

## Preface

It was around the period of World War II that Arturo Rosenblueth and Norbert Wiener were taking the first steps in the direction of systems medicine. They formed an interesting pair: Rosenblueth, a physiologist at the Harvard Medical School, and Wiener, the father of modern engineering in the United States. For this book, their conception of science is salient. They wrote, “The intention and the result of a scientific inquiry is to obtain an understanding and a control of some part of the universe.” [1] For them, as a research team, the part of the universe was physiology. An appreciation of their words is important. Understanding is not some vague, subjective explanation, but rather the precision of mathematical systems needed for the representation of relationships between measurable quantities and future predictions based on those relationships. Control is the ability to change physical behavior in a manner concomitant with the mathematical system representing the relevant phenomena.

Rosenblueth and Wiener take an active view of science: it is to change the world. In contemporary terminology, rather than science, one might say that they were describing translational science. “Translational science transforms a scientific mathematical model, whose purpose is to provide a predictive conceptualization of some portion of the physical world, into a model characterizing human intervention (action) in the physical world. Whereas the pure scientist typically tries to minimize human interference, translational science extends science to include conceptualization of human-originated action in the physical world and thereby raises epistemological issues relating to the knowledge of this intentional intervention into the natural order. Scientific knowledge is translated into practical knowledge by expanding a scientific system to include inputs that can be adjusted to affect the behavior of the system and outputs that can be used to monitor the effect of the external inputs and feed back information on how to adjust the inputs.” [2] It is this translational scientific view that Wiener brought into line with modern science during his illustrious career. In perhaps the greatest transformation of engineering epistemology since antiquity, Wiener fundamentally altered the way human beings perceive scientifically based action in the world. Teaming with Rosenblueth, he brought that transformation into medicine.

Thinking of Wiener, this book should be read in two ways. First, considering the specific definitions, theorems, and equations, it discusses a particular dynamical model for gene regulatory networks—probabilistic Boolean networks (PBNs). It covers basic model properties, inference of model parameters from data, and intervention in the model to increase the likelihood of the network being in desirable states. Taking a wider perspective, one can view the PBN model as a vehicle in which to elucidate the therapeutic goals of

translational genomics. The PBN model is rather general and includes both deterministic functional aspects and probabilistic characteristics inherent to the modeling of complex systems. Therefore, it is well suited to serve as a mathematical framework to study basic issues dealing with systems-based genomics, specifically, the relevant aspects of stochastic, nonlinear dynamical systems. These include long-run dynamical properties and how these correspond to therapeutic goals, the effect of complexity on model inference and the resulting consequences of model uncertainty, altering network dynamics via structural intervention, such as perturbing gene logic, optimal control of regulatory networks over time, limitations imposed on the ability to achieve optimal control owing to model complexity, and the effects of asynchronicity.

We do not know what models will ultimately be adopted for specific applications, but we do know that basic translational issues considered in this book will have to be confronted no matter what model is used. In translational science, we are faced with the problem of controlling complex systems in an environment of uncertainty—just the framework in which Wiener pioneered. We need to understand how the inevitable issues manifest themselves in the modeling and control of gene regulatory networks so that therapeutic control strategies can be derived and, even prior to that, so that appropriate experiments can be carried out to gain sufficient modeling information.

We have tried to unify the different strands of research that have been pursued over the last eight years and continue to be pursued. Issues such as inference, network reduction, constrained control, greedy control, and asynchronicity are just beginning to be studied. Moreover, how these are resolved in practice will depend on close interaction between biologists, physicians, mathematicians, and engineers. Only in that way will the phenomena, medical outcome, and model be brought into a coherent whole to fulfill the promise of translational science. We hope that this book provides a step in that direction.

[1] Rosenblueth, A., and N. Wiener, "The role of models in science." *Philosophy of Science*, 12, 316-321, 1945.

[2] Dougherty, E. R., "Translational science: epistemology and the investigative process," *Current Genomics*, 10 (2), 102-109, 2009.

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