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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. It addresses the continuing development of systems analysis tools based on input to state stability and related notions of detectability, regulation, and stabilization, as well as the study of 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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CONTROL OF NONLINEAR SYSTEMS

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ABSTRACT

This work focusesed on the mathematical foundations of nonlinear systems analysis and feedback control. It addressed the continuing development of systems analysis tools based on input to state stability and related notions of detectability, regulation, and stabilization, as well as the study of new theoretical questions arising from the study of biomolecular cellular mechanisms, seen as a source of inspiration for novel sensor, actuation, and control architectures.

1 Overview

This research addresses the *mathematical foundations of nonlinear systems analysis and feedback control.* Nonlinear control theory is of central importance to the Air Force mission, and the study of the associated mathematical theory is of undisputed relevance. The control of highly nonlinear systems broadly impacts applications ranging from robust feedback controllers for advanced high-performance aircraft, and reconfigurable flight control systems, to the design of autonomous aerial vehicles and of smart-munitions guidance systems.

The design and analysis of nonlinear feedback systems has recently undergone an exceptionally rich period of progress and maturation, fueled, to a great extent, by (1) the discovery of certain basic conceptual notions, and (2) the identification of classes of systems for which systematic decomposition approaches can result in effective and easily computable control laws. These two aspects are complementary, since the latter approaches are, typically, based upon the inductive verification of the validity of the former system properties under compositions (the "activation" of theoretical concepts leads to "constructive" control). It is perhaps in the first of these aspects, and in particular in the precise formulation of questions of robustness with respect to disturbances, and of stabilization conditions, formulated in the paradigm of *input to state stability*, that the PI's previous work has had the most influence, although our research covers a wide spectrum of other subjects as well. A large part of the project deals with such issues.

One relatively recent direction of the PI's research is the study of biological, and in particular intra-cellular, control and signal processing mechanisms. As a theoretician, the PI is particularly interested in *new mathematical questions in systems and control theory that arise when analyzing molecular biology models.* Evolution has resulted in robust, highly nonlinear, and hybrid feedback systems. Recent advances in genomic research are continuously adding detailed knowledge of such systems' architecture and operation, and one may reasonably argue that they will constitute a rich source of inspiration for innovative solutions to problems of control and communication engineering, as well as sensor and actuator design and integration. Thus, another major component of this project deals with problems of biological control.

The emphasis of this project is on the *development of basic principles*, and on the communication of these results to those in the engineering community (including especially other AFOSR researchers) who, in turn, employ these techniques in applications.

1.1 Input to State Stability and Related Notions

We discuss general finite-dimensional systems $\dot{x}(t) = f(x(t), u(t))$, $y(t) = h(x(t))$, in the sense of nonlinear control under standard regularity assumptions (see Section 2.1 for more details). There are two conceptually very different ways to formulate the notion of stability of such systems.

One of them, the purely *input/output approach*, relies on operator-theoretic techniques. Among the main contributions to this area, one may cite the foundational work by Zames, Sandberg, Desoer, Safanov, Vidyasagar, and others. In this approach, a "system" is a causal operator $F = F_{x(0)} : u(\cdot) \to y(\cdot)$ between spaces of signals (for fixed initial states), and "stability" is taken to mean that F maps bounded inputs into bounded outputs, or finite-energy inputs into finite-energy outputs. More stringent typical requirements in this context are that the gain

of F be finite (in more classical mathematical terms, that the operator be bounded), or that it have finite incremental gain (mathematically, that it be globally Lipschitz). The input/output approach has been extremely successful in the robustness analysis of linear systems subject to nonlinear feedback and mild nonlinear uncertainties, and in general in the area that revolves around the various versions of the small-gain theorem. Moreover, geometric characterizations of robustness (gap metric and the like) are elegantly carried out in this framework. Finally, i/o stability provides a natural setting in which to study the classification and parameterization of dynamic controllers.

On the other hand, there is the model-based, or *state-space approach* to systems and stability. In this approach, there is a standard notion of stability, namely Lyapunov asymptotic stability of the unforced system. Associated to such a system, there is the above-mentioned operator F mapping inputs (forcing functions) into state trajectories (or into outputs, if partial measurements on states are of interest). It becomes of interest then to ask to what extent Lyapunov-like stability notions for a state-space system are related to the stability, in the senses discussed in the previous paragraph, of the associated operator F. It is well-known that, in contrast to the case of (finite-dimensional) linear systems, where there is –subject to mild technical assumptions– an equivalence between state-space and i/o stability, for nonlinear systems the two types of properties are not so closely related. Even for the very special and comparatively simple case of "feedback linearizable" systems, this relation is far more subtle than it might appear at first sight: if one first linearizes a system and then stabilizes the equivalent linearization, in terms of the original system one does not in general obtain a closed-loop system that is input/output stable in any reasonable sense.

This leads one to focus on the study of the dependence of state trajectories on the size of inputs, a study which is especially relevant when the inputs in question represent disturbances acting on a system. For not necessarily linear systems, there are various possible formulations of system stability with respect to input perturbations. (For linear systems, similar considerations led to the development of gains and the operator-theoretic approach, including the formulation, when using L^2 norms, of H^∞ control.) One candidate for such a formulation is the property called "input to state stability" (ISS), introduced by the PI in 1989. In very informal terms, the ISS property translates into the statement that "no matter what is the initial state, if the inputs are small, then the state must eventually be small, and the overshoot depends on the size of the initial state." The ISS notion can be stated in several equivalent manners, which indicates that it is a mathematically natural concept: dissipation, robustness margins, or asymptotic gains.

The three most basic notions of stability in the theory of finite-dimensional linear systems are (1) internal stability (behavior of states), (2) detectability (external behavior determines how states evolve), and (3) input/output stability (transfer function has no poles in the right-hand plane). These generalize, respectively, to (1) ISS, (2) IOSS (input and output to state stability), and (3) IOS (input to output stability), for general finite-dimensional nonlinear systems. The observation that a system is internally stable if and only if it is i/o stable and detectable generalizes to "ISS equals IOSS and IOS" in an immediate fashion, providing a conceptual unity to the field.

Input to state stability proved to be a very useful paradigm in the study of nonlinear stability for systems subject to external effects, especially in connection to issues of robust and adaptive control, stochastic and hybrid versions, or in its variants for detectability and output stability (IOSS, IOS) and for integral stability (iISS).

The ISS approach differs fundamentally from the operator-theoretic ones, first of all because it takes account of initial states in a manner fully compatible with Lyapunov stability. Second, boundedness (finite gain) is far too strong a requirement for general nonlinear operators, and it must be replaced by "nonlinear gain estimates," in which the norms of output signals are bounded by a nonlinear function of the norms of inputs; the definition of ISS incorporates such gains in a natural way. Yet another way in which the approach differs from operator-theoretic quantifications of stability is that one does not focus upon the actual numerical values of gains (operator norms) but, rather, on the more qualitative question of *existence* of estimates; for (finite-dimensional) linear systems, of course, all these questions are equivalent, and they amount to the requirement that the origin should be asymptotically stable with respect to the unforced dynamics, but not so for general nonlinear systems. One may say that the ISS view is "topological" in contrast to the more "metric" view of standard operator approaches.

Recent Accomplishments

Next, we highlight next some of our recent accomplishments in the ISS area; some more details on several of these items are provided in Section 2.1.

We were able to complete the dissipation characterizations of input to output stability (IOS), of input-output to state stability, and of the integral ISS (iISS) property and its semi-global versions. ([s63],[s64],[s52]). Asymptotic-gain equivalences were found for IOS, cf. [s75], and IOSS, cf. [s74]; see [s16] for the most general results along these lines.

Proving these asymptotic characterizations requires the generalization of the Filippov-Ważewski Relaxation Theorem to infinite time intervals, a result which is of independent interest in the field of differential inclusions, see [s35] for the finite-dimensional case and [s56] for the corresponding theorem in Banach spaces. This led, in turn, to a new theorem showing that, for locally Lipschitz differential inclusions, uniform and non-uniform global asymptotic stability are equivalent, cf. [s4].

In applications such as adaptive control, often suitable tracking behavior is obtained only under assumptions of slow variation of inputs; this gave rise to the study of ISS with respect to input derivatives; the papers [s68], [s43] describe relations and differences with the ISS notion, and applications.

Measurement to error stability (MES) is a notion of partial detectability for nonlinear systems, which unifies the many concepts associated to ISS and which plays a key role in regulator theory. This notion is still poorly understood, but some progress was reported in [s58].

For nonlinear cascade systems resulting from input-output linearization, strong assumptions have to be made in order to obtain stability, typically that the driven system is ISS. The papers [s73], [s55] dealt with the case when the driven subsystem is merely integral ISS, and characterized the admissible integral ISS gains for stability. The result was used to develop a new observer-based backstepping design under suitable growth assumptions on nonlinear damping terms.

The papers [s67], [s50] introduced and studied the notion of output-input stability (OIS), which was motivated by and relates to the minimum-phase property. The definition requires the state and input to be bounded by a suitable function of the output and derivatives of the output, modulo a decaying term depending on initial conditions, and includes affine systems in

global normal form whose internal dynamics are ISS. An extension to nonlinear systems of a basic result from linear adaptive control, using this notion, was shown there as well.

A very abstract and formal ISS-like small gain theorem, in a form applicable to incremental stability, detectability, and input/output maps (possibly nonrealizable by finite-dimensional systems) was given in [s49].

In [s40], we gave an example of a globally asymptotically stable time-invariant system which can be destabilized by some integrable perturbation; this answered (in the negative) an open problem posed by Laurent Praly concerning the existence of continuously differentiable Lyapunov functions with globally bounded gradients.

The paper [s51] dealt with the design of state feedback control laws that render a closed-loop system iISS with respect to disturbances, using an appropriate concept of control Lyapunov function (iISS-CLF), whose existence is shown to lead to an explicit construction of such a control law.

In [s38], [s14], we returned to a question first addressed in our original ISS paper in 1989. For systems admitting a continuous stabilizer, we had shown that it is always possible to "robustify" the given control law so as to obtain a new feedback which is ISS with respect to actuator errors. Regularity of the feedback is essential, and for several years it was an open question to obtain a version of this result for systems which are only stabilizable by discontinuous feedback (for instance, nonholonomic mechanical systems). The breakthrough came with the realization that semiconcave control Lyapunov functions provide the key missing ingredient, and now we were able to obtain the general result, expressed in both the sampling and Euler solution senses.

The use of switching strategies for adaptive control requires the development of "LaSalle-like" invariance principles, which lead in turn to our study of ISS-like characterizations of observability of nonlinear systems, see [s59].

The goal of the PI's work in this area is highly ambitious: the complete reformulation of the foundations of nonlinear control based on ISS-like ideas. This goal is very long-term, but definitely worth the effort: the payoff will be in the development of a consistent, elegant, and ultimately design-oriented, systematic approach to the subject. Previous grants supported research which led to truly exciting advances during the last few years. However, the story is by no means complete, and we hope to be able to continue developing the theory.

1.2 Systems and Control Problems Inspired by Molecular Biology

Research in molecular biology and genomics has provided, and will continue to produce, a wealth of data describing the ingredients of cell behavior. There is a clear need to integrate this knowledge, as a prerequisite to a deeper scientific understanding as well as medical applications. Indeed, the new field of "systems biology" has arisen (see e.g. the new IEE journal *Systems Biology*) having as its goal the understanding of the basic dynamic processes, feedback control loops, and signal processing mechanisms underlying life. Conversely, since evolution has resulted in robust, highly nonlinear and hybrid feedback systems, it is reasonable to expect that the study of systems biology will constitute a rich source of inspiration for innovative solutions to control and communication engineering problems, as well as sensor and actuator design and integration. The PI has recently started the study of several mathematical questions in systems and control theory which arise from molecular biology models.

The need for mathematical models of feedback in cellular biology has been long recognized, and seminal work was done during the past 30 or more years by researchers such as Glass, Goldbeter, Kauffman, Othmer, Savageau, Segel, Tyson, and many others. What makes the present time special is the availability of huge amounts of data – generated by the genomics and proteomics projects, and research efforts dealing with the characterization of signaling networks – as well as the possibility for experimental design afforded by genetic engineering tools (gene knock-outs and insertions, PCR) and measurement technology (Green Fluorescent Protein and other reporters, as well as gene arrays).

Background

The life sciences are in the midst of a major revolution, which will have fundamental implications in biological knowledge and medicine.Work in genomics has as its objective the complete decoding of DNA sequences, providing what one may call a "parts list" for the proteins potentially present in every cell of the organism being studied. The elucidation of the three-dimensional structure of the proteins so described is the goal of the area of proteomics. The shape of a protein, in turn, determines its function: proteins interact with each other through "lego-like" fitting of parts in "lock and key" fashion, and their conformation also enhances or represses DNA expression through selective binding. One of the main themes and challenges in current molecular biology lies in the understanding of cell behavior in terms of cascades and feedback interconnections of elementary "modules" which appear repeatedly. On the other hand, the successes of systems theory have been, in large part, due precisely to its ability to analyze complicated structures on the basis of the behavior of elementary subsystems, each of which is "nice" in a suitable input/output sense (stable, passive, etc), in conjunction with the use of tools such as small gain theorems. Thus, control-oriented modeling and analysis of feedback interconnections will become an integral component of building effective models of biological systems.

One may view cell life as a huge "wireless network" of interactions among proteins, DNA, and smaller molecules involved in signaling and energy transfer. As a large system, the external inputs to a cell include physical (UV radiation, temperature) as well as chemical (drugs, hormones, nutrients) signals. Its outputs include chemicals which may in turn affect other cells, the movement of flagella or pseudopods, the activation of transcription factors, and so forth. The study of cell networks leads to the formulation of a large number of questions of a systems theory flavor. What is special about the information-processing capabilities, or input/output behaviors, of such networks, and how does one characterize these behaviors in terms familiar to control theory? What "system-theoretic modules" appear repeatedly? What are the stability properties of the various cascades and feedback loops which appear in cellular signaling networks? Inverse or "reverse engineering" issues include the estimation of system parameters (such as reaction constants) as well as estimation of state variables (concentration of protein, RNA, and other chemical substances) from input/output experiments. Generically, these questions may be viewed respectively as the identification and observer (or filtering) problems which are at the center of much of control theory.

Recent Accomplishments

Control and systems problems motivated by molecular biology tend to *resemble* similar problems that arise in engineering control or dynamical systems. However, these resemblances are oftentimes misleading, because the *precise problem formulations* may be very different from those in the respective more classical applications. This issue has driven much of the PI's interest in the subject.

There follows a quick overview of several areas of the PI's recent research. More details on selected topics are provided in Section 2.2.

Monotone Control Systems

Mitogen-activated protein kinase (MAPK) cascades represent a "biological module" or sub-circuit which is ubiquitous in eukaryotic cell signal transduction processes and is a critical component of pathways involved in cell proliferation, differentiation, movement, and death. Appearing in several variants, this system is made up of a cascade of three smaller subsystems, with certain feedback loops acting in regulatory modes. Research into MAPK cascade dynamics is a major area of interest in biology, with implications not only to natural processes but even to areas such as bio-terrorism (Bacillus anthracis, which causes of Anthrax, acts by secreting a toxin called Lethal Factor (LF), which disrupts the "connection" between the second and third subsystems in the cascade).

Our research in this area was originally motivated by work of Kholodenko, which dealt with the possible onset of oscillations under negative feedback in a MAPK cascade, specifically, the inhibitory phosphorylation of upstream SOS by p42/p44 MAPK (ERK). Since such periodic behavior has not been observed experimentally, one would like to understand what conditions guarantee the non-existence of oscillations in systems of this kind (modeled mathematically by several authors.

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 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 [s61] and [s60], 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 MAPK model studied by Kholodenko.

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 Hal Smith by Hirsh and Smale. The concept of monotone system had been traditionally defined only for systems with no external inputs (nor outputs). The first objective of the papers [s57] and [s31] 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 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 [s57] and [s31] 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.

Although motivated by MAPK cascades, the results are far more general. The paper [s13] presented a variant of the small-gain theorem from [s57] and [s31], 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. This variant was required by the study in [s37] and [s34], which 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.

Yet another application of these ideas can be found in the paper [s36], dealing with 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, [s36] added death rates due to crowding effects, 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. Using the theory of strictly monotone systems, together with basic facts about system gains, we were able in [s3] and [s47] 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. The paper [s2] deals with the application to biological models, as well as graphical tests for monotonicity.

Systems Identification and Reverse Engineering

The paper [s48] proposed a novel quantitative method for determining functional interactions in cellular signaling and gene networks. The method can be used to explore cell systems at a mechanistic level, or applied within a modular framework, which dramatically decreases the number of variables to be assayed. The topology and strength of network connections are retrieved from experimentally measured network responses to successive perturbations of all modules. In addition, the method can reveal functional interactions even when the components of the system are not all known, in which case some connections retrieved by the analysis will not be direct but correspond to the interaction routes through unidentified elements. The method was tested and illustrated using computer-generated responses of a modeled MAPK cascade and gene network.

The question of determining such interactions fits in the general framework of realization and identification theory, but is technically different because of the lack of closure under concatenation of biologically realistic inputs. (Thus, technically, the problem is no more one of semigroup representation, as classically done in control theory.) A related general question is: given a set of differential equations whose description involves unknown parameters, such as reaction constants in chemical kinetics, and supposing that one may at any time measure the values of some of the variables and possibly choose external inputs from a finitely parameterized class to help excite the system (but without assuming any semigroup closure of this class of inputs), how many experiments are sufficient in order to obtain all the information that is potentially available about the parameters? The paper [s53] established that the best possible answer (assuming exact measurements) is $2r + 1$ experiments, where r is the number of parameters. Moreover, in a precise mathematical sense, a generic set of such experiments suffices.

Finally, we continued to work on systems identification regarded as an instance of the general problem of "learning" an unknown function. The papers [s9] and [s70] took a computational learning theory approach to a problem of linear systems identification: assume that inputs are generated randomly from a known class of finite bandwith, specifically that they are (unknown) linear combinations of k known sinusoidals, and that the output of the system is observed at some single instant of time. The main result establishes that the number of samples needed for identification with small error and high probability, independently from the distribution of inputs, scales polynomially with n, the system dimension, and logarithmically with k.

Dynamics and Observers for Biochemical Networks

Among other tasks, the immune system is charged with the destruction and elimination of invading organisms and of the toxic products that they produce, as well as the destruction of virus-infected or mutated cells. One of the most challenging problems in the study of the immune system is to understand how it manages to distinguish among "self" and "other" while still being able to react fast.

One approach to this question was proposed by McKeithan, who suggested that a chain of modifications of the T-cell receptor complex, via tyrosine phosphorylation and other reactions, may give rise to both increased sensitivity and selectivity of response. This process, which he called "kinetic proofreading" because of its analogy to an older model proposed by Hopfield for DNA error correction, was modeled by McKeithan for T-cell receptor (TCR) and peptide-major histocompatibility complex (MHC) interactions by means of a certain set of nonlinear ordinary differential equations. The steady states that result are interpreted as a "signal" for antigen recognition. Thus, it was natural to ask if the steady states of this system are unique, if they are asymptotically stable, and so forth.

This led the PI to a new direction of research. The paper [s66] dealt with the theory of structure, stability, robustness, and stabilization for a class of nonlinear systems, originally studied by Feinberg, Horn, and Jackson in the 1970s and 80s, which arises in the analysis of biochemical networks. This paper extended their results, to obtain global stability conclusions that apply to the kinetic proofreading model for T-cell receptor signal transduction, as well as provided bounds on robustness under unstructured perturbations and feedback stabilization. The class of nonlinear systems that arises in this fashion is very different from others typically considered in control theory, and they are endowed with strong robustness properties.

Furthermore, when outputs are explicitly considered, problems of filtering can be posed. In [s54] and [s71], we gave necessary and sufficient condition for detectability and an explicit construction of globally convergent observers. An alternative observer, which has enhanced robustness (expressed through an ISS property) to additive disturbances, was studied in [s69].

Internal-Model Principle

One strength of control theory is that it tells us that certain structures *must* be present in systems, in order for regulation objectives to be met. Such insight can help guide experimental research, as it suggests trying to find the corresponding subsystems, and may thus help in model validation. Conversely, the absence of a critical subsystem might be an indication that the biological entity being studied does not regulate its behavior in some hypothesized sense.

In particular, and motivated by the thought-provoking paper by Doyle's group, we became interested in understanding the role of internal models in biological adaptation. Recall that the classical internal model principle (IMP due to Francis and Wonham) states that if controller regulates a system against external disturbances in some family, and if this regulation is *structurally stable* in a precise mathematical sense, then the controller must necessarily contain a subsystem which can itself generate all such disturbances (and which is driven by a suitable "error" signal). A potential drawback, when attempting to use this theorem in biological applications, is that the structural stability criterion may be impossible to check: it would imply for instance regulation even in the presence of direct connections from inputs, such as cell receptors, to outputs, such as flagellar motors. Thus, once again, one has a problem which "sounds" just like a standard problem in control theory, yet which mathematically differs in a subtle fashion.

In [s41], we gave an internal model theorem which did not require the assumption of structural stability (nor, for that matter, an a priori requirement for the system to be partitioned into separate plant and controller components). Instead, a "signal detection" capability is imposed. These weaker assumptions make the result better applicable to cellular phenomena such as the adaptation of *E.coli* chemotactic tumbling rate to constant concentrations. The "signal detection" property makes a lot of sense in biological applications (a signal must be detected with very high gain, and an action commanded, but the command may be metabolically too

expensive to be kept "on" for very long) but not necessarily in all engineering applications (we would not want, for instance, the passengers in an automobile to hit the car roof as hard as possible before an active suspension system takes over and regulates against road bumps).

Adaptive Control of Bifurcation Parameters

Some biological systems are believed to operate at a critical point between stability and instability, which brings up the issue of how bifurcation parameters may be automatically tuned to this critical value. The papers [s29] and [s30] were motivated by two such instances from the literature: neural integration in the nervous system, and hair cell oscillations in the auditory system. In both examples, the question arises as to how the required fine-tuning may be achieved and maintained in a robust and reliable way. As with the other questions illustrated here, this led to a new type of problem in control theory, related but in fact different from other work on "bifurcation control" in the literature. We formulated this question in the language of adaptive control, and presented solutions in some simple instances.

1.3 Other Nonlinear Control Research

We summarize here other recent research accomplishments by the PI in the general area of nonlinear systems.

Control of Mechanical Systems

In [s72] and [s46], we addressed questions of time-optimal control for mechanical systems with possible dissipation terms. The Lie algebras associated with these systems enjoy certain special properties. These properties were explored and are used in conjunction with the Pontryagin maximum principle to determine the structure of singular extremals and, in particular, time-optimal trajectories. The theory was illustrated with an application to a time-optimal problem for a class of underwater vehicles.

2   Selected Topics

Given the range of subjects treated, and the different methodologies employed in each case, we can only briefly cover a few selected subtopics. The published papers, and the PI's website

$$\boxed{\texttt{http://www.math.rutgers.edu/~sontag}}$$

provide technical details. For the topics treated, we do not repeat here most of the introductory material and references already discussed in the previous section.

2.1   Some Details: ISS and Related Notions

We describe first topics related to input to state stability.

IOSS and iISS Characterizations

Detectability is one of the central notions of control theory. It plays a major role in static state-feedback analysis (Lasalle's invariance principle) as well as in stabilization by means of dynamic output feedback and in observer design. Several alternative definitions are possible when trying to precisely define detectability in the context of nonlinear control. According to the specific problem under consideration, different variants are useful in capturing useful features of its linear counterpart. One version which has proved to be especially powerful for systems subject to exogenous disturbances, is to define this notion in an ISS sense, leading to what we have called "input-output-to-state stability" (IOSS). Such a notion not only allows one to extend Lasalle-type stability results to the case of non-autonomous systems, but it also provides a machinery, fully compatible with the formalism of input-to-state stability, that helps one understand issues such as minimum-phase behavior or certainty equivalence.

Although general nonlinear systems may often exhibit an overwhelming variety of behaviors, it turns out that many other "reasonable" formulations of the detectability property end up being equivalent to IOSS. Recently, we proved in work with Krichman and Wang in [s64] that IOSS is equivalent to a dissipation property. In the even more recent work [s16] with Angeli, Ingalls, and Wang, we were able to characterize IOSS as the conjunction of several important and natural weaker notions, in essence generalizing the fact (for differential equations with no controls nor outputs) that global asymptotic stability can be characterized by the combination of (neutral) stability and attractivity. For systems with inputs, such generalizations are nontrivial because, in contrast to ordinary (finite-dimensional) differential equations, there is no compactness to appeal to (even with respect to weak topologies on inputs, since we do not have any convexity properties). As an application of the results, we also obtained reformulations of the notion of integral input to state stability (iISS). Proving these results forced us, in turn, to establish facts of *independent interest in differential inclusions,* such as a generalization of the Filippov-Ważewski Relaxation Theorem to infinite time intervals, in [s35] (see also [s56] for the corresponding theorem in Banach spaces) and a theorem showing that, for locally Lipschitz differential inclusions, uniform and non-uniform global asymptotic stability are equivalent, cf. [s4]. Let us give an outline of [s16] next.

We consider systems of the following general form:

$$\dot{x}(t) = f(x(t), u(t)), \quad y(t) = h(x(t)), \tag{1}$$

where, for each $t \geq 0$, $x(t) \in \mathbb{R}^n$, $u(t) \in \mathcal{U}$, a subset of $\mathbb{R}^m$ which here we take for simplicity to be all of $\mathbb{R}^m$. We assume that the maps $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ and $h : \mathbb{R}^n \to \mathbb{R}^p$ are locally Lipschitz continuous, with $f(0,0) = 0$ and $h(0) = 0$. The symbol $|\cdot|$ denotes the usual Euclidean norms. By an *input* we mean a measurable and locally essentially bounded function $u : \mathcal{I} \to \mathcal{U}$, where, $\mathcal{I}$ is a subinterval of $\mathbb{R}$ which contains the origin. Given any input u and any $\xi \in \mathbb{R}^n$, the unique maximal solution of the initial value problem $\dot{x} = f(x, u)$, $x(0) = \xi$ (defined on some maximal open subinterval of $\mathcal{I}$) is denoted by $x(\cdot, \xi, u)$. When $\mathcal{I} = \mathbb{R}_{\geq 0}$, this maximal subinterval has the form $[0, T_{\xi,u})$. The system is said to be forward complete if for every initial state ξ and for every input u defined on $\mathbb{R}_{\geq 0}$, $T_{\xi,u} = +\infty$. The corresponding output is denoted by $y(\cdot, \xi, u)$, that is, $y(t, \xi, u) = h(x(t, \xi, u))$ on the domain of definition of the solution. The L_∞-norm (possibly infinite) of a function v defined on $\mathcal{I}$ is denoted by $\|v\|$, i.e., $\|v\| = (\text{ess}) \sup\{|v(t)|, t \in \mathcal{I}\}$. In particular, for a maximal trajectory $x(\cdot, \xi, u)$ and the corresponding output function $y(\cdot, \xi, u)$ of (1) defined on $[0, T_{\xi,u})$, $\|u\|$, $\|x\|$ and $\|y\|$ denote the L_∞ norm of $u(\cdot)$, $x(\cdot, \xi, u)$ and $y(\cdot, \xi, u)$ respectively on $[0, T_{\xi,u})$. (We make a slight abuse of notation and use sup and lim sup to mean the essential supremum where appropriate.) For a function v defined on an interval $\mathcal{I}$, if $\mathcal{I}_1 \subseteq \mathcal{I}$, we use $v_{\mathcal{I}_1}$ to denote the restriction of v to $\mathcal{I}_1$, i.e., $v_{\mathcal{I}_1}(t) = v(t)$ if $t \in \mathcal{I}_1$, and $v_{\mathcal{I}_1}(t) = 0$ otherwise. We use standard terminology on comparison functions: $\mathcal{N}$ is the class of continuous, increasing functions from $[0, \infty)$ to $[0, \infty)$; $\mathcal{K}$ is the set of $\mathcal{N}$ functions γ that are strictly increasing and satisfy $\gamma(0) = 0$; $\mathcal{K}_\infty$ is the set of $\mathcal{K}$ functions that are unbounded; $\mathcal{L}$ is the set of functions $[0, +\infty) \to [0, +\infty)$ which are continuous, decreasing, and converge to 0 as their argument tends to $+\infty$; $\mathcal{KL}$ is the class of functions $[0, \infty)^2 \to [0, \infty)$ which are class $\mathcal{K}$ on the first argument and class $\mathcal{L}$ on the second one. A positive definite function $\gamma : [0, \infty) \to [0, \infty)$ is one such that $\gamma(0) = 0$ and $\gamma(s) > 0$ for all $s > 0$. The following notions were introduced in our previous work: The system (1) satisfies the *unboundedness observability* (UO) property if, for each state ξ and control u such that $T_{\xi,u} < \infty$, it holds that $\limsup_{t \to T_{\xi,u}} |y(t, \xi, u)| = +\infty$, that is, for each state ξ and control u, $T_{\xi,u} < \infty \Rightarrow \|y\| = +\infty$. The system (1) is *input-output-to-state stable* (IOSS) if there exist some $\beta \in \mathcal{KL}$, $\gamma_u \in \mathcal{K}$ and $\gamma_y \in \mathcal{K}$ such that

$$|x(t, \xi, u)| \leq \beta(|\xi|, t) + \gamma_u(\|u\|) + \gamma_y\left(\left\|y_{[0,t]}\right\|\right) \tag{2}$$

for all $t \in [0, T_{\xi,u})$, all $\xi \in \mathbb{R}^n$ and all $u(\cdot)$. Clearly, the IOSS property implies the UO property. The following local version is also important: The system (1) is *locally IOSS* (local IOSS) if there exist $\delta > 0$ and functions $\beta \in \mathcal{KL}$, $\gamma_u, \gamma_y \in \mathcal{K}$ so that for any $\xi \in \mathbb{R}^n$, any $u(\cdot)$,

$$\max\{|\xi|, \|u\|, \|y\|\} \leq \delta \;\Rightarrow\; |x(t, \xi, u)| \leq \beta(|\xi|, t) + \gamma_u(\|u\|) + \gamma_y(\|y_{[0,t]}\|) \,\forall\, t \in [0, T_{\xi,u}). \tag{3}$$

We also say that the system (1) satisfies the *input-output limit property* (IO-LIM) if for some $\gamma_u, \gamma_y \in \mathcal{K}$,

$$\inf_{t \in [0, T_{\xi,u})} |x(t, \xi, u)| \leq \max\{\gamma_u(\|u\|), \gamma_y(\|y\|)\}$$

for all $\xi \in \mathbb{R}^n$ and all inputs $u(\cdot)$, that it satisfies the *input-output asymptotic gain property* (IO-AG) if solutions are ultimately bounded by some nonlinear gain function of $\|u\|$ and $\|y\|$, that is, for some $\gamma_u, \gamma_y \in \mathcal{K}$,

$$\limsup_{t \to T_{\xi,u}} |x(t, \xi, u)| \leq \max\{\gamma_u(\|u\|), \gamma_y(\|y\|)\}$$

for all $\xi \in \mathbb{R}^n$ and all inputs $u(\cdot)$; that it satisfies the *input-output-to-state boundedness property* (IO-BND) if for some $\sigma_0, \sigma_u, \sigma_y \in \mathcal{N}$, it holds that

$$|x(t, \xi, u)| \leq \max\{\sigma_0(|\xi|), \sigma_u(\|u\|), \sigma_y(\|y_{[0,t]}\|)\},$$

for all $\xi \in \mathbb{R}^n$ and all inputs $u(\cdot)$, and all $t \in [0, T_{\xi,u})$, and finally that it satisfies the *input-output global stability property* (IO-GS) if the functions $\sigma_0, \sigma_u, \sigma_y$ above can be taken to be of class $\mathcal{K}$. (It is not hard to see that each of the IO-AG, the IO-GS, and the IO-BND properties implies the UO condition.)

Thinking of these detectability properties as "stability modulo inputs and outputs", we can identify IOSS with asymptotic stability, IO-GS with (neutral) stability, and IO-AG with attractivity. In this context, it seems perfectly natural that IOSS should be equivalent to the combination of IO-GS and IO-AG, and indeed that is one of the decompositions which appears in our main result. Related results follow by considering other "basic" stability-like notions, such as IO-LIM. Among many others, the paper [s16] proves equivalences among the following statements:

- (IOSS)
- (IO-AG) & (IO-GS)
- (IO-AG) & (local IOSS)
- (IO-LIM) & (IO-GS)
- (IO-LIM) & (local IOSS)

We then went on to derive asymptotic characterizations of the integral input-to-state stability property. Recall that we defined a system to be *integral input-to-state stable* (iISS) if there exist functions $\beta \in \mathcal{KL}$, $\sigma \in \mathcal{K}$ and $\gamma \in \mathcal{K}$, such that, for all $\xi \in \mathbb{R}^n$ and all u, the solution $x(t, \xi, u)$ is defined for all $t \geq 0$, and

$$|x(t, \xi, u)| \leq \beta(|\xi|, t) + \gamma\left(\int_0^t \sigma(|u(s)|)\, ds\right)$$

for all $t \geq 0$. In order to obtain an interesting separation theorem, we introduced in [s16] the following properties. We say that a system (1) satisfies the *Bounded Energy Weakly Converging State* (BEWCS) property if for some σ of class $\mathcal{K}_\infty$, it holds that

$$\int_0^{+\infty} \sigma(|u(s)|)\, ds < +\infty \Rightarrow \liminf_{t \to +\infty} |x(t, \xi, u)| = 0.$$

(To be more precise, this means that for any ξ and any u for which $\int_0^\infty \sigma(|u(s)|)\, ds < \infty$, it holds that $T_{\xi,u} = \infty$, and $\liminf_{t \to +\infty} |x(t, \xi, u)| = 0$.) We say that it satisfies the *Bounded Energy Frequently Bounded State* (BEFBS) property if for some σ of class $\mathcal{K}_\infty$, it holds that

$$\int_0^{+\infty} \sigma(|u(s)|)\, ds < +\infty \Rightarrow \liminf_{t \to +\infty} |x(t, \xi, u)| < +\infty.$$

(To be more precise, for any ξ and any u for which $\int_0^\infty \sigma(|u(s)|)\, ds < \infty$, it holds that $T_{\xi,u} = \infty$, and $\liminf_{t \to +\infty} |x(t, \xi, u)| < \infty$.) (BEFBS and BEWCS each implies forward completeness.) Finally, we say that a system as in (1) is *zero-GAS* if the corresponding zero-input system $\dot{x} = f(x, 0)$ is globally asymptotically stable; that it is *zero-LS* if the zero-input system is locally (neutrally) stable; and that it is *zero-LAS* if the zero-input system is locally asymptotically stable. Then, we proved the equivalence among the following statements:

- iISS
- BEWCS and zero-LS
- BEFBS and zero-GAS

These results complete the theory of IOSS and iISS in very elegant ways, and make the concepts much easier to verify in applications. We will next introduce another important systems property, measurement to error stability (MES).

MES

   When discussing systems with outputs, the output signal typically plays one of two roles. One is that in which the outputs are considered as *measurements*. Here, one supposes that knowledge of the whole state is not available, but rather that only partial knowledge of the state can be used, and the output is meant to provide information about the state. This leads to our detectability notion of output to state stability (OSS). A second role for outputs occurs when the goal of the control design is not to regulate the behavior of the entire state, but rather only to regulate the output signal. The theory of output regulation addresses precisely this situation, that of keeping an output small. This leads, within the ISS framework, to the notion of stability of the output signal described by input to output stability (IOS). (In the case of systems with no inputs, the problem of stability of a subset of the state variables is the special case of stability of an output signal which is a projection, and it has been addressed in the ordinary differential equations literature under the name "partial stability" by Vorotnikov and others.)

   Consider now the case in which both the above situations occur. That is, there are *two* output signals, one which is measured, and the other which must be regulated. A special case of this situation has been addressed in the output regulation theory, under the name "error feedback". This theory formulates the question of regulating an output of the system (the error) with knowledge of that output only. The more general case is when there are two distinct channels playing these two roles. In the paper [s58], we generalized the notion of OSS to this situation by introducing the concept of *measurement to error stability* (MES), which can be viewed as a notion of *partial detectability* through the measurement channel. We gave a partial Lyapunov characterization of the MES property, accomplished by first comparing the MES property to a notion of output stability relative to a set. This notion, which we called *stability in three measures* (SIT) was characterized by the existence of a lower semicontinuous Lyapunov function. It was shown that the SIT property implies MES, and that the converse holds under an additional boundedness assumption. The analysis was carried out on systems described by differential inclusions – implicitly incorporating a disturbance input with compact value-set. Let us now give some details. We consider the differential inclusion

$$\dot{x}(t) \in F(x(t)) \tag{4}$$

with two output maps

$$y(t) = h(x(t)), \quad w(t) = g(x(t)),$$

and a map $\omega : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$. We take the state $x \in \mathbb{R}^n$. We assume: the set-valued map F from $\mathbb{R}^n$ to subsets of $\mathbb{R}^n$ is locally Lipschitz with nonempty compact values, the output maps $h : \mathbb{R}^n \to \mathbb{R}^{p_y}$ and $g : \mathbb{R}^n \to \mathbb{R}^{p_w}$ are locally Lipschitz, the map ω (to be used as a measurement of the magnitude of the state vector) is assumed continuous and proper, and the differential inclusion (4) is forward complete. We will denote $|\cdot|_\omega := \omega(\cdot)$. (The use of $|\cdot|_\omega$

allows a framework which includes the Euclidean norm, distance to a compact set, and more general measures of the magnitude of the state.) For each $C \subseteq \mathbb{R}^n$ we let $S(C)$ denote the set of maximal solutions of (4) satisfying $x(0) \in C$ equipped with the topology of uniform convergence on compact intervals. If C is a singleton $\{\xi\}$, we use the shorthand $S(\xi)$. We set $S := S(\mathbb{R}^n)$, the set of all maximal solutions. Given a trajectory $x(\cdot) \in S(\xi)$ for some $\xi \in \mathbb{R}^n$, we denote $y(t) = h(x(t)$ and $w(t) = g(x(t))$, for all $t \geq 0$.

Our main concept is the following one. We say that the system (4) is *measurement to error stable* (MES) if there exist $\beta \in \mathcal{KL}$ and $\gamma \in \mathcal{K}$ so that

$$|y(t)| \leq \max\{\beta(|x(0)|_\omega, t), \gamma(\|w\|_{[0,t]})\}$$

for each $x(\cdot) \in S$, and all $t \geq 0$. In the investigation of the MES property, the following notion of relative stability of the error will be useful. This is a notion of output stability which is applicable to systems with a single output y. Given a closed subset D of the state space $\mathbb{R}^n$, we say that the system (4) is *relatively error stable (RES) with respect to D* if there exists $\beta \in \mathcal{KL}$ so that for any solution $x(\cdot) \in S$, if there exists $t_1 > 0$ so that, if $x(t) \notin D$ for all $t \in [0, t_1]$, then

$$|y(t)| \leq \beta(|x(0)|_\omega, t) \qquad \forall t \in [0, t_1]. \tag{5}$$

A special case of this property occurs for a system with two outputs when the set D is defined by an inequality involving the two output maps, as follows. Let $\rho \in \mathcal{K}$. We say that the system (4) satisfies the *stability in three measures* (SIT) property (with gain ρ) if there exists $\beta \in \mathcal{KL}$ so that for any solution $x(\cdot) \in S$, if there exists $t_1 > 0$ so that, if $|y(t)| > \rho(|w(t)|)$ for all $t \in [0, t_1]$, then (5) holds. It is immediate that SIT is equivalent to relative error stability with respect to the set $D := \{\xi \in \mathbb{R}^n : |h(\xi)| \leq \rho(|g(\xi)|)\}$. Finally, we also introduced in [s58] the following relative stability property. The system (4) satisfies the *relative measurement to error bounded property* (RMEB) if there exist $\mathcal{K}$ functions ρ_1, σ_1, and σ_2 so that for any solution $x(\cdot) \in S$, if there exists $t_1 > 0$ so that, if $|y(t)| > \rho_1(|w(t)|)$ for all $t \in [0, t_1]$, then for all $t \in [0, t_1]$,

$$|y(t)| \leq \max\{\sigma_1(|h(x(0))|), \sigma_2(\|w\|_{[0,t]})\}.$$

We provided dissipation characterizations as follows. Given an open set $E \subseteq \mathbb{R}^n$, a lower semicontinuous function $V : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ is an *RES-Lyapunov function* for system (4) on E if there exist $\alpha_1, \alpha_2 \in \mathcal{K}_\infty$ so that for all $\xi \in E$, $\alpha_1(|h(\xi)|) \leq V(\xi) \leq \alpha_2(|\xi|_\omega)$, and there exists $\alpha_3 : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ continuous positive definite so that for each $\xi \in E$, $\zeta \cdot v \leq -\alpha_3(V(\xi))$ for all $\zeta \in \partial_D V(\xi)$ and all $v \in F(\xi)$, where we are denoting by $\partial_D V(\xi)$ the viscosity subdifferential of V at ξ, i.e. the (possibly empty) set of viscosity subgradients of V at ξ. We say that V is an *exponential decay RES-Lyapunov function* for system (4) on E if this property holds with $\alpha_3(r) = r$. We also specialize the above definitions for the notion of stability in three measures. Let $\rho \in \mathcal{K}$. A lower semicontinuous function $V : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ is an *SIT-Lyapunov function* for system (4) with gain ρ if there exist $\alpha_1, \alpha_2 \in \mathcal{K}_\infty$ so that for each ξ so that $|h(\xi)| > \rho(|g(\xi)|)$, it follows that $\alpha_1(|h(\xi)|) \leq V(\xi) \leq \alpha_2(|\xi|_\omega)$, and there exists $\alpha_3 : \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ continuous positive definite so that for each ξ so that $|h(\xi)| > \rho(|g(\xi)|)$, $\zeta \cdot v \leq -\alpha_3(V(\xi))$ for all $\zeta \in \partial_D V(\xi)$ and all $v \in F(\xi)$. Finally, V is an *exponential decay SIT-Lyapunov function* for system (4) with gain ρ if in addition this holds with $\alpha_3(r) = r$.

We then obtained the following theorem. For any system (4) and closed set $D \subset \mathbb{R}^n$, and denoting $E = \mathbb{R}^n \backslash D$, the following are equivalent:

- The system is relatively error stable with respect to D
- The system admits an RES-Lyapunov function on E
- The system admits an exponential decay RES-Lyapunov function on E

As a corollary (set $D = \{\xi \in \mathbb{R}^n : |h(\xi)| \leq \rho(|g(\xi)|)\}$), we have, for any $\rho \in \mathcal{K}$, that the following are equivalent:

- The system satisfies the SIT property with gain ρ
- The system admits an SIT-Lyapunov function with gain ρ
- The system admits an exponential decay SIT-Lyapunov function with gain ρ

This provides a characterization of the SIT property, which is related to MES as follows: MES implies SIT, and SIT and RMEB together imply MES. In conclusion, if (4) satisfies MES, then it admits an exponential decay SIT-Lyapunov function. Conversely, if it satisfies the RMEB property and it admits an SIT-Lyapunov function, then it satisfies MES.

ISS with Respect to Derivatives

Let us now turn to the derivative-ISS property that we studied in [s43]. In the ISS literature, inputs (thought of as "disturbances") are arbitrary (locally essentially bounded and Lebesgue-measurable) functions. Such an extremely rich set of possible input perturbations is well suited to model noise, as well as constant or periodic signals, slow parameter drift, and so on. If, on the one hand, this makes the notion of ISS extremely powerful, on the other hand it is known that ISS might sometimes be too stringent a requirement. In the output regulation literature, instead, the focus is often on "deterministic" disturbances, i.e., signals that can be generated by a finite dimensional nonlinear systems, (usually smooth). This is a class of persistent disturbances for which, roughly speaking, the following is true:

$$\|d\|_\infty \text{ small } \Rightarrow \|\dot{d}\|_\infty \text{ and derivatives of arbitrary order are also small.}$$

Under similar circumstances, for instance when cascading asymptotically stable systems, regarding the "forcing" system's state as a disturbance typically yields

$$\limsup_{t\to+\infty} |d(t)| = 0 \quad \Longrightarrow \quad \limsup_{t\to+\infty} |\dot{d}(t)| = 0.$$

Nevertheless, the classical definition of input-to-state stability completely disregards such additional information. Tracking of output references is yet another area where "derivative" knowledge is usually disregarded (the analysis is often performed only taking into account constant set-points), whereas such information could be exploited to get tighter estimates for the steady-state tracking error due to time-varying, smooth reference signals. An analogous situation also arises when parameter variations are taken into account (in adaptive control), and we expect the system to have suitably stable behavior for slow parameter drifts. The study of systems with slowly varying parameters has long been an focus of research. The analysis of such a system is usually carried out by first considering the systems corresponding to "frozen" parameters. If for all frozen parameters, the corresponding frozen systems uniformly posses certain stability properties, then it is reasonable to expect that the system with slowly varying parameters will posses the same property. A more general question is how the magnitudes of the time derivatives of the time varying parameters affect the behavior of the systems. In [s43],

we offered an ISS-like stability notion which takes into account robustness with respect to disturbances and their time derivatives. The new notion of "D^kISS" is defined through an estimate which involves the magnitudes of the inputs and their derivatives up to the k-th order. We also proposed several properties related to the D^kISS notion. All these properties serve to formalize the idea of "stable" dependence upon the inputs and their time derivatives. They differ in the formulation of the decay estimates which make precise how the magnitudes of derivatives affect the system. Finally, we illustrated by examples how these properties differ from each other and from ISS itself. Let us give some details now.

We denote by $W^{k,\infty}(J)$, for any integer $k \geq 1$ and any interval J, the Sobolev space consisting of all functions $u : J \to \mathbb{R}^m$ for which the $(k-1)$st derivative $u^{(k-1)}$ exists and is locally Lipschitz. For $k = 0$, we define $W^{0,\infty}(J)$ as the set of locally essentially bounded $u : J \to \mathbb{R}^m$. When $J = [0, +\infty)$, we omit J and write simply $W^{k,\infty}$. We say that the system (1) is *kth derivative input-to-state stable* (D^kISS) if there exist some $\mathcal{KL}$-function β, and $\mathcal{K}$-functions $\gamma_0, \gamma_1, \ldots, \gamma_k$ such that, for every input $u \in W^{k,\infty}$, the following holds:

$$|x(t,\xi,u)| \leq \beta(|\xi|,t) + \gamma_0(\|u\|) + \gamma_1(\|\dot u\|) + \cdots + \gamma_k\left(\|u^{(k)}\|\right)$$

for all $t \geq 0$. We say simply that the system is *D*ISS when it is D^1ISS and, of course, ISS is the same as D^kISS for $k = 0$. A dissipation characterization is as follows. Let $k \geq 1$. The system (1) is D^kISS if and only if there exists a smooth function $V : \mathbb{R}^n \times \mathbb{R}^{km} \to \mathbb{R}_{\geq 0}$ such that

- there exist some $\underline{\alpha}, \overline{\alpha} \in \mathcal{K}_\infty$ such that for all $(x, \mu^{[k-1]}) \in \mathbb{R}^n \times \mathbb{R}^{km}$, it holds that

$$\underline{\alpha}(|(x, \mu^{[k-1]})|) \leq V(x, \mu^{[k-1]}) \leq \overline{\alpha}(|(x, \mu^{[k-1]})|);$$

- there exist some $\alpha \in \mathcal{K}_\infty, \rho \in \mathcal{K}_\infty$ such that for all $x \in \mathbb{R}^n$ and all $\mu^{[k]} \in \mathbb{R}^{m(k+1)}$ with $\mu^{[k]} = (\mu_0, \mu_1, \ldots, \mu_k)$, it holds that

$$\frac{\partial V}{\partial x}(\cdot)f(x, \mu_0) + \frac{\partial V}{\partial \mu_0}(\cdot)\mu_1 + \frac{\partial V}{\partial \mu_1}(\cdot)\mu_2 + \cdots \frac{\partial V}{\partial \mu_{k-1}}(\cdot)\mu_k \leq -\alpha(V(\cdot)) + \rho(|\mu^{[k]}|)$$

(where "$(\cdot)$" means $(x, \mu^{[k-1]})$).

This provides a useful test for the property, and is helpful in proving a separation property analogous to those proved for IOSS and iISS and cited earlier. Clearly, if a system is D^kISS, then it is forward complete (for $u \in W^{k,\infty}$) and for some $\gamma_0, \gamma_1, \ldots, \gamma_k \in \mathcal{K}$ it holds that

$$\limsup_{t \to \infty} |x(t,\xi,u)| \leq \gamma_0(\|u\|) + \gamma_1(\|\dot u\|) + \cdots + \gamma_k(\|u^{(k)}\|).$$

If this holds, for some $\gamma_0, \ldots, \gamma_k \in \mathcal{K}$, for all $\xi \in \mathbb{R}^n$ and all $u \in W^{k,\infty}$, we say that a system satisfies the *k-asymptotic gain* (*k*-AG) property. The less obvious and more interesting converse was also shown to be true, namely, for a forward complete system (1), the following are equivalent:

- It is D^kISS
- It satisfies the k-AG property and the zero-input system $\dot x = f(x, 0)$ is (neutrally) stable

Many other results are proved in [s43], regarding stability properties of cascades as well as further characterizations. We also show there that the *DISS* property is strictly weaker than plain ISS, which is of course not surprising. (Although, interestingly, the two properties are equivalent for systems of dimension one.) Also, obviously *DISS* implies an ISS property for constant inputs, but it is perhaps less obvious that the converse does not hold (ISS with respect to constant inputs does not imply *DISS*).

Cascades

We now turn to some recent work on cascaded subsystems, with Arcak and Angeli, reported in [s55]. Constructive design methods such as backstepping and forwarding, which are based on recursive applications of cascade designs, together with the discovery of structural obstacles to stabilization such as the "peaking phenomenon" by Sussmann and Kokotović, have paved the road to major advances in nonlinear control. One of the main motivations for the stabilization of cascades came from the linear-nonlinear cascade

$$\dot{x} = f(x,z) \tag{6}$$
$$\dot{z} = Az + Bu \tag{7}$$

resulting from input-output linearization. Because global asymptotic stability (GAS) of the x-subsystem $\dot{x} = f(x,0)$ is not sufficient to achieve GAS of the whole cascade with z-feedback $u = Kz$, alternative designs which employ x-feedback were developed, such as the "feedback passivation" design of Kokotović and Sussmann. To achieve GAS by z-feedback, several authors studied general cascades in which the z-subsystem is nonlinear, and derived conditions for the x and z-subsystems that ensure stability of the cascade. Among these results, a particularly useful one is that if the x-subsystem is ISS with input z, and the z-subsystem is GAS, then the cascade is GAS. This result has been widely used for nonlinear designs based on the normal form, in which the *zero dynamics* (6) is ISS. Other results make less restrictive assumptions than ISS for the x-subsystem, but restrict the z-subsystem to be locally exponentially stable (LES). On the other hand, since the iISS property is less restrictive than ISS (because, in an iISS system, a bounded input may lead to unbounded solutions if its energy norm is infinite), [s55] analyzed the stability of nonlinear cascades in which the x-subsystem is merely iISS. The admissible iISS gains for stability were characterized from the speed of convergence of the z-subsystem. When the convergence is fast, the iISS gain function of the x-subsystem is allowed to be "steep" at zero. The paper showed that this trade-off between slower convergence and steeper iISS gain encompasses, and unifies, several results in the literature. In particular, if the x-subsystem is ISS then the slope of its iISS gain function is very gentle at zero, and tolerates every GAS z-subsystem no matter how slow its convergence is. On the other hand, if the convergence is exponential, that is if the z-subsystem is LES, then the cascade is stable for a large class of iISS gains. This class includes all iISS x-subsystems that are affine in the input z. Thus, for systems like (6)-(7), where a control law can be designed to render the z-subsystem GAS and LES, the iISS property of the x-subsystem ensures GAS of the cascade. Several results in the literature are special cases of the main result, including those that restrict the x-subsystem to be ISS and those that restrict the z-subsystem to be LES.

The paper [s55] also gave an output-feedback application of the cascade result, in the style of other work by Arcak. Due to the absence of a separation principle, it is necessary to design control laws that guarantee robustness against the observer error. A design was presented which renders the system iISS with respect to the observer error and, hence, ensures robustness

when the error is exponentially decaying. The advantage of this design over the more classical observer-based backstepping scheme is that it employs "weak" nonlinear damping terms which grow slower than previous ones, and result in a "softer" control law. Far more work is still required in this area, resulting in more general observer designs that make systems iISS with respect to observer error; see the latter discussion regarding separation principles, as well as the remarks about observers for chemical networks (which rely on an ISS property, as currently stated, and hence could potentially be greatly improved).

ISS Stabilization Under Feedback

A different direction of research is that in our work with Malisoff and Rifford, reported in [s14], which dealt with the ISS-stabilization of systems

$$\dot{x} = f(x) + G(x)u \tag{8}$$

(where f and G are locally Lipschitz vector fields on $\mathbb{R}^n$, $f(0) = 0$, and the control u is valued in $\mathbb{R}^m$; we also studied possible extensions to fully nonlinear systems). The main theorems show that, if the system (8) is globally asymptotically controllable (GAC), then there exists a feedback $K : \mathbb{R}^n \to \mathbb{R}^m$ for which

$$\dot{x} = f(x) + G(x)K(x) + G(x)u \tag{9}$$

is ISS, which, when written as $\dot{x} = f(x) + G(x)(K(x) + u)$, can be interpreted as robustness with respect to actuator errors. Recall that one of the original motivations for the introduction of the notion of ISS was to give a precise formulation of the fact that stabilizable systems may be made also stable with respect to actuator errors. This was central to showing the existence of coprime factorizations for classes of systems including feedback linearizable systems. Since a continuous stabilizing feedback K fails to exist in general, one is forced to consider discontinuous feedbacks K, so solutions of (9) are understood in the senses of sampling and of Euler solutions (each type of solution is covered by a different theorem). The results in [s14] extended our original ones (1989), which dealt with the case when the original system is stabilizable with regular feedback (interestingly, however, the actual definition of K is different, in the new paper, even when specialized to the case covered by the older work). In particular, our results apply to the example of Brockett's nonholonomic integrator.

It was a long-standing problem to obtain such generalizations, and they heavily rely upon the new techniques involving semiconcave control Lyapunov functions. Our results also strengthened our paper 1997 with Clarke et al., which constructed feedbacks for GAC systems which render the closed loop systems globally asymptotically stable. They apply in the more general situation where measurement noise may occur. In particular, our feedback K has the additional feature that the *perturbed* system

$$\dot{x} = f(x) + G(x)K(x + e) + G(x)u \tag{10}$$

is also ISS when the observation error $e : [0, \infty) \to \mathbb{R}^n$ in the controller is *sufficiently small*. In this context, the precise value of $e(t)$ is unknown to the controller, but information about upper bounds on the magnitude of $e(t)$ can be used to design the feedback. We showed these theorems: (1) If (8) is GAC, then there exists a feedback K for which (10) is ISS for Euler solutions; (2) If system (8) is GAC, then there exists a feedback K such that (10) is ISS for sampling solutions. The first theorem characterizes the uniform limits of sampling solutions of

(10); from a computational standpoint, it is also desirable to know how frequently to sample in order to achieve ISS for sampling solutions. This information is provided by the second result.

Let us provide some details of [s14]. For each $k \in \mathbb{N}$ and $r > 0$, we let $\mathcal{M}^k$ be the set of measurable $u : [0, \infty) \to \mathbb{R}^k$ with are essentially bounded, $\mathcal{M}_r^k := \{u \in \mathcal{M}^k : |u|_\infty \leq r\}$, where $|\cdot|_\infty$ is the essential supremum, and $r\mathcal{B}_k := \{x \in \mathbb{R}^k : |x| < r\}$ for each $k \in \mathbb{N}$ and $r > 0$, whose closure is $r\bar{\mathcal{B}}_k$. We also set $\mathcal{O} := \{e : [0, \infty) \to \mathbb{R}^n\}$, $\sup(e) = \sup\{|e(t)| : t \geq 0\}$ for all $e \in \mathcal{O}$, and $\mathcal{O}_\eta := \{e \in \mathcal{O} : \sup(e) \leq \eta\}$ for each $\eta > 0$. For any compact set $\mathcal{F} \subseteq \mathbb{R}^n$ and $\varepsilon > 0$, we define the compact set $\mathcal{F}^\varepsilon := \{x \in \mathbb{R}^n : \inf\{|x - p| : p \in \mathcal{F}\} \leq \varepsilon\}$. Given a continuous function $h : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n : (x, u) \mapsto h(x, u)$ which is locally Lipschitz in x uniformly on compact subsets of $\mathbb{R}^n \times \mathbb{R}^m$, we let $\phi_h(\cdot, x_o, u)$ denote the trajectory of $\dot{x} = h(x, u)$ starting at $x_o \in \mathbb{R}^n$ for each $u \in \mathcal{M}^m$. In this case, $\phi_h(\cdot, x_o, u)$ is defined on some maximal interval $[0, t)$, with $t > 0$ depending on u and x_o. A system $\dot{x} = h(x, u)$ is said to be *globally asymptotically controllable (GAC)* provided there exist a nondecreasing function $\sigma : [0, \infty) \to [0, \infty)$ and a function $\beta \in \mathcal{KL}$ satisfying the following: For each $x_o \in \mathbb{R}^n$, there exists $u \in \mathcal{M}^m$ such that $|\phi_h(t, x_o, u)| \leq \beta(|x_o|, t)$ for all $t \geq 0$; and $|u(t)| \leq \sigma(|\phi_h(t, x_o, u)|)$ for a.e. $t \geq 0$. In this case, we call σ the *GAC modulus* of $\dot{x} = h(x, u)$. In our main results, the controllers are discontinuous feedbacks, so the dynamics will be discontinuous in the state variable. Therefore, we form trajectories through sampling, and through uniform limits of sampling trajectories, as follows. We say that $\pi = \{t_o, t_1, t_2, \ldots\} \subset [0, \infty)$ is a *partition* of $[0, \infty)$ provided $t_o = 0$, $t_i < t_{i+1}$ for all $i \geq 0$, and $t_i \to \infty$ as $i \to +\infty$. The set of all partitions of $[0, \infty)$ is denoted by Par. Let $F : \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^m \to \mathbb{R}^n : (x, p, u) \mapsto F(x, p, u)$ be a continuous function which is locally Lipschitz in x uniformly on compact subsets of $\mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^m$. A *feedback* for F is defined to be any locally bounded function $K : \mathbb{R}^n \to \mathbb{R}^m$ for which $K(0) = 0$. In particular, we allow discontinuous feedbacks. The arguments x, p, and u in F are used to represent the state, feedback value, and actuator error, respectively. Given a feedback $K : \mathbb{R}^n \to \mathbb{R}^m$, $\pi = \{t_o, t_1, t_2, \ldots\} \in$ Par, $x_o \in \mathbb{R}^n$, $e \in \mathcal{O}$, and $u \in \mathcal{M}^m$, the *sampling solution* for the initial value problem (IVP)

$$\dot{x}(t) = F(x(t), K(x(t) + e(t)), u(t)) \tag{11}$$

$$x(0) = x_o \tag{12}$$

is the continuous function defined by recursively solving $\dot{x}(t) = F(x(t), K(x(t_i) + e(t_i)), u(t))$ from the initial time t_i up to time $s_i = \sup\{s \in [t_i, t_{i+1}] : x(\cdot)$ is defined on $[t_i, s)\}$, where $x(0) = x_o$. In this case, the sampling solution of (11)-(12) is defined from time zero up to time $\bar{t} = \inf\{s_i : s_i < t_{i+1}\}$. This sampling solution will be denoted by $t \mapsto x_\pi(t; x_o, u, e)$ to exhibit its dependence on $\pi \in$ Par, $x_o \in \mathbb{R}^n$, $u \in \mathcal{M}$, and $e \in \mathcal{O}$, or simply by x_π when the dependence is clear from the context. In particular, if $s_i = t_{i+1}$ for all i, then $\bar{t} = +\infty$ (as the infimum of the empty set), so in that case, the sampling solution $t \mapsto x_\pi(t; x_o, u, e)$ is defined on $[0, \infty)$. We also define the upper diameter and lower diameter of a partition $\pi = \{t_o, t_1, t_2, \ldots\}$ by $\bar{d}(\pi) = \sup(t_{i+1} - t_i)$ and $\underline{d}(\pi) = \inf(t_{i+1} - t_i)$ (sup and inf over $i \geq 0$) respectively. We let Par$(\delta) := \{\pi \in$ Par $: \bar{d}(\pi) < \delta\}$ for each $\delta > 0$. We say that a function $y : [0, \infty) \to \mathbb{R}^n$ is an *Euler solution* of (11)-(12) for $u \in \mathcal{M}$ provided there are sequences $\pi_r \in$ Par and $e_r \in \mathcal{O}$ such that

- $\bar{d}(\pi_r) \to 0$;
- $\sup(e_r)/\underline{d}(\pi_r) \to 0$; and
- $t \mapsto x_{\pi_r}(t; x_o, u, e_r)$ converges uniformly to y as $r \to +\infty$.

We say that (11) is *ISS for sampling solutions* provided there exist $\beta \in \mathcal{KL}$ and $\gamma \in \mathcal{K}_\infty$ satisfying: For each $\varepsilon, M, N > 0$ with $0 < \varepsilon < M$, there exist $\delta = \delta(\varepsilon, M, N)$ and $\kappa = \kappa(\varepsilon, M, N)$ such that for each $\pi \in \mathrm{Par}(\delta)$, $x_o \in M\bar{\mathcal{B}}_n$, $u \in \mathcal{M}_N^m$, and $e \in \mathcal{O}$ for which $\sup(e) \leq \kappa\underline{d}(\pi)$,

$$|x_\pi(t; x_o, u, e)| \leq \max\{\beta(M, t) + \gamma(N), \varepsilon\}$$

for all $t \geq 0$. We say that the system (11) is *ISS for Euler solutions* provided there exist $\beta \in \mathcal{KL}$ and $\gamma \in \mathcal{K}_\infty$ satisfying: If $u \in \mathcal{M}$, $x_o \in \mathbb{R}^n$, and $t \mapsto x(t)$ is an Euler solution of (11)-(12), then

$$|x(t)| \leq \beta(|x_o|, t) + \gamma(|u|_\infty)$$

for all $t \geq 0$.

Let $h : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n : (x, u) \mapsto h(x, u)$ be continuous, locally Lipschitz in x uniformly on compact subsets of $\mathbb{R}^n \times \mathbb{R}^m$, and so that $h(0, 0) = 0$. Recall that a *control-Lyapunov function (clf)* for $\dot{x} = h(x, u)$ is a continuous, positive definite, proper function $V : \mathbb{R}^n \to \mathbb{R}$ for which there exists a continuous, positive definite function $W : \mathbb{R}^n \to \mathbb{R}$ and a nondecreasing function $\alpha : [0, \infty) \to [0, \infty)$, which satisfy:

$$\forall \zeta \in \partial_P V(x), \quad \min_{|u| \leq \alpha(|x|)} \langle \zeta, h(x, u) \rangle \leq -W(x)$$

for all $x \in \mathbb{R}^n$. In this case, one calls (V, W) a *Lyapunov pair* for the system. (The *proximal superdifferential* (resp., *proximal subdifferential*) of a function $V : \Omega \to \mathbb{R}$ at $x \in \Omega$, where Ω is an open subset of $\mathbb{R}^n$, which is denoted by $\partial^P V(x)$ (resp., $\partial_P V(x)$), is defined to be the set of all $\zeta \in \mathbb{R}^n$ for which there exist $\sigma, \eta > 0$ such that $V(y) - V(x) - \sigma|y - x|^2 \leq \langle \zeta, y - x \rangle$ (resp. $V(y) - V(x) - \sigma|y - x|^2 \geq \langle \zeta, y - x \rangle$) for all $y \in x + \eta\mathcal{B}_n$.) We proved in 1982 that clf's always exist for GAC systems. This theorem was considerably refined by Rifford, who showed that, for any GAC system, there exists a clf V which is semiconcave on $\mathbb{R}^n \setminus \{0\}$ so that

$$\forall \zeta \in \partial_L V(x), \quad \min_{|u| \leq \alpha(|x|)} \langle \zeta, h(x, u) \rangle \leq -V(x) \tag{13}$$

for all $x \in \mathbb{R}^n$. (A continuous function $g : \Omega \to \mathbb{R}$ is *semiconcave* provided for any point $x_o \in \Omega$, there exist $\rho, C > 0$ such that $g(x) + g(y) - 2g\left(\frac{x+y}{2}\right) \leq C||x - y||^2$ for all $x, y \in x_o + \rho\mathcal{B}_n$. The *limiting subdifferential* of a continuous function $V : \Omega \to \mathbb{R}$ at $x \in \Omega$ is $\partial_L V(x) := \{q \in \mathbb{R}^n : \exists x_n \to x \ \& \ q_n \in \partial_P V(x_n) \text{ s.t. } q_n \to q\}$. If V is semiconcave, then it is locally Lipschitz, and $\emptyset \neq \partial_L V(x) \subseteq \partial^P V(x)$ for all $x \in \Omega$.) The construction of the feedback is done starting from a clf as in this result.

Let $x \mapsto \zeta(x)$ be any selection of $\partial_L V(x)$ on $\mathbb{R}^n \setminus \{0\}$ and $\zeta(0) \in \mathbb{R}^n$ be arbitrary. For each $x \in \mathbb{R}^n \setminus \{0\}$, we can choose $u = u_x \in \alpha(|x|)\mathcal{B}_m$ that satisfies the inequality in (13) for the dynamics $h(x, u) = f(x) + G(x)u$ and $\zeta = \zeta(x)$. First define the feedback $K_1 : \mathbb{R}^n \to \mathbb{R}^m$ by $K_1(x) = u_x$ for all $x \neq 0$ and $K_1(0) = 0$. Next, introduce the following functions: $a(x) = \langle \zeta(x), f(x) + G(x)K_1(x) \rangle$, $b_j(x) = \langle \zeta(x), g_j(x) \rangle$ for all $j = 1, 2, \ldots, m$, and finally

$$K_2(x) = -2V(x)(\mathrm{sign}\{b_1(x)\}, \mathrm{sign}\{b_2(x)\}, \ldots, \mathrm{sign}\{b_m(x)\})^T,$$

where g_j is the jth column of G, and where $\mathrm{sign}\{s\} = 1, -1, 0$ if $s > 0, < 0, = 0$ respectively. The proof then shows that $K := K_1 + K_2$ is so that $\dot{x}(t) = F(x(t), K(x(t) + e(t)), u(t))$ is ISS for sampling solutions. An analogous result holds for Euler solutions.

Minimum-Phase Properties

Another recent area of research dealt with notions associated to the minimum-phase property; we next describe this work, done in collaboration with Liberzon and Morse, cf. [s50]. Recall that a continuous-time linear single-input/single-output (SISO) system is said to be minimum-phase if the numerator polynomial of its transfer function has all its zeros in the open left half plane. If a linear system of relative degree r is minimum-phase, then the "inverse" system, driven by the r-th derivative of the output of the original system, is stable. (For left-invertible, multi-input/multi-output (MIMO) systems, in place of the zeros of the numerator one appeals to the so-called transmission zeros.) The notion of a minimum-phase system is of great significance in many areas of linear system analysis and design. In particular, it has played an important role in parameter adaptive control. A basic example is provided by the "certainty equivalence output stabilization theorem", which says that when a certainty equivalence, output stabilizing adaptive controller is applied to a minimum-phase linear system, the closed-loop system is detectable through the tuning error. In essence, this result serves as a justification for the certainty equivalence approach to adaptive control of minimum-phase linear systems.

For nonlinear systems that are affine in controls, a major contribution of Byrnes and Isidori was to define the minimum-phase property in terms of the new concept of *zero dynamics*. The zero dynamics are the internal dynamics of the system under the action of an input that holds the output constantly at zero. The system is called minimum-phase if the zero dynamics are (globally) asymptotically stable. In the SISO case, a unique input capable of producing the zero output is guaranteed to exist if the system has a uniform relative degree, which is now defined to be the number of times one has to differentiate the output until the input appears. (Extensions to MIMO systems are discussed in Isidori's book as well.) In view of the need to work with the zero dynamics, this definition of a minimum-phase nonlinear system prompts one to look for a change of coordinates that transforms the system into a certain normal form. It has also been recognized that just asymptotic stability of the zero dynamics is sometimes insufficient for control design purposes, so that additional requirements need to be placed on the internal dynamics of the system. One such common requirement is that the internal dynamics be ISS with respect to the output and its derivatives up to order $r-1$, where r is the relative degree. Thus, it is of interest to develop alternative (and possibly stronger) concepts which can be applied when asymptotic stability of zero dynamics is difficult to verify or inadequate.

In the paper [s50], we introduced the notion of *output-input stability (OIS)*, which does not rely on zero dynamics or normal forms. Loosely speaking, a system is OIS if its state and input eventually become small when the output and derivatives of the output are small. The class of OIS systems includes all left-invertible linear systems whose transmission zeros have negative real parts and all affine systems in global normal form with input-to-state stable internal dynamics. Conceptually, the new notion relates to the existing concept of a minimum-phase nonlinear system in much the same way as input-to-state stability (ISS) relates to global asymptotic stability under zero inputs (0-GAS), modulo the duality between inputs and outputs. An important outcome of this parallelism is that the tools that have been developed for studying ISS and related concepts can be employed to study output-input stability. If a system has a uniform relative degree (in an appropriate sense) and is detectable through the output and its derivatives up to some order, uniformly over all inputs that produce a given output, then it is output-input stable. For SISO systems that are real analytic in controls, we also showed that the converse is true, thus arriving at a useful equivalent characterization of output-input

stability. For general OIS systems in our sense, we show in the paper that stabilizing the output and its derivatives results in internal stability, as one should expect of a notion of minimum phase systems. We also established a natural nonlinear counterpart of the certainty equivalence output stabilization theorem from linear adaptive control, an intuitively appealing result that did not seem to be attainable within the boundaries of the existing theory of minimum-phase nonlinear systems. Let us provide a few technical details. (We restrict to the single-input single-output case; the vector case is similar but slightly more complicated technically.)

A smooth system $\dot{x} = f(x, u)$, $y = h(x)$, is defined to be OIS if there exist a positive integer N, a class $\mathcal{KL}$ function β, and a class $\mathcal{K}_\infty$ function γ such that for every initial state $x(0)$ and every $N - 1$ times continuously differentiable input u the inequality

$$|u(t)| + |x(t)| \leq \beta(|x(0)|, t) + \gamma(\|y^N\|_{[0,t]})$$

holds for all t in the domain of the definition of the solution, where "y^N" lists y as well as its first N derivatives, and we are taking supremum norms as usual.

For each nonnegative integer k, restricting the input u to be of class C^{k-1}, we can consider the *k-output extension* of the system, $\dot{x} = f(x, u)$, $y^k = h_k(x, u, \ldots, u^{(k-1)})$ where $h_k(x, u, \ldots, u^{(k-1)}) := (H_0(x); H_1(x, u); \ldots; H_k(x, u, \ldots, u^{(k-1)}))$ is the new output map. (For $k = 0, 1, \ldots$ define, recursively, the functions $H_k : \mathbb{R}^n \times \mathbb{R}^k \to \mathbb{R}$ by the formulas $H_0 := h$ and $H_{k+1}(x, u_0, \ldots, u_k) := \frac{\partial H_k}{\partial x} f(x, u_0) + \sum_{j=0}^{k-1} \frac{\partial H_k}{\partial u_j} u_{j+1}$. These give the derivatives of the output: if the input $u(\cdot)$ is in C^{k-1}, then along each solution $x(\cdot)$ the corresponding output has a continuous k-th derivative satisfying $y^{(k)}(t) = H_k(x(t), u(t), \ldots, u^{(k-1)}(t))$.) In other words, we redefine the output of the system to be y^k. We say that the original system is *weakly OSS of order k* if its k-output extension is OSS, and *weakly uniformly OSS of order k* if its k-output extension is uniformly OSS, in the by now standard sense of OSS as a special case of IOSS, and uniformity understood with respect to all inputs, or equivalently in a differential inclusion sense. We say that a positive integer r is the (uniform) *relative degree* of the system if the following two conditions hold: (1) for each $k < r$, the function H_k is independent of $u_0, \ldots, u_{k-1}$, and (2) there exist two class $\mathcal{K}_\infty$ functions ρ_1 and ρ_2 such that $|u_0| \leq \rho_1(|x|) + \rho_2(|H_r(x, u_0)|)$ for all $x \in \mathbb{R}^n$ and all $u_0 \in \mathbb{R}$. (If there exists such an integer r, then it is unique.) A system is defined to be *strongly minimum-phase* if it has a relative degree r and is weakly uniformly OSS of order $r - 1$

It is shown in [s50] that: (1) given any system with relative degree r and weakly uniformly OSS of order k, for some k, the system is OIS, with $N = \max\{r, k\}$; (2) conversely, if the system is OIS, then it is weakly uniformly OSS order N, and if in addition the function $f(x, \cdot)$ is real analytic in u for each fixed x, $f(0, 0) = 0$ and $h(0) = 0$, then it has a relative degree $r \leq N$. Thus, for systems with relative degree, OIS is equivalent to weak uniform OSS of order k for some $k \leq N$, and under the additional assumptions on f and h, OIS is equivalent to the existence of a relative degree $r \leq N$ plus weak uniform OSS of order k for some $k \leq N$.

2.2 Some Details: Systems/Control Problems Inspired by Molecular Biology

We describe next some control and systems problems motivated by molecular biology.

Monotone Systems and Cauchy Gains

In [s31], we consider systems that evolve in state spaces X which are subsets of Euclidean space $\mathbb{R}^n$ with an order $\succ$ induced by a closed convex cone K. Similarly, the input-value set $\mathcal{U}$

and output-value set $\mathcal{Y}$ are subsets of ordered Euclidean spaces, with orders induced by cones K^u and K^y, but we use the same symbol ($\succeq$) to denote any of the orders. We say that a system $\dot{x} = f(x, u)$, $y = h(x)$ is *monotone* provided that $h : X \to \mathcal{Y}$ is a monotone map and that the flow preserves order, i.e. the implication below holds for all $t \geq 0$:

$$u_1 \succeq u_2, \ x_1 \succeq x_2 \quad \Rightarrow \quad \phi(t, x_1, u_1) \succeq \phi(t, x_2, u_2)$$

where $u_1 \succeq u_2$ mans that $u_1(t) \succeq u_2(t)$ for all t and where $\phi(t, \xi, u)$ is the state at time t obtained if the initial state is ξ and the external input is $u(\cdot)$. The map f is defined on $\tilde{X} \times \mathcal{U}$, where $\tilde{X}$ is some open subset of $\mathbb{R}^n$ which contains X, and $f(x, u)$ is continuous in (x, u) and locally Lipschitz continuous in x locally uniformly on u. Moreover, we assume that solutions with initial states in X are defined for all $t \geq 0$ (forward completeness) and that the set X is forward invariant. For simplicity in this discussion, we will assume that the sets X and $\mathcal{U}$ are convex, and that the order cones all have nonempty interiors, although far less is needed for the results to be quoted to hold, see [s31]. Recall that the Bouligand (or "contingent") tangent cone to a set S at a point ξ is the set

$$\mathcal{T}_\xi S := \left\{ \lim_{i \to \infty} \frac{1}{t_i}(\xi_i - \xi) \,\middle|\, \xi_i \underset{S}{\to} \xi, \ t_i \searrow 0 \right\}$$

where "$\xi_i \underset{S}{\to} \xi$" means that $\xi_i \to \xi$ as $i \to \infty$ and that $\xi_i \in S$ for all i. The following is an infinitesimal characterization of monotonicity, expressed directly in terms of the vector field, which does not require the explicit computation of solutions: A system is monotone if and only if, for all ξ_1, ξ_2:

$$\xi_1 \succeq \xi_2 \text{ and } u_1 \succeq u_2 \ \Rightarrow \ f(\xi_1, u_1) - f(\xi_2, u_2) \in \mathcal{T}_{\xi_1 - \xi_2} K$$

(or, equivalently, $\xi_1 - \xi_2 \in \partial K$ and $u_1 \succeq u_2 \Rightarrow f(\xi_1, u_1) - f(\xi_2, u_2) \in \mathcal{T}_{\xi_1 - \xi_2} K$). A particular case is when $K = \mathbb{R}^n_{\geq 0}$ and $K^u = \mathbb{R}^m_{\geq 0}$ (with $\mathcal{U} = \mathbb{R}^m$). Such systems are called *cooperative systems*. Assuming that f is continuously differentiable, cooperativity if equivalent to the two properties $\frac{\partial f^i}{\partial x^j}(x, u) \geq 0$ for all $i \neq j$ and $\frac{\partial f^i}{\partial u^j}(x, u) \geq 0$ for all i, j, holding for all x, u. More general orthants must be considered, however, in order to study applications like MAPK cascades, discussed earlier. For such more general orthants, similar characterizations are given in [s31] in [s3], together with simple graph-theoretic tests. Cascades

$$
\begin{aligned}
\dot{x}_1 &= f_1(x_1, x_2, \ldots, x_N, u) \\
\dot{x}_2 &= f_2(x_2, \ldots, x_N, u) \\
&\vdots \qquad \vdots \\
\dot{x}_i &= f_i(x_i, \ldots, x_N, u) \\
&\vdots \qquad \vdots \\
\dot{x}_N &= f_N(x_N, u)
\end{aligned}
\tag{14}
$$

of monotone systems are again monotone (with respect to the obvious orders), which makes the notion particularly suitable for decomposition approaches to systems analysis and control design.

A notion of "Cauchy gain" was introduced in [s61] in order to quantify the amplification of signals by systems in a manner useful for biological applications. For monotone dynamical

systems satisfying an additional property, it is possible to obtain tight estimates of Cauchy gains. This is achieved by showing that the output values $y(t)$ corresponding to an input $u(\cdot)$ are always "sandwiched" in between the outputs corresponding to two constant inputs which bound the range of $u(\cdot)$. This additional property motivated our looking at monotone systems to start with. We say that a system has a well-defined *static Input/State (I/S) characteristic*

$$k_x(\cdot) : \mathcal{U} \to X$$

if for each constant input $u(t) \equiv \bar{u}$ there exists a (necessarily unique) globally asymptotically stable equilibrium $k_x(\bar{u})$. We say that the characteristic is *nondegenerate* if the Jacobian $D_x f(k_x(\bar{u}), \bar{u})$ is nonsingular, for all $\bar{u}$. If a characteristic exists, we also define the *static Input/Output (I/O) characteristic* as $k_y(\bar{u}) := h(k_x(\bar{u}))$. Cascades of systems with well-defined I/O characteristics also have well-defined I/O characteristics.

The key technical property for monotone systems with well-defined characteristics is as follows (there is also a multivariable version, but we provide only the scalar statement here): Suppose that a monotone single-input single-output ("SISO") system has a static I/O characteristic $k_y(\cdot)$. Then, for each initial condition ξ and each bounded input $u(\cdot)$, the following holds:

$$k_y(u_{\text{inf}}) \le \liminf_{t \to +\infty} y(t, \xi, u) \le \limsup_{t \to +\infty} y(t, \xi, u) \le k_y(u_{\text{sup}}) \,.$$

(If, instead, outputs are ordered by $\geq$, then the inequalities get reversed.) The Cauchy gain, in the sense of [s61], can be estimated from this result. For any signal ω defined on $[0, +\infty)$ and taking values in a Banach space, we defined in [s61] its "asymptotic amplitude" as follows:

$$\|\omega\|_{\text{aa}} := \limsup_{s,t \to \infty} \|\omega(t) - \omega(s)\| \in [0, \infty] \,.$$

This measures how "non-Cauchy" a function is, since $\|\omega\|_{\text{aa}} = 0$ if and only if $\lim_{t \to \infty} \omega(t)$ exists. In these terms, we defined a system as having a *Cauchy gain* $\gamma \in \mathcal{K}_\infty$ if $\|y\|_{\text{aa}} \le \gamma(\|u\|_{\text{aa}})$ for all input/output pairs u, y.

A *small-gain theorem* for monotone systems is as follows. Consider the following interconnection of two SISO dynamical systems

$$\begin{aligned} \dot{x} &= f_x(x, w), & y &= h_x(x) \\ \dot{z} &= f_z(z, y), & w &= h_z(z) \end{aligned}$$

with $\mathcal{U}_x = \mathcal{Y}_z$ and $\mathcal{U}_z = \mathcal{Y}_x$. Suppose that: (1) the first system is monotone when its input w as well as output y are ordered according to the "standard order" induced by the positive real semi-axis; (2) the second system is monotone when its input y is ordered according to the standard order induced by the positive real semi-axis and its output w is ordered by the opposite order (i.e., the one induced by the negative real semi-axis); (3) the respective static I/S characteristics $k_x(\cdot)$ and $k_z(\cdot)$ exist (thus, the static I/O characteristics $k_y(\cdot)$ and $k_w(\cdot)$ exist too and are respectively monotonically increasing and monotonically decreasing); (4) every solution of the closed-loop system is bounded; and (5) the scalar discrete time dynamical system, evolving in $\mathcal{U}_x$:

$$u_{k+1} = (k_w \circ k_y)(u_k)$$

has a unique globally attractive equilibrium $\bar{u}$. Then, the closed-loop system has a globally attractive equilibrium.

This small-gain result allows testing stability of systems of high dimension, under negative feedback, by restricting analysis to a one-dimensional discrete-time system. As a concrete illustration, let us consider the following open-loop system:

$$
\begin{aligned}
\dot{x}_1 &= \frac{v_2\,(100 - x_1)}{k_2 + (100 - x_1)} - \frac{g_1 x_1}{k_1 + x_1}\,\frac{g_2 + u}{g_4 + u} \\[2mm]
\dot{y}_1 &= \frac{v_6\,(300 - y_1 - y_3)}{k_6 + (300 - y_1 - y_3)} - \frac{\kappa_3\,(100 - x_1)\,y_1}{k_3 + y_1} \\[2mm]
\dot{y}_3 &= \frac{\kappa_4\,(100 - x_1)\,(300 - y_1 - y_3)}{k_4 + (300 - y_1 - y_3)} - \frac{v_5\,y_3}{k_5 + y_3} \\[2mm]
\dot{z}_1 &= \frac{v_{10}\,(300 - z_1 - z_3)}{k_{10} + (300 - z_1 - z_3)} - \frac{\kappa_7\,y_3\,z_1}{k_7 + z_1} \\[2mm]
\dot{z}_3 &= \frac{\kappa_8\,y_3\,(300 - z_1 - z_3)}{k_8 + (300 - z_1 - z_3)} - \frac{v_9\,z_3}{k_9 + z_3}
\end{aligned}
\tag{15}
$$

This is the model studied by Kholodenko, for MAPK cascades, from which we also borrow the values of constants (with a couple of exceptions, see below): $g_1 = 0.22$, $g_2 = 45$, $g_4 = 50$, $k_1 = 10$, $v_2 = 0.25$, $k_2 = 8$, $\kappa_3 = 0.025$, $k_3 = 15$, $\kappa_4 = 0.025$ $k_4 = 15$, $v_5 = 0.75$, $k_5 = 15$, $v_6 = 0.75$, $k_6 = 15$, $\kappa_7 = 0.025$, $k_7 = 15$, $\kappa_8 = 0.025$, $k_8 = 15$, $v_9 = 0.5$, $k_9 = 15$, $v_{10} = 0.5$, $k_{10} = 15$. Units are as follows: concentrations and Michaelis constants (k's) are expressed in nM, catalytic rate constants (κ's) in s^{-1}, and maximal enzyme rates (v's) in $nM.s^{-1}$. Kholodenko showed that oscillations may arise in this system for appropriate values of negative feedback gains. (We have slightly changed the input term, using coefficients g_1, g_2, g_4, because we wish to emphasize the open-loop system before considering the effect of negative feedback.)

To apply our small-gain theorem, we must verify that the system is monotone and has a well-defined I/S characteristic. As a cascade of a three systems, of dimensions 1, 2, and 2 respectively (the x, y, and z subsystems) it is enough to show these properties for each individual subsystem. The x subsystem is of dimension one and easy to study, so we concentrate on the y and z subsystems. Each of this has the following generic form:

$$
\left.
\begin{aligned}
\dot{x}^1 &= -u\theta_1(x^1) + \theta_2(a - x^1 - x^2) \\
\dot{x}^2 &= u\theta_3(a - x^1 - x^2) - \theta_4(x^2)
\end{aligned}
\right\} = f(x^1, x^2, u)
$$

for an appropriate constant a (where the functions θ_i's have the form $\frac{a_i r}{1 + b_i r}$), and evolving on the triangle $X = \{[x^1, x^2] : x^1 \geq 0,\ x^2 \geq 0, x^1 + x^2 \leq a\}$. The paper [s31] shows that a system of this form is monotone with respect to a suitable orthant order, and that unique global asymptotically stable equilibria exist for each constant input u. Since the complete system is a cascade of such elementary subsystems, we know that our small-gain result may be applied. Figure 1 shows the I/O characteristic of this system, as well as the characteristic corresponding to a feedback $u = \frac{K}{1+y}$, with the gain $K = 30000$. It is evident from this planar plot that the small-gain condition is satisfied - a "spiderweb" diagram shows convergence. Our theorem then guarantees global attraction to a unique equilibrium. Indeed, Figure 2 shows a typical state trajectory. A somewhat different small-gain theorem, based only on Cauchy gains and not monotonicity, was proved in [s61], and applied in particular to the model of MAPK cascades under negative feedback with parameters given in Shvartsman's work. In that reference, a bifurcation analysis is performed with respect to the feedback gain k as a parameter.
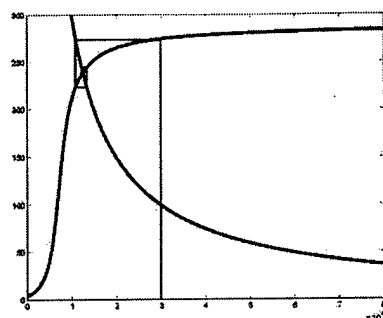
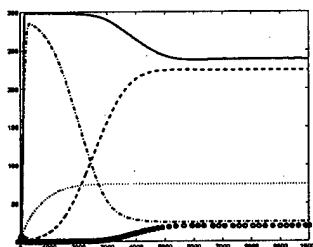Figure 1: I/O characteristic and small-gain illustration for MAPK example

Figure 2: Simulation of MAPK system under negative feedback satisfying small-gain conditions. Key: x_1 dots, x_2 dashes, x_3 dash-dot, x_4 circles, x_5 solid

Numerically, it is found that oscillations result when this parameter attains the value $k = 5.2$. The Cauchy gain approach shows that stability remains until at least $k = 3.92$, which is a very tight estimate. Keeping in mind that our results are valid even under arbitrary delays on feedback loops, this is quite remarkable.

Robust Stability and Observers for Chemical Networks

Designers strive to engineer as much robustness as possible into control systems. However, few systems perform acceptably under truly large variations in parameters. In biology, in contrast, there is often a very large variability in intracellular concentrations of chemicals, due to, for instance, unequal division among daughter cells during mitosis, gene duplications, or mutations. If functions critical to the survival of the organism are not affected, this means that evolution must have selected for appropriately robust structures. Thus, the study of biological models might provide a guide to novel robust structures for engineering applications.

The paper [s66], motivated originally by a model in immunology, represents another direction of recent research by the PI. It led to the study of classes of systems for which stability is robust independently of numerical values of parameters. The class of systems studied there

can be defined mathematically as consisting of systems of the following form:

$$\dot{x} = f(x) = \sum_{i=1}^{m}\sum_{j=1}^{m} a_{ij}\, x_1^{b_{1j}} x_2^{b_{2j}} \ldots x_n^{b_{nj}}\,(b_i - b_j) \tag{16}$$

where the constants a_{ij} are all ≥ 0, and the matrix $A = [a_{ij}]$ is irreducible (a block irreducibility assumption is sufficient for most of the results). The number m can be thought of as the number of reactions in a chemical system, and is $\leq n$, the dimension of the system (number of "species" participating in the reactions). The column vectors $b_j \in \mathbb{R}^n$ have entries $b_{1j}, b_{2j}, \ldots, b_{nj}$, which are nonnegative integers, and the matrix $B := [b_1, b_2, \ldots, b_m]$ has rank m, and none of its rows vanishes. This is viewed as a system evolving on the positive orthant $\mathbb{R}^n_+$ (which is easily seen to be forward invariant for the dynamics). The space $\mathcal{D} := \mathrm{span}\{b_i - b_j : i, j = 1, \ldots, m\}$ is the *stoichiometric subspace*. Its translates are invariant under the motions (since $\eta \cdot (b_i - b_j) = 0$ implies $\eta \cdot \dot{x}(t) \equiv 0$ for any vector η).

This type of system represents the "zero deficiency and weakly reversible" chemical networks studied by Feinberg, Horn, and Jackson in the 1970s. In their language, we are dealing with ideal mass-action kinetics, weakly reversible networks, with deficiency zero. (The latter constraint means that $m - \ell - d = 0$, where d is the dimension of the stoichiometric subspace and ℓ is the number of linkage classes, i.e., the number of connected components in the reaction graph. The irreducibility assumption corresponds to setting $\ell = 1$ for simplicity.) We assume, in addition, that there are no boundary equilibria on positive classes, that is, if a parallel translate $p + \mathcal{D}$ of $\mathcal{D}$ is such that it intersects the strictly positive main orthant, then there are no equilibria in the intersection of $p + \mathcal{D}$ and the boundary of the positive main orthant. This is a condition that is satisfied in most examples that we have encountered so far, and it is key in allowing us to obtain global stability statements in our work. As an illustration, the kinetic proofreading system studied by McKeithan is of this form. This system is described by the reactions shown in Figure 3. The variables are $T(t)$, the concentration of T-cell receptor (TCR) and $M(t)$, the
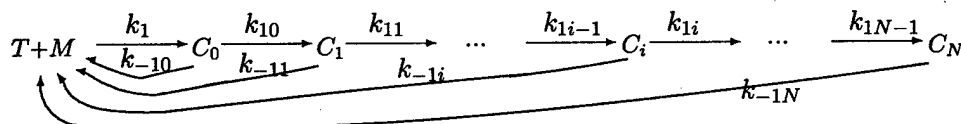

Figure 3: Kinetic Proofreading Reaction According to McKeithan

concentration of peptide-major histocompatibility complex (MHC), as well as concentrations of initial ligand-receptor and intermediate complexes $C_0(t)$ and $C_1(t), \ldots, C_N(t)$. The constants are k_1, the association rate for the reaction producing the initial ligand-receptor complex C_0 from TCR/MHC, other reaction rates $k_{1,i}$ (phosphorylation,etc.), and dissociation rates $k_{-1,i}$. This system is interesting even for the relatively trivial case $N = 0$: writing $x_i(t)$, $i = 1, 2, 3$ for the concentrations of T, M, C_0 respectively, we arrive to the equations:

$$\begin{aligned}
\dot{x}_1 &= -k_+ x_1 x_2 + k_- x_3 \\
\dot{x}_2 &= -k_+ x_1 x_2 + k_- x_3 \\
\dot{x}_3 &= k_+ x_1 x_2 - k_- x_3.
\end{aligned}$$

where we wrote k_+, k_- instead of k_1, k_{-10} respectively. In the general formalism shown above, these equations would be obtained as follows. The complexes $T + M$ and C_0 give rise to the

vectors b_1 and b_2 respectively, which list the species entering in the complex (first and second in first complex, third in the second complex), and the matrix A indicates the graph of the reaction:

$$T + M \leftrightarrow b_1 = \begin{pmatrix} 1 \\ 1 \\ 0 \end{pmatrix} , \quad C_0 \leftrightarrow b_2 = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} , \quad A = \begin{pmatrix} 0 & k_- \\ k_+ & 0 \end{pmatrix} .$$

We then have that

$$f(x_1, x_2, x_3) = (a_{21} x^{b_1} (b_2 - b_1) + a_{12} x^{b_2} (b_1 - b_2) = k_+ x_1^1 x_2^1 x_3^0 \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix} + k_- x_1^0 x_2^0 x_3^1 \begin{pmatrix} 1 \\ 1 \\ -1 \end{pmatrix} .$$

McKeithan postulated that the immune recognition signal is determined by the steady states of this system, and showed that steady states are unique, under the simplifying assumption that all constants are the same: $k_{1,i} \equiv k_1$, $k_{-1,i} \equiv k_{-1}$. This motivated the PI to ask several basic theoretical questions, dealing with the structure of the set of steady states, in general, and the analysis of stability (are there periodic orbits, as in other chemical examples like Belousov-Zhabotinsky reactions? what about possible chaotic behavior?). Among the results shown in [s66], not just for the system above but also for any system (16) of the general type being considered, are the fact that the set E of equilibria is an embedded submanifold, and the state space is foliated into invariant sets (stoichiometry classes) which are transversal to the manifold E; moreover, positive steady states are unique in each leaf (stoichiometry class), all trajectories converge to the set of equilibria, and, moreover, there is global asymptotic stability, relative to each leaf, of the positive steady state. The original papers of Feinberg et. al. provided many of the basic techniques needed in order to develop the theory, but substantial additional effort was needed in order to prove the global statements. In addition, the paper [s66] provided estimates of robustness to unmodeled dynamics, and gave extensions to some non-ideal mass action kinetics, and also gave solutions to a stabilization problem (using inflows and outflows).

Suppose now that we include a measurement function $h : \mathbb{R}^n \to \mathbb{R}^p$ into the specification of the system. Specifically, we will assume that the output coordinates are monomials, i.e. $h(x) = \mathrm{col}\,(x_1^{c_{11}} x_2^{c_{12}} \cdots x_n^{c_{1n}}, \ldots, x_1^{c_{p1}} x_2^{c_{p2}} \ldots x_n^{c_{pn}})$ where the $p \times n$ matrix of exponents $C = (c_{ij})$ has all its entries nonnegative integers. (This choice of output functions allows one to include reaction rates as well as measurements of single concentrations.) As usual, we define an *observer* for any system $\dot{x} = f(x)$, $y = h(x)$ to be another system $\dot{z} = g(z, y)$, $\hat{x} = \hat{h}(z)$ which estimates internal states (in this case, chemical concentrations). That is, we assume that for all initial conditions $x(0), z(0)$ of the composite system, solutions are well-defined for all $t \geq 0$, and $|\hat{x}(t) - x(t)| \to 0$ as $t \to +\infty$. Even though we are dealing with potentially highly nonlinear systems, in our work with Madalena Chaves cf. [s54] and [s71], we gave necessary and sufficient conditions for detectability, and an explicit construction of globally convergent observers. The observer has the following very simple form:

$$\dot{z} = f(z) + C'(y - h(z)) \qquad (\hat{x} = z)$$

which, of course, resembles a Luenberger observer (or "deterministic Kalman filter") — but which has the transpose of C as a particular gain matrix. (Interestingly, other observers, for instance using gains based on linearized systems or on extended Kalman filters, can be shown by counterexample to not always result in global convergence, for these same systems.) The proof is based on showing that the system with inputs $\dot{z} = f(z) + C'(u - h(z))$ is ISS, relative not

to "$z = 0$ and $u = 0$" but to suitable equilibria; this is, in turn, done by using an entropy-like ISS-Lyapunov function. As a bonus, one obtains an automatic robustness to observation noise, expressed in ISS-like terms. This is one of the few instances where one can obtain globally convergent observers for a nontrivial class of nonlinear systems (not linearizable by output injection). It remains to see if such observers are useful in interesting engineering applications, but we did perform experiments (described in Chaves' recently completed Ph.D. thesis under the P.I.'s direction) validating the use of these observers in some simple chemical reactions. (We used NMR data to actually measure all concentrations, thus providing a cross-check for the estimates.) In [s69], we introduced a variant, based on log-barrier functions, that trades slower observer convergence for a larger margin of robustness.

Internal Model Principle

As discussed earlier, in [s41] we provided an internal model theorem (in the sense of proving *necessity* of internal models) which is suitable for applications in which the goal is adaptation (disturbance rejection) with signal detection. Let us give some details now. We dealt with single-input single-output systems Σ, affine in inputs: $\dot{x}(t) = f(x(t)) + u(t)g(x(t))$, $y(t) = h(x(t))$ with f and g smooth vector fields and h a scalar smooth function, satisfying $f(0) = h(0) = 0$. Given a class $\mathcal{U}$ of functions $[0, \infty) \to \mathbb{R}$ (such as for example the set of all constant functions), we say that Σ *adapts* to inputs in $\mathcal{U}$ (a more appropriate technical control-theoretic term would be "asymptotically rejects disturbances in $\mathcal{U}$") if the following property holds: for each $u \in \mathcal{U}$ and each initial state, the solution exists for all $t \geq 0$ and is bounded, and the corresponding output $y(t) = h(x(t))$ converges to zero as $t \to \infty$. We say that Σ *contains an output-driven internal model of* $\mathcal{U}$ if there is a change of coordinates which brings the system into the following block form:

$$\begin{aligned}
\dot{z}_1 &= f_1(z_1, z_2) + ug_1(z_1, z_2) \\
\dot{z}_2 &= f_2(y, z_2) \\
y &= \kappa(z_1)
\end{aligned}$$

(the subsystems with variables z_1 and z_2 correspond respectively to Σ_0 and Σ_{IM} in Figure 4), and in addition the subsystem with state variables z_2 is capable of generating all functions

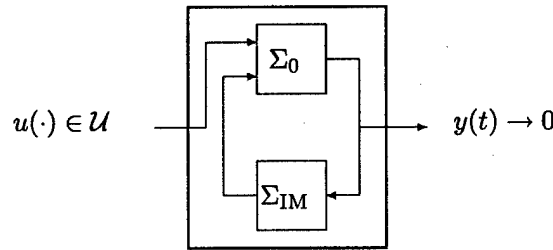Figure 4: Decomposition of Σ into Σ_0 and Σ_{IM}, the Latter Driven by $y(t)$

in $\mathcal{U}$, meaning the following property: there is some scalar function $\varphi(z_2)$ so that, for each possible $u \in \mathcal{U}$, there is some solution of $\dot{z}_2 = f_2(0, z_2)$ which satisfies $\varphi(z_2(t)) \equiv u(t)$. The precise meaning of "change of coordinates" is as follows. There must exist an integer $r \leq n$, differentiable manifolds Z_1 and Z_2 of dimensions r and $n - r$ respectively, a smooth function

$\kappa : Z_1 \to \mathbb{R}$, vector fields F and G on $Z_1 \times Z_2$ which take the partitioned form

$$F = \begin{pmatrix} f_1(z_1, z_2) \\ f_2(\kappa(z_1), z_2) \end{pmatrix}, \quad G = \begin{pmatrix} g_1(z_1, z_2) \\ 0 \end{pmatrix}$$

and a diffeomorphism $\Phi : \mathbb{R}^n \to Z_1 \times Z_2$, such that

$$\Phi_*(x)f(x) = F(\Phi(x)), \quad \Phi_*(x)g(x) = G(\Phi(x)), \quad \kappa(\Phi_1(x)) = h(x)$$

for all $x \in \mathbb{R}^n$, where Φ_1 is the Z_1-component of Φ and star indicates Jacobian. Our result holds under additional conditions on the vector fields defining the system. The first condition is the fundamental one from an intuitive point of view, namely that the system is able to detect changes in the input signal: Assumption 1: a uniform relative degree exists. This means that there exists some positive integer r such that $L_g L_f^k h \equiv 0 \, \forall k < r - 1$ and $L_g L_f^{r-1} h(x) \neq 0 \, \forall x \in \mathbb{R}^n$ where $L_X h$ is the Lie derivative of a function h along the direction of the vector field X. (The integer r is the relative degree of Σ; the assumption amounts to the statement that the output derivatives $y^{(k)}(t)$ must be independent of the value of the input at time t, for all $k < r$, but that $y^{(r)}(t) = b(x(t)) + a(x(t))u(t)$ for some function $a(x)$ which is everywhere nonzero.) The next two conditions are of a technical nature. They are automatically satisfied for linear systems. For nonlinear systems, we need such conditions in order to guarantee the existence of a change of variables exhibiting the system Σ_{IM}. (See the paper for ways of weakening these assumptions.) Assuming that the degree is r, we introduce the following vector fields: $\tilde{g}(x) = \frac{1}{L_g L_f^{r-1} h(x)} g(x)$, $\tilde{f}(x) = f(x) - \left(L_f^r h(x)\right)\tilde{g}(x)$, $\tau_i := \mathrm{ad}_{\tilde{f}}^{i-1} \tilde{g}, i = 1, \ldots r$, where ad_X is the operator $\mathrm{ad}_X Y = [X, Y] = $ (Lie bracket). The assumptions are then: Assumption 2: τ_i is complete, for $i = 1, \ldots, r$, and Assumption 3: the vector fields τ_i commute with each other. Finally, we must define the allowed classes of inputs $\mathcal{U}$. As usual in control theory, we assumed that inputs are generated by *exosystems*. That is, there is given a system Γ: $\dot{w} = Q(w)$, $u = \theta(w)$ evolving on some differentiable manifold, Q a smooth vector field, and θ a real-valued smooth function such that the input class $\mathcal{U}$ consists exactly of those inputs $u(t) = \theta(w(t))$, $t \geq 0$, for all possible solutions of $\dot{w} = Q(w)$. (For example, if we are interested in constant signals, we pick $\dot{w} = 0$, $u = w$ and if we are interested in sinusoidals with frequency ω then we use $\dot{x}_1 = x_2$, $\dot{x}_2 = -\omega^2 x_1$, $u = x_1$.) We assumed that the exosystem is Poisson-stable. This means that the exosystem is almost-periodic in the sense that trajectories keep returning to neighborhoods of the initial state. We then proved that, if Assumptions 1-3 hold and the system Σ adapts to inputs in a class $\mathcal{U}$ generated by a Poisson-stable exosystem, then S contains an output-driven internal model of $\mathcal{U}$.

3 Recent Publications

2004

1. "Some new directions in control theory inspired by systems biology," *Systems Biology*, 2004, to appear.

2. (with D. Angeli and J.E. Ferrell, Jr.) "Detection of multi-stability, bifurcations, and hysteresis in a large class of biological positive-feedback systems," *Proceedings of the National Academy of Sciences USA* **101**(2004): 1822–1827.

3. (with D. Angeli) "Multistability in monotone I/O systems," *Systems and Control Letters* **51**(2004): 185–202.

4. (with D. Angeli, B. Ingalls and Y. Wang) "Uniform global asymptotic stability of differential inclusions," *Journal of Dynamical and Control Systems* **10**(2004): 391-412.

5. (with M. Chaves and R.J. Dinerstein) "Steady-states of receptor-ligand dynamics: A theoretical framework," *J. Theoretical Biology* **227**(2004): 413–428.

6. (with G. Enciso) "Monotone systems under positive feedback: multistability and a reduction theorem," *Systems and Control Letters*, to appear.

7. (with G. Enciso) "On the stability of a model of testosterone dynamics," *Journal of Mathematical Biology*, to appear.

8. (with P. Berman and B. DasGupta), "Randomized approximation algorithms for set multicover problems with applications to reverse engineering of protein and gene networks," in *Proc. 7th. Int. Workshop on Approximation Algorithms for Combinatorial Optimization Problems, Cambridge, MA, Aug. 2004*, to appear in *Lec. Notes Comp. Sci.*, Springer-Verlag, NY.

9. (with D. Ocone and P. Kuusela) "Learning-complexity dimensions for a continuous-time control system," *SIAM J. Control and Optimization*, to appear.

10. (with D. Angeli and P. De Leenheer) "Monotone chemical reaction networks," submitted.

11. (with M. Malisoff) "Asymptotic controllability and input-to-state stabilization: The effect of actuator errors," in *Optimal Control, Stabilization, and Nonsmooth Analysis* (de Queiroz, M., M. Malisoff, and P. Wolenski, eds.), Springer-Verlag, Heidelberg, 2004, pp. 155–171.

12. (with D. Angeli) "Interconnections of monotone systems with steady-state characteristics," in *Optimal Control, Stabilization, and Nonsmooth Analysis* (de Queiroz, M., M. Malisoff, and P. Wolenski, eds.), Springer-Verlag, Heidelberg, 2004, pp. 135–154.

13. (with D. Angeli and P. De Leenheer) "A small-gain theorem for almost global convergence of monotone systems," *Systems and Control Letters* **52**(2004): 407–414.

14. (with M. Malisoff, and L. Rifford) "Asymptotic controllability implies input to state stabilization," *SIAM J. Control and Optimization*, to appear.

15. (with M. Chaves and R.J. Dinerstein) "Optimal length and signal amplification in weakly activated signal transduction cascades," submitted.

16. (with D. Angeli, B. Ingalls and Y. Wang) "Separation principles for input-output and integral-input to state stability," *SIAM J. Control and Opt.*, to appear.

17. (with D. Angeli and P. De Leenheer) "A tutorial on monotone systems- with an application to chemical reaction networks," *Proc. 16th Int. Symp. Mathematical Theory of Networks and Systems (MTNS 2004)*, to appear.

18. (with B. DasGupta and J. Hespanha) "Aggregation-based approaches to honey-pot searching with local sensory information," in *Proceedings American Control Conf.*, Boston, June 2004, to appear.

19. (with B. DasGupta and J. Hespanha) "Computational complexities of honey-pot searching with local sensory information," in *Proceedings American Control Conf.*, Boston, June 2004, to appear.

20. (with A. Kiyatkin, and B.N. Kholodenko) "Inferring dynamic architecture of cellular networks using time series of gene expression, protein and metabolite data," *Bioinformatics* (2004), in press.

21. (with D. Angeli) "An analysis of a circadian model using the small-gain approach to monotone systems," submitted.

22. (with M. Chaves and R.J. Dinerstein) "Gains and optimal design in signaling pathways," submitted.

23. (with J.L. Mancilla-Aguilar, R. García, and Y. Wang) "Representation of switched systems by perturbed control systems" submitted.

24. (with J.L. Mancilla-Aguilar, R. García, and Y. Wang) "Uniform stability properties of switched systems with inputs" submitted.

25. (with G. Enciso) "A remark on multistability for monotone systems" submitted.

26. (with D. Angeli and P. De Leenheer) "Monotonicity and convergence in chemical reaction networks" submitted.

27. (with M. Andrec, B.N. Kholodenko, and R.M. Levy) "Inference of signaling and gene regulatory networks by steady-state perturbation experiments: Structure and accuracy," submitted.

2003

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