Safety Factor in Cardiac Propagation

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***Abstract*—Safety factor is a term that has been used for quite some time in cardiac electrophysiology, to refer to the robustness of propagation. It has had several definitions but none have been entirely satisfactory. In this paper, we will present discuss what is wrong with previous versions, a propose a new formulation. The new formulation is verified for a wide range of scenarios.**

I. Introduction

Cardiac safety factor (SF) is generally defined to be the excess charge delivered to a cell, beyond the amount required to cause an action potential. A value of one means that exactly enough current was delivered, while less than one indicates propagation failure. The first attempt to define SF was by [1]. Leon and Roberge later posited a version based on local cellular excitation [2] and Shaw and Rudy followed with the most well known version [3], which was later tweaked [4]. This most recent formulation shall be referred to as SF_{R}. A rather recent study[5] using SF_{R} revealed many issues with the computation. SF_{R} was only verified in one-dimension [3], [6] so SF_{R} properly may not capture the dynamics of successful propagation in higher dimensions. While the concept of SF is straight forward, its computation is not.

II. Mathematical Derivation of Safety Factor

By conserving charge flowing into a cell, the following expression must hold

$$Q_{in} - Q_{out} = C_m \Delta V_m + Q_{ion} - Q_{stim} \tag{1}$$

where C_m is the membrane capacitance, Q_{in} and Q_{out} are the charges entering and leaving a cell through gap junctions, and Q_{ion} is the charge passing through membrane channel proteins. Q_{stim} is the current injected by an intracellular stimulus electrode if present. Note that Q_{in} and Q_{out} are both positive quantities as defined by earlier formulations.

The expression for SF used by [4] and [5] is given by:

$$SF_{\mathrm{R}} = \frac{C_m \Delta V_m + Q_{out}}{Q_{in}} = 1 - \frac{Q_{ion}}{Q_{in}} \tag{2}$$

where the rightmost equality is an identity which follows from (1). Note that when reexpressed this way, the dependency on Q_{out} disappears.

Computationally, splitting charge into influx and efflux can become nontrivial for unstructured grids. Efflux may be present at a node while influx is occurring at an adjacent node Thus, interpolation must be done along edges and in time to properly decompose the charge into two components.

A. New Formulation for Safety Factor

We propose a new formulation of SF which is simply the net current entering a cell divided by the threshold current required to fire a cell:

$$SF_{\mathrm{VB}} = \frac{Q_{in} - Q_{out}}{Q_{thr}(t_A)} = \frac{\frac{1}{\beta}\int_{t_A} \nabla \cdot \overline{\sigma}_m \nabla V_m \, dt}{Q_{thr}(t_A)} \tag{3}$$

where t_A is the interval from 1% V_m take off to the point at which the ionic current is zero, representing the interval before the activation of the sodium channels. Q_{thr} is the minimum charge required to elicit an action potential in a single isolated cell, which is dependent on the exact state of the cell. Two equivalent versions of SF_{R} are given, the last being in a form suitable for experimental computation since it can be measured by estimating the Laplacian.

The computation of this formula depends on the history of a particular cell since threshold depends on the level of refractoriness. Thus, Q_{thr} must be individually calculated for each cell. However, Q_{thr} can easily be determined from isolated experiments on a single cell given initial conditions, The threshold is close to linear with respect to t_A since the subthreshold membrane acts like a passive RC circuit to a large degree.

SF_{VB} was tested using a similar experimental design to the [5] study: a $2\,mm$-long strand of Purkinje cells was attached to a $2 \times 4\,mm$ piece of myocardial tissue (see Fig. 1). A monodomain finite element formulation was used, details of which can be found in [7]. An edge length of $5\mu m$ was used for all elements to reduce discretization error. Ion dynamics were described by the modified Beeler-Reuter model in the myocardium [8] and the DiFrancesco-Noble model [9] in the Purkinje strand. The complex architecture known to exist at PVJs was ignored. Strand width was studied over the range $60 - 120\,\mu m$.

The distribution of SF_{VB} during Purkinje-to-myocardium propagation with a $120\,\mu m$ strand is shown in Fig. 1. As expected, SF_{VB} was minimal near the PVJ, where the preparation was most vulnerable to propagation failure, and increased as the wavefront curvature became larger. At the tissue boundary, there was a sharp increase in SF_{VB} due to the lack of

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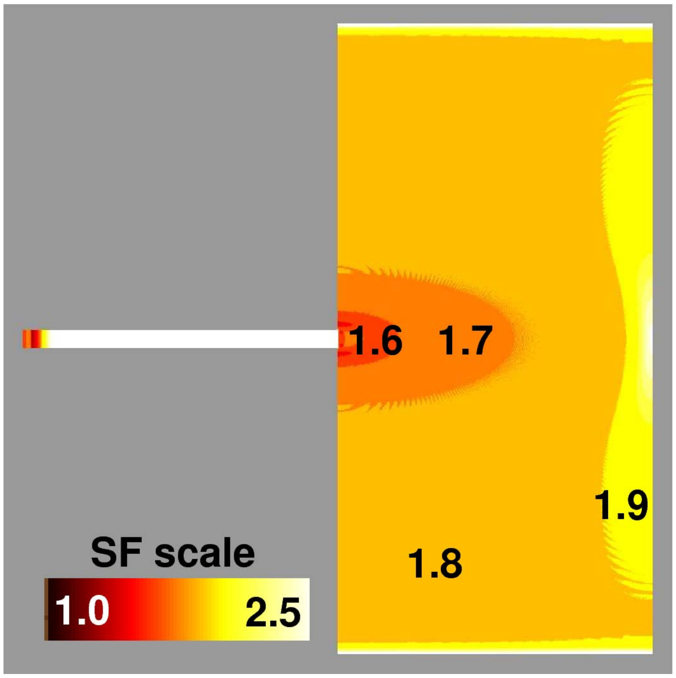

Fig. 1. Safety factor distribution for simulated tissue set up with 120 μm strand width. Propagation was initiated at the left end of the strand. Color indicates safety factor.

downstream cells to be excited. Fig. 2 shows SF_{VB} from strand to myocardium, including the centre of the PVJ as strand width was varied. Where propagation was unsuccessful, SF_{VB} dropped below unity at the PVJ and the failed stimulus decayed exponentially into the surrounding tissue.

III. Discussion

SF_{VB} is the direct ratio of the charge available at a given node to the charge required for that node to achieve the depolarization threshold. A value less than 1 indicates propagation fail since the cell cannot achieve the threshold voltage. Quantitatively, $SF_{\text{VB}} = 1.7$ indicates an 70% charge surplus and $SF_{\text{VB}} = 0.9$ indicates a 10% shortfall which will result in failed conduction. SF_{VB} is also direction dependent, with longitudinal propagation have a higher safety factor.

Our version of SF behaves as one intuitively expects. It increases near borders and was a minimum near the junction. It does not rely on decomposing current into influx and efflux, and can been approximated experimentally by using Laplacian electrodes

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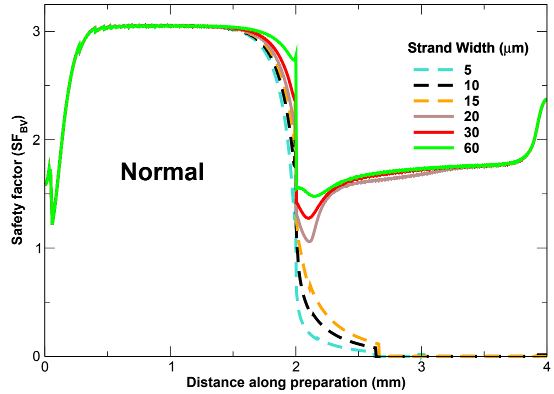

Fig. 2. SF_{VB} along the horizontal axis, from stimulation site ($0\,mm$) through PVJ ($2\,mm$) to myocardial boundary ($4\,mm$). Failed propagation is indicated with dashed lines.

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