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# Introduction

Mathematical modeling has been used for decades to help scientists understand the mechanisms and dynamics behind experimental observations. Designing models requires experimental data, and knowledge or a hypothesis about how the components of the system are connected. Neurogastrobiology is largely an empirical science, much of it incomprehensible and unpredictable, because of a deficient theoretical foundation. Investigations into different aspects of morphology, electrophysiology, neurophysiology, neuropharmacology, and biomechanics have mostly utilized reductionist approaches to analyze the interactions of neuromuscular and regulatory mechanisms at molecular levels, leaving unstudied the operative integration of component processes involving electromechanical, chemoelectrical and electrochemical coupling. Our understanding of how the gastrointestinal tract regulates the flow of its contents in normal and diseased states will remain fragmentary and semi-quantitative, with correspondingly limited clinical applicability, until a theory that unifies the fine- and large-scale effects has been developed and demonstrated to adequately predict physiological behaviors.

Existing models of the gastrointestinal system have proven helpful in predicting behavior under experimental conditions. However, most models suffer from biological naiveté: they can validate experimental hypotheses, but generally cannot provide any information about system function beyond that which the experimenters had already proposed to be true. New models are being developed that incorporate detailed dynamics for sets of interactions with varying degrees of complexity. Computational power can solve large sets of equations over multicellular networks, to effectively bridge the gap among subcellular, cellular, tissue, organ and system-level features. The range

of problems that are being addressed is growing steadily, utilizing modeling methods that differ in their modularity and mathematical implementation. However, the current deficit in scientists equally trained and prepared to understand mathematics and biology/medicine hampers the development and application of computer simulations methods in biology.

A range of mathematical models and numerical methods related to specific questions of neurogastrobiology with applications to the studies of gastrointestinal motility are presented in this book. The extent to which the models provide a clear understanding of how fine-scale mechanisms produce large-scale effects are analyzed using computer simulations. Attempts have been made to gain insight into the physics of complex wave phenomenon in the gut by offering new explanations for experimental data and re-interpreting old observations using novel conceptual views on hierarchical conjugation in low excitable biological media. With this approach we have tried to eliminate many of the mistakes and misinterpretations of physiological findings that have dominated the field for several decades. One regrettable consequence of this is the prominence of gastrointestinal motor disorders in medicine and the limited effectiveness of existing methods to treat it.

The focus of this book is on neurobiological aspects of intestinal motility. A “bottom-up” approach is employed in the text. This means that to understand the function of a system, it is first necessary to understand the function and behavior of its components and their interactions. Such an approach is appealing because it suggests a modular organization in the gastrointestinal system, which is intuitively useful in understanding possible interactions among different components and their emergent properties. An ordered design process is used to understand biological processes in smooth muscle fibers, neurons and neuronal networks, and myoelectrical activity and signal transduction mechanisms.

This strategy appears to be the best method to build a feasible model of the gut. The challenging question is how to manage the computational complexity of the model. The processes are described by nonlinear systems of partial and ordinary integro-differential equations that can only be solved numerically and simulated on a computer. It is not our intention to provide a detailed study of numerical implementations, but rather to introduce

concepts of how numerical algorithms are designed and what are the requirements to be met in order to achieve the desired accuracy and efficiency in calculations.

The resultant equations include parameters and constants, such as mechanical and cable electrical properties of the longitudinal and circular smooth muscle syncytia, rates of chemical reactions for the conversion of acetylcholine, noradrenaline and serotonin, and activation thresholds, which are, in most cases, unknown and must be identified using the available data. The procedure of parameter identification requires solving the model with a set of “guessed” input values. The results of simulations are then compared with experimental data. If the results do not match, a new guess is made and the process is repeated. This process can be computationally demanding, especially when using a large number of parameters and variables. However, it could be rationalized by using efficient search methods or by optimization-based techniques. The inability to find a suitable parameter set might indicate that the equations are not a correct representation of the system. In such cases, the simulation results may question the original hypothesis from which the model was derived and predict the need for new changes to the model. Thus, numerical experimentation can lead to testable quantitative or qualitative predictions that distinguish between *in vivo* and *in vitro* experimental methods.

Finally, after the model has been numerically validated, it can serve as a gnostic tool to explore a wide range of experimental conditions in a virtual environment; to understand the impact of physiological variables in ways that cannot be adequately represented in even the most complex animal models; to predict the effects of intrinsic/extrinsic interventions before expensive bench experiments are run; to reproduce and study “analytically” the effects of different classes of drugs; and to facilitate the investigation of issues of clinical safety and efficacy.

Numerical studies play a crucial role in elucidating, explaining and understanding complex biological phenomena when seen together with experimental and existing knowledge. New successes emerge as the opportunity to use mathematical and computational models in biosciences continue to grow. Collaboration between modelers and experimentalists will result in accelerated integration of these methodologies into mainstream biology.