CONTROL OF NONLINEAR SYSTEMS

Eduardo D. Sontag
SYCON – Rutgers Center for Systems and Control
Department of Mathematics, Rutgers University
New Brunswick, NJ 08903
sontag@control.rutgers.edu
http://www.math.rutgers.edu/~sontag

ABSTRACT

This small grant provided a semester of graduate student support for the further development of the theory of monotone systems. Systems with inputs and outputs was introduced in recent work by the PI, and this extension allows the modeling of many basic components of complex biological signaling pathways. Extensions to deal with the effect of delays and diffusion terms were studied in this project.

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14. ABSTRACT

This Final Report summarizes accomplishments of the grant research. The work focuses on the mathematical foundations of nonlinear systems analysis and feedback control. The emphasis is on monotone input/output systems, and underlying new theoretical questions arising from the study of biomolecular cellular mechanisms, seen as a source of inspiration for novel sensor, actuation, and control architectures.

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1 Introduction

This project concerns mathematical foundations of nonlinear systems analysis and feedback control, with a focus on monotone systems. This small grant provided one semester of graduate student support (Fall 2004). We describe the basic background in the rest of the report. Papers reporting on the results of this research are in preparation for journal submission.

2 Monotone Control Systems

Small-gain theorems are routinely used in control theory in order to guarantee stability. However, classical small-gain theorems cannot be used, at least in any obvious "off the shelf" fashion, if the location of the closed-loop steady-states depends on the precise gains of the feedback law (or if there are multiple such states). Negative (or "inhibitory") feedback in molecular biology (similar situations arise in engineering) is almost never of the form $u = -k(x - x^*)$, which would preserve the equilibrium x^*. Rather, it may take a form such as "$1/(k + x)$" so that the closed-loop steady state depends on the actual value of the parameter k. For example, the equilibrium $x = 4$ in $\dot{x} = -x + 4$ gets moved to $x = 1$ under the inhibitory feedback resulting in $\dot{x} = -x + 4/(3 + x)$. In previous work,* we introduced the notions of *asymptotic amplitude* for signals, and associated *Cauchy gains* for input/output systems, and provided a Lyapunov-like characterization which allows the estimation of gains for state-space systems. We then stated a small-gain theorem expressed in terms of Cauchy gains, and used these results to obtain a very tight estimate of the onset of Hopf bifurcations in the biological MAPK model. The results on Cauchy gains allowed us to deal with a restricted type of MAPK cascade (single-phosphorylation at each stage). However, a fuller, and more realistic, model was harder to analyze. The breakthrough came when we realized (with David Angeli) that each subsystem in the cascade is a *monotone system with inputs*, with respect to an appropriate partial order in states.

Monotone systems are dynamical systems $\dot{x} = f(x)$ for which trajectories preserve a partial ordering in $\mathbb{R}^n$. They include the subclass of *cooperative* systems, for which different state variables reinforce each other (positive feedback) as well as certain more general systems in which each pair of variables may affect each other in either positive or negative, or even mixed, forms. Among the classical references in this area are the textbook by Smith and major papers by Hirsh and Smale. The concept of monotone system had been traditionally defined only for systems with no external inputs (nor outputs). They have played a central role in control theory, since important aspects of the analysis of the Riccati matrix equations of filtering and optimal control can be formulated in terms of monotone flows, as discussed in Reid's classical work.

The first objective of our previously published papers was to extend the notion of monotone systems to *systems with inputs and outputs*, and then to provide easily verifiable infinitesimal characterizations of monotonicity (expressed in nonsmooth analysis terms, via Bouligand tangent cones). This is by no means a purely academic exercise, but it is a necessary first step

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*A detailed list of references was provided in the Final report for F49620-01-1-0063. An exposition of much of this work, including references to the original research papers, can be found in: Eduardo D. Sontag, "Some new directions in control theory inspired by systems biology," *Systems Biology* 1(2004): 9–18.

in the study of interconnections, especially including feedback loops, built up out of monotone components.

We also introduced the notion of steady-state response for every constant input, or static input/output characteristic, and showed, in particular, that such responses are always well-defined for the basic MAPK subsystems, no matter what are the form of the kinetics or the numerical values of parameters. (This fact requires a careful proof –even if biologists always assume it to be true– as it amounts to proving a global stability result for a nonlinear system.) Cascades of monotone systems are easily shown to be monotone, and steady-state responses also behave well under composition, but negative feedback typically destroys the monotonicity of the original flow, and also potentially destabilizes the resulting closed-loop system. The main result in our Trans Autom Control 2002 paper with Angeli was a small-gain theorem for negative feedback loops involving monotone systems with well-defined i/o characteristics, and applied, in particular, to MAPK cascades. Susequently, we presented in other papers a variant of the small-gain theorem suitable for "almost global" (meaning that the domain of attraction is open dense) stability of monotone control systems which have well-defined "almost" i/o characteristics. and applied to presented small-gain theorems guaranteeing the lack of oscillatory or more complicated behavior in a large class of Lotka-Volterra systems with predator-prey interactions as well as chemostats, which describe the interaction between microbial species which are competing for a single nutrient. For chemostats, a well-known fact is the so-called "competitive exclusion principle," which states roughly that in the long run only one of the species survives. This is in contrast to what is observed in nature, where several species seem to coexist. This discrepancy has lead many researchers to propose modifications to the model that bring theory and practice in better accordance. In particular, in later work with deLeenheer we studied the effect of crowding, and for such modified systems, presented an easily checkable condition on coefficients which guarantees the existence of a global attractor.

A very different line of research deals with *positive* feedback loops. Starting with systems which have a well-defined i/o characteristic and are also monotone, positive feedback preserves monotonicity but, in general, introduces multiple steady states. Multi-stationarity by positive feedback is a mechanism that has been long proposed as a molecular-biological basis for cell differentiation, development, and periodic behavior described by relaxation oscillations, since the classic work by Delbrück, who suggested in 1948 that multi-stability could explain cell differentiation, and continuing to the present, in work in the literature. Using the theory of strictly monotone systems, together with basic facts about system gains, we were able with Angeli (2003 Syst Ctr Lett paper) to show that the location and, more importantly, stability properties of steady states, can be determined easily from a planar plot, and a theorem guarantees that every trajectory, except at most for a set of measure zero of initial conditions, converges to one of the steady states so identified. We also gave a discussion of hysteresis behavior, as well as a subtle counterexample showing that monotonicity plays a crucial role, and cannot be dispensed with as an assumption. In a Proc Natl Acad Sci 2004 paper, we explained the application to biological models, as well as graphical tests for monotonicity.

3 Open problems addressed in this research, and preliminary results

There are many open problems yet to be studied for these small-gain theorems. Is not always simple to verify in terms of parameters of the original system (indeed, must of the work in these applications went toward obtaining such estimates). A more systematic manner of verification, especially for systems which are only monotone after reduction by conserved quantities (e.g., due to stoichiometric constraints, and are hence only "implicitly" monotone) is very much needed in order to deal with large-scale realistic examples in signaling networks. A 2004 Conf Dec and Control paper by the PI dealt with this issue (that work was not supported by this grant, which only provided a semester of graduate student support, but the PI's students Enciso and Wang have now continued this work and papers are being prepared for submission).

As mentioned earlier, another line of research on monotone systems deals with *positive* feedback loops. For systems with a well-defined i/o characteristic and monotone, positive feedback preserves monotonicity but, in general, introduces multiple steady states. Multi-stationarity by positive feedback is a mechanism that has been long proposed as a molecular-biological basis for cell differentiation, development, and periodic behavior described by relaxation oscillations. This is of interest not only in biology, but is one of the basic mechanisms for oscillations in systems of engineering interest as well. We showed in our previous work that the location and stability properties of steady states can be easily determined from a planar plot, and gave a theorem guaranteeing that generically trajectories converge to one of these steady states. In work with graduate student Enciso, we have now obtained broad generalizations of these ideas, extending them to the multiple i/o case.

Finally, we were able, with graduate students Wang and Enciso to extend many of our results on small-gain and multistability of monotone i/o systems to systems with delays and with diffusion. Clearly, both delays (in transport or communication) and spatial effects are ubiquitous in biological as well as in many engineering systems. Several papers are in preparation.