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Hybrid modeling of electrical and optical behavior in the heart

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ABSTRACT

Optical mapping of transmembrane potential using voltage-sensitive dyes has revolutionized cardiac electrophysiology by enabling the visualization of electrical excitation waves in the heart. However, the interpretation of the optical mapping data is complicated by the fact that the optical signal arises not just from the surface, but also from some depth into the heart wall. Here, we review modeling efforts, in which the diffusion of photons is incorporated into the computer simulations of cardiac electrical activity ("hybrid" modeling), with the goal of improving our understanding of optical signals. We discuss the major accomplishments of hybrid modeling which include: (i) the explanation of the optical action potential upstroke morphology and prediction of its dependence on the subsurface wave front angle, (ii) the unexpectedly low magnitudes of optically recorded surface potentials during electrical shocks, and (iii) the "depolarization" of the core of the spiral wave and odd dual-humped optical action potentials during reentrant activation. We critically examine current optical mapping techniques and controversies in our understanding of electroporation during defibrillation. Finally, we provide a brief overview of recent theoretical studies aimed at extending optical mapping techniques for imaging intramural excitation to include transillumination imaging of scroll wave filaments and depth-resolved optical tomographic methods.

1. Introduction

Optical mapping of transmembrane potential using voltage-sensitive dyes has revolutionized cardiac electrophysiology (for review see [9,10]). Unlike electrodes, the dyes can be introduced into the tissue through coronary blood flow without causing tissue damage. They bind to the cardiac myocyte membrane and respond to changes in the transmembrane potential by changing their excitation and fluorescence spectra. The resulting voltage-dependent variations in light intensity can be recorded using photodiode arrays or fast CCD cameras, with each frame in such a recording being a snapshot of the transmembrane voltage distribution in the area of interest. The use of optical sensors instead of electrodes has significantly simplified data recording with high spatial and temporal resolution. It has allowed measurement of both depolarization and repolarization (repolarization is difficult to study using electrical methods because the signal, or T-wave, is very small), and enabled observation of the polarization induced during a strong electrical shock, which was not possible using conventional electrical mapping techniques.

At first glance, optical mapping appears to be limited to the heart surface. Yet, as we have learned more about the method, it has become clear that the optical signal arises not just from the surface, but also from some depth into the heart wall. To understand the implications of this depth-dependent signal, mathematical modelers are starting to incorporate optical diffusion of photons into their computer simulations of the heart's electrical activity ("hybrid" modeling), with the hope of improving the agreement between theory and experiment and aiding the interpretation of optical mapping results. The improved understanding of voltage-sensitive optical signals has set the stage for the next technological step: 3D intramyocardial optical mapping. In this paper, our goal is to review hybrid models of optical mapping in the heart, and to critically examine current methods, results, and conclusions arising from these simulations.

2. Averaging over depth

Due to light penetration into the myocardium, optical action potentials recorded from the heart surface contain contributions from the subsurface layers [11]. The simplest way to account for the optical properties of the signal is to average over depth [2,12,13]. In this model, the optical signal, V_{optical}, is the weighted average of the transmembrane potential, V_m, at different distances, z, below the tissue surface. If we use a single exponential weighting function, the optical signal is

$$V_{\text{optical}} = \frac{\int_0^\infty V_m(z)\, e^{-z/\delta} dz}{\int_0^\infty e^{-z/\delta} dz}. \quad (1)$$

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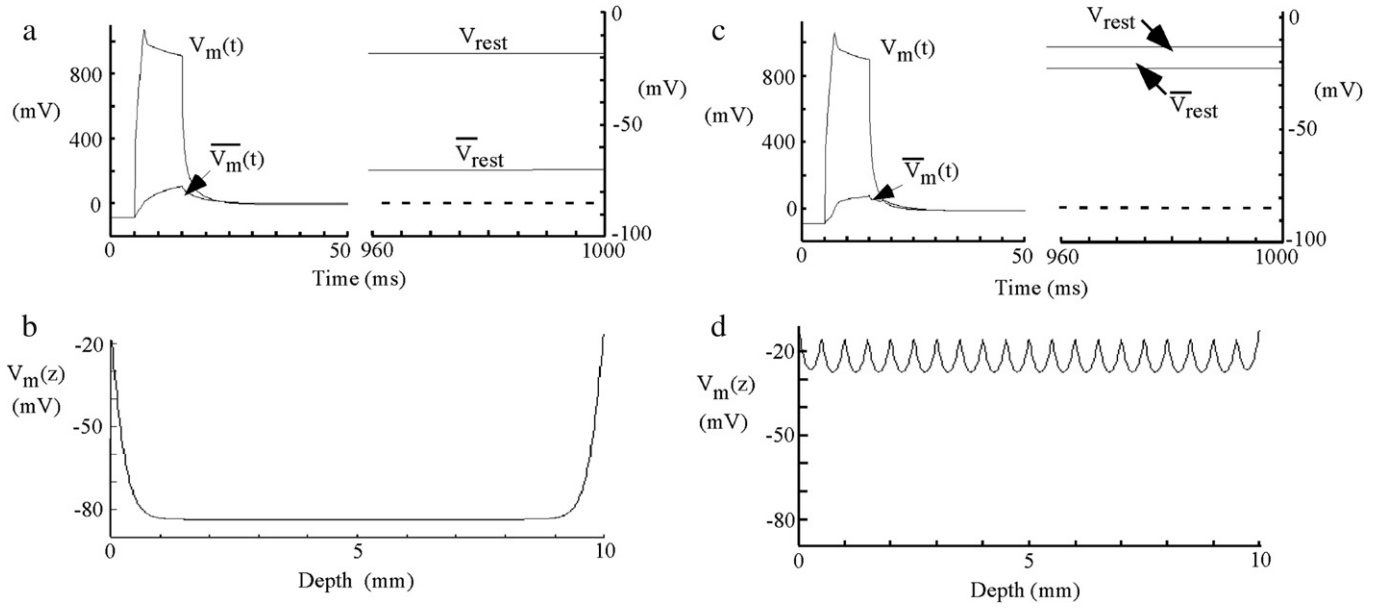

Fig. 1. The transmembrane potential produced during and after a strong shock in homogeneous (a and b) and heterogeneous (c and d) tissue. V_m at the surface during the shock is over 800 mV, but is less than 200 mV in the signal averaged over depth, $\bar{V}_m$ (a and c). After the shock, the homogeneous tissue returns to rest (−85 mV) everywhere except near the tissue surfaces (0 and 10 mm), where it is depolarized by electroporation (b). The heterogeneous tissue is electroporated and depolarized throughout (d). From [1].

In this model, δ determines the depth over which averaging occurs and has a value on the order of half a millimeter (see below) [2,14–16].

The parameter δ introduced in Eq. (1) arises from two factors: the decay of the illumination light as it enters the tissue, and the decay of the fluorescent light as it exits the tissue. Assuming exponential decay of illumination and fluorescent light with decay constants δ_i and δ_f, respectively, one can readily derive a rough estimate of the decay constant in Eq. (1):

$$\delta = \frac{\delta_i \delta_f}{\delta_i + \delta_f}. \tag{2}$$

In general δ_f is larger than δ_i because the fluorescent light has a longer wavelength than the incident light, and longer wavelengths penetrate deeper into the tissue.

Eq. (1) is applicable only when lateral blurring is negligible, so the transmembrane potential is 1D (varying only with depth), and when the myocardial surface is illuminated uniformly. One example of such a situation is when a uniform electric field is applied to a homogeneous slab of tissue, so V_m decays exponentially with depth into the tissue with an electrical length constant λ, $V_m(z) = V_m(0)\, e^{-z/\lambda}$. Substitution of this expression into Eq. (1) gives

$$V_{\text{optical}} = V_m(0)\, \frac{\lambda}{\lambda + \delta}. \tag{3}$$

If $\delta \gg \lambda$, the optical signal underestimates the surface transmembrane potential by a factor of about λ/δ. If $\delta \ll \lambda$, the optical signal is approximately equal to the surface transmembrane potential. If δ is about 0.5 mm and λ is about 0.1 mm in the direction perpendicular to the myocardial fibers (typical for cardiac tissue), the optical signal underestimates the surface transmembrane potential by about a factor of 1/5.

Such averaging may explain in part why experimentalists often observe unexpectedly small transmembrane potentials when measured optically, during defibrillation-strength shocks [17,16,18]. According to Janks and Roth [12], who analyzed the optical signal produced during a strong shock, averaging over depth could be one of the reasons why large polarizations were not observed in the experiments: they could have been large at the tissue surface but much smaller in the optical signal (Fig. 1(a), (c)). This effect of depth averaging is consistent with the experimental observations by Sharifov and Fast [19,20], who found significantly larger polarizations when using surface staining of the dye instead of global staining.

Depth averaging, however, is insufficient to explain findings by Neunlist and Tung [17], Al-Khadra et al. [16] and Kodama et al. [18], who have observed evidence of electroporation (including depolarization of the resting potential [21]) without observing a large polarization during the shock. If just the surface tissue is electroporated, the depolarization of the resting potential should also fall exponentially with depth (Fig. 1(b)), so its effect should also be suppressed in the optical signal (Fig. 1(a)), which is not the case in their experiments [22].

One possible explanation of this contradiction is that heterogeneities cause large transmembrane potentials throughout the tissue, so that electroporation is widespread and the resting potential is depolarized everywhere (Fig. 1(d)) [1]. In this case, the optical signal during the shock would be small because of averaging over adjacent depolarized and hyperpolarized regions. This hypothesis, however, is not supported by the propidium iodide uptake experiments that show electroporation only in a thin layer near the myocardial surface [23]. Clearly other factors could also affect the optical signal at such large transmembrane potentials, such as a nonlinear response of the dye, dye bleaching, etc. [24]. A recent study by Zemlin et al. [25] suggests that the resolution of this controversy may require a more fundamental paradigm shift. Their study shows that the surface polarization is significantly smaller than predicted by the existing theories. Any definitive conclusions about electroporation during defibrillation will require other methods to detect electroporation besides optical mapping.

When imaging more complex phenomena such as reentrant wave fronts, optical averaging can have many subtle and interesting effects. For instance, Efimov et al. [26] observed "double-humped" action potentials during reentry. They hypothesized that the two peaks may "represent the signatures of two activation wave fronts propagating above and below the filament, which in this area is close to the epicardial surface." Several researchers