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Chaos and bifurcation in a stochastic model of the calyx of Held

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Abstract—The calyx of Held is a giant glutamatergic synapse in the auditory system. Short-term plasticity (either facilitation and depression) have been observed experimentally and in proposed biophysical models of the system. Because of the large number of discrete release site for the vesicles (which in turn drive the gating process at the synapse), the random process of vesicle release is modelled as a continuous differential equation. We propose a new stochastic discrete model of vesicle release and show that even for large pools of release sites, the short-term plasticity of the system deviates from the continuous model as the number of available docked vesicles decreases. We compare results of this new stochastic-discrete biophysical model with the previous deterministic-contiunous biophysical model and with models derived from synaptic transmission data obtained from the rat cortex.

1. Introduction

Synaptic transmission of an action potential (AP) between neurons is governed by the lossy electrical transmission of the AP voltage pulse along the synaptic pathway. At the post-synaptic terminal this electrical impulse triggers the release of chemical neurotransmitters which cross the gap junction and initiate the corresponding electrical signal at the output neuron. Successful transmission depends on the availability of sufficient neurtransmitter at particular vesicle docking sites located at the output terminus of the synapse. A large synapse, such as the calyx of Held, may have as many as 3000 such release sites, while smaller synapses in the cortex may have only between one and ten.

Of course, for the AP arriving at the synaptic output terminus to be successfully propagated to the output neuron there must be sufficiently many release sites with docked vesicles. Stimulation with a train of action potentials may deplete this pool of docked vesicles and therefore decrease the post-synaptic potential (PSP) observed at the output neuron. This depletion of docked vesicles provides a model for experimentally observed synaptic depression (that is, inhibition of PSP response) which provides an example of short-term plasticity in neural information processing. For the calyx of Held this phenomenon has been verified in [1].

In this paper we describe a model of short-term synaptic depression in the calyx of Held [1]. This model represents the population of vesicle release sites, and the fraction of these which are occupied, as a continuous quantity. Change of that quantity is governed by a differential equation. This is a reasonable approximation to make for the calyx of Held, as the number of release sites is fairly large. However, for cortical synapses the population is much smaller. We adapt the model presented in [1] for the case of a small population and when each site is released and refilled stochastically. We explore the dynamics of this system and show that the qualitative behaviour is similar to that observed in the cortical synapse of a rat [4].

In the next two sections we introduce our model, and describe our analysis. In Sec. 4 we conclude.

$\tau_r =$	2.5 sec.		
$n_e =$	0.056		
$k =$	193200		
$\alpha =$	4		
$C_0 =$	0.034 mM		
$\tau_f =$	0.0252 sec.	$n_f =$	0.091
$\tau_i =$	8 sec.	$n_i =$	0.003
$\tau_b =$	0.6 sec.	$n_b =$	0.21
$\tau_D =$	0.05 sec.	$n_D =$	3.3

Table 1: Parameter values (from [1]) used to simulate the calyx of Held. For details of the model, see Sec. 2. Note that the standard unit for calcium concentration in this model is milli-M.

2. Model

We first describe the biophysical model of synaptic transmission at the calyx of Held presented in [1]. We then describe our adaptations of this model for finite populations of vesicle release sites.

In the calyx of Held the number of vesicle docking sites is large (of the order of 1800-3000 [1, 3]) and that population can be approximated as a continuous variable. Let $n(t)$ denote the fraction of available docking sites with a docked vesicles, and let $p(t)$ denote the probability of a given vesicle being released upon arrival of an AP. Let the δ-function denote the arrival of action potentials ($\delta(t) = 0$ for $t \neq 0$ and $\int_{-k}^{k} \delta(t)dt = 1$) at time t_s. The vesicle population is then controlled by the continual reoccupation of empty docking

sites (with rate τ_r) and the incremental response n_e to an AP. Hence,

$$\frac{dn}{dt} = (1-n(t))\left[\frac{1}{\tau_r} + n_e\delta(t-t_s)\right] - T(t)\delta(t-t_s) \quad (1)$$

$$p(t) = 1 - \exp\left(-k([\mathrm{Ca}^{2+}]_i)^{\alpha}\right) \quad (2)$$

$$T(t) = n(t)p(t) \quad (3)$$

where $T(t)$ is proportional to the quantity of neurotransmitter released after an AP, and $[\mathrm{Ca}^{2+}]_i$ is the amount of calcium ions present in the synapse. The parameters k and α are determined experimentally and dictate the rate of release. The availability of calcium ions is modelled by the following system of four ordinary differential equations

$$[\mathrm{Ca}^{2+}]_i = C_0 c_1(t) \quad (4)$$

$$\frac{dc_1}{dt} = \frac{c_2(t)-c_1(t)}{\tau_f} + n_f\delta(t-t_s) \quad (5)$$

$$\frac{dc_2}{dt} = \frac{i(t)}{\tau_i} + \frac{b(t)}{\tau_b} - [n_i + n_b T(t)]c_2(t)\delta(t-t_s) \quad (6)$$

$$\frac{di}{dt} = -\frac{i(t)}{\tau_i} + n_i c_2(t)\delta(t-t_s) \quad (7)$$

$$\frac{db}{dt} = -\frac{b(t)}{\tau_b} + n_b T(t)c_2(t)\delta(t-t_s) \quad (8)$$

where the various parameters τ_f, τ_i, τ_b, n_f, n_i, n_b control the relative rates of the various terms and C_0 is a constant of proportionality. The Eqns. (5) and (6) account for calcium facilitation and suppression and the $i(t)$ and $b(t)$ terms in Eqn. (6) are the activity in the inactivated and blocked calcium channels. One can note that Eqns. (6), (7) and (8) form a closed system such that c_2+i+b is constant. Finally, the PSP is given by

$$R(t) = T(t)(1-D(t)) \quad (9)$$

$$\frac{dD}{dt} = -\frac{D(t)}{\tau_d} + (1-D(t))n_d T(t) \quad (10)$$

where $D(t)$ models desensitisation of the output. The various parameters in this model are assigned values (adopted from [1]) according to Table 1.

This is the model proposed by [1], in Fig. 1 we illustrate the model behaviour. One can observe short term depression of the PSP in response to continued stimulation at a fixed frequency. To account for the effect of the finite pool size we modify this system as follows.

Let N_D denote the total number of docking sites, and $n_d^{(k)}$ the occupancy state of docking site k, $k = 1, \ldots, N_D$

$$n_d^{(k)} = \begin{cases} 1, & \text{if site } k \text{ is occupied} \\ 0, & \text{otherwise} \end{cases}$$

and analagous to Eqn. (1), we now have that

$$n(t) = \frac{1}{N_d}\sum_k^{N_d} n_d^{(k)}(t) \quad (11)$$

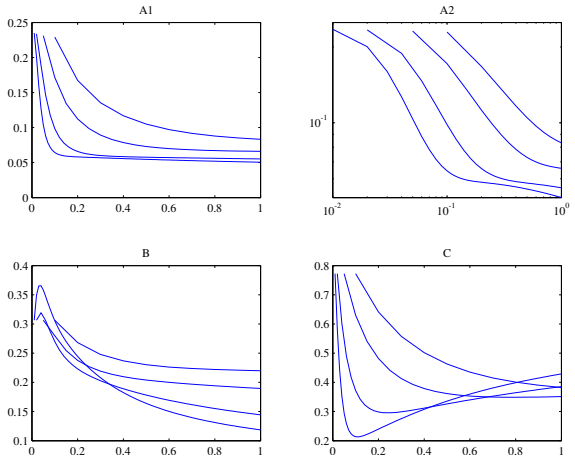

Figure 1: Short term synaptic depression in the continuous model of the calyx of Held. In this figure we recalculate the results presented in [1]. Panel (A1) and (A2) show the time course of the PSP response for stimulation at a constant rate (from top to bottom, that it 10, 20, 50 and 100 Hz). The lower panels show the release probability $p(t)$ (B) and the docking site occupancy $n(t)$ (C).

The individual vesicle docking sites' occupancy and their tally $n(t)$ are now defined to be constant between AP events. Upon the arrival of an AP, an occupied docking site discharges its vesicle and become empty with probability $p(t)$, given by Eqn (2), above. The probability of an unoccupied docking site acquiring a vesicle is given by $q(t)$

$$q(t_s) = \int_{t_{s-1}^+}^{t_s^-} \frac{(1-n(t))dt}{\tau_r} + n_e(1-(n(t_s^-)) - T(t) \quad (12)$$

which is obtained by integrating the rate equation (1) over the interval between successive APs t_{s-1} and t_s. Since we make the approximation that $n(t) = n(t_{s-1}^+) = n(t_s^-)$ for all $t \in (t_{s-1}, t_s)$ we can simplify this to give the transition probability

$$q(t_s) = (1-(n(t_s^-))\left(\frac{1}{\tau_r} + n_e\right) - T(t). \quad (13)$$

This dynamic can be summarised in the following transition matrix

	$n_d^{(k)}(t_{s-1}) = 0$	$n_d^{(k)}(t_{s-1}) = 1$
$n_d^{(k)}(t_s) = 0$	$1-q(t_s)$	$p(t_s)$
$n_d^{(k)}(t_s) = 1$	$q(t_s)$	$1-p(t_s)$

(14)

The remaining equations (2)-(10) are unchanged.

Figure 2 illustrates the release process for stochastic-discrete simulations with $N_d = 3000$ and with $N_d = 6$. For large N_d the ensemble average and the single realisation are close, and close to the results obtained with the continuous model (Fig. 1). Nonetheless, the initial rate of depression

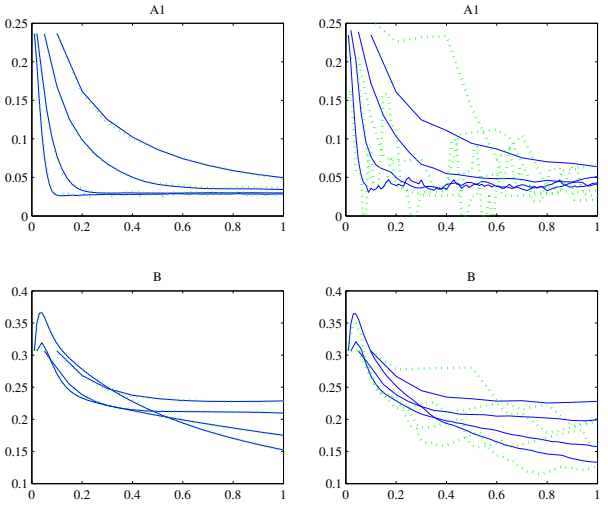

Figure 2: Short term depression in the stochastic-discrete model of synaptic transmission. On the left are results for $N_d = 3000$ and on the right for $N_d = 6$. The upper panels (labelled A1) depict PSP for stimulation at 10, 20, 50 and 100 Hz. The lower panels show the release probability $p(t)$ (panels B). In each case we illustrate an ensemble average of 50 trials (solid blue lines) and single random representative (green dashed line).

in the discrete model is faster and more abrupt, particularly at 100 Hz. This is plausible because when the docking sites are depleted of vesicles, the continuous model and the equivalent discrete model diverge. That is, the relatively small number of docked vesicles, rather than the large number of total docking sites, becomes important. For the case $N_d = 6$ the small sample effect and quantisation in the output are both evident. In the next section we explore this model in more detail and study it's behaviour compared to real time series data.

3. Dynamics

In [4] we describe a computational study of time series data collected from single pairs of cortical neurons in rats. The data (described in more detail in [2] and in [4]) is obtained from 300 μm slices of the somatosensory cortex of Wistar rats (12–21 days old). Brief current pulses (4 ms, 0.6-1.5 nA) were used to stimulate presynaptic APs, and the resulting EPSPs were recorded in the postsynaptic cell. The stimulation sequence was designed to appear "naturalistic" and followed a doubly stochastic, inhomogeneous Poisson process. Typical data from this procedure is depicted in Fig. 3 along with representative model performance.

From this figure we see that the experimental data and

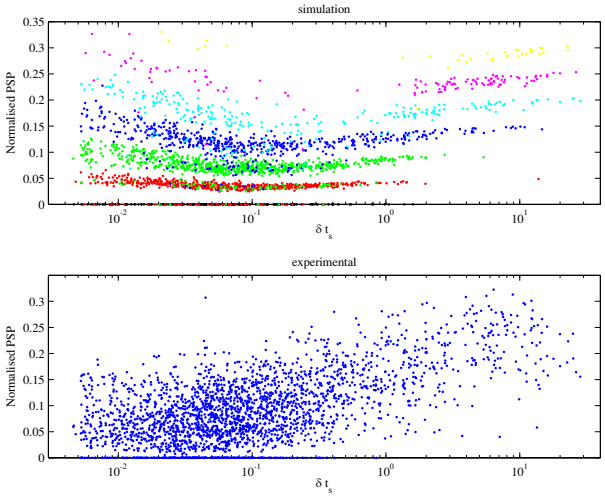

Figure 3: The upper panel depicts the model response ($N_d = 6$) to a simulated naturalistic sequence of APs. The lower panel depicts the response of a rat cortical synapse to the same sequence. Horizontal axis is the time interval between successive APs (log scale) and the vertical axis is the corresponding PSP. In the upper panel quantisation as a result of the limited number of vesicle docking sites is evident. To emphasise this feature, data points are colour coded based on the number of docked vesicle in the model upon the arrival of the AP (0, black; 1, red; 2, green; 3, blue; 4, cyan; 5, magenta; 6, yellow). The same feature is not immediately obvious in the experimental data. Nonetheless, Fig. 4 does demonstrate that similar quantisation can be found in the experimental data.

the biophysical model described here share similar features. The most striking difference between the biophysical model and the data is the quantisation evident in the model. Nonetheless, in Fig. 4 we compute stimulation interval dependent histograms and show that the same banding (quantisation) evident in the model is also present in the experimental data, albeit somewhat obscured by noise.

In order to probe whether the short term depression evident in the models (Fig. 1 and 2) is also present in the data we need to reconstruct, from the data, an approximation to the dynamical system underlying the data. In Fig. 5 we illustrate the result of this calculation. The modelling procedure is described at length in [4], and full details are available from the first author. In brief, we construct an ensemble of radial basis models to predict the next PSP from the last d_e PSPs and the current stimulation interval $t_s - t_{s-1}$. This ensemble is then averaged (using a procedure detailed in [4]) to remove statistical anomalies, and we find that the result is both robust and repeatable. For sufficiently large d_e we find that the results are also fairly robust between different values of d_e. In [4] we show that these models exhibit a wide range of dynamic behaviour, including bifurcation in

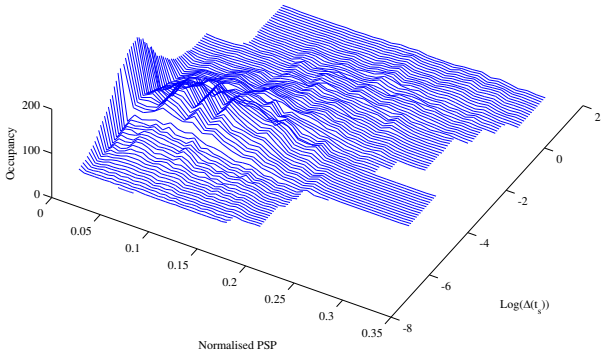

Figure 4: Banded histograms for the experimental data in Fig. 3. For discrete bands of interspike intervalues separate histograms are computes and plotted. This ensemble display highlights the same quantisation evident in the model is also present in the data. Note the characteristic repeating ridges in the histograms, corresponding to the quantisation resulting from the small discrete number of possible occupied release sites.

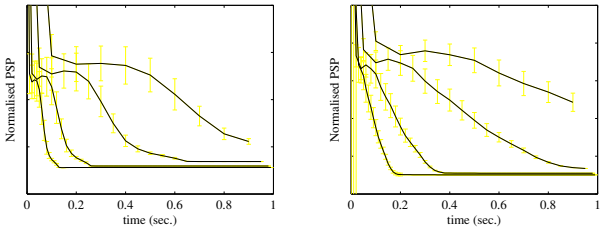

Figure 5: Short term depression in the data driven model of synaptic transmission. The model is built from the data in Fig. 3 and 4 and depends on an embedding dimension d_e. On the left are results for $d_e = 13$ and on the right results for $d_e = 19$. Each panel depicts mean PSP for stimulation at 10, 20, 50 and 100 Hz (compare with previous figures labelled A1). In each case we illustrate an ensemble average of 50 trials (solid black lines) and standard deviation (yellow bars). Responses have the same basic characteristics as Fig. 1 and 2 and are robust to changes in d_e.

asymptotic dynamics and chaotic dynamics. In the current discussion we focus only on the short term depression of the synaptic response to stimulation at a fixed frequency.

From Fig. 5, we find that the short term depression in the biophysical models is also evident in the model built directly from the data. In Fig. 5 the depression is most accentuated at the highest frequencies. However, the data-driven models do have additional characteristics that are not well explained from the biophysical model. In all model simulations we observe a slight, but systematic recovery following stimulation at a fixed frequency (that is, the curves in Fig. 5 are not non-increasing). This feature, if genuinely representative of the data, would not be expected to occur in the biophysical models as these models are constructed only to show depression. Finally, we note that the variance between trials (shown as bars in Fig. 5) is comparable to experimental variation in data reported from [1] in the calyx of Held. Nonetheless, it remains to be determined whether this variance in Fig. 5 is stochastic or related to the nonlinear determinism suggested by [4].

4. Conclusion

From the data driven perspective, the focus of this report, and [4] are slightly different. In [4] we constructed bifurcation diagrams and showed that models of synaptic transmission built from experimental data can exhibit a rich range of bifurcations and chaos. The focus was on examining the asymptotic behaviour for a wide range of stimulation rates (the stimulation interval $t_s - t_{s-1}$) and we showed that varying the stimulation rate can lead to behaviour changing from stable period-one to higher order periodic dynamics or apparently chaotic variation. In the current analysis we also examine variation in dynamics as a function of stimulation rate (10, 20, 50, or 100 Hz). But in this work we are interested in short term plasticity, and therefore we focus on the manner of convergence to what is assumed to be a stable fixed value. We show that our biophysical model agrees well with both the experimental data and the data driven model derived from the experiment.

Acknowledgments

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