



Editorial

Introduction to the special issue on systems biology

The 21st century has been recognized as the century of biology, and new technologies and methods are vastly accelerating the pace of discovery in biology and medicine with a growing impact on our lives. New developments and discoveries in biology do, however, often depend on an interdisciplinary approach that encompasses, among others, chemistry, physics, mathematics and the systems sciences. These interdisciplinary approaches have led to more integrative and more holistic analyses, in which not only the components are studied, but the connections between, and regulations of the components are important. This approach has come to be known as “systems biology”, and systems sciences have played a crucial role in that field. In this special issue, the role of systems and control theory for systems biology is emphasized. The objective is to present the latest results in this field, to highlight the contributions of the systems and control community to systems biology, and to attract further interest to systems biology from this community.

The call for papers for the special issue was very well received, and a total number of 53 papers were submitted. This pleasing response shows the growing interest of the systems and control community in the area of systems biology. Out of the submitted papers, 23 contributions have been included in this special issue and a number of additional papers have been transferred to regular issues of the journal.

The topics covered in the special issue are rather broad and comprise the analysis of biological networks including gene regulatory networks and general biochemical network and especially robustness consideration in such networks, general modeling questions for biological systems, optimality investigations and oscillation and synchronization phenomena at the cellular and subcellular level. In addition novel questions related to synthetic biology, the combination of science and engineering to design and build novel biological functions and systems, are being discussed.

Network analysis is an important topic in systems biology and four papers of this special issue focus on this topic. A decomposition approach into subsystems is explored by Buzi et al. in a study of models for autocatalytic networks, which makes them amenable to Lyapunov stability analysis. The authors show that robustness is related to how easily the attractor regions can be identified. Zavlanos et al. address the question of network inference of gene regulatory networks while enforcing stability constraints. A framework based on piecewise affine differential systems is proposed by Chaves and Gouze to model, in a qualitative fashion, gene regulatory networks. Ederer et al. introduce a novel application of Gibbs energy analysis to establish a stability criterion for biochemical networks.

Biological systems all share a large degree of robustness. This is the topic of two papers in this issue. Waldherr and

Allgöwer deal with the robustness analysis problem of biochemical network models. They develop a method based on polynomial programming to compute a parameter region of guaranteed robustness. In this region, the system maintains either stability or instability, the latter being for example related to oscillatory behavior. An LMI framework is introduced for calculating the globally asymptotic stable equilibrium points for gene regulatory networks by Chesi.

The availability of suitable models is the basis for a model-based analysis and design. Six papers in this special issue discuss various aspects in this context. The work of Koutroumpas et al. contributes to the modeling of DNA replication, a field challenged by discrepancies between model predictions and experimental observations. This effect, known as the random gap problem, can be reproduced by a Markov Process, underlining the hypothesis of a limiting factor in the DNA replication process. Kiparissides et al. describe a holistic “closed-loop” approach to the iterations between computational model building and optimal experimental design. The approach is demonstrated on a hybridoma culture problem. The derivation of biologically meaningful, simplified models, for system analysis and design from high-dimensional nonlinear models is the topic of the paper of Anderson et al. They derive a set of efficient computational tools that are then applied on a model of the Epidermal Growth Factor (EGF) signalling pathway. Palanthandalam-Madapusi and Goyal revisit an established mechanical model of DNA, which is based on continuum mechanics but highly sensitive to the assumed constitutive law. They present an elegant way to express the model equations in state-space form, where the unknown constitutive law corresponds to an unknown input. By incorporating data, the constitutive law can then be approximated. A classical challenge in systems biology regards the reconstruction of networks from input-output data, for which Yuan et al. present novel results. They extend the existing approaches for LTI systems to incorporate noise and nonlinear dynamics, two common features of biological systems. Their method in addition penalizes higher complexity orders, thus counteracting the common problem of overfitting. Alamir et al. report an application to epileptic seizure control using a model in which the brain is described by a network of interconnected oscillators. Their work points the way to EEG-based feedback control therapies. One logical extension of modeling methodologies is to address the growing interest in spatially distributed phenomena. Arcak reports on the application of LMI methods to the derivation of a condition for spatial uniformity for asymptotic properties in reaction-diffuse networks underlying biochemical processes.

Very often biological function is related to nonlinear effects. One of the most important ones being nonlinear oscillations and synchronization, topics that are discussed in five papers. Franci et al. focus on neuron synchronization causing neurological

diseases. They show how the system can be represented by a Kuramoto model, which allows one to deduce the robustness of its phase-locking property as well as conditions on the control law in order to achieve desynchronization. In Hori et al. existence conditions of periodic oscillations in large-scale cyclic gene regulatory networks are investigated. In particular a new graphical and analytical criterion is introduced that allows one to analyze cyclic gene regulatory networks composed of any number of genes. Wang and Doyle III describe a method for computing the rate of synchronization in a network of coupled oscillators. Their work details an application to a network consisting of locally coupled nodes that also receive a common globally entraining cue. Synchronization is also the subject in the paper of Ramirez et al.: They consider a network of coupled cells that emerges in diabetes, and derive sufficient conditions for synchronization on coupling strength and the proportion of cells that are active in the overall network. A further result is motivated by synchronizing neuron dynamics: Kashima et al. discuss coupled piecewise affine systems and present a sufficient condition for oscillations in this type of systems, usually difficult to analyze. Importantly, their condition can be reformulated as a criterion on the coupling topology, facilitating the application to large systems.

Optimality issues are being treated in three contributions. Goelzer et al. consider the problem of medium distribution within a cell, and reformulate it in terms of complex optimization. By regarding the cell as a connection of subsystems, they are able to identify limiting factors for the cell's growth rate. Jungers et al. develop a method for randomly computing the decomposition of admissible elementary flux vectors that are used to describe a metabolic network. Boolean networks have been used to study very large scale gene regulatory networks, where often the level of detail is lacking. Kobayashi and Hiraishi describe a method for reducing the optimal control policy in probabilistic Boolean networks to an integer linear programming problem.

Over the last few years synthetic biology has emerged as the combination of science and engineering to design and build novel biological functions and systems. The implementation of a gene regulatory network is one goal of synthetic biology, giving rise to control problems in vivo as considered by Menolascina et al. These authors design a control law and demonstrate its performance on a benchmark network in yeast. Despite the nonlinearities and time delays present in the system, the results show good accordance with the model predictions.

The field of applications for systems biology is remarkably diverse and encompasses for example also a method to enhance the immune system response in malaria dynamics based on newly defined state jumps as introduced in the contribution of Chang et al. They show, among others, that malaria immunity can be enhanced very efficiently by use of a closed-loop control scheme, compared to open-loop control schemes as is typically suggested in the literature.

We hope the readers of *Automatica* will find the special issue interesting and stimulating, and we expect that the included papers contribute to further advance the area of systems biology.

Finally, the guest editors would like to thank all the authors who have submitted papers to the special issue and the many reviewers involved in the refereeing of the submissions. In particular we want to thank the excellent associate editors of the special issue (Murat Arcak, Graziano Chesi, Denis Dochain, Jürgen Hahn, Mike Henson, Pablo Iglesias, Elling Jacobsen and Rick Middleton) for their invaluable help in putting this special issue together.

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