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

†Peter A. Murray and ‡Frances K. Skinner [1],

†*Edward S. Rogers Sr. Dept. of Electrical and Computer Engineering,*

†‡*Toronto Western Research Institute, University Health Network,*

‡*Depts. of Medicine (Neurology), Physiology and* †‡*Institute for Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada*

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 develop a protocol to fit a three-state phenomenological kinetic scheme to a more complex six-state kinetic scheme that describes synaptic depression. We are able to capture inhibitory 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.

1 Introduction

In the hippocampal cortex, networks of interneurons connected with GABAergic inhibitory synapses are critically involved in several network rhythms associated with learning and memory [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 postsynaptic mechanisms. For example, postsynaptic mechanisms could involve desensitization of $GABA_A$ receptors [1, 5]. 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 brain processing. 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, and compare them with simulations using the more complex kinetic scheme. In this way, we can determine whether the simpler scheme with the computed parameters captures network phenomena.

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[1] Corresponding author: Toronto Western Research Institute, University Health Network, 399 Bathurst St., MP 13-317, Toronto, Ontario, Canada, M5T 2S8. Phone: 416-603-5800x5107; FAX 416-603-5745; email: fskinner@uhnres.utoronto.ca

2 Methods

2.1 Synaptic Gating Models

Previously we incorporated a six-state kinetic scheme into 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 [7,10], and develop a method to link it to more complex kinetic schemes. The simple 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] and involves eight parameters as compared to three (U_{SE},τ_D,τ_S) for the simpler scheme above. For the intrinsic properties, we use the hippocampal interneuron model from [11].

2.2 Network Simulator

We re-designed our in-house neuronal network simulator, NNET [9], 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. The applied current to the presynaptic cell was varied randomly such that the action potential frequency of the presynaptic cell was between 0 and 70Hz. The applied current was held constant for a random length of time and a new current was chosen every 0 to 100ms for a total stimulation time of 1500ms. Nine different random patterns were used. This random 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 U_{SE} parameter was varied between 0 and 1 in 0.05 increments. The τ_D parameter was varied in 2000ms blocks starting at 0 with 50ms resolution until a minimum error was found. See Figure 1(C) for an example of the error surface produced by this method. The error function used was the mean square of the 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 postsynaptic cell was set at its resting potential (-65mV in this case). Additional details of the procedure are given in [8].

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 as the correlation between square unit pulses centred upon the action potential peaks with a fixed width of 20% of the shorter of the two periods [12].

We repeated the procedure for two additional versions of the complex scheme where the parameter values were different.

3 Results

3.1 Parameter Fitting

A particular case (for the control version of the complex scheme) is shown in Figure 1. The average minimum error for the parameter fitting is 0.34mV. The error surface calculated is shown in Figure 1(C). 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 for the case illustrated in Figure 1. The two systems both show coherent solutions and harmonic locking dynamics in similar parameter regions suggesting that the simple scheme captures the essential dynamics of the complex scheme. Highly correlated regions and harmonic locking regions for the simple scheme

encompass 33% and 65% respectively of the corresponding parameter region in the complex scheme and with less optimal parameters it was much less (See Figure 2). This was also true for the other two cases [8]. Given that the three cases refer to control and modulation of $GABA_A$ receptors by anaesthetic drugs, we can better understand drug-modulation at the network level with the simpler scheme.

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. We can now fully explore the effects of short-term synaptic depression on larger networks and the effect of different degrees of desensitization in the complex scheme.

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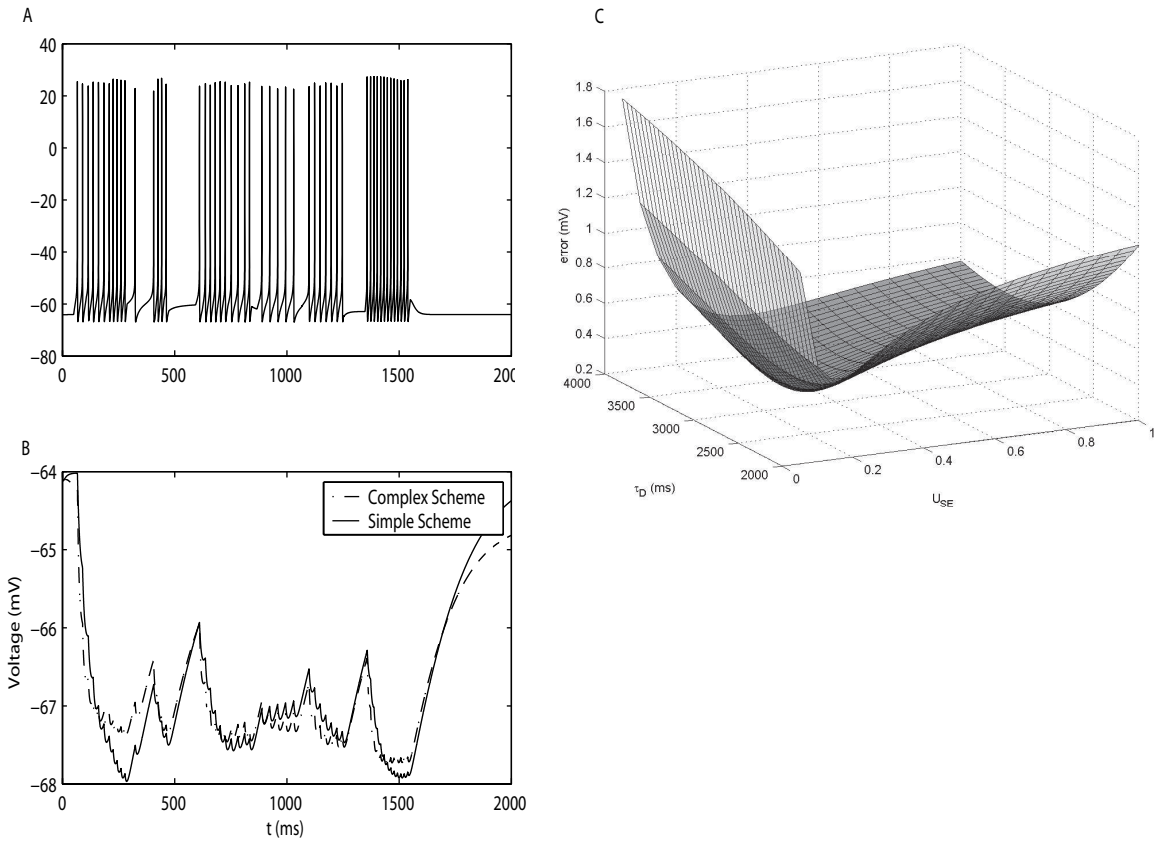

Fig. 1. Derivation of Parameters for Simple Scheme. (A) Example of an input stimuation pattern generated in the presynaptic neuron. (B) Resulting IPSPs in the postsynaptic neuron using the complex six-state scheme and the best fit simple scheme. (τ_D=3250, U_{SE}=0.35,τ_S=150) (C) Error surface for a range of τ_D and U_{SE} parameters showing the minimum error of 0.34 at (τ_D=3250, U_{SE}=0.35). See [2] for descriptions of variables in complex scheme.

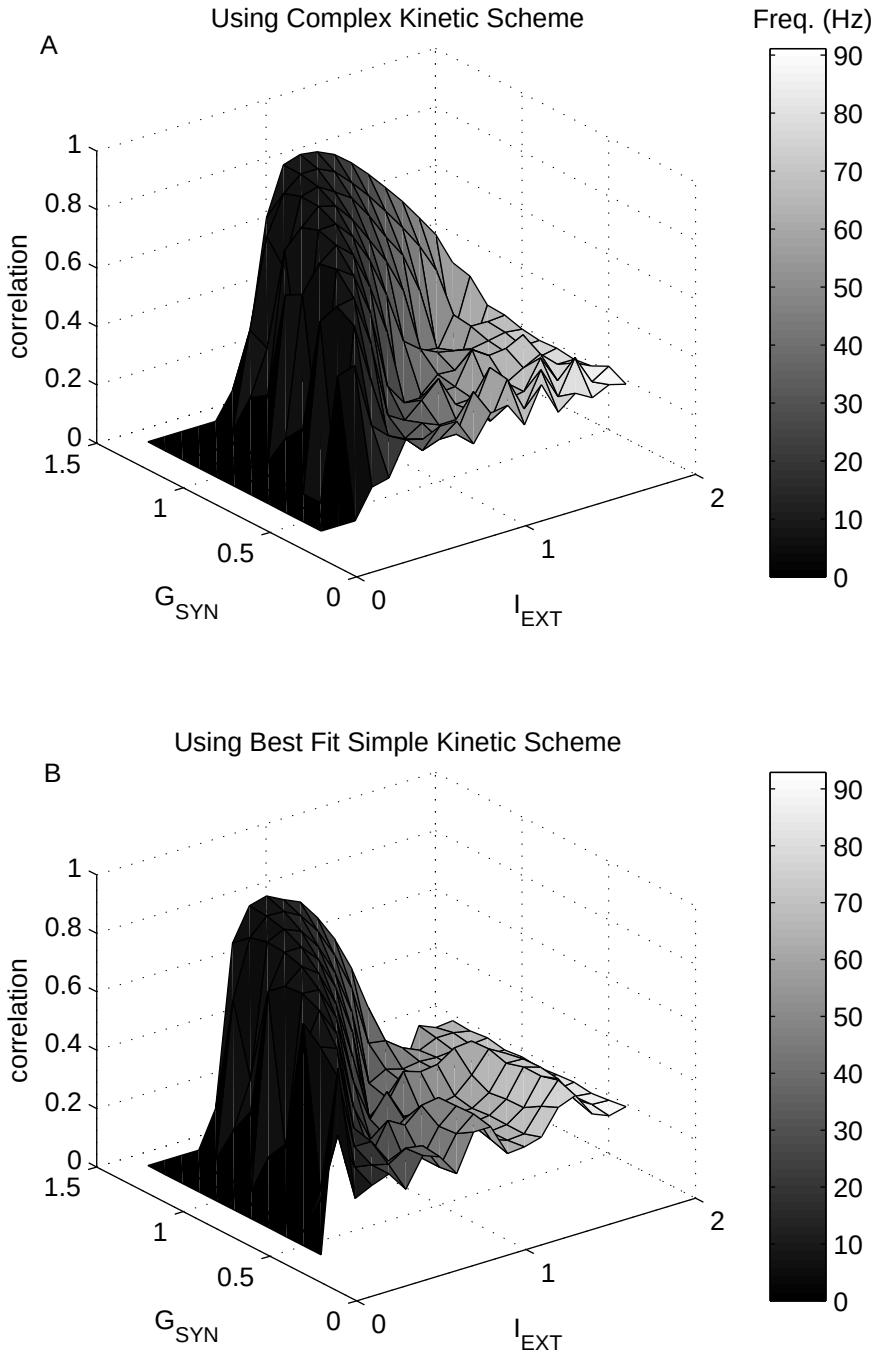

Fig. 2. Correlation maps for two cell inhibitory networks using (A) the complex six-state scheme, and (B) the best fit simple kinetic scheme (see Fig. 1(B)).