

REALIZATION AND CONTROL PROBLEMS FOR BIOCHEMICAL REACTION NETWORKS

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Abstract. Several problems of realization and control for rational positive systems are formulated which are motivated by problems of cell biology and by rational drug design. The systems are realistic models of biochemical reaction networks.

Key Words. Cell biology, biochemical reaction networks, rational positive systems, realization, control.

1. INTRODUCTION

How can control and system theory effectively contribute to cell biology? Now that the genome is known for many living organisms the next major challenge in biology is to understand how a cell regulates its chemical network. Cell biology is part of the *life sciences*, the currently used term for biology and medicine.

The approaches of cell biology so far are primarily descriptive. There is an extensive literature on how the cell consists of molecules and the reactions of these molecules. This is necessary basic knowledge. Most of the literature on regulation of biochemical reactions/systems focusses attention on the influence by certain molecules or chemical substances on the rate of one particular reaction. *Systems biology* is the approach in which one considers the dynamic behavior of a network of chemical substances in a cell which are in direct interaction with each other, rather than one particular chemical substance. Within systems biology there is both attention for static properties like steady states and sensitivity coefficients, see [10], and for dynamic behavior such as oscillations, see [11]. However, the problems and questions studied in control and system theory are not addressed in biology. In particular, problems involving dynamic behavior and its control are not addressed, attention in systems biology is often restricted to a steady state analysis. Several problems and questions of control and system theory are therefore discussed below. These problems are part of the research program of the author and are carried out in cooperation with coworkers.

The motivation for research into cell biology with

control and system theory, is to increase the understanding of the functioning of the cell, to aid in rational drug design, and to aid biotechnology. Rational drug design refers to the procedure by which medical drugs are determined. This includes the formulation of a realistic mathematical model, the determination of enzymes which to inhibit, the determination of chemical substances which can inhibit an enzyme, the determination of possible side effects, and the testing of the drug. Biotechnology aims at improving the production, possibly with living organisms, of particular chemical substances. The expectation is that medicine and biotechnology are to benefit considerable from a research effort with control and system theory.

2. EXAMPLES

For the dynamic behavior of unicellular organisms, plants, animals, and humans, or of parts of these organisms, biologists and mathematical biologists have formulated mathematical models in the form of differential equations or dynamic systems.

A particular example currently studied by the author and co-workers is the glycolysis in the unicellular organism *Trypanosoma brucei*. The mathematical model may be found in the publications [4, 12]. The dynamic system consists of a system of differential equations with each component of the vector field being a sum of rational functions, of which the numerator and the denominator polynomial each have positive coefficients. Such a system will be called a *rational positive system*. The rationality of the system is realistic because its dynamic behavior exhibits the

saturation of concentrations typically found in living organisms. An alternative model for biochemical reaction networks is a polynomial positive system, see for example [17].

Further study is required into a classification of dynamic systems for biochemical reaction networks and into the necessary conditions for such dynamic systems like mass conservation or dissipation. Biologically interesting are also dynamic systems based on non-mass action kinetics and on statistical thermodynamics.

Books with information on biology and on cell biology include [1, 5]. Books on enzyme kinetics include [7, 10, 16]. Classes of dynamic systems which model biochemical reaction networks based on mass action kinetics are described in [8, 9, 13].

3. SYSTEMS

A *rational positive system for a cell reaction network* is defined as a dynamical system, as understood in system theory, defined by the differential equation

$$\dot{x}(t) = N \text{Diag}(r(x(t), x_{ex}))u(t) + Bv(t), \quad (1)$$

$$x(t_0) = x_0, \text{ or, per component } i \in \mathbb{Z}_n,$$

$$\dot{x}_i(t) = \sum_{j=1}^m (N_{i,j}^+ - N_{i,j}^-) r_j(x(t), x_{ex}(t)) u_j(t) + B_i v(t) \quad (2)$$

$$= f_i(x(t), x_{ex}, v(t), u(t)), \quad x_i(t_0) = x_{i,0},$$

$$z(t) = H \text{Diag}(r(x(t), x_{ex}))u(t), \quad (3)$$

with the definitions,

$$n, m \in \mathbb{Z}_+, \quad n_v, n_{ex}, n_z \in \mathbb{N},$$

$$X = \mathbb{R}_+^n, \text{ the state set,}$$

$$X_{ex} = \mathbb{R}_+^{n_{ex}}, \text{ the set of external concentrations,}$$

$$V = \mathbb{R}_+^{n_v}, \text{ the set of the external input rate,}$$

$$U = \mathbb{R}_+^m, \text{ the input set of enzyme concentrations,}$$

$$N \in \mathbb{Z}^{n \times m}$$

called the *stoichiometric matrix*,
with decomposition,
 $N = N^+ - N^-, \quad N^+, N^- \in \mathbb{N}^{n \times m},$
 $u : T \rightarrow U, \text{ an input function,}$
representing the enzyme concentration,
 $z : T \rightarrow \mathbb{R}^{n_z},$
the outflow rate of the system,
 $r : X \times X_{ex} \rightarrow \mathbb{R}^m, \quad \forall j \in \mathbb{Z}_m,$

$$r_j(x, x_{ex}) = \frac{p_j^+(x, x_{ex})}{q_j(x, x_{ex})} - \frac{p_j^-(x, x_{ex})}{q_j(x, x_{ex})},$$

$$(p^+/q), (p^-/q) \in \mathbb{R}_{+,s}(x, x_{ex}).$$

4. PROBLEMS AND APPROACHES

In this section several problems of control and system theory are described which are of interest to the understanding of biochemical reaction networks and to control for rational drug design and for biotechnology.

The first problem area is decomposition of dynamic systems for biochemical reaction networks. As is well known from linear positive systems and from positive matrices, any linear positive system can be associated with a directed graph. The same association can be formulated for nonlinear positive systems. One then distinguishes strongly connected classes, also called irreducible classes, and their relation. Thus, a positive system can be decomposed into a finite set of irreducible subsystems which are related by a directed graph. In the context of control and system theory one studies the graph of a positive system with inputs and outputs, which usually neither researchers in positive matrices nor researchers in biology do. The reader should also note that the graphs displayed in papers by biologists cover only part of a biochemical reaction network and are almost always incomplete. The full network is much more dense than the one displayed. The graph of a network is used in every problem described below. An entry into the literature on graphs and dynamic systems are the books by K. Murota, [14, 15].

The second problem area is that of dynamical system properties of positive systems. Though this is only of indirect interest to control and system theory, it is useful in the study of examples. Questions to be investigated include: (1) Does there exist a steady state for a particular concentration of enzyme inputs? (2) Is a steady state unique? (3) How to compute a steady state? It is clear that the decomposition of the network as described above in Problem Area one has to be used in the study of this problem.

The third problem area is realization of subclasses of positive systems. Problems and questions are (1) to determine necessary and sufficient conditions on the observed functions for the existence of a realization in the particular class of systems considered; (2) to formulate necessary and sufficient conditions for minimality of the class of systems considered; (3) to classify all minimal realizations. These problems will be useful for determining the essential properties of the class of systems considered, for the problem of identifiability, for the existence of control laws because of the concept of controllability, and for the existence of observers because of the concept of observability. A first approach to these problems is stated in the paper [21]. The realization problem for linear positive systems has been discussed by many authors, see [18, 19] for an entry into the literature.

A fourth problem area is system reduction of positive systems. Realistic models of biochemical reaction networks are large. The number of enzymes in small

organisms is of the order of a few 100 to 1000, in *E. coli* it is about 6000, and in humans possibly 25.000. The number of chemical substances, which is directly related to the dimension of the state space of a dynamic system, is somewhat less than the number of enzymes. Thus a realistic model of a full network is of the order of a few hundred to about 20.000. It is likely that through evolution, organisms have developed a structure for the control of these reaction networks. Because of the many feedback loops, the conjecture is that the dynamics can be simplified considerably. The problem is thus how to reduce a large-order positive systems to a low-order positive systems such that the input-output behaviors of both systems are close in a to-be-specified norm. An investigation on this problem has been started at CWI and the Vrije Universiteit for this problem. The approach is difficult because the systems both have to be positive, including positivity of the input and output functions.

The fifth problem area is the construction of observers. It is a fact that in general one cannot measure directly the actual concentrations in a cell. But experiments in biochemistry are carried out in artificial environments. Biochemists are familiar with the concept of system identification but use different terms. A source on this is [7, Ch. 3]. Experiments can also be carried out with groups of cells. For the system identification procedure it is necessary to have an observer available. A positive observer for a positive system is a dynamic system which is a positive system, which has zero-error dynamics, and for which the estimation error is globally asymptotically stable. The main problems are (1) to formulate a concept of detectability; (2) to construct the positive observer; and (3) to prove global asymptotic stability. This program has been carried out for linear positive systems, see [20], and for Horn-Jackson networks of polynomial type, [6]. More research is required on the characterization of detectability and on the construction of observers of rational positive systems.

The sixth problem area is control of positive systems. The first problem is the change of the underlying graph of the system due to feedback. A characterization is needed of the class of control laws which, when applied to the system, leave the graph of the system unchanged or invariant. Next a characterization is needed of the graphs which one can obtain after feedback, in case there is no invariance of the graph. A second problem is to determine which components of the input to put to zero so as to achieve a particular zero controlled-output component. A third problem is noninteracting control. A biochemical reaction network can be very large and with many inputs and outputs. Yet the cell succeeds in using the network effectively to carry out its functions. If the outflow of a particular chemical substance is to be increased or decreased then the cell increases a particular set of enzymes. Since a cell cannot reason, the information on which set of enzymes to increase must

be encoded in the genome. For researchers of control theory it is therefore a problem of reverse engineering to find out which inputs, enzyme concentrations, effect which controlled-outputs. This corresponds to the analysis of a closed-loop system after a noninteracting control problem has been solved, also called a decoupling problem. A fourth problem is to discover the control objectives which the cell strives for based on the current functioning of the cell. This may help in the understanding of the noninteracting control and the robustness of the network. That the cell functions robustly with respect to many variations in inputs and parameter values has been observed. But a quantitative measure of robustness can probably be obtained from the dynamical system and calculations.

5. TOWARDS A CONTROL AND SYSTEM THEORY FOR POSITIVE SYSTEMS

The aim of the author is to develop control and system theory for several subclasses of positive systems. A sketch of the theory follows.

The system theory of a subclass of positive system requires the concepts of reachability (controllability) and observability. The realization problem for each subclass of positive systems requires attention. For linear positive systems progress on the realization problem has been made but the characterization of minimality is still missing, see [19].

Positive systems admit a decomposition in terms of irreducible subsystems which ordinary linear systems do not possess. The decomposition and the underlying graph play a major role in the formulation of system theoretic concepts. The order relation of states is a major concept for the study of dynamic system properties like existence of steady states and global asymptotic stability, [2, 3].

Control theory of subclasses of positive system requires a synthesis procedure. Necessary and sufficient conditions for the existence of control laws such that the closed-loop system attains prespecified control objectives, requires the concept of reachability and stabilizability. Similarly, the existence of observers requires the concepts of observability and detectability.

6. CONCLUDING REMARKS

The main contribution of this paper is to list problems of control and system theory which need attention to advance the state of knowledge for control of biochemical reaction networks: (1) Decompositions of biochemical reaction networks as dynamic systems with inputs and outputs. (2) Dynamical system properties. (3) Realization of subclasses of positive systems. (4) System reduction of positive systems. (5) Construction of observers for positive systems. (6) Control of positive systems, including determination of zeroing particular controlled-output components and noninteracting control. Research is in progress on many

of these problems but much remains to be done.

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