Modeling of Disease - Molecular Level: Overview

Definition

Though molecular and cellular level modeling is the first step in the long ladder of multiscale modeling for clinical translational application, it may be regarded as the critical scale: "Where the rubber meets the road." The idiom from automotive engineering refers to the critical endpoint where all the ancillary engineering - fuel system, chassis, pistons, etc. - is finally tested. In the realm of translation, this point comes when we translate basic research results to the clinical setting. The physician (though not the surgeon) intervenes at the molecular scale, using pharmacological agents to alter physiological activity only observed at far higher scales: the macroscopic realms of clinical tests and of signs and symptoms. Given the vast scale gap between molecular treatments and macroscopic outcome, there is enormous difficulty in understanding causal relations, so as to design better drugs and better drug combinations. Multiscale modeling can help make these connections in order to provide a basis for rational pharmacotherapeutics.

Detailed Description

This section includes entries of three types:

- Techniques
  : These simulations are performed largely using techniques used elsewhere in computational neuroscience. However, some techniques have been introduced or expanded in the context of their use in translational studies.
- Locations
  : Partitioning of the nervous system can be done at many scales, from organelle to major brain area.
- Diseases
  : We make note of a few neurological and psychiatric illnesses that have been examined at this scale.

Techniques

Standard techniques of molecular and cellular computational neuroscience are utilized for clinical and translational modeling. The techniques that are applicable to simulation at the molecular and cellular level are listed here by their coverage in entries of this encyclopedia (loosely grouped from micro to macro):

- Stochastic Simulators
- Gillespie Algorithm for Biochemical Reaction Simulation
- Deterministic Reaction-Diffusion Simulators
- Modeling of Bimolecular Reactions
- Modeling of Enzyme Kinetics
- Modeling Ion Concentrations
- Second Messenger Modeling
- Cable Equation
- Equivalent Cylinder Model (Rall)
- Modeling Synapses
- Modeling the Axon
- Numerical Integration Methods
- Action Potential Initiation

In this section, we add two additional methods that have been applied to clinical translational problems.
"Polypeptide and Protein Modeling for Drug Design" takes us down to the lowest of the multiple scales used in computational neuroscience. Polypeptide modeling largely utilizes ball-and-spring modeling, staying above the level of quantum mechanical representations. Individual atoms or atomic groups (e.g., amino acids) are represented as moving in

a force field largely determined by the chemical bonds connecting them. This research has direct importance for clinical translation because the lock-and-key fit of a ligand (a drug) to a target is dependent on the physical relations of the interacting species.

"Application of Declarative Programming in Neurobiology" demonstrates the novel use of a Declarative Programming Language to address problems in Alzheimer's disease and in fear conditioning. Declarative Programming is distinguished from the familiar Imperative Programming languages which we commonly utilize. Imperative programs implement an algorithm. Declarative programs describes relationships between elements, defining what computations are possible amount these elements.

Locations

Disease strikes at many locations and at many scales. Parsimony and clinical efficacy depend on finding the proper scale and proper locus for clinical investigation and for clinical intervention - in some cases these are not the same location. A recent example from oncology is illustrative: a renal cancer and a leukemia were previously classified according to organ system and therefore treated by different subspecialists with different therapeutic approaches. These cancers have now been found to share the same tumor mutation and to benefit from similar treatments. As in this oncology example, protean neurological diseases will also express widely. For example, diseases of mitochondria such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonic epilepsy with ragged red fibers; the ragged fibers being broken mitochondria) produce neurological disorders across many neural systems, beyond the already broad scope of their acronyms.

In addition to connoting locations in the brain and body (macroscale), disease localization also needs to consider the locus in the cell: particular organelles such as mitochondria, particular classes of molecules such as ion channels, and particular specialized subcellular spaces such as synapses and spines. Some of these locations are covered elsewhere in these volumes: note sections on "Ion Channel Types and Modeling," "Synaptic Dynamics," and entry on "Dendritic Spines." It is to be expected that disorders of spine shape, and of proteins involved in synaptic plasticity, will produce neurological or psychiatric disorders. In this section, we consider the modeling of pharmacotherapeutic manipulation of ion channels in "Neuropharmacological Modeling, Pharmacogenomics, and Ion Channel Modulation."

A literal route to clinical application is described here in "Brain Extracellular Space: A Compartment for Intercellular Communication and Drug Delivery." The blood-brain barrier and the extracellular space represent the major pathways for delivery of pharmacological agents. Due to therapeutic index (therapeutic concentration/toxic concentration ratio), it is important to consider how a particular drug can be delivered so as to arrive at adequate concentrations at the site of disease, without being present at excessive concentration at other locations.

At the cellular level, neurological disease has substantial overlap with disease in other excitable tissues. It is particularly valuable to consider the extensive work that has been done in cardiology, here represented by "Cardiac Excitable Tissue Pathology (Ion Channels)" and "Cardiac Excitable Tissue Pathology (Ischemia)." Cardiology models are generally more mature than those in neurology. They also have direct analogies to diseases of the brain: e.g., myocardial infarction and stroke; arrhythmias and epilepsies. Similarly, excitable tissue is important in the islets of the pancreas and in other endocrine systems, where production and release of hormone is directly analogous to production and release of neurotransmitters: see entry on "Endocrine Cell Function and Dysfunction." A broader physiological perspective, relevant to many of these cell types, is presented here in "Neuropharmacological Modeling, Alterations in Ionic Homeostasis."

Many neurological diseases present outside of the brain or involve the brain in its association with the body. In particular, the enteric nervous system (ENS) and autonomic nervous system (ANS) are prone to disorders and will be important areas for modeling in the future. In the present section, we feature an entry on "Pathological Changes in Peripheral Nerve Excitability," to consider disorders in the peripheral nervous system (PNS). It is important to note that myopathies (muscle diseases) also fall within the bailiwick of neurology and will benefit from modeling, some of which can be borrowed from the cardiology literature.

At the subcellular level, signaling occurs through second and third through nth messengers. There has been considerable modeling at this scale, but not as much looking at dysfunction. These topics are covered in detail in the section on " Biochemical Signaling Pathways and Diffusion." Particular note should be made of the major role of calcium as a second messenger, covered in eight entries in that section. Certainly, dysregulation of calcium control will play a major role in the production and expression of disease.

All disease is to a greater or lesser extent multifactorial. Patient susceptibility is determined in substantial part by the genome and its control, as well as by the epigenome and metagenome, representing additional genomes that are

involved (mitochondrial, bacterial - commensal or pathological, viral). In a neuron, communication between genome and synapse is particularly complex, insofar as this is information flow between the organism's two primary loci of information storage. Synaptic changes depend on elaboration, transport, and insertion of membrane proteins, which start with signals at the synapse that trigger changes in transcription. In the present section, we cover the role of second messengers in providing communication with the cell nucleus: transcriptional control dysfunction, modeling, and evaluating potential pathology in the linkage between the cell and its nucleus at the molecular and organelle scales.

Diseases

Evaluation of individual diseases is the natural approach for clinical translation - as an end goal we want to know how to treat a particular disease or even a particular patient (personalized medicine) or subgroup of patients (precision medicine). We highlight here four diseases, although there are several others where some cellular/molecular modeling progress has been made, and many more where such progress is greatly needed.

A model of molecular dependencies in Alzheimer's is presented in "Application of Declarative Programming in Neurobiology to Decipher Normal and Pathological Processes." A model of ALS is presented in "Amyotrophic Lateral Sclerosis and Axonal Pathologies."

As a lens through which to view computational neuroscience, disease modeling presents a number of difficulties. First, diseases are generally multiorgan, both in production and in expression. For example, we present here an entry on "Brain Ischemia and Stroke." Stroke is most often caused by atherosclerosis, a disease of blood vessels. A translational model would ideally include the cellular changes of the arterial wall and the changes in hemodynamics, along with factors that include the blood-brain barrier (which breaks) and the role of a broad dispersion of harmful neurohumoral agents. Stroke frequently co-occurs with myocardial infarction (MI). These coincident disorders, in brain, heart, and local microvasculature, affect one another, e.g., MI reduces cardiac output and therefore increasing the extent of an incipient stroke. Another difficulty in providing a unified model of a disease is that the disease may involve many disparate variants: hemorrhagic vs bland stroke, thrombotic vs embolic stroke, and cortical stroke (grey matter) vs internal capsule (white matter) stroke.

As mentioned in the "Definition" section above, modeling at molecular and cellular levels is only the lowest rung in the multiscale ladder of both downward and upward causality. Disparate viewpoints at different scales represent a challenge but are a necessary stage in the development of future unified multiscale views, as can be illustrated by the case of epilepsy - contrast the entry in the section: "Epilepsy: Abnormal Ion Channels" with the perspective presented in entries on "Epilepsy: Computational Models," "Slow Oscillations, and Epilepsy: Network Models," "Epilepsy, Neural Population Models of."

How are we to build multiscale models out of these disparate pieces? Ideally it would be possible to embed one scale within the model for the higher scale, thereby creating a single unified multiscale model, In many cases this is not possible, so that the models remain separate, with each level informing the other via emergent properties discovered at the lower level. In the case of epilepsy research, emergences from the effect of a drug on a detailed model of an ion channel can be used to change the parameterizations of an ion channel, which could then be directly embedded in a compartmental model. Emergences from the compartment model can then be used in a reduced model or to modify an integrate-and-fire model. Either of these models (or both as in a hybrid network) can be directly embedded to produce large network models. Emergences from the network can then be used to modify a mean-field model. While this upward sequence is difficult, the downward sequence is even more difficult: we want to follow the scales back down in order to apply lessons learned from the population model in order to eventually suggest changes to drug effect at the polypeptide level.

Conclusions

These initial efforts aimed at understanding the base scale of molecular and cellular interactions for understanding brain disease should be considered in the context of the wider field of computational systems biology, a field concerned with multiscale modeling across organ systems and medical specialties. Systems biology has been catapulted forward with the realization that the massive amounts of data being collected as genomes, proteomes, and other omes will not be interpretable without contexts, contexts that can only be provided by sophisticated computational models. Further future

hope springs from the potential of computer simulation to provide personalized or precision medicine; physiological data from a particular patient would be used to adapt simulation parameters for simulation, just as anatomical data for a particular patient is currently used to provide specifics of beam targeting in radiation therapy.