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The Promise of Cardiac Neuromodulation: Can Computational Modeling Bridge the Gap?

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Neurocardiology is a rapidly progressing scientific and clinical field which shows significant promise in the prevention and treatment of arrhythmias[1]. Computational modeling has been a backbone technique in the study of arrhythmia mechanisms since the 1960s, with the natural evolution toward multi-scale models[2,3] spanning from the molecular cell to the whole heart to the population level. Despite this explosion in cardiac computational modeling fueled by advances in processing power, computational models of neurocardiology remain limited, likely due to the complexity and interplay between numerous feedback mechanisms involved. Prior studies modeled how the cardiac autonomic nervous system (ANS) influences high-level cardiac physiology[4,5] but models directly linking the cardiac ANS to cardiac electrophysiology are lacking.

In this issue of *J. Physiology*, Yang et al. present a novel model of neurocardiology that is not only multi-scale but also multi-disciplinary. This approach differs from prior studies which typically only model the downstream effects of sympathetic and parasympathetic modulation on cardiac myocytes, with pre-specified changes in heart rate, ion channel expression, calcium cycling. In this study, the authors directly simulate both neuronal and cardiac electrophysiology simultaneously. The neuronal electrophysiology models[6] for the sympathetic and parasympathetic cardiac nervous system are directly coupled to cardiac electrophysiology models incorporating both sinoatrial node (SAN)[7] and ventricular myocyte models[8,9]. The advantage of such an approach is that the inputs modulating the myocyte models are dynamically derived during each time point in the simulation instead of being pre-set by the modeler, which may allow for richer emergent and potentially more physiological behaviors.

Building the cardiac ANS model alone is a significant contribution. The authors base their ANS model on prior descriptions in the literature[1,4,5,10] to reproduce the multiple distinct networks of cardiac control consisting of 3 layers: the central nervous system (CNS), intrathoracic nervous system (ITNS), and the intrinsic cardiac nervous system (ICNS), which is further broken down into 2 sub-networks (the sympathetic S-ICNS and

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parasympathetic P-ICNS). Each of these networks is simulated in detail as individual neurons coupled at synapses, with bi-directional feedback between the ITNS, S-ICNS, and P-ICNS subnetworks. The outputs of the S-ICNS and P-ICNS networks are then linked as inputs into the SAN and ventricular myocyte models to dynamically affect heart rate and modulate cellular electrophysiological properties.

Using this model, the authors systematically test the isolated and combined effects of sympathetic and parasympathetic inputs on heart rate (HR), action potential duration (APD), and intracellular calcium load. These *in silico* experiments are well designed and derive several expected physiological results including increasing HR and decreased APD with isolated sympathetic surge, decreasing HR with isolated parasympathetic input, as well as the blunting of sympathetic effects with the addition of parasympathetic input. The model also demonstrates an enhanced propensity for delayed after-depolarization mediated triggered activity in a 1D cable with sympathetic stimulation, especially in a diseased state with heart failure cellular remodeling. This systematic approach is a strength of *in silico* experimentation where interventions can be modeled cleanly in a manner that may be impossible *in vitro* or *in vivo*.

Multi-scale modeling is an ambitious endeavor and this study has several limitations. The SAN and ventricular myocyte models used were from rabbit not human due to the availability of existing sympathetic / parasympathetic inputs. While the model produced broadly sensible results, there were several aspects which did not fully correspond to available experimental data. For example, the model predicted an increased HR that reached a steady state with constant sympathetic stimulation, while experiments by Wang et al[11] showed a gradual decline despite continued sympathetic activity. The authors discuss this limitation and hypothesize how the model could be improved to include β1-adrenergic receptor desensitization by PKA as a possible contributing mechanism. The model also showed no prolongation of APD with isolated parasympathetic stimulation, which is inconsistent with Yamakawa et al[12]. The heart failure models only incorporate cellular changes although chronic cardiac injury can lead to remodeling of the cardiac ANS, including of the vagus nerve itself[13]. The study also incorporates atomic-scale molecular dynamics simulations to derive β- adrenergic receptor – norepinephrine interaction affinities and rates. However, the parameter results have varied by an order-of-magnitude from experimental measurements, which need further investigation of this discrepancy.

Lastly, while there are feedback loops within the ANS model (afferent connections between the ITNS and S-ICNS, and sub-connections between the S-ICNS and P-ICNS), there is no clear afferent feedback present from myocardium back up to the ANS. This need for feedback at each level of modeling is highlighted in a recent review of neurocardiology by Gurel et al[14], detailing the differences between open-loop and closed-loop systems. The true advantage of simultaneously simulating both ANS electrophysiology and cardiac myocyte electrophysiology as opposed to simply pre-programing autonomic input on rails is the opportunity for feedback loops and emergent behaviors to develop. It would be important for future models to incorporate such bi-directional feedback. For example as the authors note, increasing HR and contractility could impact systemic blood pressure, which the ANS then responds to via carotid and aortic baroreceptors.

Nevertheless, Yang et al take a bold step toward a tractable multi-scale multi-disciplinary model of neurocardiology. This work provides a strong prototype for the continued development of more sophisticated computational models with increased feedback mechanisms. Future iterations could be a powerful tool for the development of new cardiac ANS therapies.

Supplementary Material

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