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Computational modeling of cardiac optogenetics: Methodology overview & review of findings from simulations ☆

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ABSTRACT

Cardiac optogenetics is emerging as an exciting new potential avenue to enable spatiotemporally precise control of excitable cells and tissue in the heart with low-energy optical stimuli. This approach involves the expression of exogenous light-sensitive proteins (opsins) in target heart tissue via viral gene or cell delivery. Preliminary experiments in optogenetically-modified cells, tissue, and organisms have made great strides towards demonstrating the feasibility of basic applications, including the use of light stimuli to pace or disrupt reentrant activity. However, it remains unknown whether techniques based on this intriguing technology could be scaled up and used in humans for novel clinical applications, such as pain-free optical defibrillation or dynamic modulation of action potential shape. A key step towards answering such questions is to explore potential optogenetics-based therapies using sophisticated computer simulation tools capable of realistically representing opsin delivery and light stimulation in biophysically detailed, patient-specific models of the human heart. This review provides (1) a detailed overview of the methodological developments necessary to represent optogenetics-based solutions in existing virtual heart platforms and (2) a survey of findings that have been derived from such simulations and a critical assessment of their significance with respect to the progress of the field.

1. Introduction

Cardiac optogenetics is an exciting new field in which cells in the heart are genetically modified to express light-sensitive proteins (opsins) so that low-energy light can be used to induce transmembrane current, providing a means for electrophysiological control [1,2]. Many different types of opsins exist, including ionic channels and pumps that produce different types of membrane current (i.e., depolarizing or hyperpolarizing) when illuminated with light in a particular wavelength range [3–8]; this rich diversity means that optogenetics enables numerous useful applications in opsin-expressing tissue, including eliciting or suppressing action potentials (APs) with exquisite spatiotemporal specificity. Thus far, this versatile approach has been implemented using transgenic animals (with global cardiac expression) and in cells, tissue, and organs that have been light sensitized by gene or cell delivery [9–13]. Beyond its irrefutable appeal as a basic science tool, it remains to be seen whether optogenetics-based solutions may provide an alternative to electrotherapy to treat cardiac arrhythmias [14,15]. Computer modeling provides an avenue to narrow the scope of experimental investigations by helping to pinpoint which light-based therapy innovations are most likely to make a difference in the clinic. The aim of this review is to summarize the work that has been done so far towards virtual cardiac optogenetics, i.e. the incorporation of optogenetic tools in realistic simulations of the heart. First, we provide a comprehensive overview of the methodological approach for integrating new features at the sub-cellular (protein), cellular, tissue, and organ scales of biophysically-detailed cardiac models; then, we highlight interesting and relevant findings that have emerged from simulations of cardiac optogenetics to date.

2. Methodology overview

Simulations conducted in detailed models of the heart (ventricular, atrial, or whole-heart) are increasingly recognized as an essential aspect of the investigation of cardiac disease [16–19], with applications ranging from mechanistic analysis of rhythm disorders [20–29] or pump dysfunction [30–33] to the development of novel therapeutic methodologies [34–36]. Excitingly, the emergence of models reconstructed from medical images

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(obtained via magnetic resonance, computed tomography, etc.), which incorporate patient-specific detail about cardiac geometry and structural remodeling, has opened up new avenues for translating results from simulations into insights relevant to clinical applications [37–43]. Since optogenetics has emerged at a time when such a rich and robust set of tools for cardiac computational modeling exists, there is great enthusiasm to discover what might be learned about this exciting new technology if it can be explored in biophysically-detailed models of the heart [1,14,15]; to achieve this goal, new methodologies have been developed to represent light sensitization and optical stimulation at multiple spatial scales [44], as summarized in Fig. 1. At the protein scale (I), the light- and voltage-sensitive electrical properties of opsins expressed in the sarcolemma are represented; at the cell scale (II), the integration of opsins in individual myocytes or exogenous donor cells is modeled; at the tissue scale (III), the heterogeneous spatial distribution of opsin-expressing cells resulting from light sensitization must be represented; finally, at the organ scale (IV), it is necessary to capture the application of optical stimuli to the heart, taking into account light-matter interactions resulting in photon scattering and light attenuation. This section provides a detailed review of different methodologies that have been devised, either in the context of cardiac optogenetics or for other multiscale heart modeling studies.

2.1. Modeling cardiac optogenetics at the protein scale

The first step towards multiscale simulation of cardiac optogenetics is the development of accurate models of the light- and voltage-dependent electrophysiological behavior of opsins. Initial efforts in this direction have focused on the algal blue light-sensitive protein channelrhodopsin-2 (ChR2), the most widely used excitatory opsin in optogenetics research. ChR2 forms a light-sensitive cation channel that is permeable to H^+, Na^+, K^+, and Ca^{2+}, with a reversal potential of approximately 0 mV [3]. Analysis of spectral characteristics revealed that ChR2 energy absorption is maximal for light with a wavelength of approximately 480 nm [45]. Hegemann et al. formulated the first mathematical description of the ChR2 photocycle [46], proposing a Markov model with states representing open, closed, and refractory channel configurations; a rapid closed-to-open transition in the presence of blue light was found to be necessary to achieve a simulated ChR2 current (I_{ChR2}) consistent with experimental measurements. Based on experiments in voltage-clamped ChR2-expressing cells revealing I_{ChR2} with a distinct a peak-and-plateau morphology, potentiated by the irradiance of the optical stimulus, it was inferred that a model with at least four states (including a second open state associated with a refractory light-adapted channel configuration) was required to fully reproduce the photosensitive properties of ChR2 [45,47].

Recent efforts by Williams et al. [48] led to characterization of both light- and voltage-sensitive properties of ChR2 photocurrent and its operation in cardiomyocytes. Based on experimental data, an extended version of the four-state model by Nikolic et al. [47] was put forward, that includes voltage rectification and voltage dependence of kinetic parameters. The inclusion of an empirical scaling function to represent ChR2's voltage rectification was found to be essential in accurately reproducing the behavior of I_{ChR2} during the different phases (upstroke, notch, plateau, repolarization) of light-triggered cardiac action potentials (APs). Experimental validation was enabled by an "optical AP clamp" to extract the I_{ChR2} waveform during light-triggered cardiac AP [48,49]. This approach involves measuring the total membrane current in a ChR2-expressing cell with membrane voltage clamped to a specific AP morphology and recreation of the optical stimulus used to trigger the AP; by comparing currents in the presence and absence of illumination, the dynamic I_{ChR2} during the AP can be extracted.

Fig. 2 A shows photocurrent traces in response to 5 blue light pulses of different intensity for the ChR2 model by Williams et al. in cells clamped to resting $V_m = -80$ mV. Fig. 2B shows the response to both electrical and optogenetics-based stimuli in a simulated cardiomyocyte [50]: first, two electrically-paced APs; then, two APs prolonged by the application of strong light stimuli during the plateau phase (200 and 400 ms long, each delivered

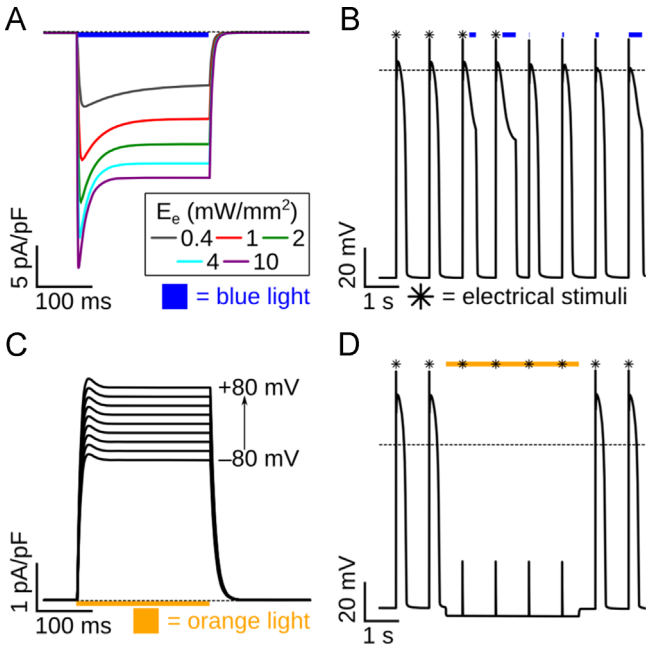

Fig. 2. Simulated response to optogenetics-based stimulation of opsin-expressing human cardiomyocytes. (A) ChR2-mediated photocurrent (I_{ChR2}) in response to 200 ms of blue-light illumination with a range of irradiance (E_e) levels; I_{ChR2} is modeled as described by Williams et al. [48] and incorporated in a human ventricular myocyte [50] clamped to $V_m = -80$ mV. (B) Result of electrical and optogenetics-based stimulation in the human ventricular myocyte. Both light-based action potential (AP) prolongation (beats 3 and 4) and purely light-elicited APs (beats 5 to 8) are shown. Blue light pulses had $E_e = 10$ mW/mm^2. (C) NpHR-mediated photocurrent (I_{NpHR} in response to 200 ms pulses of orange light ($E_e = 1.4$ mW/mm^2) in ventricular myocytes clamped to a range of V_m values. The formulation used to model I_{NpHR} is provided Table 1. (D) Optogenetics-based "silencing" of electrical stimuli that would otherwise have induced APs. The orange light pulse had $E_e = 1.4$ mW/mm^2. Electrical stimuli were transmembrane current pulses (strength: 32.4 μA/cm^2, duration: 1 ms); NpHR-based silencing failed when stronger and/or long-lasting electrical stimuli needed to be countered by light. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

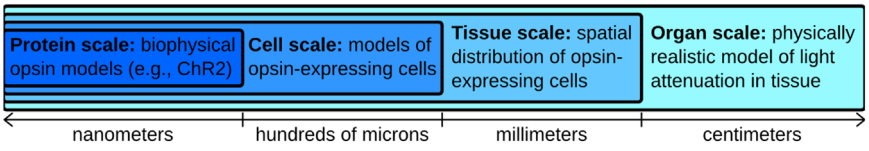

Fig. 1. Schematic showing new methodologies that must be integrated with the existing approach to multiscale cardiac modeling. Changes required at four discrete spatial scales are highlighted.

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