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the spatial Hodgkin-Huxley system**

by

*Henry Tuckwell, and Jürgen Jost*

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# Inhibition of repetitive activity by weak noise in the spatial Hodgkin-Huxley system

Henry C. Tuckwell and Jürgen Jost

*Max Planck Institute for Mathematics in the Sciences, Inselstr. 22, 04103 Leipzig, Germany*

We consider the response of the Hodgkin-Huxley (HH) spatial system in the weak noise regime near the bifurcation to repetitive spiking. The signal is restricted to a small segment and noise occurs over a region which may overlap or not the signal region. As in the point model, weak noise can inhibit or terminate the spiking activity with a minimum in spike count as noise level increases, but only if signal and noise overlap in space. If signal and noise are applied on disjoint intervals, then weak noise has no effect on the spiking activity, no matter how large its region of application.

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Recent studies of the HH-system of ordinary differential equations (ODE's) with stochastic input have revealed new and interesting phenomena [1, 2]. In particular, at mean input current densities near the critical value for repetitive firing, it was found that weak noise could strongly inhibit spiking with a minimum in the firing rate as the noise level increased from zero [1, 2]. It is of interest to see if these phenomena extend to the spatial HH-system where in addition there exist many possibilities for the spatial distributions of the mean input (signal) and of the noise. It will be shown that the spatial HH system exhibits quite similar but more complex behavior than the ODE system. The spatial Hodgkin-Huxley system [3] consists of the cable partial differential equation for nerve membrane voltage

$$C_m V_t = \frac{a}{2R_i} V_{xx} + \bar{g}_K n^4 (V_K - V) + \bar{g}_{Na} m^3 h (V_{Na} - V) + g_l (V_l - V) + I(x, t)$$

and differential equations for  $m, h, n$  describing the sodium and potassium conductances. (Subscripts are used to denote partial differentiation.) Thus  $m_t = \alpha_m(V)(1 - m) - \beta_m(V)m$  with similar equations for  $n$  and  $h$ . Initial and boundary conditions must of course be specified. The quantities  $C_m, \bar{g}_K, \bar{g}_{Na}, g_l$ , and  $I(x, t)$  are respectively the membrane capacitance, maximal potassium conductance, maximal sodium conductance, leak conductance and applied current density for unit area (1sq cm).  $R_i$  is the intracellular resistivity,  $a$  is the fiber radius, all times are in ms, all voltages are in mV, all conductances per unit area are in mS/cm<sup>2</sup>,  $R_i$  is in  $\Omega$ cm,  $C_m$  is in  $\mu$ F/cm<sup>2</sup>, distances are in cm, and current density is in  $\mu$ A cm<sup>-2</sup>.  $n(x, t)$ ,  $m(x, t)$  and  $h(x, t)$  are the potassium activation, sodium activation and sodium inactivation variables. Their evolution is determined by the voltage-dependent coefficients  $\alpha_n(V) = \frac{10-V}{100[e^{(10-V)/10}-1]}$ ,  $\beta_n(V) = \frac{1}{8}e^{-V/80}$ ,  $\alpha_m(V) = \frac{25-V}{10[e^{(25-V)/10}-1]}$ ,  $\beta_m(V) = 4e^{-V/18}$ ,  $\alpha_h(V) = \frac{7}{100}e^{-V/20}$ ,  $\beta_h(V) = \frac{1}{e^{(30-V)/10}+1}$ . The

following standard parameter values are used throughout:  $a = 0.0238$ ,  $R_i = 34.5$ ,  $\bar{g}_K = 36$ ,  $C_m = 1$ ,  $\bar{g}_K = 36$ ,  $\bar{g}_{Na} = 120$ ,  $g_l = 0.3$ ,  $V_K = -12$ ,  $V_{Na} = 115$  and  $V_l = 10$ . For the initial values,  $V(x, 0) = 0$ , the resting level, and for the auxiliary variables the equilibrium resting values are used, for example  $n(x, 0) = \alpha_n(0)/(\alpha_n(0) + \beta_n(0))$ . The boundary conditions were set as zero-derivative at both end points.

The corresponding system of ordinary differential equations (ODE's) has been the subject of a very large number of studies and analyses, as for example in references [4–11] but there have been relatively few articles on the spatial or partial differential equation (PDE) system [12, 13]. In this article we focus on the HH system in one space dimension, which is most accurate for a nerve cylinder, usually of uniform diameter. This simple geometry can nevertheless be used to gain some insight into the properties of neurons with complex anatomy by appealing to such methods as [9] mapping from a neuronal branching structure to a cylinder, thus reducing the multi-segment problem to solving a cable equation in one space dimension.

We first consider the spatial HH-system with a deterministic input  $I(x, t) = \mu(x, t)$  where  $\mu(x, t) = \mu > 0$ ,  $0 < x < x_1 < L$ ,  $t > 0$ , and  $\mu(x, t) = 0$ , otherwise. That is, a constant current is applied indefinitely over a (small) region near the origin, heuristically representing a soma-dendritic region which is attached to an axon which extends from  $x = x_1$  to  $x = L$ . In the calculations the length was set at  $L = 6$ . With the stimulus extending to  $x_1 = 0.2$  the result for  $\mu = 4$  is a solitary spike; with  $\mu = 6$ , a doublet of spikes propagates along the nerve cylinder. For  $\mu$  greater than some critical value, there ensues a train of regularly spaced spikes, as for example when  $\mu = 7.5$ , corresponding to repetitive (periodic) firing in the HH-system of ODE's. In order to quantify the spiking activity, the maximum number  $N$  of spikes on  $(0, 6)$  is employed. There is a sudden increase in the value of  $N$  as  $\mu$  increases through a critical value, which depends on  $x_1$ , paralleling the appearance of a limit cycle solution in the ODE system. Such dependence of  $N$  on

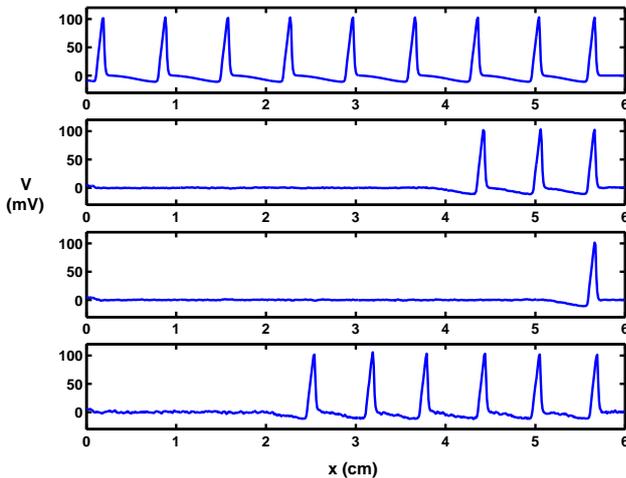


FIG. 1: Showing examples of the inhibitory effects of noise on regular spiking in the spatial HH system for a mean current density near the bifurcation to repetitive spiking. Here  $V$  is plotted against  $x$  at  $t = 160$  ms. In the top record there is no noise ( $\sigma = 0$ ), in the second and third records, relatively small noise of amplitude  $\sigma = 0.1$ , and in the bottom record, a larger noise of amplitude  $\sigma = 0.3$ . For parameter values, see text.

$\mu$  was found for two values of  $x_1$ , viz 0.1 and 0.2, with critical values of  $\mu$  at about 6 and 6.5, respectively. In consideration of the behavior of the HH system of ODE's with noise, it was then of interest to examine the effects of noise on the spike counts near the bifurcation points for the PDE case.

The HH-system of PDE's was therefore considered with applied currents (consisting of "signal" plus noise) of the following form  $I(x, t) = \mu(x, t) + \sigma(x, t)w(x, t)$  on subsets of a cylindrical nerve cell extending from  $x = 0$  to  $x = L$ . Here  $\{w(x, t), x \in [0, L], t \geq 0\}$  is a two-parameter white noise with covariance function  $\text{Cov}[w(x, s), w(y, t)] = \delta(x - y)\delta(t - s)$ . The functions  $\mu(x, t)$  (as above) and  $\sigma(x, t)$  are deterministic and specify the spatial (and temporal) distributions of the mean and variance of the noisy input. For the random component  $\sigma(x, t) = \sigma > 0$ ,  $0 < x_2 < x < x_3 \leq L$ ,  $t > 0$  and  $\sigma(x, t) = 0$ , otherwise. The numerical integration of the stochastic system is performed by discretization using an explicit method, shown to be accurate by comparison with analytical results in similar systems [14].

In Figure 1 are shown examples of the effects of noise with the following parameters:  $\mu = 6.7$ ,  $x_1 = 0.1$ ,  $x_2 = 0$ , and  $x_3 = L = 6$ . That is, the noise component is  $\sigma$  on the whole interval  $(0, L)$ . In the top record there is no noise and there are 9 spikes. In the middle two records, with a noise level of  $\sigma = 0.1$  there is a significant diminution of the spiking activity, with only 1 spike in one case and 3 in the other. With the noise turned up to  $\sigma = 0.3$  (bottom record) the number of spikes is greater, but still less than

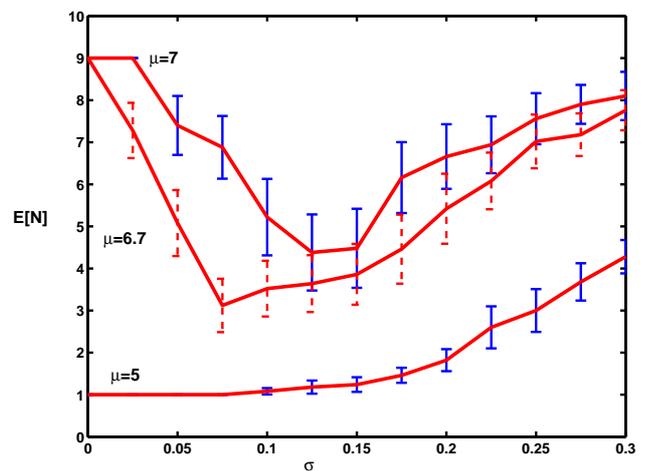


FIG. 2: Showing the effects of increasing noise on mean numbers of spikes as a function of noise level for various values of the mean level of excitation  $\mu$  on  $(0, 0.1)$ . Noise of amplitude  $\sigma$  is applied on  $(0, L)$ . The bottom curve is for a value of  $\mu$  well below the critical value at which repetitive firing occurs, whereas the upper two curves, where minima occur, are for  $\mu$  near the bifurcation point. 95% confidence limits are shown for the mean (50 trials).

in the noise-free case, there being 6 in the example shown.

Mean spike counts were obtained with  $x_1 = 0.1$ , at various  $\sigma$  for  $\mu = 5, 6.7$  and 7. The first of these values is less than the critical value for repetitive firing and the other two values are close to and just above the critical value. The number of trials for each point in the following is 50, which is sufficient to show the main effects. Figure 2 shows plots of the mean spike counts,  $E[N]$ , as explained above, versus noise level. This figure may be compared with Figure 5 in [2]. For  $\mu = 5$ ,  $E[N]$  increases monotonically as  $\sigma$  increases from 0 to 0.3. When  $\mu = 6.7$ , which is very close to the critical value for repetitive firing, a small amount of noise causes a substantial decrease in firing with the appearance of a pronounced minimum near  $\sigma = 0.075$ . For  $\mu = 7$ , where indefinite repetitive firing occurs without noise, a similar reduction in firing activity occurs for small values of  $\sigma$ , with a minimum near  $\sigma = 0.15$ , after which spiking activity increases monotonically for values of  $\sigma$  up to the largest value employed,  $\sigma = 0.3$ . The occurrence of minima with increasing noise level has been referred to as *inverse stochastic resonance* [1] as it has a character opposite to stochastic resonance [15]. In some trials, with large  $\sigma$ , *secondary phenomena* were observed [13, 14], in which noise-induced pairs of spikes emerged outside the signal region and interfered with the emitted train.

With a larger region of excitation (signal) so that  $x_1 = 0.2$ , mean spike counts were similarly obtained with various noise amplitudes for values of  $\mu = 5, 6.2$  and 6.5. Again, the first of these values is less than the critical

value for repetitive firing (see Figure 2) and the other two close to or just above the critical value. The system responses were similar to those for  $x_1 = 0.1$ . These findings parallel those found for the HH system of ODE's and although there is no standard bifurcation analysis for the PDE system, it is probable that most of the arguments which apply to the system of ODE's apply, in some sense, to the PDE's.

In order to explore the mode of spike failure, we examined the early behavior of the voltage near the source of action potential. The voltage paths in cases of failure are close to those for the repetitive spike train until just before the 2nd or 3rd etc spike is about to form, whereupon the trajectory wanders on a path away from threshold. Consequently, the spike train terminates prematurely as the system thereafter stays at low levels of depolarization, destroying the possibility of further spikes.

It is of interest to see how varying the extent of the noise around the signal region affects the propagation of action potentials. It was at first surprising to find that, with  $x_1 = 0.1$ ,  $x_2 = 0.1$  and  $x_3 = 0.2$ , when there was weak noise just to the right of the excitatory stimulus, no reduction in spike count occurred. Thus, it seemed that weak noise at the source of the spiking could cause a significant reduction in spike count, but noise with the same magnitude and extent over a region disjoint from the region of excitation, tended to have little or no effect on spike propagation. In a systematic investigation, with the mean excitation fixed at  $\mu = 6.2$  for  $0 < x < 0.2$ , noise of strength  $\sigma = 0.1$  was applied for  $x_2 < x < x_3$  where  $x_3 - x_2$  was fixed at 0.2 and  $x_2$  varied from 0, corresponding to complete overlap, to 0.2, corresponding to zero overlap. The results, which are shown in Figure 3, provide a clear demonstration of the significance of the degree of overlap of (weak) noise and signal. Histograms of spike counts on 50 trials enabled the determination of the fraction of trials on which there was interference of the spike train by noise. For example, with complete overlap ( $x_2 = 0, x_3 = 0.2$ ) there were 11 of 50 trials with a full complement of 9 spikes as in the noise-free case, representing interference, mainly in the form of inhibition, by noise in 78% of trials. In contrast, with  $x_2 = 0.12$  and  $x_3 = 0.32$ , giving 40% overlap, there were 9 spikes in all 50 trials, indicating zero interference. The probability of interference (as a %) versus degree of overlap is plotted in the left panel of Figure 3. This probability is seen to remain at zero until the overlap is 40% and then increases monotonically to achieve the value near 80% when the overlap is complete. In the right panel of Figure 3 are plotted the mean spike counts versus amount of overlap along with 95% confidence intervals. The mean spike count remains at 9 until the overlap is greater than 40%. The results of Figure 3 illustrate dramatically the importance of overlap of signal and weak noise for the latter to have an inhibitory effect on spiking. That is, a spike may traverse a region of weak noise, but if the same

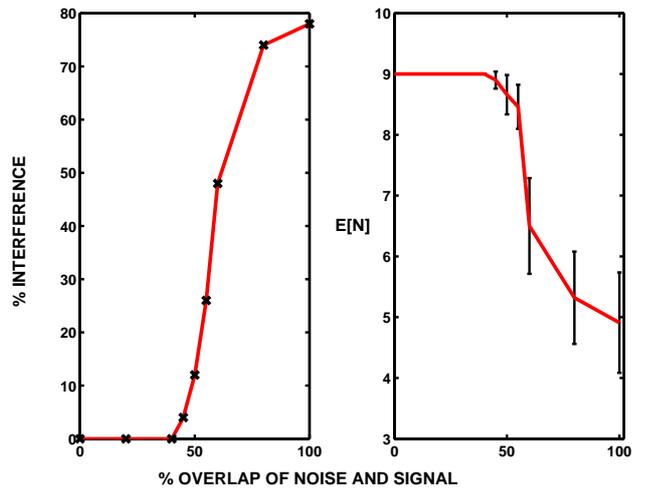


FIG. 3: *Left panel.* The fraction of trials during which weak noise interfered with the spike train is plotted against the % overlap of the regions where the signal  $\mu > 0$  and the noise amplitude  $\sigma > 0$ . Parameter values are  $x_1 = 0.2$ ,  $\mu = 6.2$  and  $\sigma = 0.1$ . *Right panel.* The corresponding expected number of spikes  $E[N]$  is plotted against % overlap of signal and noise. 95% confidence limits are shown based on 50 trials.

noise is applied at the source of the spike, there is a considerable chance of a reduction or cessation of spiking.

The mathematical theory of stochastic nonlinear stochastic PDE's of the type we are concerned with is abstract [16, 17] and there is a paucity of results concerning traveling wave solutions in the presence of noise [18]. In order to obtain some mathematical insight into the phenomena just described, we should distinguish two different regimes in the model equations. We have the small region  $0 < x < x_1$  where an external current is applied and where consequently the spikes are generated, and the large region  $x_1 < x < L$  where no such current is applied and where the spike is propagated. The first region was found to be much more sensitive to perturbations than the second. The spatial Hodgkin-Huxley equations belong to the class of reaction-diffusion systems, and some general theory can be applied, see e.g. [19], [20]. The typical nonlinear effects are generated from the nonlinear reaction term and the linear diffusion term. In the first regime, where the spike is generated, the reaction dominates the behavior. Therefore, the effects of perturbations are similar to those in the non-spatial Hodgkin-Huxley equations which constitute a system of nonlinear ordinary differential equations. In particular, noise when applied at a particular part of the periodic trajectory that corresponds to the regular spiking can destroy an incipient spike, see [2]. The second regime is modelled as a travelling wave solution of the Hodgkin-Huxley equations, see [21]. Here, a travelling wave is a solution of the above PDE system that depends only  $\xi = x - \theta t$ . With

$W(\xi) = V(x, t)$  and  $'$  denoting a derivative w.r.t.  $\xi$ , on introducing the auxiliary function  $Z = W'$ , we obtain the first order system  $W' = Z$  and

$$\frac{a}{2R_i} Z' = -(\theta C_m Z + \bar{g}_K n^4 (V_K - W) + \bar{g}_{Na} m^3 h (V_{Na} - W) + g_l (V_l - W)).$$

The changes for the remaining equations are obvious. The existence of travelling waves for such systems has been investigated in [22]. The difference with the ordinary Hodgkin-Huxley equation consists in the term  $\theta Z$  on the right hand side. According to the analysis of [23], this has the consequence that the fast reaction dynamics corresponding to the propagated spike branches off from the vicinity of the equilibrium set  $\bar{g}_K n^4 (V_K - W) + \bar{g}_{Na} m^3 h (V_{Na} - W) + g_l (V_l - W) = 0$  at positions that are different from the original rest state  $V = 0$ . Therefore, the region at the incipient spike where the solution slowly traverses a narrow region of its basin of attraction, as analyzed in [10], is avoided. Consequently, the travelling wave is much less sensitive to perturbations than the spike generation. This yields a qualitative explanation of our numerical findings.

The inhibitory effect of noise on spiking has been experimentally demonstrated in the squid axon [24]. Such an inhibitory effect has been explained in transitions from one attractor, a limit cycle, to another, being a stable rest point [2, 10]. In the present article we have found that similar but more complex phenomena occur in the HH PDE (cable) system. There are two new effects in the spatial HH system that cannot arise in the ODE system and which clearly demonstrate the utility of spatial models as providing more realistic insights into the behavior of real neurons. Firstly, with regard to the spatial distributions of the signal and the noise, our results suggest that in the HH system the inhibition of spiking by noise of small amplitudes (here for  $\sigma < 0.3$ ) is significant if the region of signal generation and the region of occurrence of noise overlap, possibly only to a minor degree. However, if signal and noise were on disjoint intervals, then weak noise had no effect. This was the case even when the noise extended along the major part of the cable. Thus, weak noise can prevent the generation of action potentials (at their source), but not their propagation. It will be of much interest to explore the mathematical reasons for this behavior in more detail. Secondly, in spatial models (or real neurons), secondary effects may be induced by noise if it is sufficiently strong. For example, noise may itself lead to the generation of (usually pairs

of) action potentials at locations which are possibly remote from the regions of application of a signal. This was seen previously [12] and in the Fitzhugh-Nagumo system [14]. Noise induced action potentials can sometimes just be spurious or they can annihilate previously generated spikes which they encounter. Future work on these complex phenomena involving noise is needed for the elucidation of their role, not just in the relatively simple HH model, but in more realistic models of central nervous system neurons such as [25].

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