Credibility, Replicability, and Reproducibility in Simulation for Biomedicine and Clinical Applications

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Abstract

Modeling and simulation in computational neuroscience is currently a research enterprise, used to better understand neural systems, but not yet directly applicable to the problems of patients with brain disease. In order to be used for clinical applications, there must not only be considerable progress in the field, but also a concerted effort to use best practices so as to be able to demonstrate model credibility to the FDA, to clinics and hospitals, to doctors, and to patients. In doing this, we can learn lessons from long-standing practices in other areas of simulation (aircraft, computer chips), from software engineering, and from other areas of biomedicine, notably biomechanics. We introduce some basic concepts that will be important in the development of credible clinical neuroscience models: Reproducibility & Replicability, Verification & Validation, Software/Model Configuration Control, and general Procedures & Processes for Credible Mechanistic Multiscale-Modeling. We also discuss how garnering strong community involvement can promote model credibility. Finally, in addition to direct usage with patients, we note the potential for simulation usage in the area of Simulation-Based Medical Education, an area in which to date been primarily

reliant on physical models (mannequins) and scenario-based simulations rather than on numerical simulations.

Introduction

One hallmark of science is reproducibility. An experiment that cannot be reproduced by others may result from statistical aberration, artifact, or fraud. Such an experiment is not credible. Therefore, reproducibility is the first stage to ensure credibility of an experiment. However, reproducibility alone is not sufficient. For example, an *in vitro* experiment is generally performed to advance or aid the understanding of *in vivo* conditions. However, the *in vitro* results will in some cases be inapplicable to the living tissue due to the artifact of isolation: a single cell or a tissue slice extracted from its environment will not function in precisely the way it functioned in residence. In medicine, animal models of a disease or treatment are frequently used, but may not be credible due to the many differences between the human and the monkey, rat, or other animal.

Credibility of a simulation, model or theory depends strongly on the projected model use. This is particularly true in going from research usage to clinical usage. In research, innovation and exploration are desirable. Computer models will be used in research to introduce or explore new hypotheses which have not been thought of before, ideally providing a new paradigm to test experimentally. In this setting, the most important models may in some cases be the less credible ones -- these are the models that stretch understanding by challenging the common view of how a particular system works to offer a paradigm shift. Here, *prima facie* credibility is in the eye of the beholder, representing the views of the community (the dominant paradigm).

In the clinical realm, by contrast, establishing credibility is of paramount importance. For pharmaceuticals, credibility is currently established through evidence-based medicine (EBM), ideally through double-blind trials with large numbers of patients. The downside of this statistical approach is that it necessarily lumps together the large number of disparate patients required to achieve statistical significance. In some cases, this has resulted in tragedy as a subgroup with particular genetics has a fatal response to a drug that is beneficial in the overall group (*e.g.,* rofecoxib, brand-name Vioxx). As EBM gives way to precision medicine, pharmaceutical credibility will be established in each subgroup to enhance safety. However, in order to establish pharmaceutical reliability for personalized medicine (precision with a subgroup of n=1), data-mining will not work since there is by definition no one else to compare this patient to. The only way to predict the response of that individual patient to a particular treatment will be through simulating that patient's individual response based on their genetics and various levels of epigenetics up through brain connectomics. The patient simulation would provide a prediction of the response of that patient's unique physiodynamics to a particular drug, surgical approach, or stimulation paradigm. The credibility of such models will be essential.

In addition to pharmacotherapy, brain disease treatment also utilizes other therapeutic modalities, ranging from neurosurgery to the talk therapy of psychiatry and clinical psychology. While the latter will likely remain beyond the range of our modeling efforts, neurosurgery has already begun to benefit from modeling efforts to identify locations and pathways for epilepsy ablation surgery. Another set of therapeutic approaches that are likely to benefit from modeling are the electrostimulation therapies that are finding increased use in both neurology and psychiatry -- deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct/alternating current stimulation (tDCS/tACS), and electroconvulsive

therapy (ECT). Neurorehabilitation will also benefit from modeling to help identify procedures to encourage neuroplasticity at locations where change will have the greatest effect for relief of deficit.
In most respects, the issues of credibility, replicability, reproducibility for computational neuroscience simulation are comparable to those faced by researchers using simulation to study other organ systems. However, the complexity of the brain and several special features provide unique challenges. As with modeling of other organ systems, there are a large number of scales from molecular (angstrom) level up through tissue levels (centimeters). Many experiments extend from the lowest to highest scales, for example evaluating performance on a memory task as a drug modifies ion channel activity at the molecular level. Compared to other organ systems, there is a particularly broad range of temporal scales of interest: 100 microseconds of sodium channel activation up to years of brain maturation and learning. In addition to physical scales of the central nervous system (CNS) itself, brain research includes further investigative levels of cognition, information, and behavior. An additional aspect of nervous system organization involves overlap between scales, which prevents encapsulation of one scale for inclusion in the higher scale. For example, spatiotemporal activity in apical dendrites of neocortical pyramidal cell (subcellular level) are co-extensive in both spatial and temporal scales with the scales of the local network (supracellular level).

In this paper, we will focus on the many issues of model credibility from a biomedical and clinical perspective. We will use *model* here forward to mean mathematical model, primarily analyzed *in silico* via a *simulation*, the numerical instantiation of a mathematical model on a computer. We will identify explicitly when discussing other types of models: verbal models, animal models, physical models, *etc.* Currently, there are still relatively few models of brain disease, and those still remain in the research domain, rather than being critical clinical tools. Therefore, we are largely developing and considering policy and practice for clinical computational neuroscience, based on the current uses of computational neuroscience in basic biomedical research, and on the clinical usage of simulations in other domains of medicine. In doing this, we will introduce some basic concepts that are important in development of credible models: Reproducibility & Replicability and Verification & Validation. In addition to direct usage with patients, we note the great potential for simulation in the area of simulation-based medical education (SBME), an area in which the *simulations* have to date been primarily physical models (body dummies) and scenarios rather than numerical simulations.

Reproducibility and Replicability indicate Reliability

Replicability is the ability to achieve a fully identical result. Replicability is a design desideratum in engineering when one wants to make sure that a system being distributed runs identically to a prototype system.(R. A. McDougal, Bulanova, and Lytton 2016; Drummond 2009; Crook, Davison, and Plesser 2013) Reproducibility, in contrast, is the ability of a simulation to be reproduced by others. Replicability and reproducibility are inversely related. A turnkey system, provided on a dedicated hardware or a dedicated virtual machine, will run identically every time and therefore be fully replicable. However, such a system will not be reproducible by outsiders, and may in some cases have been encrypted in order to make it difficult to reverse engineer. Generally, the higher level the representation, the more readily other groups can reproduce and understand a simulation, but the less likely they are to obtain an identical result -- lower replicability and usability. Representations using equations -- algebra, linear algebra, calculus -- are identical worldwide and therefore can provide the greatest degree of reproducibility by any group anywhere. However, differences in numerical algorithms used in computer implementations of the equations will lead to somewhat different results for different instantiations of the equations. From there one goes through various levels of software representations including dedicated packages providing a declarative description of a simulation, or dedicated packages with procedural descriptions. The former will generally be more understandable and more easily ported than the latter. A general-purpose interpreted language such as

Python will provide a more easily understood and reproduced simulation than will a compiled language such as C or FORTRAN. Finally, we reach the level of a turn-key system which is likely to only provide machine code with no easily understood (source) code provided and little likelihood of reproducibility.

Some difficulties with precise replicability of simulations are common to many different simulation systems. In particular, a model that uses pseudo-random numbers will not replicate precisely if a different randomizer is used, if seeds are not provided or if randomizers are not handled properly when going from serial to parallel implementations. One difficulty peculiar to neural simulation is related to the strong nonlinearities (and numerical stiffness) associated with action potential spike thresholding due to positive feedback through fast voltage-gated activation of sodium channels leading to further membrane depolarization. Spiking networks are sensitive to round-off error since a single time-step change in spike time will propagate to produce changes in the rest of the network.(London et al. 2010)

In general, specific simulation programs have enhanced reproducibility by providing purpose-built software to solve the particular problems of the computational neuroscience domain. These packages will generally couple ordinary differential equation solvers (ODEs) for simulating individual neurons with an event-driven queuing system to manage spike event transmission to other neurons in neuronal networks. These facilities are provided by a number of neuronal network simulators such as BRIAN (Goodman and Brette 2008), PyNN (Davison et al. 2008), and NEST (Plesser et al. 2015), which allow spiking neurons to be connected together in networks of varying size. (Note that these simulators are very different from the Artificial Neural Networks used in deep learning which do not implement spiking neurons). Some other packages also add the ability to do more detailed cellular simulation for the individual neurons by adding the partial differential equations (PDEs) needed to simulate the internal chemophysiology that complements the electrophysiology of spiking. Packages such as NEURON (Carnevale and Hines 2006) and MOOSE (Dudani et al. 2009) provide this additional functionality. However, many simulations in computational neuroscience are still carried out using general purpose mathematical software, e.g., Matlab, or more general computer languages such as FORTRAN, C or C++, limiting their reproducibility, reusability, and extensibility.

Since computational neuroscience simulations are often very large, extensibility to high performance computing resources (HPCs) is also desirable. Some current simulator tools offer a direct path to these larger machines. NetPyNE, a declarative language built on top of NEURON, provides a general description of a network that can be run directly either on a serial processor or, via MPI (message passing interface), on an HPC (William W. Lytton et al. 2016). The Neuroscience Gateway Portal provides a shared, NSF-supported resource that simplifies HPC for a variety of simulators, including NetPyNE, NEURON, NEST, BRIAN and others, by obviating the need for the user to know MPI usage (Carnevale et al. 2014).

Journal articles should permit reproducibility since equations are given in the methods section. However, full details are generally not provided due to the enormous complexity of detail with many different cell types and complex network connectivity (R. A. McDougal, Bulanova, and Lytton 2016). Furthermore, parameters and equations may be given for one figure but not for all figures shown. Papers may also have typographical or omission errors. And even when the paper version is complete and entirely without error, errors are likely to creep in when reproduction is attempted and the model is typed or scanned to get it back into a computer. For all of these reasons, an electronic version of a model is both more accurate and more immediately usable than a paper copy. Some journals, and many individual editors or reviewers in the field,

require software sharing as part of the publication process. However, some authors resist this mandate desiring to retain exclusive access to their intellectual property.

Databases of models and parts of models have become important in encouraging reproducibility in computational neuroscience (Gleeson et al. 2017). Additional value is added by utilizing formal model definitions such as ModelML, CellML, NeuroML, VCML, SBML (Moraru et al. 2008; Hucka et al. 2003; Lloyd et al. 2008; Zhang, Bakshi, and Prasanna 2007; Cannon et al. 2014; Gleeson et al. 2010). Major databases are being provided by the Human Brain Project, the Allen Brain Institute, the International Neuroinformatics Coordinating Facility, and others. Other databases include the NeuroMorpho.Org database of neuronal morphologies, the ModelDB database of computational neuroscience models (see this issue) in a variety of simulation packages and languages, and the Open Source Brain database for collaborative research (Gleeson et al. 2012; Gleeson, Silver, and Cantarelli 2015; Gleeson et al. 2018) We discuss these resources further below under "Role of the Community."

A recent initiative to encourage reproducibility in science is the new *ReScience Journal* (rescience.github.io), which only publishes papers that replicate computational studies. By hosting the journal on github, new implementations are directly hosted along with the paper, and any ancillary materials identifying provenance or providing documentation. Recently Shimoura *et al.* ported the classic Potjans-Diesmann cortical microcircuit model from NEST to BRIAN, reproducing and confirming the primary results (Cordeiro et al. 2018).

Good Practices Contributing to Simulation Credibility

Verification and Validation (V&V)

Verification and validation (V&V) helps users demonstrate the credibility of a computational model within the context of its intended use. This is accomplished by assessing the quantitative and qualitative aspects of the model that influence model credibility. The process of establishing the model's capability to represent the real system is accomplished through the processes of verification, validation, uncertainty propagation, and sensitivity analysis. Of these, V&V represent the most well-known, and potentially confused, aspects of model assessment.

Computational models may be implemented using open-source or commercial (off-the shelf) software, custom (in-house) code, or a combination of the two (modified off-the shelf software). Verification provides assurance that a computational model accurately represents the underlying mathematical equations and their solution on a specific code platform. Software implementation of model concepts should follow best practices of the developing organization, using established software quality assurances practices and processes such as those described in the Capability Maturity Model Integration (https://www.sei.cmu.edu/cmmi/). In the case of ground-up model development, this ensures proper construction, error checking, and version management has been followed, and is communicated to the user. Verification also focuses on confirmation of parameter specification, and the accurate translation of model data from model data sources into the model application.

The verification process is divided into two sequential steps: code verification and calculation verification. *Code verification* ensures that the numerical algorithms implemented by the code developer are a faithful representation of the underlying physical or conceptual model. In other words, code verification establishes

the reliability of the source code in representing the conceptual model, including relevant physics, for the problem. During this phase, benchmark problems with analytical solutions are typically employed to ensure that the computer code generates the correct solution at the specified order of accuracy. For example, a common reference example in Computational Fluid Dynamics (CFD) is laminar flow in a straight pipe with circular cross-section, whose analytical solution is well-known.(Stern, Wilson, and Shao 2006) CFD modeling techniques are used for neurosurgical modeling of cerebral artery aneurysms.(Babiker et al. 2013) Unfortunately, for most Computational Neuroscience applications no analytic solutions are available. Therefore, one is restricted to comparing results from one numerical approximation to that of another without reference to any ground truth (Brette et al. 2007).

Next, *calculation verification* aims to estimate numerical errors associated with the conceptual model implementation, *i.e.,* the computational model representing the target application. Going back to the laminar pipe flow example, one would generalize the geometry, material properties, and loading conditions such that the problem no longer has an analytical solution but can be solved numerically. Various aspects of the model numerics are investigated and refined until the model is deemed to be accurate within a pre-specified tolerance. Upon completion of the calculation verification step, the user has established (and should document) that due diligence has been followed to ensure a software-bug free implementation of the model concepts with contextually substantiated parameter values.

Everyday vernacular often equates or confuses the terms “verification” and “validation”. As described in the previous paragraphs, *verification* seeks to ensure that the quality of the implementation of the conceptual model. Similarly, *validation* seeks to assess how well the conceptual model and its implementation on a specified code platform represent the real-world system for a defined application. More rigorously stated, validation is an assessment of the degree the model and simulation is an accurate representation of the response of the real system within the intended context of application. In this case, validation is a comparative process that defines a qualitative or quantitative measure of how the model differs from an appropriate experimental or other data source, i.e. a *referent*. Validation also helps to ensure that the computational model has *sufficient* rigor for the context of use. Since a more rigorous model is not necessarily more credible, this optimizes the investment of resources to achieve validation.

The definition of an appropriate referent is a critical aspect of model validation. Ideally, a validation referent is associated with the context of use of the real system in that it should consist of data that is obtained for a system with high similarity to the system being modeled and represent data obtained within an environment similar to that of that real system. It should also be considered of high quality by the model end-user community and represent data not used in model development, separating *design data* from *testing data* (also called fit vs benchmark data, or calibration vs validation data). This is not always possible, and clarity must be communicated regarding the limitations imposed due to inadequacies of the validation referent. Practitioners should also keep in mind that a model validation, or the understanding of the variability of the model in predicting the real world response, exists only in the area of the referents used in the validation process, as illustrated by the Validation Domain in Fig. 1. The Application Domain shown in Fig. 1 establishes the range of input and output parameters relevant to the context of use of the computational mode. As application of the model deviates from the situational context described by the referent, the influence of the model validation information should also change.

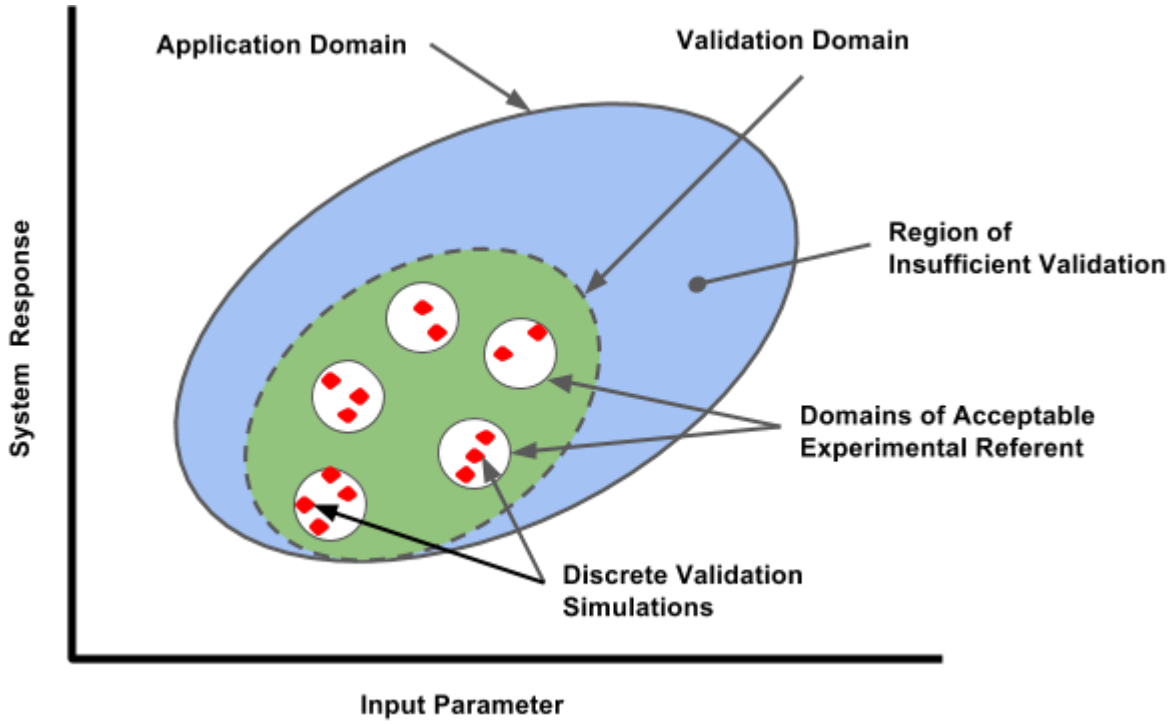

Figure 1. Validation domain of a computational model for range of input parameters and outputs (system responses). Red diamonds represent the validation set points, where comparisons between the computational model and applicable referents were conducted by discrete simulations performed in each referent sub-domain. The range of parameters evaluated establish the Validation Domain (green ellipse), which will define the extent of the Application Domain (large blue ellipse) where model performance has established credibility. Applications of the model outside of the Application Domain lack validation and have lesser credibility.

In most cases, the more quantitative the comparison, the stronger the case that a model and simulation is contextually valid. Organizations such as the American Society of Mechanical Engineers have developed standards to guide the model practitioner in performing successful model validation activities. These comparisons range from qualitative, graphical comparative measures, to quantitative comparative measures relying on statistical analysis of referent and model variance, the latter obtained over a wide range of input parameter variation (Oberkampf and Roy 2010). In practice, the end-user community and regulatory agencies should play a role in assessing the applicability of the validation comparison based on the context of expected application and the influence the model has on critical decision-making.

Aspects of Good Practice for Credibility

Software Aspects

Credibility of simulation results require reliability of simulation protocols and software tools. Good software practices include version control; clear, extensive documentation and testing; use of standard (thoroughly tested) software platforms; and algorithms for particular types of numerical solutions. It is also desirable to rely on existing industry standards and guidelines, and to compare simulation results against competing implementations. To maintain the highest level of credibility, one would establish and follow these practices at every step of the development, V&V, and during utilization of the simulation tools.

Version control is an approach for preserving model development and use histories, including tracing the provenance of model parameters and scope of applicability. There exists a large number of version control systems (VCS) which provide on-site, remote, or distributed solutions (*e.g.,* GIT, SVN, Mercurial). In general terms, these systems provide tools for easy traceability of changes in individual files, attribution of modifications and updates to the responsible author, and versioning of specific snapshots of the complete system. Use of a VCS is recommended for both development (troubleshooting of bugs) as well as the day-to-day use of the modeling tools (monitoring of modeling progress).

One of the important aspects of establishing model credibility that is often overlooked in the computational science community is testing of the model scripts and binary codes. Researchers tend to focus their attention on V&V in the context of simulation results, but omit testing the functionality of the software modules themselves. This process can be implemented as a suite of tests which verify functionality of individual functions and modules (unit tests) and their integration within the system (integration tests). It is common practice to automate the testing procedures using any of the existing automated testing frameworks and perform these tests after each version update.

While VCS provides modeling tool traceability, extensive documentation adds usability and insight into the model structure and its expected behavior. Good documentation practice requires maintenance of a detailed electronic laboratory notebook (e-notebook), which ideally provides automatic coordination with software versions and data output. The notebook will also include informative records of model development and implemented assumptions, model mark-up, detailed descriptions of the input and output formats, and testing procedures. Depending on the complexity of the modeling tools and/or approach, the model description may be augmented with case studies, verification problems, and tutorials to ensure that other researchers/practitioners use the model as intended by the original authors.

It should be noted that even models developed and used strictly following the aforementioned guidelines, could have some application bugs and usability issues. Thus, it is important to also cross-verify simulation results using alternative execution strategies and competing model implementations (*e.g.,* run the simulation using both NEURON and NEST). This step would reduce the chance of obtaining spurious simulation results, while simultaneously also providing a greater insight into the obtained results. In addition to the inter-model verification, some of the simulation steps could be governed by generally-applicable or discipline-specific standard operating procedures, guidelines, and regulations. These guidelines should be adopted to conform to existing standards and promote the reproducibility and in turn credibility.

Developing Credible Mechanism-Oriented Multiscale Models: Procedure and Process

In science, explanation can be inductive, proceeding from repeated observation. Ideally, however explanation precedes prediction, permitting deductive reasoning (Hunt et al. 2018). Simulation of a mechanistic multiscale model provides an explicit way of connecting a putative explanatory mechanism to a phenomenon of interest.

Credibility and reproducibility can be enhanced by taking note of the many factors and workflows required to build a credible simulation to be used in a clinical application. One of these, often overlooked, is the role of exploratory (incredible) simulations in building credible simulations. We would argue that most of the simulations that have been done in computational neuroscience are of the exploratory kind, and that we can now begin winnowing and consolidating these to create credible simulations for clinical application.

Unfortunately, the problems in biology and particularly in neuroscience are characterized by 1. imprecise, limited measures; 2. complex observations whose relevance is sometimes unclear; 3. sparse, incommensurable and sometimes contradictory supporting information; and 4. high degree of uncertainty (left of the ranges in Fig. 2). These limitations contrast with the more solid information, concepts, observables and lower uncertainty associated the "classical" engineering of man-made devices such as computers, cars and aircraft.

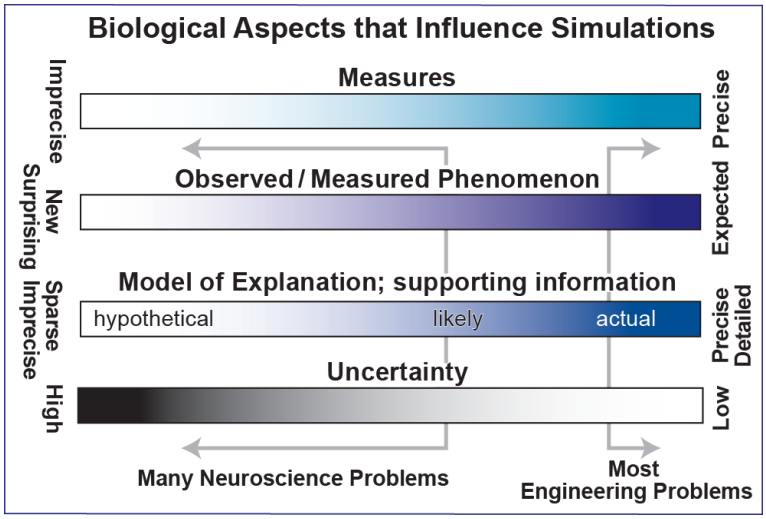

Figure 2. Spectra to characterize biological aspects of interest. Classical engineering problems lie at the right side of each range, working with precise measures, strong expectations, detailed information and low uncertainty. Unfortunately, most neuroscience problems lie far to the left with weak measures, unclear phenomenology, sparse information and high uncertainty.

As can be seen in Fig. 3, the procedures that we identify for the building of a credible simulation involve many sub-workflows and processes. One can spend years in Box **d**, building tools and running exploratory simulations that only lay the groundwork for future credible models. Nonetheless, it is important not to lose site of the goals, which is to explain brain phenomenology at one or more levels of description: electrical rhythms, movement, behavior, cognition, *etc.*

The first task is to specify phenomena to be explained **(a)**. From this perspective, potentially relevant biological aspects are then organized together with relevant information and data into incipient explanations (**c**). In the computational neuroscience community, there are multiple perspectives regarding what information is to be considered relevant. For example, some argue that dendritic morphology and the details of ion channels are critical for understanding cortical networks (Amunts et al. 2017), while others consider that one need only consider simplified spiking cells(Cain et al. 2016) (Diesmann, Gewaltig, and Aertsen 1999) (Potjans and Diesmann 2014), and still others that it is best to work with high-level dynamical representations of populations (Shenoy, Sahani, and Churchland 2013) or mean-field theory (Robinson, Rennie, and Rowe 2002). Indeed all of these perspectives can be regarded as part of the explanatory modeling that will find its way into new concepts of: 1. what is considered to be a relevant observation or measurement (arrow from **c** to **a**) and 2. what will be considered to be the form of an eventual causal explanation (arrow from **c** to **b**). Development of this incipient explanation will involve establishing mappings and drawing analogies between features of the explanation and particular measurements. These mappings and analogies may then be extended to provide working hypotheses and to actual preliminary biomimetic simulations for the eventual causal explanations.

A set of additional considerations (**d**) provide the bridge from the exploratory activities of **c** to final credible models of **e**. Although illustrated towards the bottom, these aspects of project formulation should also be

considered from the very beginning. For example, in computational neuroscience, potential use cases are still being developed and differ considerably across the four major clinical specialties with interest in this area. Some of these are considered below -- they will include epilepsy surgery; rational phamacotherapeutics in epilepsy, schizophrenia and other diseases; use of electrical and optogenetic stimulation; and changes in the approach to physiatry. As the field identifies the users, specific use cases, requirements and specifications, we will identify a variety of phenomena to be considered (arrow from **d** to **a**). For example, if users will have access to electroencephalography (EEG) data but not electrocorticography (ECoG) data, that difference in the observables will alter not only the type of software to be developed (**d** and **e**) but also alter the types of explanations that are to be sought (arrow from **d** to **b**). Use cases will also need to be organized based on expectations, separating near-term and long-term needs. Many new users, use cases and applications will arise since all specialties and subspecialties have an interest in better understanding the innervation of their organ system of interest (Barth et al. 2017) (Samineni et al. 2017) (Ross et al. 2018) (Vaseghi et al. 2017).

While identification of users and use cases remains relatively underdeveloped in computational neuroscience, the development of simulation tools is quite sophisticated. The need to combine a variety of numerical techniques (ODEs, PDEs, events, graph theory, information theory *etc.*) has resulted in the development of a number of simulation platforms. The software and numerical descriptions in **d** are needed both for development of exploratory simulations in **c** and for the resultant credible software in **e**. These simulation techniques have been developed over more than a half century, starting with the pioneering work of Hodgkin and Huxley (Hodgkin and Huxley 1952), Rall (Rall 1962), Fitzhugh (Fitzhugh 1961), and others. Today we have a large variety of simulators with different strengths (Bower and Beeman 2012) (Goodman and Brette 2008) (Carnevale and Hines 2006) (Davison et al. 2008) (Plesser et al. 2015) (Brette et al. 2007) (Tikidji-Hamburyan et al. 2017) that can be used individually or in combination, *cf.* MUSIC (Djurfeldt et al. 2010).

During the final stage of credible model development (**e**), we demonstrate that the model provides the desired outputs to represent observations (arrow from **e** to **a**). A typical requirement is that simulation outputs agree with target phenomenon measurements within some tolerance. Since the simulation system will be multi-attribute and multiscale, it will at the very least begin providing mechanism-based, causal understanding across measures. To the extent that the model is truly biomimetic, direct mappings will exist to specific biological counterparts (arrow from **e** to **b**). Although **e** appears to be the end of the road, actual practice will require that the resulting software system undergoes many rounds of verification, validation, refinement and revision before even being released to users. From there, continued credibility requires continuing work on documentation, tutorials, courses, bug reports and bug fixes, requested frontend enhancements, and identified backend enhancements.

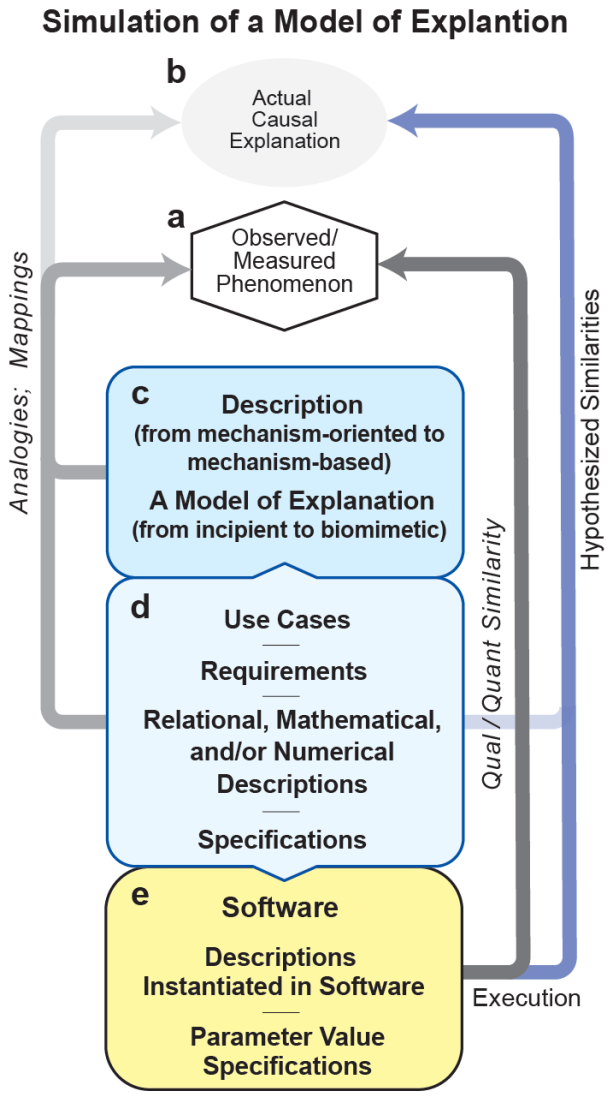

Figure 3. Mechanistic multiscale modeling process; (a) Observables of phenomena to be explained. (b) causal explanation to be discovered; (c) process (workflow) to identify and organize related information into descriptions, this process will involve simulation; (d) meta-modeling workflows required for defining the extent of the final model (e) credible simulation which matches target phenomenon within some tolerance.

Role of the Community

Community involvement is important in order to to establish the credibility of models and modeling and simulation processes. The peer-review publication process serves as a traditional starting point for engaging the community. However, sharing the models themselves, along with the data used to build and evaluate them, provides greater opportunities for both the discipline-specific and the broader communities to directly assess their credibility. The role of sharing models and related resources has been acknowledged in the neurosciences community (Callahan et al. 2017; R. A. McDougal, Bulanova, and Lytton 2016). These related resources include the documentation of the model (commonly provided in English) and its implementation encoded in its original markup (if in a formal language). With access to the model and its associated data and documentation, interested parties can then assess the reproducibility and replicability of the models and the simulation workflow first-hand. Further, reuse of the models and extensions of the modeling and simulation strategies for different applications can reveal previously unknown limitations and

reinforce strengths of the model. Each of these various community contributions help build up the credibility of a model.

It is also important to note the necessity of cross-community fertilization to establish a common ground for credible modeling and simulation practices, to conform to and evolve standards that promote a unified understanding of model quality. Such standards enable individuals to easily exchange and reuse a given model on its own or in combination with other models. Especially in multi-scale modeling efforts, for example connecting the molecular, organelle, cellular, and tissue-level processes to predict potential drug targets (Neymotin, Dura-Bernal, Lakatos, et al. 2016; Neymotin, Dura-Bernal, Moreno, et al. 2016),(Anwar 2017), the ability to trust and build upon existing models can accelerate the development of these larger-scale efforts. Organizations, such as the Committee on Credible Practice for Modeling and Simulation in Healthcare (Mulugeta and Erdemir 2013), are leading efforts to establish such standards.

Most community involvement has come through the establishment of databases and other resources that have encouraged submissions from the overall community of researchers. For example, the Scholarpedia resource established by Izhikevich and collaborators has hosted articles on computational neuroscience concepts and techniques that have been used to share concepts, modeling techniques, and information about particular modeling tools (Wilson 2008; Seidenstein, Barone, and Lytton 2015; Gewaltig and Diesmann 2007). The Open Source Brain project provides a central location for collaborators working on modeling the nervous system of particular brain areas or of whole organisms, notably the OpenWorm project for modeling the full nematode nervous system (Szigeti et al. 2014). The Human Brain Project, an EU project based in Switzerland, has established a number of "Collaboratories" to encourage community involvement in coordinated projects. One of these projects aims to identify the parameters underlying individual synaptic events recorded in voltage clamp experiments (Lupascu et al. 2016). The Allen Brain Institute, another large modeling and data collection center, shares all results with the community, even before publication. Most of the major simulator projects encourage contributions from the community to provide either simulator extensions or additional analytic tools. For example, the SenseLab project hosts a SimToolDB alongside ModelDB for sharing general simulation code (Nadkarni et al. 2002). ModelDB itself is a widely used resource which specifically solicits model contributions and then provides a starting point for many new modeling projects that are extensions or ports of existing models (Robert A. McDougal et al. 2016; Peterson et al. 1996).

The above databases are used to provide completed models that are designed to be stand-alone but could also in the future be used as components of larger models. By contrast, anatomical cell models or ion channel models are generally made available as starting points for other models and are used in combination to build models at higher scales. Examples of these include the NeuroMorpho.Org database of neuronal morphologies and the Channelpedia database of voltage-sensitive ion channels (Ranjan et al. 2011; Ascoli, Donohue, and Halavi 2007).

The availability of these valuable resources is a testament to the successful engagement of the computational neuroscience community. Now the challenge is to provide mechanisms for choosing among the existing hundreds of models. Here again, community involvement can play a critical role by providing the feedback and assessments of a model and its credibility to aid others in deciding whether or not to re-use that model.

Use of Simulation in Medical Education

Simulation-based medical education (SBME) is rapidly growing in application for training medical students, residents, and in some cases for planning highly-specialized medical and surgical procedures (Jones, Passos-Neto, and Braghiroli 2015; Yamada, Fuerch, and Halamek 2017). However, the use of the word *simulation* here differs from our usage. SBME is referring to *simulated reality*, ranging from purely paper exercises based on protocols, to re-enactments with live actors of physical exams or major disasters, to detailed computer-based virtual reality training similar to video games. Virtual-reality simulators make use of some numerical simulation to establish the trajectory of a football in a video game or the elasticity of tissue in a surgical simulator. Nonetheless, the technologies and tools used to administer SBME have been slower to adapt to current advances in modeling and simulation technologies, including mechanistic multiscale modeling. This has been especially problematic in neurology because of the added complexity of the symptoms associated with neurological conditions. Even the most advanced mannequins and computer-generated simulations have very limited capacity to produce a realistic focal neurological deficit or combination of signs and symptoms (Ermak et al. 2013; Micieli et al. 2015; Konakondla, Fong, and Schirmer 2017). Additionally, the fidelity and credibility of these models and simulations can vary significantly.

Epilepsy is one of the most successfully modeled disorders in neurology and neurosurgery (W. W. Lytton 2008). In particular, Jirsa and colleagues have pioneered models of individual patients prior to epilepsy surgery, an example of modeling for personalized medicine (Jirsa et al. 2017; Bernard and Jirsa 2017; Proix et al. 2017; W. W. Lytton 2017). Such simulations could now be extended into training protocols for neurology and neurosurgery residents, offering an opportunity for melding educational simulation with computational neuroscience.

Current SBME efforts in this domain have utilized a mannequin to train medical students to manage differential diagnoses and emergency procedures for handling status epilepticus and acute stroke (Ermak et al. 2013). The mannequin used in that SBME study was not actually designed for neurology training and was not capable of mimicking visible, or electrographic, signs of stroke or seizures. Instead the designers focused on a different level of verisimilitude, asking the student to read into the scenario to assess the medical condition based on data from charts and simulation actors playing the part of family members, with a focus on recognition and management of the neurological emergency. Debriefing of students was conducted in accordance with the ten conditions (*i.e.,* best practices) for effective implementation of SBME (Barry Issenberg et al. 2005). On this basis, the authors concluded that the proposed protocol provided a framework for how SBME can be used in neurology, despite the shortcomings of current technology. However, the simulation necessarily falls short on the tenth condition of effective implementation of SBME: the degree to which the simulation has a “real-life” feel.

In the future, life-like and highly immersive SBME will facilitate the learning of highly-demanding and dangerous medical procedures, including emergencies and recovery from mistakes, in the way that is currently done with simulators used to train pilots, astronauts and flight controllers. Ideal neurology and neurosurgery (and eventually psychiatry and physiatry) SBME systems must be able to perform the task it advertises, in its entirety, separate novices from experts and have these learned skills be transferable to patient care (Konakondla, Fong, and Schirmer 2017). The predictive validity of the simulation can then be

assessed by comparing performance measured under simulation condition and with real patients (Konakondla, Fong, and Schirmer 2017).

Another example of SBME in clinical neuroscience training is the Neuro-Touch surgical training system developed by the National Research Council of Canada (Konakondla, Fong, and Schirmer 2017), built around a stereoscope with bimanual procedure tools that provide haptic feedback and a real-time computer-generated virtual tissue that responds to manipulation. As the surgeon is working through a surgical scenario, the simulator records 13 metrics that are currently being collected for detailed analysis in order to develop benchmarks that differentiate medical students, junior or senior residents and attending neurosurgeons. However, because the evaluation is only being conducted within the confines of the simulations, the authors warn that the insights that may be drawn should only be viewed as the skill level of the learner using the simulator, and not a clear indication of skill performance. There have been examples in aircraft simulators where a particular technique which served to "game" the simulator resulted in a fatal accident when used in real life (Wrigley 2013). Hence, mastery of the simulation by a junior physician may only indicate that the learner has learned the behavior of the simulator and should not be interpreted as the learner having matched the skill level of a seasoned neurosurgeon. Furthermore, substantial work would be needed to determine whether seasoned practitioners can have similar benefits as early learners for acquiring medical skills and improving clinical care.

The Neurological Exam Rehearsal Virtual Environment (NERVE) virtual patient SBME tool was developed to teach first- and second-year medical students how to diagnose cranial nerve deficits. This virtual patient SBME was found to be an effective teaching tool (Reyes 2016) when evaluated using a questionnaire-based validation test specifically designed for virtual patient simulators (Huwendiek et al. 2014). An interesting future extension would be to provide an underlying simulator that would take account of the many complex neurological deficits found in patients due to the anatomical confluence of tracts in the brainstem. Such a simulator would be useful for neurology residents as well as for medical students.

Overall, although there are works that show great promise for SBME to prepare healthcare providers to successfully complete difficult medical procedures (Yamada, Fuerch, and Halamek 2017), the nuances of designing and implementing credible SBME tools and curricula should not be underestimated. This has proven to be especially challenging in neurology (Ermak et al. 2013; Chitkara et al. 2013; Fuerch et al. 2015; Konakondla, Fong, and Schirmer 2017). As Micieli et al. pointed out, when simulators are not adequately designed to give the practitioner appropriate feedback and decision-making information, the number of errors can rise significantly, which in turn can increase risk to the patient (Micieli et al. 2015). Considering that there are about 400,000 medical error related deaths every year in the US, it is paramount to design and implement credible SBME systems and curricula that are targeted at improving clinical outcomes (Jones, Passos-Neto, and Braghiroli 2015; Konakondla, Fong, and Schirmer 2017). In doing so, we suggest that SBME systems and curricula begin to incorporate multiscale models that simulate realistic physiologic responses that physicians can expect to encounter clinically.

In an effort to advance both the technologies and methodologies applied in SBME, the Society for Simulation in Healthcare (SSH) recently established the Healthcare Systems Modeling & Simulation Affinity Group. The Committee on Credible Practice of Modeling and Simulation in Healthcare (Mulugeta and Erdemir 2013) has been collaborating with the SSH community by providing guidance on how to design and implement explicit multiscale computational models into traditional SBME systems. Additionally, the Congress of Neurological Surgeons have formed a Simulation Committee to create simulations for resident

education (Konakondla, Fong, and Schirmer 2017). The US FDA and the ASME have also been working to publish standards and guidelines for regulatory submissions involving computational models and simulations for healthcare applications (Hariharan et al. 2017).

There are no SBME systems currently available that incorporate computational models to simulate realistic physiologic response of virtual patients and mannequins to brain disease and to interventions. In order to use SBME to train medical students and practitioners to appropriately respond to these medical conditions, we need to move towards the incorporation of physiologically accurate mathematical models into the overall architecture of SBME systems and curricula.

Use of Modeling in Clinical Domains of Brain Disease

Simulations in the clinical neuroscience domain have largely focused on accounting for the neural activity patterns underlying brain disease. Testing the predictions arising from simulation is dependent on technological advances in neuromodulation, pharmacology, electrical stimulation, optogenetic stimulation, *etc*. Neuropharmacological intervention is generally systemic with effects wherever receptors are found, often peripherally as well as centrally. Although targeted treatment with an implanted cannula is possible, it is not currently used clinically. By contrast, electrical stimulation can be highly targeted with local placement of electrodes. Development of closed-loop systems and devices for brain stimulation (Dura-Bernal et al. 2015), are currently being used and show promise in treating a wide range of neurological diseases and disorders including Parkinson, depression, and other disorders (Choi et al. 2015) (Johansen-Berg et al. 2008; Shils, Mei, and Arle 2008). Nontargeted electrostimulation using transcranial electrodes is also being widely used but remains controversial, and still lacks precise clinical indications (Lafon et al. 2017; Huang et al. 2017; Santos et al. 2017; Esmaeilpour et al. 2017; Lefaucheur et al. 2014). Consideration is also being given to future use of optogenetic stimulation therapies that would offer still greater precision compared to electrical stimulation -- targeting not only a particular area but a particular cell type or set of cell types within that area (Samineni et al. 2017; Kerr et al. 2014; Vierling-Claassen et al. 2010)

Successful application of models in the clinical domain will depend on the use of credible practices to develop, evaluate, document and disseminate models and simulations, using the principles outlined above. However clinical applications will also need to be verified and validated by trial in the clinical context in order to be utilized.

As an illustrative case for evaluating the credibility of a simulation study, we consider a mechanistic multiscale model of multi-target pharmacotherapy for disorders of cortical hyperexcitability (Neymotin, Dura-Bernal, Lakatos, et al. 2016). The study assessed hyperexcitability in an exploratory manner. We therefore did not pre-define a single clinical context but left ourselves open to exploration of cortical activation for dystonia and seizures. Dystonia is a movement disorder that produces involuntary muscle contractions and involves pathology in multiple brain areas including basal ganglia, thalamus, cerebellum, and sensory and motor cortices. We focused only on primary motor cortex, noting that this was one common output area for potentially distributed pathology.

The multiscale model included molecular, cellular, and network scales, containing 1715 compartmental model neurons with multiple ion channels and intracellular molecular dynamics. Data used to develop the model was taken from a large number of sources including different species, different preparations (slice, cell culture, *in vivo, ex vivo*), different age animals, different states, different conditions. None of the data was taken from the clinical disorders in question due to limitations of human experimentation. As the model lacked a description of the motor output, the simulations could not be systematically evaluated in the context

of dystonia. We suggested that the model may be applicable to epilepsy due to the appearance of the cortical activity patterns in the simulations. Beta activation in the cortex was used as a surrogate feature to evaluate whether simulations can account for activity patterns relevant to dystonia. The model lacked representations of spinal cord or limb, as well as many pharmacological parameters, particularly with respect to role of neuromodulators (known unknown), brain states (less known unknown) and metabolic parameters. Simulations reproduced patterns of heightened cortical activity seen in dystonia. The corresponding pathological parameter sets were identified by independent random variations in parameters. These simulations demonstrated degeneracy, meaning that there were many combinations of parameters that yielded the pathological syndrome.

The primary result was that no individual parameter alteration could consistently distinguish between pathological and physiological dynamics. A support vector machine (SVM) machine learning approach separated the physiological from pathological patterns in different regions of high-dimensional space, suggesting multitarget routes from dystonic to physiological dynamics. We interpreted these results as suggestive of the need for a multitarget drug-cocktail approach to intervene in dystonia. In order to enable replication and aid in reproducibility of the model, we utilized Mercurial, a versioning system which was used to track parameter variations and match to corresponding simulations (Hinsen, Läufer, and Thiruvathukal 2009; Waltemath et al. 2013). The model was disseminated via publication and meeting presentations with the code made available via ModelDB resource (reference #189154). Limited documentation was also made available at a level conforming to ModelDB requirements, consistent with practices generally accepted by the Computational Neuroscience community. Due to the nature of the clinical domain, the parameter provenance was partial; details of parameter sources were included in the paper. Model replicability was tested by ModelDB curators, but was not tested directly by the manuscript reviewers. There have not yet been any third-party studies reproducing the model. There are unexploited opportunities to compare the model with alternative implementations, for example by considering a simpler modeling formalisms for single-neuron activity. Credibility of the simulations and insights from the results would be enhanced by follow-on work that reproduces the simulations using similar or alternative implementations. Of course, these studies would have to follow the replicability and reproducibility principles outlined here to enable a meaningful comparison of simulations towards improving credibility.

As a contrast to above examination of the credibility practices as applicable to a mechanistic multiscale model, we considered these issues in the context an individualized phenomenological model of seizure propagation by Proix and colleagues (Proix et al. 2017), implemented using The Virtual Brain platform (Sanz-Leon et al. 2013). The study was aimed at demonstrating that patient-specific virtual brain models derived based on information from diffusion magnetic resonance imaging (MRI) technique have sufficient predictive power to improve diagnosis and surgery outcome in cases of drug resistant epilepsy. Data from individual patient tractography and EEG was utilized to parameterize the each individual model separately. The diffusion MRI-based connectivity observed between the parcellated brain regions in each individual was used to setup the patient-specific connectivity matrix that related distinct autonomous oscillators ("Epileptors") at each brain region. The resultant patient-specific virtual brain model was evaluated for its consistency in predicting seizure-like activity patterns in that patient.

Considering that the Epileptor model is a phenomenological description of oscillatory patterns of activity in a bulk tissue (neural mass model), there are no explicit parameters or variables that directly arise from specific molecular, cellular and metabolic pathways. However, the autonomous oscillator model switched between interictal and ictal states because of a slow *permittivity variable* that was hypothesized to relate to

local tissue metabolism. Alternative connectivity matrices and weightings were considered based on data from control subjects, shuffling the data, changing the weights while preserving the topology of the connectivity, and log-transformation. Based on these validations, the authors demonstrated that prediction of seizure patterns was improved when the patient-specific topology of the connectivity matrix was utilized. The study also considered alternative models based on fast coupling, no time scale separation, and a generic model that shows saddle-node bifurcation. Based on the simulations considering these alternative models, the authors concluded that weak coupling is necessary for the predictions on the recruited networks.
The Virtual Brain platform is made available in a public repository using the widely-employed git distributed version control system. The model and the results were disseminated as part of the published manuscript as well as through conference presentations and posters. While the manuscript was peer-reviewed, it is not readily apparent if the model was tested directly in simulations by the manuscript reviewers. Credibility of the simulations and insights from the results would be enhanced by follow-on work that reproduces the simulations based on data from additional patients, as well as using alternative model formalisms that incorporate details at the biochemical or cellular scales. In order to permit a meaningful comparison, such follow-on studies would have to follow the replicability and reproducibility principles outlined here.

As the computational models of neurological conditions become increasingly reproducible and credible, the potential for utilizing the model simulations for therapeutic development becomes a viable proposition. For example, development of safe and therapeutically effective neurostimulation protocols requires identification of suitable, if not necessarily optimal, ranges of parameters, e.g., strength, duration, frequency, waveform, location, iterations, schedule, reference activity, *etc.* It is not feasible to evaluate the large and high-dimensional stimulus parameter space empirically through experimentation in animals or in humans to identify the most appropriate stimulation protocol. Hence, computational modeling and simulation of the response of micro- and macro-scale neural circuits in the brain to neurostimulation becomes an essential component of the stimulation development workflow. The simulation-based approach can narrow down the ranges of stimulation parameters appropriate for each neurological context, potentially in a patient-specific fashion. In this manner, credible practice computational models can transform the intractable challenge of developing effective neurostimulation approaches into a feasible pursuit of techniques for testing and implementing prioritized ranges of desirable neurostimulation parameters.

Actionable Recommendations and Conclusions

The potential of modeling and simulation in clinical application and medical education are promising. However, this potential is mainly being tapped in the areas that are close to traditional engineering domains, such as computational fluid dynamics and stress analysis. For this reason areas of medicine that are related to blood flow, biomechanics and orthopedics have benefited most. By contrast, the brain has an idiosyncratic evolved set of mechanisms that are extremely difficult to reverse engineer and which draw on many areas of engineering, some of which have not been invented yet. Therefore, computational neuroscience remains primarily in the research domain, with only fragmented translations from computational neuroscience to clinical use or to medical education. As medical practice moves toward precision and then personalized healthcare, multiscale modeling will be necessary for simulating the specific patient's response to a disease and treatment. To move towards this goal, we must cultivate credible modeling and simulation practices taken from traditional areas of engineering.

Model Configuration Management

Since many models will be built within the context of a simulation platform, we refer here to "Model configuration." However, all of these points apply *a fortiori* to models being built from scratch in a general-purpose programming language.

1. Use *version control*: git or mercurial (hg) are preferred. github can be used to host projects (Dabbish et al. 2012). In shared projects version control establishes who is responsible for which pieces of code.
2. Use an *electronic notebook* (enotebook) with clear documentation of every stage of model development (including mistakes)
3. Include *provenance* of parameters in enotebook and via version control -- parameters may be changed due to new experimental data and it is valuable to have a clear record of when and why the change was made and what the consequence was for the model.
4. Perform testing of model components: for example, demonstrate that the cell-types show proper firing characteristics before incorporating into networks.
5. Later in the process develop a test suite for further testing. Ideally, model testing should be performed at every version update. A test suite can be linked to standard testing frameworks to automate this testing.
6. Whenever possible, use reliable model development platforms such as NEST, BRIAN, NEURON, MOOSE, NENGO, PyNN, *etc.* This will increase the likelihood of accurate simulation and will enhance sharing. Similarly model components should be taken from reliable databases of morphologies, channels and other components.
7. Later in the process, encourage other groups to compare simulation results on alternative platforms or with different implementations.

Verify and Validate Models

1. Simulation platform developers generally verify the adequacy of the numerics. Some simulators offer alternative numerical solvers which can be tested to assess qualitative similarity of results. For example, one problematic area is the handling of fixed and variable time steps for spike handling in networks.(W. W. Lytton and Hines 2005)
2. Verify algorithms you develop. For example, when developing a neuronal network, make sure that the network design is correct before moving to actual simulation.
3. Verify that the results make sense -- verify that the simulation is a reasonable implementation of the conceptual model. It is tragically easy to move on to the analysis phase of the study without first looking at the raw output to make sure it is reasonable.
4. Validate based on data from a real-world system. In some cases, it may be important to distinguish simulation results from same model for different situations, *e.g., in vitro* slice *vs. in vivo* background activation.
5. Test robustness of a model to parameter changes in order to ascertain whether a particular result is only seen with a particular set of parameter choices.

Although all of these steps are valuable, it is important to understand that higher model fidelity and V&V rigor do not automatically translate to higher credibility.

Share Models and Data

1. Submit models to shared databases such as ModelDB or via github. Share widely -- you can submit the same model to various databases and submit components such as cells and ion channel definitions to component databases.
2. Document thoroughly -- the Methods section of a paper will provide an overall gloss but will not generally go into sufficient detail with regard to software design and use. Comment code. Provide a README on how to launch the simulation.
3. Disseminate -- publish, of course, and present posters and talks to various audiences. In a multidisciplinary area such as computational neuroscience, the same model will say different things to different audiences -- physiologists, anatomists, cognitive neuroscientists, neurologists, psychiatrists, other modelers.
4. Join communities via organizations such as Society for Neuroscience, Computational and Systems Neuroscience (CoSyne), Organization for Computational Neuroscience (OCNS).
5. Obtain independent reviews of models. This is difficult and time consuming but some grants are now providing funding explicitly to pay for consultants to review models.

Define Context of Use and Simulation Requirements

We distinguished above between *exploratory models*, done by an individual researcher in order to provide ideas and new hypotheses, and *context models*, purpose-built models for external users in a given environment, for example clinical or medical education use. In the latter case, it is essential to be clear about who the users are and which usage patterns (sets of use cases) are to be targeted and which ones are to be excluded or to be left as part of longer-term goals. However even exploratory models can benefit from these considerations, envisioning yourself (and perhaps your experimental collaborator) as the user.

1. Identify the *users*. Even if you are the only user at the beginning of the project, you will be sharing the model later, so you may want to take account of other users who are not as familiar with your domain. For clinical use, a clinical assistant for epilepsy would be different for neurosurgeons vs neurologists.
2. Identify the *context of use*. For example, will this model primarily be used to study dynamics, or will it be extended into information theory or will it be expected to perform a memory function, *etc.*
3. Identify *intended uses.* You may have one intended use for yourself as a modeler to generate new theoretical hypotheses and another for your experimental colleague. In the context of a educational application, an SBME for medical students will be very different than an application for residents or for continuing medical education.
4. Attempt to identify *usage patterns* -- it is often the case that underprepared users who have not read the manual use a program in unintended, and sometimes dangerous, ways.

Translation of computational neuroscience models for clinical and medical education use

In the preceding sections we have given examples of particular clinical and educational/training scenarios that may be ripe for the introduction of simulation technology. Here we list both those already mentioned and others that have potential for future applications. This list is by no means complete.

1. Education: Integration of modeling into mannequins and online virtual patients to reproduce neurological deficits in SBME. Initial versions of this would not require mechanistic multiscale modeling but could be done with phenomenological modeling. Future versions would incorporate mechanistic modeling in order to also incorporate the time-course of signs and symptoms (dynamics of the system).
2. Training: Virtual reality simulators with haptic feedback for neurosurgery training.
3. Personalized patient simulations to decide on surgery vs interventional radiology (coiling) for aneurysms.
4. Clinical decision making: Personalized patient simulations to decide on surgical approach for epilepsy surgery.(Jirsa et al. 2017)
5. Simulation for seizure prediction in Epilepsy Monitoring Unit (EMU).
6. Personalized patient simulation to determine therapies for Parkinson disease to include combinations of surgical, electrical and pharmacological therapy (Grill and McIntyre 2001; Kerr et al. 2013; Holt and Netoff 2017; Hammond, Bergman, and Brown 2007; Van Albada et al. 2009; Shils, Mei, and Arle 2008)
7. Head, brain and neural modeling for understanding effects of different kinds of electrical stimulation including transcranial stimulation (Huang et al. 2017; Esmaeilpour et al. 2017; Lafon et al. 2017).
8. Modeling vagal and peripheral nerve stimulation for treatment of systemic disorders (NIH SPARC program, commonfund.nih.gov/sparc).
9. Psychiatry: identifying the varying roles of disorder in dopaminergic, glutamatergic, inhibitory and other deficits in schizophrenia to develop new multi-target therapies (Lisman et al. 2010).
10. Neurorehabilitation (physiatry) Modeling the interface between neural and musculoskeletal models to treat spasticity or dystonia (van der Krogt et al. 2016).

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References

Amunts, Katrin, Christoph Ebell, Jeff Muller, Martin Telefont, Alois Knoll, and Thomas Lippert. 2017. "The Human Brain Project: Creating a European Research Infrastructure to Decode the Human Brain." *Neuron* 92 (3). Elsevier:574–81.

Anwar, A. 2017. "Capturing Intracellular Ca2+ Dynamics in Computational Models of Neurodegenerative Diseases." *Drug Discovery Today. Disease Models*, In press.

Ascoli, Giorgio A., Duncan E. Donohue, and Maryam Halavi. 2007. "NeuroMorpho.Org: A Central Resource for Neuronal Morphologies." *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* 27 (35). Soc Neuroscience:9247–51.

Babiker, M. Haithem, Brian Chong, L. Fernando Gonzalez, Sachmanik Cheema, and David H. Frakes. 2013. "Finite Element Modeling of Embolic Coil Deployment: Multifactor Characterization of Treatment Effects on Cerebral Aneurysm Hemodynamics." *Journal of Biomechanics* 46 (16):2809–16.

Barry Issenberg, S., William C. Mcgaghie, Emil R. Petrusa, David Lee Gordon, and Ross J. Scalese. 2005. "Features and Uses of High-Fidelity Medical Simulations That Lead to Effective Learning: A BEME Systematic Review." *Medical Teacher* 27 (1). Taylor & Francis:10–28.

Barth, Bradley B., Craig S. Henriquez, Warren M. Grill, and Xiling Shen. 2017. "Electrical Stimulation of Gut Motility Guided by an in Silico Model." *Journal of Neural Engineering* 14 (6):066010.

Bernard, C., and V. Jirsa. 2017. "Virtual Brain for Neurological Disease Modeling." *Drug Discovery Today. Disease Models*, In press.

Bower, James M., and David Beeman. 2012. *The Book of GENESIS: Exploring Realistic Neural Models with the GEneral NEural SImulation System*. Springer Science & Business Media.

Brette, Romain, Michelle Rudolph, Ted Carnevale, Michael Hines, David Beeman, James M. Bower, Markus Diesmann, et al. 2007. "Simulation of Networks of Spiking Neurons: A Review of Tools and Strategies." *Journal of Computational Neuroscience* 23 (3). Ecole Normale Superieure, Paris, France.: Springer:349–98.

Cain, Nicholas, Ramakrishnan Iyer, Christof Koch, and Stefan Mihalas. 2016. "The Computational Properties of a Simplified Cortical Column Model." *PLoS Computational Biology* 12 (9). Public Library of Science:1–18.

Callahan, Alison, Kim D. Anderson, Michael S. Beattie, John L. Bixby, Adam R. Ferguson, Karim Fouad, Lyn B. Jakeman, et al. 2017. "Developing a Data Sharing Community for Spinal Cord Injury Research." *Experimental Neurology* 295 (September):135–43.

Cannon, Robert C., Padraig Gleeson, Sharon Crook, Gautham Ganapathy, Boris Marin, Eugenio Piasini, and R. Angus Silver. 2014. "LEMS: A Language for Expressing Complex Biological Models in Concise and Hierarchical Form and Its Use in Underpinning NeuroML 2." *Frontiers in Neuroinformatics* 8. Frontiers Media SA.

Carnevale, Ted, and Michael Hines. 2006. *The NEURON Book*. New York: Cambridge University Press.

Carnevale, Ted, Amit Majumdar, Subha Sivagnanam, Kenneth Yoshimoto, Vadim Astakhov, Anita Bandrowski, and Maryann Martone. 2014. "The Neuroscience Gateway Portal: High Performance Computing Made Easy." *BMC Neuroscience* 15 (Suppl 1). BioMed Central Ltd:P101.

Chitkara, Ritu, Anand K. Rajani, John W. Oehlert, Henry C. Lee, M. S. Epi, and Louis P. Halamek. 2013. "The Accuracy of Human Senses in the Detection of Neonatal Heart Rate during Standardized Simulated Resuscitation: Implications for Delivery of Care, Training and Technology Design." *Resuscitation* 84 (3):369–72.

Choi, Ki Sueng, Patricio Riva-Posse, Robert E. Gross, and Helen S. Mayberg. 2015. "Mapping the 'Depression Switch' During Intraoperative Testing of Subcallosal Cingulate Deep Brain Stimulation." *JAMA Neurology* 72 (November):1252–60.

Cordeiro, V. L., C. C. Ceballos, C. Romaro, and A. C. Roque. 2018. "Reimplementation of the Potjans-Diesmann Cortical Microcircuit Model: From NEST to Brian." *bioRxiv*. biorxiv.org. https://www.biorxiv.org/content/early/2018/01/16/248401.abstract.

Crook, Sharon M., Andrew P. Davison, and Hans E. Plesser. 2013. "Learning from the Past: Approaches for Reproducibility in Computational Neuroscience." In *20 Years of Computational Neuroscience*, 73–102. Springer.

Dabbish, Laura, Colleen Stuart, Jason Tsay, and Jim Herbsleb. 2012. "Social Coding in GitHub: Transparency and Collaboration in an Open Software Repository." In *Proceedings of the ACM 2012 Conference on Computer Supported Cooperative Work*, 1277–86. CSCW '12. New York, NY, USA: ACM.

Davison, Andrew P., Daniel Brüderle, Jochen Eppler, Jens Kremkow, Eilif Muller, Dejan Pecevski, Laurent Perrinet, and Pierre Yger. 2008. "PyNN: A Common Interface for Neuronal Network Simulators." *Frontiers in Neuroinformatics* 2. Frontiers Research Foundation:11.

Diesmann, M., M. O. Gewaltig, and A. Aertsen. 1999. "Stable Propagation of Synchronous Spiking in Cortical Neural Networks." *Nature* 402 (6761). Nature Publishing Group:529–33.

Djurfeldt, Mikael, Johannes Hjorth, Jochen M. Eppler, Niraj Dudani, Moritz Helias, Tobias C. Potjans, Upinder S. Bhalla, Markus Diesmann, Jeanette Hellgren Kotaleski, and Örjan Ekeberg. 2010.

"Run-Time Interoperability between Neuronal Network Simulators Based on the MUSIC Framework." *Neuroinformatics* 8 (1). Springer:43–60.

Drummond, Chris. 2009. "Replicability Is Not Reproducibility: Nor Is It Good Science." In *Proceedings of the Evaluation Methods for Machine Learning Workshop*.

Dudani, Niraj, Subhasis Ray, Siji George, and Upinder S. Bhalla. 2009. "Multiscale Modeling and Interoperability in MOOSE." *BMC Neuroscience* 10 (Suppl 1). BioMed Central Ltd:P54.

Dura-Bernal, Salvador, Amit Majumdar, Samuel A. Neymotin, Subhashini Sivagnanam, Joseph T. Francis, and William W. Lytton. 2015. "A Dynamic Data-Driven Approach to Closed-Loop Neuroprosthetics Based on Multiscale Biomimetic Brain Models." In *IEEE Interanationl Conference on High Performance Computing 2015 Workshop: InfoSymbiotics/Dynamic Data Driven Applications Systems (DDDAS) for Smarter Systems, Bangalore, India*, edited by Ieee.

Ermak, David Matthew, Douglas W. Bower, Jody Wood, Elizabeth H. Sinz, and Milind J. Kothari. 2013. "Incorporating Simulation Technology into a Neurology Clerkship." *The Journal of the American Osteopathic Association* 113 (8):628–35.

Esmaeilpour, Zeinab, Paola Marangolo, Benjamin M. Hampstead, Sven Bestmann, Elisabeth Galletta, Helena Knotkova, and Marom Bikson. 2017. "Incomplete Evidence That Increasing Current Intensity of tDCS Boosts Outcomes." *Brain Stimulation*, December. https://doi.org/10.1016/j.brs.2017.12.002.

Fitzhugh, R. 1961. "Impulses and Physiological States in Theoretical Models of Nerve Membrane." *Biophysical Journal* 1 (6). Elsevier:445–66.

Fuerch, Janene H., Nicole K. Yamada, Peter R. Coelho, Henry C. Lee, and Louis P. Halamek. 2015. "Impact of a Novel Decision Support Tool on Adherence to Neonatal Resuscitation Program Algorithm." *Resuscitation* 88 (March):52–56.

Gewaltig, Marc-Oliver, and Markus Diesmann. 2007. "NEST (NEural Simulation Tool)." *Scholarpedia Journal* 2 (4):1430.

Gleeson, Padraig, Matteo Cantarelli, Boris Marin, Adrian Quintana, Matt Earnshaw, Eugenio Piasini, Justas Birgiolas, et al. 2018. "Open Source Brain: A Collaborative Resource for Visualizing, Analyzing, Simulating and Developing Standardized Models of Neurons and Circuits." *bioRxiv*. https://doi.org/10.1101/229484.

Gleeson, Padraig, Sharon Crook, Robert C. Cannon, Michael L. Hines, Guy O. Billings, Matteo Farinella, Thomas M. Morse, et al. 2010. "NeuroML: A Language for Describing Data Driven Models of Neurons and Networks with a High Degree of Biological Detail." *PLoS Computational Biology* 6 (6). Public Library of Science:e1000815.

Gleeson, Padraig, Andrew P. Davison, R. Angus Silver, and Giorgio A. Ascoli. 2017. "A Commitment to Open Source in Neuroscience." *Neuron* 96 (5):964–65.

Gleeson, Padraig, Eugenio Piasini, Sharon Crook, Robert Cannon, Volker Steuber, Dieter Jaeger, Sergio Solinas, Egidio D'Angelo, and R. Angus Silver. 2012. "The Open Source Brain Initiative: Enabling Collaborative Modelling in Computational Neuroscience." *BMC Neuroscience* 13 (Suppl 1). BioMed Central Ltd:O7.

Gleeson, Padraig, Angus Silver, and Matteo Cantarelli. 2015. "Open Source Brain." *Encyclopedia of Computational Neuroscience*. Springer, 2153–56.

Goodman, Dan, and Romain Brette. 2008. "Brian: A Simulator for Spiking Neural Networks in Python." *Frontiers in Neuroinformatics* 2. Frontiers Research Foundation:5.

Grill, Warren M., and Cameron C. McIntyre. 2001. "Extracellular Excitation of Central Neurons: Implications for the Mechanisms of Deep Brain Stimulation." *Thalamus & Related Systems* 1 (3):269–77.

Hammond, C., H. Bergman, and P. Brown. 2007. "Pathological Synchronization in Parkinson's Disease: Networks, Models and Treatments." *Trends in Neurosciences* 30 (7). Elsevier:357–64.

Hariharan, Prasanna, Gavin A. D'Souza, Marc Horner, Tina M. Morrison, Richard A. Malinauskas, and Matthew R. Myers. 2017. "Use of the FDA Nozzle Model to Illustrate Validation Techniques in Computational Fluid Dynamics (CFD) Simulations." *PloS One* 12 (6):e0178749.

Hinsen, K., K. Läufer, and G. K. Thiruvathukal. 2009. "Essential Tools: Version Control Systems." *Computing in Science Engineering* 11 (6):84–91.

Hodgkin, Alan L., and Andrew F. Huxley. 1952. "A Quantitative Description of Membrane Current and Its Application to Conduction and Excitation in Nerve." *The Journal of Physiology* 117 (4). Wiley Online

Library:500–544.
Holt, A. B., and T. I. Netoff. 2017. “Computational Modeling to Advance Deep Brain Stimulation for the Treatment of Parkinson’s Disease.” *Drug Discovery Today. Disease Models*, In press.
Huang, Yu, Anli A. Liu, Belen Lafon, Daniel Friedman, Michael Dayan, Xiuyuan Wang, Marom Bikson, Werner K. Doyle, Orrin Devinsky, and Lucas C. Parra. 2017. “Measurements and Models of Electric Fields in the in Vivo Human Brain during Transcranial Electric Stimulation.” *eLife* 6 (February). https://doi.org/10.7554/eLife.18834.
Hucka, Michael, Andrew Finney, Herbert M. Sauro, Hamid Bolouri, John C. Doyle, Hiroaki Kitano, Adam P. Arkin, et al. 2003. “The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models.” *Bioinformatics* 19 (4). Oxford Univ Press:524–31.
Hunt, Anthony C., Ahmet Erdemir, Feilim MacGabhann, William W. Lytton, Edward A. Sander, Mark K. Transtrum, and Lealem Mulugeta. 2018. “The Spectrum of Mechanism-Oriented Models for Explanations of Biological Phenomena.” *arXiv [q-bio.QM]*. arXiv. http://arxiv.org/abs/1801.04909.
Huwendiek, Sören, Bas A. De Leng, Andrzej A. Kononowicz, Romy Kunzmann, Arno M. M. Muijtjens, Cees P. M. Van Der Vleuten, Georg Friedrich Hoffmann, Burkhard Tönshoff, and Diana H. J. M. Dolmans. 2014. “Exploring the Validity and Reliability of a Questionnaire for Evaluating Virtual Patient Design with a Special Emphasis on Fostering Clinical Reasoning.” *Medical Teacher*, October, 1–8.
Jirsa, V. K., T. Proix, D. Perdikis, M. M. Woodman, H. Wang, J. Gonzalez-Martinez, C. Bernard, et al. 2017. “The Virtual Epileptic Patient: Individualized Whole-Brain Models of Epilepsy Spread.” *NeuroImage* 145 (January):377–88.
Johansen-Berg, H., D. A. Gutman, T. E. J. Behrens, P. M. Matthews, M. F. S. Rushworth, E. Katz, A. M. Lozano, and H. S. Mayberg. 2008. “Anatomical Connectivity of the Subgenual Cingulate Region Targeted with Deep Brain Stimulation for Treatment-Resistant Depression.” *Cerebral Cortex* 18 (June):1374–83.
Jones, Felipe, Carlos Eduardo Passos-Neto, and Odonne Freitas Melro Braghiroli. 2015. “Simulation in Medical Education: Brief History and Methodology.” *Principles and Practice of Clinical Research* 1 (2). http://ppcr.org/journal/index.php/ppcrjournal/article/view/12.
Kerr, Cliff C., Daniel J. O’Shea, Werapong Goo, Salvador Dura-Bernal, Joseph T. Francis, Ilka Diester, Paul Kalanithi, Karl Deisseroth, Krishna V. Shenoy, and William W. Lytton. 2014. “Network-Level Effects of Optogenetic Stimulation in a Computer Model of Macaque Primary Motor Cortex.” *BMC Neuroscience* 15 (Suppl 1). BioMed Central Ltd:P107.
Kerr, Cliff C., Sacha J. Van Albada, Samuel A. Neymotin, George L. Chadderdon, P. A. Robinson, and William W. Lytton. 2013. “Cortical Information Flow in Parkinson’s Disease: A Composite Network/field Model.” *Frontiers in Computational Neuroscience* 7 (39):39.
Konakondla, Sanjay, Reginald Fong, and Clemens M. Schirmer. 2017. “Simulation Training in Neurosurgery: Advances in Education and Practice.” *Advances in Medical Education and Practice* 8 (July):465–73.
Krogt, Marjolein Margaretha van der, Lynn Bar-On, Thalia Kindt, Kaat Desloovere, and Jaap Harlaar. 2016. “Neuro-Musculoskeletal Simulation of Instrumented Contracture and Spasticity Assessment in Children with Cerebral Palsy.” *Journal of Neuroengineering and Rehabilitation* 13 (1):64.
Lafon, Belen, Asif Rahman, Marom Bikson, and Lucas C. Parra. 2017. “Direct Current Stimulation Alters Neuronal Input/Output Function.” *Brain Stimulation* 10 (1):36–45.
Lefaucheur, Jean-Pascal, Nathalie André-Obadia, Andrea Antal, Samar S. Ayache, Chris Baeken, David H. Benninger, Roberto M. Cantello, et al. 2014. “Evidence-Based Guidelines on the Therapeutic Use of Repetitive Transcranial Magnetic Stimulation (rTMS).” *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology* 125 (November):2150–2206.
Lisman, John E., Hyun Jae Pi, Yuchun Zhang, and Nonna A. Otmakhova. 2010. “A Thalamo-Hippocampal-Ventral Tegmental Area Loop May Produce the Positive Feedback That Underlies the Psychotic Break in Schizophrenia.” *Biological Psychiatry* 68 (1):17–24.
Lloyd, Catherine M., James R. Lawson, Peter J. Hunter, and Poul F. Nielsen. 2008. “The CellML Model Repository.” *Bioinformatics* 24 (18). Oxford Univ Press:2122–23.
London, Michael, Arnd Roth, Lisa Beeren, Michael Häusser, and Peter E. Latham. 2010. “Sensitivity to Perturbations in Vivo Implies High Noise and Suggests Rate Coding in Cortex.” *Nature* 466

(7302):123–27.
Lupascu, Carmen A., Annunziato Morabito, Elisabetta Merenda, Silvia Marinelli, Cristina Marchetti, Rosanna Migliore, Enrico Cherubini, and Michele Migliore. 2016. “A General Procedure to Study Subcellular Models of Transsynaptic Signaling at Inhibitory Synapses.” *Frontiers in Neuroinformatics* 10 (June):23.
Lytton, William W., Alexandra Seidenstein, Salvador Dura-Bernal, Felix Schurmann, Robert A. McDougal, and Michael L. Hines. 2016. “Simulation Neurotechnologies for Advancing Brain Research: Parallelizing Large Networks in NEURON.” *Neural Computation* 28:2063–90.
Lytton, W. W. 2008. “Computer Modelling of Epilepsy.” *Nature Reviews. Neuroscience* 9 (8). Department of Physiology, State University of New York, Downstate Medical Center, Brooklyn, New York, USA. billl@neurosim.downstate.edu: Nature Publishing Group:626–37.
———. 2017. “Computers, Causality and Cure in Epilepsy.” *Brain: A Journal of Neurology* 140:516–26.
Lytton, W. W., and M. L. Hines. 2005. “Independent Variable Timestep Integration of Individual Neurons for Network Simulations.” *Ncomp* 17:903–21.
McDougal, R. A., A. S. Bulanova, and W. W. Lytton. 2016. “Reproducibility in Computational Neuroscience Models and Simulations.” *IEEE Transactions on Bio-Medical Engineering* 63:2021–35.
McDougal, Robert A., Thomas M. Morse, Ted Carnevale, Luis Marenco, Rixin Wang, Michele Migliore, Perry L. Miller, Gordon M. Shepherd, and Michael L. Hines. 2016. “Twenty Years of ModelDB and beyond: Building Essential Modeling Tools for the Future of Neuroscience.” *Journal of Computational Neuroscience*, 1–10.
Micieli, Giuseppe, Anna Cavallini, Paola Santalucia, and Gianfranco Gensini. 2015. “Simulation in Neurology.” *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 36 (10):1967–71.
Moraru, I. I., J. C. Schaff, B. M. Slepchenko, M. L. Blinov, F. Morgan, A. Lakshminarayana, F. Gao, Y. Li, and L. M. Loew. 2008. “Virtual Cell Modelling and Simulation Software Environment.” *IET Systems Biology* 2 (5):352–62.
Mulugeta, Lealem, and Ahmet Erdemir. 2013. “Committee on Credible Practice of Modeling and Simulation in Healthcare.” In *ASME 2013 Conference on Frontiers in Medical Devices: Applications of Computer Modeling and Simulation*, V001T10A015–V001T10A015. American Society of Mechanical Engineers.
Nadkarni, Prakash, Jason Mirsky, Emmanouil Skoufos, Matthew Healy, Michael Hines, Perry Miller, and Gordon Shepherd. 2002. “Senselab: Modeling Heterogenous Data on the Nervous System.” In *Bioinformatics: Databases and Systems*, 105–18. Springer, Boston, MA.
Neymotin, Samuel A., Salvador Dura-Bernal, Peter Lakatos, Terence D. Sanger, and William W. Lytton. 2016. “Multitarget Multiscale Simulation for Pharmacological Treatment of Dystonia in Motor Cortex.” *Frontiers in Pharmacology* 7 (June):157.
Neymotin, Samuel A., Salvador Dura-Bernal, Herman Moreno, and William W. Lytton. 2016. “Computer Modeling for Pharmacological Treatments for Dystonia.” *Drug Discovery Today. Disease Models* 19:In press.
Oberkampf, William L., and Christopher J. Roy. 2010. *Verification and Validation in Scientific Computing*. Cambridge University Press.
Peterson, Bret E., Matthew D. Healy, Prakash M. Nadkarni, Perry L. Miller, and Gordon M. Shepherd. 1996. “ModelDB: An Environment for Running and Storing Computational Models and Their Results Applied to Neuroscience.” *Journal of the American Medical Informatics Association: JAMIA* 3 (6). American Medical Informatics Association:389–98.
Plesser, Hansekkehard, Markus Diesmann, Marc-Oliver Gewaltig, and Abigail Morrison. 2015. “NEST: The Neural Simulation Tool.” In *Encyclopedia of Computational Neuroscience*, edited by Dieter Jaeger and Ranu Jung, 1849–52. Springer New York.
Potjans, Tobias C., and Markus Diesmann. 2014. “The Cell-Type Specific Cortical Microcircuit: Relating Structure and Activity in a Full-Scale Spiking Network Model.” *Cerebral Cortex* 24 (3):785–806.
Proix, T., F. Bartolomei, M. Guye, and V. K. Jirsa. 2017. “Individual Brain Structure and Modeling Predict Seizure Propagation.” *Brain: A Journal of Neurology* 140:651–54.
Rall, W. 1962. “Electrophysiology of a Dendritic Neuron Model.” *Biophysical Journal* 2:145–67.
Ranjan, Rajnish, Georges Khazen, Luca Gambazzi, Srikanth Ramaswamy, Sean L. Hill, Felix Schürmann, and Henry Markram. 2011. “Channelpedia: An Integrative and Interactive Database for Ion Channels.”

Frontiers in Neuroinformatics 5 (December):36.
Reyes, R. 2016. “An Empirical Evaluation of an Instrument to Determine the Relationship Between Second-Year Medical Students’ Perceptions of NERVE VP Design Effectiveness and Students' Ability to Learn and Transfer Skills from NERVE.” University of Central Florida. http://stars.library.ucf.edu/etd/4893/.
Robinson, P. A., C. J. Rennie, and D. L. Rowe. 2002. “Dynamics of Large-Scale Brain Activity in Normal Arousal States and Epileptic Seizures.” *Physical Review. E, Statistical, Nonlinear, and Soft Matter Physics* 65 (4). American Physical Society:041924.
Ross, Shani E., Zhonghua Ouyang, Sai Rajagopalan, and Tim M. Bruns. 2018. “Evaluation of Decoding Algorithms for Estimating Bladder Pressure from Dorsal Root Ganglia Neural Recordings.” *Annals of Biomedical Engineering* 46 (2):233–46.
Samineni, Vijay K., Aaron D. Mickle, Jangyeol Yoon, Jose G. Grajales-Reyes, Melanie Y. Pullen, Kaitlyn E. Crawford, Kyung Nim Noh, et al. 2017. “Optogenetic Silencing of Nociceptive Primary Afferents Reduces Evoked and Ongoing Bladder Pain.” *Scientific Reports* 7 (1):15865.
Santos, Michele Devido Dos, Vitor Breseghello Cavenaghi, Ana Paula Machado Goyano Mac-Kay, Vitor Serafim, Alexandre Venturi, Dennis Quangvinh Truong, Yu Huang, et al. 2017. “Non-Invasive Brain Stimulation and Computational Models in Post-Stroke Aphasic Patients: Single Session of Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation. A Randomized Clinical Trial.” *Sao Paulo Medical Journal = Revista Paulista de Medicina* 135 (5):475–80.
Sanz-Leon, P., S. Knock, M. Woodman, L. Domide, J. Mersmann, A. McIntosh, and V. K. Jirsa. 2013. “The Virtual Brain: A Simulator of Primate Brain Network Dynamics.” *Frontiers in Neuroinformatics* 7:10.
Seidenstein, Alexandra H., Frank C. Barone, and William W. Lytton. 2015. “Computer Modeling of Ischemic Stroke.” *Scholarpedia Journal* 10 (3). https://doi.org/10.4249/scholarpedia.32015.
Shenoy, Krishna V., Maneesh Sahani, and Mark M. Churchland. 2013. “Cortical Control of Arm Movements: A Dynamical Systems Perspective.” *Annual Review of Neuroscience* 36 (1). Annual Reviews 4139 El Camino Way, PO Box 10139, Palo Alto, California 94303-0139, USA:337–59.
Shils, J. L., L. Z. Mei, and J. E. Arle. 2008. “Modeling Parkinsonian Circuitry and the DBS Electrode. II. Evaluation of a Computer Simulation Model of the Basal Ganglia with and without Subthalamic Nucleus Stimulation.” *Stereotactic and Functional Neurosurgery* 86 (1):16–29.
Stern, Fred, Robert Wilson, and Jun Shao. 2006. “Quantitative V&V of CFD Simulations and Certification of CFD Codes.” *International Journal for Numerical Methods in Fluids* 50 (11). John Wiley & Sons, Ltd.:1335–55.
Szigeti, Balázs, Padraig Gleeson, Michael Vella, Sergey Khayrulin, Andrey Palyanov, Jim Hokanson, Michael Currie, Matteo Cantarelli, Giovanni Idili, and Stephen Larson. 2014. “OpenWorm: An Open-Science Approach to Modeling Caenorhabditis Elegans.” *Frontiers in Computational Neuroscience* 8. Frontiers Media SA.
Tikidji-Hamburyan, Ruben A., Vikram Narayana, Zeki Bozkus, and Tarek A. El-Ghazawi. 2017. “Software for Brain Network Simulations: A Comparative Study.” *Frontiers in Neuroinformatics* 11:46.
Van Albada, S. J., R. T. Gray, P. M. Drysdale, and P. A. Robinson. 2009. “Mean-Field Modeling of the Basal Ganglia-Thalamocortical System. II: Dynamics of Parkinsonian Oscillations.” *Journal of Theoretical Biology* 257 (4). Elsevier:664–88.
Vaseghi, Marmar, Siamak Salavatian, Pradeep S. Rajendran, Daigo Yagishita, William R. Woodward, David Hamon, Kentaro Yamakawa, Tadanobu Irie, Beth A. Habecker, and Kalyanam Shivkumar. 2017. “Parasympathetic Dysfunction and Antiarrhythmic Effect of Vagal Nerve Stimulation Following Myocardial Infarction.” *JCI Insight* 2 (16). https://doi.org/10.1172/jci.insight.86715.
Vierling-Claassen, Dorea, Jessica A. Cardin, Christopher I. Moore, and Stephanie R. Jones. 2010. “Computational Modeling of Distinct Neocortical Oscillations Driven by Cell-Type Selective Optogenetic Drive: Separable Resonant Circuits Controlled by Low-Threshold Spiking and Fast-Spiking Interneurons.” *Frontiers in Human Neuroscience* 4. Frontiers Research Foundation:198.
Waltemath, Dagmar, Ron Henkel, Robert Hälke, Martin Scharm, and Olaf Wolkenhauer. 2013. “Improving the Reuse of Computational Models through Version Control.” *Bioinformatics* 29 (6). Oxford Univ Press:742–48.
Wilson, Charles. 2008. “Up and down States.” *Scholarpedia Journal* 3 (6):1410.
Wrigley, Sylvia. 2013. “Negative Training: When the Simulator Lies.” In *Why Planes Crash Case Files:*

2001. Fear of Landing.

Yamada, Nicole K., Janene H. Fuerch, and Louis P. Halamek. 2017. “Simulation-Based Patient-Specific Multidisciplinary Team Training in Preparation for the Resuscitation and Stabilization of Conjoined Twins.” *American Journal of Perinatology* 34 (6):621–26.

Zhang, Cong, Amol Bakshi, and Viktor K. Prasanna. 2007. “ModelML: A Markup Language for Automatic Model Synthesis.” In *2007 IEEE International Conference on Information Reuse and Integration*. https://doi.org/10.1109/iri.2007.4296640.