Reduced Kinetic Schemes of Short-term Synaptic Plasticity in Inhibitory Network Models ⋆

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Abstract

GABAergic, inhibitory interneurons are critical controllers of brain rhythms. Short-term synaptic plasticity affects neuronal network dynamics that give rise to these rhythms. We incorporated a three-state phenomenological kinetic scheme that describes synaptic depression into inhibitory network simulations. We developed a protocol to fit the phenomenological scheme to a more complex six-state kinetic scheme. We are able to capture the network dynamics using our "reduced" simpler scheme as compared with using the more complex scheme. Using such simpler schemes, we will be able to explore the effects of short-term depressions as described by more complex kinetic schemes on network dynamics.

Keywords: hippocampus, synchrony, neuronal network, synaptic depression, $GABA_A$ synapse.

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1 Introduction

GABAergic inhibitory cells or interneurons play key roles in brain processing, such as memory, learning, sleep processes and epilepsy, as expressed by various brain rhythms. Specifically, in the hippocampal cortex, networks of interneurons connected with inhibitory synapses have been found to be critically involved in several network rhythms [6]. Computer simulations of mathematical models allow one to explore which physiological mechanisms might be relevant to the formation of these rhythms.

Short-term plasticity has been shown to be a functionally important synaptic property [3]. Some interneuronal types (e.g., hippocampal basket cells) exhibit short-term synaptic plasticity in the form of synaptic depression. Synaptic depression occurs as a result of both pre- and post-synaptic mechanisms. For example, postsynaptic mechanisms could involve desensitization of $GABA_A$ receptors [1,5]. Multi-state kinetic schemes have been developed to describe short-term plasticity. While it has been demonstrated how short-term plasticity might contribute functionally to neural coding and sensory-motor programs, it is unclear how details of more complex kinetic schemes (e.g., [4]) might contribute to network dynamics that underlie information processing in the brain.

In this work, we develop a way to link parameters in a simple, phenomenological kinetic model of short-term plasticity to a more complex kinetic scheme involving receptor desensitization. We then use these parameters in simulations of model inhibitory networks of hippocampus, and compare them with simulations using the more complex kinetic scheme. In this way, we can determine whether the simpler

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scheme with the computed parameters captures network phenomena.

2 Methods

2.1 Synaptic Gating Models

Previously we incorporated a six-state kinetic scheme in inhibitory network models [2]. The complexity of the scheme makes it computationally expensive to perform larger network simulations as well as difficult to perform any mathematical analysis. To circumvent this, we use a much simpler phenomenological kinetic scheme developed by Markram and Tsodyks [7, 9] and develop a method to link it to more complex kinetic schemes. The scheme is described by the following equations:

$$I_{Syn} = g_{syn} S (V - V_{syn}) \tag{1}$$

$$\frac{dS}{dt} = \alpha U_{SE} F(V_{pre}) R - \frac{S}{\tau_S} \tag{2}$$

$$\frac{dR}{dt} = \frac{1 - S - R}{\tau_D} - \alpha U_{SE} F(V_{pre}) R, \tag{3}$$

where I_{Syn} is the synaptic current, g_{syn} is the maximum synaptic conductance, V and V_{pre} are the membrane voltages of the post- and pre-synaptic cells respectively, V_{syn} is the synaptic reversal potential, S is the open state, R is the recovered or closed state, $1 - S - R$ is the inactive state, $F(V_{pre}) = 1/\{1 + exp[-(V_{pre} - \theta/2]\}$, where θ is a threshold set to 0 mV,τ_S and τ_D are the decay and recovery time constants respectively, α is the activation rate (assumed to be 1), and U_{SE} is a parameter representing the utilization of synaptic efficacy under a pre-synaptic model of synaptic depression [7]. The complex six-state kinetic scheme we use is

given in [1]. For the intrinsic properties, we use the hippocampal interneuron model from [10].

2.2 Network Simulator

We re-designed our in-house neuronal network simulator, NNET [8] to allow the underlying current equations to be easily implemented separately and chosen at runtime for a particular simulation. The main assumption of the program is a current balance equation based model of the form:

$$C\frac{dv}{dt} = \sum I_{Cell} + \sum I_{Connection}, \tag{4}$$

where I_{Cell} represents currents local to one cell such as ionic channels or external applied current and $I_{Connection}$ represents currents between cells such as electrical or chemical synapses. The new version of NNET is freely available with source code upon request.

2.3 Stimulation Protocol

In the original work, Markram and Tsodyks fit the model to experimental data using a pulse train followed by a recovery pulse. The protocol was repeated for different pulse train frequencies. However, we found that the slow dynamics of the complex kinetic scheme were sometimes not exposed with this protocol. Inspired by the verification protocol used by Markram and Tsodyks, a "random" stimulation pattern was used with randomly varying frequencies and durations using maximum boundaries of 70Hz and 100ms respectively. Four different random patterns were used. This more complicated stimulation proved sufficient to expose the slow dynamics

of the complex kinetic scheme as well as its frequency dependence. An example of input stimulation is shown in Figure 1(A).

2.4 Parameter Fitting

The parameters for the simple kinetic scheme were found by varying U_{SE} and τ_D to create an error map. The error function used was the mean square of the percent difference in inhibitory postsynaptic potentials (IPSPs). In order to discretize the IPSPs, we used the minimum post-synaptic potential between pre-synaptic events. The third parameter, τ_S was set formulaically from equation 1 in [1]. The initial conditions in the simple and complex schemes were set such that a certain level of desensitization was already reached. The postsynpatic cell was set at its resting potential (-65mV in this case).

2.5 Verification

To determine whether the parameters we obtained for the simple scheme captured appropriate network dynamics, we performed simulations using two-cell mutually and self inhibited networks and compared them with previous network simulations using the complex scheme [2]. We used a correlation measure defined in [11] and used in [2]. The measure is defined as the correlation between square unit pulses centered upon the action potential peaks with a fixed width of 20% of the shorter of the two periods.

3 Results

3.1 Parameter Fitting

The average minimum error for the parameter fitting is 0.4%. As shown in figure 1(B), the simple kinetic model does a good job following the complex model for many different frequencies. Note that the fit depends on the choice of initial conditions. In particular, the contribution of the desensitized state requires that the initial conditions be chosen such that 90% is initially in the $(1 - S - R)$ state in the simple scheme and in the slow desensitized state of the complex scheme [1]. This value was chosen as it reflects the steady state of the complex scheme in network simulations.

3.2 Verification

Figure 2 shows correlation maps of the complex (A) and the simple (B) synaptic gating schemes as the synaptic strength and excitatory input are varied. The two systems both show coherent solutions and harmonic locking dynamics in similar parameter regions suggesting that the simple scheme approximately captures dynamics of the complex scheme. Correlations above 0.6 for the simple scheme encompass 42% of the corresponding parameter region in the complex scheme (See Figure 2). In contrast, less optimal parameters result in smaller regions of overlap and/or harmonic locking patterns not being expressed in the same parameters regimes.

4 Discussion and Conclusions

We have developed a way to determine parameters for a simple phenomenological three-state kinetic scheme from a complex six-state kinetic scheme. In particular, slow transitions to and from desensitized states can be captured with appropriate initial conditions. This "reduction technique" can be applied to other complex kinetic schemes. An important consequence of this work is that larger network simulations can now fully explore the effects of short-term synaptic depression on network dynamics. As we can fit the phenomenological scheme to different degrees of desensitization in the complex scheme, the result of this on network dynamics can also be examined.

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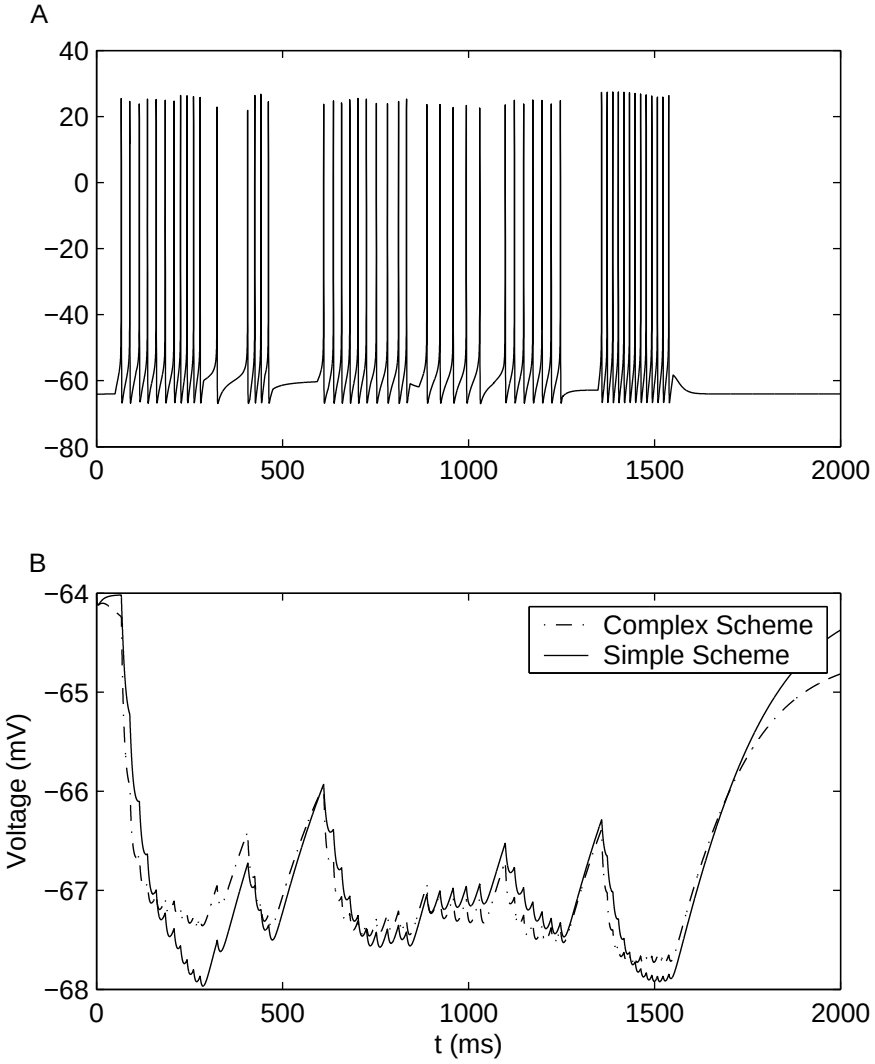

Fig. 1. Derivation of Parameters for Simple Scheme. (A) Example of an input stimuation pattern generated in the presynaptic neuron. (B) Resulting IPSPs in the postsynaptic neuron using the complex six-state scheme and the best fit simple scheme. ($\tau_D = 3250, U_{SE} = 0.35, \tau_S = 150$) See [2] for descriptions of variables in complex scheme.

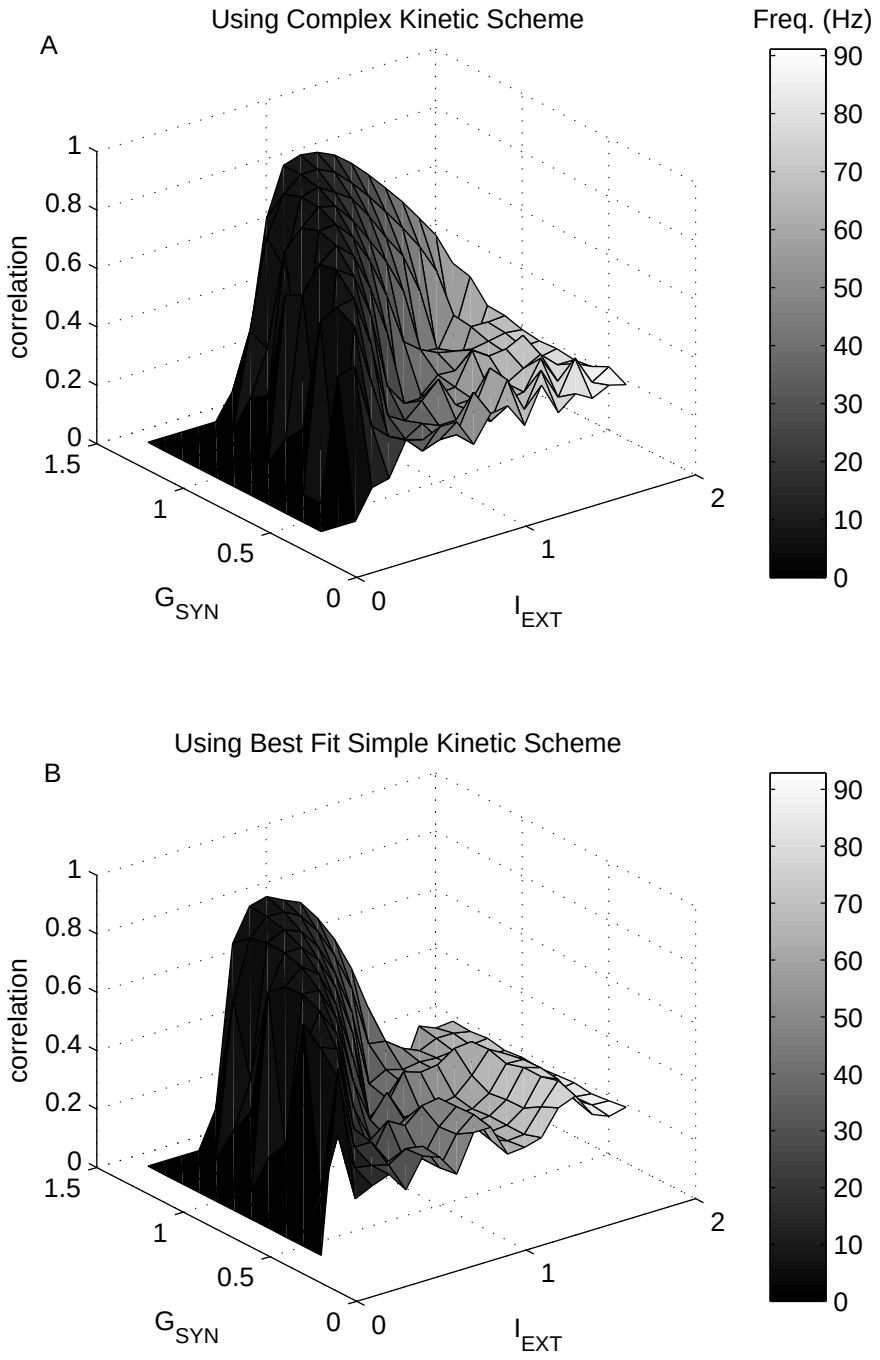

Fig. 2. Correlation maps for two cell inhibitory networks using (A) the complex six-state scheme, and (B) the best fit simple kinetic scheme (see Fig. 1(B)).