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Linear Time Variant Model of Synapse/Neuron and its Adaptation Method; Application on Predicting Hippocampus CA1 Neuron's PSP

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***Abstract*— In this paper, development of a linear model of a neuron/synapse, along with a method for its parameter optimization is addressed. Spike input and output was assumed in the model. The developed system was utilized for modeling behavior of a single cell hippocampal neuron. Utilizing this method, the model's parameter was adapted to reproduce cell's output using the same input spike train which was applied to the hippocampus cell. The results showed that the EPSP and spiking patterns of the hippocampus cell's output can be reproduced by 96% accuracy employing approach of this study. Due to simplicity of the proposed system, modeling of a large scale network can be easily achieved. Results of a simulation study for a case when there are 80 synapses is provided.**

I. Introduction

Neurons along with synapses are the computational building units of human nervous system. In particular, synapses play significant role in generating neurons response to a stimuli or series of stimulus. It is well studied that depending on temporal pattern of stimulus, dynamics of a synapse changes by forming short and long term substrates for synaptic response [1, 3, 4, 5]. There are many researches published on mathematical modeling of synaptic response considering different aspects of neural cells. The models have considered cellular chemistry, ionic channels property, synaptic transmission, and electro-chemical properties in response to stimulus under different spatial-temporal condition of synapse and its counterpart neuron. In summary, while some of the presented models, detail biological plausibility, the others focuses on computational efficiency. No need to mention that in all of these models nonlinear properties of synaptic responses are mathematically described by utilization of nonlinear equations.

In the field of neural engineering in general and biomimetic devices for enhancing functionality of impaired hippocampus in particular, there are many challenges ranging from developing computational platform for executing mathematical models for processing signals to materials interacting with live cells. This paper focuses only on mathematical modeling and computational challenges concerning biomimetic hippocampal devices. Three major topics are covered in this paper:

a) Model of synapse/neuron. Previously published mathematical models of synaptic transmission are nonlinear rendering adjusting their parameter for input-output modeling of hippocampal neurons/synapses to be infeasible utilizing of-the-shelf optimization algorithms. The nonlinear properties of synapse/neuron models for spiking stimulus makes it extremely difficult not impossible for tuning the models parameters. This is because nonconvexity of dynamical models provides unpredictable convergence time, and non unique solution for the problem in hand. Though, mathematically a nonlinear system can be replaced by an infinite order convex/concave system, Yousefi et al [2] showed that nonlinearity in synapse/neuron can be replaced by a finite order linear model system without degradation of synapse/neuron response performance. Yousefi et al linear model of synapse/neuron incorporated a set of linear differential equations with the order of Eight. Albeit the model increased computational cost of the model, it has provided a convex synapse/neuron model offering predictable training time. The hippocampal synapse/model model of this study is based on linear system introduced in [2] which will briefly described in section II.

b) Measuring closeness of spiking signals. Measuring quality of spike-in spike-out model for processing hippocampal signals requires an objective function with which similarity between output of live cells and output of the model is compared. Due to spiking nature of system's inputs and outputs of the system, one-to-one comparison between spiking signals does not provide meaningful similarity measure. Thus some of previous researches have been focused on similarity measurements derived from *temporal distribution* of the spikes i.e. rate of spike. Another approach is to form a comparison measure based on neuron's membrane potential at the time of spike. Since at the time of spike membrane potential must be above firing threshold and at any other times the cross membrane voltage should stay below firing threshold therefore similarity measure function based on the mentioned two constraints provides a convex representation of closeness of desired and target spiking outputs. In this paper, measuring closeness of two spike train is addressed by development of convex objective function which is based on fully or partially observed membrane potential.

c) Model Predictive Control method for estimating parameters of the model − employing experimental data − has been utilized [7]. A single layer spike-in spike-out model of hippocampus is proposed and training algorithm is formulated for estimating unknown parameters of the model. Efficiency of the model and training algorithm is explored through two examples. In the first example, a model with

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known parameters is assumed and data is generated based on the model. It is demonstrated that the proposed training method can estimate the free parameters of the model given input-output data. The second example considers a realistic scenario by utilizing data recoded from a rat brain's hippocampus. A single layer neural model for the data is assumed and model's parameters are estimated.

II. Methods and Algorithms

A. Facilitation Depression Model and its Linearization

In modeling level, Facilitation-Depression - FD - model of synapse dynamics proposed by Tsodyks et al [5] and Dittman et al [3] was employed. The model is a lump sum description of synaptic mechanisms and in general the model predicts synapse output to be highly correlated with multiplication of facilitation and depression factors. Synapse by FD model can be described by:

$$\partial F_t/\partial t = -(F_t - F_0)/\tau_f + (1 - F_t) * \Delta F * \delta(t - t_{ap}) \quad (1)$$

$$\partial N_t/\partial t = -(N_t - 1)/\tau_r - F_{t^+} * N_t * \delta(t - t_{ap}) \quad (2)$$

$$\partial G_t/\partial t = -G_t/\tau_g + N_{max} * F_{t^+} * N_t * \delta(t - t_{ap}) \quad (3)$$

$$\partial K_t/\partial t = -K_t/\tau_k + N_{max} * F_{t^+} * N_t * \delta(t - t_{ap}) \quad (4)$$

$$V_t = G_t - K_t \quad (5)$$

where F_t is facilitation dynamics in response to input spikes i.e. APs, and N_t is the portion of release-ready vesicles. G_t and K_t describes α-synapse function for PSP - V_t - emerging from released vesicles. The derived equation for PSP consists of $F_{t^+} * N_t$ term making PSP to be non-linearly dependent to the state variables of the synapse stated in the equations 1 through 5. The approach presented in [2] was utilized to generate linear space model for the synapse. In summary, the discrete linear synapse can be described by the following difference equations:

$$X_{n+1} = (A_s + 1_{ap}(n) * A_t) * X_n + (B_s + 1_{ap}(n) * B_t) \quad (6)$$

$$X_n = [F_n \quad L_n \quad N_n \quad R_n \quad Q_n \quad M_n \quad H_n \quad G_n \quad K_n]' \quad (7)$$

$$V_n = [0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 1 \quad -1] * X_n = C * X_n \quad (8)$$

In the equations (6)-(8), X_n is the synapse state space vector consisting of F_n facilitation, L_n a slack variable, N_n vesicles ready for release, R_n, Q_n, M_n, and H_n slack variables, G_n, and K_n PSP related variables. V_n is the neuron's membrane potential.

Membrane potential of a neuron is the summation of PSPs caused by individual synapses. A neuron fires an action potential if it is not in the refractory period and if its membrane potential is above firing threshold. This can be modeled by the following equations:

$$V(n) = \sum_m V^m(n) + \mathrm{Ref}^o(n) + U^e(n) \quad (9)$$

$$U^e_{n+1} = (1 - \Delta t/\tau_a) * U^e_n + K * \Delta t * I^e(n) \quad (10)$$

$$\mathrm{Ref}^o_{n+1} = (1 - \Delta t/\tau_{ref}) * \mathrm{Ref}^o_{n+1} + \mathrm{Ref}_{\mathrm{amp}} * 1^o_{ap}(n) \quad (11)$$

$$\text{If } V(n) > V_{th} \ \cap \ V(n) - V(n-1) > 0 \rightarrow 1^o_{ap}(n) = 1 \quad (12)$$

The simulation results of the study show that the linear (approximate) model of the synapse does not impose any error if the time gap between input APs exceeds 3 msec. In addition the error between the output of approximate and non-approximate models is less than 5% when time interval between input APs are less than 3 msec. Linear properties of the approximate model in addition to its high performance makes it a strong candidate for processing large scale neural signals. In general, tuning parameters of nonlinear model of synapse/neuron is achieved in an unpredictable time; parameters of the stated linear approximate model can be estimated for input-output modeling of neural activities in a very short and predictable time.

B. Model Predictive Control method for parameter estimation

The synapse/neuron model presented in the previous section provides linear state space model of the combined synapse and neuron dynamic behaviors. However spiking property of input and the output of the model renders parameter estimation of the model to be a complex task. In order to address parameter estimation of the model two scenarios are considered:

1. EPSP of the post-synaptic neuron is known

In this scenario, since the states of the model are fully observed therefore parameter estimation of the model becomes a fitting problem and it can be solved by Model Predictive Control − MPC − method. It worth mentioning that if EPSP has been observed over the time period of T, then N_m number of unknown parameters can be estimated by solving $N_s \times T$ set of linear equations. There is also a need for implicit conditions which guarantees the membrane potential of the neuron is above firing threshold at time of spikes. Therefore:

$$\text{minimize } O = \sum_{n=0}^{\infty} f(x(t)) \quad (13)$$

subject to:

$$V_{n=n_{spike}} > v_{threshold} \quad (14)$$

$$V_{n\neq n_{spike}} < v_{threshold} \quad (15)$$

$$X(n+1) = (A_s + A_t * 1_{ap}(n)) * X(n) + (B_s + B_t * 1_{ap}(n)) \quad (16)$$

$$N_{max} < 1, \quad N_{max} > 0 \quad (17)$$

$$\Delta F < 1, \ \Delta F > 0 \quad (18)$$

In the equation (13) the objective function O is replaced with a non zero number which converts the estimation into a feasibility problem.

2. EPSP is only observed at the time of firing

Second scenario is when EPSP is not fully observed and rather it is only observed when neuron fires. This makes states of the space-state model to be unknown which have to be estimated along with other unknown parameters of the system. To be able to estimate both state variables and unknown parameters of the model, a two step procedure is considered. In the first stage parameters are assumed to be known and state variables are estimated and in the second stage with known state variables unknown parameters are updated. Furthermore, training procedure is performed between two consecutive spikes. This is because state-space system is time variant and it varies at the time of input spike.

III. Simulations and Case Study

Two sets of data were employed to validate effectiveness of the model and also parameter estimation algorithm: a)

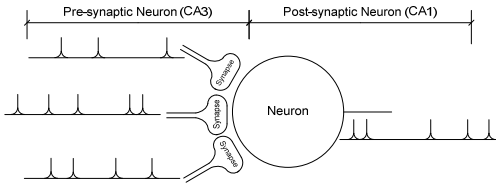

Figure 1: Multiple synapses connected to a neuron

artificially generated data using the model, and b) hippocampal recordings of live cells. The goal was to tune the parameters of the model by the input−output data either generated officially or recorded from live cells.

In the first set of experiments, it was assumed that parameters of the model are all known and EPSP was generated using the known model. Specifically, a random patterns of spikes were provided to the input of the system i.e., synapse and EPSP was produced. After having set of EPSPs and the input spike patterns, the parameters of the system was estimated.

For the purpose of second set of experiments, the recordings were made from hippocampus CA1 pyramidal cell under whole-cell patch clamp configuration. Input was made via electrical stimulation of the CA3 axons, so the result of synaptic activation in the CA1 cell was observed and recorded.

In the equations 1 through 12 stated in the section II, only two parameters are unknown namely N_{max} and ΔF. These parameters provide long and short term potentiating factors and they are estimated from the data during training. The other parameters were assumed to be fixed and known.

A. Model adaptation using artificially generated data

In this simulation a single neuron with 10 synapses were networked such that synapses were receiving random spike input and providing PSP to the post-synaptic neuron (feed forward connection). Neuron's output was only observed at the time of firing assuming all parameters of the system is known. Therefore the goal was set to estimate N_{max} and ΔF of each synapse utilizing the same input spikes and the time of neuron's spike time. Figure 2 provides training progress and performance of the trained network. Referring to the Figure 2.b almost all unknown ΔF parameters are precisely

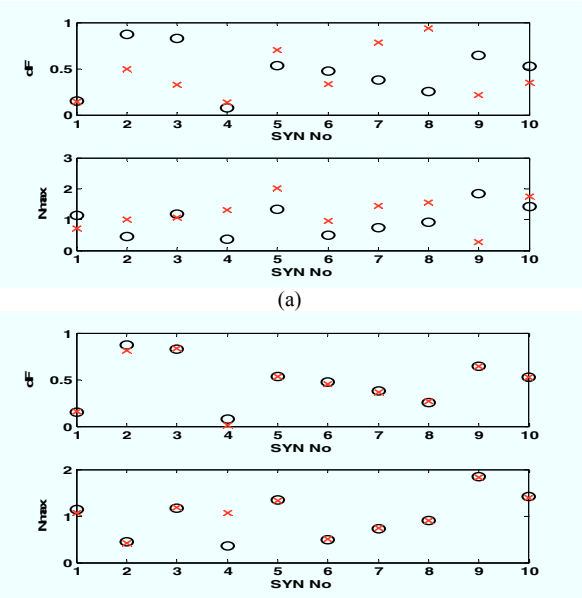

Figure 2a, 2b: unknown parameters of the system before training (a), and trained parameters (b).

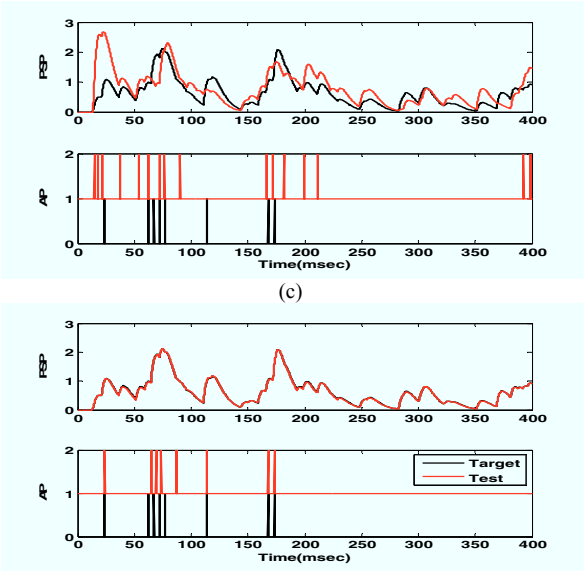

Figure 2c, 2d: membrane potential and output spikes before training (a), and trained membrane potential and target spikes (b).

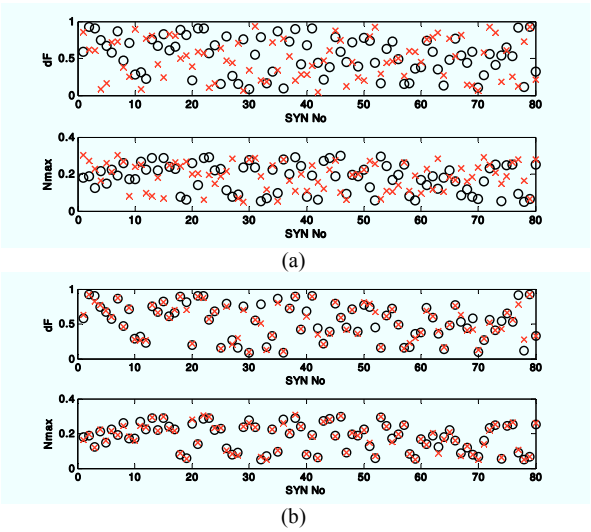

Figure 3: Eighty synapses with 160 unknowns, unknown parameters of the system before training (a), and trained parameters (b).

estimated and only one out of ten N_{max} parameters has not converged to the target value. This is something expected because the objective is to have neuron to fire at the desired spike time and since the goal has been reached the procedure has stopped.

The same type of simulation was performed to show that the method of this study can be scaled up by utilizing more synapses and neurons. Single neuron with 80 synapses networked and unknown parameters were estimated. Figure 3 shows the parameters before and after training. The 160

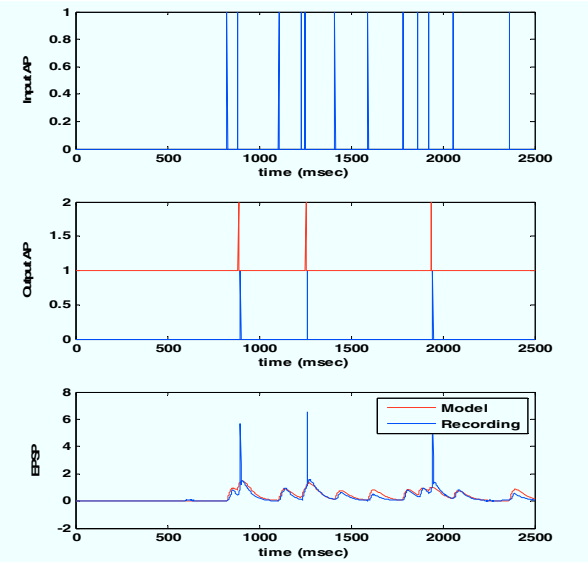

Figure 4: top is the input stimulus applied to the CA3, middle is the firing times of the model and cell, bottom is the generated EPSP by the model and recorded from the cell.

parameters of the model estimated in less than one second utilizing an average desktop computer.

B. Model adaptation using recordings of the hippocampal CA3-CA1 recorded data

Data collected from CA1 neuron by applying Poisson distributed stimulus to the CA3 axon. The data collection was made by patch clap configuration in which rat slice thickness was 0.4 millimeter. It was assumed that only a single synapse and single neuron is sufficient for modeling the input output behavior of CA3-CA1 connections. The plan was to step up the number of synapses until the model generates the desired EPSP and spike timings. Figure 4 demonstrates the recorded data and the hippocampus cell's EPSP and the model predicted EPSP and spike times.

The model's parameters after training is shown in the table I. The other known parameters of the model are also shown in the table I.

Table 1: Model Parameters

Parameter		**Value**
$\boldsymbol{\tau_F}$	Facilitation Time Constant	250 msec
$(\Delta \boldsymbol{F}, \boldsymbol{F_0})$	Facilitation Increment Factor	(**0.37238**,0)
$\boldsymbol{\tau_R}$	Vesicle Recovery Time Constant	350 msec
$\boldsymbol{N_{max}}$	Maximum Number of Release Sites	**2.649**
$(\boldsymbol{\tau_g}, \boldsymbol{\tau_k})$	Time Constant of EPSP	(40, 29) msec

IV. Conclusion

In this paper we presented application of linearized synapse model defined by Facilitation and Depression. If the time interval of the spikes inputting to the synapse remains above three milliseconds then the prediction error of a linear synapse model does not exceed five percent. So it makes utilization of linear synapse model to be an advantage when there is a need for scaling up the size of the spiking neural network. In this scenario, parameter estimation of the model can be achieved in a predictable time comparing to when the synapse model is nonlinear and its parameter estimation is achieved in an unpredictable time.

The method of this study didn't require defining a specific mathematical function for measuring closeness of two spike patterns rather implicit constraints for the membrane potential at the time of spike was added to the objective function. The objective function combined with its constraints is a convex function however due to time variability of state space model, the parameter update has to be performed in between two consecutive spike intervals. In all of the simulation tasks of this study the parameters of the system converged to a steady-state value.

The whole-cell recoding of CA3-CA1 hippocampal neurons was modeled by a single synapse and a neuron. The estimated parameters of the neuron provided capability for predicting very precise cell's firing time. At the same time the estimated EPSP had below two percent error compared to the one recorded from live cell. This makes utilization of state-space based model for predicting synapse/neuron's response to be attractive because all states of the synapse and neuron will be observable. It is worth mentioning that kernel based models for modeling EPSP can only provide prediction of EPSP with no details on synapse/neuron's intermediate states.

Field potential recording of hippocampal cells involves interaction of multiple layers of neurons with many synapses. when field potential is recorded, the EPSP from inter-layers are unobserved. State-Space modeling of field potential recordings, requires the MPC to be extended for multi-layers. Though, in the current work strength of MPC for estimating unobserved states of the synapse/neuron was explored, it is planned to estimate unobserved inter-layer neuron's EPSP along with the other synapse and neuron' parameters. The later will be the work for future.

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