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Invited Review

Neuronal modeling with intracellular calcium signaling

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Abstract: Cytosolic Ca^{2+} ions play an important role in the regulation of numerous aspects of cellular activity in virtually all cell types. There is a complex interaction between the neuronal electrical signals on plasma membrane and the chemical signals of intracellular calcium. Each neuron can be considered as a binary membrane system with plasma membrane and endoplasmic reticulum membrane, and the neuronal endoplasmic reticulum can be regarded as a neuron-within-a-neuron. This review explores the simulation modeling of neuronal dynamics mutually coupled with the intracellular calcium signaling released from endoplasmic reticulum through the inositol 1,4,5-trisphosphate receptor calcium channels. We show that a current trend is to include the intracellular calcium dynamics into the neuronal models, and the frontier of this research is now shifting to spatial neuronal models with diffusing intracellular calcium. It is expected that more important results will be obtained with the neuronal models incorporating the intracellular calcium dynamics, especially the spatial models considering the calcium diffusion both in soma and dendritic branches.

Key words: neuron; channel; calcium signals; noise; network

胞内钙信号作用的神经模型

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摘 要：细胞溶质内的游离钙离子在许多细胞活动中发挥着重要的作用。对于神经元，细胞膜上的神经电信号和胞内钙离子化学信号之间有着复杂的相互作用，每个神经元都可看作为一个含有细胞膜和内质网膜的双膜系统，而神经细胞的内质网则可视为神经元内的神经元。本综述探讨了神经元膜上神经电信号与内质网钙通道释放的胞内钙信号相耦合的动力学模型。我们认为，计算神经动力学的一个研究方向是考虑包含胞内钙动力学的神经元模拟，而且该研究前沿转向考虑胞内钙波扩散运动的空间神经元模型。包含内质网钙动力学的神经模型，尤其是考虑胞体和树突内钙扩散的空间神经元模型，将加深我们对神经动力学的认识。

关键词：神经元；离子通道；钙信号；噪音；网络
中图分类号：Q421；Q422；Q424；O415.6；O414.22

Cytosolic Ca^{2+} ions play an important role in the regulation of numerous aspects of cellular activity in virtually all cell types [1−5]. This versatility arises through the diverse mechanisms by which Ca^{2+} signals are modulated to act over very different time and distance scales. Neurons use both extracellular and intracellular calcium signals to regulate a great variety of neuronal processes, including excitability, associativity, neurotransmitter release, synaptic plasticity, and gene transcription [2]. A well established mechanism is the regulation of the external calcium influx through voltage-gated calcium channels or ligand-gated ion channels. For example, at synaptic junctions the voltage-gated channels are used to trigger the release of neurotransmitter and to contrib-

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ute to dendritic action potentials. At postsynaptic sites, the neurotransmitters can induce a calcium influx using ligand-gated channels such as the NMDA receptors [6–8].

Although much is known about the influx regulation of external calcium, there is less study on the mechanisms and roles of the intracellular calcium released from the internal calcium stores, such as the endoplasmic reticulum (ER) in neurons [9]. The ER is a continuous network distributed throughout the neuron, including the soma, dendrite and axon, as a high calcium concentration store. Throughout the ER the inositol 1,4,5-trisphosphate receptors (IP_3R) or ryanodine receptors (RyR) are distributed [10,11]. These receptor channels are responsible for releasing calcium ions from the ER upon the binding of calcium ions on the receptors.

As a result, there is a mutual interaction between the neuronal electrical signals on plasma membrane and the chemical signals of intracellular calcium. The extracellular Ca^{2+} influx during a neuronal action potential can cause the opening of IP_3R or RyR channels to release calcium ions from ER [10,11]. The changes of calcium concentrations in cytosol or ER will modulate the various calcium activated channels on plasma membrane and affect the neuronal excitability [12]. In recent years, there is an increasing interest for neuron modelers to simulate the interaction among the neuronal electrical signals and intracellular calcium signals. This review explores the simulation modeling of neuronal dynamics modulated by the intracellular calcium released from ER IP_3R channels.

1 The concept of neuron-within-a-neuron

Entry of external Ca^{2+} through voltage-operated or receptor-operated channels plays a major role in neuronal activities, but there also is an important contribution of Ca^{2+} released from the ER. The ER is a continuous membrane network that extends throughout the neuron (Fig. 1). The ER maintains a large concentration gradient of Ca^{2+} that can be released in a regenerative manner, thus allowing information to spread long distances through Ca^{2+} waves. This regenerativity is mediated by either IP_3R or RyR, which displays a process of Ca^{2+}-induced Ca^{2+} release. One of the important factors determining the sensitivity of these two Ca^{2+} channels is the content of Ca^{2+} in the ER lumen. During a neuronal spike, the Ca^{2+} that enters from the outside is taken up by the ER, which then becomes primed, i.e., the IP_3Rs and the RyRs become sufficiently sensitive to release the accumulated Ca^{2+} back into the cytosol. In effect, the ER provides a short-term memory of neural activity by integrating the brief Ca^{2+} pulses associated with each discharge. When the accumulated Ca^{2+} reaches the critical threshold for regenerative release, the large explosive and global release of Ca^{2+} could provide the neuron with information concerning previous levels of neuronal activity.

Indeed, the ER network has many properties resembling those of the plasma membrane. Both systems are highly nonlinear. The ER rapidly integrates large amounts of excitatory and inhibitory inputs and triggers an action potential when the membrane potential declines below a critical threshold. Likewise, the excitability of the ER membrane is highly variable and also has to reach a critical threshold before it will elicit a regenerative Ca^{2+} wave. These two membranes are intimately tied together through a variety of reciprocal interactions to regulate specific neuronal processes such as excitability, associativity, transmitter release, synaptic plasticity, and gene transcription [6–8].

Thus, both structurally and functionally the ER may be considered as ‘a neuron-within-a-neuron’. The concept of a neuron-within-a-neuron was first suggested by Berridge in 1998 [2]. The basic idea is that neuronal Ca^{2+} signaling depends upon a binary membrane system, i.e. the outer plasma membrane and the internal ER membrane (Fig. 1). The outer plasma membrane integrates external information (e.g. excitatory and inhibitory inputs) and generates fast propagating action potentials using voltage-dependent Na^+ and Ca^{2+} channels. The ER system monitors internal signals, e.g. Ca^{2+} and the inositol 1,4,5-trisphosphate (IP_3) messengers, and can produce slowly propagating regenerative Ca^{2+} signals using a conduction system based on the IP_3Rs.

2 Release of calcium from ER store

In many cells ER stores are the primary source of Ca^{2+} ions. The IP_3R channel opens upon the binding of both Ca^{2+} ion and IP_3, a messenger generated in response to binding of numerous extracellular ligands to Gq- and tyrosine-kinase-coupled cell-surface receptors [10]. Cells have developed an active Ca^{2+} propagation mechanism, involving Ca^{2+}-induced Ca^{2+} release, by which diffusing Ca^{2+} ions released from an open channel can bind to nearby IP_3R channels to open them, inducing more ER Ca^{2+} release. This regeneration process will be terminated because high Ca^{2+} concentrations cause

excessive Ca^{2+} binding on IP_3R channel to close the channel. Finally, cytosolic calcium declines as cellular pump process drives Ca^{2+} ions back into ER and out of the cell. Governed by such nonlinear reaction-diffusion processes, complex spatiotemporal waves of Ca^{2+} concentration are generated (Fig. 2).

At rest the cytosolic Ca^{2+} is maintained very low (50–100 nmol/L), but much higher concentrations are generated upon the opening of IP_3Rs. Ca^{2+} ions in the cytosol move by passive diffusion alone. This process

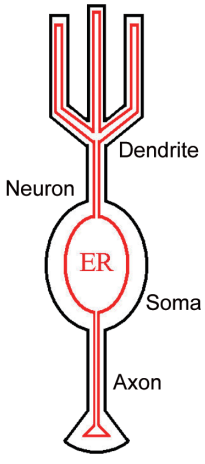

Fig. 1. Binary membrane system of neuronal Ca^{2+} signaling with the outer plasma membrane (black lines) and the internal ER membrane (red lines). The ER is a continuous network that extends to all parts of the neuron, including soma, dendrite and axon, which can be treated as a neuron-within-a-neuron.

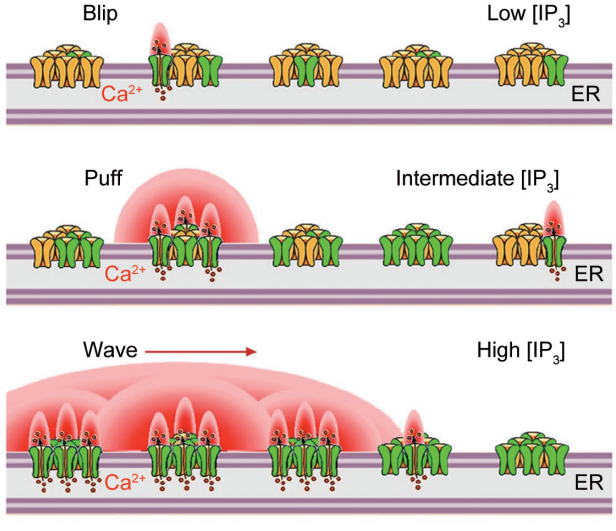

Fig. 2. The hierarchy structure of Ca^{2+} signals release from ER IP_3R channels: blips from single IP_3R, puffs from a cluster of IP_3Rs and global waves spreading through the cell. The figure which was modified from Parker *et al*., 1996 [19], is kindly provided by Prof. Ian Parker in UC Irvine.

is modified by the presence of endogenous mobile and immobile Ca^{2+} buffers that bind free Ca^{2+} and generally slow down its effective rate of diffusion, steepening Ca^{2+} microdomains around an open Ca^{2+} channel [13]. Thus, the Ca^{2+} concentration near the channel mouth may be 100 μmol/L or more, whereas concentrations as close as one or two μm fall below 1 μmol/L [3, 12, 14]. Ca^{2+} ions therefore have only a restricted "range of action", on the order of 5 μm [15]. However, the positive regulation of IP_3R by Ca^{2+} enables long-range signaling through the generation of actively propagating Ca^{2+} waves which travel at a few dozen μm/s by successive cycles of Ca^{2+} release, diffusion, and dynamics of Ca^{2+}-induced Ca^{2+} release [16, 17].

Imaging technology shows that IP_3R channels are distributed on ER membrane in highly localized clusters on hundred-nanometer scale, spaced a few micrometers apart [18–20]. Thus, the intracellular Ca^{2+} signals show a hierarchy structure (Fig. 2) [1, 17, 21, 22]. Weak activation by low IP_3 concentration evokes localized elevations of cytosolic Ca^{2+} concentration, which arises stochastically and autonomously at discrete release sites. These events are of variable size. The smallest involve Ca^{2+} flux through single IP_3R, and are called blips [23–26]. Larger events (puffs) involve concerted opening of multiple channels clustered at spacing of a few dozen nanometers within individual release sites [18, 19, 24, 25]. These puff events were first observed in *Xenopus* oocytes [18] and have now been observed in numerous other cell types, e.g. cultured tumor cells, secretory cells, and neurons [1, 27, 28], suggesting they are a ubiquitous feature of IP_3/Ca^{2+} signaling. With higher IP_3 concentration, Ca^{2+} released at one site can trigger Ca^{2+} release at adjacent sites, leading to the generation of Ca^{2+} waves that propagate in a saltatory manner [17, 24, 29].

3 Calcium-activated ion channels

Release of Ca^{2+} from the ER modulates neuronal excitability by altering Ca^{2+}-dependent ion channel currents. The Ca^{2+}-dependent ion channels include the calcium-activated potassium channels (K_{Ca}) [3, 30], store-operated calcium (SOC) channels [31], calcium-release-activated calcium (CRAC) channels [32], and calcium-dependent chloride channels (Fig. 3). As an example we simply review the K_{Ca} channels [3, 30]. We discuss the two classes of K_{Ca} channels that have distinct intrinsic affinities for Ca^{2+}, i.e. the voltage- and Ca^{2+}-activated large conductance K^+ channels (BK_{Ca}) and Ca^{2+}-activated small

conductance K^+ channels (SK_{Ca}).

BK_{Ca} channels are involved in a diversity of physiological processes ranging from regulation of smooth muscle tone to modulation of neurotransmitter release [33, 34]. BK_{Ca} channels are activated by the cooperative effects of two distinct stimuli, membrane depolarization and cytoplasmic Ca^{2+}. Both stimuli converge allosterically on the gating apparatus of the channels, with increasing Ca^{2+} concentrations shifting the activation curve from highly positive potentials (> 100 mV) into the physiological voltage range [35]. Robust activation of BK_{Ca} channels at membrane potentials around 0 mV requires values for Ca^{2+} concentration > 10 μmol/L [36], as are known to only occur in the immediate vicinity of active Ca^{2+} sources, particularly Ca_V channels.

According to the distance, there are two classes of BK_{Ca} channels in neurons: those tightly associated with Ca_V channels in Ca^{2+} nanodomains and those located more distantly from Ca^{2+} sources. The macromolecular BK_{Ca}-Ca_V complexes that physically link a Ca^{2+} source and a Ca^{2+}-dependent effector may be in the 10 nm range. Formation of macromolecular complexes between BK_{Ca} and Ca_V channels not only provides a simple mechanism for reliably delivering micromolar Ca^{2+} to BK_{Ca} channels without affecting other Ca^{2+}-dependent signaling processes, but also puts the activity of BK_{Ca} channels under tight control of the Ca_V partner. Distinct from localization in Ca^{2+} nanodomains, some

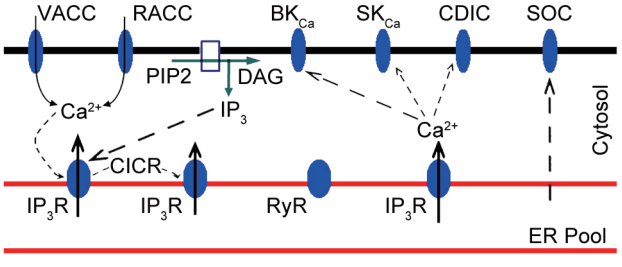

Fig. 3. Neural Ca^{2+} signaling. The extracellular Ca^{2+} ions can enter the neuron through voltage-activated Ca^{2+} channels (VACC) or receptor-activated Ca^{2+} channels (RACC). Metabotropic neurotransmitters stimulate the formation of IP_3 from PIP2, which acts on IP_3R channels to release Ca^{2+} from the ER pool. On ER membrane there are also RyR channels. Both the IP_3Rs and the RyRs are sensitive to Ca^{2+}. The process of Ca^{2+}-induced Ca^{2+} release (CICR) will set up propagated Ca^{2+} waves. The increase of intracellular Ca^{2+} alters Ca^{2+}-dependent ion channels (CDIC) on plasma membrane, including the BK_{Ca} and the SK_{Ca} channels. The store-operated calcium (SOC) channel is controlled by the Ca^{2+} concentration in ER.

BK_{Ca} channels may also be located more distant from Ca_V channels and be operated by a global increase in Ca^{2+}.

SK_{Ca} channels are widely expressed in the central nervous system (CNS), where they are important for intrinsic excitability, dendritic integration, and contributing to synaptic plasticity [37–39]. SK_{Ca} channels are gated solely by intracellular Ca^{2+} ions [40, 41]. SK_{Ca} channel activity shows a steep dependence upon Ca^{2+}. Unlike BK_{Ca} channels, where there may be a single coassembled Ca_V channel fueling a single BK_{Ca} channel, SK_{Ca} channels likely are contained within a microdomain with more than a single Ca^{2+} source providing the Ca^{2+} for SK_{Ca} channel activation. Due to their intrinsically higher Ca^{2+} sensitivity, SK_{Ca} channels may be located as far as several dozen nanometers away from the Ca^{2+} sources that are still capable of providing essential Ca^{2+} to open SK_{Ca} channels.

4 Modeling of intracellular calcium dynamics

Since the first observations of Ca^{2+} oscillations, the experimental investigation of their molecular mechanism has been accompanied by numerous modeling approaches. One of the most attractive features about models is their ability to make experimentally testable predictions. That Ca^{2+} oscillations can occur in the presence of a constant level of IP_3 and that the self-amplification of Ca^{2+} release from the ER into the cytoplasm lies at the basis of Ca^{2+} oscillations were for example first predicted theoretically [42]. However, this early model assumed that Ca^{2+} oscillations require the existence of 2 types of pools, some sensitive to IP_3 and others possessing RyR and thereby sensitive to Ca^{2+}. This turned out not to be necessary as the IP_3R is itself sensitive to both Ca^{2+} and IP_3.

Models of the IP_3R play a central role not only for understanding channel kinetics, but also as building blocks for constructing larger-scale models of cellular Ca^{2+} signaling. Several IP_3R models [43–49] have been developed to describe experimental data obtained from IP_3R reconstituted in bilayer membranes, with broad application of the De Young-Keizer model [44] in particular. However, there are significant differences in the behavior of reconstituted IP_3Rs in bilayer membrane [50] versus that of IP_3Rs in their native environment of the nuclear envelope [51, 52], and only a few models have incorporated IP_3R data obtained on nucleus membranes [52–54]. Shuai *et al.*[55] have suggested a dynamic

IP_3R model that successfully reproduces data obtained from patch-clamp recordings of nuclear IP_3Rs and is sufficiently simple. The channel model consists of four identical, independent subunits, each of which has an IP_3-binding site, together with one activating and one inactivating Ca^{2+} binding site. A feature of the model is that channel opening may occur if either three or four of the subunits of the tetramer are in an activated state, i.e. binding both IP_3 and the activating Ca^{2+} ion, but not the inhibitory Ca^{2+} ion.

With the IP_3R channel models many computational calcium models have been developed in the past 20 years. They differ by the precise oscillations that they aim to describe, as determined both by the cell type and by the agonist. Models also vary according to the level of description, from the blip modeling with a single IP_3R channel for calcium release [56–60], to the puff modeling with several dozen IP_3R channels distributed in a cluster on ER membrane [59–64], and to the global calcium oscillations and waves [16, 65–71]. For the blip and puff modeling the stochastic channel open/closing dynamics must be considered. The simple models are dimensionless model, and more realistic models consider the diffusion-reaction process of free calcium, stationary and mobile calcium buffers in a two or three-dimensional cell body.

5 Dimensionless somatic neuron models

Sixty years ago, Hodgkin and Huxley proposed a single-compartment somatic neuron model [72]. The classic Hodgkin-Huxley model neglects the neuron's spatial structure and focuses entirely on how its various ionic currents contribute to subthreshold behavior and spike generation. These models have led to a quantitative understanding of many dynamical phenomena including phasic spiking, bursting, and spike-frequency adaptation [73, 74]. More than 50 years after Hodgkin and Huxley analyzed the squid axon, simple neuron models still offer surprising power on neuronal dynamics.

The dimensionless models to couple the electrical excitability and intracellular calcium oscillation have been discussed several decades ago [75]. Chay *et al.* consider in detail different Hodgkin-Huxley-type models with the modulation of intracellular calcium [75–79]. One of the models is for R15 Aplysia neurons [76, 79]. The R15 neurons model contains a Na^+ current, an L-type Ca^{2+} current, a cationic nonselective inward current, whose strength depends on the level of luminal Ca^{2+} concentration. With the model it has been shown that the intracellular calcium oscillation can induce the electrical bursting with a much higher spiking frequency. With the bifurcating diagrams, they discussed how neuronal spiking can be transformed to periodic bursting or chaotic behavior with the change of model parameters [77].

Shuai *et al.* propose a sensory cell with the basal membrane contains voltage-sensitive Ca^{2+} channels, voltage-sensitive and Ca^{2+}-activated K^+ channels [80, 81]. While the free intracellular calcium concentration in the sub-membrane space is treated as a dynamic variable, which changes with time following two terms, the influx of extracellular Ca^{2+} ions into the cell through the voltage-sensitive calcium channel and efflux of free intracellular Ca^{2+} ions from the sub-membrane space to the extracellular medium by the pump action and to the intracellular medium by absorption. With the model, the functional differences between A- and B-receptors of weakly electric fish *G. petersii* are explained [80, 81].

Kusters *et al.* consider the cell membrane potential depending on the inward rectifier potassium channels, the L-type Ca^{2+} channels, SOC channels, and Ca^{2+}-dependent chloride channels [82]. The Cl^- channel current increases with cytosolic Ca^{2+} concentration, causing a depolarization to the Nernst potential of Cl^- ions near −20 mV. The SOC channel current increases when the concentration of Ca^{2+} in the ER decreases [83]. The model shows that the coupling of the two oscillation systems, i.e. the periodic firing of membrane action-potential and the periodic oscillation of intracellular Ca^{2+} released from the ER, leads to a rich behavior, including multiple stable and unstable states and hysteresis, in agreement with experimental observations [83].

The modeling results also indicate that a high Ca^{2+} buffer concentration can alter the characteristic regular firing of cerebellar granule cells and that a transition to various modes of oscillations occurs, including bursting [84]. These simulation results suggest that cytosolic Ca^{2+} buffering capacity can tightly modulate neuronal firing patterns leading to generation of complex patterns and therefore that Ca^{2+}-binding proteins may play a critical role in the non-synaptic plasticity and information processing in the CNS.

6 Spatial somatic neuron models

Beyond the dimensionless neuronal models, one can simulate the spatial neuron models. Comparing to the

fast spreading of action potential on plasma membrane, the spreading speed of intracellular Ca^{2+} wave is very slow at several dozen μm/s, thus the spatial models in a two or three-dimensional cell body can only describe the Ca^{2+} diffusion dynamics.

Fletcher and Li consider a single spherical soma model with the ion channels evenly distributed on the cell surface [85]. With the spherical soma the Ca^{2+} dynamics has been simulated in a three-dimensional cell body with two compartments, only the cytosol and ER. Both compartments are assumed to exist at every space point inside the cell, giving rise to a bidomain model. The cytosol and ER are separated by the ER membrane, which contains IP_3R channels, SERCAs, and a nonspecific Ca^{2+} leak. This approach retains a correct account of the amount of Ca^{2+} entry into the cell and generates a realistic Ca^{2+} profile in the whole cell including the shell area. The Ca^{2+} dynamics are governed by the partial and differential equations and boundary conditions. Rapid Ca^{2+} buffering effect is considered in the cytosol and ER also.

At the plasma membrane electrical activity drives Ca^{2+} ions into the cytosol through Ca^{2+} channels, whereas Ca^{2+} ions are extruded by the plasma membrane Ca^{2+} ATPases and Na^+-Ca^{2+} exchangers. The membrane electrical activity is governed by seven channel currents, including a TTX-sensitive Na^+ current, an L-type Ca^{2+} current, a delayed rectifier K^+ current, an inward rectifier K^+ current, a small-conductance Ca^{2+}-activated K^+ current, a cAMP-activated nonspecific cation current, an SOC current that is inhibited by high Ca^{2+} concentration in ER. Such a model not only can account for the various experimental results, but also predicts a bursting mechanism which has not been reported in experiments [85].

7 Dendritic neuron models

An interesting problem is how the spatial structure of a neuron contributes to its dynamics and function. In order to answer it, one has to design the morphologically realistic models based on anatomical reconstructions. These models extend the cable theory of Rall, who showed mathematically that dendritic voltage attenuation spreads asymmetrically [86]. This phenomenon allows dendrites to compute the direction of synaptic activation patterns, and thus provides a mechanism for motion detection. When voltage-dependent conductances are taken into account, numerical integration over the spatially discretized dendrite, the compartmental model, is needed to solve the resulting high-dimensional system of equations [87–90]. For complex dendritic trees, more than 1 000 compartments are required to capture the cell's specific electrotonic structure, e.g. the spike back propagation in pyramidal neurons [91].

Combining with Ca^{2+} dynamics, Loewenstein and Sompolinsky show that the temporal integration can be achieved at a single neuron level [92]. The calculation and memory of position variables by temporal integration of velocity signals is essential for posture, the vestibule ocular reflex and navigation [93]. Integrator neurons exhibit persistent firing at multiple rates, which represent the values of memorized position variables. A widespread hypothesis is that temporal integration is the outcome of reverberating feedback loops within recurrent networks [94, 95]. However, Loewenstein and Sompolinsky show that a single neuron can be a neural integrator [92].

In the Loewenstein-Sompolinsky model the Ca^{2+} wave-fronts within single neurons can generate graded persistent activity and temporally integrate incoming inputs. The diffusion of Ca^{2+} together with its nonlinear autocatalytic dynamics give rise to wave-fronts of high Ca^{2+} concentrations along dendritic processes of neuron [96]. These fronts propagate at a speed that is proportional to the synaptic input to the cell, resulting in instantaneous front locations that vary in proportion to the temporal integration over previous inputs. Ultimately, information stored in the Ca^{2+} signals must be decoded by the membrane potential at the axon hillock and communicated by action potentials. In the model, a Ca^{2+}-dependent cationic current has been incorporated into the neuron model. The Ca^{2+}-dependent cationic channels are open solely in regions of the dendrite where Ca^{2+} concentration is high. Consequently, the total amount of depolarizing current depends on the location of the Ca^{2+} front along the dendrite. As a result, the Ca^{2+}-dependent currents translate the location of the fronts into concomitant persistent spiking activity [92].

8 Neuronal network models

The neurons couple to each other to consist complex networks [6–8]. There are different coupling mechanisms, including active chemical synaptic interaction, electrotonic coupling through gap junctions, electrical field effects (i.e. ephaptic transmission), and ionic interactions (e.g. increases in the extracellular concentration of K^+).

At the network level much richer dynamics can be found. As the first step one can consider the dimensionless somatic Ca^{2+}-neuron networks.

Bondarenko and Chay consider a neuronal network coupled by synaptic connection with intracellular Ca^{2+} dynamics in each dimensionless neuron [97]. The neurons are either excitatory or inhibitory, and so there are three types of couplings: purely excitatory AMPA, purely inhibitory GABA, and mixed connections. These synaptic connections are modified by the intracellular Ca^{2+} of the presynaptic cell, which in turn depends on the Ca^{2+} ions coming from the Ca^{2+} channel in the plasma membrane and that released from ER. On the neuronal membrane there are three types of channels, including the voltage-dependent Ca^{2+} channels, the voltage-independent Ca^{2+} channels, and the delayed-rectifying time-dependent K^+ channels. The Ca^{2+} concentrations in cytosol and ER are also simulated in the model. The neural network model can produce different types of activities, including spontaneous propagating waves which are observed in the experiments. Such a wave motion can be important for the processes of learning and recognition in neural ensembles.

Loewenstein *et al.* present a dynamic mechanism by which the electrical coupling of identical nonoscillating cells can generate synchronous membrane potential oscillations [98]. They demonstrate this mechanism by constructing a biologically feasible model of electrically coupled cells, characterized by an excitable membrane and intracellular Ca^{2+} dynamics. They show that strong electrical coupling in this network generates multiple oscillatory states with different spatial-temporal patterns. In many studies it usually has been assumed that electrotonic coupling serves as a synchronizing device, or as a fast excitatory pathway. Loewenstein *et al.* suggest that in addition, electrical coupling can serve as a generator of oscillatory activity with the interaction of intracellular Ca^{2+} [98].

9 Noise effects on neuronal dynamics

In the past decades, constructive effects of noise in nonlinear neuronal systems have been investigated extensively in the context of noise-induced transition and noise-induced synchronization [99–103]. Noise-induced transition means that noise may lead to the appearance of new regimes which are not observed in the corresponding noise-free system [99]. An example is the noise-induced spiking or bursting in neural models [101]. Noise-induced synchronization means that a common external noise input to two independent systems could give rise to synchronized motion of both systems [101, 102].

Due to the clustered distribution of IP_3R channels on ER membrane, the IP_3Rs show a strong stochastic channel dynamics, resulting in a strong stochasticity in Ca^{2+} signals. Besides the noisy intracellular Ca^{2+} signals, there are also the noisy currents due to the stochastic dynamics of channels on plasma membrane and the noisy inputs from coupled neurons in the networks. A general question is how the neurons can work with the binary membrane system, either at the single neuron level or at the network level, to exploit these various stochasticities positively and to process neuronal information precisely.

Lang *et al.* discuss the generation and synchronization of bursts in intrinsically spiking neurons due to stimulation with random intracellular Ca^{2+} fluctuations [104]. It is demonstrated that sufficiently strong noise could induce qualitative change in the firing patterns of a single neuron from periodic spiking to bursting modes. Furthermore, it is found that a pair of uncoupled and nonidentical spiking neurons, subjected to a common noise, can exhibit synchronous firing in terms of noise-induced bursting. The synchronization is overall enhanced with the noise intensity increasing, and synchronization transitions are exhibited at intermediate noise levels.

10 Conclusions and future trends

As described in this review, both the plasma membrane and the ER membrane form a binary membrane neuron system. The mutual interaction between the neuronal electrical signals on plasma membrane and the chemical signals of intracellular Ca^{2+} regulates a variety of neuronal processes. The concept of a neuron-within-a-neuron becomes all the more interesting because the ER membrane, like the plasma membrane, has both integrative and regenerative properties that could play important roles in neural signaling [2].

Since Hodgkin and Huxley proposed the neuron model in 1952 [72], the quantitative neuronal models explain and organize the rapidly growing amount of experimental data, and make lots of testable predictions. As the neuronal models and experiments become more closely interwoven, the more realistic neuronal models are required. Thus, a current trend in neuronal simulations is to include the intracellular Ca^{2+} dynamics into

the models.

In this review we show that in recent years there are an increasing number of neuronal models on the mutual interaction among the neuronal electrical signals and the intracellular Ca^{2+} signals. However, most of these models are dimensionless. The frontier of this interest is now shifting to spatial neuronal models coupled with diffusing Ca^{2+}.

With the spatial models, one can discuss not only the slow Ca^{2+} diffusion dynamics, but also the questions how the hierarchy Ca^{2+} signals, i.e. the local blips and puffs, and global waves, module neuronal activity differently. As reviewed in the paper, the effective coupling range is in nanodomain between BK_{Ca} and Ca_V channels, and also can be in microdomain between SK_{Ca} and Ca_V channels. In order to simulate these different couplings with different distances, one has to go beyond the dimensionless neuronal models and consider the spatial structure of the neuron.

With the spatial models, it is also possible to explain why both the voltage-gated ion channels on the plasma membrane and the IP_3R channels on the ER membrane have to be at the right place in the right group to couple to each other and to endow individual neurons with their specific character, and how the biophysical properties of channels together with their spatial distribution can define the signalling characteristics of a neuron [105, 106]. It is expected that more important results and conclusions will be obtained with the spatial model to incorporate the Ca^{2+} diffusion in soma and dendritic branches at the single neuron level or at the network level.

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