Hybrid Stochastic and Deterministic Simulations of Calcium Blips

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ABSTRACT Intracellular calcium release is a prime example for the role of stochastic effects in cellular systems. Recent models consist of deterministic reaction-diffusion equations coupled to stochastic transitions of calcium channels. The resulting dynamics is of multiple time and spatial scales, which complicates far-reaching computer simulations. In this article, we introduce a novel hybrid scheme that is especially tailored to accurately trace events with essential stochastic variations, while deterministic concentration variables are efficiently and accurately traced at the same time. We use finite elements to efficiently resolve the extreme spatial gradients of concentration variables close to a channel. We describe the algorithmic approach and we demonstrate its efficiency compared to conventional methods. Our single-channel model matches experimental data and results in intriguing dynamics if calcium is used as charge carrier. Random openings of the channel accumulate in bursts of calcium blips that may be central for the understanding of cellular calcium dynamics.

INTRODUCTION

Calcium signaling regulates numerous cellular functions as diverse as gene expression, secretion, muscle contraction, and synaptic plasticity. A major class of Ca^{2+} signals are triggered by the binding of extracellular ligands to cell surface receptors, resulting in the activation of well-known second messenger pathways (1–5) to evoke Ca^{2+} release from intracellular storage compartments—principally the endoplasmic reticulum (ER) and the sarcoplasmatic reticulum. Information is encoded in the spatiotemporal patterning of the resulting increases in cytosolic Ca^{2+} concentration, which may be organized as localized transients (6), propagating waves (7–11), and global oscillations (1,12–15).

Inositol 1,4,5-trisphosphate (IP_3) receptor channels (IP_3R) are present in the ER membrane and regulate the liberation of Ca^{2+} in response to the binding of Ca^{2+} and IP_3 to receptor sites on the channel: that is to say, the open probability of the IP_3R channel depends on the cytosolic calcium concentration as well as the IP_3 concentration (see (16–19) for reviews). This feedback provides a self-amplifying release mechanism (calcium-induced calcium release), so that the calcium flux increases nonlinearly with concentrations of IP_3 and Ca^{2+}. In particular, Ca^{2+} released by one channel diffuses in the cytosol and thus increases the open probability of neighboring channels, thereby enabling complex spatiotemporal signals.

Experimental observation of local, random release events called ''puffs'' indicates that IP_3R channels are grouped into clusters on the ER membrane containing a few tens of channels (20–23), whose opening is concerted by local diffusion of Ca^{2+} and calcium-induced calcium release between adjacent channels. These clusters in turn are randomly distributed across the ER membrane at spacings of a few micrometers. Puffs are now considered to be elemental events of Ca^{2+} signaling (24), underlying global oscillations and waves. Subsequent theoretical studies demonstrated that the observed local calcium elevations are not random due to the small numbers of Ca^{2+} ions, but rather due to the random binding and dissociation of Ca^{2+} and IP_3 at the regulatory binding sites of the IP_3R (see (11,25–29) and (30) for the ryanodine receptor channel).

It is therefore important for the understanding of calcium signaling, to develop accurate models for stochastic transitions of single channel states. The available experimental data are of two categories: First, there are patch-clamp experiments of single channel currents. IP_3Rs are inserted into bilayer membranes or are studied in the nuclear membrane and exposed to fixed concentrations of Ca^{2+} and IP_3. It is crucial to note that in these experiments a charge carrier different from calcium is used, so that the ions moving through the channel do not bind to receptor sites on the channel and thereby modify the channel gating. Recordings of single-channel currents are then analyzed to obtain, for instance, open probabilities, mean open and mean close times. Several IP_3R models (31–36) have been developed to describe experimental data obtained from IP_3Rs reconstituted in bilayer membranes, with the De Young-Keizer model (32) in particular being widely applied. However, there are significant differences in behavior of the reconstituted IP_3Rs versus that of IP_3Rs in their native environment of the nuclear envelope (37,38), and only a few models have incorporated IP_3R data obtained for the latter (39,40). On the other hand, models that do exist for nuclear receptors are not dynamic

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models, i.e., they cannot elucidate channel kinetics. Therefore, we have developed a DeYoung-Keizer-like model based on data obtained from patch-clamp of nuclear IP_3Rs that consistently reproduces experimental data (41). The model comprises four identical, independent subunits, each with nine different states. A channel opens when at least three of its subunits undergo a conformational change to an active state after binding IP_3 and Ca^{2+}.

In a second type of experiment, one studies IP_3R channels under physiological conditions in intact cells by using fluorescent indicator dyes to monitor Ca^{2+} liberation into the cytosol. The resolution of such imaging techniques is sufficient to detect presumptive single-channel signals (christened ''blips'') (6,21), but it is difficult to study these events in isolation because the opening of one channel usually triggers openings of multiple adjacent channels in the cluster (42). Because the blips form the smallest fundamental building block from which cellular calcium signals are generated, it is important to understand the behavior of IP_3Rs under physiological conditions where the gating of an individual channel is modulated by the large ($>$1000-fold) changes in local Ca^{2+} concentration that result from Ca^{2+} flux through that channel.

To that end, we simulate stochastic IP_3R channel state dynamics under conditions of no Ca^{2+} feedback (K^+ as the charge carrier), and where Ca^{2+} is the charge carrier. The latter events we refer to as ''blips with calcium carrier.'' The transitions during a patch-clamp experiment (i.e., no Ca^{2+} feedback) can be simulated by a Markovian scheme with constant transition rates. A standard method (two-state Markovian scheme) is to compile a list of all transitions of the channel in models such as the DYK, and fix a sufficiently small time-step *dt*. The occurrence of each of the stochastic transitions during a specific simulation time step is determined by comparison of a computer random number with the product of the corresponding rate and *dt* (27,43). Another, much more efficient method, is the so-called Gillespie algorithm, which determines the time of each transition by using one random number, while a second random number is used to determine the specific next reaction that is to occur (44). Thus, it needs as many steps (and twice as many random numbers) as transitions occurring, which is far less than for the standard method.

While the Gillespie method provides an efficient means for the study of stochastic channel transitions, the simulation of blips with calcium carrier poses a number of additional problems, which we will briefly outline.

1. The spatiotemporal evolution of free calcium and calcium-binding buffers needs to be simulated simultaneously with the evolution of channel states. In this work, we consider the diffusion and chemical reactions of these species as deterministic processes. This strategy should be principally proven by simulating the full system stochastically and comparing the results with those from the reduction approach. In view of the large number of calcium ions and buffer proteins our assumption is, however, generally accepted (35,43,45) and we will not address its validity in the current publication.
2. The spatial extent of a channel is ~10–30 nm. Strong currents of calcium through the membrane lead to very localized calcium concentrations around an open channel. On the other hand, released calcium diffuses rapidly over distances of several micrometers. To cope with the resulting range of length scales we chose the finite element method and resolve the calcium profile at nanometer scales close to the channel mouth, while utilizing larger and computationally more tractable grid lengths far from the channel.
3. The timescale of calcium flux upon opening of a channel is in microseconds. This timescale cannot be ignored since the binding of calcium to the channel can occur on timescales as short as tens of microseconds. However, simulations need to trace the evolution for many seconds to achieve statistically significant estimates of stochastic channel gating. This gap of timescales necessitates an efficient time-stepping method including time adaptivity for both the stochastic and deterministic equations of our model.
4. A fourth problem, which is at the focus of this article, is that huge and fast concentration changes upon channel openings and closings have a strong impact on the stochastic dynamics of channel binding and unbinding. As mentioned above, the rate of calcium binding may increase by three orders of magnitude upon channel opening owing to the enormous local calcium concentration increase. This implies that the classical Gillespie algorithm, which rests on the assumption of time-independent rates between succeeding stochastic events, cannot be used. Instead, we chose a special, so-called hybrid method to couple stochastic and deterministic simulations. This method was described recently for ordinary differential equations (ODEs) coupled to Markov processes (46,47) and allows for an adaptive step-size integration of the deterministic equations while at the same time accurately tracing the stochastic reaction events.

In this article, we describe the application of the hybrid method introduced by Alfonsi et al. (46) to the calcium system and thus for the first time, to our knowledge, to a spatially extended system described by partial differential equations (PDEs). A second novelty of our approach is the following: The hybrid method assumes that all stochastic events cause a change in the deterministic variables, which is not the case in the Ca^{2+} system. A special feature of the Ca^{2+} system is that the binding/unbinding of Ca^{2+} ions and IP_3 may not change the open/close state of a channel. Therefore, we devised a new hybrid method by combining the adaptive simulation scheme of the deterministic reaction-diffusion dynamics and the simulation technique for stochastic