Mathematical and Informatics Challenges to Translating Cardiovascular Models to Clinical Care

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Integrative computational models of the cardiac myocyte and whole-heart function are now being applied to understand the molecular, cellular and structural basis of heart disease. Descriptions of myocyte membrane currents and transporters are now highly refined, and attention is shifting to understanding the ways in which intra-cellular signaling and mitochondrial energy production couple to and modulate membrane excitability and Ca^{2+}-cycling in health and disease. The ever increasing biophysical detail and complexity of these cell models now raises important questions about the ways in which they are best formulated and tailored to the specific biological questions being addressed. We will present our view of the major mathematical and computational challenges we now confront when developing and applying myoycte models. These questions include use of deterministic versus stochastic ordinary and partial differential equation models, strengths and limitations of each modeling approach. The past decade has also seen major advances in development of integrative models of whole-heart function that incorporate biophysical models of the myocyte as well as heart geometry, fiber and sheet structure. Models of the human heart are now being developed, and an important question is how they can be used to guide the selection of therapy tailored to the needs of the individual. By definition, models can only be personalized using data that can be measured in the patient. This is currently limited to magnetic resonance, ultrasound, and computed tomography imaging of heart geometry, motion, and location and shape of structural abnormalities such as infarcts. In light of these limitations, an important challenge is to discern those disease settings in which generation of arrhythmia is dominated by perturbed structure rather than perturbed cellular function. A more general challenge is to determine application areas where whole-heart models *are* or *are not* "massively under-determined". Finally, it is important that models be shared so that published results can be reproduced and more extensive model validation performed by the community. XML-based model description languages have been explored as a solution to the problem of model dissemination. However, they have practical limitations regarding the class of models they can represent, and do not address the problems raised above. We will present a different approach to model publication that is based on the reproducible research and workflow composition system called Galaxy. Galaxy makes it possible to share models, save parameter sets, perform simulations, provide links (URLs) to simulation results, and document the history of steps taken when performing a simulation. Galaxy has the potential to provide transparency to the modeling process.