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DYNAMICAL SYSTEMS AND CONTROL THEORY INSPIRED BY MOLECULAR BIOLOGY

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14. ABSTRACT

This project aims to develop new concepts, theory, and algorithms for control and signal processing using ideas inspired by molecular systems biology. Cell biology provides a wide repertoire of systems that are strongly fault-tolerant, nonlinear, feedback-rich, and truly hybrid, while making effective use of highly heterogeneous sensing and actuation channels. Advances in genomic/proteomics and molecular systems biology research are continually adding detailed knowledge of such systems' architecture and operation, thus offering, in principle, a powerful source of inspiration for innovative solutions to problems of control and communication, sensor and actuator design, and systems integration.

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DYNAMICAL SYSTEMS AND CONTROL THEORY
INSPIRED BY MOLECULAR BIOLOGY

AFOSR FA9550-11-1-0247

Final Performance Report, 08/15/2013-08/14/2014

Eduardo Sontag, Department of Mathematics, Rutgers University

Objectives: This ultimate aim of our work is to develop new concepts, theory, and algorithms for control and signal processing using ideas inspired by molecular systems biology. Cell biology provides a wide repertoire of systems that are strongly fault-tolerant, nonlinear, feedback-rich, and truly hybrid, while making effective use of highly heterogeneous sensing and actuation channels. Advances in genomic/proteomics and molecular systems biology research are continually adding detailed knowledge of such systems' architecture and operation, thus offering, in principle, a powerful source of inspiration for innovative solutions to problems of control and communication, sensor and actuator design, and systems integration.

Status/Progress:

During the final year of this grant, the PI and his collaborators largely completed the research started in the first year, resulting in significant new results, which were documented in submitted papers, on the formulation of an approach to stochastic monotone control systems and on the development and application of tools including contraction theory to the study of stability. The effort during the grant period involved the PI as well as graduate students Zahra Aminzare, Maja Skataric, and Michael de Freitas, the latter two of whom completed their Ph.D. theses in 2014. The thesis by de Freitas completed the work started early on in this project and provided a general small-gain theorem for random dynamical systems with inputs and outputs, motivated by bio-molecular systems. Work with Aminzare provided new results on contractions for distributed and interconnected systems, and was motivated by a molecular binding model. Work with Margaliot and Tuller developed new notions of "weak" contractions, motivated by problems from protein translation machinery. Work with Skataric and Nikolaev dealt with the use of singular perturbation tools to show that scale invariance is subject to fundamental limitations, again motivated by a set of questions arising from a concrete biological context.

A brief technical discussion of recent work follows. The previous reports for years 1 and 2 should be consulted for discussion of work conducted previous to the start of the last period.

Contraction theory

As described in previous reports, contraction theory is a powerful tool for analyzing nonlinear dynamical systems. A system is contracting if all the trajectories in some region of the state space converge to each other at an exponential rate. This implies many desirable properties including convergence to an attractor, and entrainment to a periodic excitation. Contraction theory has found numerous applications in control theory, observer design, synchronization of coupled oscillators, and more. Recent extensions include notions of partial contraction, analyzing a network of interacting contracting elements, LaSalle-type principles for contracting systems, Lyapunov-like characterization of incremental stability, and applications of pseudo-contraction to study contraction to a subset of the state-space (e.g., the set of states with equal coordinates). We have continued to study many of these topics.

Two papers have been published or submitted during this period: [8] and [6], in which we studied a notion of "weak" contraction that allows contraction up to an arbitrarily small transient in time, and applied these ideas to the entrainment of translation elongation to intra-cellular signals such as tRNAs levels and other factors affecting translation.

Motivated by an important biochemical example, we developed new theorems regarding the synchronization of agents, interconnected by diffusive links, in a journal paper [3] under review (a conference version, with a summary as well as additional material, will appear in [4]). In these papers, we discuss the application of contraction to synchronization of diffusively interconnected components described by nonlinear differential equations. We provide estimates of convergence of the difference in states between components, in the cases of line, complete, and star graphs, and Cartesian products of such graphs. We base our approach on contraction theory, using matrix measures derived from norms that are not induced by inner products. Such norms are the most appropriate in many applications, but proofs cannot rely upon Lyapunov-like linear matrix inequalities, and different techniques, such as the use of the Perron-Frobenious Theorem in the cases of L^1 or L^∞ norms, must be introduced.

In [1] we studied the special case of L^2 norms and generalizations to reaction-diffusion partial differential equations. We also prepared a long expository paper on contraction theory and applications to nonlinear stability for presentation at an invited Tutorial at the upcoming 2014 IEEE Conference on Decision and Control [2]. This paper provides a self-contained introduction to some of the basic concepts and results in contraction theory, discusses applications to synchronization and to reaction-diffusion partial differential equations, and poses several open questions.

Random dynamical systems

In the 1980s, L. Arnold conceived an elegant and deep approach to the foundations of random dynamics. His paradigm of a *Random Dynamical System* (RDS for short) is based on an ultimately simple idea: view an RDS as consisting of two ingredients, a stochastic but autonomous "noise process", and a classical dynamical system that is driven by this process. The noise process is described by a measure-preserving dynamical system. It is typically probabilistic, representing for example environmental perturbations, internal variability, randomly fluctuating parameters, model uncertainty, or measurement errors. But the formalism allows for deterministic periodic or almost-periodic driving processes as well. The resulting theory, developed since by many authors, provides a seamless integration of classical ergodic theory with modern dynamical systems, giving a theoretical framework parallel to classical smooth and topological dynamics (stability, attractors, bifurcation theory, and so forth), while allowing one to treat in a unified way the most important classes of dynamical systems with randomness —random differential or difference equations (basically, deterministic systems with randomly changing parameters), or stochastic ordinary and partial differential equations (white noise or, more generally, martingale-driven systems as studied in the Itô calculus). In previously reported work, we introduced a notion of random dynamical systems with inputs, providing several basic definitions and results on equilibria and convergence. The main goal has been all along to propose a new RDS-based formalism for random control systems, that is, systems with inputs (and outputs), which we abbreviate RDSI (or RDSIO).

Our motivation for studying RDS with inputs and outputs arises from the need to provide foundations for a constructive theory of interconnections and feedback for stochastic systems, one that will eventually generalize successful and widely applied deterministic approaches to the analysis and design of dynamic networks. Interconnection theory has proved very useful for the analysis of even deterministic systems with no inputs. It has been very successful when combined with tools from passivity theory, input-to-state (ISS) stability, and monotone systems with inputs and outputs. The key need is to have an appropriate class of systems that are CICS (converging-input converging-state) coupled with what are generically called "small-gain theorems" (essentially, asking that the feedback loop results in a contraction in an appropriate sense). CICS theorems were proved in the previous year and have been already published. The final step in this project was achieved with the successful statement and proof of a small-gain theorem for monotone RDSI, and this was the main result of de Freitas' Ph.D. thesis, and is reported in the recently submitted paper [5].

Scale-Invariance

We have largely completed our program of theoretical developments concerning the scale-invariance property in enzymatic networks. The phenomenon of fold-change detection, or scale-invariance, is exhibited by a variety of sensory systems, in both bacterial and eukaryotic signaling pathways. A common theme in the systems biology literature is that certain systems whose output variables respond at a faster time scale than internal components give rise to an approximate scale-invariant behavior, allowing approximate fold-change detection in stimuli. Indeed, in our own results reported in previous grant periods, and already published, we argued that all 3-node scale-invariant enzymatic networks are based upon this mechanism. The paper [7] established a fundamental limitation of such a mechanism, showing that there is a minimal fold-change detection error that cannot be overcome, no matter how large the separation of time scales is. To illustrate this theoretically predicted limitation, we discussed two common biomolecular network motifs, an incoherent feedforward loop and a feedback system, as well as a published model of the chemotaxis signaling pathway of Dictyostelium discoideum.

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Publications

[1] Z. Aminzare, Y. Shafi, M. Arcak, and E.D. Sontag. Guaranteeing spatial uniformity in reaction-diffusion systems using weighted l_2-norm contractions. In *A Systems Theoretic Approach to Systems and Synthetic Biology I: Models and System Characterizations*, pages 73–101. Springer-Verlag, 2014.

[2] Z. Aminzare and E.D. Sontag. Contraction methods for nonlinear systems: A brief introduction and some open problems. In *Proc. IEEE Conf. Decision and Control, Los Angeles, Dec. 2014*, 2014. To appear.

[3] Z. Aminzare and E.D. Sontag. Synchronization of diffusively-connected nonlinear systems: results based on contractions with respect to general norms. 2014. Submitted.

[4] Z. Aminzare and E.D. Sontag. Using different logarithmic norms to show synchronization of diffusively connected systems. In *Proc. IEEE Conf. Decision and Control, Los Angeles, Dec. 2014*, 2014. To appear.

[5] M. Marcondes de Freitas and E.D. Sontag. A small-gain theorem for random dynamical systems with inputs and outputs. 2014. Submitted.

[6] M. Margaliot, E.D. Sontag, and T. Tuller. Entrainment to periodic initiation and transition rates in a computational model for gene translation. *PLoS ONE*, 9(5):e96039, 2014.

[7] M. Skataric, E.V. Nikolaev, and E.D. Sontag. Scale-invariance in singularly perturbed systems. In *Proc. IEEE Conf. Decision and Control, Los Angeles, Dec. 2014*, 2014. To appear.

[8] E.D. Sontag, M. Margaliot, and T. Tuller. On three generalizations of contraction. In *Proc. IEEE Conf. Decision and Control, Los Angeles, Dec. 2014*, 2014. To appear.

Personnel Supported During Duration of Grant: Eduardo Sontag, Professor, Rutgers University; Michael de Freitas, Graduate Student, Rutgers University; Zahra Aminzare, Graduate Student, Rutgers University.

Honors & Awards Received (over grant period): Elected Fellow of the American Mathematical Society for Industrial and Applied Mathematics; and of the International Federation of Automatic Control.

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