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Rule-based firing for network simulations

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Abstract

We have developed a rule-based firing model that reproduces some of the complexity of real neurons with little computational overhead and isolation of postsynaptic state variables that are likely to be critical for network dynamics. The basic rule remains the same as that of the integrate-and-fire model: fire when the state variable exceeds a fixed threshold. Additional rules were added to provide adaptation, bursting, depolarization blockade, Mg-sensitive NMDA conductance, anode-break depolarization, and others. The implementation is event driven, providing additional speed-up by avoiding numerical integration.

Keywords: Computer simulation; Computer modeling; Neuronal networks; Event-driven simulation

1. Introduction

The large computational size of compartmental models makes them difficult to use in large network simulations. Additionally, these large single neuron models are themselves so complex as to be difficult to manipulate and difficult to understand, distracting from the focus on a particular parameter's effect on network dynamics. A typical synaptic effect, for example, will depend not only on the weight and intrinsic time constant of the synaptic mechanism, but also on the filtering provided by postsynaptic membrane and voltage-sensitive membrane mechanisms. Furthermore, as all of these effects are combined postsynaptically, it becomes difficult to disambiguate them so as to separate, for example, the influence of AMPA from the influence of NMDA.

For these reasons, leaky integrate-and-fire neurons have been a favored alternative to compartmental modeling when working with networks. Integrate-and-fire neurons have been elaborated in various ways in order to provide additional biological detail and to improve computational efficiency [2,3]. One useful efficiency technique is to bypass numerical integration, avoiding linked differential equations to create a much faster event-driven network [9,10].

The basic rule of an integrate-and-fire neuron is to fire when the state variable exceeds a fixed threshold. We propose an augmentation of the integrate-and-fire model that utilizes a series of rules to incorporate additional biological detail. The influence of individual synaptic receptors are represented in the model by individual state variables, making it easy to manipulate and follow their separate influence on network firing. Despite this added complexity, the implementation remains event driven, retaining the associated efficiencies.

2. Methods

The rule-based model is event driven: state variables are only updated when an event is received. External events arrive from other neurons; internal events indicate an internal state update: e.g., the end of the refractory period. External inputs produce a step increment in an internal state variable that corresponds to a particular receptor: separate state variables are maintained for AMPA, NMDA, $GABA_A$ and $GABA_B$ inputs. Each of these state variables decays exponentially back towards zero with its own time constant. These synaptic state variables are added to resting membrane potential (RMP) and to an adaptation state variable to arrive at a final V_m which is compared to threshold to determine if firing takes place.

For easy comparison to both biology and to compartmental models, parameters and state variables are

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expressed in biological units. Rule-based model parameterization can then be readily matched to a compartmental model, by setting, for example, RMP and E_{AMPA} to the values used in a compartmental model.

Additional speed-up is obtained through use of table look-up to avoid run-time calculation of exponential decays and other response wave forms. Additionally, random variables are precalculated and stored in arrays so as to avoid calls to computationally expensive pseudo-randomization routines.

The techniques and simulations described here are implemented in the NEURON simulator (www.neuron.yale.edu) [4]. Although NEURON is a compartmental model simulator, it features an efficient event queue utilizing a splay-tree algorithm [5,6]. The NEURON integrator can be turned off during event-driven simulations so as to offer no time- and minimal space-overhead. Individual neuron integrators can also be turned on to run hybrid networks with both compartmental and rule-based cells [7].

3. Results

Fig. 1 shows rule-based model response to AMPA synapses from a set of 4 independent Poisson random-spike generators. The response to each input is a voltage jump after an axonal delay. Weight W_{AMPA} determines the size of the voltage step whose amplitude is also proportional to the distance from the E_{AMPA} reversal potential: $V^{step}_{AMPA} = W_{AMPA}(V - E_{AMPA})/E_{AMPA}$. Note that W_{AMPA} is a unitless weight, not a conductance. W_{AMPA} converts a driving force to a step voltage increment due to the AMPA activation. The step is scaled by distance from the reversal potential E_{AMPA}. The step is added to a calculated ongoing V_{AMPA} which is a state variable that represents the summed AMPA synaptic potential. Following a step, V_{AMPA} decays with time constant τ_{AMPA}. In Fig. 1, there is an imposed period firing each 100 ms in addition to the firings due to threshold crossings. These imposed "externally driven" firings are simply read out of a precalculated firing time vector. In this simulation, one of the periodic external spikes is dropped due to the refractory period from the prior spike (oblique arrow).

In addition to the various V_{syn} synaptic state variables (syn = AMPA, NMDA, $GABA_A$ or $GABA_B$), there is an intrinsic negative-going AHP state variable V_{AHP} which is stepped more negative whenever a spike occurs. As well as its effect on V_m, the negative of the V_{AHP} is scaled to provide a value that directly augments the refractory period. V_{AHP} thereby serves double duty: providing a long (I_{AHP}-like) adaptation via V_m (dependent on the parameter τ_{AHP} and a short (I_C-like) adaptation via refractory period lengthening. An additional adaptation mechanism is provided by decrementing the synaptically driven V_{syn} state variables after each spike. Because the units are rule-based, their firing tends to be highly regular which in a network setting could produce unwanted coincidences. As a symmetry-breaking procedure, jitter can be added as a small additional random delay in spike firing time.

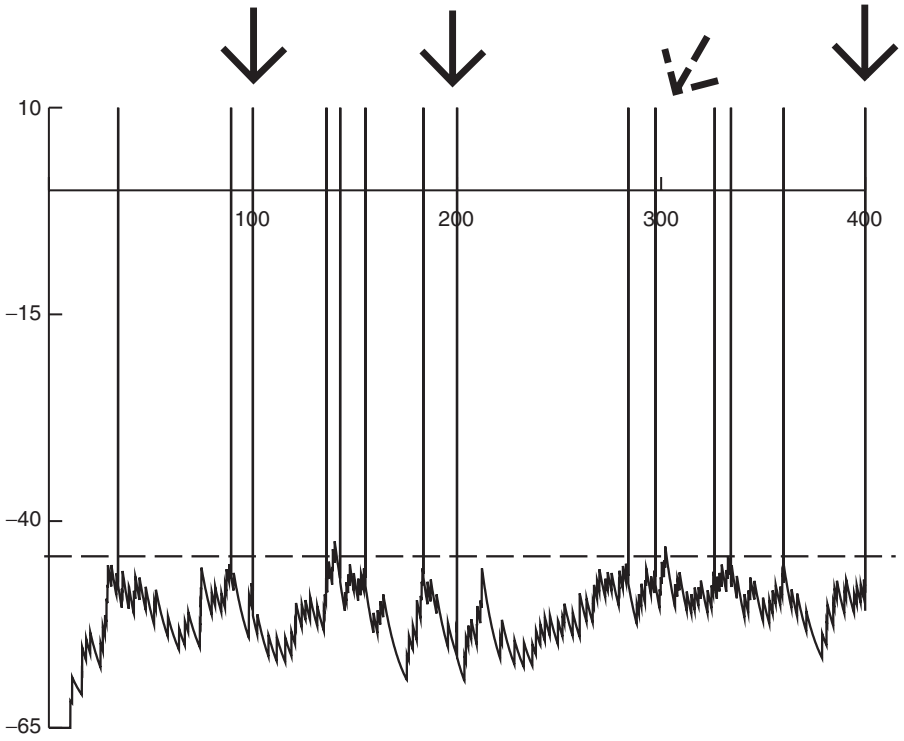

Fig. 1. Irregular firing in response to independent Poisson generators with superimposed directed firing at 100 ms intervals (down vertical arrow) Spike missed at 300 ms due to refractory period (down oblique arrow).

The rule-based model can also produce bursting. Grossly, burst spiking can be divided into two distinct types: (1) driven bursts riding on top of powerful synaptic stimulation; (2) intrinsic bursts produced by the mechanisms of the neuron itself. Both of these burst types can be produced by the rule-based model (Fig. 2). Intrinsic bursting is determined by a rule that is parameterized for burst length and intra-burst spike frequency. Here again, the bursts can be varied by adding jitter.

Fig. 2 also illustrates the application of two other rules. In the Hodgkin–Huxley model, as in reality, depolarization blockade of spiking occurs when voltage rises beyond the domain where sodium channel activation and deactivation occur, preventing the characteristic action potential oscillation. In the rule-based model, depolarization blockade follows a rule: no spike is generated if V_m exceeds a fixed upper limit (upward arrow in Fig. 2B). Fig. 2 also demonstrates the influence of NMDA activation, with its tendency to produce longer and stronger depolarizing effects in the presence of postsynaptic depolarization. In the rule-based model, this influence is instantiated using the equation developed to describe Mg^{2+} unblocking [6]. Note that the use of realistic units (mV) for voltage rules allows us to use the standard equation.

We have begun to utilize the rule-based model units in networks. Fig. 3 shows a synfire chain with 12 000 cells separated into 20 groups (columns) of 600 cells each. The raster plot shows activation of the first chain (bottom left)

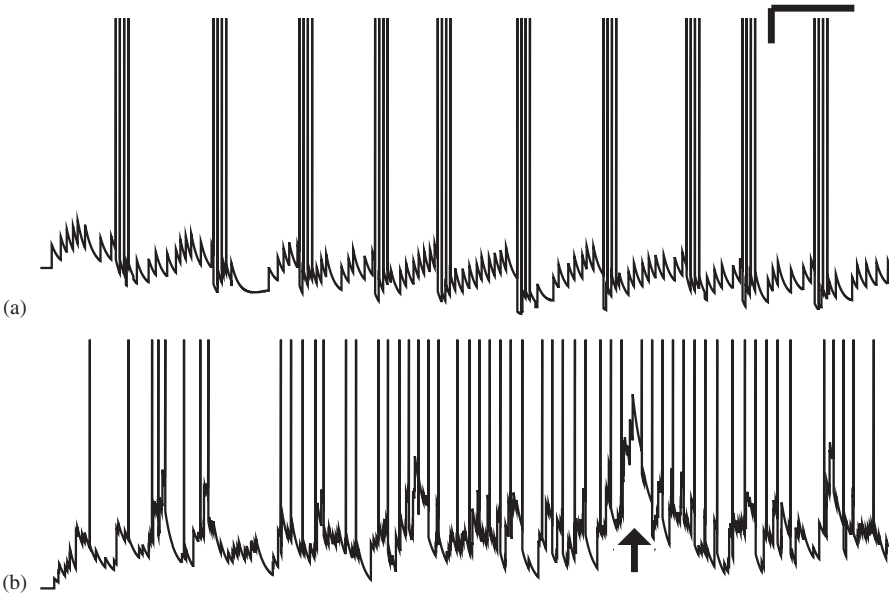

Fig. 2. Bursting. (a) Highly regular intrinsic bursts driven by fairly regular AMPAergic activation with no NMDA and no jitter, and (b) irregular bursting due to varying input with strong NMDA component. Arrow shows one example of depolarization spike blockade. Scale 15 mV; 100 ms.

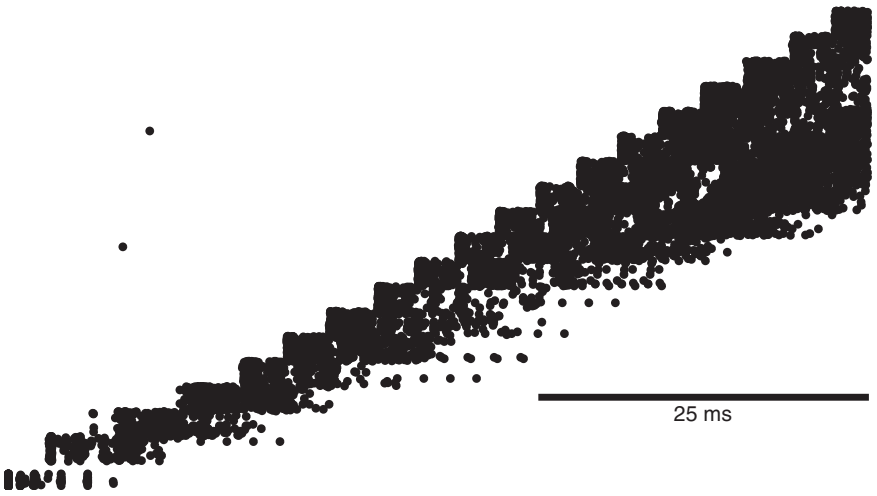

Fig. 3. Raster plot of synfire chain of 10 000 excitatory and 2000 inhibitory cells.

by stimulation. Activation persists within each column and then spread to the neighboring column. The prolongation of activation in each column amplifies as one goes from column to column. This 100 ms/27 787 spike simulation required 19.86 s on a 2.4 GHz 64-bit Opteron AMD processor.

Since these network simulations have no integrator overhead, they can run arbitrarily fast, depending on the amount of spiking in the model. As spike frequencies increase, queue overhead imposes increasing computational burden. This dependency on activity patterns makes it difficult to benchmark the simulation against other model types, requiring that the average firing of two implementations be matched on a per-cell-type basis (compartmental models of some cell types will be far more computationally intensive than those for others).

In general, we can expect substantial speed ups over integrated simulations unless event frequencies approach the inverse of the time-step required for numerical integration of compartmental models. A typical time-step for a fixed time-step integration would be 0.025 ms. This corresponds to a 40 kHz integration frequency (sampling rate). Network complexity analysis shows that this event frequency would occur in a network with a convergence of 1000 cells each actively spiking at 40 Hz. Although pyramidal cells have order 10 000 synaptic boutons, the convergence is considerably less due to redundant connectivity. Additionally, under most conditions the several thousand presynaptic cells would not be expected to all be simultaneously strongly activated. Also it is worth noting that a fixed time-step integration will alias spike input times to the nearest time-step boundary while an event-driven simulation will preserve input timing [8].

4. Discussion

In addition to advantages of speed, the rule-based model lays out neural parameters explicitly so as to permit easy manipulation. By contrast, in a compartmental model, phenomena such as adaptation and postinhibitory rebound are dependent on several voltage-sensitive ion channels, each of which has its own complex parameterization, three-steps removed from the network phenomenon of interest [1]. Alteration of one of these channel-level parameters will typically have multiple effects, altering not only the neuron-level phenomenon of interest but often profoundly altering other neuron responses as well. For example, altering adaptation by changing the strength of one or more of the many potassium channels responsible for adaptation will change burst-firing patterns as well.

The rule-based framework can incorporate further rules as needed for particular cell types with characteristic firing patterns. These patterns can be incorporated into the rule base either by constructing an analytically calculable dynamical rule or by providing a simple cut-and-paste spike form. Jitter and length variation rules can be added to prevent stereotypy.

An alternative approach to producing additional complexity in the rule-based model would be to provide further intrinsic mechanisms comparable to the intrinsic AHP mechanism that is currently being used. Although an rule-based model with multiple intrinsic mechanisms could begin to approach the complexity of a numerically integrated single-compartment model, the event-driven implementation means that the individual channels do not interact via mutual dependence of voltage as they would in a compartmental model. Any dependence on voltage or other state variable must be instantaneous, as is, for example, the voltage dependence of the NMDA response.

Hybrid networks can be developed that incorporate rule-based units alongside compartmental-model cells in a single network. Hybrid networks will be valuable to confirm the accuracy of the rule-based implementation by comparing spike patterns with compartmental-model activity in the same network context. A full compartmental-model network could be seeded with a few rule-based units, each wired to have the same inputs as a single compartmental unit. Parameters would then be modified either manually or automatically to produce the same activity as the matched compartmental models. The compartmental cells could then be replaced in part or whole with the rule-based units. Hybrid networks also allow observation of the complex activity of compartmental models (e.g., dendritic interactions) in the context of the large networks made possible by the rule-based units [7,8].

Acknowledgements

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Mark Stewart received a B.S. in chemistry and biology in 1983, his Ph.D. in neuroscience in 1989 and M.D. in 1991. His graduate work was done at the State University of New York, Downstate Medical Center, where he was hired to the faculty in 1993 after a postdoctoral fellowship with R.K.S. Wong. His research interests began with the neural basis for the hippocampal theta rhythm, stretched to include work in brain slices and dissociated single cells from subiculum and other parahippocampal regions, and returned to whole animal model systems with studies of autonomic and immune consequences of seizure activity. He compares computational neuroscience to his teenage son: the field has developed sufficiently to go beyond the storage of facts from biological experiments; it has started to "talk back" with model-based predictions of biology such as axonal gap junctions.