Web-based Supplementary Materials for "Practical Estimability Analysis and Optimal Design in Dynamic Multi-scale Models of Cardiac Electrophysiology"

Web Appendix A: Design Optimization Algorithm

The information matrix associated with an experimental design can be expressed as a weighted sum of experiment-specific information matrices: $M(\boldsymbol{w}) = \sum_{j=1}^{J} w_j M_j$, where $\boldsymbol{w} = [w_1, \ldots, w_J]$ is a vector of weights that sum to one. The design optimization task is to select the weights that minimize an optimal design criterion, denoted $\Psi[M(\boldsymbol{w})]$. In order to accomplish this, consider an iterative algorithm where, at each iteration, the current design weights $\boldsymbol{w}$ are reweighted the direction of $\boldsymbol{w}'$ by some prespecified amount $0 < \alpha \ll 1$: $(1-\alpha)M(\boldsymbol{w}) + \alpha M(\boldsymbol{w}')$.

The weights $\boldsymbol{w}'$ are selected at each iteration to minimize the change in the value of the optimal design criterion, which is expressed relative to α as follows:

$$\frac{\Psi[(1-\alpha)M(\boldsymbol{w}) + \alpha M(\boldsymbol{w}')] - \Psi[M(\boldsymbol{w})]}{\alpha}. \tag{1}$$

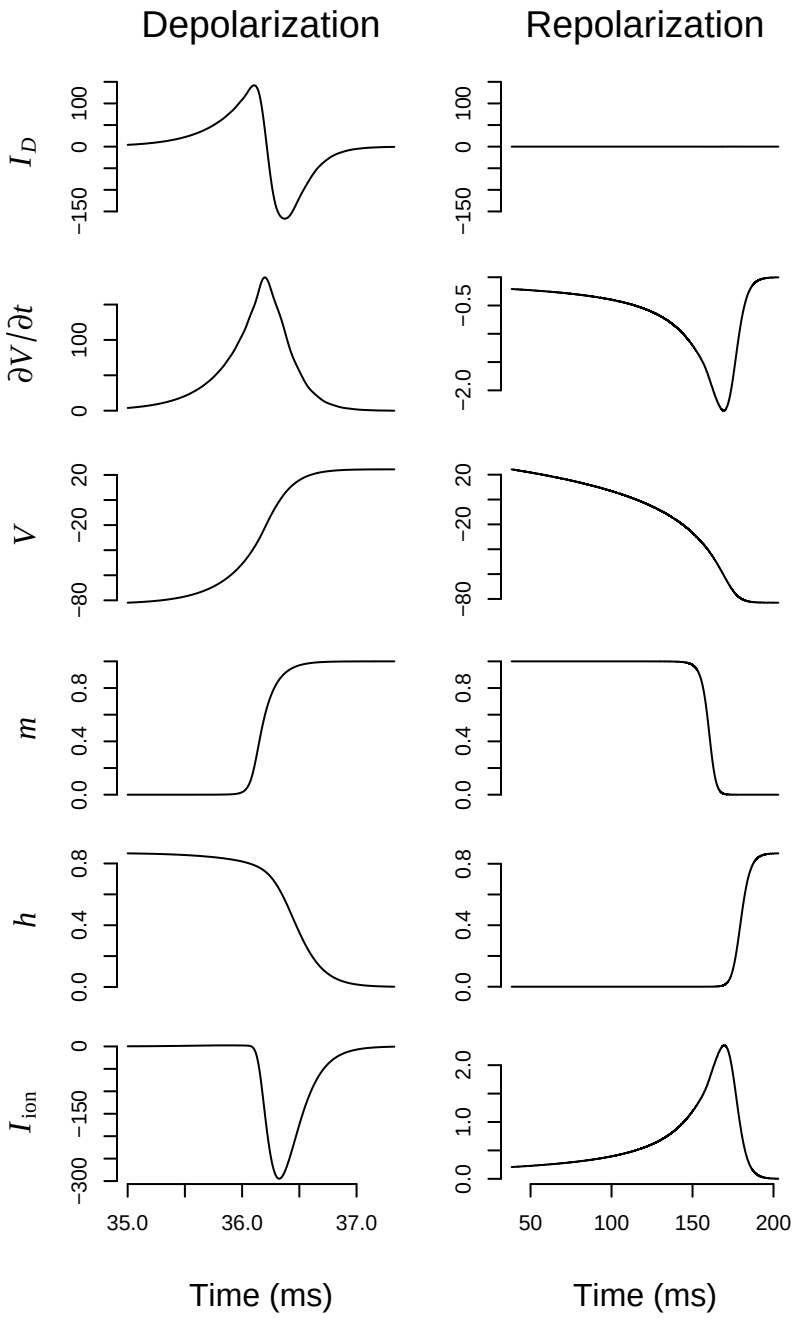
The limit of the above expression as $\alpha \to 0$ is a directional derivative that, for some optimal design criteria including the D- and A-optimality criteria, has a closed expression of the form $C - \varphi(\boldsymbol{w}, \boldsymbol{w}')$, where C is a scalar constant. The expression $\varphi(\boldsymbol{w}, \boldsymbol{w}')$ is called the *sensitivity function*, and represents the negative change (up to constant C) in the associated optimal design criterion that results from an infinitesimal change in $\boldsymbol{w}$ in the direction of $\boldsymbol{w}'$. When no closed expression for the sensitivity function is available (e.g., the K-optimality criterion), the limit of (1) can be approximated using a finite difference (i.e., for small value of α).

Thus, at each step of the iterative algorithm, $\boldsymbol{w}'$ is selected to maximize $\varphi(\boldsymbol{w}, \boldsymbol{w}')$. How-

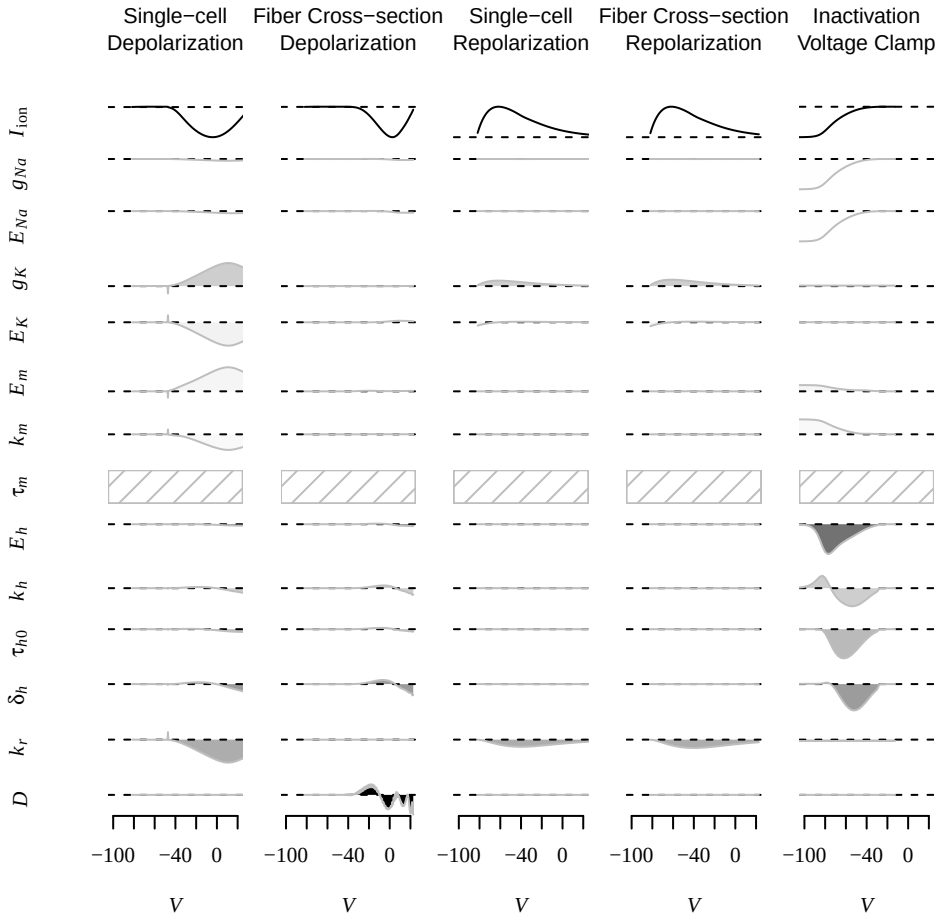
ever, even this is a difficult problem since $\boldsymbol{w}'$ can take an infinite set of values. To overcome this, Fedorov and Leonov (2013) recommend selecting $\boldsymbol{w}'$ from the set of J *atomized* weight vectors, i.e., those that assign all weight to just one type of experiment. The same authors provide rationale for this, and argue that the resultant algorithm produces optimal weights under certain conditions. Specifically, the algorithm can be used to identify A- and D-optimal designs, because the A- and D-optimality criteria are convex and smooth functions of the design weights. The K-optimality criterion is not necessarily convex or smooth in the design weights. However, we nevertheless use a modified version of the optimization algorithm to identify K-efficient weights by evaluating the algorithm over many random initializations.

References

Fedorov, V. V. and Leonov, S. L. (2013). *Optimal Design for Nonlinear Response Models*. Chapman & Hall/CRC Biostatistics Series. Taylor & Francis.



Web Figure 1: Action potential propagation model solutions.



Web Figure 2: Augmented sensitivity plot for the 12 parameters of the modified cardiac ion-channel model (τ_m replaced by a $1/10^{th}$ scaled version of τ_h). The uppermost row of panels plot the model solution (solid black lines) for I_{ion} as a function of V during depolarization and repolarization, and in single-cell and fiber midpoint experiments. Dashed black lines mark the y-axis origin. Solid gray lines represent the sensitivity values for the corresponding parameter and experiment type. In each row of panels, the intensity of the shaded regions is constant, and represents the degree of linear dependence of the corresponding parameter sensitivity values on that of the other parameters. Lighter shading indicates greater dependence and reduced identifiability and estimability. When no shading is visible in one or more rows, the model is not estimable, or only weakly estimable.