Comments to the Editor

Cardiac Muscle Is not a Uniform Syncytium

We read with interest the study by Aslanidi et al. (1), which implements a multidimensional mathematical model of the Purkinje-ventricular junction (PVJ), and applied our earlier formulation of the safety factor of conduction (SF) (2), to find that there is an optimal velocity that is neither too fast nor too slow through which impulses can travel across the PVJ. Despite the authors' successful use of SF, we were surprised to read in the Discussion subsection entitled Optimal Velocity that they believe that conduction in purely cardiac tissue (not across a PVJ) cannot have an optimal velocity, and furthermore that our earlier findings can be ''an artifact of numerical approximation'' (p. 32 in Aslanidi et al. (1)).

In the same subsection of the Discussion in Aslanidi et al. (1), the authors make a critical assumption in SF computation that is not consistent with cardiac physiology or histological structure. They assume that cardiac tissue is a uniform syncytium. This incorrect assumption is made when the authors present a simple theoretical analysis revealing that ''a maximum [SF] in a *uniform* tissue is not feasible.'' (p. 32 of Aslanidi et al. (1), emphasis added). They then add a caveat stating that ''It is also possible that the previous study (2) actually implemented a *nonuniform* model with differential coupling within and between cells…. If so, the relationship shown between SF and [diffusion coefficient] fits into our theoretical analysis'' (p. 32 of Aslanidi et al. (1)).

It is well understood that cardiomyocytes contain, at otherwise impermeable cell-cell borders, intercellular gap junction coupling that makes the tissue nonuniform on the cellular scale. Consequently, conduction in cardiac tissue is inherently discontinuous (3,4). In normal myocardium, the resistivity represented by gap junctions at intercalated disk structures that span well less than a micron, is similar to the resistivity of the entire cardiomyocyte cytoplasm that spans 100 μm or more (reviewed in (5)). When gap junction coupling decreases, the discontinuity further increases at the intercalated disks (6). The intrinsic discontinuous nature of cellular conduction due to gap junctions and cell-size differences has been well studied with computational models of cardiac muscle (7–10) and is also elegantly discussed by Spach (11).

In our earlier publication (2), we focused on safety factor and the discontinuous nature of conduction and devoted an entire Appendix to the discussion of spatial discretization and distribution of fiber resistivity. We refer Aslanidi et al. (1) and the readers to this aspect of our article, as it is not discussed in their article. Achieving numerical accuracy of a uniform model by simply decreasing the spatial step in a one-dimensional simulation, as Aslanidi et al. did, unfortunately violates the intrinsic discontinuity that exists in cardiac tissue. As we discussed in Shaw and Rudy (2), our results were checked with a model containing 21 discretization elements per cell, interconnected with the same myoplasmic resistance, and with gap junction elements concentrated at the ends of each cell to represent the higher resistance of gap junction at the intercalated disk.

We agree with the general conclusion of Aslanidi et al. (1) that discontinuities in cardiac substrate result in an optimal conduction velocity. However, it is important to emphasize that when the discontinuous nature of cardiac substrate is considered, even in a one-dimensional fiber consisting solely of cardiomyocytes interconnected via gap junctions (true to the actual structure), an optimal conduction velocity also exists (2). We thank Aslanidi et al. for pointing to us the need to clarify the importance of developing a model that is true to the cardiac substrate. In computational modeling of cardiac electrophysiology, numerical accuracy is not good enough; biological accuracy is important as well.

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Submitted December 16, 2009, and accepted for publication March 17, 2010.
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0006-3495/10/06/0001/02 $2.00
doi: 10.1016/j.bpj.2010.03.030

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