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Systems biology of the heart: hype or hope?

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Systems biology, the approach that combines reduction and integration to explore dynamic structure–function interrelations across biomedically relevant spatio-temporal scales, is applied to heart research.

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Whether one subscribes to the view that *systems biology* is a field of study, a set of techniques, or a conceptual approach, it has become a mainstream element of biomedical research. Although there seems to be no universally acceptable definition for the term yet, the smallest common denominator is perhaps that systems biology considers the *mutual interactions between a biological entity and its parts.*[1] This can be derived directly from the definitions of *biology* (contracted from *bios* [Greek for "life"] and *logos* [Greek for "word, study"]: "the study of life") and *system* (according to Ludwig von Bertalanffy, "an entity that maintains its existence through the mutual interaction of its parts").[2]

Systems biology, whether targeting the level of populations, whole organisms, organs, tissues, cells, or subcellular components, builds on a combination of experimental, theoretical, and computational techniques. These are applied, from the outset, with the aim to support both "reductionist" (attempting to understanding the nature of complex systems by reducing them to the interactions of their parts) and "integrationist" (focusing on systems-level properties and how those shape lower level behavior) approaches for studying the dynamic interplay of biological structure and function within the biological system of interest. This synthesis of formerly disparate (and, at least apparently, opposing) approaches to biomedical research requires novel concepts and tools, in particular for tackling the challenge associated with conducting research that requires investigation at multiple levels of structural complexity (e.g., study how cells, integrated into tissues, support organ function). Another interesting aspect is that parts of a system at one level (e.g., cells in a muscle) constitute systems in their own right at a lower level of structural complexity (e.g., for the investigation of calcium handling effects on cross-bridge formation).[3]

Biological research, whether aiming primarily to reduce or to integrate, relies on *models*. By definition, models *are simplified representations of reality*.

This definition applies to all models, whether conceptual, experimental, or computational. As the extent and scope of simplification will differ between models, there is no one-to-one map between "reality" and "model." Thus, if we are interested in the effects of pharmacological modulation of one ion channel on heart rhythm, we will need a multitude of models across various levels of structural complexity (e.g., protein-affinity tests, patch clamp and single-cell electrophysiology studies, isolated heart- and animal-based research, patient testing) and even at the same level of structural complexity (e.g., test dose–response curves in cells from different parts of a heart, including pacemaker, conduction, and working myocardium, or in different species).

Thus, simplification is a central feature of model systems and determines both their utility and their limitations. Imagine, for a moment, a situation where a model captured absolutely *all* features of reality: such a "clone" would be no easier to understand than the original itself; it would lose the power to help in revealing novel insight over and beyond what is apparent from the original already and would be fraught (in biomedical research

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at least) with the methodological and ethical restrictions that will have raised the need of having a model system in the first place. Those concerns are among the reasons for which we do not conduct pharmacological testing on humans before other simplified systems will have provided (simplified) answers to the likelihood of having therapeutic effects in the absence of overriding negative consequences (for a more detailed illustration, see Mirams and Noble[17]). Of course, even testing in human volunteers will not give a definitive answer on possible (in particular rare) side effects, as one human is also just a partial representation (a model) of the entire species.

From understanding models as tools that are of use for some but not all purposes (no tool ever is), the challenge arises to pick "the right one" for a purpose. This needs to be driven by an appreciation of the relevance of models in a given setting (applicability to the question at hand), their quality (e.g., in terms of representing essential features of the original, and hence supporting reproducibility of findings), and cost (not just in terms of money, but also with regard to training needs and ethical considerations). Everything else being equal, *models should be as simple as possible, yet as complex as necessary to address a given question.*[4]

While all of the above applies equally to conceptual, experimental, and computational models, the development and validation of the latter is an area that deserves further discussion. It is easy to regard bio-mathematical modeling as any of a wide range of activities: (i) completely futile because of the complexity of biological systems; (ii) an exercise in restating what we already know; (iii) a necessary and complementary component to other research tools; and presumably many more.

It is easy to sympathize with (i), given that there is so much we do not yet know about biological structures and functions and their dynamic interplay. Even the data we already have obtained are often not included in model representations, in part because of genuine arguments in favor of simplification and in part because we do not have the algorithms and computing power to extract and use relevant information. In that sense, statement (ii) is only half-true, at best. It is also at least half-wrong, as the complexity of multiple feed-forward and feed-back pathways in complex biological systems (see (i)) can be hard to penetrate or know, even if we have the relevant underlying information. Computer models, with their capability of observing basic laws, such as conservation of mass, charge, and momentum, are a potentially amazing aide in the knowledge-generation process. Of course, all a computer model can do (at best) is to offer an assessment of *plausibility*. This argues in favor of (iii), as different types of models should be used in direct iteration, with experimental data providing input for both model generation and validation.

One goal of systems biology, therefore, would appear to be the generation of models that are relevant for the range of questions we need to address, representative of the reality we wish to capture, reproducible and robust, and reasonable in terms of the different facets of costs involved.[3] A good illustration of how this view is starting to change the way we conduct biomedical investigations is the European Community-funded Virtual Physiological Human (VPH) initiative, which is focused on developing and implementing biophysically based computational models to aid clinically relevant research and development.[5] The success of this initiative, which forms part of the worldwide Physiome effort (http://www.physiome.org.nz/), has been based on the integration of vast arrays of data, to extract information, and to turn this into practically applicable knowledge related to various parts and processes of the human body. One of the most prominent examples of the successful use of this approach has been the modeling of the heart.

Cardiac computational modeling has benefited from the fact that it targets an organ whose function displays a high degree of spatial and temporal regularity, for which a wealth of high-quality structural and functional data exists at multiple levels of spatio-temporal integration (including, for example, histology, computed tomography, magnetic resonance imaging, patch clamp, and electrocardiology). Its leading position among organ models is also related to the long history of computational modeling (from the first biophysically based cell models in the 1960s, to bulk three-dimensional (3D) geometry models in the 1990s, and most recently, highly detailed histo-anatomical models) and to the high relevance of this as a target for biomedical exploration. This has led to highly successful uses of computational modeling as a predictive tool, for instance in the assessment of pharmacological effects on the heart. Thus, Mirams *et al.* performed simulations using

cellular models that integrated preclinical information on multi-channel block for various pharmacological compounds, showing that this could be used to improve the reliability of early cardiac safety prediction beyond current methods.[6] In another recent example, Moreno *et al*. used similar models to simulate the interaction kinetics of the anti-arrhythmic drugs flecainide and lidocaine with cardiac sodium channels, predicting clinically relevant concentrations at which flecainide and lidocaine will exacerbate, rather than ameliorate, arrhythmia.[7] These studies illustrate effective virtual drug-screening, using models of drug–channel interactions, to predict the effects of pharmacological compounds on heart rhythm and, hence, clinical utility and marketability.

Even though the above examples illustrate that heart models are becoming predictive, much remains to be done in this field. Thus, while modern histo-anatomically structured "heart" models are now based on imaging data at *para*-cellular resolution,[8] they do not usually include the atria or the big vessels, most of them are static (i.e., not considering the all-essential pump function of the heart), and very few represent any cell population other than myocytes (even though cardiac nonmyocytes, mainly fibroblasts, outnumber muscle cells even in the healthy heart, with potentially important functions beyond structural support roles usually ascribed to connective tissue[9]).

Going down in structural complexity, the above advances in 3D models that incorporate structural detail in the micro-to-macro domain (cell to organ) are not yet matched by representations in the nano-to-micro range (protein / membrane systems to whole cell). Arguably, the lack of insight into 3D nano-structures is one of the current bottlenecks on the way to bridging insight from subcellular networks to systems' behavior. This is being addressed now using advanced nanoscopic imaging modalities, such as electron microscopic tomography (based on back-projecting multiple 2D electron microscopy images, obtained over a wide range of viewing directions, to reproduce 3D data sets with a resolution of $\sim$5 nm or better, sufficient to visualize macromolecular assemblies)[10] and interferometric photoactivated localization microscopy (combination of photoactivated localization microscopy with single-photon, simultaneous multiphase interferometry that provides sub-20 nm 3D protein localization with high molecular specificity).[11] It stands to expect, therefore, that we will have highly structured 3D models of cells to support spatially resolved simulation of intracellular activity before the end of this decade.

Combined, this poses an enormous challenge, requiring dynamic structure–function data that span huge spatial and temporal domains (on the order of 10^{-9}–10^{0} m from ion channel pore to whole body, and 10^{-9}–10^{7} s from protein configuration changes to disease development). In addition, there is a need for a unified set (or, at least, for a set of definitions to allow interaction)[12] of nondeterministic computational models accounting for variability and stochastic behavior at multiple levels of structural and functional complexity. An essential, but currently lacking, instrument for seamless incorporation of cardiac experimental data into computational models is a clearly defined minimum information standard to govern recording, annotating, and reporting of data. Attempts to establish reporting standards that are acceptable to (and, hence, hopefully adhered to by) the greater research community are currently occurring across many scientific disciplines. For cardiac electrophysiological experimentation specifically, a standard for reporting Minimum Information for a Cardiac Electrophysiology Experiment (MICEE) was proposed in the autumn of 2011.[13] The ultimate goal of MICEE is to develop a useful interface that facilitates dissemination of the minimum information necessary for reproduction of cardiac electrophysiology research, allowing for easier comparison and utilization of findings by others (including computational modelers). Improving experimental and theoretical modelling techniques across the above spatio-temporal ranges, and implementing reporting and dissemination standards, could be perceived as "mission impossible." We would argue that it is "mission imperative," as there is simply no alternative to the quantitative study of dynamic structure–function interactions in complex systems if we wish to advance, and make more efficient, biomedical research and development.

As mentioned above, state-of-the-art computational modeling needs continuous iteration with experimental (both basic and clinical) research to avoid tapping into the *plausibility trap*, by which a quantitatively plausible explanation is taken for proof of a matter. Computational models are useful

for hypothesis formation, for guiding experimental approaches, and for data analysis and interpretation, but the proof of the pudding is in the eating. In fact, when computational models *fail* to reproduce observed behavior, they can be most useful for the stimulation of new insight, as it is when our best-conceived expectations are proven wrong that we learn the most. Such "failures" in theoretical models can drive novel biomedical research, to determine whether input data, boundary conditions, interpretations, or model implementations are missing relevant aspects. As an illustration of this iterative approach, the studies by Lei and Kohl[14] and Cooper *et al.*[15] into stretch-induced acceleration of cardiac pacemaker function initially explored the effects of cell swelling (considered, at the time, as a suitable experimental model of stretch), finding an unexpected slowing of pacemaker rate. This was explained using computational models and highlighted the limitations of the original experimental technique. A new experimental approach to axially stretch pacemaker cells was then applied, which indeed revealed the expected rate acceleration, known to occur in native tissue. The compatibility of cell electrophysiological responses with tissue behavior was explored in further computational modeling, and a stretch-activated ion channel was identified as a plausible substrate underlying the response. This example demonstrates how computational and experimental models, if conducted in direct iteration, can advance our understanding of biological systems. It also highlights the role that advanced engineering techniques play in this setting (they are for *reduction* what computational modeling is for *integration*).

To conclude, systems biology is a valuable approach to biomedical research, with the potential to identify the dynamic cross-talk between *entity* and *parts*, as they affect each other through structural and functional interaction across all levels relevant for biomedicine. This is the hype. Models, used in this discovery process, are simplified representations of reality. This is reflected in the popular quote by George Box, "All models are wrong."[16] What is usually forgotten is his additional comment: "... the practical question is how wrong do they have to be to not be useful."[16] The art, therefore, lies in the appropriate matching of tasks and tools, and systems biology is helping us in getting better at doing that. This is the hope.

Conflicts of interest

The authors declare no conflicts of interest.

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