using time series of gene expression, protein and metabolite data", Bioinformatics, Vol. 20(12), pp. 1877-1886., 2004.

[4] G. Szederkényi, J. R. Banga, A. A. Alonso. "Inference of complex biological networks: distinguishability issues and optimization-based solutions", BMC systems biology, Vol. 5(1), 177., 2011.

[5] G. Szederkényi, A. Magyar, K. Hangos, "Analysis and control of polynomial dynamic modelswith biological applications", New York, NY: Academic Press, 2018.

[6] U. Alon, "An Introduction to Systems Biology: Design Principles of Biological Circuits", Chapman & Hall, CRC, 2007.

[7] H. G. Frøysa, H. J. Skaug, G. Alendal, "Experimental design for parameter estimation in steady-state linear models of metabolic networks", Mathematical Biosciences, Vol. 319., 108291., 2020.

[8] L. Ljung, T. Glad, "On global identifiability for arbitrary model parametrizations", Automatica, Vol. 30(2), pp. 265-276.,

[9] T. Glad, "Nonlinear state space and input-output descriptions using differential polynomials", In Descusse, J., M. Fliess, A. Isidori and D. Leborgne (Eds), Lecture Notes in Control and Information Science, Vol. 122., Springer Berlin.

[10] H. W. Lenstra, "Integer Programming with a Fixed Number of Variables", Math. Oper. Res., 8, pp. 538–548., 1983.

[11] M. Grötschel, L. Lovász, A. Schrijver, "Geometric Algorithms and Combinatorial Optimization", Springer-Verlag, Algorithms and Combinatorics 2, 1988.

[12] A. J. Barvinok, "A Polynomial Time Algorithm for Counting Integral Points in Polyhedra When the Dimension is Fixed", Math. Oper. Res., 19., pp. 769–779., 1994.

[13] M. Köppe, "A primal Barvinok algorithm based on irrational decompositions", SIAM Journal on Discrete Mathematics, Vol. 21(1), pp. 220–236., 2007.

[14] S. Verdoolaege, et. al., "Counting Integer Points in Parametric Polytopes Using Barvinok's Rational Functions", Algorithmica, Vol. 48(1), pp. 37–66., 2007.

[15] J. B. Lasserre, "Integer programming, Barvinok's counting algorithm and Gomory relaxations", Operations Research Letters, Vol. 32(2), pp. 133-137., 2004.

[16] J. A. De Loera et. al., "Effective lattice point counting in rational convex polytopes", J. Symb. Comput., 38., pp. 273–1302., 2004.

[17] T. G. Kurtz, "The Relationship between Stochastic and Deterministic Models for Chemical Reactions", The Journal of Chemical Physics, 57(7), 1972., 2976-2978.

[18] D. F. Anderson et. al., "Stochastic analysis of chemical reaction networks with absolute concentration robustness", J. R. Soc. Interface, 11(90), 2014.

[19] D. F. Anderson, T. G. Kurtz, "Continuous time Markov chain models for chemical reaction networks", In: H. Koeppl et. al. (eds) "Design and analysis of biomolecular circuits: engineering approaches to systems and synthetic biology", Springer, Berlin, 2011., 3–42.

[20] A. Condon, et. al., eds. "Algorithmic Bioprocesses", Springer Science and Business Media, 2009.

[21] H. Zhang, S. A. Billings, Q. M. Zhu, "Frequency response functions for nonlinear rational models", International Journal of Control, Vol. 61., pp. 1073–1097., 1995.