Emergence of Deterministic Calcium Dynamics from Spatially Coupled Stochastic Microdomains in Cardiac Myocytes

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Abstract

Recent multiscale models of cardiac calcium dynamics have demonstrated that stochastic channel behavior can be captured using aggregated calcium release units (CaRUs), bridging subcellular variability and whole-cell responses. However, such mean-field approaches do not explicitly resolve spatial interactions between microdomains, limiting their ability to assess how local stochastic dynamics give rise to coherent global behavior. In this work, we introduce a two-dimensional spatial extension of a previously validated Scalable Aggregate Calcium Release Unit (SACaRU) framework, enabling explicit modeling of diffusion-mediated coupling between calcium release sites. The cell is represented as a 2D network of coupled units, each incorporating stochastic Markov Chain formulations for L-type Calcium Channels (LCCs) and Ryanodine Receptors (RyRs) within a modified human ventricular electrophysiological model. The computational strategy combines domain decomposition and operator splitting. Local stochastic dynamics are independently solved for each unit using a binomial tau-leaping scheme, while a global diffusion step updates cytosolic calcium concentrations and mediates coupling between neighboring units. This approach is implemented in parallel, allowing efficient simulation of large spatial networks while preserving stochastic fidelity at the subcellular level. Simulations demonstrate that diffusion-mediated coupling promotes synchronization across calcium release units, leading to the emergence of deterministic-like global calcium dynamics despite intrinsically stochastic local behavior. This transition is accompanied by a marked reduction in variability and recovers coherent whole-cell calcium transients consistent with previously reported multiscale behavior. This work extends mean-field multiscale models by incorporating explicit spatial structure, providing a scalable framework to investigate how microdomain coupling shapes the emergence of global cardiac dynamics and enabling future studies in physiologically realistic geometries.

1. Introduction

Cardiac excitation–contraction coupling depends on the tightly regulated dynamics of intracellular calcium (Ca^{2+}). Following membrane depolarization, L-type calcium channels (LCCs) provide a trigger for the opening of clustered ryanodine receptors (RyRs), resulting in calcium-induced calcium release (CICR) from the sarcoplasmic reticulum (SR). LCCs and RyRs are organized in localized calcium release units (CaRUs), where the interaction of a small number of channels gives rise to stochastic calcium release events, including calcium sparks and calcium waves [1–4]. These local events are spatially distributed throughout the myocyte and collectively determine the global calcium transient and electrophysiological response.

Computational cardiac models have traditionally described whole-cell calcium handling using deterministic formulations, in which ionic currents and intracellular concentrations represent population averages [5, 6]. Such models efficiently reproduce macroscopic electrophysiological behavior but do not explicitly represent fluctuations arising from the stochastic gating of individual channels. Conversely, stochastic subcellular models represent CaRUs containing relatively small numbers of LCCs and RyRs and can reproduce local calcium-release phenomena and their spatial interactions through calcium diffusion [7, 8]. The computational cost of simulating large numbers of spatially coupled stochastic units, however, remains a major challenge for multiscale whole-cell modeling [4].

An important question is therefore how stochastic dy-

namics at the microdomain scale give rise to the apparently deterministic behavior observed at the cellular scale. In previous work, we developed a Markov Chain (MC)-based formulation of the L-type calcium current and incorporated it into the human ventricular model of ten Tusscher and Panfilov [6, 9]. More recently, this formulation was extended to a Scalable Aggregate Calcium Release Unit (SA-CaRU), allowing the number of LCCs and RyRs to be systematically varied within a single stochastic unit. This model demonstrated a transition from stochastic to deterministic-like calcium dynamics as the effective number of channels increased, with deterministic-like behavior emerging around $O(10^2)$ LCCs under control conditions [10].

However, the SA-CaRU represents an aggregate, mean-field description in which spatially separated CaRUs are not explicitly resolved. The present work extends this framework to a two-dimensional spatial network of 16×16 CaRUs, preserving stochastic LCC and RyR dynamics within each unit while introducing calcium-diffusion coupling between neighboring units. The resulting model allows us to investigate whether coherent deterministic-like whole-cell dynamics can emerge from spatially distributed CaRUs that remain intrinsically stochastic at the local scale. We further employ a parallel computational strategy to make the simulation of the coupled network tractable.

2. Methods

The proposed framework extends the previously developed stochastic CaRU formulation [10] to a spatially distributed network of coupled units. The underlying human ventricular electrophysiological model and stochastic formulations for LCCs and RyRs, including the Markov Chain and binomial τ-leaping approaches, are retained from previous studies [6, 9, 10] and are therefore not described in detail here. The present work focuses on the spatial organization of the CaRUs, calcium-diffusion coupling between neighboring units, and the parallel computational implementation.

2.1. Two-Dimensional Spatial Model

The stochastic CaRU was extended to a two-dimensional 16×16 grid, resulting in 256 spatially coupled CaRUs. Each unit contains four LCCs and 20 RyRs, yielding a total of 1024 LCCs and 5120 RyRs across the network. Thus, the same total numbers of LCCs and RyRs used in the aggregate formulation are preserved, while the channels are distributed among spatially distinct and intrinsically stochastic CaRUs.

Calcium coupling between neighboring units is introduced through diffusion in the intracellular ($[Ca]_i$), subspace ($[Ca]_{ss}$), and sarcoplasmic reticulum ($[Ca]_{SR}$) compartments. For each compartment, the local calcium dynamics are augmented by a diffusion term,

$$\frac{\partial [Ca]}{\partial t} = F([Ca], t) + D\nabla^2 [Ca]_{free}, \qquad (1)$$

where $[Ca]$ denotes the total calcium concentration and only the free fraction $[Ca]_{free}$ contributes to diffusion. $F([Ca], t)$ represents the local calcium fluxes and D is the corresponding diffusion coefficient. The spatial Laplacian is discretized using a finite-difference scheme with $\Delta x = \Delta y = 0.5$ μm. Neumann boundary conditions are applied at the boundaries of the spatial domain.

This formulation couples neighboring stochastic CaRUs through calcium exchange while preserving the local stochastic dynamics of each unit.

Figure 1 illustrates the spatially coupled network, where each CaRU exhibits stochastic local dynamics and exchanges calcium with its neighboring units.

2.2. Numerical and Parallel Implementation

The coupled electrophysiological and calcium-diffusion equations were solved using the explicit Euler method with a time step of $\Delta t = 10^{-3}$ ms. The spatial domain was discretized with $\Delta x = \Delta y = 0.5$ μm, with diffusion coefficients set to $D_i = D_{ss} = 0.4$ μm^2/ms and $D_{SR} = 0.12$ μm^2/ms [11]. The diffusion terms were evaluated using the finite-difference formulation described above.

To reduce the computational cost of simulating multiple stochastic CaRUs, the model was implemented using the Message Passing Interface (MPI). The local dynamics of individual CaRUs were distributed among processing cores and solved concurrently. After each local integration step, calcium concentrations were exchanged between neighboring units and the diffusion terms were evaluated to update the coupled system. This procedure was repeated throughout the simulation, preserving the stochastic dynamics of each CaRU while enabling parallel computation of the complete 16×16 network.

2.3. Computational Experiments

The spatially distributed model was evaluated using a 16×16 network comprising 256 stochastic CaRUs, with four LCCs and 20 RyRs per unit, corresponding to a total of 1024 LCCs and 5120 RyRs. To assess the emergence of global deterministic behavior, this configuration was compared with a single aggregate CaRU containing the same total number of LCCs and RyRs. Thus, the comparison preserves the overall LCC population while changing its spatial organization from an aggregated representation to a network of locally stochastic units.

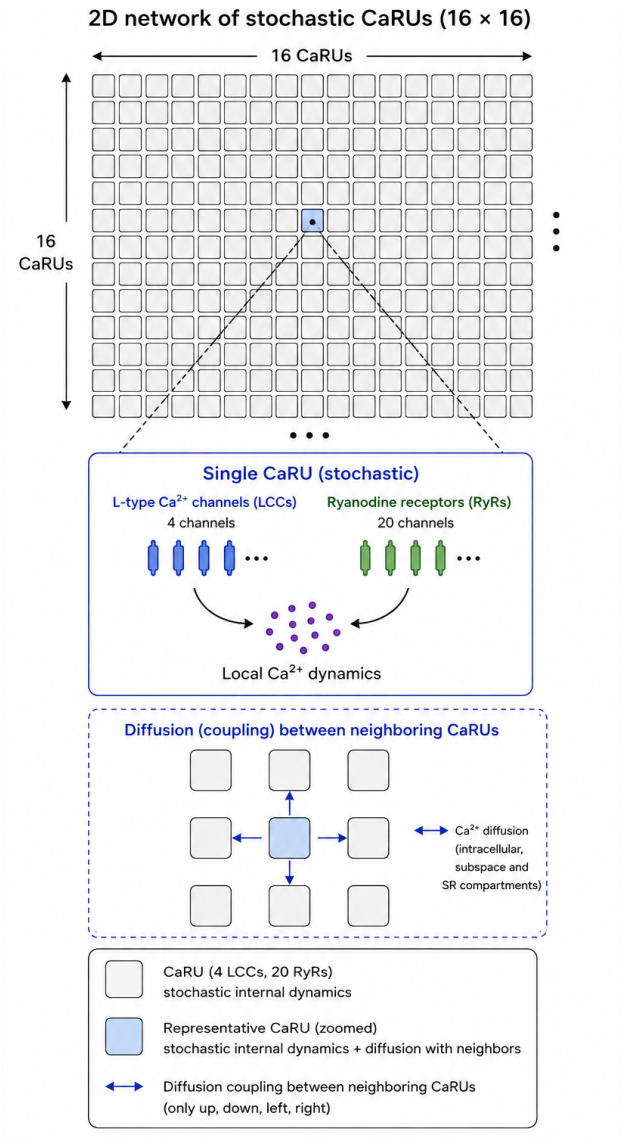

Figure 1. Two-dimensional network of 256 stochastic CaRUs coupled by calcium diffusion between neighboring units.

For each configuration, 50 stochastic realizations were simulated under 1-Hz pacing and compared with the corresponding deterministic reference model. The action potential (AP), intracellular free calcium concentration ($[Ca]_i^{free}$), L-type calcium current (I_{CaL}), and sarcoplasmic reticulum calcium release current (I_{rel}) were evaluated. The spatially distributed simulations were used to determine whether diffusion-mediated coupling between locally stochastic CaRUs could recover coherent whole-cell dynamics consistent with the deterministic formulation.

3. Results

The results evaluate whether diffusion-mediated coupling of spatially distributed stochastic CaRUs can recover coherent whole-cell dynamics. The 16×16 spatial model is compared with the aggregate and deterministic references while preserving the same overall LCC and RyR populations, allowing the effect of spatially distributed local stochasticity on global cellular behavior to be assessed.

3.1. Emergence of Deterministic Whole-Cell Dynamics

The spatially coupled 16×16 model was compared with an aggregate 1×1 CaRU containing the same total population of 1024 LCCs and 5120 RyRs. While the aggregate configuration concentrates all channels in a single unit, the spatial model distributes them among 256 CaRUs, with four LCCs and 20 RyRs per unit.

Figure 2 shows the whole-cell responses obtained from the 50 stochastic realizations of the spatial model, together with the aggregate stochastic and deterministic references.

Despite the strong stochasticity of the individual CaRUs, the spatially coupled network produces coherent whole-cell responses that closely follow the deterministic reference. This behavior is observed in the action potential (AP), free intracellular calcium concentration ($[Ca]_{i_{free}}$), L-type calcium current (I_{CaL}), and sarcoplasmic reticulum calcium release current (I_{rel}). Thus, distributing the same overall channel population across spatially coupled stochastic microdomains recovers deterministic-like whole-cell dynamics while retaining local stochasticity.

4. Discussion and Conclusions

The results extend the previously developed stochastic CaRU framework by showing that deterministic-like whole-cell dynamics can emerge from spatially distributed stochastic units. Unlike the aggregate formulation, where a large channel population is represented within a single CaRU, the proposed model distributes the same LCC and RyR populations across 256 units, each retaining substantial local stochasticity. The results indicate that diffusion-mediated coupling between spatially distributed stochastic microdomains is sufficient to recover coherent deterministic-like whole-cell dynamics.

This spatial formulation provides a computational link between stochastic calcium dynamics at the microdomain scale and whole-cell electrophysiology. The parallel implementation facilitates the simulation of larger spatial networks while preserving the stochastic dynamics of individual CaRUs. Future work will extend the framework toward more physiologically realistic cellular geometries and heterogeneous spatial organization.

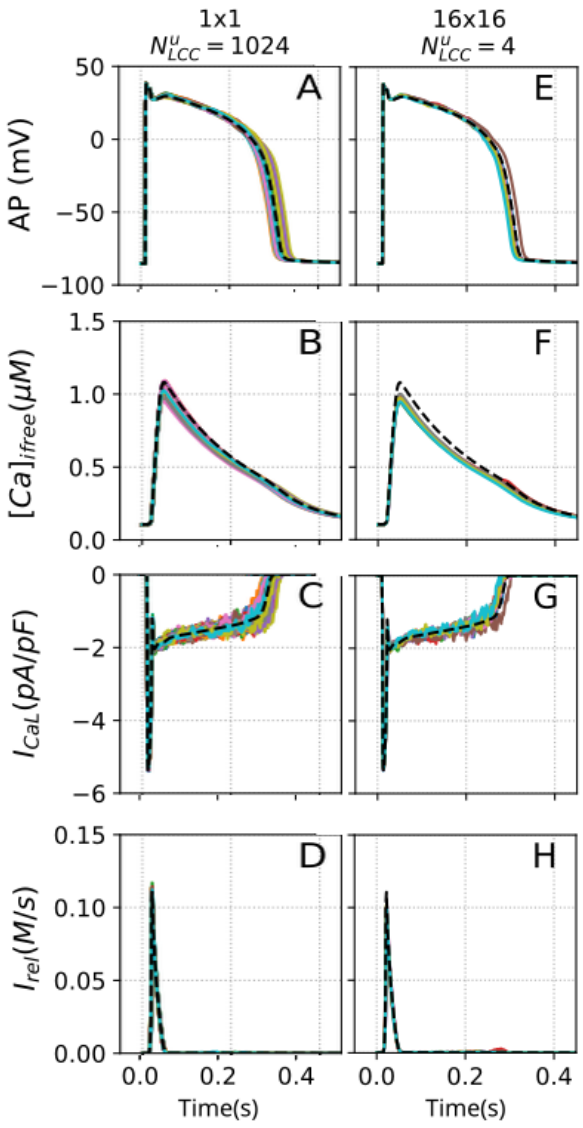

Figure 2. Whole-cell responses for the aggregate 1×1 CaRU (1024 LCCs) and spatially coupled 16×16 network (4 LCCs/CaRU). Colored curves show 50 stochastic realizations; the black line shows the deterministic reference.

In conclusion, the proposed two-dimensional model demonstrates that coherent deterministic-like cellular dynamics can emerge from the diffusion-mediated coupling of locally stochastic CaRUs, providing a scalable framework for investigating the multiscale organization of cardiac calcium dynamics.

Acknowledgments

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