

Supporting Information

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SI Text

Macroscale Ephaptic Model. In this section, we present the ephaptic variant of the macroscale model (Eqs. 8 and 9) described in the main text. It can be derived by macroscopic first principles or by homogenization. Consider functions $\phi(x)$ and $\phi_c(x)$ that are defined for all x and that represent the intracellular and cleft potentials in the neighborhood of myocytes around x . Similarly, let $w_{\text{side}}(x)$ and $w_{\text{end}}(x)$ be the gating variables along the sides and ends of cells near x . As derived in ref. 1, if these functions vary slowly over the length scale of cells, they obey the following macroscale equations:

$$C\partial_t\phi(x) = \frac{A\sigma_{\text{cyt}}}{S} \left(1 - \frac{1}{1+\kappa}\right) \partial_{xx}\phi(x) - \frac{1}{S\ell R_c} \phi_c(x) - I_{\text{ion,side}}(\phi(x), w_{\text{side}}(x)), \quad [\text{S1}]$$

$$C\partial_t[\phi(x) - \phi_c(x)] = \frac{1}{2AR_c} \phi_c(x) - I_{\text{ion,end}}(\phi(x) - \phi_c(x), w_{\text{end}}(x)), \quad [\text{S2}]$$

$$\partial_t w_{\text{side}}(x) = g(\phi(x), w_{\text{side}}(x)), \quad [\text{S3}]$$

$$\partial_t w_{\text{end}}(x) = g(\phi(x) - \phi_c(x), w_{\text{end}}(x)), \quad [\text{S4}]$$

where $\kappa = \ell g_{\text{GJ}}/\sigma_{\text{cyt}}$ is a nondimensional parameter comparing gap-junctional and cytosolic conductances.

Of particular importance for our multiscale model is the nonephaptic version of these equations, corresponding to their behavior as $R_c \rightarrow 0$. In this limit, $\phi_c(x) \equiv 0$, $w_{\text{side}}(x) = w_{\text{end}}(x)$, and $I_{\text{ion,side}}$ and $I_{\text{ion,end}}$ must be combined into a single I_{ion} , simplifying Eqs. S1–S4 to the nonephaptic macroscale model, Eqs. 8 and 9, given in the main text.

Numerical Methods. In this section we present a discretization of our multiscale model, adaptivity criteria, operators for transferring the state variables from one dynamically constructed grid to another, and a simple second-order accurate time-stepping method for the semidiscrete equations.

Nonuniform gridding and notation. Consider a linear strand of myocytes partitioned into blocks of m cells. To avoid confusion, we refer to biological cells as myocytes and computational cells of our macroscopic finite volume method as blocks. As depicted in Fig. 2, we choose the ends of blocks to align exactly with the ends of myocytes. At any instant in time, each block is either resolved or unresolved, as per the adaptivity criteria detailed below. If unresolved, the m myocytes therein are represented by a single node. At this node, the stored potential and gating variables represent an average value over the m myocytes. If resolved, a block has n interior nodes and two boundary nodes for each of the m myocytes therein. At interior nodes, intracellular potential and gating variables for the side membranes are stored. At boundary nodes, intracellular potential and gating variables for the end membranes are stored. Let $\Delta x_{\text{macro}} = m\ell$ and $\Delta x_{\text{micro}} = \ell/n$ be the grid spacings in the unresolved and resolved regions, respectively.

If the i th block is resolved, let $\phi_{j,k}^i$ represent the potential corresponding to the k th node within the j th myocyte of the i th block. This node corresponds to the physical position

$x = (k - \frac{1}{2})\Delta x_{\text{micro}}$ within the j th myocyte. Here, $1 \leq j \leq m$ and $1 \leq k \leq n$. For convenience, we use $k = 1/2$ and $k = n + 1/2$ to denote quantities defined at the left and right ends of cells, respectively. The notation for w is identical. We also define potentials for $k = 0$ and $k = n + 1$, which correspond to ghost nodes that are used to impose Neumann boundary conditions at the ends of the cells. These values are defined via linear extrapolation of the interior and boundary values, i.e., $\phi_{j,0}^i := 2\phi_{j,1/2}^i - \phi_{j,1}^i$ and $\phi_{j,n+1}^i := 2\phi_{j,n+1/2}^i - \phi_{j,n}^i$, respectively.

If the i th block is unresolved, let ϕ^i and w^i represent the potential and the gating variables at the single node within that block. To simplify the presentation of the discrete equations, we sometimes refer to the potential within the i th block as $\phi_{j,k}^i$ even when block i is unresolved. In this case, $\phi_{j,k}^i := \phi^i$.

To refer to neighboring myocytes, we define $\phi_{0,k}^i := \phi_{m,k}^{i-1}$ and $\phi_{m+1,k}^i := \phi_{1,k}^{i+1}$. Note that if block $i - 1$ is unresolved, then $\phi_{0,k}^i = \phi^{i-1}$. Likewise, if block $i + 1$ is unresolved, then $\phi_{m+1,k}^i = \phi^{i+1}$.

Semidiscretized equations. The semidiscretized equations are described, block by block, as follows:

If the i th block is resolved, then

$$C\partial_t\phi_{j,k}^i = \frac{A\sigma_{\text{cyt}}}{S} \frac{\phi_{j,k-1}^i - 2\phi_{j,k}^i + \phi_{j,k+1}^i}{\Delta x_{\text{micro}}^2} - I_{\text{ion,side}}(\phi_{j,k}^i, w_{j,k}^i) \quad [\text{S5}]$$

for $1 \leq k \leq n$,

$$C\partial_t(\phi_{j,1/2}^i - \phi_{c,j-1}^i) = \sigma_{\text{cyt}} \frac{\phi_{j,1}^i - \phi_{j,1/2}^i}{\Delta x_{\text{micro}}/2} - g_{\text{GJ}}(\phi_{j,1/2}^i - \phi_{j-1,n+1/2}^i) - I_{\text{ion,end}}(\phi_{j,1/2}^i - \phi_{c,j-1}^i, w_{j,1/2}^i), \quad [\text{S6}]$$

$$C\partial_t(\phi_{j,n+1/2}^i - \phi_{c,j}^i) = \sigma_{\text{cyt}} \frac{\phi_{j,n}^i - \phi_{j,n+1/2}^i}{\Delta x_{\text{micro}}/2} - g_{\text{GJ}}(\phi_{j,n+1/2}^i - \phi_{j+1,1/2}^i) - I_{\text{ion,end}}(\phi_{j,n+1/2}^i - \phi_{c,j}^i, w_{j,n+1/2}^i), \quad [\text{S7}]$$

$$\partial_t w_{j,k}^i = g(\phi_{j,k}^i, w_{j,k}^i) \quad \text{for } 1 \leq k \leq n, \quad [\text{S8}]$$

$$\partial_t w_{j,1/2}^i = g(\phi_{j,1/2}^i - \phi_{c,j-1}^i, w_{j,1/2}^i), \quad [\text{S9}]$$

$$\partial_t w_{j,n+1/2}^i = g(\phi_{j,n+1/2}^i - \phi_{c,j}^i, w_{j,n+1/2}^i), \quad [\text{S10}]$$

$$\phi_{c,j}^i = \begin{cases} \sigma_{\text{cyt}} R_c \mathcal{A} \left(\frac{\phi_{j,n}^i - \phi_{j,n+1/2}^i}{\Delta x_{\text{micro}}/2} + \frac{\phi_{j+1,1}^i - \phi_{j+1,1/2}^i}{\Delta x_{\text{micro}}/2} \right), & \text{or} \\ 0 \end{cases} \quad [\text{S11}]$$

where the top entry of the braces in Eq. S11 is used if both biological cells adjacent to the (i,j) th cleft are resolved. Eq. S5 is a second-order accurate discretization of the partial differential

equation, Eq. 1, and Eqs. S6 and S7 are second-order accurate discretizations of the boundary conditions, Eqs. 2 and 3. Note that the coupling to neighboring unresolved blocks is contained in the gap-junctional terms in Eqs. S6 and S7. We remark that in our model, cleft potentials can be nonzero only when both neighboring myocytes to a given cleft are resolved. Specifically, the clefts at the leftmost and rightmost ends of a contiguous block of resolved cells are set to have zero potential.

If the i th block is unresolved, then

$$C\partial_t\phi^i = \frac{1}{S\ell + 2A} \frac{\ell}{\Delta x_{\text{macro}}} \times \left(\left\{ \begin{array}{l} A\sigma_{\text{cyt}} \left(1 - \frac{1}{1+\kappa}\right) \frac{\phi^{j-1} - \phi^j}{\Delta x_{\text{macro}}} \\ Ag_{\text{GJ}}(\phi_{m,n+1/2}^{j-1} - \phi^j) \end{array} \right\} + \left\{ \begin{array}{l} A\sigma_{\text{cyt}} \left(1 - \frac{1}{1+\kappa}\right) \frac{\phi^{j+1} - \phi^j}{\Delta x_{\text{macro}}} \\ Ag_{\text{GJ}}(\phi_{1,1/2}^{j+1} - \phi^j) \end{array} \right\} \right) - I_{\text{ion}}(\phi^j, w^j), \quad \text{[S12]}$$

$$\partial_t w_i = g(\phi_i, w_i), \quad \text{[S13]}$$

where the top entry of each brace is used if the appropriate neighboring block is unresolved and the bottom entry is used if that neighboring block is resolved.

Adaptivity criteria. In our adaptive multiscale model, we choose to resolve the i th block if certain “feature detection” criteria are met. Specifically, block i is resolved if

$$|\max_{j,k} -\min\{\phi_{m,n+1/2}^{j-1}, \phi_{j,k}^j, \phi_{1,1/2}^{j+1}\}| > 10 \text{ mV}, \quad \text{or} \quad \text{[S14]}$$

$$\max_j |\phi_{c,j}^j| > 1 \text{ mV}. \quad \text{[S15]}$$

That is, blocks are resolved if the gradient of potential is steep enough or if there is a nontrivial cleft potential. We also resolve blocks immediately neighboring those selected by the rules above. We leave all other blocks unresolved. These criteria were chosen so that sharp wave fronts are preferentially resolved. In our simulations, the nonuniform grid is regenerated between, but not within, each time step.

Interpolation and restriction operators. When the adaptivity criteria prescribe that an unresolved block should subsequently be resolved, the values of the potential and gating variables at the new grid points are set to be equal to those of the previously unresolved block. Note that this simple interpolation procedure results in all clefts in the interior of the newly resolved block having potential 0 mV. Likewise, when the adaptivity rule prescribes a resolved block should subsequently be unresolved, the variables are restricted onto the coarser grid through simple averaging.

Time stepping. In all simulations, potentials and gating variables are updated using a second-order accurate Strang operator-splitting scheme with $\Delta t = 5 \cdot 10^{-4}$ ms. All spatial derivatives, describing cytoplasmic and gap-junctional coupling, are treated implicitly via the Crank–Nicolson method, and all reaction terms, describing the ion channel dynamics, are treated via the explicit trapezoidal rule, an explicit second-order Runge-Kutta method.

1. Hand P, Peskin C (2010) Homogenization of an electrophysiological model for a strand of cardiac myocytes with gap-junctional and electric-field coupling. *Bull Math Biol* doi:10.1007/s11538-009-9499-2.