Comments to the Editor

Response: Optimal Velocity Can Arise from Various Discontinuities

It is generally accepted that the excitation of the heart involves propagation of action potentials (APs) through a discontinuous and anisotropic network of electrically coupled cells. In their comment on our article (1), Shaw and Rudy (2) emphasize the importance of considering such discontinuities in computational modeling of cardiac tissue, and bring our attention to the fact that results presented in their earlier article (3) were based on simulations of a discontinuous model, where an optimal AP conduction velocity (corresponding to the maximal safety factor, SF) is feasible.

We are grateful to Shaw and Rudy for clarifying the latter fact, as it was not obvious from their original article (3), which stated:

> ''For computations in this report, $\Delta x = 100$ μm (entire cell length) is used as the discretization element with R_i reflecting the lumped contribution of axial and gap junction resistance ($R_i = R_{myo} + R_g/\Delta x$). When intracellular detail is sought, a smaller Δx of 21 computation elements per cell ($\Delta x = 4.76$ μm) is used with R_g concentrated at the edge elements of the cells.''

From their article (3), it was unclear whether ''intracellular detail is sought'' in their Fig. 7 illustrating the optimal velocity. Therefore, in our article (1) we have written:

> ''It is also possible that the previous study (3) actually implemented a nonuniform model with differential coupling within and between cells (see description in their Appendix), as it is not explicitly stated which model they used in simulations showing the existence of a maximal SF.''

The comments by Shaw and Rudy (2) clarify this misunderstanding. With this clarification, we note that their original article (3) likely did not mean to suggest that a conduction velocity maximum exists in a uniform cardiac tissue.

We should also emphasize that, in our article (1), it was never stated that cardiac tissue is a uniform syncytium. The statement made in the Optimal Velocity section of the Discussion is correct, i.e., that ''a maximum [SF] in uniform tissue is not feasible''—and this statement can apply to any uniform tissue, not necessarily cardiac. In the context of our article (1), the statement can also refer to any ''uniform continuous model of cardiac tissue,'' as our analytical analysis has been applied to such a model. We agree that continuous models are not the best idealization of cardiac tissue, as discrepancies between continuous models and more accurate discontinuous models (e.g., in the AP conduction velocity and maximum upstroke velocity) at weak intercellular coupling can be substantial (4–6). However, at normal or even moderately low values of the intercellular coupling the macroscopic behavior of the discontinuous cardiac tissue can be described using the continuous cable approximation (4,5). Hence, although models that account for subcellular heterogeneities—such as the one-dimensional strand model used by Shaw and Rudy (3)—provide a high degree of biological accuracy for a wide range of the intercellular coupling values, larger scale three-dimensional simulations of cardiac tissue often rely on uniform reaction-diffusion mono- or bidomain models (7,8) in order to remain computationally efficient. Importantly, macroscale heterogeneities and anisotropy can be incorporated into such models. Thus, to maintain a balance between biological accuracy and computational efficiency we used a macroscopically heterogeneous and anisotropic reaction-diffusion model for the three-dimensional ventricular wedge in our study (1).

In our view, conclusions made by Shaw and Rudy (2,3) and us (1) are similar, and can now be formulated more clearly:

1. A maximum SF in a uniform tissue (or a uniform continuous tissue model) is not feasible.
2. Cardiac tissue is not intrinsically uniform, and hence, potentially always has an optimal SF and an optimal conduction velocity.
3. Specific value of the optimal conduction velocity is defined by the nature and scale of the underlying tissue heterogeneity.

These conclusions are based on different models that considered discontinuities at various scales: either microscopic heterogeneity between intra- and intercellular coupling (3), or macroscopic differences in electrical coupling, tissue dimensions, and anisotropy across the Purkinje-ventricular junction (1). Thus, although biological accuracy cannot always be maintained at all scales within a single study, comparing results from various studies that use different models to consider various scales (i.e., subcellular, cellular, tissue, and whole organ) can lead to more general and more reliable conclusions.

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