EPSRC Workshop on Computational Neuroscience

WARWICK, UK

DECEMBER 2008

- **FIRSTLY THANKS TO THE ORGANIZERS JIANFENG, DIMITRIS AND DAVID FOR THEIR KIND INVITATION**

STOCHASTIC EFFECTS IN SOME NONLINEAR NEUROBIOLOGICAL DYNAMICAL SYSTEMS

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TOPICS

1. FITZHUGH-NAGUMO STOCHASTIC PARTIAL DIFFERENTIAL EQUATION MODEL

   A. SIMULATION
   B. ANALYTICAL METHOD

2. EFFECTS OF NOISE ON HH RHYTHMIC SPIKING

   1. SIMULATION OF THE ODES: INVERSE STOCHASTIC RESONANCE
   2. MOMENT METHOD FOR THE ODES
   3. SIMULATION SOLUTIONS OF THE PDE: ISR
   4. SPIKE GENERATION IN A MODEL NEURON (VERY BRIEFLY)

See also Nottingham Meeting of Steve Coombes & Markus Dahlem January 9

SPREADING CORTICAL DEPRESSION: DETERMINISTIC & STOCHASTIC MODELING IN 2 SPACE D

PART 1:
FITZHUGH-NAGUMO SPDE MODEL NEURON

- **FN system is simpler than HH and has some similar properties – used also for heart dynamics and many other things eg EEG, Spreading depression**

First objectives

- **(1) determine effects of noise on transmission of solitary waves (action potentials)**

- **(2) compare properties of numerical solutions of spde with those analytically determined**

- **References:**

  Neural Computation **20, 3003 (2008)**

  Physica A **387, 1455 (2008) – for analytical method in case of small perturbations**

INTRODUCTION TO STOCHASTIC PDES AS NEURON MODELS

- FOR NEURAL MODELING THE SIMPLEST SOMEWHAT REALISTIC MODEL OF A NEURON IS THE LIF (LEAKY INTEGRATE AND FIRE) MODEL
- (1) STEIN BIOPHYS J 1965

  dV=-sdt + a_EdN_E – a_IdN_I

- (2) TUCKWELL J THEOR BIOL 1979
- dV=-sVdt + a_E(V_E-V)dN_E – a_I(V_I-V)dN_I
- HERE THE N'S ARE USUALLY POISSON PROCESSES.
- THESE MODELS ARE CALLED "LEAKY" BECAUSE BETWEEN INPUT EVENTS THE MEMBRANE POTENTIAL DECAYS TOWARDS RESTING LEVEL

- **Because jumps lead to differential-difference or integral equations, the most studied forms of these models are the smoothed versions – diffusion approximations where the membrane potential is continuous and all relevant equations are differential equations. If reversal potentials are neglected this gives the Ornstein-Uhlenbeck process (OUP)**

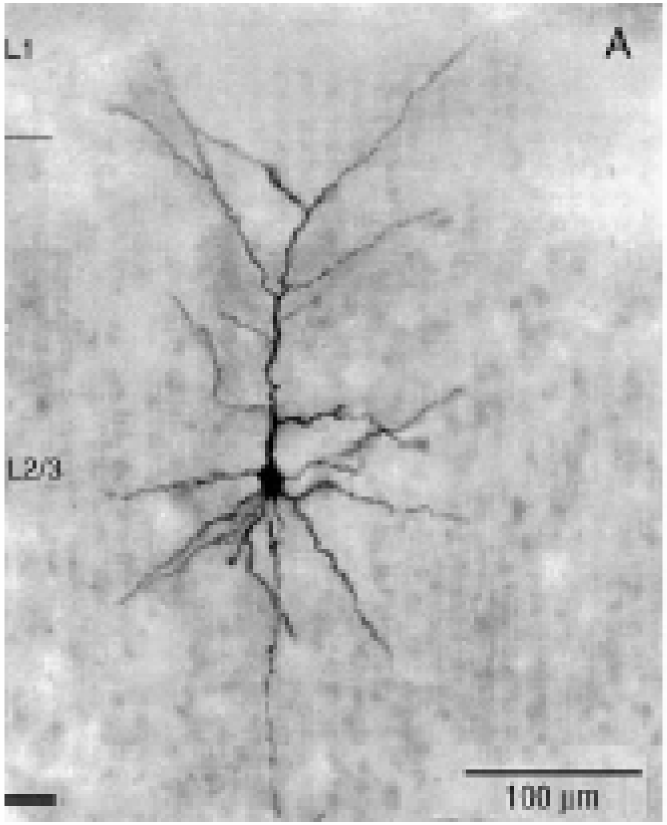
- **However, simulation is just as facile with the discontinuous models.**

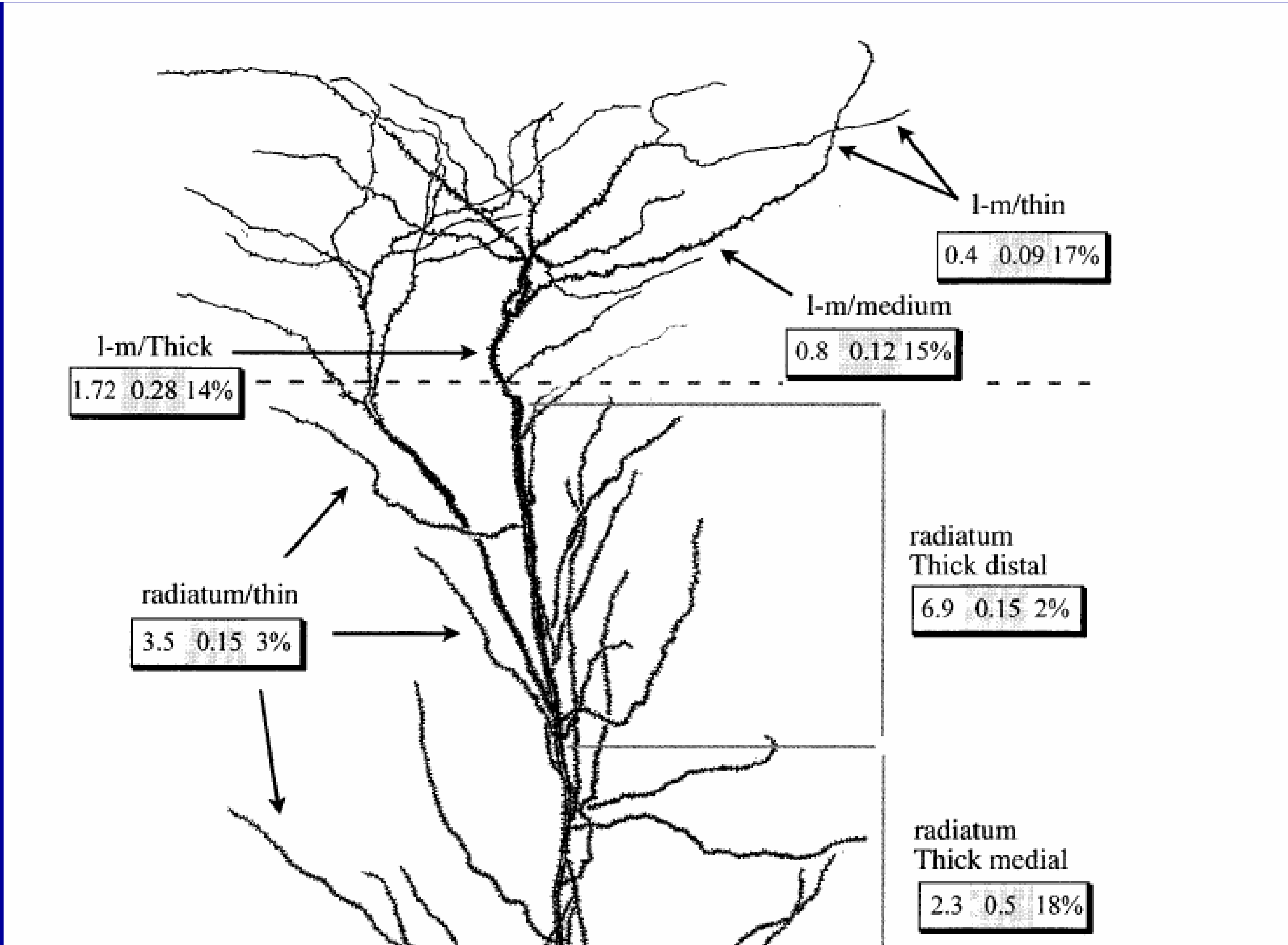
For the OUP the stochastic DE for subthreshold voltages is linear

$$dX=(m - aX)dt + s dW$$

where m is the mean input rate, a is the reciprocal of the time-constant (typically 3-30 msec), s is the standard deviation of the input and W is a standard Wiener process or BM (mean 0, variance t).

- **HOWEVER IT SEEMS THAT NEURONS CAN NOT BE ACCURATELY REPRESENTED BY A SINGLE POINT MODEL. INTEGRATION PHENOMENA DEPEND STRONGLY ON SPATIAL LOCATION. Below is a typical layer 2/3 pyramidal neuron of the rat barrel cortex D.Feldmeyer, et al J.Physiol.538 (3) (2002) 803. The next 2 pages show synaptic distributions on a hippocampal pyramid (Megias et al, 2001).**

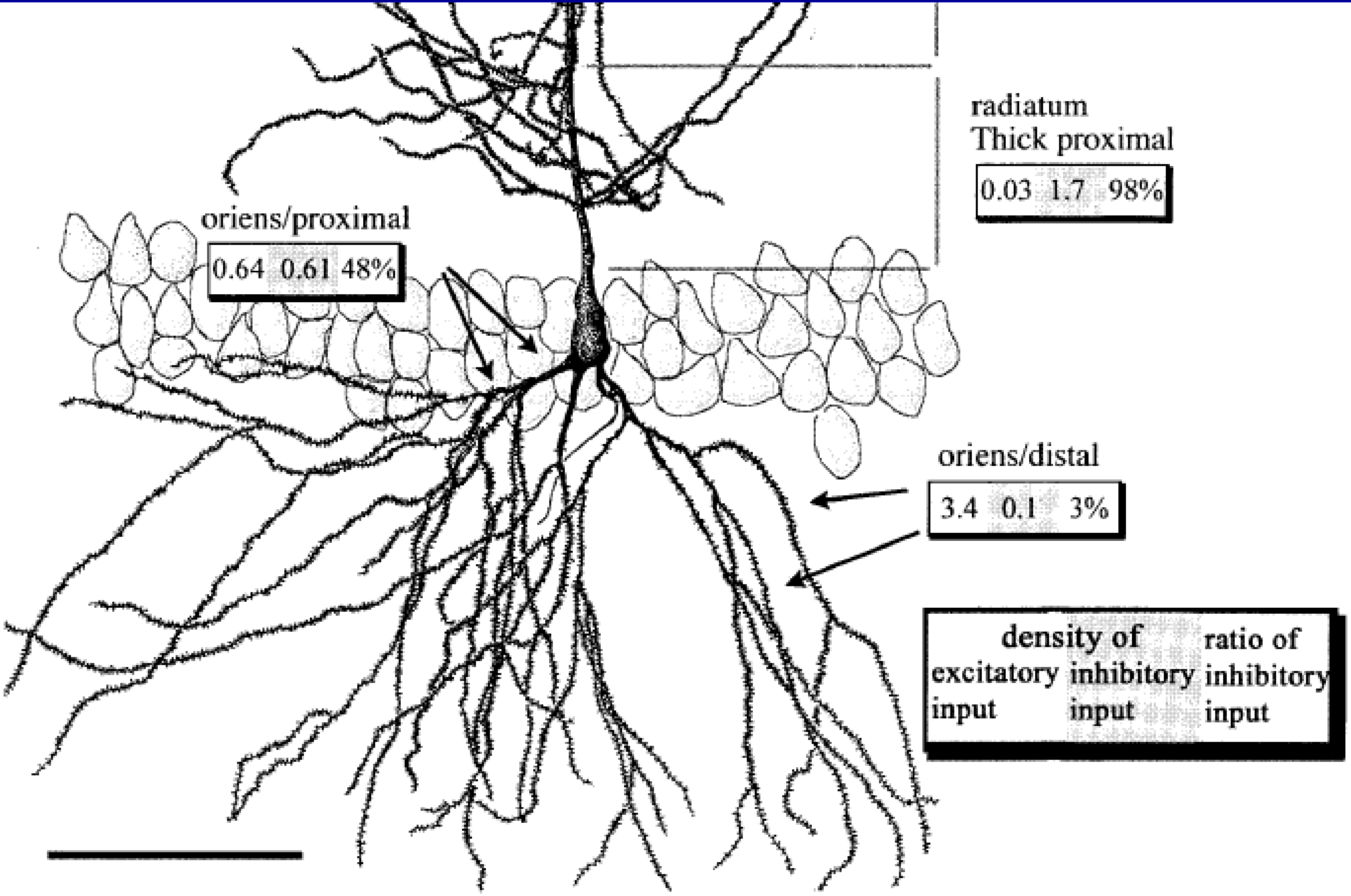




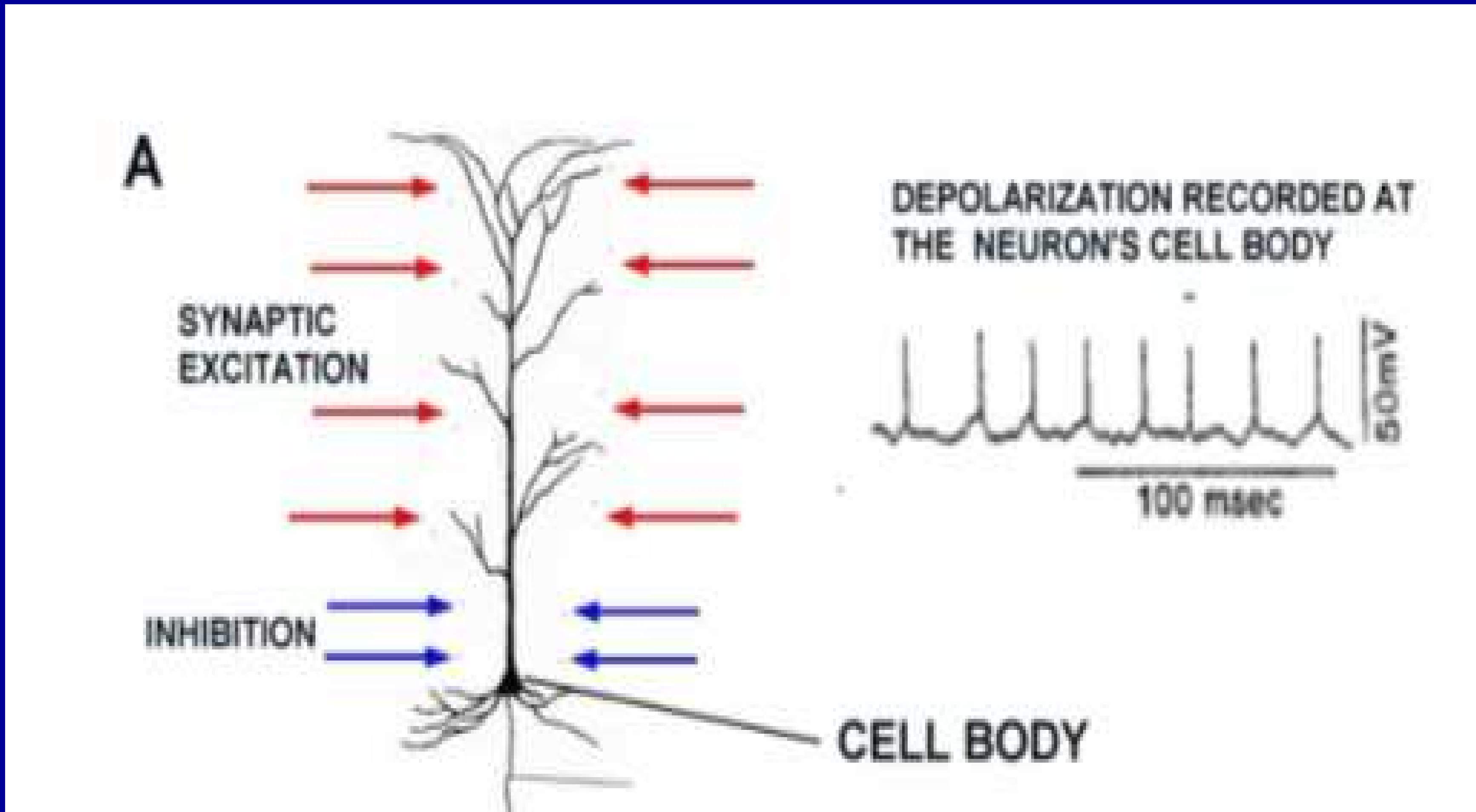
l-m/thin
0.4 0.09 17%
l-m/medium
0.8 0.12 15%
l-m/Thick
1.72 0.28 14%
radiatum/thin
3.5 0.15 3%
radiatum
Thick distal
6.9 0.15 2%
radiatum
Thick medial
2.3 0.5 18%

LOWER PART

KEY: ABC=EX /MIC,IN /MIC, %INHIB



SCHEMATICALLY WE HAVE ROUGHLY IN THE PARADIGM P-CELL CASE



- **Thus it is hard to construct an accurate electrophysiological model of a neuron without taking into account the spatial extent of the cell.**

- **There are packages like GENESIS and NEURON, for trying to incorporate the details of a neuron's anatomy, but systematic analysis is a problem due to the large number of parameters**

- **Problem 1.**

  The main difficulty is the extensive branching of dendrites.

- **Problem 2.**

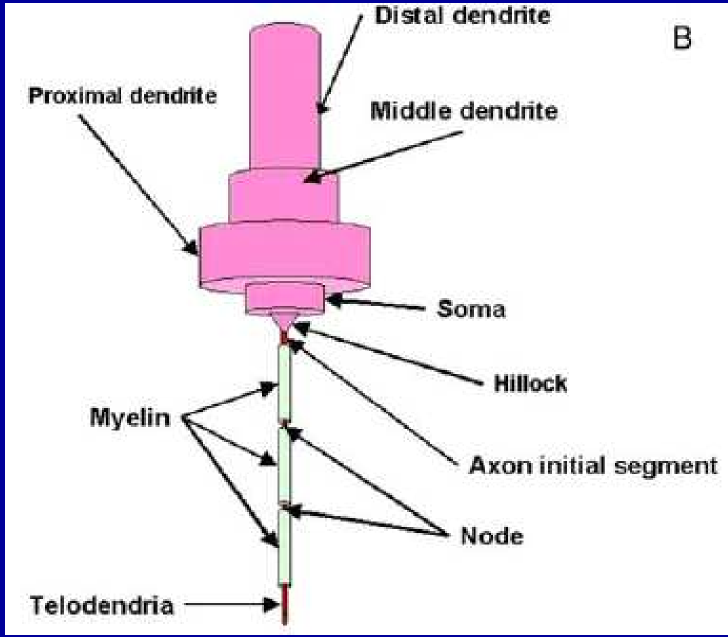
  The other main difficulty is to have any idea of the details in space-time of the synaptic inputs. It's hard to see how these could be measured, except in really simple cases.

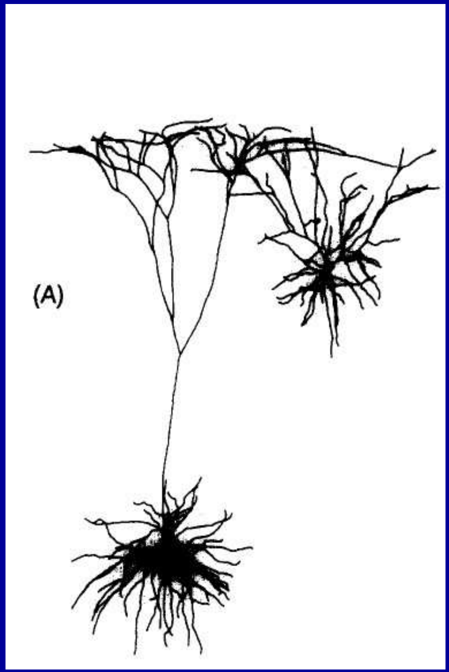
- **The first problem has been overcome by various authors by simplifying the geometry.**

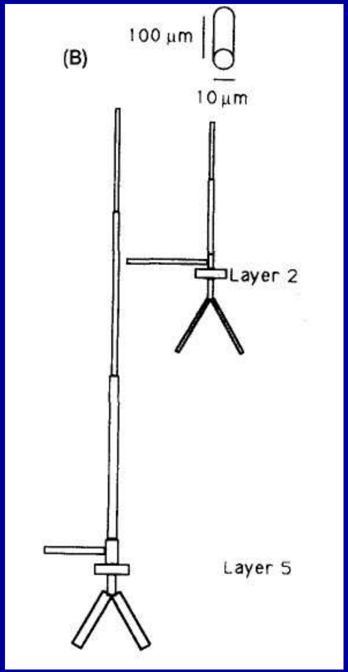
Some of the first attempts with cylinders of various radii were for motoneurons Dodge & Cooley, IBM J. Res. Devel. 17 (1973) 219.; Traub, Biol Cyb 25, 163-167 (1977).

A similar approach was adopted for a rat barrel pyramid in Iannella, Tuckwell and Tanaka Math Biosci 188 (2004) 117–132. >>>>

In 1993 Bush and Sejnowski obtained a reduced P-cell model: *Journal of Neuroscience Methods,* 46 (1993) 159-166







- **However, under certain constraints on the branching properties, the potential over a dendritic tree can be mapped onto that of an "equivalent cylinder" (Rall, 1968; Walsh & Tuckwell, 1985)**

- **This means that one can get some insight into spatial effects using a neuron model with one time and one space dimension – that is a "cable", which may be linear or nonlinear.**

- The spatial LIF models corresponding to an OUP model are linear cable equations + threshold conditions with a Gaussian white noise or Poisson stimuli.

- Case (1) at a single point 0<x<L, W is a 1-parameter Wiener process.
- - see Wan & Tuckwell, Biol Cyb 33, 39-55 (1979)

$$\frac{\partial V}{\partial t} = -V + \frac{\partial^2 V}{\partial x^2} + \delta(x - x_0)\left[a + b\frac{dW}{dt}\right],$$

Case (2) distributed where W is a 2-parameter WP. Here alpha and beta may depend on x and t.

-see Tuckwell & Walsh, Biol Cyb 49, 99-110 (1983)

$$\tilde{V}_t = -\tilde{V} + \tilde{V}_{xx} + \alpha + \beta W_{xt}, \qquad a < x < b,$$

- **In either case, for these linear models, on finite spatial intervals, one may use separation of variables and obtain solutions for the subthreshold regime as infinite sums of Ornstein-Uhlenbeck processes. Usually only the first few terms contribute significantly – see Tuckwell, *Introduction to Theoretical Neurobiology* volume 2 (CUP, 1988).**

- **For recent analytical results for some two-component <u>linear</u> cable models involving a two-parameter OUP see**

Tuckwell, Physica A 368, 495 (2006) and

Mathematical Biosciences 207, 246 (2007)

In the latter article the ISI density was shown to be strongly dependent on the spatial distributions of excitation and inhibition.

- **Despite the complexity of ionic currents in CNS neurons, it is expeditious and helpful to first consider the classical FN and HH PDE models. Here we consider the spatial stochastic FN model – stochastic spatial HH is considered in Section 2.3**

- **With nonlinear spatial models such as Hodgkin-Huxley or Fitzhugh-Nagumo, the situation is not as simple as for the linear passive cables, but one has the advantage that threshold conditions are inbuilt.**

- **For small perturbations about a stable equilibrium point, perturbative expansions do provide a good approximation as we will demonstrate for FN.**

Stochastic FN equations and solutions by simulation

In general form, for one space dimension, the FN model can be written, with voltage variable $u(x,t)$ and a recovery variable $v(x,t)$,

$$u_t = D_1 u_{xx} + \kappa u(u-a)(1-u) - \lambda v + I(x,t) \tag{1}$$

$$v_t = D_2 v_{xx} + \epsilon' [u - pv + b], \tag{2}$$

where $x \in (0, L)$ is the space variable and $t > 0$ is time. Initial and boundary conditions must also be specified. The quantities κ, λ, ϵ', p, D_1 and D_2 are positive and usually taken to be constants, although they could vary with both x and t. The parameter b can be positive, negative or zero. The applied current or input signal $I(x,t)$ may be due to external or intrinsic sources. In the majority of applications $D_1 = 1$ and D_2=0, which will be the case in this article.

In the model of Fitzhugh (1969), the parameterization was

$$u_t = u_{xx} + u - \frac{u^3}{3} - v + I(x,t) \tag{3}$$

$$v_t = 0.08(u - 0.8v + 0.7). \tag{4}$$

Two-parameter white noise

The stochastic input current terms of this paper contain the two-parameter random white noise process $w = \{w(x,t)\}$, where by definition

$$w(x,t) = W_{xt},$$

where $W = \{W(x,t)\}$, for values of $x \in [0, x_1]$ and $t \in [0, t_1]$, is a two-parameter Wiener process or Brownian motion. Properties of W and w parallel those of the usual one-parameter Wiener process or Brownian motion and the usual Gaussian white noise. $W(x,t)$ is a Gaussian random variable with mean zero and variance xt and covariance $\mathrm{Cov}[W(x,s), W(y,t)] = min(x,y)min(s,t)$ so that

$$\mathrm{Cov}[w(x,s), w(y,t)] = \delta(x-y)\delta(s-t).$$

Sample paths of W are (continuous) surfaces and for a fixed value of one of the parameters, the process is the usual one-parameter Wiener process.

SPATIAL FN WITH 2-PARAM WHITE NOISE

GENERAL EXPLICIT NUMERICAL METHOD WORKS WELL (VERIFIED WITH EXACT RESULTS FOR LINEAR AND NONLINEAR SPDE)

CONSIDER THE SPDE

$$u_t = Du_{xx} + f(u) + \sigma w(x,t)$$

Suppose the space interval is $0 \le x \le L$ and the time interval is $0 \le t \le T$. Then put $\Delta x = L/m$ and $\Delta t = T/n$ and let $x_i = (i-1)\Delta x$ for $i = 0, 1, \ldots, m$, and let $t_j = (j-1)\Delta t$ for $j = 0, 1, \ldots, n$. Approximating u at the grid point (x_i, t_j) by $u_{i,j}$ the simulation proceeds by the following scheme:

$$u_{i,j} = u_{i,j-1} + \delta[u_{i-1,j-1} - 2u_{i,j-1} + u_{i-1,j-1}] + \Delta t f(u_{i,j-1}) + \sigma\sqrt{\Delta t/\Delta x} N_{i,j},$$

where

$$\delta = \frac{D\Delta t}{(\Delta x)^2}$$

and where the $N_{i,j}$'s are a collection of independent standard (zero mean, unit variance) normal random variables which will be generated by a computer routine. The method generally works well if $\delta < 0.5$ and particularly well if $\delta \approx 0.2$.

Simulation of the original FN model with white noise

We are interested firstly in the effects of noise on the propagation of an action potential so we consider an FN system with the original parameterization as in (3), (4) and let

$$I(x,t) = \sigma(x)w(x,t),$$

that is, driftless white noise with amplitude which may depend on position. Sealed end conditions will usually be employed. In order to start an action potential we apply a current J at $x = 0$ for $0 \leq t \leq t^*$. The boundary conditions are thus

$$u_x(0,t) = J, \quad 0 < t \leq t^*,$$

$$u_x(0,t) = 0, \quad t > t^*$$

$$u_x(L,t) = 0, \quad t > 0.$$

For initial conditions for the general system of SPDE's $u_t = D_1 u_{xx} + f(u,v) + \sigma w(x,t)$ and $v_t = D_2 v_{xx} + g(u,v)$ we choose suitable equilibrium values

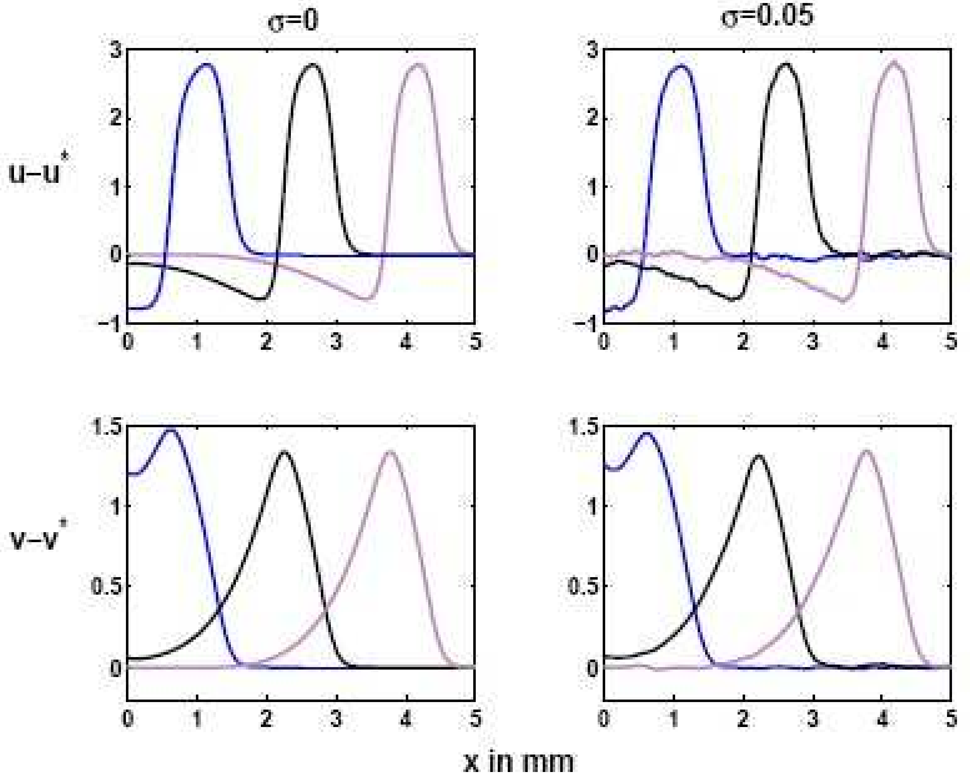
$$u(x,0) = u^*, \quad v(x,0) = v^*, \quad 0 < x < L,$$

where u^* and v^* satisfy

$$f(u^*,v^*) = 0, \quad g(u^*,v^*) = 0.$$

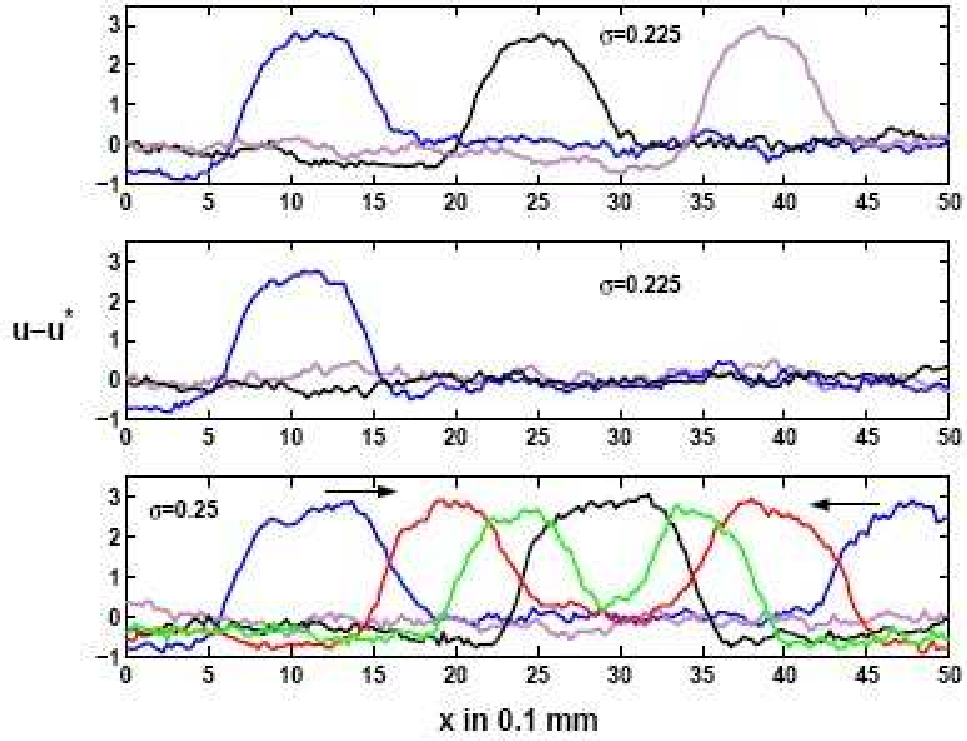
For the standard FN model (3),(4), these equilibrium values are $u^* = -1.1994$ and $v^* = -.6243$, being the unique real solution of $u - u^3/3 - v = 0$ and $0.08(u - 0.8v + 0.7) = 0$.

RESULTS 1



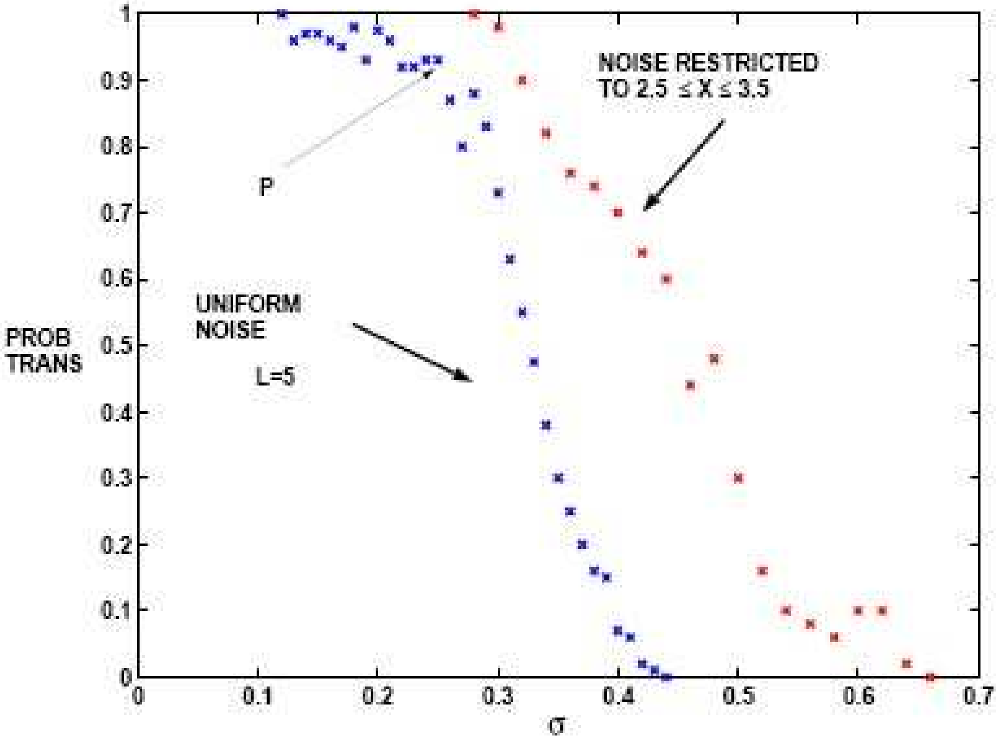
Simulated solutions of the FN system with original parameters as in (3),(4). The variables are plotted versus distance at 0.75 msec (blue), 1.5 msec (black) and 2.25 msec (purple). In the left column there is no noise and in the right column a small uniform noise of $\sigma = 0.05$.

RESULTS 2



Simulated solutions of the FN system with original parameters as in (3),(4) for larger (uniform) noise amplitudes. $u - u^*$ is plotted versus distance at 0.75 msec (blue), 1.5 msec (black) and 2.25 msec (purple). In the top two examples, $\sigma = 0.225$ whereas in the bottom figure $\sigma = 0.25$. For $\sigma = 0.25$, $u - u^*$ is also shown for 1.1 msec (red) and 1.3 msec(green) illustrating the annihilation of the original wave by a left-going noise-induced wave.

EFFECTS OF NOISE ON RELIABILITY OF TRANSMISSION

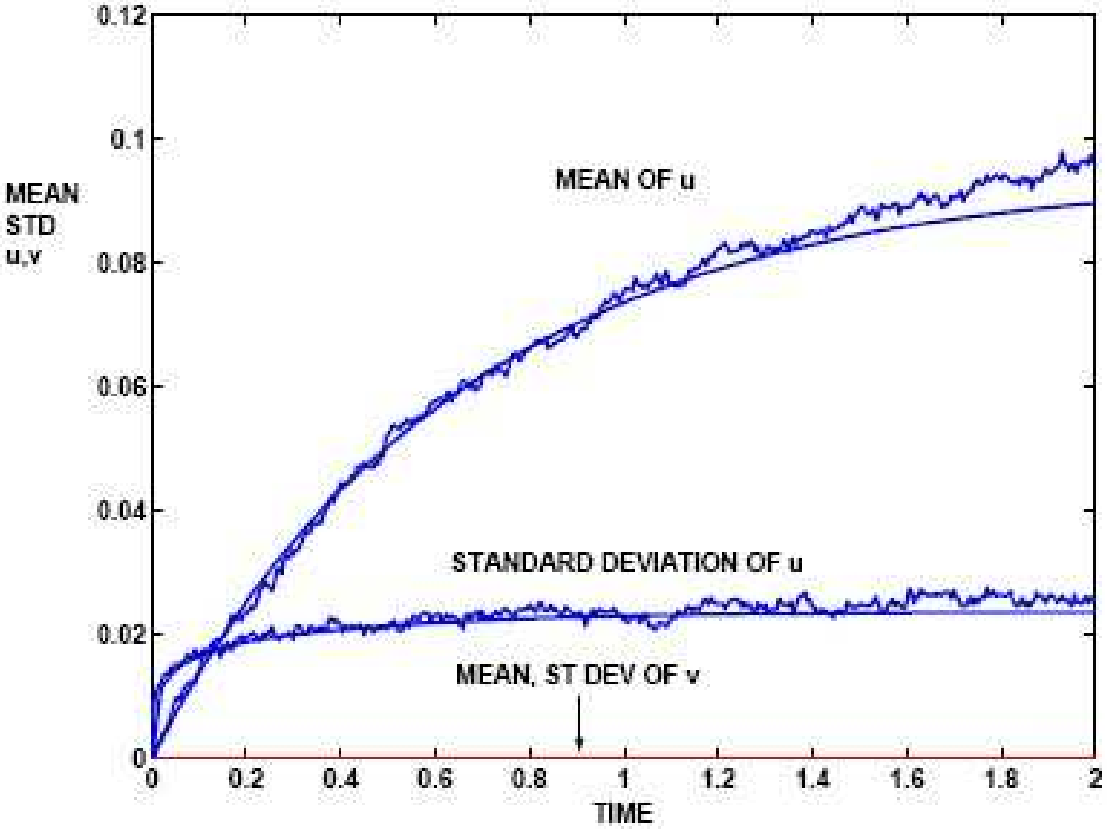


The probability of faithful transmission of the action potential versus noise amplitude. Blue crosses are for uniform noise whereas red crosses are for the case of noise restricted to a small region. 100 trials per point. The point P demarcates for the uniform case the regime for smaller σ where the noise essentially kills the oncoming wave from the regime for larger σ where the noise is sufficiently strong to give rise to non-local large often disruptive responses.

The results for uniform noise (blue crosses) can be divided into two regimes, to the left and right of the point P. The rate of decline of p_{trans} as σ increases from 0.12 to about 0.26 is slower by a factor of about 4.5 than that as σ increases from 0.26 to 0.40. Examination of the sample paths shows that there are two kinds of transmission failure. One is due purely noise interference occuring at the smaller values of σ and resulting in the annihilation of the traveling wave. The other occurs when the noise itself starts a secondary disturbance of sufficient magnitude that it may grow into a substantial response, which may take the form of another wave or multiple waves.

- Such phenomena could never arise in a point model as all the action potentials arise at a single point, develop at a single point and go nowhere!

COMPARISON OF ANALYTICAL AND NUMERICAL SOLUTIONS



Mean and standard deviation of u and v at $x = L/2$ as obtained by simulation of the two-component system (10), (11) with uniform white noise. For parameter values, see the text. The same quantities are also shown calculated analytically and are depicted by smooth blue curves. Values of v from simulation are shown but are extremely small for this parameter set.

- This last set of analytical results was obtained using a perturbation expansion for the SPDE. Such calculations are very lengthy, but useful to check numerical approximations. Briefly we have...

ANALYTICAL METHOD

- **CONSIDER WITH EPSILON SMALL**

$$u_t = u_{xx} + g(u) + \epsilon(\alpha + \beta W_{xt}), 0 < x < L, t > 0.$$

- **AND ASSUME g(u_0)=0,**

Try a perturbation expansion

$$u(x,t) = u_0 + \epsilon u_1(x,t) + \epsilon^2 u_2(x,t) + \mathrm{O}(\epsilon^3)$$

- **Substitute in the PDE and equate coeffs of powers of epsilon**
- **This gives a recursive set of linear SPDEs for u_1, u_2 etc**
- **The first is**

$$\frac{\partial u_1}{\partial t} = \frac{\partial^2 u_1}{\partial x^2} + \gamma u_1 + \alpha + \beta \frac{\partial^2 W}{\partial x \partial t}.$$

- **with solution,**

$$u_1(x,t) = \alpha \int_0^t \int_0^L G(x,y;t-s)\mathrm{d}y\mathrm{d}s + \beta \int_0^t \int_0^L G(x,y;t-s)\mathrm{d}W(y,s),$$

where G is the Green's function for

$$\frac{\partial \tilde{u}}{\partial t} = \frac{\partial^2 \tilde{u}}{\partial x^2} + \gamma \tilde{u},$$

- **and the second is**

$$\frac{\partial u_2}{\partial t} = \frac{\partial^2 u_2}{\partial x^2} + \gamma u_2 + \frac{\rho}{2!} u_1^2$$

so that

$$u_2(x,t) = \frac{\rho}{2} \int_0^t \int_0^L G(x,y;t-s) u_1^2(y,s)\mathrm{d}y\mathrm{d}s.$$

- **First and second order moments**

$$\mathrm{E}[u(x,t)] = u_0 + \epsilon \mathrm{E}[u_1(x,t)] + \epsilon^2 \mathrm{E}[u_2(x,t)] + \mathrm{O}(\epsilon^3).$$

$$K(x,s;y,t) = \mathrm{Cov}[u(x,s), u(y,t)]$$

- **are evaluated using the Green's function for the cable equation but the calculations are very laborious past 3rd powers of epsilon**

AN EXAMPLE SHOWING LINEAR VERSUS NONLINEAR (ANALYTICAL)

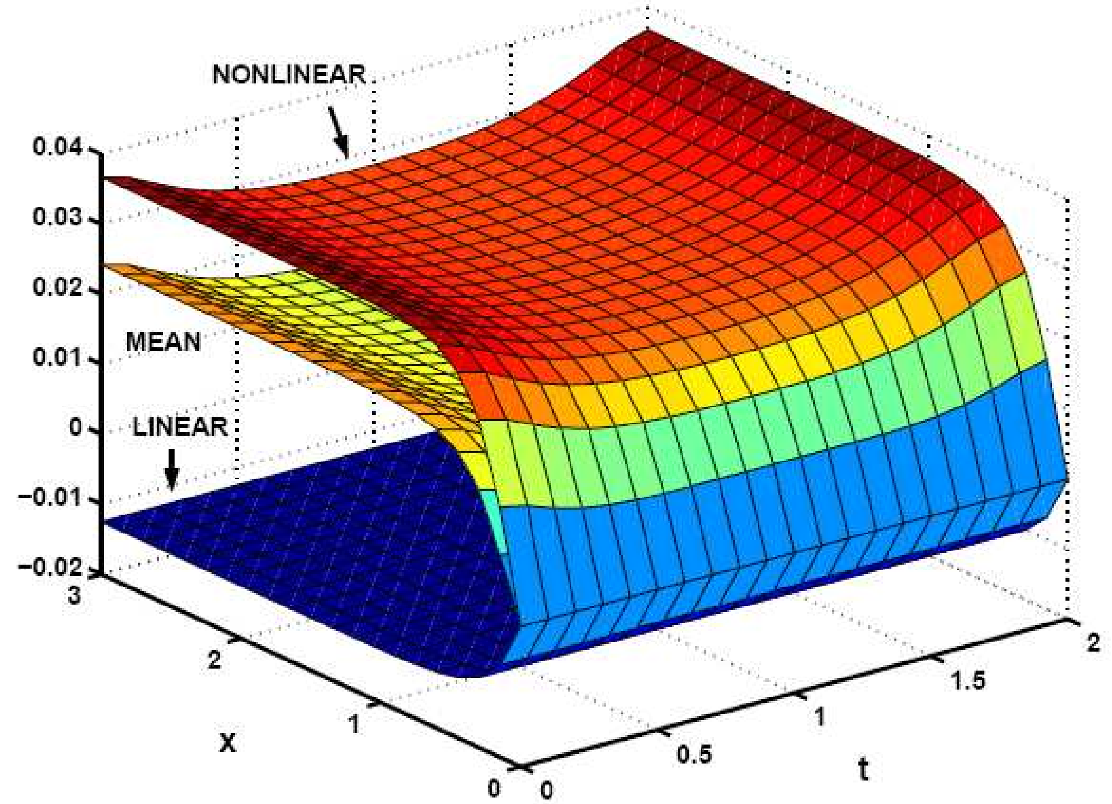


Figure 6: Computed mean of the voltage variable $u(x,t)$ satisfying (13) with net inhibition ($\alpha < 0$) at various x and t. Mean computed from (14). Also shown are the total nonlinear and linear contributons. For parameter values see text.

ONE CAN SEE WHEN THE SERIES IS NOT CONVERGING BY EXAMINING THE STATIONARY DISTRIBUTION RELATIVE TO EQUILIBRIA

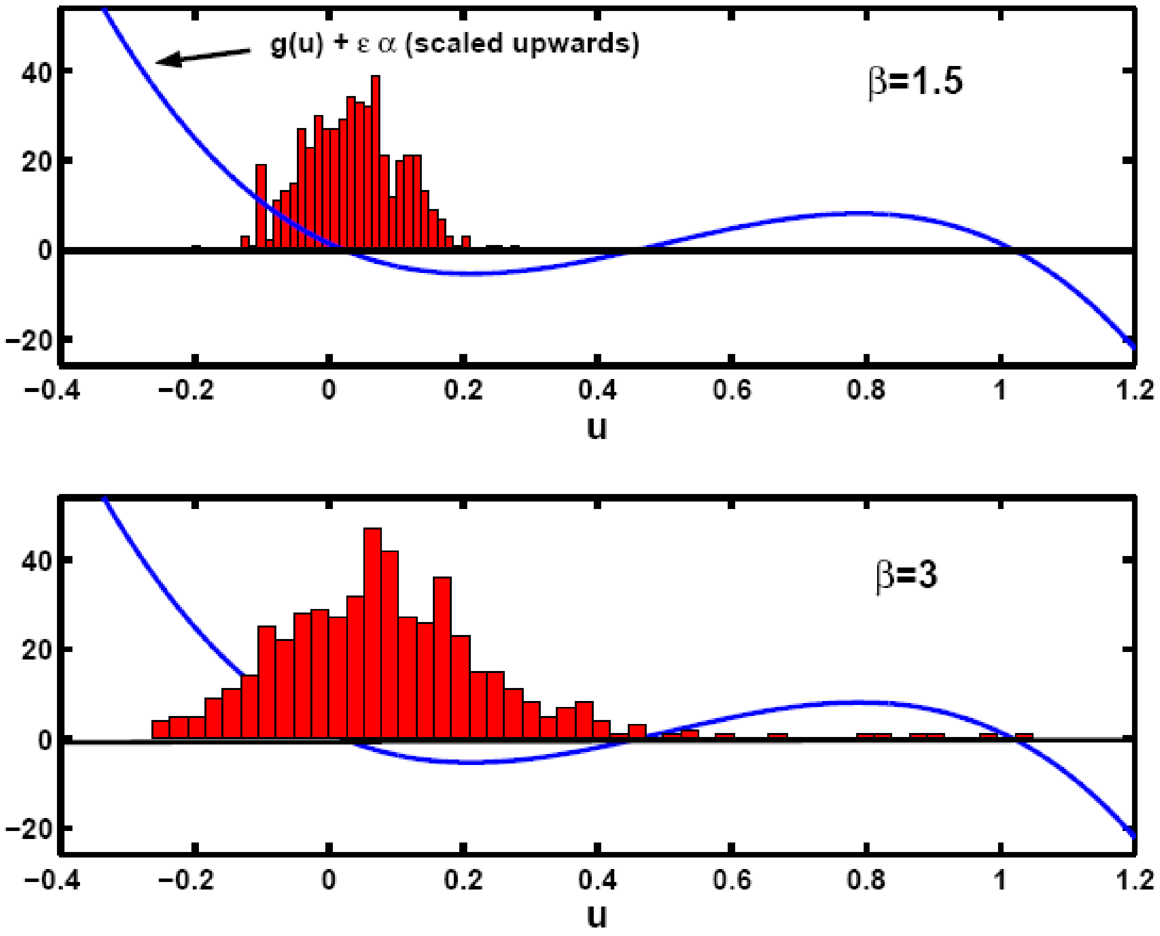


Figure 8: Histograms of the long-term values of $u(0,t)$ shown in relation to the source function $g(u)+\epsilon\alpha$ (scaled) for two values of β in the case where $\alpha = 1$. For $\beta = 1.5$ the analytical method is accurate but not for $\beta = 3$. For

PART 2: NOISE AND THE POINT AND SPATIAL HH MODEL

JOINT WITH BORIS GUTKIN (ENS, PARIS) AND JUERGEN JOST (MIS, MPI, LEIPZIG)

- We firstly consider two types of stimulation of an HH (point) model neuron.

- (1) Additive or “current” noise

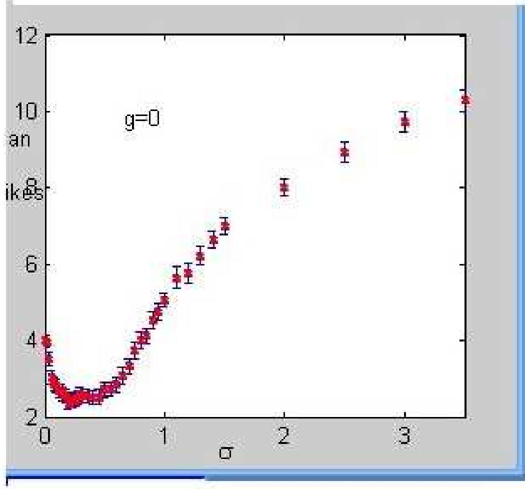
- (2) Conductance based noise, more akin to synaptic input.

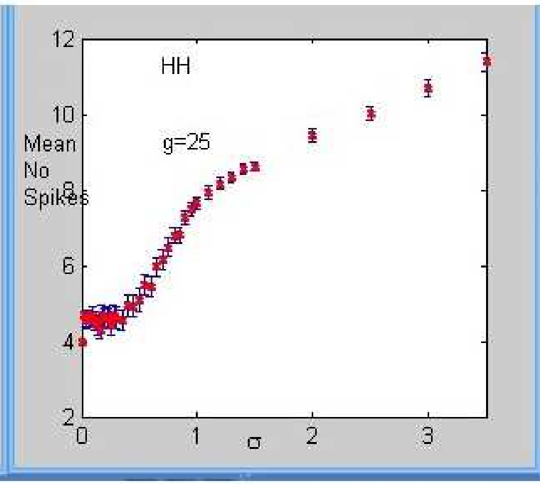
BACKGROUND

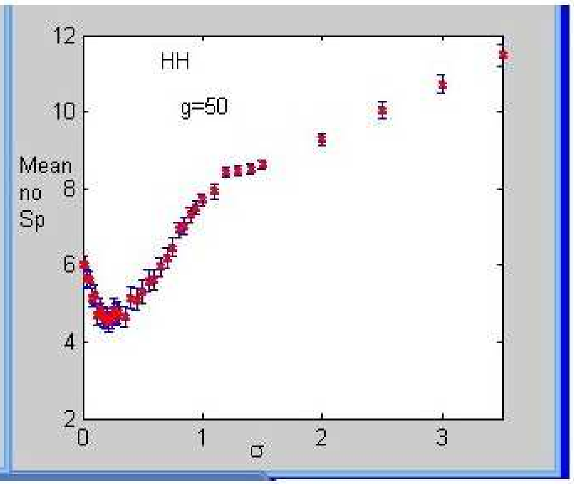
- **As a prelude to this study, we had been considering the effects of noise on coupled type 1 (QIF) neurons –see Gutkin, Jost & Tuckwell**
  Theory in Biosciences 127, 135-139 (2008)
  Europhysics Letters 81, 20005 (2008)

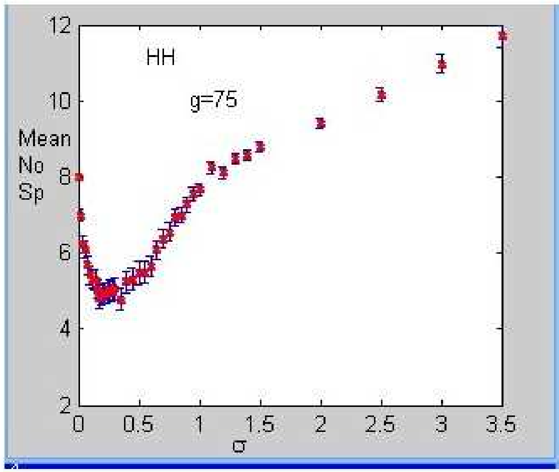
  We commenced a similar study of coupled HH neurons and some of the results are shown on the next page

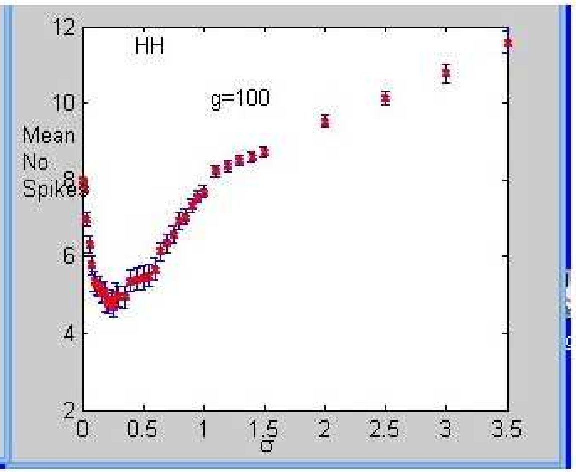
  Initially we had thought that the minima had been due to coupling but found the same occurred with zero coupling. This led us to a systematic study of single HH neurons with noise.


g=0
an
ikes
σ


HH
g=25
Mean
No
Spikes
σ


HH
g=50
Mean
no
Sp
σ


HH
g=75
Mean
No
Sp
σ


HH
g=100
Mean
No
Spikes
σ

(1) SDE model for HH with additive noise

$$\mathrm{d}V = \frac{1}{C}\{[\mu + \bar{g}_{\mathrm{K}} n^4 (V_{\mathrm{K}} - V) + \bar{g}_{\mathrm{Na}} m^3 h (V_{\mathrm{Na}} - V) + g_1 (V_1 - V)]\,\mathrm{d}t + \sigma\,\mathrm{d}W\}$$

$$\mathrm{d}n = [\alpha_n (1 - n) - \beta_n n]\,\mathrm{d}t$$

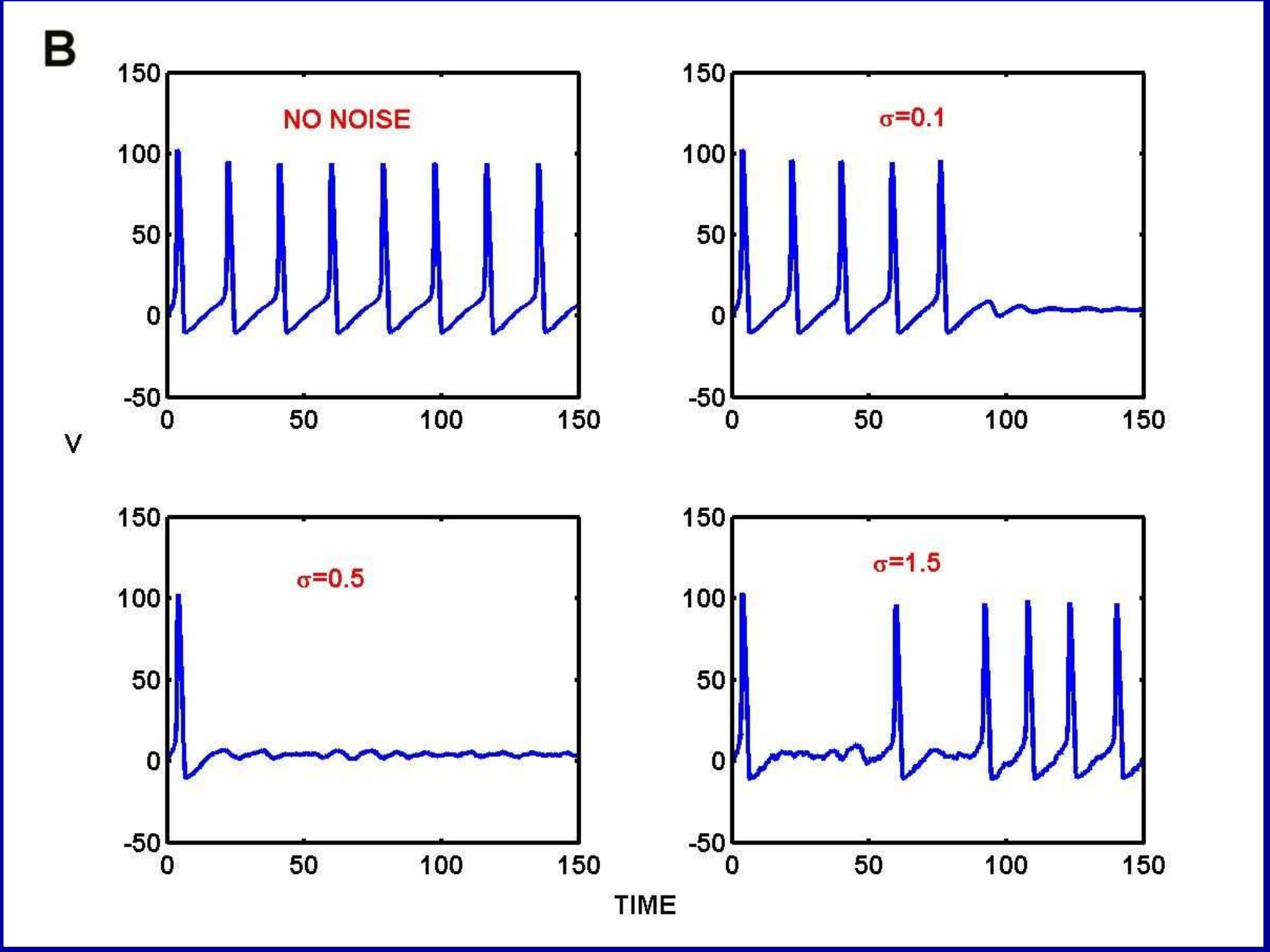
$$\mathrm{d}m = [\alpha_m (1 - m) - \beta_m m]\,\mathrm{d}t$$

$$\mathrm{d}h = [\alpha_h (1 - h) - \beta_h h]\,\mathrm{d}t,$$

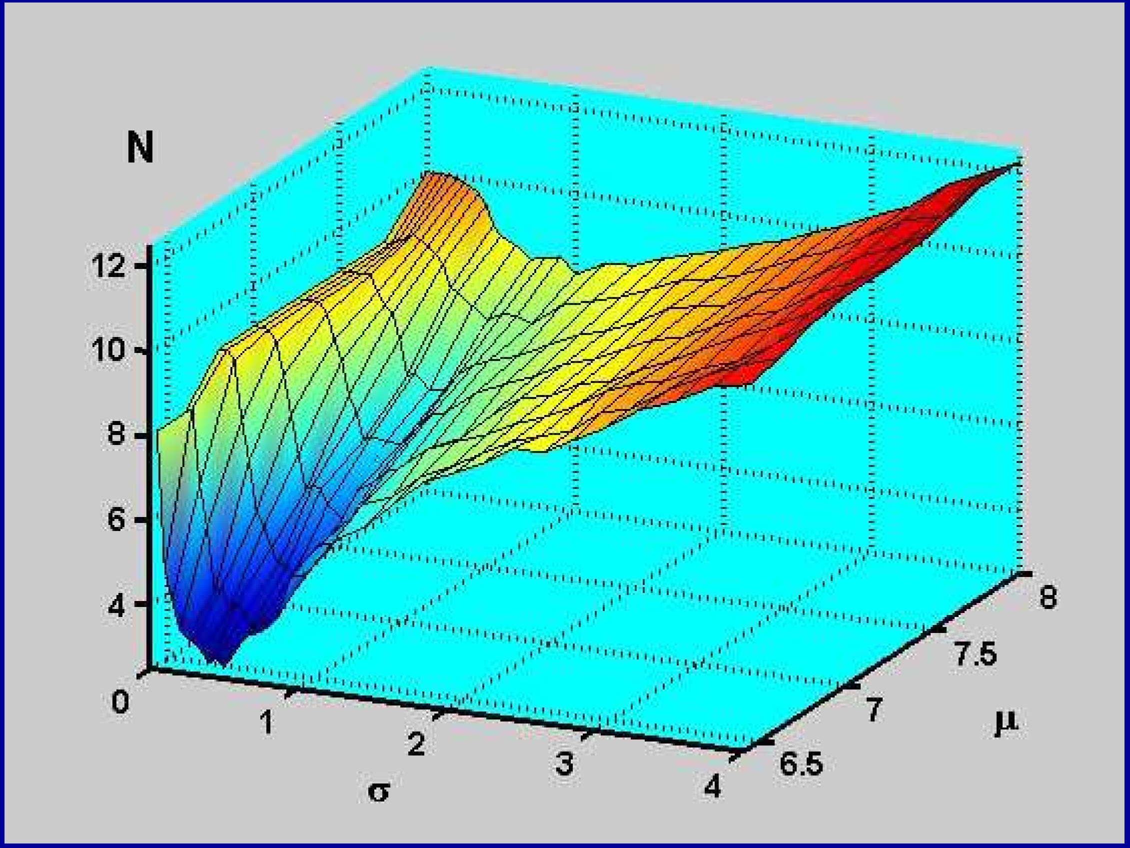
where C is the membrane capacitance in $\mu\mathrm{F/cm}^2$, V is the depolarization from resting membrane potential in mV and V_{K} and V_{Na} are the Nernst equilibrium potentials (mV) for potassium and sodium ions. The constants $\bar{g}_{\mathrm{K}}$ and $\bar{g}_{\mathrm{Na}}$ are the maximal membrane conductances, in $\mathrm{mS/cm}^2$, for potassium and sodium.

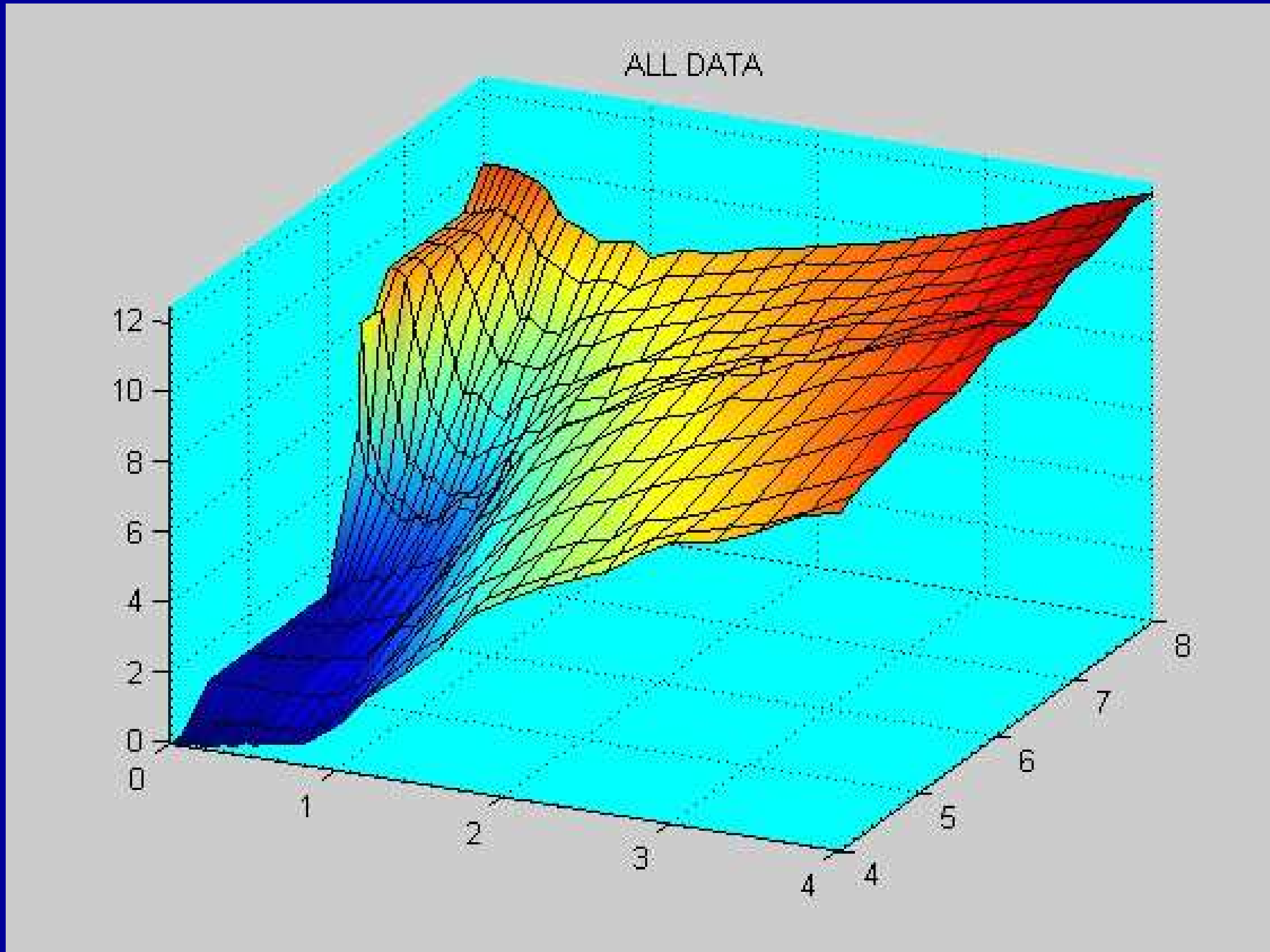
- USING STANDARD PARAMETER VALUES THE CRITICAL VALUE OF μ TO INDUCE REPETITIVE FIRING (HOPF BIFURCATION) IS ABOUT 6.44. WE EXAMINED SPIKE TRAINS FOR VARIOUS VALUES OF μ

AND σ AND GOT RESULTS SUCH AS THESE (μ=6.6):

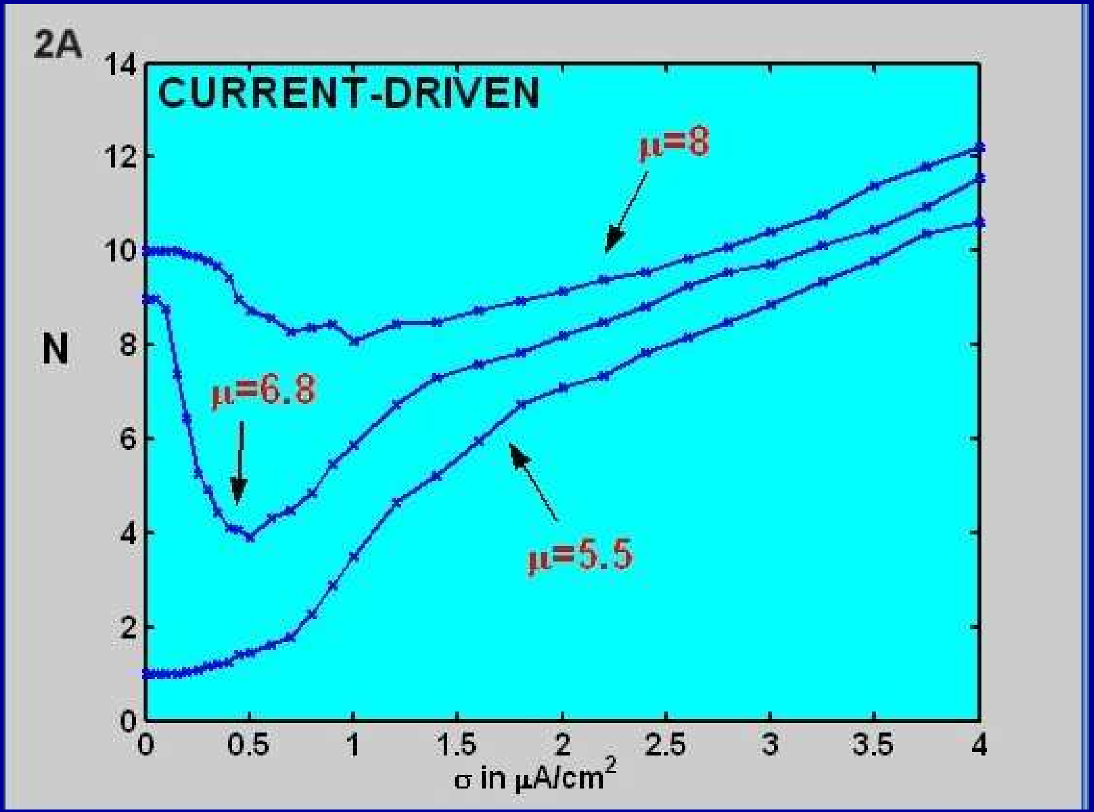


PLOTTING NUMBER OF SPIKES, N, VERSUS μ AND σ FOR VALUES OF μ GREATER THAN 6.44 GAVE THE FOLLOWING PICTURE. THESE RESULTS ARE BASED ON 500 TRIALS FOR EACH POINT. A DISTINCT MINIMUM OCCURS AS σ INCREASES AWAY FROM ZERO WHEN μ IS NEAR THE CRITICAL VALUE. A MORE COMPLETE PICTURE FOLLOWS.




ALL DATA
12
10
8
6
4
2
0
0
1
2
3
4
4
5
6
7
8

SOME PARTICULAR RESULTS HELP TO ILLUSTRATE WHAT IS GOING ON



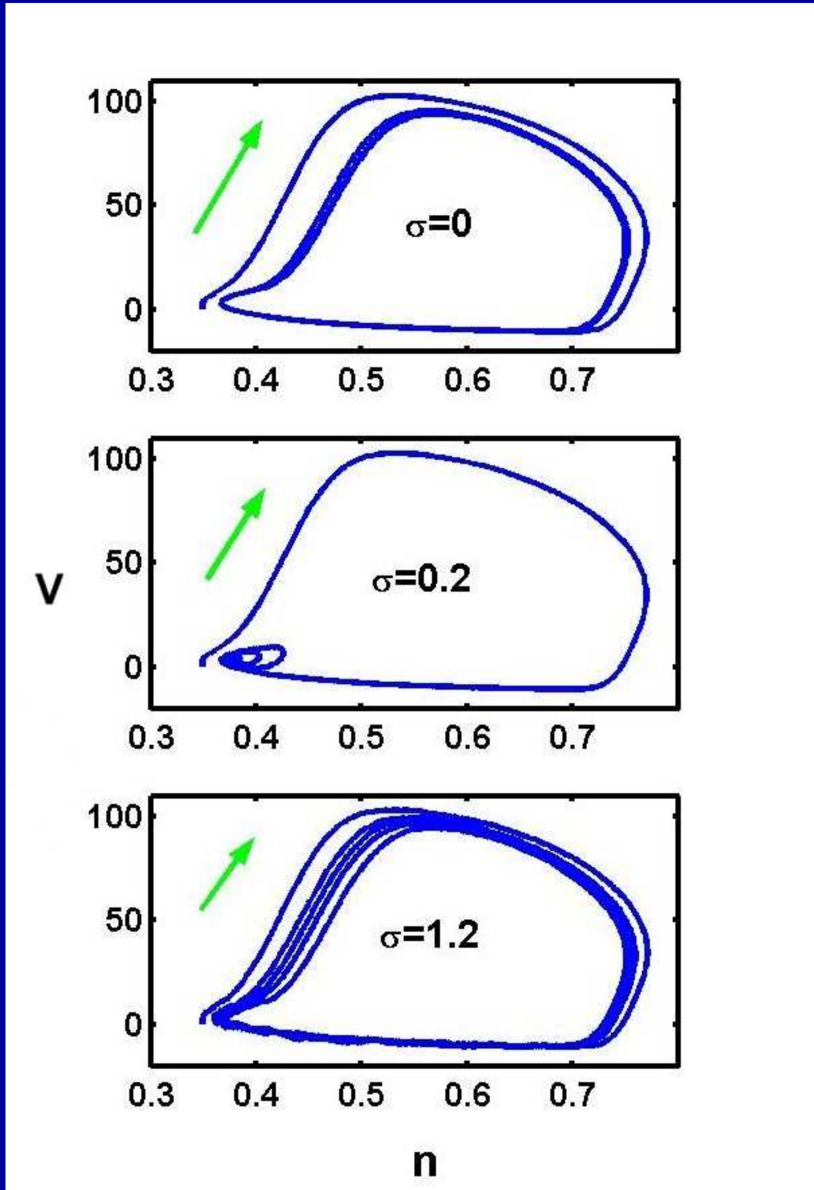
- IT IS CLEAR THAT AT CERTAIN VALUES OF THE MEAN CURRENT, THE RESPONSE UNDERGOES A DISTINCT MINIMUM AS THE NOISE VARIES.

BECAUSE STOCHASTIC RESONANCE, FAMILIAR IN MANY SENSORY SYSTEMS, ENTAILS A MAXIMUM IN THE RESPONSE (OFTEN MEASURED BY A SIGNAL TO NOISE RATIO), THIS PHENOMENON IS CALLED "INVERSE STOCHASTIC RESONANCE".

THE EXPLANATION LIES IN THE NATURES OF THE ATTRACTORS OF WHICH, FOR MEAN CURRENTS GREATER THAN THE CRITICAL VALUE, THERE ARE TWO : A STABLE REST STATE AND A STABLE LIMIT CYCLE.

JUST PAST THE CRITICAL VALUE THE BOA FOR THE LIMIT CYCLE IS SMALL AND A SMALL NOISY SIGNAL (OR ANY)

CAN KICK THE DYNAMICS INTO THE BOA OF THE STABLE REST POINT – THUS TERMINATING THE SPIKING. THIS IS ILLUSTRATED IN THE FOLLOWING PICTURE.


σ=0
σ=0.2
σ=1.2
V
n
100
50
0
0.3
0.4
0.5
0.6
0.7

We have sought explanations of these phenomena in terms of the variance of the process: the idea is that if the variance becomes large in one of the basins of attraction then the process has a large chance to exit and either stop or start spiking

To approach this analytically we have found the moment equations for an hh neuron with noise – in the additive noise case there are 14 de’s.

INTRODUCTION TO THE MOMENT METHOD

WITH ONE-DIMENSIONAL DIFFUSION PROCESSEES DEFINED BY AN SDE

$$dX = a(X,t)dt + b(X,t)dW$$

IT IS OFTEN POSSIBLE TO MAKE PROGRESS IN SOLVING THE KOLMOGOROV OR FOKKER-PLANCK EQUATION (LINEAR PDE) FOR THE TRANSITION PROBABILITY DENSITY FUNCTION. HOWEVER, IN COMPLEX MULTIDIMENSIONAL CASES IT IS DESIRABLE TO HAVE APPROXIMATE ANALYTICAL TECHNIQUES.

ONE SUCH METHOD IS TO CONSTRUCT A SYSTEM OF DETERMINISTIC ORDINARY DIFFERENTIAL EQUATIONS FOR THE MEANS AND COVARIANCES.

WE FOLLOW RODRIGUEZ AND TUCKWELL, PRE 54, 5585 (1996),

- **NEURAL (NETWORK) DYNAMICAL SYSTEMS CAN OFTEN BE PUT IN THE FOLLOWING FORM.**

Let $\mathbf{X}=\{\mathbf{X}(t),t\geqslant 0\}=\{(X_1(t),X_2(t),\ldots,X_n(t)),t\geqslant 0\}$, with $n\geqslant 1$, be an n-dimensional random process with components satisfying the stochastic differential equations

$$dX_j(t)=f_j(\mathbf{X}(t),t)dt+\sum_{k=1}^{m} g_{jk}(\mathbf{X}(t),t)dW_k(t),$$

where $j=1,2,\ldots,n$ and $m\geqslant 1$. The $W_k=\{W_k(t),t\geqslant 0\}$, $k=1,2,\ldots,m$ are standard Wiener processes (that is, they each have zero mean, initial value zero with probability one, and variance equal to t at time t) which we assume are independent.

Define the n means for the various components

$$\overline{X_j}(t) = E[X_j(t)],$$

where $j = 1, \ldots, n$, and the n^2 quantities

$$K_{ij}(t) = E[(X_i(t) - \overline{X_i}(t))][(X_j(t) - \overline{X_j}(t))],$$

where $i, j = 1, \ldots, n$. Of these n^2 quantities there are n variances,

$$V_j(t) = E[(X_j(t) - \overline{X_j}(t))]^2,$$

where $j = 1, \ldots, n$, and $\frac{1}{2}n(n-1)$ distinct covariances, $K_{ij}(t)$ with $i < j$.

- **Applying this to the expressions for the means gives**

$$\frac{dm_j}{dt} = f_j(\mathbf{m}, t) + \frac{1}{2} \sum_{l=1}^{n} \sum_{p=1}^{n} \left\{ \frac{\partial^2 f_j}{\partial x_l \partial x_p} \right\}_{(\mathbf{m}, t)} C_{lp} \,.$$

and to the covariances gives

$$
\begin{aligned}
\frac{dC_{ij}}{dt} = & \sum_{k=1}^{m} \left\{ g_{ik} g_{jk} \right\}_{(\mathbf{m},t)} + \sum_{l=1}^{n} \left\{ \frac{\partial f_i}{\partial x_l} \right\}_{(\mathbf{m},t)} C_{lj} + \sum_{l=1}^{n} \left\{ \frac{\partial f_j}{\partial x_l} \right\}_{(\mathbf{m},t)} C_{il} \\
& + \frac{1}{2} \sum_{l=1}^{n} \sum_{p=1}^{n} \left\{ g_{jk} \frac{\partial^2 g_{ik}}{\partial x_l \partial x_p} + \frac{\partial g_{ik}}{\partial x_l} \frac{\partial g_{jk}}{\partial x_l p} + \frac{\partial g_{ik}}{\partial x_p} \frac{\partial g_{jk}}{\partial x_l} + g_{ik} \frac{\partial^2 g_{jk}}{\partial x_l \partial x_p} \right\}_{(\mathbf{m},t)} C_{lp}.
\end{aligned}
$$

FOR HH THE COMPONENTS ARE X1=V, X2=n, X3=m AND X4=h.

- **The means are m_1, m_2, m_3, m_4**

  and there are 4 variances C_11, C_22, C_33 and C_44 together with another

  6 covariances C_12, C_13, C_14, C_23, C_24, C_34 = 14 1st and 2nd order moments.

For example, C_24 = Cov (n(t), h(t))

FAIRLY LENGTHY CALCULATIONS GIVE FOR EXAMPLE THE DE'S FOR THE MEAN AND VARIANCE OF THE VOLTAGE VARIABLE

$$\begin{aligned}\frac{dm_1}{dt} &= \frac{1}{C}\Big[\mu + \overline{g}_K m_2^4(V_K - m_1) + \overline{g}_{Na} m_3^3 m_4 (V_{Na} - m_1) + g_L(V_L - m_1)\\ &-4\overline{g}_K m_2^3 C_{12} - 3\overline{g}_{Na} m_3^2 m_4 C_{13} - \overline{g}_{Na} m_3^3 C_{14}\\ &+6\overline{g}_K m_2^2 (V_K - m_1) C_{22} + 3\overline{g}_{Na} m_3 m_4 (V_{Na} - m_1) C_{33}\\ &+3\overline{g}_{Na} m_3 (V_{Na} - m_1) C_{34}\Big].\end{aligned}$$

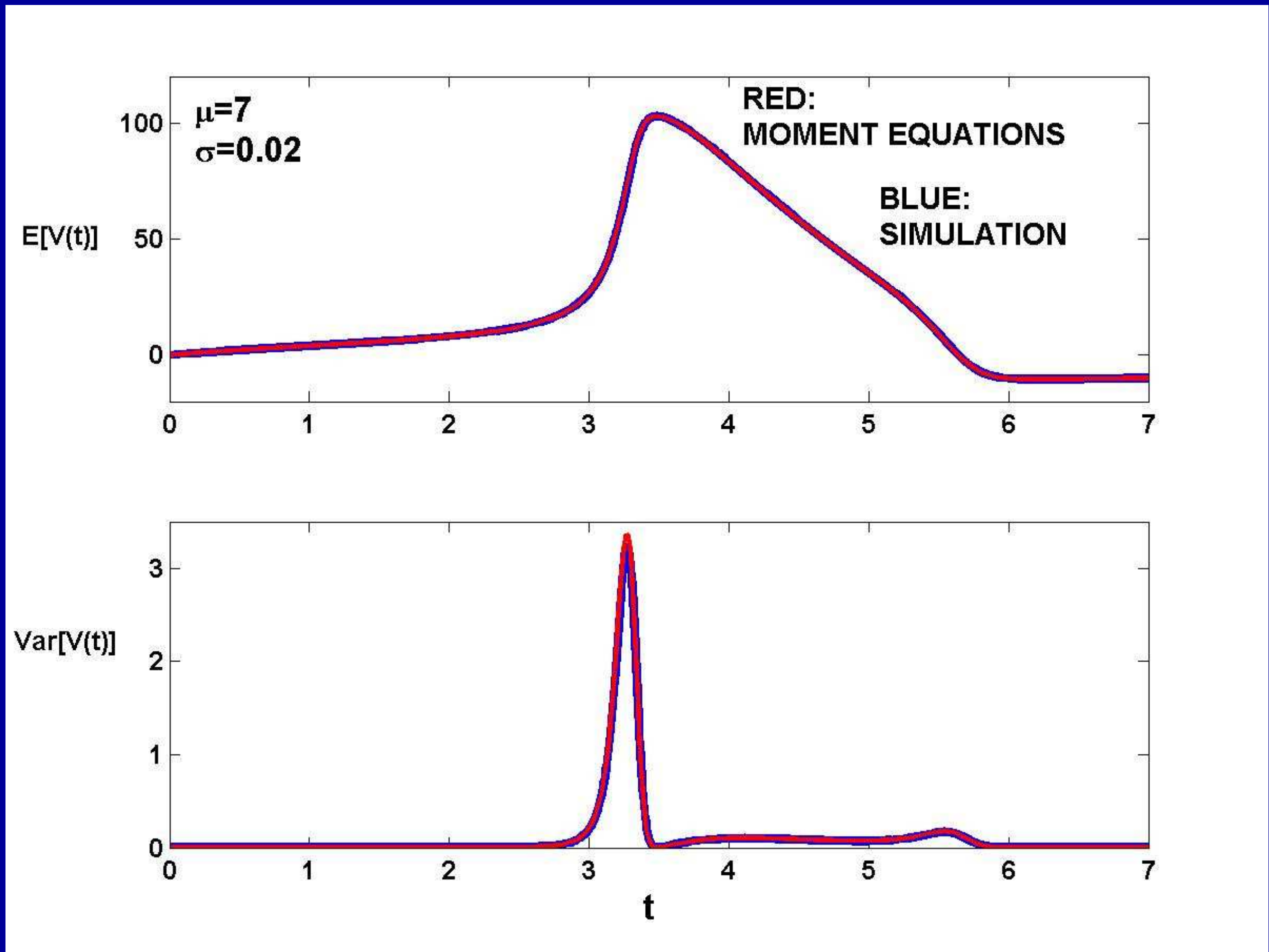
$$\begin{aligned}\frac{dC_{11}}{dt} &= -\frac{2}{C}\left[\overline{g}_K m_2^4 + \overline{g}_{Na} m_3^3 m_4 + g_L\right] C_{11}\\ &+\frac{8}{C}\overline{g}_K m_2^3 (V_K - m_1) C_{12}\\ &+\frac{6}{C}\overline{g}_{Na} m_3^2 m_4 (V_{Na} - m_1) C_{13}\\ &+\frac{2}{C}\overline{g}_{Na} m_3^3 (V_{Na} - m_1) C_{14} + \left(\frac{\sigma}{C}\right)^2\end{aligned}$$

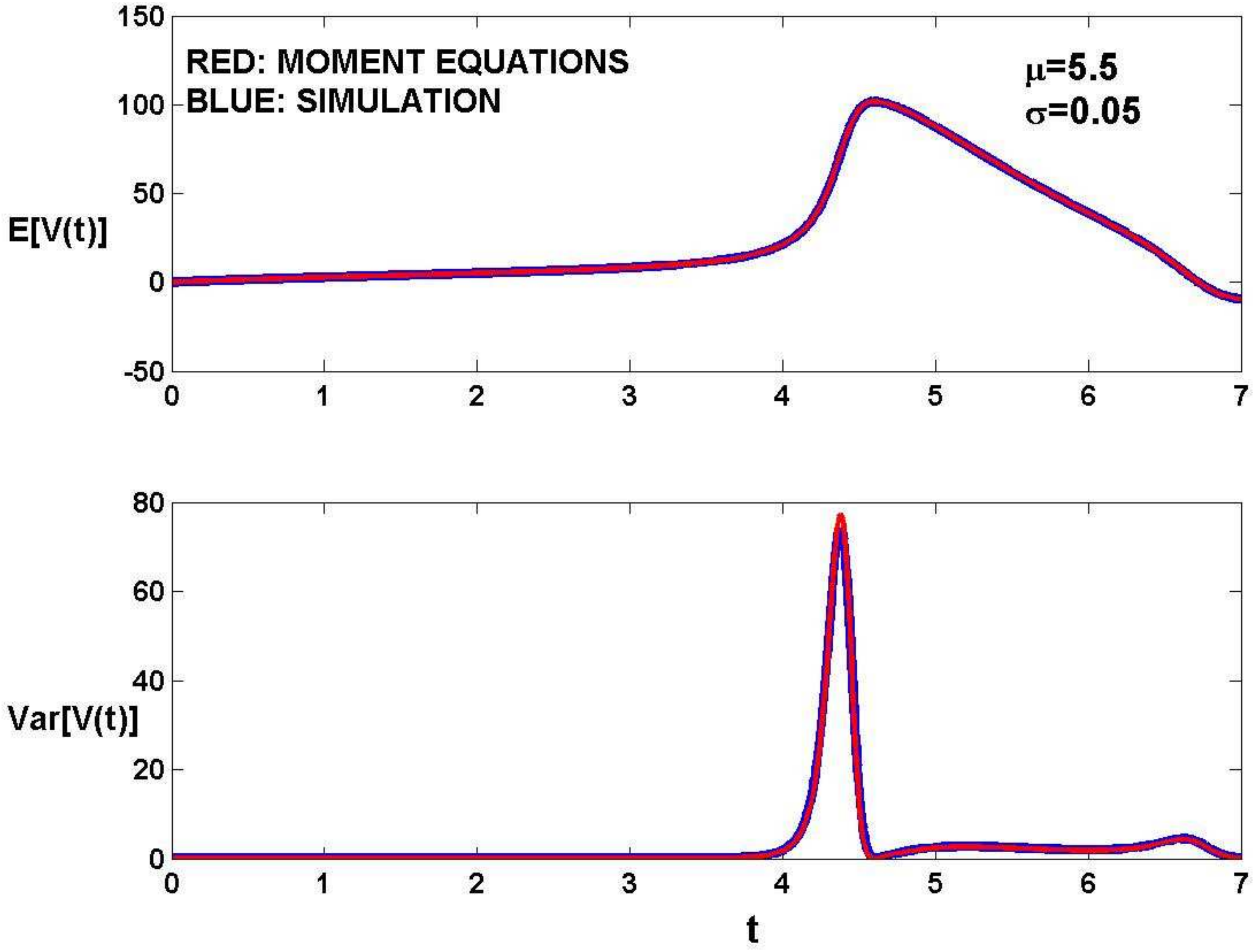
- **OTHER EQUATIONS INVOLVE THE ALPHA'S AND BETA'S AND THEIR DERIVS E.G.**

$$
\begin{aligned}
\frac{dm_2}{dt} &= \alpha_n(m_1)(1-m_2)-\beta_n(m_1)m_2 \\
&\quad +\Big[\big(\alpha_n''(m_1)(1-m_2)-\beta_n''(m_1)m_2\big)C_{11} \\
&\quad -2\big(\alpha_n'(m_1)+\beta_n'(m_1)\big)C_{12}\Big]
\end{aligned}
$$

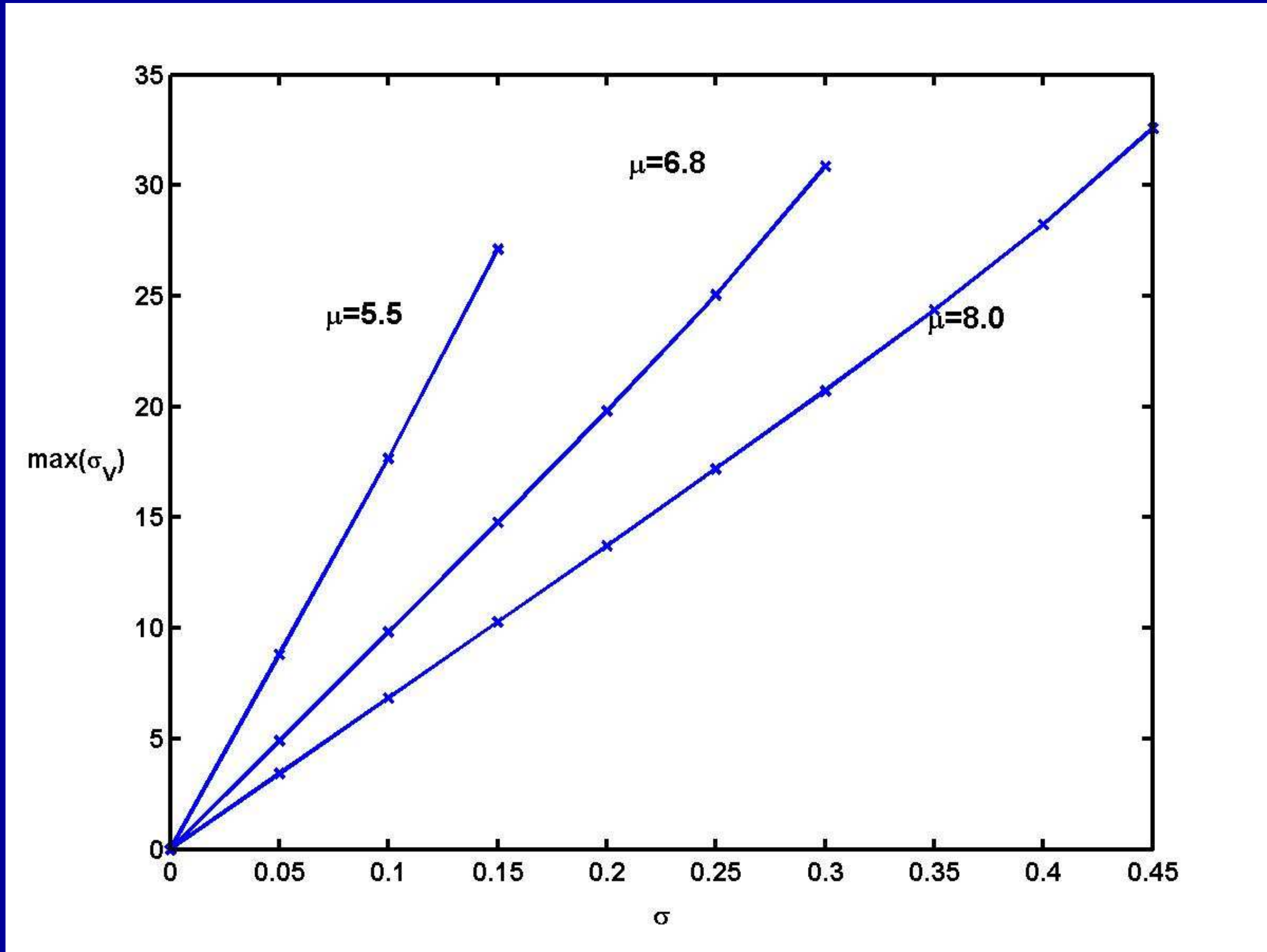
$$
\begin{aligned}
\frac{dm_3}{dt} &= \alpha_m(m_1)(1-m_3)-\beta_m(m_1)m_3 \\
&\quad \Big[\big(\alpha_m''(m_1)(1-m_3)-\beta_m''(m_1)m_3\big)C_{11} \\
&\quad -2\big(\alpha_m'(m_1)+\beta_m'(m_1)\big)C_{13}\Big]
\end{aligned}
$$

FOLLOWING SHOW THE MEAN AND VARIANCE OF THE VOLTAGE: THE FIRST TWO SETS OF RESULTS ARE FOR SMALL NOISE AND SHOW THE EXCELLENT AGREEMENT BETWEEN ANALYTICAL AND SIMULATION RESULTS

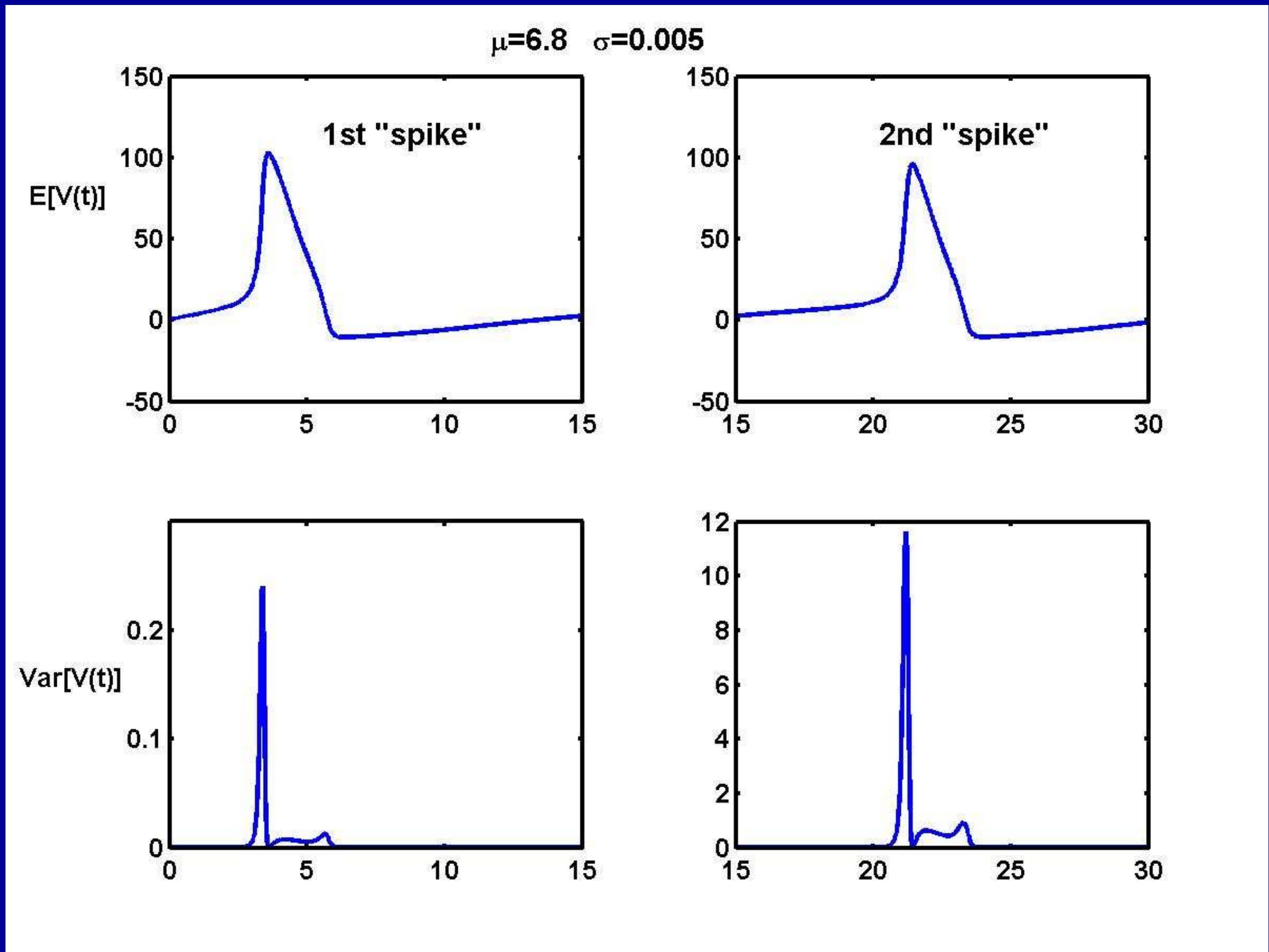



RED: MOMENT EQUATIONS
BLUE: SIMULATION
μ=5.5
σ=0.05
E[V(t)]
150
100
50
0
-50
0 1 2 3 4 5 6 7
Var[V(t)]
80
60
40
20
0
0 1 2 3 4 5 6 7
t

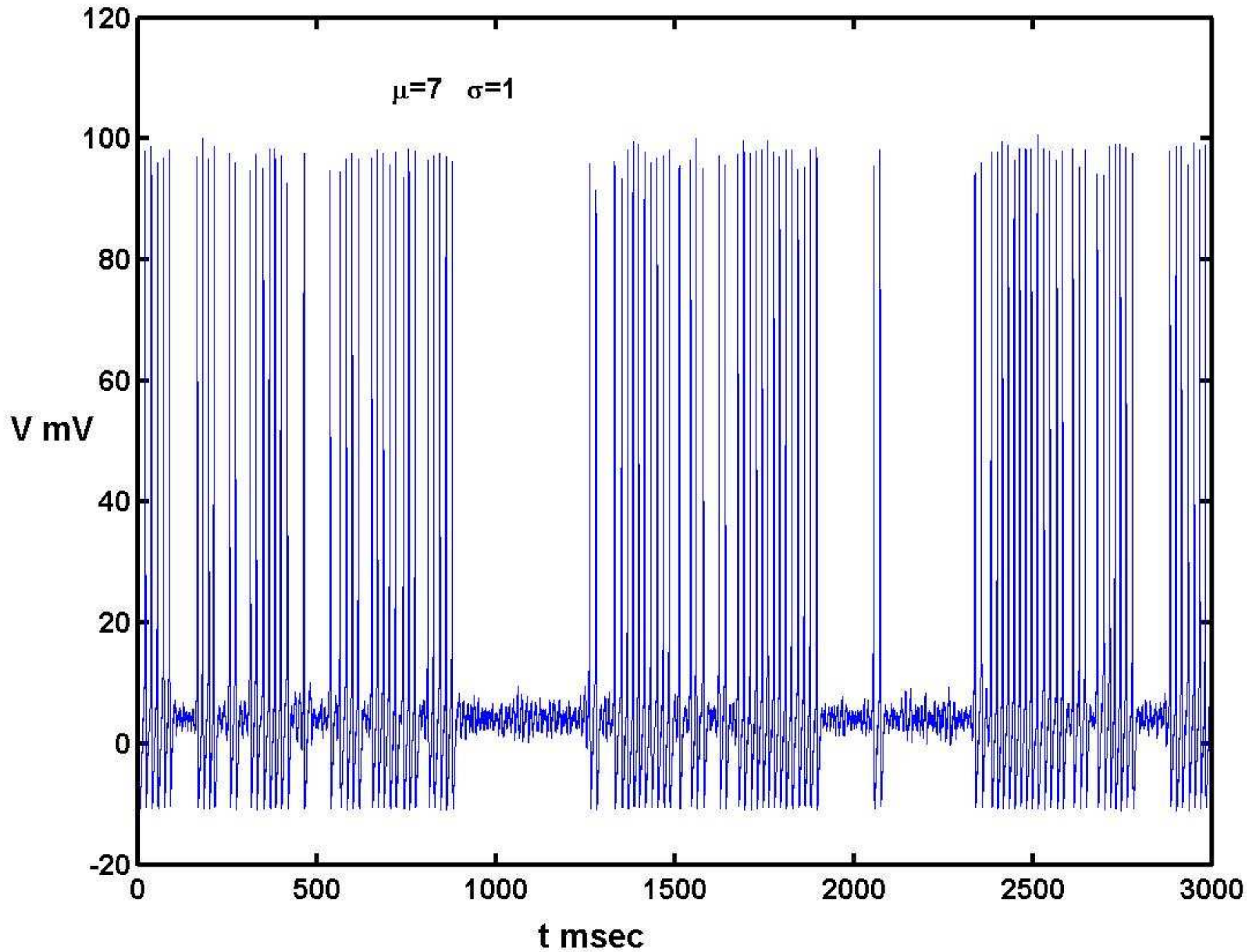
THIS SHOWS HOW THE VARIANCE OF V DEPENDS ON SIGMA FOR VARIOUS MU: THE GRAPHS STOP WHEN THE METHOD FAILS



THIS SHOWS HOW A SMALL NOISE MAY STOP THE SPIKING AFTER 1 SPIKE

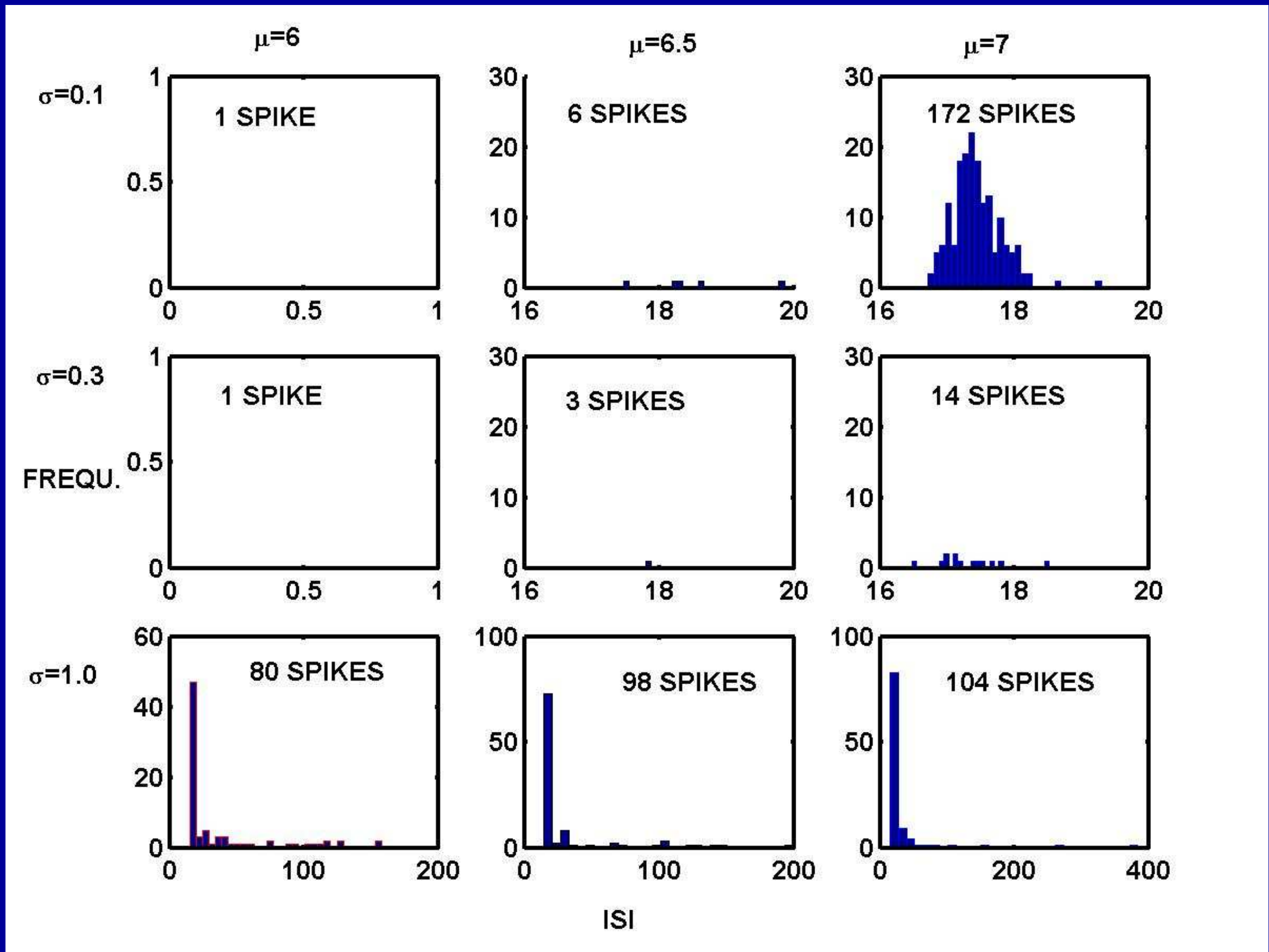


LONG DURATION EXAMPLE – LARGE NOISE SWITCHING FROM LIM CYCLE TO REST



LONG DURATION 3000 msec - SUMMARY

JUST SUB **JUST SUP** **SUP**



- **Hence one sees that there is a “competition” between the tendency of noise to stop the spiking and the tendency for it to induce spiking.**

Theory: use exit-time theory for Markov processes

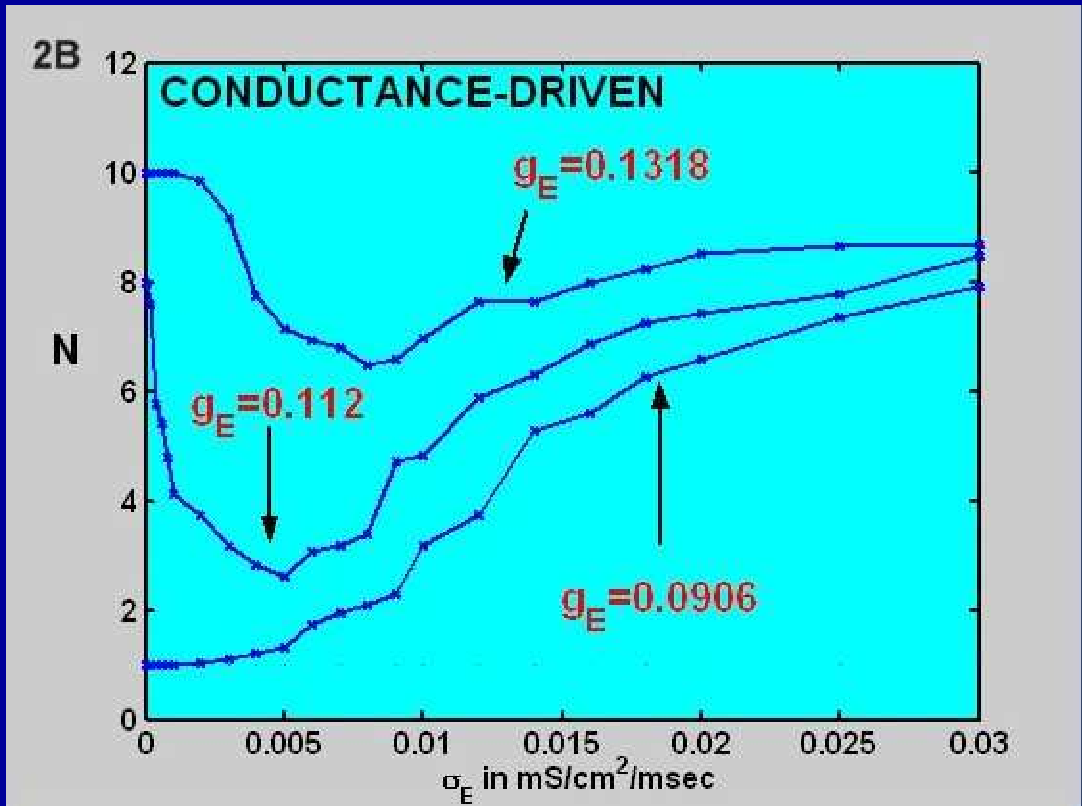
- **Theorem:** The process switches from spiking to non-spiking states (and vice-versa) in a finite time with probability one. The expected times which the system remains in one or the other state are the solutions of linear partial differential equations given below
- **Sketch proof**
- The process has an infinitesimal operator L. That is, the transition density p satisfies a Kolmogorov equation
- $\partial p / \partial t = Lp$
- The prob p_L of leaving the BOA BL of the limit cycle satisfies
- $Lp_L = 0$ on BL (*)
- with boundary condition
- $p_L = 1$.
- The solution of * is p_L = a constant. Hence, because process is continuous, $p_L = 1$ throughout BL.
- Similarly for the prob p_R of leaving the BOA BR of the rest state. Standard theory gives that the expected time to stay in the spiking state satisfies $LF_L = -1$ on BL with boundary condition $F_L = 0$.

  Similarly for the expected time to leave BR. The behaviour of the system is thus characterized by a sequence of alternate exit times from BL and BR.

(2) We also considered HH model with conductance-based noise: n, m and h equations the same as before

$$
\begin{aligned}
dV &= \left(\frac{1}{C}[\overline{g}_K n^4(V_K - V) + \overline{g}_{Na} m^3 h(V_{Na} - V) \right. \\
&\quad \left. + g_L(V_L - V)] + I_c(t)\right) dt \\
dg_E &= -\frac{1}{\tau_E}\left[g_E - \overline{g}_E\right] dt + \sigma_E dW_E(t) \\
dg_I &= -\frac{1}{\tau_I}\left[g_I - \overline{g}_I\right] dt + \sigma_I dW_I(t)
\end{aligned}
$$

RESULTS: WE OBTAINED A SIMILAR RESULT WITH COND-BASED NOISE: VOILA!



2.3 INCLUDING SPATIAL EXTENT: THE HODGKIN-HUXLEY SPDE

HH PDE

$$C\frac{\partial V}{\partial t} = \frac{a}{2R}\frac{\partial^2 V}{\partial x^2} + I(x,t)$$

where a = radius, C = membrane capacitance/unit area, R= specific resistance of intracellular material.

The current I may consist of ionic components, applied currents or synaptic input.

We use the usual HH ionic terms

$$I_i = \overline{g}_K n^4(V_K - V) + \overline{g}_{Na} m^3 h(V_{Na} - V) + g_L(V_L - V)$$

The applied current is

$$I_A(x,t) = \mu(x,t) + \sigma(x,t)w(x,t)$$

where w is a standard two parameter white noise.

HH SPDE

In the following the mean is $\mu(x,t) = 6.5$ for all

$$t > 0$$

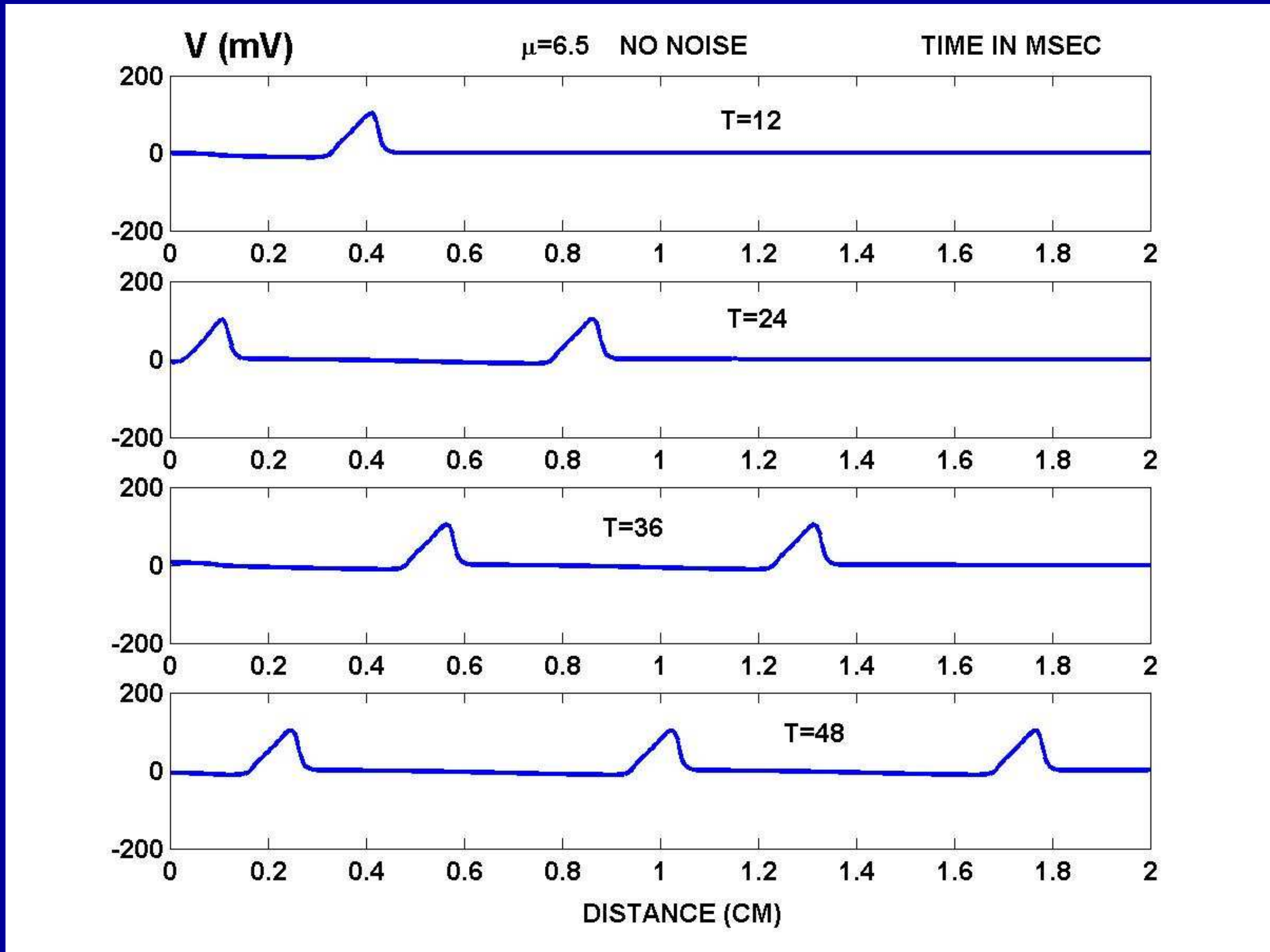
and

$$0 < x < 0.1.$$

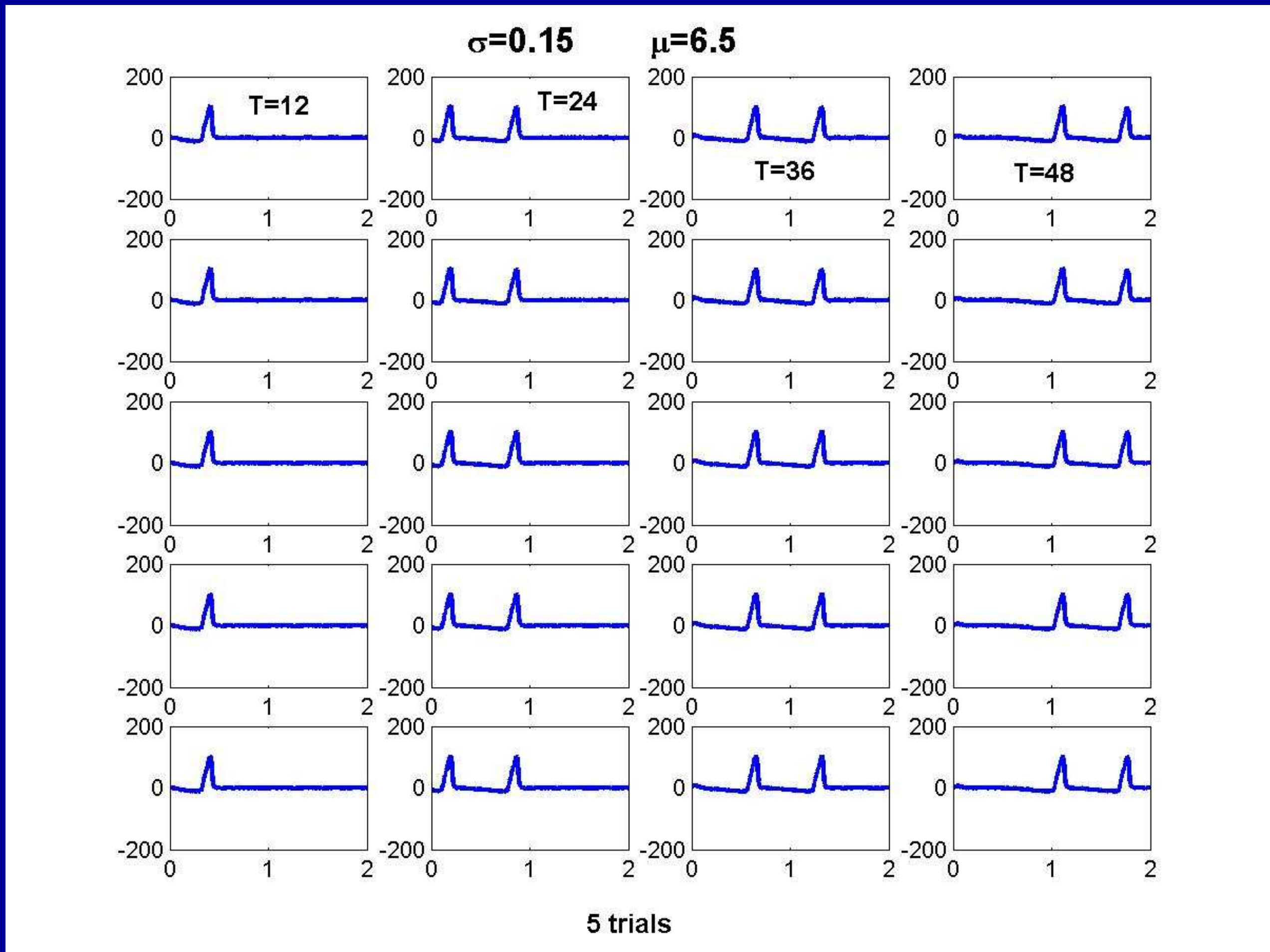
This is sufficient to ensure a train of spikes. The noise amplitude is a constant for all x and t.

Standard HH parameters are employed and an explicit integration method whose accuracy was checked (see below).

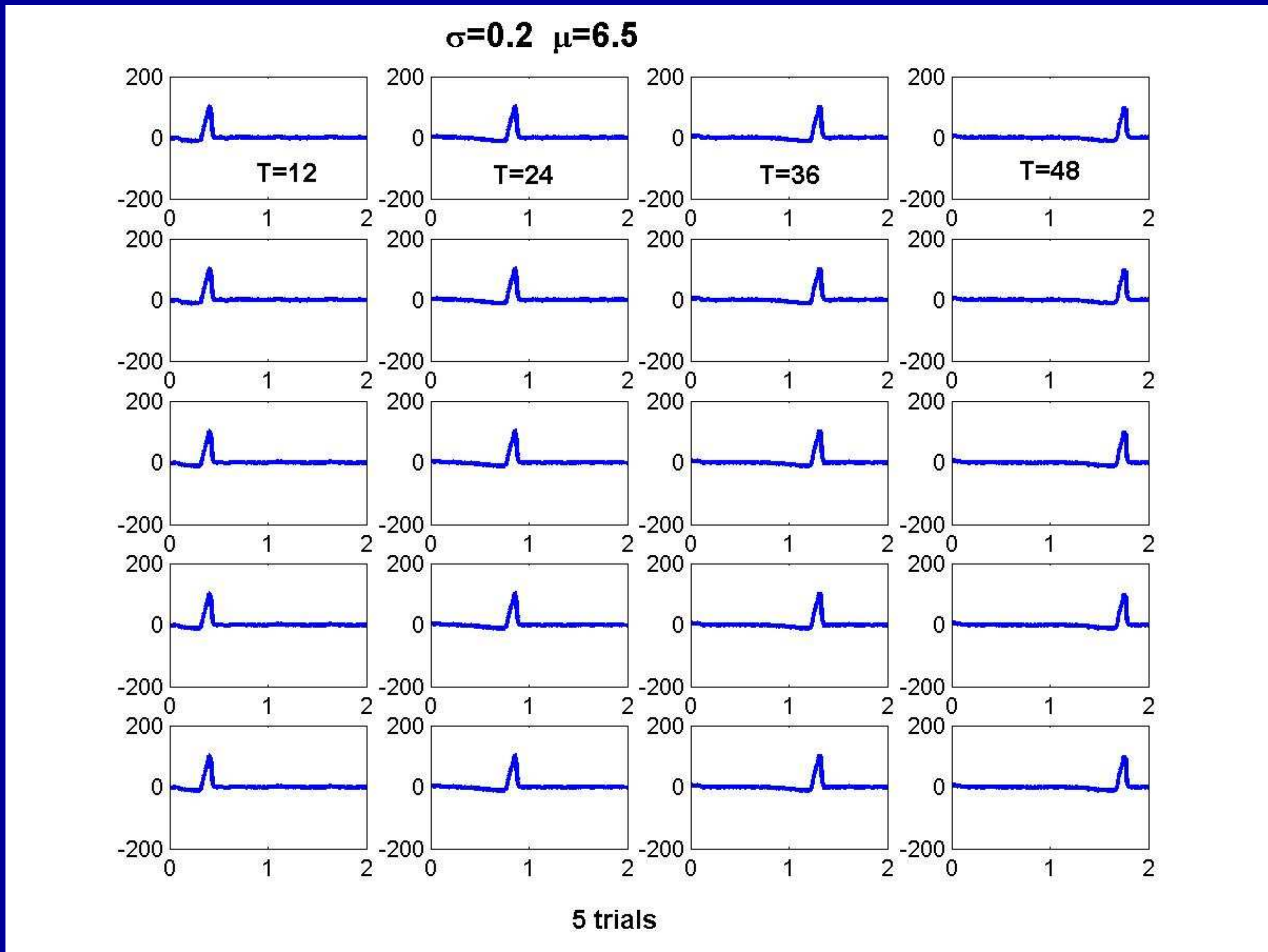
RESULTS 1 : no noise: TRAIN OF AP's



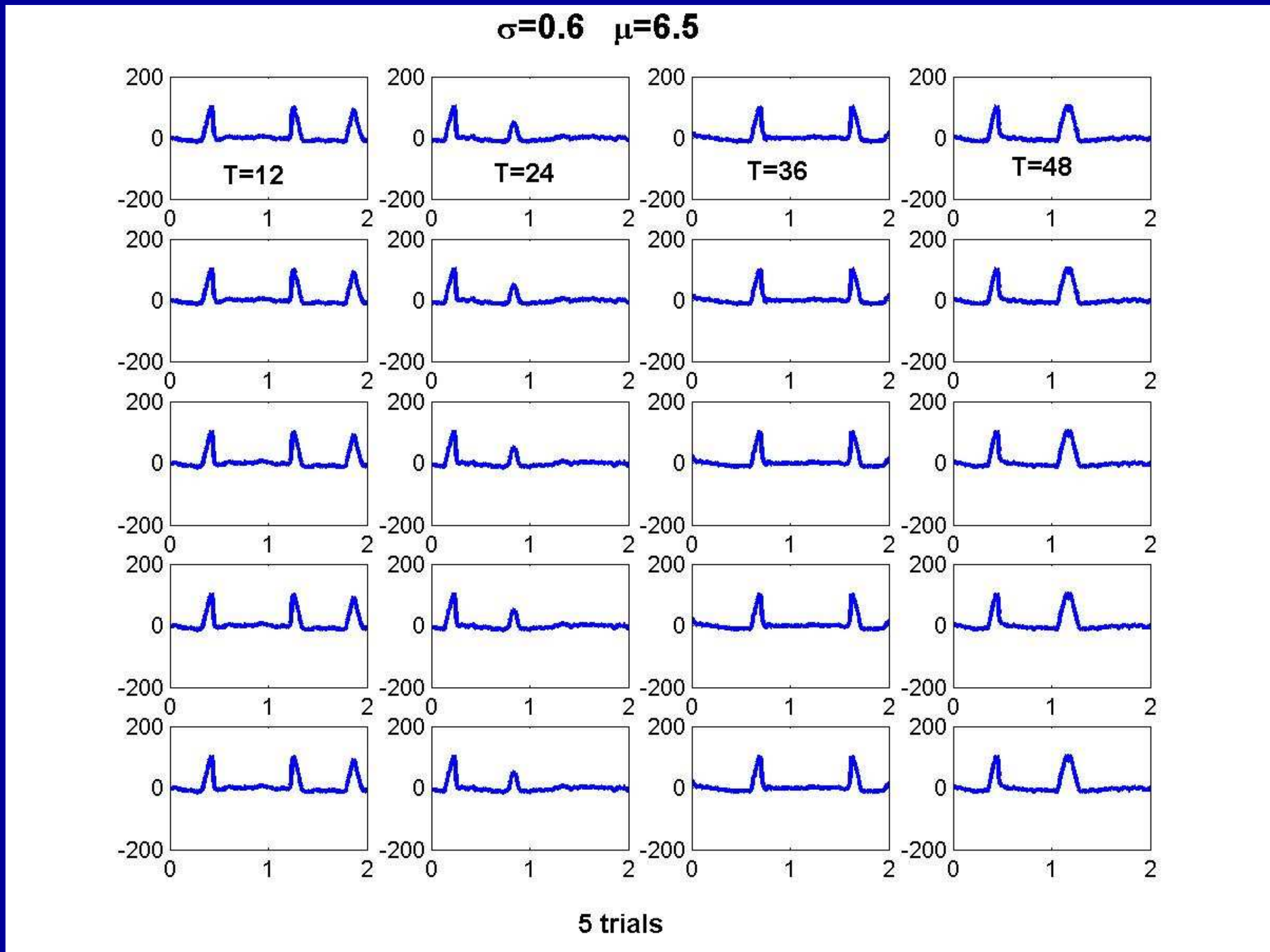
RESULTS 2



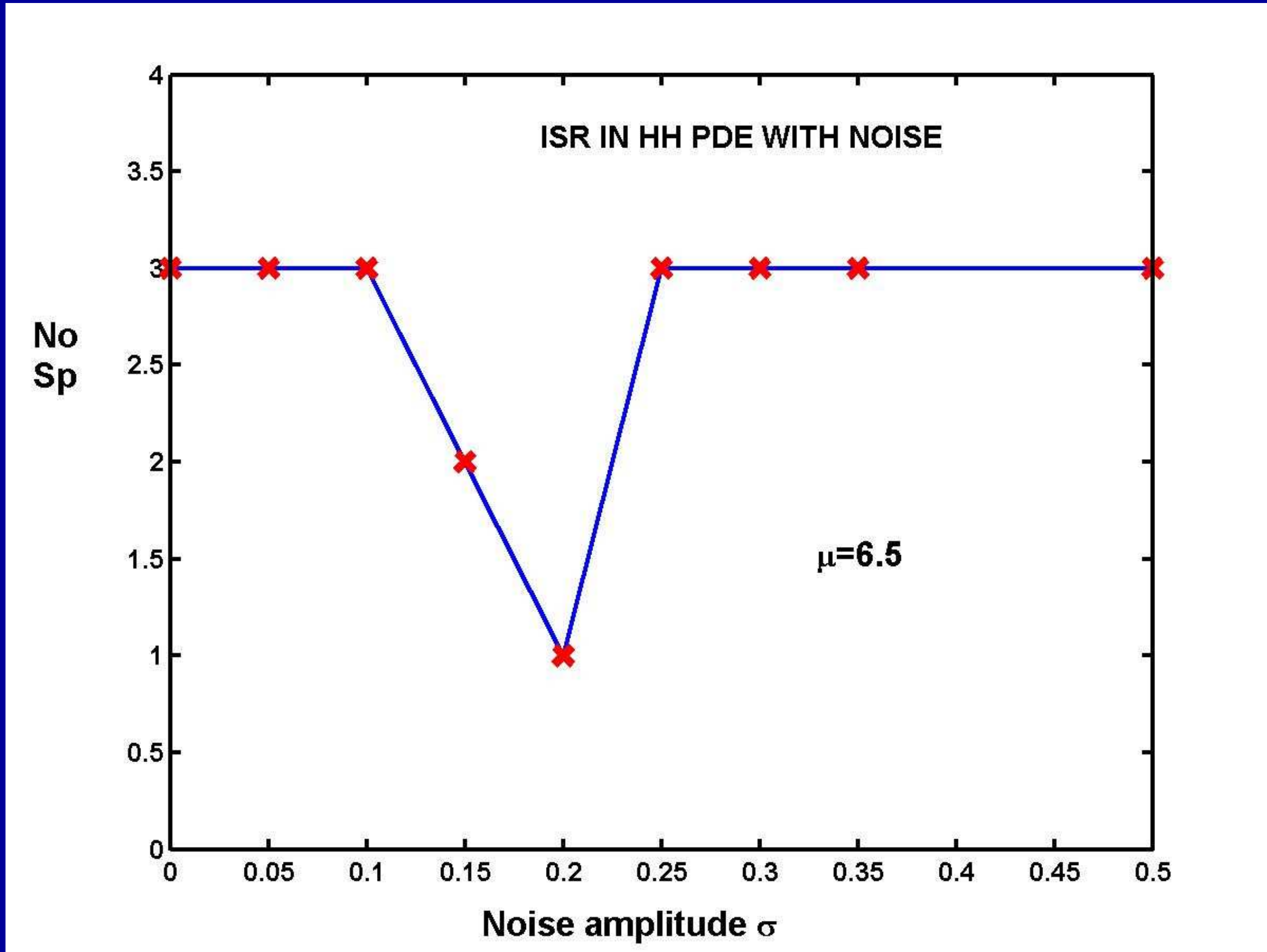
RESULTS 3



RESULTS 4

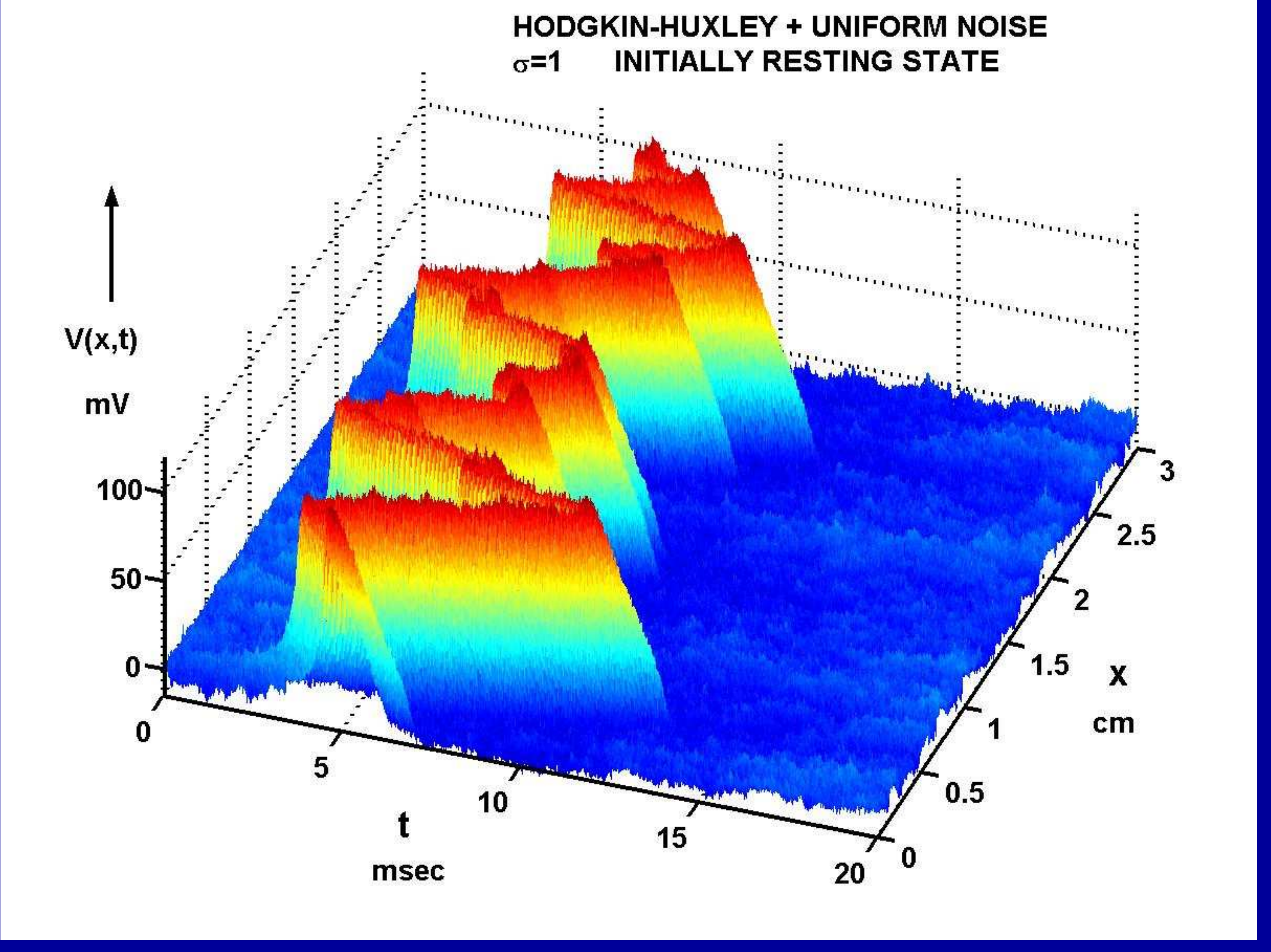


RESULTS 5

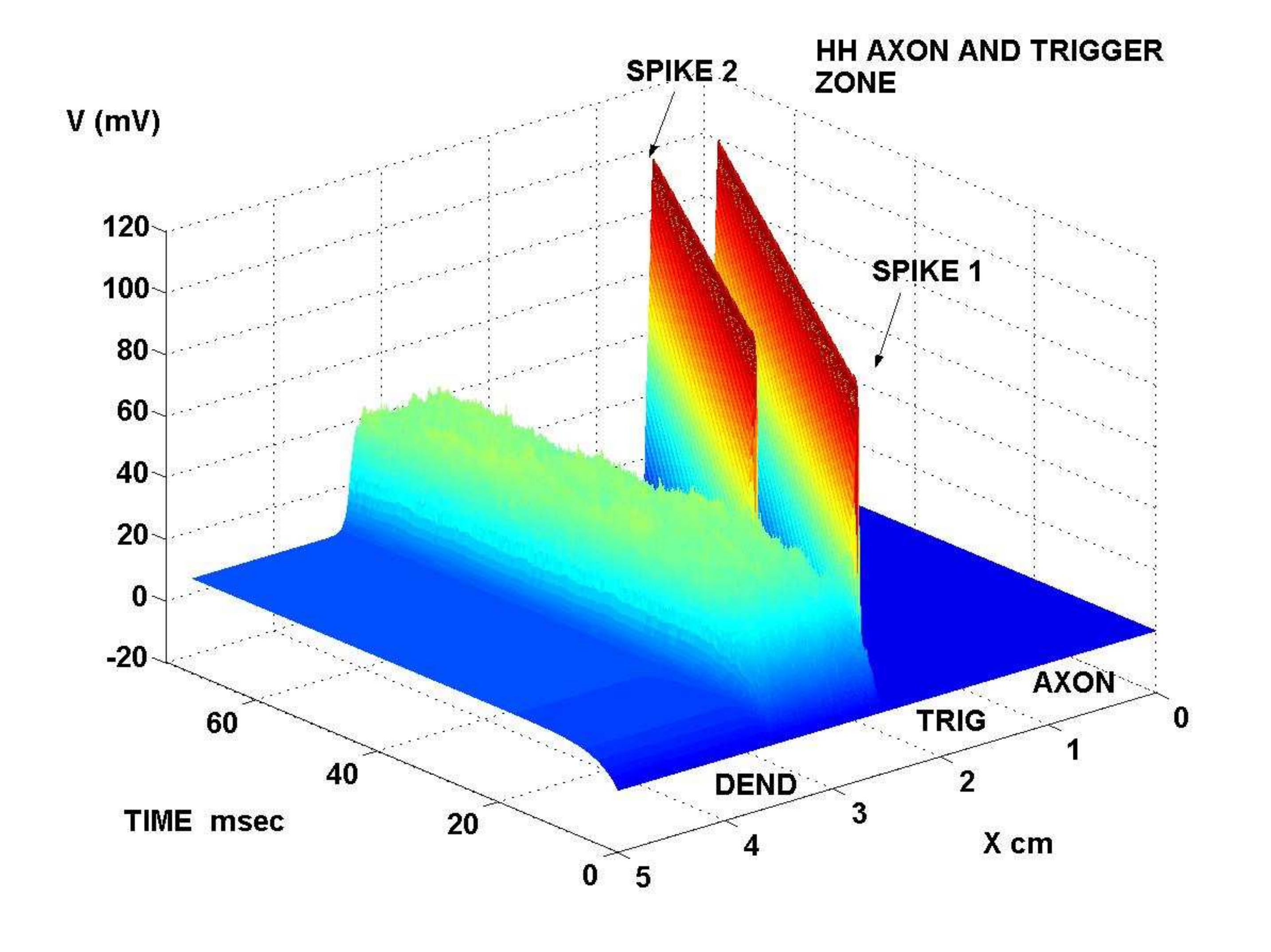


ISR IN HH PDE WITH NOISE
μ=6.5
No Sp
Noise amplitude σ
0
0.5
1
1.5
2
2.5
3
3.5
4
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5

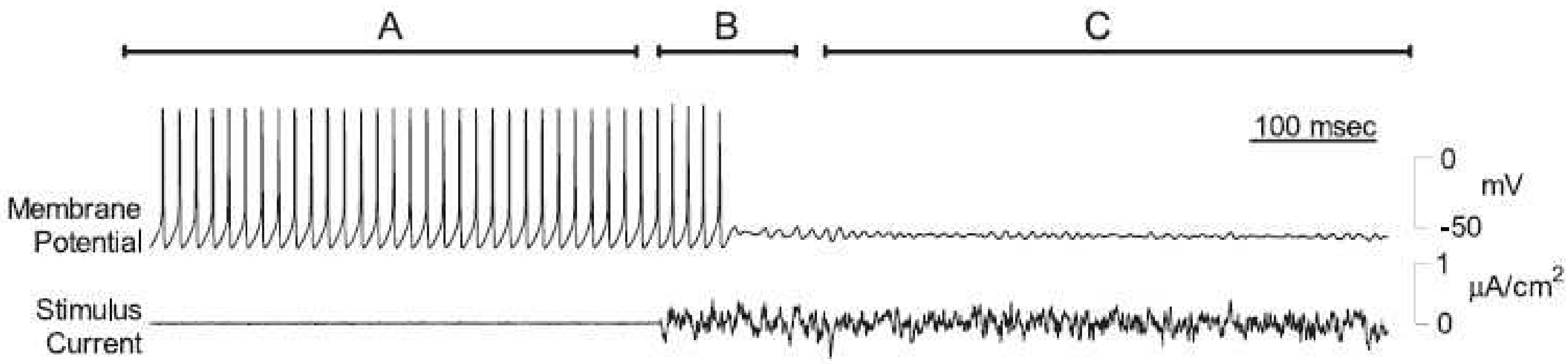
WAVE INTERFERENCE



Wave instigation at t-zone: preliminary result



EXPERIMENTAL CONFIRMATION OF THE SILENCING OF NEURONAL ACTIVITY BY NOISE CAME IN 2006 ON SQUID AXON – AN ARTICLE BY Paydarfar, Forger & Clay: Noisy inputs and the induction of on-off switching behavior in a neuronal pacemaker. J. *Neurophysiol.* 96, 3338-3348. 8 AXONS WERE EXAMINED.



THESE PHENOMENA ARE EXPECTED TO OCCUR WHEN A STABLE REST POINT AND A STABLE LIMIT CYCLE CO-EXIST.

THE IMPLICATIONS FOR NEURAL ACTIVITY REMAIN TO BE FULLY EXPLORED. THE RESULTS FOR NOISE IN THE PDES MAY BE RELEVANT TO TRANSMISSION OF DENDRITICALLY INSTIGATED SPIKING

APART FROM IN SINGLE CELL PACEMAKER ACTIVITY THERE MAY BE APPLICATIONS IN

- BRAIN OSCILLATIONS INCLUDING EPILEPSY
- CARDIOLOGY
- CELL KINETICS – TUMOR GROWTH (P53)
- ASTROPHYSICS
- ECOLOGY
- CLIMATOLOGY

IN ALL OF WHICH STABLE LIMIT CYCLES ARE FOUND.

END