

# RESPONSE VARIABILITY OF TYPE-1 NEURONS TO PERIODIC AND RANDOM PULSATILE INPUT

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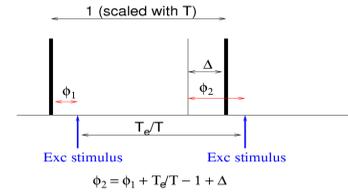
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## Abstract

Globus pallidus (GPe) and subthalamic nucleus (STN) neurons of the basal ganglia communicate with inhibitory and excitatory efferents respectively, but individual cells are not necessarily reciprocally connected [1]. Examining previous models [2] reveals that neurons with both type-1 and type-2 phase response curves (PRCs) could be involved in the GPe-STN circuitry. *In vivo* and *in vitro* GPe recordings show spike time variability that may be due to stochastic external synaptic input, periodic input, or intrinsic membrane noise. In an effort to systematically understand the variability caused by various intrinsic and extrinsic factors (including periodic and stochastic [3]), we report here some modeling work on response properties of type-1 neurons (with period  $T_0$ ) to periodic ( $T_f$ ) and random (with Gaussian noise with width  $\sigma$ ) external pulsatile input by using piecewise linear approximations to the corresponding

typical PRCs. 1:1 phaselocking is achieved for  $r (=T_f/T_0) < 1$ , but large enough that  $r > 1-A$ , where  $A$  is the maximum phase advancement of the PRC. The stability of this state depends also on the skewness of the PRC (parametrized by  $M$ ). PRCs with right skewness allow synchrony for stronger stimuli, but left skewed PRCs limit the stability region to  $A < 2(1-M)$ . Thus left skewed PRCs can show a bigger parametric region displaying a variable spike output. The neuron's desynchronizing mechanism and the firing rate variabilities are studied around but outside of 1:1 locked state. For  $r$  close to unity, the coefficient of variation (CV) of the interspike intervals is a sensitive function of the skewness factor  $M$ . But for weaker stimuli or for  $r \ll 1$ , CV is high but confined to a narrow range. The results are extended to two and large number of uncoupled neurons with type-1 PRCs that are receiving common periodic and/or random inputs.

## SYNCHRONY FOR PERIODIC DRIVING

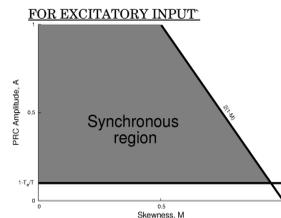


### TWO PIECE LINEAR PRC: SYNCHRONY WITH PERIODIC INPUT

Left skewness promotes synchrony with external input.

Right skewness can destabilize synchrony. For synchrony, the skewness must be less than  $1-A/2$ .

$A$  must also be bigger than  $1-T_e/T$ .



### FOR EXCITATORY INPUT

Existence condition:  
 $1 - A < \frac{T_e}{T} < 1$

Stable fixed point:  
 $\phi^* = M + \frac{1-M}{A} \left( A + \frac{T_e}{T} \right)$

Stability condition:  
 $0 < A < 2(1-M)$

### INHIBITORY INPUT

Existence condition:  
 $1 < \frac{T_i}{T} < 1 + A$

Stable fixed point:  
 $\phi^* = \frac{M}{A} \frac{T_i}{T}$

Stability condition:  
 $0 < A < 2M$

### THREE PIECE LINEAR PRC: SYNCHRONOUS STATE FOR PERIODIC INPUT

The slow rising phase below  $M_0$  does not alter the conditions for synchrony with external periodic input. But another fixed point can exist for  $A < A_0$ , as well as a different fixed point for inhibitory input as given below when  $A > A_0$ :

For inhibitory input:

Existence condition:  
 $1 < \frac{T_i}{T} < 1 + A$

Stable fixed point:  
 $\phi^* = \frac{M}{A} \frac{T_i}{T}$

Stability condition:  
 $0 < A < 2M$

For inhibitory input:

Existence condition:  
 $1 + A_0 < \frac{T_i}{T} < 1 + A$

Stable fixed point:  
 $\phi^* = M_0 + \frac{M - M_0}{A - A_0} \left( -A_0 + \frac{T_i}{T} \right)$

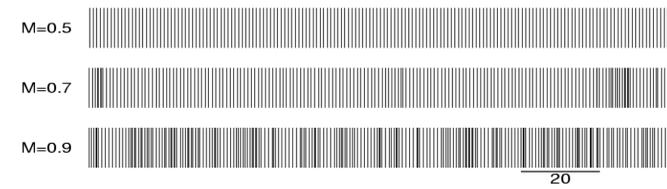
Stability condition:  
 $A_0 < A < A_0 + 2(M - M_0)$

## Results

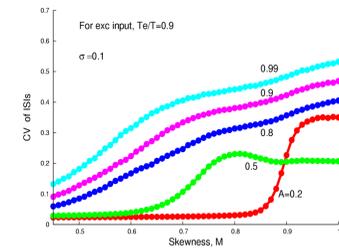
### LEFT SKEWNESS INCREASES COEFFICIENT OF VARIATION

#### EFFECT OF SKEWNESS ON SPIKE VARIABILITY

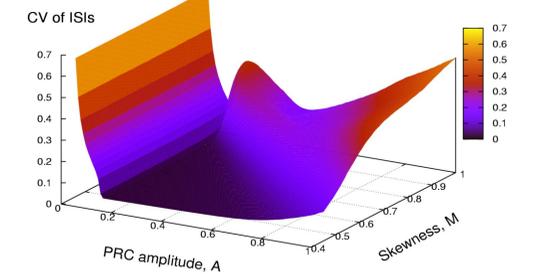
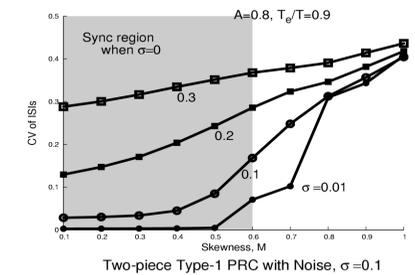
$A=0.8, T_e/T=0.9, \sigma=0.1$



**Above Left:** ISI sequences for increasing values of skewness when Gaussian width of the stimulus period is 0.1. Coefficient of variation increased with skewness. **Above Right:** For bigger noise levels, the output CV increases above that of the input at relatively weaker skewness values.

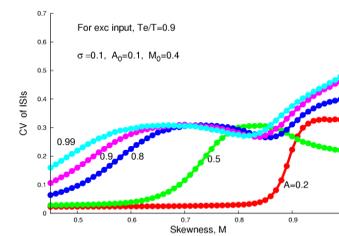
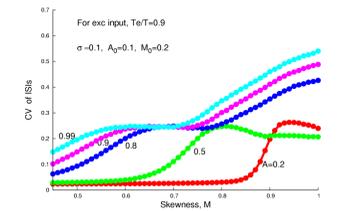


**Left:** CV as a function of skewness for different stimulus levels. **Right:** A parametric plot showing CV (color scale) as a function of both  $A$  and  $M$ . The local peak is related to the fine structure of the distribution function.



The region on the left that shows rapid changes in the CV fails to satisfy existence condition for synchrony:  $1-A < T_e/T < 1$ .

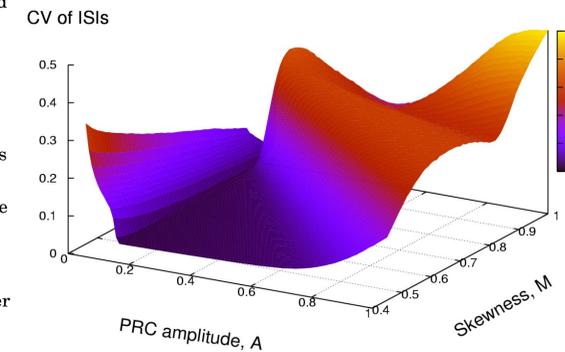
#### EFFECT OF $M_0$ ON SPIKE TIME VARIABILITY



$M_0$  does not alter the synchronization condition between  $A$  and  $M$ , but the spike time variability is altered modestly by  $M_0$ .

Increasing  $M_0$ , while keeping  $A_0$  constant, has the effect of prolonging the residence time of the cell in the unlocked state, and hence contributes to the CV: Bigger  $M_0$  leads to larger CV.

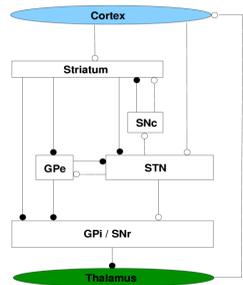
Three-piece Type-1 PRC with noise,  $A_0=0.1, M_0=0.4, \sigma=0.1$



## Introduction

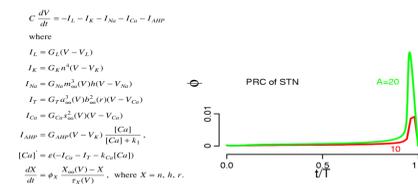
### BASAL GANGLIA CIRCUITRY

Subthalamic nucleus (STN) and globus pallidus external segment (GPe) neurons are spontaneously oscillatory and show considerable output spike time variability.



### STN MODEL [2] EQUATIONS AND PHASE RESPONSE CURVE FOR EXC INPUT

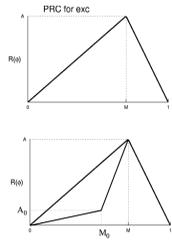
The STN's PRC shows left skewness. Our goal is to study the role of skewness in synchrony and spike variability for external periodic/random input.



## Model

### TWO PIECE LINEAR PRC

Typical type-1 phase response curves show positive responses (or phase advancements) for excitatory synaptic input. Integrate-and-fire model, and the STN model [2] are a few examples. STN model shows large skewness. We wish to parametrize the skewness in our study. We approximate the PRC with two piece-wise linear curves with a maximum PRC value of  $A$  occurring at an input phase of  $M$ .



$$\phi_{n+1} = \phi_n + R(\phi_n) + \frac{T_e}{T}$$

$$R(\phi) = \begin{cases} \frac{A}{M} \phi & \text{if } 0 < \phi < M \\ A - \frac{A}{1-M} (\phi - M) & \text{if } M < \phi < 1 \end{cases}$$

### INCORPORATING NOISY DRIVING

We assume that the external period is noisy with a mean of  $T_e$  and a Gaussian deviation of  $\sigma$ . Only the ratio  $T_e/T$  (where  $T$  is the intrinsic oscillation period) enters the analysis, since the phase is scaled with  $T$ .

### THREE PIECE LINEAR PRC

We also consider the PRC with a third linear branch on the left that has maximum response of  $A_0$  at an input phase of  $M_0$ .

For CV calculations, a total of 200,000 iterations were used after discarding the initial 1000 iterations.

$$R(\phi) = \begin{cases} \frac{A_0}{M_0} \phi & \text{if } 0 < \phi < M_0 \\ \frac{A - A_0}{M - M_0} (\phi - M_0) & \text{if } M_0 < \phi < M \\ A - \frac{A}{1-M} (\phi - M) & \text{if } M < \phi < 1 \end{cases}$$

## References:

1. K. C. Loucif, C. L. Wilson, R. Baig, M. G. Lacey, and I. M. Stanford, *J. Physiol.* **567**:977-987, 2005.
2. D. Terman, J. E. Rubin, A. C. Yew, and C. J. Wilson, *J. Neurosci.* **22**:2963-2976, 2002.
3. B. Ermentrout and D. Saunders, *J. Comput. Neurosci.* **20**:179-190, 2006.

## Conclusions:

1. Two piece-wise linear type-1 PRC synchronizes with external excitatory periodic input when  $0 < A < 2(1-M)$ . For inhibitory input, the condition is  $0 < A < 2M$ . Three piece-wise linear PRC can, in addition show synchrony for  $A < A_0$ .

2. Left skewness increases the CV for excitatory input.

3. High CV is also realized when the condition  $1-A < T_e/T < 1$  fails.