2011 50th IEEE Conference on Decision and Control and
European Control Conference (CDC-ECC)
Orlando, FL, USA, December 12-15, 2011

Kalman Filter Tracking of Intracellular Neuronal Voltage and Current

Yina Wei, *Student Member, IEEE*,Ghanim Ullah, Ruchi Parekh, Jokubas Ziburkus, Steven J. Schiff, *Member, IEEE*

Abstract— **The nervous system encodes and processes information with the activities of neurons. The response of a single neuron is complex and depends on the interactions between its previous state, its intrinsic properties, and the stimuli it receives. Experimentally, we utilize the patch clamp technique to monitor neural membrane voltages, but the underlying stimuli, including the external current or synaptic current from other neurons, cannot be fully observed. In this paper, we used computational models as an alternative to tackle these challenges. We employed an ensemble Kalman filter to reconstruct unobserved intracellular variables and parameters only from measured membrane potentials in a CA1 pyramidal neuron model that follows Hodgkin-Huxley dynamics. We found that the tracking of intracellular neuronal voltage and current was close to their true values whether the observations are from model generated data or real experimental data. In addition, we retrieved the experimentally inaccessible dynamics of the neuron, such as the changes of sodium and potassium gating variables, which helps to understand their roles in generating action potentials. Our study provides a powerful framework for observing dynamics underlying neural activity and seeking better real-time neuronal control.**

I. INTRODUCTION

The neuron, an electrically excitable cell, is the fundamental biological unit in the brain [1]. The response of a single neuron is complex and depends on the interactions between its previous state, its intrinsic properties, and the external stimuli or synaptic currents it receives [2]. Although we can measure single neuron properties via patch clamp techniques, the underlying input current and neural dynamics are not directly measurable. Computational models have been increasingly used as an alternative to tackle these challenges that are encountered in such experiments. Previous studies on the input-output relationship of a neuron have been carried out by conventional filters [4], artificial neural networks [2], and a numerical model [3]. These approaches are helpful to establish a quantitative relationship between neuron response and input stimulus. However, in a typical computational model, we obtain a solution from integration without considering its uncertainty. The measurements of real experimental data may contain noise from recording equipment, and there are ubiquitous sources of neuronal noise including membrane channel stochasticity, branch point conduction failure, and probabilistic transmitter release [26]. Therefore, brain measurements are always uncertain.

The Kalman filter has emerged as an effective way to infer experimentally inaccessible variables from noisy measurements [5][6]. Although the Kalman filter was originally derived for linear systems, the various modification of Kalman filter, such as the ensemble Kalman filter [7], and the unscented Kalman filter [8][9] are more suitable for complex nonlinear neural dynamics. Such techniques have led to great successes in many other complex areas, such as aircraft engine health estimation, aircraft model estimation, robot navigation, financial forecasting, and weather prediction before they were applied to neurons [10][11][12][16]. Recently, our laboratory extended such approaches in assimilating spatiotemporal neuronal data [12], and tracking seizure dynamics with real experimental data [14][15]. To our knowledge, the ensemble Kalman filter has not yet been used to model the input-output relationship in a single neuron.

In this paper, we aim to reconstruct input current and neural dynamics from a neuron model using only the membrane potential measurement from a CA1 pyramidal cell. We experimentally applied input current to the neuron and recorded its membrane potential. The pyramidal neuron model is described as a nonlinear dynamic system that follows modified Hodgkin-Huxley equations. We assumed the input stimulus is unknown, and reconstructed the underlying stimulus and the neural dynamics using the intracellular recordings from single neuron by an ensemble Kalman filter, in particular the unscented Kalman filter (UKF). This paper is organized as follows. Section II presents the neuron model of the pyramidal cell and the implementation of the UKF algorithm. Section III presents the main results of this work. Finally, section IV presents conclusions and the future work.

II. MATERIALS AND METHODS

A. The Neuron Model

We modeled the pyramidal cell using a single compartment model. The dynamics of the compartment is modeled as a nonlinear system following a modified Hodgkin-Huxley

Yina Wei is with Center for Neural Engineering, Department of Engineering Science and Mechanics, Penn State University, PA 16802 USA (email: yxw170@psu.edu).

Ghanim Ullah is with Theoretical Biology and Biophysics, Los Alamos National Laboratory, NM 87545 USA (email: gullah@lanl.gov).

Ruchi Parekh is with Center for Neural Engineering, Department of Engineering Science and Mechanics, Penn State University, PA 16802 USA (email: ruchisparekh@gmail.com).

Jokubas Ziburkus is with Department of Biology and Biochemistry, University of Houston, Texas 77204 USA (email: jziburkus@uh.edu).

Steven J Schiff is with Center for Neural Engineering, and Departments of Engineering Science and Mechanics, Neurosurgery, and Physics, Penn State University, PA 16802 USA (email: sschiff@psu.edu).

This work was in part supported by NIH Grants R01MH50006 and K02MH01493, and the endowment funds of Harvey F. Brush.

formalism that describes how action potentials in neurons are generated [17]. This model reveals the key dynamics of ion flow across the cell membrane underlying the action potential by four coupled nonlinear ordinary differential equations:

$$\frac{dV}{dt} = \frac{1}{C}(I_{ext} - I_{Na} - I_K - I_l) \tag{1}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m \tag{2}$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h \tag{3}$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \tag{4}$$

where I_{ext} is the external injected current or synaptic current from other neurons, I_{Na} and I_K are the sodium and potassium currents across the voltage-gated ion channels, I_l is the leak current that is linearly related to the leak conductance. These currents can be expressed as:

$$I_{Na} = G_{Na} m^3 h (V - E_{Na}) \tag{5}$$

$$I_K = G_K n^4 (V - E_K) \tag{6}$$

$$I_l = G_l (V - E_l) \tag{7}$$

where the variables and parameters can be found in table I.

TABLE I: Model Variables and Parameters

Symbol	Units	Description
V	mV	Membrane potential
m		Activating sodium gate
h		Inactivating sodium gate
n		Activating potassium gate
C	$1uF/cm^2$	Membrane capacitance
G_{Na}	$32mS/m^2$	Maximal conductance of sodium current
G_K	$10mS/m^2$	Maximal conductance of potassium current
G_l	$0.1mS/m^2$	Conductance of leak current
E_{Na}	$55mV$	Reversal potential of sodium current
E_K	$-90mV$	Reversal potential of potassium current
E_l	$-70mV$	Reversal potential of leak current

The activation and inactivation variables m, h, and n range between 0 and 1 representing the fraction of channels in closed and open states. The parameters α_m, β_m, α_h, β_h, α_n, β_n are rate constants of the ion channel state transitions that are dependent on V [18][19].The equations of these rate constants are from the pyramidal cell model of Gloveli(2005) [18], as shown in Table II.

TABLE II: The Opening and Closing Rate Constants

$\alpha_m = \frac{0.32(54+V)}{(1-exp(-(V+54)/4))}$	$\beta_m = \frac{0.28(V+27)}{(exp((V+27)/5)-1)}$
$\alpha_h = 0.128exp(-(50+V)/18)$	$\beta_h = \frac{4}{(1+exp(-(V+27)/5))}$
$\alpha_n = \frac{0.032(V+32)}{(1-exp(-(V+52)/5))}$	$\beta_n = 0.5exp(-(57+V)/40)$

B. The Unscented Kalman Filter

The Kalman filter is the most well known data assimilation tool that estimates the internal system states x from observations y for linear systems [5][6]. Estimating the stimuli and unobserved states in a neuron model is a nonlinear estimation problem. The unscented Kalman filter (UKF) provides an optimized framework to reconstruct and predict model state for nonlinear systems [8][9]. Let the nonlinear estimation problem be

$$x_k = F(x_{k-1}, u_k) + q_k \tag{8}$$

$$y_k = H(x_{k-1}) + r_k \tag{9}$$

where q and r are the process and measurement zero mean Gaussian noises with covariance matrices Q and R respectively. F and H are the process and observation functions with system states x, input u, and output y.

The Kalman filter works in two steps (Fig1): first it estimates the system state and covariance from model only (prediction); then it assimilates noisy measurements to update the system state and covariance (correction). The key of the UKF is to produce several sigma points around the current state estimate based on its covariance, and to propagate these points through the nonlinear map and capture an estimation of the mean and covariance (Fig1) [10]. The procedure of the UKF is shown as follows:

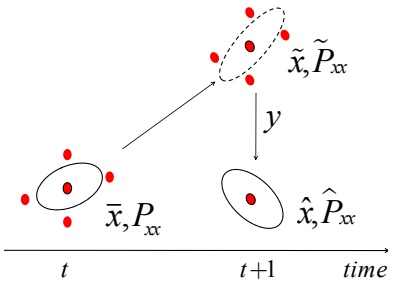


Fig. 1: Iterative diagram of the unscented Kalman Filter

1) First, suppose x is a N-element vector, and choose the sigma points from their mean $\bar{x}$ and covariance P_{xx} at time t.

$$X_i = \bar{x} + (\sqrt{NP_{xx}})_i^T \qquad (i = 1, 2, \ldots, N) \tag{10}$$

$$X_i = \bar{x} - (\sqrt{NP_{xx}})_i^T \qquad (i = N+1, \ldots, 2N) \tag{11}$$

2) Propagate each sigma point from time step t to $t+1$ through the known nonlinear functions F and H yielding transformed points and the observations.

$$\tilde{X}_i = F(X_i) \qquad \tilde{Y}_i = H(X_i) \tag{12}$$

3) Estimate the new mean and covariance based on transformed points.

$$\tilde{x} = \frac{1}{2N}\sum_{i=1}^{2N} \tilde{X}_i \qquad \tilde{y} = \frac{1}{2N}\sum_{i=1}^{2N} \tilde{Y}_i \tag{13}$$

$$\tilde{P}_{xx} = \frac{1}{2N}\sum_{i=1}^{2N}(\tilde{X}_i - \tilde{x})(\tilde{X}_i - \tilde{x})^T + Q \tag{14}$$

$$\tilde{P}_{xy} = \frac{1}{2N}\sum_{i=1}^{2N}(\tilde{X}_i - \tilde{x})(\tilde{Y}_i - \tilde{y})^T \tag{15}$$

$$\tilde{P}_{yy} = \frac{1}{2N}\sum_{i=1}^{2N}(\tilde{Y}_i - \tilde{y})(\tilde{Y}_i - \tilde{y})^T + R \tag{16}$$

4) Update the *a posteriori* state estimate mean and covariance matrix at time $t+1$ using the Kalman filter equations:

$$K = \tilde{P}_{xy}\tilde{P}_{yy}^{-1} \tag{17}$$

$$\hat{x} = \tilde{x} + K(y - \tilde{y}) \tag{18}$$

$$\hat{P}_{xx} = \tilde{P}_{xx} - K\tilde{P}_{xy}^T \tag{19}$$

Here, K is the Kalman gain matrix and y is the measurement. Then the updated $\hat{x}$ and $\hat{P}_{xx}$ will be used for the next iteration.

C. The Implementation of UKF

To implement the UKF into the neuron model, we set the augmented state vector x as a $N = p + n$ dimension vector composed of p parameters and n dynamic variables. If p parameters are tracked in the system, then the first p rows of state vector x follow the parameter function $\lambda_k = \lambda_{k-1}$. In this paper, to reconstruct the input current of the neuron, we consider I_{ext} as a time-varying parameter and insert it into the state vector. Therefore, the process equations of the Kalman filter would be:

$$\dot{x} = \begin{bmatrix} \dot{I}_{ext} \\ \dot{V} \\ \dot{m} \\ \dot{h} \\ \dot{n} \end{bmatrix} = \begin{bmatrix} 0 \\ (I_{ext} - I_{Na} - I_K - I_l)/C \\ \alpha_m(1-m) - \beta_m m \\ \alpha_h(1-h) - \beta_h h \\ \alpha_n(1-n) - \beta_n n \end{bmatrix} + q \tag{20}$$

Since the only measured variable is the membrane potential (V) of the pyramidal cell, the measurement equations would be:

$$y = Cx + r \tag{21}$$

where $C = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 \end{bmatrix}$

By augmenting the observed state variables with unobserved state variables and system parameters, the UKF can estimate and track both unobserved variables and system parameters.

The covariance matrix for process noise Q and observation noise R should be positive semi-definite symmetric matrixes with off-diagonal elements valued as zero. In our case, Q is a 5×5 matrix as shown in Eq.(22) , where Q_1 is the process noise covariance for parameters and Q_2 is the process noise covariance for variables. We suppose the process noise of variables is uncorrelated with each other. Therefore, the off-diagonal elements are set to be zero. R is a 1×1 matrix for the measurement noise covariance.

$$Q = \begin{bmatrix} Q_1 & 0 & 0 & 0 & 0 \\ 0 & Q_2 & 0 & 0 & 0 \\ 0 & 0 & Q_2 & 0 & 0 \\ 0 & 0 & 0 & Q_2 & 0 \\ 0 & 0 & 0 & 0 & Q_2 \end{bmatrix} \tag{22}$$

The tracking results are highly dependent on Q, R and initial values. We chose Q and R that gave us the best results in two ways:

1) The Chi-squared (χ^2) test is often used as a diagnostic of the statistical model that gives information about Q and R in the KF [21]. Based on the definition of χ^2 in KF [21], the χ^2 in this paper can be defined by

$$\chi^2 = (y - \tilde{y})^T(\tilde{P}_{yy})^{-1}(y - \tilde{y}) \tag{23}$$

The mean of χ^2 should be around 1, reflecting the innovation is consistent with the innovation covariance. It tests whether there is model data mismatch.

2) Although the χ^2 test works well on model generated data, the model cannot be perfect for the real experimental data. We seek to minimize the root mean square error (RMSE), which reflects how well the predicted values fit the experimental data.

$$RMSE = \sqrt{\sum_{i=1}^{N}(x_i - \hat{x}_i)^2/N} \tag{24}$$

We plotted RMSE as a function of Q and R, and chose the set that gave us the lowest RMS errors for both voltage and current, suggesting the best fitting.

All simulations were carried out using MATLAB. The integration time-step is 0.01ms while the membrane potential of the neuron was measured each 0.1ms.

D. Experimental Data

Cells to be patched were identified based on morphological characteristics and the location of the cell body within hippocampal layers. After being patched, cells were injected with negative current to hold them at -75 to -80 mV. Negative and positive square wave current pulses were injected in increments of 50-100 pA for 500 ms to determine the membrane properties of the cells [18][20][24].

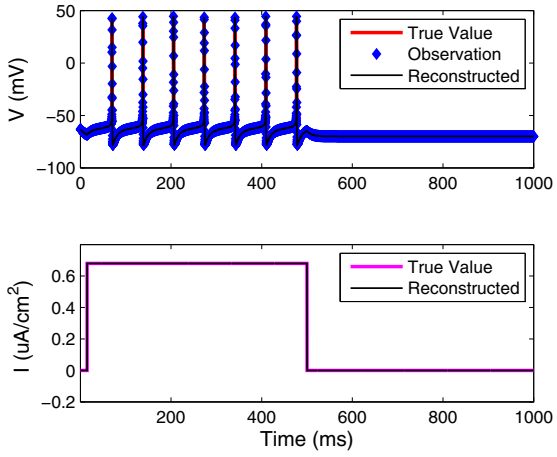
III. RESULTS

In our study, we tracked the input stimuli and neural dynamics, within UKF framework by assimilating the membrane potential measurements in two cases: 1) model generated data; 2) real experimental data.

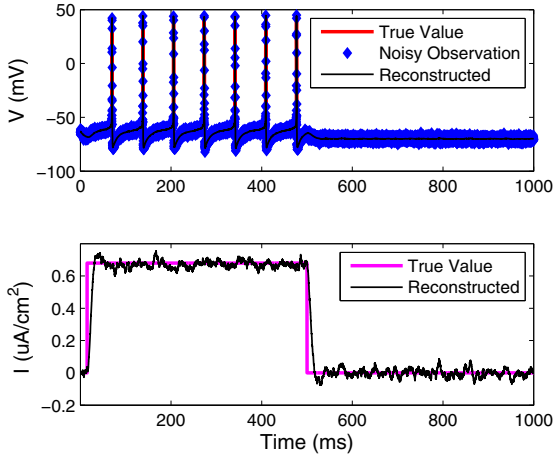
A. Model Generated Measurements

In this section, the observations are based on simulation only, generated by corrupting membrane potentials (V) with white Gaussian noise to mimic experimental data. By comparing the estimated values with the true values, we can evaluate the performance of the tracking.

1) Step Current: typically, in the experiment, negative and positive step current are injected into a neuron to determine the passive and active properties of the cells and confirm the cell-type, such as excitatory pyramidal cell or inhibitory basket cell [20][24].



(a)



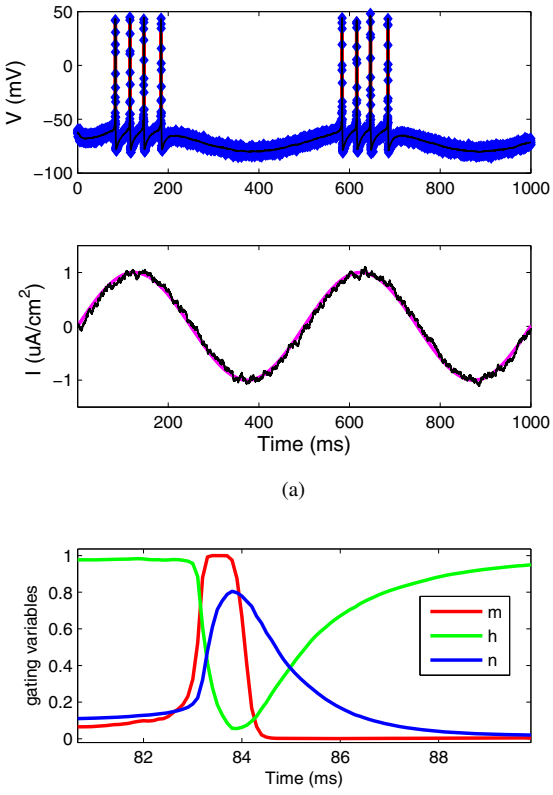
(b)

Fig. 2: Assimilating noise-free (a) and noisy observations (b) with unknown step current injection: measured membrane potentials (blue dots), true value of membrane potentials (red) and input current (pink), reconstructed membrane potentials and input current (black).

When the pyramidal cell is stimulated by positive step current, it generates a series of action potentials. Here, the observations are the membrane potential and simulated by injecting positive current into the cell. We first showed the tracking performance from noise-free observation (Fig 2a). The intracellular voltage and input current were reconstructed with excellent accuracy from noise-free observation (Fig 2a). The RMS errors of membrane voltage and input current are close to zero, suggesting the reconstruction is comparable to previous studies [3].

We then showed that the UKF can successfully reconstruct the input current from noisy measurements. In Fig 2b, the observations are corrupted by 20% measurement noise, corresponding to noise strength $d = 1.5$. Therefore, the covariance of measurement noise $R = d^2$ is 2.25. The choice of $Q_1 = 0.0625$ and $Q_2 = 0.0001$ gives us a χ^2 close to 1. When the observation is noise-corrupted, the reconstructed voltage and input current still have a good approximation to their true values. The RMS errors of voltage and input current are also very small, reflecting high estimation accuracy.

2) Periodic Current: we mimic background oscillatory drive by injection of sinusoidal current waveforms. When the neuron is stimulated by an unknown sinusoidal current, it generates a periodic firing pattern of response spikes. The effect of periodic current can modulate the firing frequency of the neuron.



(a)

(b)

Fig. 3: Assimilating the noisy observation with unknown periodic current injection. (a). measured membrane potentials (blue dots), true value of membrane potentials (red) and input current (pink), reconstructed membrane potentials and input current (black). (b). estimated neural dynamics corresponding to the first spike in (a).

Intracellular sinusoidal currents were injected in the neuron model. The frequency of the waveform was 2 Hz and the intensity was 1 $\mu A/cm^2$. The observed membrane voltage was corrupted by 20% measurement noise with noise strength $d = 1.9$. Therefore, the covariance of measurement noise $R = d^2$ is 3.61. The choice of $Q_1 = 0.16$ and

$Q_2 = 0.0001$ gives us a χ^2 close to 1.

Results showed that the reconstructed voltage and current from the noisy observation approximates their true values (Fig 3a). We also reconstructed the inaccessible neural dynamics, such as the voltage gated ionic channels, Na^+ and K^+ (Fig 3b). Once the unobserved neural dynamics is available, we can establish a closed loop feedback controller to manipulate the membrane voltage based on such estimates [22].

B. Real Experimental Measurements

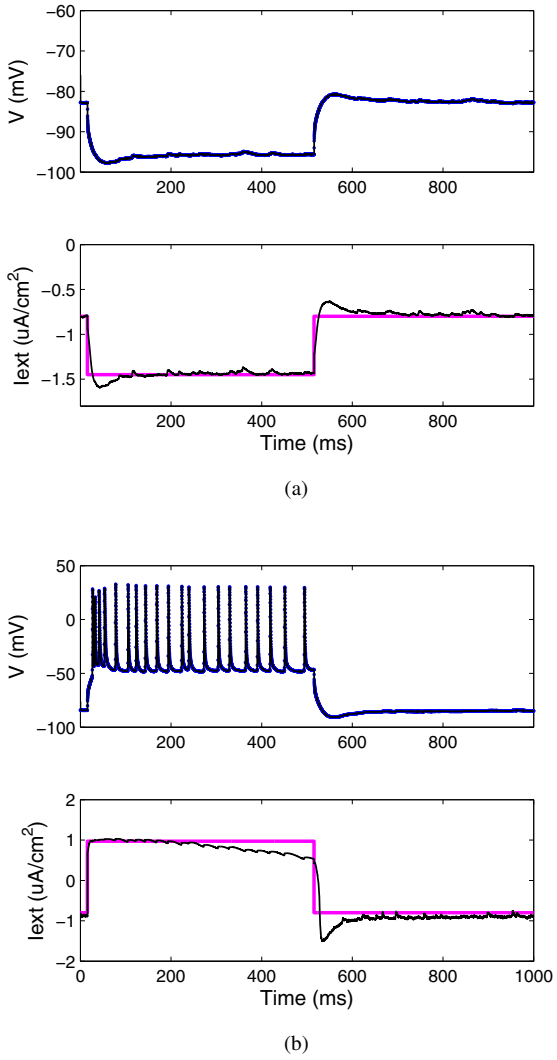


Fig. 4: Assimilating intracellular experimental data with unknown step current injection. The neuron response in pyramidal cell is generated by injecting negative (a) or positive (b) step current from 15.5ms to 515.5ms. Measured experimental data at the pyramidal cell (blue dot); estimated trajectory of membrane voltage and input current (black).

We have shown that the UKF can be used to reconstruct the global dynamics of the biophysical neuron model using model generated data as the observation. However, the model is always an imperfect representation of nature. The real experimental data is also more complicated than the model generated noisy data. Here, we tracked the real experimental data from *in vitro* patch clamp recordings by the UKF approach.

In Fig 4, after a whole cell patch, the pyramidal cell was held at -83 mV by negative current. Negative and positive square wave current pulses were injected in increments of 70pA for 500ms. Here, we chose $R = 0.0001$, $Q_1 = 0.001$ and $Q_2 = 0.0001$ that gave us the best tracking results.

Results showed that the UKF framework can successfully reconstruct membrane voltage and input current from experimental data with this simple neuron model. The reconstructed input currents are a good approximation of negative (Fig 4a) and positive (Fig 4b) step currents injected into the neuron in the experiment. We noticed that the reconstructed positive current decreased (Fig 4b) during 500ms injection. This is because the model is not ideal for the pyramidal cell. The drift comes from the lack of frequency adaptation current in the model, such as M-type current or medium afterhyperpolarization (mAHP) current. The decrease in the frequency of spiking in the experiment is mostly due to this kinds of current. Since the goal of this study was to assimilate complex neuronal dynamics using the simplest model, we have ignored this feature in the model for this preliminary report. The filter compensate for this current by the drift in the estimated current as shown. Such knowledge would be constructive in further optimizing similar models in the future. In addition, the sodium and potassium gating variables were also reconstructed. We have noticed that these reconstructed gating variables sometimes are not within their physiological range of 0 and 1. Since the model is simple, the tracking still works very well. However, it is useful to employ constrained Kalman filtering techniques [23][25] to project the gating variables in the range of 0 and 1 for a more complex model.

IV. CONCLUSIONS AND FUTURE WORKS

In this paper, the Kalman filter was introduced to reconstruct the input stimulus and neural dynamics from noisy neuronal measurements. This method has successfully reconstructed the input-output relationship in a single neuron with both model generated data and experimental data from *in vitro* patch clamp recordings. The marriage of the ensemble Kalman filter and the neuron model in this paper also provides a powerful strategy to generate control signals based on the measured and estimated variables. A discussion of the use of ensemble Kalman filtering in dynamic clamp was presented in [14]. By setting a reference voltage, we can estimate the current required to inject. For example, if the reference voltage is set to a constant value below the threshold of the action potential, then the controller can annihilate the action potential propagation from one neuron to others. This preliminary study provides an intriguing set of results towards future observing and controlling neuron dynamics.

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