Editorial: What Biomedical Engineers Can Do to Impact Multiscale Modeling (TBME Letters Special Issue on Multiscale Modeling and Analysis in Computational Biology and Medicine: Part-2)

I. Problem

In virtually every scientific endeavor, computational models are used to aid the design and predict aspects of the physical world around us. Engineers see modeling as a necessary tool for developing research questions and designing tools. In biology and medicine, scientists have long used conceptual models to explain relatively uncomplicated data, and increasingly computational models are recognized as an important platform for discovery and translation of complex data. We cannot, however, ignore the large number of skeptics who often question the usefulness of biocomputational models, as their ultimate impact is still debatable.

II. History

In 2003, a U.S. government working group of program officers specifically overseeing modeling and analysis portfolios across NIH and NSF convened to discuss the status of computational modeling in biomedical research. The group recognized that because individual portfolios were small, there was a need to support each other's programs through joint efforts and collaboration, resulting in the formation of the Interagency Modeling and Analysis Group (IMAG). Subsequently, in 2004, IMAG released the first interagency solicitation for multiscale modeling of biomedical, biological, and behavioral systems [1], which resulted in the formation of the Multiscale Modeling Consortium (MSM) in 2006. The MSM Consortium began working group discussions and started populating the IMAG wiki in 2007 [2]. IMAG and the MSM have since grown to include ten government agencies in the U.S. and Canada, and over 60 research projects.

Also in 2006, the Japanese government launched the Next-Generation Integrated Simulation of Living Matter project (ISLiM) [3]. In 2007, IMAG released a three-year multiscale modeling initiative [4]. In the same year, there began a swelling interest from the international community to coordinate international efforts for multiscale, physiome modeling between the U.S., Europe, and Japan. The European Commission had just completed a consensus study that became the roadmap for the Virtual Physiological Human (VPH) initiative [5]. In 2008, IMAG worked with the E.C. to produce a special call for International Cooperation on VPH [6]. Almost at the same time of its release, the European Commission announced the eligibility of U.S. researchers to receive grant funding from the E.C. [7]. These funding opportunities created a tremendous wave of momentum for the multiscale modeling communities worldwide, spawning much growth in research activity as indicated in the lists of special journal publications described in the editorials of this special issue.

III. Impact of Modeling

As interest in modeling and especially multiscale modeling of biological systems continued to grow within the IMAG MSM Consortium, the EC VPH, the Japanese ISLiM, and other communities promoting biocomputational modeling; audiences in the general biomedical research arena remained less excited and receptive. This sentiment has been observed repeatedly in grant and journal reviews, in the development of funding initiatives, and in discussions with the general community-–usually not published in print, though a recent review touches on the challenges facing the fields of biochemical modeling and systems pharmacology [8].

To better understand this dichotomy, in December of 2009 IMAG held the first IMAG Futures Meeting. This meeting was an opportunity to assess the impact of biocomputational modeling in the *broader* research and policy endeavor, and to discuss these issues in the context of current challenges and opportunities for biomedical, biological, and behavioral systems. This meeting included government and scientific leaders, as well as attendees interacting via worldwide videocast. The discussions were grouped along five levels of biological organization: 1) population; 2) whole body; 3) cell–tissue–organ; 4) pathways and networks; and 5) atomic and molecular. Participants in each group represented diverse biological fields, and represented modelers, nonmodelers, experimentalists, policy makers, academia, and industry. Participants were charged to describe how models succeeded or failed to make a difference in the broader research endeavor, discuss issues surrounding the acceptance of models, and illustrate major challenges and opportunities. Participants were encouraged to reflect on their own fields and expertise and call attention to issues that are unique to each scale as well as issues that may span across scales. Discussions indicated that models that had the greatest impact (from time of model development) were at the smallest (atomic and molecular) and largest (population) scales. At these scales, there was a stronger culture of community-collected data, community-developed codes, as well as an urgency for obtaining model

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predictions (e.g., to determine who should receive the next H1N1 vaccine). In the middle scales, there existed more diverse and disparate experimental data, biological mechanisms, and computational and mathematical methods, making the impact less apparent and more incremental. Participants concluded that for models to be useful and have an impact on research and policy, models must be integrated and adopted into research, training, and policy development. They noted that the complexity of biological data continues to grow and frequently defies intuition and predictability. To effectively drive the design of experiments and develop testable hypotheses in all domains and scales, modeling is inevitable. The IMAG Futures meeting discussions with added postmeeting public commentary produced the IMAG Futures report, which is posted on the IMAG wiki [9].

IV. Charge to Biomedical Engineers

Many of the specific recommendations detailed in [9] were used to push the envelope for multiscale modeling in the latest IMAG initiative [10], released in April 2011. This funding opportunity attempts to promote technological bridges between scales, available data, biological domains, disciplines, and expertise. Biomedical engineers by training are equipped to reach outside the box and integrate the diverse knowledge, data, and methodologies necessary to achieve successful multiscale modeling. The key, however, is to overcome the underlying sociological obstacles that are preventing the skeptics from appreciating the true potential of these models.

It is the onus of the modeler to describe and explain their models in a manner that is understandable to the potential users of the model. The modeler must convey the usefulness of the model, at the same time emphasize that the model itself is not the solution, but a tool or platform for iterative research. Mechanistic, mathematical models help define the structure of the system. These models can at the same time systematically archive and integrate data, analyze and identify gaps in our knowledge; and communicate, share, and transfer information of the system without losing important details. A model provides a framework for capturing the complexity and quantifying uncertainty of the biological system-–essentially extending the human mind to better understand the physiology of the system or assist in making decisions for medical policy and treatment.

The model must be useful from the point of view of the end user, the experts of the system. Are the user's needs and requirements being addressed? Are there success stories that provide convincing evidence that the model can indeed correctly predict outcomes not (easily) obtained through experiments?

Biomedical engineers are well positioned to change the culture of biomedical research. Science needs to move from using models to explain experimental findings to using models as a tool to discover new information about a system—to build testable hypotheses. Biomedical engineers should be ready to demonstrate how modeling can efficiently and economically drive scientific experimentation, data acquisition, and technology development. Likewise, biomedical engineers should show that modeling has the potential to accelerate translation from basic science to clinical medicine. For example, models can be efficiently used to predict the boundaries for safety and efficacy of drugs and medical devices, in particular in the face of the multifactorial diseases we face today.

Finally, biomedical engineers should work to integrate mathematical modeling into all aspects of biomedical research. The IMAG Futures Report [9] indicated that this integration is inescapable—it is only a matter of time, but we should work to accelerate the process. Modeling in fact promotes interdisciplinary research and training. The pipeline of scientists and medical practitioners must learn to integrate the use of models into all aspects of their profession.

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