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Yoga for the sinoatrial node: Sarcoplasmic reticulum calcium release confers flexibility

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Given the central role of the sinoatrial (SA) node in determining heart rate, there is a long history of attempts to understand the rhythmic spontaneous beating of SA nodal cells. Since its discovery in 1979 [1], the inward "funny" current (I_f) has held a prominent place in the understanding of this process. In fact, many textbooks and review articles refer to I_f as the "pacemaker current" [2,3], a term that implies primacy. The properties of I_f make it seem almost ideally suited for pacemaking: it slowly activates at the negative membrane potentials of diastole, and the inward current it supplies can drive a slow depolarization towards the action potential threshold [4]. This mechanism, whereby spontaneous beating results from voltage and time-dependent changes in ionic currents, has been termed a membrane clock, or M-clock.

However, the hypothesis that the funny current plays a dominant role in pacemaking has not gone unchallenged. In recent years, studies from several groups have suggested that periodic spontaneous release of Ca^{2+} from the sarcoplasmic reticulum (SR) plays a critical role in SA nodal pacemaking [5,6]. According to this hypothesis, local release of SR Ca^{2+} near the cell membrane leads to Ca^{2+} extrusion from the cell via the Na^+–Ca^{2+} exchanger (NCX). Because NCX is electrogenic, Ca^{2+} removal results in an inward current that contributes to diastolic depolarization. This general mechanism has been called the Ca^{2+}-clock.

Although experimental evidence supports a role for each mechanism, considerable controversy continues to exist regarding the relative importance of each in driving and controlling sinoatrial nodal cell (SANC) pacemaking [7–9]. Several factors contribute to the ongoing controversy. One is that either mechanism offers a reasonable explanation for changes in heart rate due to autonomic regulation. The voltage dependence of I_f depends on cAMP, and changes in cAMP levels due to adrenergic or muscarinic stimulation could conceivably explain changes in heart rate due to sympathetic or parasympathetic activation. Similarly, several proteins involved in Ca^{2+} regulation, including phospholamban and L-type Ca^{2+} channels, are phosphorylated by protein kinase A (PKA), and phosphorylation after

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β-adrenergic stimulation would be expected to cause increased spontaneous Ca^{2+} release, and therefore rate acceleration.

A more fundamental difficulty is the fact that the M-clock and Ca^{2+}-clock mechanisms are tightly linked to one another. Each system on its own is complex, containing many interdependencies between its components and non-linear relationships between the components and overall cellular behavior. Intuitive understanding is further obscured by the bidirectional interactions between the M-clock and the Ca^{2+}-clock due to membrane currents that either respond to or alter intracellular [Ca^{2+}]. This complexity makes it difficult to draw definitive conclusions, even from seemingly straightforward experiments. For instance, evidence in favor of the Ca^{2+}-clock mechanism includes the fact that ryanodine, an agent that inhibits SR Ca^{2+} release, slows the baseline beating rate and attenuates the acceleration resulting from β-adrenergic stimulation [5,8]. A possible alternative interpretation, however, is the fact that disruptions in normal intracellular Ca^{2+} handling will alter the activity of Ca^{2+}-dependent adenylyl cyclases, and thereby change cAMP levels in the cell. Links between the M-clock and the Ca^{2+}-clock make the interpretation of many such experimental interventions quite challenging.

Mathematical modeling has often been used as a tool to gain insight into complex systems, and this strategy has been applied successfully to pacemaking in the SA node. The behavior of a model, however, depends on the assumptions and data that are considered when building the model, and many of the same controversies and differences in interpretation have migrated from the experimental to the modeling literature. In an interesting simulation study in this issue of the *Journal* [10], Maltsev and Lakatta took a different approach. They attempted to step away from the details of specific experiments and ask a more general question: does the collection of channels and transporters by itself influence the ability of a myocyte to exhibit robust pacemaking and to respond to changes in physiological conditions? Rather than performing simulations with biophysically detailed models containing all well-known ion transport mechanisms, they constructed simpler models, which enabled a more complete exploration of each model's parameter space. This allowed them to explore not just a single model of the system, but a large population of models, potentially allowing them to gain insight into the system in a more general way, rather than understanding simply a specific incarnation. The results of their analysis suggest that while either I_f or the Ca^{2+} f-clock can drive pacemaking in the absence of the other, the funny current can do so more reliably across a wider range of parameter values, whereas the Ca^{2+}-clock provides greater flexibility in autonomic-dependent changes in rate.

1. Modeling has been used to examine specific aspects of pacemaking mechanisms

Mathematical modeling of SA nodal cells has a long history, beginning with models developed in the early 1980s [11,12]. In subsequent years, ion transport pathways have become more clearly defined, and models have generally increased in complexity to reflect new knowledge about the channels, transporters, and pumps that may contribute to pacemaking. Contemporary mathematical models of SA nodal cells generally contain

dozens of differential equations and dozens of model parameters that control specific pathways [13–16]. Simulations performed with these models have generated significant insight into several aspects of SA nodal physiology, including: (1) changes in SA nodal firing with adrenergic or cholinergic stimulation [13–16]; (2) drugs or interventions that can slow or prevent pacemaking [17]; and (3) possible ionic current differences between central and peripheral SA nodal cells [18,19].

Models of SA nodal cells are built using voltage clamp data, and are subsequently validated by comparing simulation results against additional experimental data. These validations generally include baseline firing rate and action potential characteristics, and may also include changes that occur with drugs, adrenergic stimulation, or cholinergic stimulation. Following this validation, the authors of a study frequently simulate additional experimental protocols to generate novel model predictions. Although this strategy has been successful and has led to significant insights, particularly when simulations have been combined with new experiments, the conventional modeling approach has several limitations. The validation process is often incomplete and guided by whichever experimental studies are most familiar to the investigators. A model may therefore be consistent with some experimental results, but, unbeknownst to the developers, inconsistent with other data. Similarly, subsequent analysis of the validated model to generate novel predictions is hypothesis driven and may miss key insights that a more systematic model analysis could provide. In addition, most investigations ignore variability between individuals and consider the published model to represent a typical sample. This can potentially limit the scope of conclusions drawn from the model and does not allow for ready analysis of differences between individuals in, for example, responses to drugs. As a result, while these traditional models have certainly proved useful and will continue to do so in the future, complementary strategies are needed for a more complete analysis.

In their study, Maltsev and Lakatta [10] addressed some of these limitations. Instead of working with a biophysically detailed mathematical model of the SA nodal myocyte, they seemingly took a step backwards by working with minimal models of pacemaking cells that contained only 4 or 5 ion transport mechanisms. Somewhat counterintuitively, this step backwards provided the authors with important advantages. The simplicity of their models allowed them to explore the models exhaustively, which meant they could draw general rather than context-specific conclusions.

2. The approach employed in the present study has generated new insight

In an attempt to define and explore the essential components for a physiological pacemaker, Maltzev and Lakatta [10] developed a number of different frameworks for minimal models of the SA nodal cell, each containing only 4 or 5 different components. Individual components were either membrane currents or the formulation for SR Ca^{2+} uptake and release, and formulations were from the authors' published, more comprehensive model [14]. For each model type, they created a large set (10,000 for those with 4 parameters, 100,000 for those with 5) of models with different parameter values but the same components. This allowed them to explore the full range of behaviors that the model architectures were capable of generating, and in particular whether they could generate

reasonable pacemaking activity and recapitulate observed changes in pacemaking upon autonomic stimulation. The large number of different formulations for each model type allowed them to calculate two important metrics for each: (1) the “robustness” of a model type was defined as the percentage of model sets that exhibited reasonable pacemaking at baseline and under cholinergic and beta-adrenergic stimulation; and (2) model “flexibility” was calculated as the ratio of the rate under β-adrenergic stimulation to the rate under cholinergic stimulation, averaged across all model sets that produced adequate pacemaking.

They found that fairly robust pacemaking could be achieved by adding any of the Ca^{2+} clock, the funny current, or the T-type Ca^{2+} current to a basic framework of the L-type Ca^{2+} current, NCX, and the rapid delayed rectifier K^+ current. While the 4-component models with the T-type or funny current were more robust in terms of more frequently generating reasonable pacemaking, they were less flexible in their response to autonomic modulation than those including the Ca^{2+} clock. This suggests potentially mutually supportive roles for I_f and the Ca^{2+}-clock in pacemaking, with the funny current potentially serving as a consistent driving mechanism, and the Ca^{2+} clock more able to drive modulations in behavior, especially at faster rates. Therefore, this study supports a significant role for the Ca^{2+}-clock in pacemaking, but at the same time also suggests an important yet distinct role for I_f.

A model containing both the Ca^{2+}-clock and the funny current was both robust and flexible in response to autonomic modulation, but interestingly the most flexible of the robust 5-component model types was the one containing the Ca^{2+}-clock and the T-type current. The ability of the T-type current to play a major role in generating robust, flexible pacemaking is interesting in that, unlike I_f or the Ca^{2+}-clock, it is neither directly autonomically modulated in their model, nor is it widely considered to play a leading role in pacemaking. This is an example of how this sort of undirected, broadly sampling approach can lead to new ideas about mechanisms.

In exploring areas such as the potentially complementary roles for I_f and the Ca^{2+}-clock in pacemaking, as well as the arguably surprising role of the T-type current, the results of this study provide new conceptual insight into pacemaking. The ability of their method to improve our understanding also suggests that similar approaches based on analyzing large sets of models could be of use in future studies, not only of SANC pacemaking, but also in other areas of model-based research.

3. The present study builds on new trends towards “population-based” modeling

To place the study by Maltsev and Lakatta [10] into a broader context, we note that the work builds on an important emerging trend in research that uses mathematical modeling to understand physiological processes. Arguably initiated by Marder and colleagues in computational neuroscience [20–22], this new paradigm emphasizes that researchers should move beyond simulations with a single model that is considered representative of a typical biological sample. Instead, simulation studies are likely to be more informative when they consider a population of models, each with different properties [23,24], and several recent

publications from a number of laboratories have made important contributions to this effort [25–30]. It is worthwhile to consider some of the lessons learned from these studies, and to discuss how the results of Maltsev and Lakatta add to our understanding.

First, an obvious benefit of population-based modeling is that, when parameters are varied over a meaningful range, the simulations generate predictions regarding how the sample responds to changes in conditions. This strategy has proven to be useful for comparing models of the same cell type in order to identify where predictions diverge [27,31]. The present work [10] extends this idea by demonstrating that minimal models containing particular combinations of transport mechanisms are inherently more robust than minimal models containing other combinations.

Second, population-based modeling studies have recently provided insights into pathological behaviors, such as variability in the response to pro-arrhythmic drugs [32], prolongation of atrial action potentials due to K^+ channel variants [33], and altered ventricular physiology in heart failure [34]. Although pathological conditions were not explicitly considered in the present work, one can easily envision how the approach could be extended to examine arrhythmic disorders such as sick sinus syndrome or sinus tachycardia.

Third, this general strategy can be useful for inferring reasonable ranges of parameter values. If models that are consistent with experimental results are selected from a large population, this procedure can narrow down acceptable ranges for particular parameters [30,35,36], and it can identify correlations between parameters that are necessary to produce specific model behaviors [37]. This current study did not systematically explore the characteristics of the parameter combinations producing the most realistic results, but the structure of these parameter sets represents an avenue for future work that may provide insight into how various ion transport pathways are regulated.

4. The limitations of the present study suggest avenues for future research

Some limitations of Maltsev and Lakatta's study [10] should be mentioned because these limitations suggest ideas for future research. One is that although several different combinations of components were examined, and maximal rates of ion transport were varied over wide ranges, only one formulation, from an existing model [14], was used for each component. If a particular formulation misses a critical biophysical detail, then the importance of that component may be consistently under- or over-estimated in the analysis. A second limitation is the fact that minimal models were used. The minimal models may facilitate thorough analyses and conceptual understanding, but they are less able to generate experimentally-testable predictions than are more biologically complete models.

These limitations suggest that a similarly systematic, population-based examination of more complete models could build on the results of this study, not only by expanding upon its conclusions, but also by suggesting novel experiments capable of resolving controversies that previous experimental work has failed to untangle. And if such a study examined multiple SA nodal cell models built by different groups, the comparison could address the

issue of whether particular formulations influenced the general conclusions of the present study.

Despite these limitations, the study is a novel and instructive application of a systematic, population-based modeling strategy. It succeeds in providing insight into the controversial mechanisms of SANC automaticity, specifically by suggesting complementary roles for the funny current and the Ca^{2+}-clock in providing robustness and flexibility, respectively. The paper is likely to be relevant both to readers interested in SA nodal physiology, as well as to readers interested more broadly in how quantitative analyses can facilitate mechanistic understanding.

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