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GUEST EDITORIAL

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Editorial for the special issue “Control-theoretic approaches for systems in the life sciences”

Since its dawn, systems-and-control theory has been strongly and deeply interlaced with the life sciences, as is emphasized by the work of some of its greatest pioneers. Norbert Wiener presented *Cybernetics* in his book as *Control and Communication in the Animal and the Machine*, thus stressing the remarkable similarities between engineering mechanisms and regulation in living beings. Ludwig von Bertalanffy, the founder of *General Systems Theory*, advocated the use of mathematical approaches and system-level thinking in the study of biology, and was a biologist himself.

The approaches developed within the realm of systems-and-control theory can be successfully employed to better understand the functioning of systems in the life sciences at all scales, from biochemical reaction networks to biological systems, from biomedical systems to ecological networks and epidemic phenomena. Novel rigorous methods can guide the control, optimization, and bottom-up design of systems in synthetic biology, as well as the development of approaches for biomedicine and of strategies for the control of epidemics. Systems in the life sciences are characterized by a high level of complexity, steep nonlinearities, and largely uncertain dynamics: their features pose many challenges that can inspire the development of new theory in robust and nonlinear control.

This special issue has collected recent advances and new exciting ideas at the frontiers between systems-and-control theory and the life sciences, presented by renowned research teams worldwide. The scope of the special issue includes several complementary aspects, ranging from systems biology and synthetic biology (modeling, analysis, control, and design of biochemical and biological systems at all scales) to the analysis and management of ecological networks, from the study of biomedical systems (including disease management and the design and analysis of novel treatments) to the analysis and the control of epidemiological systems (embracing the study of their dynamics and approaches to suppress or mitigate the spread of contagion). Attention is devoted to modeling, identification, parameter estimation, as well as to analysis, control, and optimization. The special issue embraces both work with novel theoretical approaches and work that advances theoretical contributions with meaningful applications.

1 | EPIDEMIOLOGICAL SYSTEMS: ANALYSIS, CONTROL, AND OPTIMIZATION

The COVID-19 pandemic has highlighted the importance of mathematical and systems-and-control approaches to understand, manage, and control health emergencies, to predict the trend of epidemics and to plan effective strategies that curb the contagion. Indeed, several contributions of the special issue revolve around models for epidemics and infectious diseases and tackle their analysis and their control to suppress the contagion and eradicate infections, resorting to nonpharmaceutical interventions as well as vaccination.

Eduardo D. Sontag proposes “An explicit formula for minimizing the infected peak in an SIR epidemic model when using a fixed number of complete lockdowns”; his work deals with the careful timing of nonpharmaceutical interventions, such as physical distancing, with the aim of minimizing the peak in the number of infected individuals, and provides an insightful, explicit, and easily computable rule for the timing of a fixed number of complete lockdowns of prespecified lengths.

In their work “Change time estimation uncertainty in nonlinear dynamical systems with applications to COVID-19,” Rijad Alisic, Philip E. Paré, and Henrik Sandberg analyze the detectability of sudden parameter changes for nonlinear dynamical systems in the presence of measurement noise, so as to assess the impact of individual nonpharmaceutical interventions or viral mutations on the epidemic spread, and look for the most informative data sample allowing to discriminate at best between different output trajectories, revealing, for example, that monitoring the number of infected (instead of recovered/deceased) is preferable.

"Semi-Markov models of epidemics over networks with time delays" are proposed by Mohammad Ghousein, Emmanuel Moulay, and Patrick Coirault, who modify Markov models for epidemics by including minimum viral incubation period and recovery period as time delays affecting the states, leading to a more general class of systems that loses the Markovian property; sufficient conditions for the global exponential stability of the resulting time-delay probabilistic dynamical models are offered via Lyapunov theory.

"A time-varying network model for sexually transmitted infections accounting for behavior and control actions" is proposed by Kathinka Frieswijk, Lorenzo Zino, and Ming Cao, whose stochastic network model for the spread of sexually transmitted infections includes asymptomatic infections, as well as behavioral choices related to the use of protective measures and their time evolution depending on the perceived risk and on persuasion due to exchange of opinions; different control actions (awareness campaigns, routine screening, and partner notification) are investigated along with their effectiveness.

Francesco Parino, Lorenzo Zino, Giuseppe C. Calafiore, and Alessandro Rizzo, in their article "A model predictive control approach to optimally devise a two-dose vaccination rollout: A case study on COVID-19 in Italy," face the challenge of optimally planning massive two-dose vaccination rollouts by leveraging a nonlinear model predictive control strategy that accounts for both healthcare and socioeconomic costs, which they apply to the 2021 COVID-19 vaccination campaign in Italy by considering a tailored epidemic model with parameters inferred from real data.

2 | THERAPY DESIGN FOR INFECTIOUS DISEASES

Moving from the between-host scale of epidemiological models that describe contagion spreading in a population to the in-host treatment of diseases, the paper "Scheduling collateral sensitivity-based cycling therapies toward eradication of drug-resistant infections," by Josephine N. A. Tetteh, Sorin Olaru, Hans Crauel, and Esteban A. Hernandez-Vargas, explores the control-theoretic aspects and implications of facing drug-resistant pathogens through the sequential use of drugs where resistance to the former drug induces sensitivity to the next (collateral sensitivity); a switched system formulation allows to optimally tailor the order and time of cycling between drugs to the pathogen population present in the host.

3 | BIOLOGICAL SYSTEMS: ANALYSIS OF METABOLIC AND GENETIC REGULATORY NETWORKS

Systems-and-control theory offers powerful tools to gain insight into the behavior of biological systems, including their response to perturbations, their stability properties, and their ability to give rise to sustained and synchronized oscillations.

In his paper "Sign-sensitivity of metabolic networks: Which structures determine the sign of the responses," Nicola Vassena follows a structural approach to investigate the sign of the responses of metabolic networks to external perturbations, affecting both reaction rates and metabolite concentrations at the equilibrium, exclusively based on the network stoichiometry, without any information about the parameter values; subnetworks that have a crucial role in determining the sign sensitivity are identified and shown to be associated with kernel vectors of the stoichiometric matrix and thus independent of the chosen kinetics.

Nicolas Augier, Madalena Chaves, and Jean-Luc Gouzé deal with "Weak synchronization and convergence in coupled genetic regulatory networks: Applications to damped oscillators and multistable circuits": they consider a general model of genetic networks, compare the equilibria and stability properties of different interconnections based on either homogeneous or heterogeneous coupling, and find conditions for weak synchronization, applied to the synchronization of damped oscillators and to the control of multistable systems.

4 | BIOLOGICAL SYSTEMS: CONTROL

Control-theoretic approaches allow us to govern, enhance, and improve biological phenomena at various scales, ranging from gene regulation and metabolism to the control of cell populations and their growth, and enables the design of biological mechanisms with the desired behavior. In a biological context, control strategies can aim at optimality, but most often need to face huge uncertainty and environmental variability, which requires fundamental robustness properties.

Virginia Fusco, Davide Salzano, Davide Fiore, and Mario di Bernardo present a feedback strategy for the “Embedded control of cell growth using tuneable genetic systems”: they control the density of a microbial population, where cells self-regulate their growth rate, by tuning the production of a growth inhibitor protein based on the information on the population density obtained from a quorum sensing mechanism, they show that the set-point can be flexibly changed online, and they test the robustness of the designed controller with respect to disturbances and parameter variations due, for example, to cell-to-cell variability.

“Self-regulation in a stochastic model of chemical self-replication” is investigated by Alessandro Borri, Massimiliano d’Angelo, and Pasquale Palumbo, who analyze burst noise propagation in the context of gene expression and investigate the impact of feedback on noise attenuation, both within a computational numerical framework based on a stochastic simulation algorithm and within an approximated analytical framework that replaces nonlinear terms with linear ones to enable closed-loop solutions for first- and second-order moments.

Debojyoti Biswas, Sayak Bhattacharya, and Pablo A. Iglesias investigate “Enhanced chemotaxis through spatially regulated absolute concentration robustness” and introduce a control mechanism to enhance the efficiency of chemotaxis (the directional motility of cells in response to spatial chemical gradients) in amoeboid cells, whose movement is enabled by protrusions driven by the stochastic threshold crossing of an underlying excitable system, by suppressing undesirable protrusions in the wrong directions; the control action couples an absolute concentration robustness mechanism to the cellular signaling machinery.

The work “Optimal control of probabilistic Boolean control networks: A scalable infinite horizon approach” by Sonam Kharade, Sarang Sutavani, Sushama Wagh, Amol Yerudkar, Carmen Del Vecchio, and Navdeep Singh deals with the optimal control of large-scale gene regulatory networks, modeled as probabilistic Boolean control networks based on Markov decision processes, with the aim of developing therapeutic intervention strategies that alter gene regulation dynamics so as to avoid diseased states.

Nicolas Augier and Agustín G. Yabo deal with the “Time-optimal control of piecewise affine bistable gene-regulatory networks,” where the goal is to minimize the time that a piecewise affine bistable genetic toggle switch needs to transition between its two stable steady states, and show that time-optimal transitions pass through an undifferentiated state, which has fundamental importance in cell biology in relation to fate differentiation of cells and has applications in synthetic biology, biotechnology, and gene therapy.

The paper “Optimal periodic resource allocation in reactive dynamical systems: application to Microalgal production” by Olivier Bernard, Liu-Di Lu, and Julien Salomon focuses on a periodic resource allocation problem applied to a dynamical system, which is inspired by the optimization of a mixing strategy to enhance the growth rate in a microalgal raceway system; the control is represented by a permutation applied on the system to reallocate the resources to the different activities.

5 | BIOLOGICAL SYSTEMS: OBSERVER DESIGN AND ESTIMATION

Estimating the state of a biological system based on experimentally measured quantities is fundamental.

Alex dos Reis de Souza, Denis Efimov, Andrey Polyakov, Jean-Luc Gouzé, and Eugenio Cinquemani discuss “State observation in microbial consortia: A case study on a synthetic producer-cleaner consortium”; they frame an observability analysis and propose state estimators for each component of a system describing a two-strain microbial consortium that involves both producers and cleaners; they deal with observer design and they assess the advantage of measuring a fluorescent reporter in addition to the total biomass, even though measuring total biomass alone is enough to make the system detectable.

6 | BIOLOGICAL SYSTEMS: IDENTIFICATION AND MODEL ORDER REDUCTION

System identification and the generation of reduced order models are of crucial importance in systems and synthetic biology.

Francesco Montefusco, Anna Procopio, Declan G. Bates, Francesco Amato, and Carlo Cosentino tackle the “Scalable reverse-engineering of gene regulatory networks from time-course measurements”: they propose a computationally efficient method for topological inference of biological interaction networks from experimental data, which combines system identification based on instrumental variables with a regularization strategy to deal with over-parameterized systems, and can simultaneously exploit multiple time series from multiple experiments and be applied to large-scale networks with thousands of nodes.

Gemma Massonis, Julio R. Banga, and Alejandro F. Villaverde propose “AutoRepar: a method to obtain identifiable and observable reparameterizations of dynamic models with mechanistic insights”; their approach automatically re-parameterizes nonlinear ODE models to guarantee their structural identifiability and observability, so that the values of the model parameters and state variables can be inferred from data without ambiguities and the models can provide reliable predictions and insight.

“Robustness guarantees for structured model reduction of dynamical systems with applications to biomolecular models” are offered by Ayush Pandey and Richard M. Murray, who focus on the robustness properties of the error in model reduction in the presence of uncertainties; they compute robustness guarantee metrics for a class of reduced models of engineered biological systems in uncertain environments, and propose an automated model reduction method to find the best possible reduced model, which is applied to gene expression systems with limited resources and to circuits for bacterial population control.

7 | SYSTEMS-AND-CONTROL APPROACHES IN BIOMEDICINE

Developing parameter identification, state estimation, and control approaches for biomedical systems is key to provide robust and theoretically grounded support to healthcare workers in the clinical practice.

“Parameter identification and state estimation for a diabetic glucose-insulin model via an adaptive observer” are considered by Roberto Franco, Héctor Ríos, Alejandra Ferreira de Loza, Louis Cassany, David Gucik-Derigny, Jérôme Cieslak, and David Henry, who design an LMI-based adaptive observer for patients with type 1 diabetes mellitus, using Bergman’s minimal model, to simultaneously estimate states and parameters corresponding to the insulin-dependent glucose disappearance rate in the presence of parameter uncertainties and food intake regarded as an external disturbance; the estimates are based on intravenous glucose measurements and the approach is validated in the UVA/Padova metabolic simulator.

Luca Ranghetti, Daniel E. Rivera, Penghong Guo, Antonio Visioli, Jennifer Savage Williams, and Danielle Symons Downs discuss “A control-based observer approach for estimating energy intake during pregnancy” aimed at regulation of gestational weight so as to prevent risks for both the mother and her unborn child; an energy balance model predicts gestational weight based on physical activity and unmeasured disturbances associated with energy intake, and two different control-based observer formulations, relying on internal model control and model predictive control, are proposed and tested on real data.

“Nonlinear dynamic modelling and model predictive control of thrombin generation to treat trauma-induced coagulopathy” are investigated by Damon E. Ghetmiri and Amor A. Menezes: they propose a nonlinear dynamic coagulation model including the complex biochemical reactions of clotting and demonstrate the effectiveness of a model predictive control scheme that administers blood proteins as system inputs to robustly automate clinical interventions for trauma-induced coagulopathy, even in the presence of experimentally observed uncertainties involving nonlinearities and delays.

8 | ECOLOGICAL SYSTEMS: DECISION-MAKING AND POPULATION CONTROL

Two contributions deal with decision-making in populations and with the control of ecological systems.

Leonardo Stella and Dario Bauso investigate “The impact of irrational behaviors in the optional prisoner’s dilemma with game-environment feedback”, where players can choose to cooperate, defect or abstain, their behavior can be irrational according to prospect theory (capturing, e.g., reference dependence or loss aversion), and environmental effects exert a feedback over the population dynamics; the system is analyzed in the context of evolutionary games, with applications to opinion dynamics in society (elections) and collective decision-making in honeybee swarms.

“Cyclic control equilibria for switched systems with applications to ecological systems” are discussed by Alejandro L. Anderson, Pablo Abuin, Antonio Ferramosca, Esteban A. Hernandez-Vargas, and Alejandro H. Gonzalez, who investigate permanence regions for switched systems under arbitrary waiting-time constraints and their (un)suitability as control targets, and propose a case study concerning population control and the stabilization of communities in an ecological system.

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