

Perspectives on Sharing Models and Related Resources in Computational Biomechanics Research

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Abstract

The role of computational modeling for biomechanics research and related clinical care will be increasingly prominent. The biomechanics community has been developing computational models routinely for exploration of the mechanics and mechanobiology of diverse biological structures. As a result, a large array of models, data, and discipline-specific simulation software has emerged to support endeavours in computational biomechanics. Sharing computational models and related data and simulation software has first become a utilitarian interest and now it is a necessity. Exchange of models, in support of knowledge exchange provided by scholarly publishing, has important implications. Specifically, model sharing can facilitate assessment of reproducibility in computational biomechanics, and can provide an opportunity for repurposing and reuse, and a venue for medical training. The community's desire to investigate biological and biomechanical phenomena crossing multiple systems, scales, and physical domains, also motivates sharing of modeling resources as blending of models developed by domain experts will be a required step for comprehensive simulation studies as well as the enhancement of their rigor and reproducibility. The goal of this article is to understand current perspectives in the biomechanics community for the sharing of computational models and related resources. Opinions on opportunities, challenges, and pathways to model sharing, particularly as part of the scholarly publishing workflow, were sought. A group of journal editors and a handful of investigators active in computational biomechanics were approached to collect short opinion pieces as part of a larger effort of the IEEE EMBS Computational Biology and the Physiome Technical Committee to address model reproducibility through publications. A synthesis of these opinion pieces indicates that the community recognizes the necessity and usefulness of model sharing. There is a strong will to facilitate model sharing and there are corresponding initiatives by the scientific journals. Outside the publishing enterprise, infrastructure to facilitate model sharing in biomechanics exists and simulation software developers are interested in accommodating the community's needs for sharing of modeling resources. Encouragement for the use of standardized markups, concerns related to quality assurance, acknowledgement of increased burden, and importance of stewardship of resources are noted. In the short-term, it is advisable that the community builds upon recent strategies and experiments with new pathways for continued demonstration of model sharing, its promotion, and its utility. Nonetheless, the need for a long term strategy to unify approaches in sharing computational models and related resources is acknowledged. Development of a sustainable platform supported by a culture of open model sharing will likely evolve through continued and inclusive discussions bringing all stakeholders at the table, e.g., by possibly establishing a consortium.

Keywords

computational biomechanics, model sharing, model exchange, simulation, reproducibility

1 Motivation

Computational modeling has greatly augmented our understanding of the role of mechanics on biological function, and now it is a widely utilized strategy for biomechanics research. The reach of computational biomechanics spans practically all organs and tissue types, from brain [1] to cardiovascular system [2], and from respiratory function [3] to musculoskeletal response [4]. Simulations have been utilized to explore the etiology of diverse pathologies such as osteoarthritis [5], osteoporosis [6], and cardiovascular [7] and cerebrovascular [8] aneurysms, to name a few. Predictive modeling has elaborated on the consequences of traumatic injuries to organ systems [9]. Simulation-based design of effective and safe innovations, ranging from rehabilitation strategies [10] to cardiovascular stents [11] and orthopaedic implants [12], has become possible. In silico approaches have also penetrated medical care, e.g., physics-based modeling of arterial flow is an emerging clinical tool for patient-specific diagnosis of heart function [13]. Under these circumstances, computational biomechanics can be considered as a viable alternative to minimize experimentation including cadaver testing, animal studies, and research on human subjects. Its role in basic and applied science, and in translation of technologies and innovations to the medical field will likely expand.

The fundamental product of scientific conduct is the generation of new knowledge and scholarly publishing is the common medium for knowledge exchange. In computational biomechanics, models, data (for development and evaluation of models), simulation software, simulation workflows, and simulation results are intermediaries to biomechanics knowledge. Access to these intermediate products of the modeling and simulation lifecycle can have significant impact on the perceived quality of scientific findings and can dramatically improve the efficiency of subsequent scientific conduct and translation of scientific knowledge to the application domain. An important benefit of model sharing is the increased reproducibility potential of a modeling and simulation study [14]. Computational biomechanics relies on virtual representations with detailed definitions of anatomical, structural, and physiological properties, which are driven by lifelike loading and boundary conditions. Simulations use advanced software capturing the physics of the body, organs, joints, tissues, and cells, down to the molecular level. The constraints of publication venues and the reliance on a natural language may unintentionally prevent adequate descriptions of model components and simulation steps [15]. Consequently, someone who is interested in rebuilding the model or at least repeating the simulations to understand the reproducibility of a computational study will likely be at a disadvantage. A model, when provided in its original form, is complete and defined in a formal language. This representation removes the potential for errors in interpretation, i.e., when the developer describes the model and when the prospective user interprets the developer's description to regenerate the model and reproduce simulation results. Another important and obvious benefit of model sharing is the opportunity for repurpose and reuse. Future users of a model, if it is available, can focus on the scientific question or clinical application rather than rebuilding the model from scratch. Development of biomechanics models can be labor intensive and time consuming. Availability of virtual specimens, subjects, and populations offers the promise to increase the efficiency of computational biomechanics as a discipline. Representation of biomechanics, a persistent phenomenon coupled to biological function, is a necessity for multi-system and multi-scale modeling and simulation [16]. Interdisciplinary groups have an

increasing need for biomechanics models for more holistic explorations of body, organ, tissue, and cell behavior [17]. It is not surprising that modeling communities and funding agencies promote sharing of models for such purposes [18,19]. Finally, access to models and relevant data and software provides diverse training opportunities. An engineer may learn about modeling and simulation techniques, i.e., strategies for anatomical and mechanical representations of biological structures. A scientist in training can use the model to understand the biomechanical behavior of organs and tissues. A physician may perform surgical simulations with the model, for rehearsal or to understand the biomechanical consequences of an intervention [20]. All these benefits already motivate sharing in computational biomechanics despite its potential burden on the scientific workflow. Plus, with our increased dependency on computational modeling and simulation for research and clinical care, sharing of models and related products is becoming a necessity rather than a leisure activity.

The biomechanics community has been responsive to the emerging need for sharing computational models and related products. Simulation software, which are free and open source have been developed and are gaining traction. It is now possible to access highly sophisticated biomechanics software enabling capabilities for cardiovascular fluid flow simulations [21], finite element analysis of tissue deformations [22], and musculoskeletal movement simulations [23], among many others. Some of these software are available for any type of use, including commercial; some others are restricted for academic use only. Infrastructure to host modeling and simulation projects have been launched and are publicly available [24]. Many investigators have already used these platforms to disseminate data and models that are relevant to biomechanics research [25]. Scientific journals targeting biomechanics audiences have started to encourage the sharing of data, models, and software and have provided some guidance. All these initiatives are partially in response to the requirements of funding agencies, which are increasingly aware of the value of sharing data and models and have incorporated such activities as a condition of funding [19]. All stakeholders are adjusting to this changing landscape and as a result, acceptance of sharing products of scientific conduct, including computational models, seems to be accelerating. On the other hand, the biomechanics community at large may still have reservations about sharing models. Such reservations can only be addressed if anecdotal experiences, which seem to point towards cultural issues, technical capabilities, economic burden, and fragmentation of the modeling enterprise, are documented clearly.

The goal of this document is to understand current perspectives of key stakeholders on the sharing of computational models and related materials in biomechanics. The activity emerged from a larger effort of the IEEE EMBS Computational Biology and the Physiome Technical Committee to address model reproducibility through publications [18]. Elaboration of opinions, from individuals at the front lines of scholarly communication and from teams at the heart of modeling and simulation infrastructure, will help elucidate the expectations for sharing in computational biomechanics, clarify emerging opportunities, and define imminent and long-term challenges. Consolidation of such perspectives will eventually provide a pathway to realize model sharing in a structured and sustainable manner, supporting existing knowledge exchange platforms of scholarly publishing with a model exchange culture.

2 Solicitation of Perspectives

A group of editors of scientific journals relevant to biomechanics were approached along with several members of the biomechanics community who have been active in model sharing. An invitation was sent by the first author of this commentary to a total of 8 journals and 6 prominent members of the biomechanics community. The invitation described the goal of the commentary as to curate opinions of journal editors and leaders and stakeholders in the biomechanics community on opportunities, challenges, and pathways for model sharing. It instructed invitees to write a short paragraph on model sharing and reproducibility within the context of their activities in the community and possibly in relation to the journals with which they have been associated. They were asked to limit their contribution to approximately 300 words but not more than 500 words plus references, and focus on how they think model sharing can be incorporated into our scientific workflow and how this may impact the quality of research, translation, and training. They were encouraged to identify and discuss any requirements, obstacles, success stories, and behavioral changes in a forward-thinking manner such that a sustainable ecosystem can be established for model sharing, reproducibility, and reuse. The invitees were reminded that the goal was to incorporate all these opinion pieces in the commentary verbatim with an introduction (to describe motivation and the process of acquiring opinion pieces) and a discussion (to synthesize the contributions and augment with supporting information). In a follow-up communication, the invitees were encouraged to include their co-editors and collaborators to their individual opinion piece to provide a group perspective; to cite any relevant editorials and publications that may help them to convey their message and may provide a more comprehensive view of the ecosystem and culture in regard to model, data, and software sharing; to provide a perspective beyond model sharing, to include data and software sharing as well; and to keep the document focused on high priority opportunities, challenges, and success stories.

3 Individual Opinion Pieces

Editors from 6 scientific journals and 4 groups prominently involved in model sharing responded to the inquiry. Their individual perspectives on opportunities, challenges, and pathways for model sharing in biomechanics are provided below with minor edits, i.e., for consolidation of citations and for clarification of acronyms.

Perspective from Peter J. Hunter and Gerhard A. Holzapfel (as Editors in Chief, Biomechanics and Modeling in Mechanobiology [26])

Any discussion of model sharing needs to be clear about terminology: (i) A model simulation is **repeatable** when re-running it produces a consistent result (within appropriate error bounds if the model is stochastic), and that of course is the bare minimum requirement. (ii) More usefully, a model is **reproducible** when its outputs can be reproduced by a machine from an unambiguous statement of the model equations, together with specified values of the model parameters, initial conditions and boundary conditions. Markup languages such as CellML [27], SBML [28], NeuroML [29] and FieldML [30] are designed to encode a model in unambiguous and declarative form (if a model is encoded in a procedural language like Matlab, it is difficult to then incorporate it into another model). The markup language SED-ML [31] is designed to specify the simulation protocol for running the model with specified

inputs and outputs. Note that not all models are biophysically based and there is a place for the rule-based based approach common in ‘agent based’ modeling. In fact most models will have some type of ‘black box’, often in the form of an empirically derived constitutive relation. (iii) A model is **reusable** when it can be used as an independent model or as a module within another model. This requires that the appropriate use of the model is well documented and that its limitations are clear, and that the model is semantically annotated (often with community derived ontologies) to provide the biological and biophysical meaning of all of its variables and components. (iv) A model is **discoverable** when it has been annotated with metadata that describe the purpose and use of the model sufficiently to allow the model to be retrieved via a webservice. (v) A model is **validated** when its predictions under specified conditions match experimental observations.

It is the role of peer-reviewed journal publications to assess the level of model validation, but the publishing process is currently failing to ensure that published models are reproducible, reusable and discoverable. For models that are based on algebraic and/or ordinary differential equations, there are well-established standards [27–29], model repositories [32], and freely available software [33]. However, for spatial modelling, typically using finite element methods to solve partial differential equations, the creation of standards is much more difficult and is discussed elsewhere in this volume. We advocate a step in this direction for the biomechanics community by establishing a database of all commonly used material constitutive laws based on the CellML standard (see, for example, Fibre Dispersion Law [34], which is based on Gasser et al. [35]). The visualisation of these constitutive laws should use a three-dimensional view of a homogeneous material cube that can be tested in silico with standard biomechanics protocols. Such a facility will shortly be available via the Physiome model repository.

Perspective from Leslie M. Loew (as former Editor in Chief, Biophysical Journal [36] and as Principal Investigator, Virtual Cell Project [37])

The Biophysical Society and *Biophysical Journal* are fully committed to transparency, reproducibility, and data sharing for all the research that we publish. I am about to end my 5 year term as Editor in Chief and am most proud of the measures that we have taken, in collaboration with the Society, to insure that Research Reproducibility is a hallmark of every paper (see Loew et al. [38]). We’ve done this by developing a comprehensive set of “Guidelines for the Reproducibility of Biophysics Research” [39]. This is a living document that has been updated and modified over the past two years as new technologies and data sharing resources emerge. The two basic principles that these “Guidelines” strive to ensure are:

1. Research results should be reported with sufficient detail to enable replication of the study in other laboratories (using supporting information as necessary).
2. Data or material produced in a published study should be readily disseminated and openly accessible whenever feasible (either as supporting material, through deposition in databases or repositories, or through the author’s website and laboratory).

How are these principles translated into practice for the particular challenges associated with software and model sharing? Here are excerpts from the Biophysical Journal Guidelines that address these specific issues:

“4.6 COMPUTATIONAL SYSTEMS AND PHYSIOLOGICAL MODELS. SBML and CELLML are two emerging standards for encoding computational models related to systems biology and physiology. To assure public access to such computational models, authors should, where applicable, deposit their models in the CellML Model Repository or the Biomodels Database. Other public databases for models developed in NEURON (<http://senselab.med.yale.edu/modeldb/default.asp>) or VCell (<http://vcell.org>) should also be utilized where applicable. When this is not possible (e.g., in the case of MatLab or other code), authors should include their model code as a file in the online Supporting Material.”

“4.8 SOFTWARE. Authors must declare the location and accessibility of any custom code and software central to the main claims of their paper. We recommend deposition of source code on GitHub together with a listing on Zenodo, which will assign a Digital Object Identifier (DOI) to make the upload uniquely citeable; this DOI should be reported in the manuscript.”

How can we achieve better compliance with journal guidelines for model sharing? I am opposed to regulations by granting agencies to compel authors to adhere to rigid requirements: in our diverse research fields one size fits all approaches are just unworkable. However, a strong and coherent partnership between editors, model authors and software developers can work. In particular, software developers can provide the tools to make these operations as painless as possible. I am the Principal Investigator for a comprehensive software environment for modeling cell physiology called Virtual Cell [37], giving me an additional perspective with which to address issues of model and software sharing. For example, when our users publish a paper containing a VCell model, we encourage them to make their models public through the VCell database and provide access instructions within the published paper. Users are also encouraged to fully annotate their models to facilitate searching for and reuse of model components. VCell supports export of models into standard formats such as SBML [40] and users are urged to deposit them in the Biomodels Database hosted by the European Bioinformatics Institute [41]. Ultimately, as the community comes to appreciate the value of verifiable and reusable models, authors will be fully incentivized to routinely comply with these best practices.

Perspective from John Middleton and Christopher R. Jacobs (as Editors, Computer Methods in Biomechanics and Biomedical Engineering [42])

Model sharing during the journal submission/review process is considered to be a good idea and such requirements will no doubt increase as software systems become more embedded within both the research and commercial environment. Sharing of models/software/data has been attempted in the past and of course many large internationally used software packages have been successfully developed along the lines of knowledge sharing and such packages now form the basis of many biomechanical simulation journal submissions. The sharing of

simulation software can indeed work very well particularly in cases which can be well defined and where the fundamental physical equations of the system lend themselves to the application of modelling techniques such as the finite element method (FEM). Here further checks such as accuracy/convergence/validation can be quantified which can add further assurance to the results presented.

However with more complex simulation systems, particularly in the ever expanding area of life sciences, such as cell mechanics, contact, nonlinear response and biodynamics, it will become increasingly difficult for an author and reviewer to agree on both the physical nature of the problem (mathematical/numerical definition) and the subsequent techniques used to generate and solve the simulated process. Likewise careful consideration needs to be given to how data is generated during the simulation process and in what format the resulting output is prepared and presented. (Very often colour plots can be most confusing and not easy to interpret).

In essence, model sharing is considered to be a progressive idea and one that the Journal of Computer Methods in Biomechanics and Biomedical Engineering would support. The area of computational biomechanics/biosimulation/tissue modelling is one that will continue to expand and find further application throughout the life sciences. The understanding and sharing of such techniques provides the opportunity for software developers to share both existing science and new and novel methods which will further enhance the successful development of accurate and validated computational simulation systems. From the reviewers point of view, model sharing can also provide a degree of reproducibility which can give confidence in the results together with a guide to the accuracy and quality of the resulting presentation of output.

(A warning: Many individuals and others have developed simulation packages where it may not be clear how software, data generation or the resulting output have been prepared and coded. Here it may be difficult to access source coding or to be able to apply diligence/confidence to results which may indeed be reproducible. FEM techniques can be notoriously difficult to reproduce and great care must be taken in that the person providing the shared data states clearly and fully what is being shared.)

Perspective from Perumal Nithiarasu, Rainald Löhner and Guowei Wei (as Editors, International Journal for Numerical Methods in Biomedical Engineering [43])

Model sharing in biomechanics and biomedical engineering is becoming an essential route to innovation. By openly sharing new and state of the art models (theoretical, computational and physical), research groups can accelerate inventions for the benefit of the community. Our expertise is in the area of computational model development. Developing and testing a new computational model is a mammoth task and sharing a computational model (codes) will certainly benefit many upcoming researchers and the community.

However, a number of challenges should be considered before finding the best way of sharing new models (note that there are many open source initiatives already available). Our experiences dictate that simply sharing a computational model in this area will be counterproductive. Before models are shared, they should be benchmarked against other models and reality [44]. A model in the area of biomedical engineering will be as good as the

data used in the model. The model can only be reliable if uncertainties related to the data input and boundary and initial conditions are reduced. We think that before a model is accepted for sharing, the models should be benchmarked by a group of researchers on real and reliable data. The model should be shared along with all the necessary inputs so that others can reproduce identical results.

As seen in the aforementioned reference, International Journal for Numerical Methods in Biomedical Engineering has already taken initiatives towards benchmarking of models. The editorial board members of the journal are supportive of this direction and one special issue has been published on benchmarking already. In addition to groups coming together to produce benchmark solutions, the journal has started sharing data. We don't believe anything is stopping the journal from sharing the models (codes). However, an internationally accepted standard of sharing the models will be useful for the future. An established method of sharing models will avoid populating the community with misleading and incorrect models.

Perspective from Beth A. Winkelstein and Victor H. Barocas (as Co-Editors, Journal of Biomechanical Engineering [45])

Archival journals play an important role in the preservation and sharing of data and models. With the advent of supplemental material and long-term storage of electronic information, journals are uniquely situated to extend their existing roles as the stewards of scientific information and the arbiters of reproducibility. Both of these roles, however, must evolve with the demands and opportunities of the times.

In the context of information storage, the sheer volume of data that now can be generated and must be vetted, stored, and accessed efficiently would have been unimaginable just a few years ago. An additional challenge comes from the wide array of journals. Each journal has its own criteria for acceptance, its own scope and audience, its own storage mechanism, and its own dissemination policies. Researchers publish work with similar themes and model content in different journals so as to achieve the largest possible audience and impact for their work. One must ask, therefore, how the same model is to be shared among multiple journals, often with different publishers, in a way that promotes critical analysis, implementation, and advancement of the work. It also may be that the format of a model most useful to one community is not the same as that best suited to another. It is therefore our duty as researchers, modelers, and editors to work together to develop better mechanisms for transfer of knowledge across traditional boundaries.

In the context of reproducibility, modeling presents a unique challenge. When one writes a manuscript about, e.g., a biaxial experiment, one does not provide the testing device and the sample; rather, one provides a description of what device was used, how the samples were obtained, and what protocols and analytical methods were used *so that the reader can reproduce the experiment*. In contrast, a computational modeling paper can also provide the code that was used to do the study as well as any necessary supporting files. It is incumbent upon our community as a whole to define what a sharable model is and then, definition in hand, to enact appropriate guidelines and practices.

Finally, we observe that the change from physical to digital data storage has made possible a centralized archive that could be lost for a variety of reasons. In the era of print-only media, every library had a copy of the journal. An all electronic journal, however, exists only where the publisher's server is (or in the cloud). In light of this potential vulnerability, a central federal archive or a broadly distributed archive housed, e.g., by a consortium of academic and commercial partners, may be the best solution in the long run.

Perspective from Farshid Guilak (as Editor in Chief, Journal of Biomechanics [46])

In the field of biomechanics, we are witnessing unprecedented growth in the sheer rate and volume of our research output. New techniques are now available that provide high-throughput spatial and temporal acquisition of biomechanical, imaging, and biological data. Simultaneously, rapidly increasing computational power has made computational modeling at spatial and temporal resolutions that were not possible only a few years ago.

With this increasing wealth of data and computational ability, it is important to realize that we have potentially introduced new sources of error into our research that can influence the rigor and reproducibility of scientific reports in potentially unpredictable manners. This broader issue has also been brought to bear by the National Institutes of Health (NIH), which has provided a set of principles and guidelines designed to improve research rigor and reproducibility [47]. A number of different issues are addressed in these guidelines, but particularly relevant to the field of biomechanics are the topics of transparency in reporting in research, as well as the facilitation of data and material sharing. Even with the increasing pressure from journals to keep publications succinct, the highly interdisciplinary field of biomechanics is well poised to address these issues, particularly with respect to issues relating to the lack of details in being reported in methods and results. The increased ability to share methodologic details, process, and data collected will be critical to improving reproducibility, and supports the NIH recommendation that datasets be deposited in repositories where they be bidirectionally linked to the published article.

To address these issues, the *Journal of Biomechanics* has introduced a number of tools for Content Innovation to allow presentation, sharing, and storage of detailed methods and large datasets and models in archival journal articles [48]. These tools are described in detail elsewhere, but include online instruments such as the *Interactive Plot Viewer*, *3D Geometric Shape and Model Viewer*, *Virtual Microscope*, *Interactive MATLAB Figure Viewer*. In brief, these tools allow free-standing online viewing, manipulation, and downloading of data, figures, models, and large image/movie datasets.

To accompany the archiving of datasets and models, it will be critical to develop and evolve standards for the reporting of various experimental and computational studies/methods (e.g., Guilak et al., 2000 [49]; Erdemir et al., 2012 [15]). With increasing reliance on electronic publishing, such large datasets can be directly linked to published manuscripts. Such information is not limited simply to individual datasets but can also complex computational models, detailed mathematical derivations, computational algorithms/software, and interrelated multimodal, multidimensional datasets (e.g., combined mechanical/biological/imaging/etc.). Allowing full access to the methods, models, and data in the archival format that journals provide will ensure the biomechanics makes continuing strides in rigor and reproducibility.

Perspective from Joy P. Ku, Jennifer L. Hicks and Scott L. Delp (as developers of OpenSim [50] and SimTK [51])

In the musculoskeletal modeling community, sharing models, data, and software has had a transformative impact on research and training. For example, BJ Fregly, Darryl D’Lima, and colleagues shared a rich set of experimental data and models for predicting knee joint contact forces. Researchers have downloaded these resources over 9000 times [52], and the data provide a benchmark for validating simulation algorithms [53–56]. Our group develops and shares OpenSim [23], an open source musculoskeletal modeling and simulation software package. The software, and accompanying models and data, have supported over 900 scientific publications, provided the technology needed for over 120 grant submissions, and helped teach biomechanics in K-12 through graduate programs. While the benefits to the community seem clear, most models, software, and data produced by the community still are not shared.

Our 2015 survey of 49 leaders in the field revealed that fears of not being properly cited, fears of misuse, and the time and effort required for sharing and maintaining the resource are the largest barriers to sharing. But the experiences and successes in our community and others point towards several ways we can overcome these barriers, including creating and publicizing rewards for sharing and developing infrastructure that eases the burden of sharing.

Tapping into academia’s rewards structure—for example, using contributions to open science as a criteria for promotion, awards, and grants—would accelerate sharing. There are also existing benefits of sharing that should be promoted more broadly. For instance, an analysis of our laboratory’s research demonstrates that studies in which models, data, and simulations are shared receive significantly more citations than similar papers without shared resources. Piwowar and Vision also found this to be the case in their analysis of gene expression microarray data [57]. For many researchers, a demonstrable increase in publication impact could override the occasional instance of not being cited by someone who uses their resource. Thus, we need to better highlight this benefit within the community, for example, by creating algorithms to automatically compile and promote such statistics.

The benefits may still be outweighed, though, by the extra effort required to share the resource [58,59]. For example, it took over a week to prepare a model from one of our recent studies [60] such that it could be successfully and easily re-used. Here is where technology and investments in shared infrastructure could help. For example, the SimTK repository [51] we developed provides a website for easily uploading and downloading shared resources; communicating with users; tracking usage; and building collaborations. Hundreds of researchers use the site to share their models and tools and are relieved of the burden of developing and maintaining such infrastructure within their own labs.

We need leaders to show the way—individuals who commit to sharing their own research outputs and advocate for increased sharing. Even small actions can help shift the norm. We encourage members of the community to share a dataset, advocate for fellow researchers who share resources to receive awards or promotions, or recognize the value of resource sharing

in grant applications. Science is a team sport. By working together to build collective resources, we can accelerate progress.

Perspective from Michael Sacks (as former Editor, Journal of Biomechanical Engineering [45] and former Chair, New Directions Committee, Summer Biomechanics, Bioengineering & Biotransport Conference [61])

At the New Directions Committee held at the Summer Biomechanics, Bioengineering & Biotransport Conference in 2016, we discussed and approved a proposal to establish a “global biomechanics wiki” that will act as a Biomechanics Modeling Wiki (BMW). It is hoped that this will become a comprehensive multi-disciplinary library of computational models and data coupled with a database of experts. The plan is to have data entered as wiki entries and moderated blogs. The present format includes: 1) Develop a comprehensive multi-disciplinary library of computational models, data, and expertise. 2) Format: Online Wiki entries and moderated blogs. 3) Coordination with community: start with ASME BED, add BMES, ESB later on. 4) Industry outreach: industrial partner program. 5) Regulation/guidance: NIH, FDA, ISO. 6) Collaboration with BME journals: introduce a mechanism for data submission as supplementary materials.

The content structure is: 1) Consolidate existing data from published sources / prominent groups. 2) Review of computational medicine related efforts. 3) Focus on all computational scales: system -> organ -> tissue -> cell. 4) Initial focus on cell/tissue and organ via continuum modeling. 5) Simulations - models, geometry, model parameters; simulation cases; boundary conditions: flow conditions, loads, stresses; benchmark test cases; documentation; code / algorithm library; verification and validation steps, approaches, guidelines. 6) Databases - in vitro, ex-vivo, in vivo experiments; material testing data (AFM, biaxial, micropipette aspiration); example clinical data.

Currently, the site is built on the Python programming language using its web framework, Django. The data models are stored in the database using PostgreSQL. A popular Javascript library, AngularJS, is being used to implement dynamic features to the site as well as data interaction features. Every web view loads the necessary components to serve its functions. Currently, a substantial section of the BMW has been developed. Of particular interest to BED members will be the Expertise Database Module. Users can create their own expertise entry with a list of fields to fully describe the expertise of the user. The entries are searchable and indexed. An expertise entry is similar to a user profile. We have also been coordinating with ASME to coordinate with their related efforts. It is anticipated that a beta version will be available for review by BED members by early spring 2018. We are also coordinating with ASME and BED to establish the BMW as part of a larger ASME effort and to secure stable funding.

Perspective from Jeffrey A. Weiss, Gerard A. Ateshian and Steve A. Maas (as developers of FEBio [22,62,63])

FEBio is a freely available software suite for the simulation of mechanics, reaction and transport in solids, mixtures, and fluids. The mathematical framework is based on discretization of coupled partial differential equations that vary in space and time. Discretization and solution of the discretized nonlinear equations is based on the finite

element method. This requires generation of a geometric model and specification of boundary conditions, initial conditions and material properties. The results include the values of field variables as a function of space and time. The FEBio software suite includes software packages for model generation (PreView) and postprocessing/visualization of results (PostView).

To reproduce the results of a FEBio simulation presented in an archival publication, users must have access to the input file to FEBio that contains the information above. This is a text file and can vary in size up to about 1 GB depending on model size. Typical sizes are much smaller (a few MB). In addition, users need access to the specific version of FEBio that was used in the publication so that they can run the analysis and reproduce the results, so we make sure that previous versions remain available. The results from a FEBio simulation are stored in a binary file, and these files vary in size but can be several GB. The results are typically examined using PostView. For reproducibility and model sharing related to archival publication, our users have provided the FEBio input file as Supplementary Data or they have provided the input file and/or the results via an independent web location. To facilitate reproducibility, we are working with the SimTK development team at Stanford to provide the ability to easily perform FEBio analyses online. We welcome any journal-specific features that make it easier for readers to reproduce published results from FEBio simulations, and we would be very happy to work with those involved to achieve this goal.

Perspective from Andrew D. McCulloch (as Investigator, National Biomedical Computation Resource [64])

National Biomedical Computation Resource (NBCR) [64] is an NIH-supported Biomedical Technology Research Resource established in 1994 to facilitate access by biomedical scientists to the computing power of the national supercomputer centers. Since that time, NBCR has led the development of new tools and methods for multi-scale modeling of biomedical problems spanning scales of biological organization from molecule and cell to tissue and organ system. By developing integrated tools and workflows, the NBCR aims to promote interdisciplinary collaboration and the development and reuse of new multi-scale models of important biomedical problems. In addition to disseminating tools and workflows, the center also provides regular training courses and opportunities on its software tools.

Some of these tools include the Adaptive Poisson-Boltzmann Solver, APBS [65], a software package for modeling biomolecular solvation by solving the continuum models for describing electrostatic interactions between molecular solutes in salty, aqueous media. BrownDye uses Brownian dynamics to simulate association reactions of biomolecules [66]. It can be used to estimate second-order rate constants of association and transition probabilities among binding sites. SMOL provides an efficient way to solve the Smoluchowski diffusion equation using the Finite Element Tool Kit (FETK), also developed at the NBCR. CSMOL is an instance of SMOL designed for sub celling modeling. CellPack [67] allows users to create three-dimensional models of the cellular mesoscale by solving the optimal packing of molecular structures in the cell microanatomy. And Continuity [68] is a problem-solving environment for multi-scale modeling in biomechanics and electrophysiology that integrates systems models of cellular dynamics with finite element models of tissue and organ physiology. Continuity also has built-in access to a model database allowing users to share models.

Diverse driving biomedical projects on problems such as infectious diseases, systems pharmacology of cardiac arrhythmias and contractile filament energetics in heart failure define the priorities for developing new tools and workflows that integrate these modeling tools to cross scales. NBCR investigators have been developing workflows with the Kepler framework for problems such as drug design. In a recent development, NBCR investigators used the recent theory of “milestoning” to combine molecular dynamics and Brownian dynamics simulations [69] to create concentric spheres around the receptor through which to track the molecule’s circuitous path as it approached the receptor protein. The rate constants found using this composite method agreed well with experimental and theoretical values.

4 Further Thoughts

The opinion pieces presented as part of this work were aimed for developing a communal understanding of the sharing of computational models and related resources in biomechanics and how model sharing may fit into scholarly publishing workflow. These perspectives were received from a handful of contributors and therefore it is arguable that the opinions may not necessarily represent the biomechanics community as a whole. Nonetheless, insights from various journal editors, scientists, and resource providers from the biomechanics world at least establish a cross-sectional view on the culture and ecosystem of sharing models and related resources.

Opinion contributors acknowledged the potential benefits of sharing computational models, related data, and simulation software. For the members of the scholarly publishing community, the emphasis was understandably on the role of sharing for assessment of the reproducibility of a study at hand. Some also noted the added benefits on training, i.e., understanding new methods from shared models and code, and on potential acceleration of inventions by reuse. Perspectives from those who are at the frontlines of sharing, i.e., who develop infrastructure and who routinely share resources, provided data on reuse. Such data confirmed the potential outreach of models when they are shared, e.g., hundreds of publications based on repurposing of models, thousands of downloads. Similar to the publishing community, providers of infrastructure also indicated the impact of model sharing on training and research, i.e., to teach a modeling technique or to validate a new strategy of simulation.

Editors from various scientific journals described initiatives of their publication platforms to facilitate sharing of models used in publications. Many publishing platforms already support mechanisms for the authors to provide supplementary materials along with their scientific article. While models and related resources can be submitted as such, use of existing repositories and public databases are also recommended. Some journals have also started providing online tools for presentation, sharing, and storage of rich content, which may otherwise be difficult to document as part of a publication. The editors encourage the use of standards (for model markup) and provide pointers to existing initiatives. Nonetheless, they also acknowledge that a model and supporting simulation code used by study authors may not conform to standards. In some cases, guidance on obtaining digital object identifiers for shared materials are now available as part of author instructions. It should be noted that acquisition of digital object identifiers for models and related resources will likely enhance discoverability of the shared material in the long term. Efforts to clarify terminology relevant to model sharing and its impact,

to develop databases, to evolve reporting guidelines, and to build model benchmarking strategies are noted as important activities to enhance the sharing culture.

A fundamental and important concern seems to be related to the extent of sharing. In computational biomechanics, models commonly include representations of anatomy, physiological properties, and inputs such as loading and boundary conditions to drive simulations. When a model is shared, all this information is included as part of the definition of the model. Nonetheless, the foundational data to develop these representations, to provide input parameters, and to evaluate model performance can also be part of dissemination. Sharing of submodels, e.g. constitutive representations of material behavior and related coefficients and data as part of a comprehensive organ model, may also facilitate their reuse. Computational models can be stand alone, i.e., incorporating embedded solvers for execution. Alternatively, they may rely on separate custom made or off-the-shelf commercial simulation software. In the latter case, dissemination of the model by itself has to rely on the assumption that the user of the model will also have access to the simulation software. Model providers may want to consider sharing simulation code along with the model, or providing guidance on how to access such code. Studies in computational biomechanics increasingly rely on multiscale models and large scale simulations, which in many cases dictate the use of high performance computing [70]. Even when disseminated, simulations with models of this nature can be hard to replicate. Sharing of simulation results will likely be helpful for these type of computational models. In addition, simplified and computationally feasible models that capture biological and physiological abstraction and simulation workflow of their detailed counterparts can be shared as a supplement. This sharing strategy may assist those who may be interested in evaluating the quality of a computational study or who may want to learn and practice advanced modeling and simulation techniques in a more accessible manner. Determination of the scope of sharing models and related resources will likely drive future development and expansion of mechanisms to support dissemination.

Individual perspectives portrayed various mechanisms for sharing models and related resources, supporting infrastructure to create a sharing culture, and challenges associated with these. Many alternative repositories exist to host computational models and relevant data and software. Journal sites, for example, provide the means for authors of computational biomechanics studies to upload their models, data, and simulation code, and investigators have started to use them for dissemination of their models and data [71]. Federally funded and publicly available repositories are also solutions that are independent from the publication enterprise. SimTK is a noteworthy example of such a repository with prominence in the biomechanics community [51]. A large variety of computational models have been shared through SimTK including cardiovascular models [72], finite element representation of joints [73], and musculoskeletal models [74], among many others. Models disseminated in such repositories can be associated with multiple publications and provide the capacity to acquire separate digital object identifiers for models and data for enhanced discoverability. Institutional repositories are also amenable to the sharing of data and models and have been used to disseminate data and models in biomechanics [75]. In addition, general purpose data repositories, whether commercially available, e.g. Figshare [76], or through non-profit entities, e.g., Dryad [77], can be used for resource sharing in computational biomechanics. As a last resort, models, data, and software can be shared through laboratory sites [78] or dedicated websites [79]. Whatever the choice of the sharing platform, one needs to consider advantages and disadvantages related to maintenance and longevity. The diversity of

platforms also indicate the fragmentation of the model and data sharing space and the potential difficulty of consolidating similar models into more comprehensive, structured, and specialized databases. There are disease specific initiatives to consolidate diverse simulation strategies and model types, e.g., for multiscale modeling of heart failure [68]. It is also encouraging that the community is motivated to curate related models, e.g., commonly used material constitutive laws, cardiovascular models, and to identify strategies to overcome this challenge. The development and expansion of mark-up languages, data formats, and model exchange tools will likely support such initiatives and increase the reuse potential of shared models.

Access to simulation software is also instrumental to support model sharing and its reuse, and for assessment of the reproducibility of a computational biomechanics study. The biomechanics community has successfully delivered special purpose software (free and open source software or software for academic use) for finite element analysis, e.g., FEBio [62], for simulations of blood flow, e.g., SimVascular [80], and for musculoskeletal movement simulations, e.g., OpenSim [50]. Multiscale modeling and simulation initiatives have also provided software components for simulation of biomechanics coupled with cellular function, e.g., Continuity [81] for heart electrophysiology that also provide means to access model databases. It is now possible not only to share a computational model for download but also provide a complete platform where interested parties can repeat simulations online using a cloud-based instantiation of the model, simulation software, and computing hardware. This concept is not necessarily new in biomedical computing but in biomechanics, examples of this strategy have just emerged [73].

In the opinion pieces, some insight and a few concerns were noted in regard to the burden and risk of sharing computational models. An obvious and considerable cost of sharing research outputs is the development, maintenance, and further expansion of dissemination infrastructure. Repositories not only need to co-exist but also to interface with each other and with publication platforms to support discoverability and achieve redundancy. This capacity is imperative when the same model and its derivatives are used for different scholarly work and may need to be provided through a unified source or at least in a traceable fashion. In addition, studies blending multiple models, data, and simulation software from different resources will likely require cross-referencing between repositories. Example platforms that are mentioned in the opinion pieces indicate that journals, independent repositories, and academic institutions are prepared for the storage capacity, bandwidth, and persistency requirements of dissemination, including that of models. An investment in cross-referencing the platforms, possibly through the use of data registries [82], may be helpful to achieve coherence in model sharing culture. With access to multiple platforms, the model provider can share the same model through different venues. For example, different versions of a model can be shared at the author's project site and a specific version (relevant to the published study) can be submitted to journals. Such an approach will achieve redundancy, when and if one of the dissemination site fails. To support the ecosystem of model sharing, federal agencies may provide platforms that are specific to dissemination of models, i.e., analogous to PubMed Central [83] where scholarly articles are deposited and possibly similar to the public-private partnership of NIH Data Commons [84]. A comprehensive approach to curate models at the national (or worldwide) level can assist curation of special collections of models, which appears to be within the interests of the community.

The concern about the quality of shared computational models is a valid one. As raised by one of the commentators, an option is to adopt controlled release of computational models to the

community following comprehensive benchmark testing by developers and by a third party. This approach has the seeming advantage of preventing overpopulation of the computational biomechanics ecosystem with low quality models and data. On the other hand, a stringent benchmarking criteria and workflow may increase the regulatory burden and prevent timely dissemination of useful and innovative models. The open source software community's motto "release early, release often" [85] can be applied for sharing models and related resources in biomechanics. This strategy will provide the opportunity for continuing review of models, by the users, throughout the lifecycle of the model. This philosophy has been known to enable development of high quality, consumer level, general purpose or specialized open source software [86]; its capacity to serve the computational biomechanics community is yet to be seen. A balance between early dissemination and quality considerations can also be achieved. Computational models, which are already disseminated publicly "as is, under no warranty" can go through a certification process when and if needed. A model that meets quality criteria for a specific application or set of applications can be branded and registered as such in order to provide the community some confidence. In the broad biomedical community, relevant initiatives exist and can be utilized for computational biomechanics as well. For example, the U.S. Food and Drug Administration launched a program to qualify medical device development tools including computational models [87]. Activities of and guidance from multidisciplinary organizations like the Interagency Modeling and Analysis Group (IMAG) and Multiscale Modeling Consortium [88], and the Committee on Credible Practice of Modeling & Simulation in Healthcare [89] can also be utilized to establish a certification process for quality assurance of shared computational models [14]. For example, informed by this Committee, the IMAG multiscale modeling funding initiative incorporated a requirement for grantees to establish metrics for a third-party review of their models through a model credibility plan [19]. The underlying idea is that as a first step in model sharing, credibility of the model and the trust with the model end user are established.

The burden of model sharing on developers, reviewers, and users of computational models should not be underestimated. One of the commentaries noted the additional effort required, particularly when the goal of model developers is beyond the publication of a computational study but also to make the model available to others for prospective simulations [60]. Ideally, this effort includes preparing a download package for the model and related resources, identifying a repository to host the package, uploading the package to the repository, developing and providing additional documentation, e.g., a users' guide, and being prepared to maintain the model, e.g., respond to questions from the community who may be interested in using the model. A reviewer, who may be assigned to evaluate a computational biomechanics study, also faces significant burden [90]. The reviewer may want to download the model, acquire the simulation software, check the repeatability of simulations by running the test use cases, and evaluate the source mark-up of the model to understand model parameter space that may not have been fully described in the scholarly manuscript. Despite the increased burden, all these activities will facilitate discovery, assessment for repurposing, and reuse of the models, preventing reinvention of the wheel for a prospective simulation study. It is promising that those involved with model sharing in computational biomechanics (as a provider or a reviewer) seem to acknowledge the benefits of the process to augment quality, visibility, and potential impact of a simulation study in spite of the increased workload [90].

An overlooked issue of sharing models and related resources is the management of intellectual property. Similar to many creative work, intellectual property associated with computational models is likely to be protected by copyright. Simulation software, which models rely on, may have components that are protected by copyright and patents. At the time of dissemination, the ownership of the model and related resources and the permissions to use, adapt, and redistribute (essentially, the licensing terms) should be specified. Many options exist, from free and open source licenses that are permissive, e.g. MIT license [91], to licenses restricting commercial use but acknowledging academic freedoms, to proprietary terms routinely adopted in industrial simulation software and models, e.g. as in the Living Heart Project [92]. The conditions on prospective use, modification, and distribution of the models have important practical implications when a user wants to utilize multiple models or simulation software, which may have incompatible licensing. This situation is becoming routine in multiscale modeling, where investigation of a problem requires models at spatial scales that range from atomistic and cellular levels to those of tissues, organs and the body [17]. Incompatible licensing may inadvertently introduce significant restrictions on broad dissemination and may place computational models behind unaffordable paywalls. Collaborative efforts between those who share models and others who provide software, repositories and related resources may aim for arrangements to accommodate or to relax license restrictions such that simulation platform can be made available with the model. In a recent cloud computing pilot study, a collaboration of this nature was demonstrated, and a simplified knee joint model was shared with the community along with the simulation platform [73]. Such initiatives can serve as examples and discussion platforms for guidance on management of intellectual properties.

Promotion of a model sharing culture has been challenging. Incentives and recognition may facilitate compliance with the sharing policies and expectations of journals, funding agencies, and the community at large. Journals in computational biomechanics and in the general scientific domain strongly recommend sharing of data, models, and software, with some even mandating it as a condition of publication [93]. Recent funding programs in modeling and simulation also have similar mandates as a condition of support [19]. These direct incentives may accelerate model sharing but raise understandable concerns in the community due to their potential interpretation as a strong-armed approach. In computational biomechanics, early adopters of the model sharing practice were self-motivated and their anecdotal experience indicate some level of recognition, albeit in an implicit way, e.g., established visibility in the discipline and increased citations. Institutions, journals, societies, and funding agencies have some responsibility for official recognition of individuals that are promoting model sharing. Academia can formalize dissemination of resources as part of promotion criteria. Journals and scientific societies can establish award mechanisms for model sharing activities as they do for publications. Eventually, the sharing of models and related resources can be a natural component of computational biomechanics research, as routine as writing a scientific article on a simulation study.

5 Conclusions

Niche computational models of the present are potential commodities of the future for routine applications in computational biomechanics. The availability of models and related resources will provide the opportunity for others to understand their capacity, to evaluate their quality, and to repurpose them for different use cases without the burden of re-creation. The biomechanics

community has recognized this opportunity and with some success, has managed to establish the foundations of a sharing culture for computational modeling and simulation. The community has also been aware of the difficulties in model sharing as many groups tried to fit model exchange strategies to the workflow of scholarly research. Synergistic but sometimes redundant or conflicting initiatives and guidance exist. Nonetheless, the infrastructure and the mindset for sharing models are maturing; simulation software, accommodating open science, are evolving; and more data have become available to build computational models. Differences in opinions can be observed in terms of what to share; why to share and how; and when to share. Yet, all these seem to establish a healthy push-pull relationship within the community and among different stakeholders that will move the model sharing culture towards a unified understanding supported by a sustainable platform. In the short-term, it is advisable that the community continues demonstration of model sharing, its promotion, and its utility. The community should also reflect upon its past experiences, be courageous to try out new strategies, and invest in continued communication to establish model sharing as a common component of scholarly work in biomechanics and to enhance discoverability, accessibility, and quality of models of biological structures.

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Conflict of Interest

AE, GAH, LML, JM, CRJ, FG, JPK, JLH, SLD, explicitly indicated that they had no conflicts of interest with the content of this article. PJH, PN, RL, GW, BAW, VHB, MS, JAW, GAA, SAM, ADM, GCYP did not report any conflicts of interest with the content of this article.

Author Roles

AE designed the commentary, acquired individual opinion pieces, assembled the document, wrote the first draft of the full manuscript. GCYP conceptualized the activity, engaged the community, coordinated in person discussions, and edited the draft. Individual opinion pieces were provided by PJH & GAH; LML; JM & CRJ; PN, RL & GW; BAW & VHB; FG; JPK, JLH & SLD; MS; JAW, GAA & SAM; and ADM. All co-authors were given the opportunity to review and edit the draft of the full manuscript and agree with its contents.

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