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Editorial

Special Issue on "Biological Networks"

Rudiyanto Gunawan [1,*] and Neda Bagheri [2,*]

[1] Department of Chemical and Biological Engineering, University at Buffalo, 302 Furnas Hall, Buffalo, NY 14260, USA

[2] Department of Chemical and Biological Engineering, Center for Synthetic Biology, NSF-Simons Center for Quantitative Biology, Northwestern Institute for Complex Systems, Northwestern University, Technological Institute, 2145 Sheridan Road, E154, Evanston, IL 60208, USA

* Correspondence: rgunawan@buffalo.edu (R.G.); n-bagheri@northwestern.edu (N.B.); Tel.: +1-716-645-0952 (R.G.); +1-847-491-2716 (N.B.)

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Networks of coordinated interactions among biological entities govern a myriad of biological functions that span a wide range of both length and time scales—from ecosystems to individual cells, and from years (e.g., the life cycle of periodical cicadas) to milliseconds (e.g., allosteric enzyme regulation). For these networks, the concept of "the whole is greater than the sum of its parts" is often the norm rather than the exception. Meanwhile, continued advances in molecular biology and high-throughput technology have enabled a broad and systematic interrogation of whole-cell networks, allowing for the investigation of biological processes and functions at unprecedented breadth and resolution, even down to the single-cell level. The explosion of biological data, especially molecular-level intracellular data, necessitates new paradigms for unraveling the complexity of biological networks and for understanding how biological functions emerge from such networks. These paradigms introduce new challenges related to the analysis of networks in which quantitative approaches such as machine learning and mathematical modeling play an indispensable role. The Special Issue on "Biological Networks" showcases advances in the development and application of in silico network modeling and analysis of biological systems. The Special Issue is available online at: https://www.mdpi.com/journal/processes/special_issues/Biological_Networks.

Identifiability and Design of Experiments for Biological Network Models

A well-known challenge in the development of computational models of biological networks is the identifiability of model parameters. A model is said to be structurally identifiable when its parameters can, in principle, be extracted from measurements of the output responses of the model. The lack of structural identifiability implies that any attempt to determine model parameters from measurement data is futile. The paper by Villaverde and Banga [1] focuses on assessing structural identifiability by using the concept of observability. More specifically, for certain initial conditions, structurally unidentifiable models can mistakenly be ascertained to be identifiable. The paper provides illustrations of such challenges through biochemical model examples and proposes a procedure to overcome this complication.

Even in cases where a model is structurally identifiable, the accuracy of parameter estimates can remain poor. A concept related to structural identifiability is *practical identifiability*, which addresses concerns of parameter uncertainty. A key factor that controls parameter uncertainty is the design of experiments. Two papers in this Special Issue explore the model-based optimal design of experiments (MBDOE) via the Fisher information matrix (FIM). The paper by Sinkoe and Hahn [2] showcases the importance of optimizing experiments for improving the practical identifiability of model parameters, especially in connection to dynamic biological data and modeling. More specifically, the paper describes the application of the FIM-based D-optimality criterion and the Morris method for computing

parametric sensitivities, to optimize dynamic input functions to the interleukin-6 signaling model. In silico implementations of the optimal input functions show great promise in significantly reducing parametric uncertainty.

A high degree of model nonlinearity (curvatures) can negatively affect the performance of FIM-based experimental designs. The paper by Manesso et al. [3] addresses this issue by introducing a new multi-objective optimization (MOO) framework. This framework identifies Pareto optimal experiments that balance maximizing the information content of experimental data through the FIM with minimizing model curvatures. A proof of concept using a biochemical network model of baker's yeast fermentation illustrates the benefits of using the proposed MOO MBDOE over a number of FIM-based optimal designs and other experimental designs that also consider model curvatures.

Dynamic Biological Network Modeling

Two papers in the Special Issue present new biological network models that span multiple scales. The paper by Ruggiero et al. [4] presents a dynamic model of tuberculosis (TB) granuloma activation describing host-TB pathogen interactions. The model captures the local immune system response to *Mycobacterium tuberculosis*, the dynamics of matrix metalloproteinase-1 and collagen in granuloma, and the leakage of bacteria from granuloma. By changing the values of parameters in the model, the authors are able to assess how perturbations in the immune response (as well as HIV co-infection) affect granuloma activation.

The paper by Lee et al. [5] looks at the modeling of NF-κb signaling dynamics induced by lipopolysaccharide (LPS) in the presence of a cytokine secretion blocker. Parameter estimation based on average single-cell flow cytometry data points to a previously unidentified action of the cytokine secretion blocker, which was validated in additional experiments and subsequent model refinement. The iterations between computational modeling and experimental design highlight how the process of inferring biological networks can lead to new testable hypothesis and insights.

Network-Based Biological Systems Analysis and Optimization

Biological network models enable a systematic and comprehensive analysis and optimization of biological systems, as showcased by three papers in the Special Issue. The paper by Perumal and Gunawan [6] introduces a new dynamic sensitivity analysis that can account for cellular heterogeneity. The analysis, termed molecular density function perturbation (MDFP), introduces time-dependent in silico perturbations to the molecular concentrations of biological species in the network. The application of MDFP to a mathematical model of programmed cell death signaling stimulated by a tumor necrosis factor ligand points to key events in the signaling pathway that determine the cell-to-cell variability in the response to the stimulus.

The paper by Widiastuti et al. [7] outlines a model-driven strategy to estimate and improve the production capability of microbes based on an in silico analysis of genome-scale metabolic networks. The strategy explores the use of *Zymomonas mobilis* to produce succinic acid. The genome-scale metabolic network model enables a combinatorial deletion analysis, leading to the identification of four gene deletions that would amplify succinic acid molar yield by 15 times.

The review paper by Faraji and Voit [8] focuses on the metabolic modeling of crop science with a specific focus on bioenergy crops. In comparison to microbes and animal cells, mathematical modeling of plant metabolisms is still in its infancy, but is expected to become a standard tool in the future. The paper delves into unique challenges and constraints in modeling plant metabolic networks, as well as limitations and mitigating strategies in using popular modeling formalisms to capture the physiological characteristics of plant systems. A case study involving lignin biosynthesis in switchgrass illustrates how mathematical modeling can serve as a powerful tool for strain improvement through the generation of a library of virtual strains.

Network-Based Biological Data Analytics

Biological networks are crucial in the interpretation and analysis of biological data. The paper by Vargason et al. [9] demonstrates how univariate (one variable at a time) statistical analysis is often suboptimal as it does not account for the correlation of data structure arising from an underlying biological network. By using clinical data for autism spectrum disorder as case studies, multivariate analyses were demonstrated to be much more efficacious than univariate approaches.

The paper by Padmanabhan et al. [10] highlights how the network of cellular pathway crosstalk can provide better biomarkers with improved diagnosis and prognosis accuracy. The work presents a procedure to construct a cellular pathway crosstalk reference map, by combining information on chemical, genetic and domain interactions and transcription factors. The reference map is personalized by utilizing each patient's single nucleotide polymorphisms. In the application to the Alzheimer's disease (AD) dataset from the Alzheimer's Disease Neuroimaging Initiative, the authors show how using the patient-specific cellular pathway crosstalk as an additional feature significantly improves the accuracy in assessing the risk of mild cognitive impairment progression to AD.

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