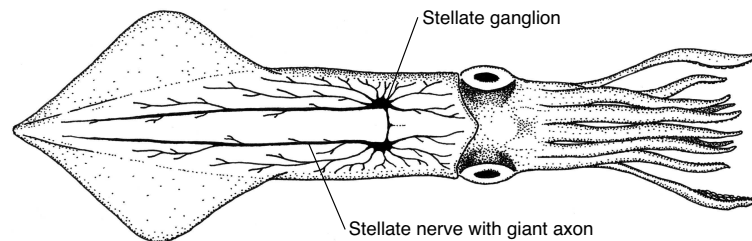


# Response of the Hodgkin-Huxley model in the high-input regime

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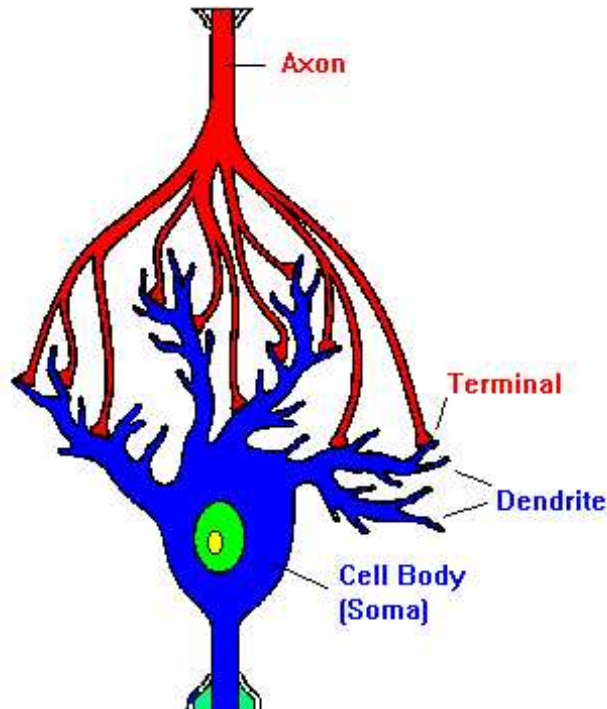
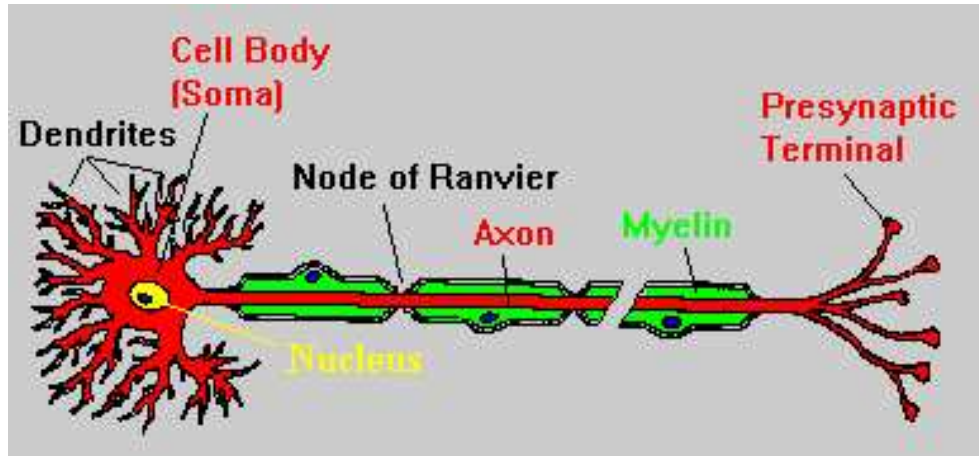


# Summary

- Brief introduction of the HH model
- Characterization of the stochastic stimulation protocol
- Analysis of the neuronal responses for different noise levels
- Looking for coherence in the neuronal response
- Influence of correlations on the coherent response
- Conclusions and open problems



# The neuron in brief



A neuron in the brain cortex has many ( $\sim 10,000$ ) synaptic connections, but not all active. The neuron receives 300 – 1,000 postsynaptic inputs of amplitude  $\sim 0.5 - 1$  mV at a frequency  $\sim 100$  Hz, it responds each 10 – 40 inputs by emitting an action potential of duration 1 – 2 msec and amplitude  $\sim 100$  mV.

# The Hodgkin-Huxley model



*Hodgkin*

The HH model reproduces the time evolution of the membrane potential and of the ionic currents measured experimentally for a giant squid axon.



*Huxley*

# The Hodgkin-Huxley model



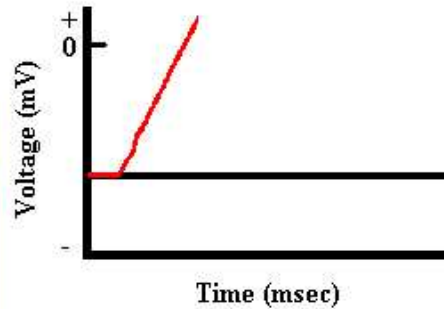
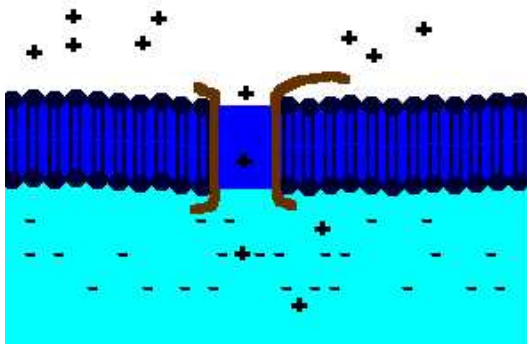
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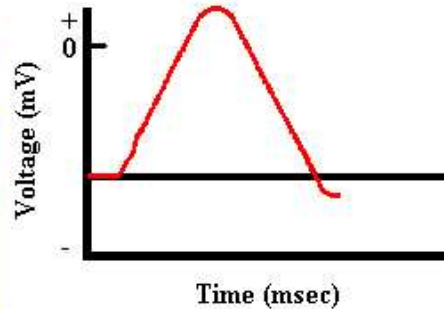
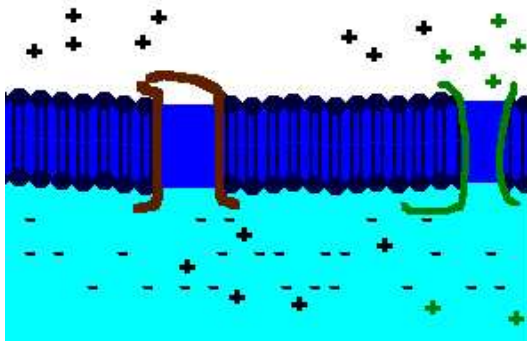
Huxley

## Membrane Depolarization



$Na^+$  enters inside the cell

## Membrane Repolarization



$K^+$  leaves the cell

# The Hodgkin-Huxley model

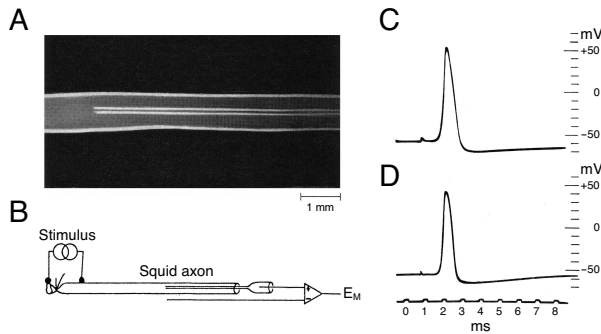


Hodgkin

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Huxley



$C = 1 \mu F/cm^2$  - Membrane capacitance

$V$  - Membrane Potential (mV)

$I_j$  - Ionic channel currents ( $\mu A/cm^2$ )

$$C\dot{V} = \sum_j I_j + I_{syn} = -g_{Na}m^3h(V - V_{Na}) - g_Kn^4(V - V_K) - g_L(V - V_L) + I_{syn}$$

$$\dot{x} = \alpha_x - x(\alpha_x + \beta_x) \quad x = n, m, h \quad \text{gating variables}$$

$\alpha_x = \alpha_x(V)$  and  $\beta_x = \beta_x(V)$  are highly nonlinear functions.

# The Hodgkin-Huxley model



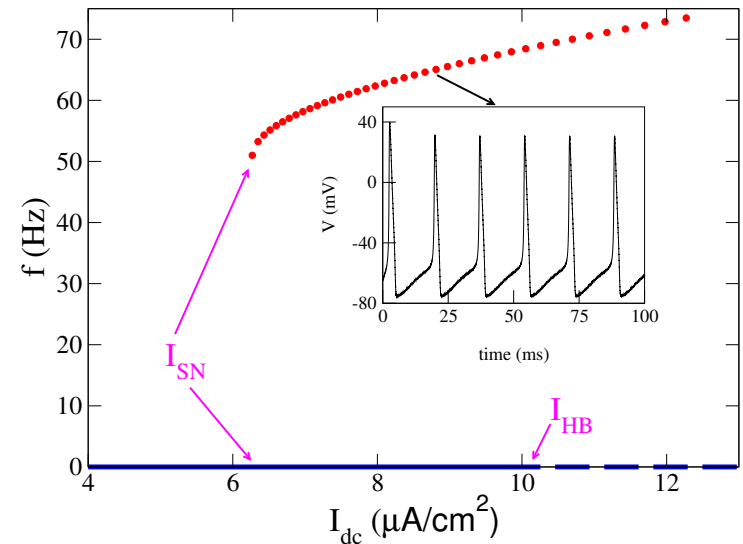
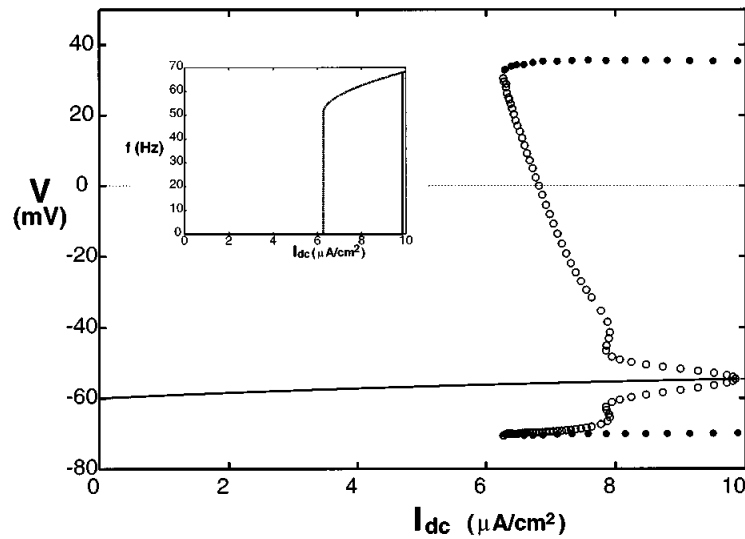
Hodgkin

The HH model reproduces the time evolution of the membrane potential and of the ionic currents measured experimentally for a giant squid axon.



Huxley

Constant Current Synaptic Input  $I_{syn} = I_{dc}$



# High-input regime

- Instead of a constant current  $I_{dc}$ , we consider  $N_E$  excitatory (EPSP) and  $N_I$  inhibitory postsynaptic inputs (IPSP), each corresponding to a voltage kick  $\Delta V = 0.5 \text{ mV}$ .



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- Firstly **independent** inputs are considered, and then also the effect of **correlations** among the inputs is analyzed.

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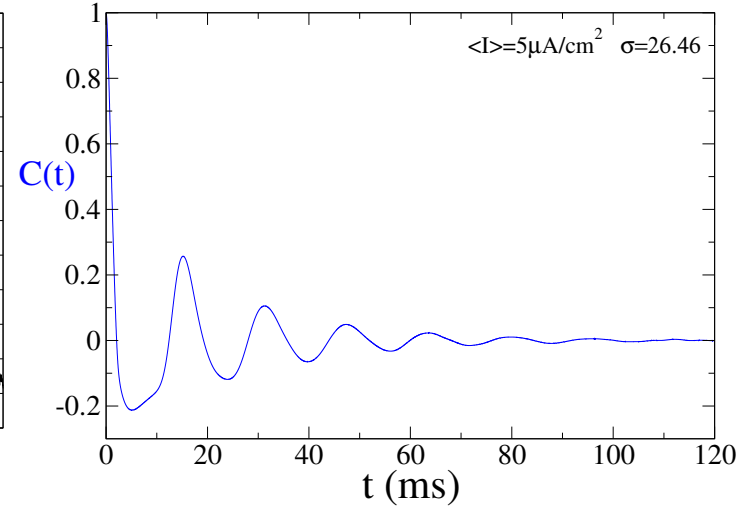
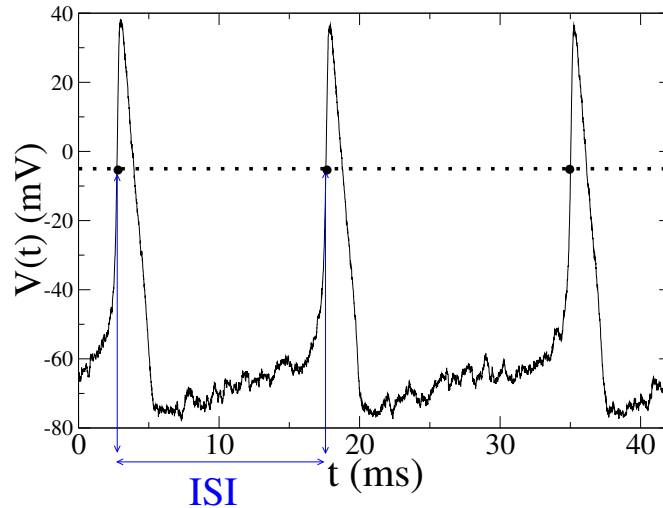
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At these frequencies the **net input spike count** within a temporal window  $\Delta T$  ( $\geq 1 \text{ msec}$ ) is essentially **Gaussian distributed** and it can be characterized by its average  $\mu = \nu(N_E - N_I)\Delta T$  and variance  $V = \nu(N_E + N_I)\Delta T = \nu\sigma^2\Delta T$ .

The response of the neuron is examined for **fixed** average input current  $\bar{I} = C\Delta V\nu(N_E - N_I)$  by varying only  $\sigma$  and therefore the standard deviation of the noise.



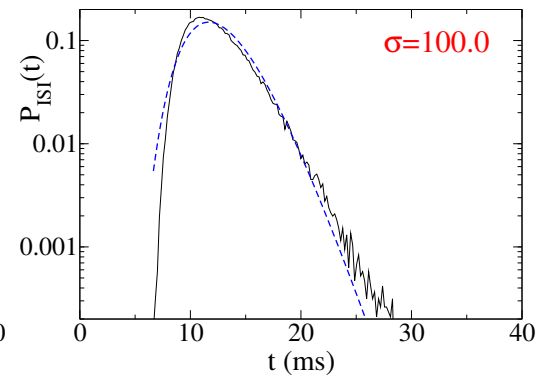
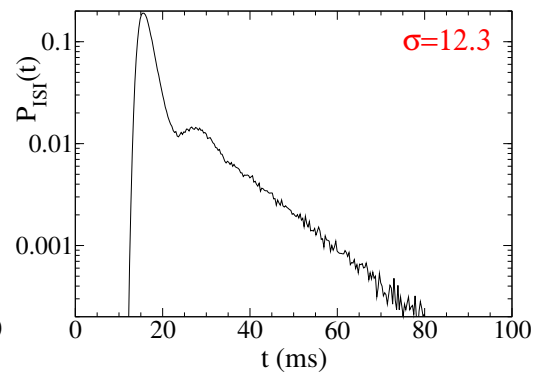
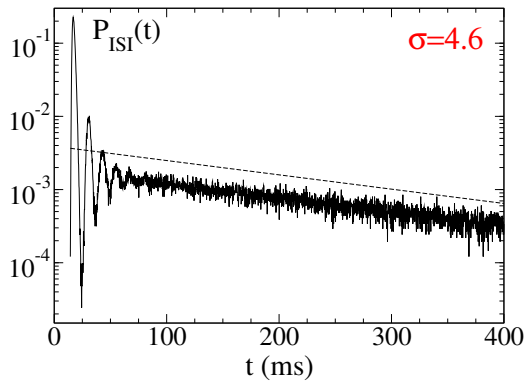
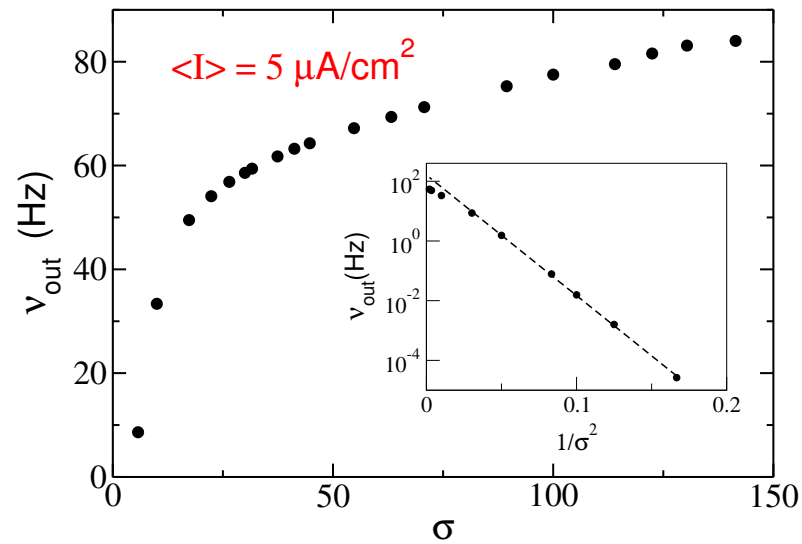
# Statistical and dynamical indicators



- ISI distribution  $\rightarrow P_{ISI}(t)$ ;
- $CV = \frac{Std(ISI)}{\langle ISI \rangle}$   $\rightarrow$  coefficient of variation of the ISIs:  
Poisson distribution  $\rightarrow CV = 1$  \*\*\* regular sequence  $\rightarrow CV = 0$ ;
- $\tau_c = \int_0^\infty C^2(t) dt$   $\rightarrow$  correlation time,  $C(\tau) = \frac{\langle V(t+\tau)V(t) \rangle - \langle V \rangle^2}{\langle V^2 \rangle - \langle V \rangle^2}$
- Conditional entropies (not discussed here)

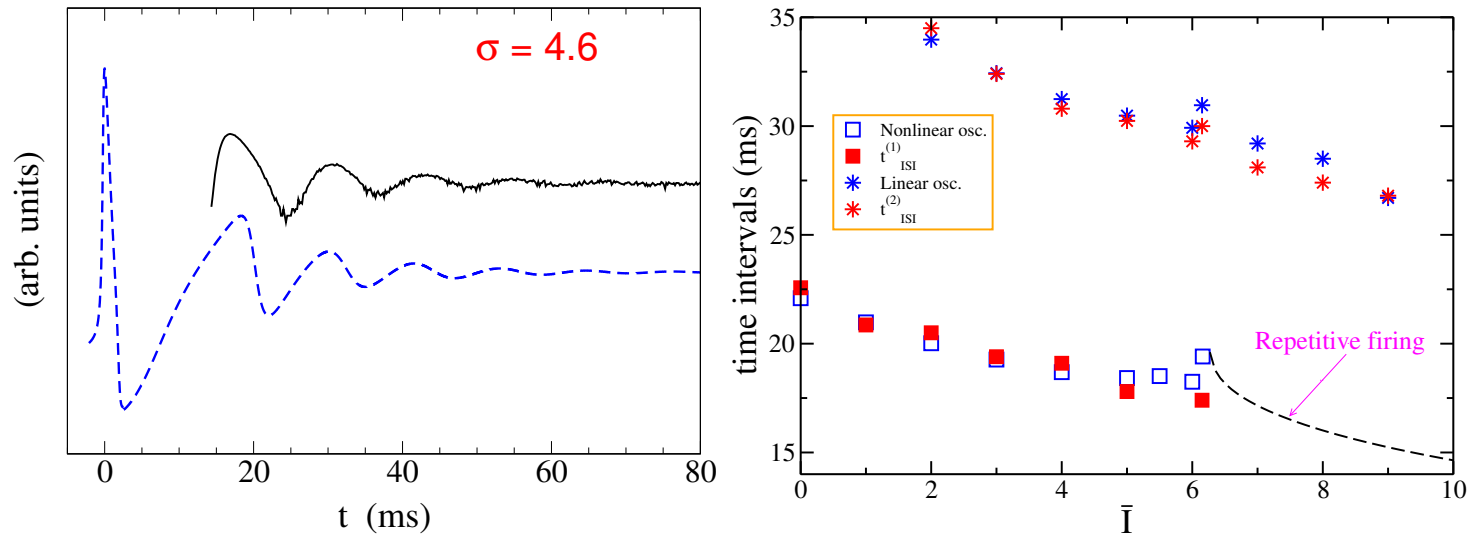
# Response of the silent neuron

The HH neuron is in the silent state, i.e. the average input current  $\bar{I}$  is smaller than  $I_{SN}$ .



# Response of the silent neuron

## Spikes triggered by relaxation oscillations



The neuronal spiking is enhanced in correspondence of the maxima of the relaxation oscillations following a spike emission.

The first oscillation has a **nonlinear origin**, while the period of the subsequent ones can be obtained via a **linear analysis** around the stable fixed point solution (focus).



# Response of the silent neuron

## Firing activated by noise

Two mechanisms compete:

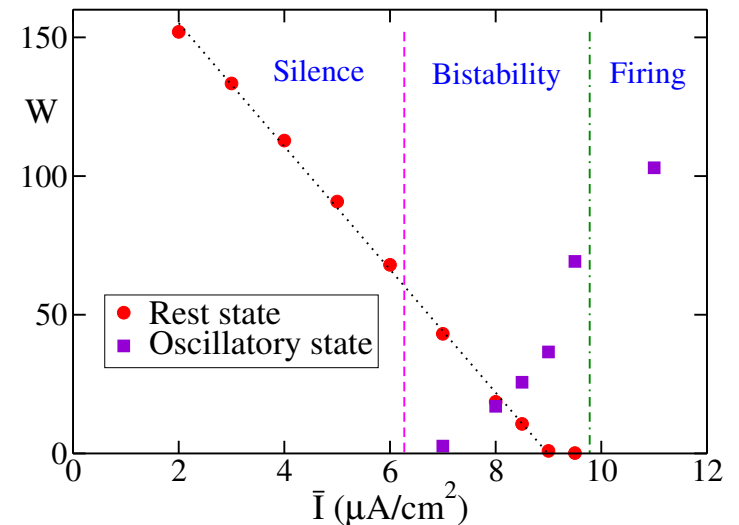
- the HH dynamics tends to relax towards the rest state;
- noise fluctuations lead the system towards an excitation threshold.

The dynamics of  $V(t)$  resembles the overdamped dynamics of a particle in a potential well under the influence of thermal fluctuations, and the firing times can be expressed in terms of the Kramers expression (for sufficiently small noise)

$$t_a \propto e^{W_S/\sigma^2}$$

the time distribution is Poissonian ( $CV = 1$ ).

- for  $\sigma < \sqrt{W_S}$  → Activation Process
- for  $\sigma > \sqrt{W_S}$  → Diffusive Dynamics





# Response of the silent neuron

## High noise limit

The effect of noise fluctuations on the neuron dynamics is twofold:

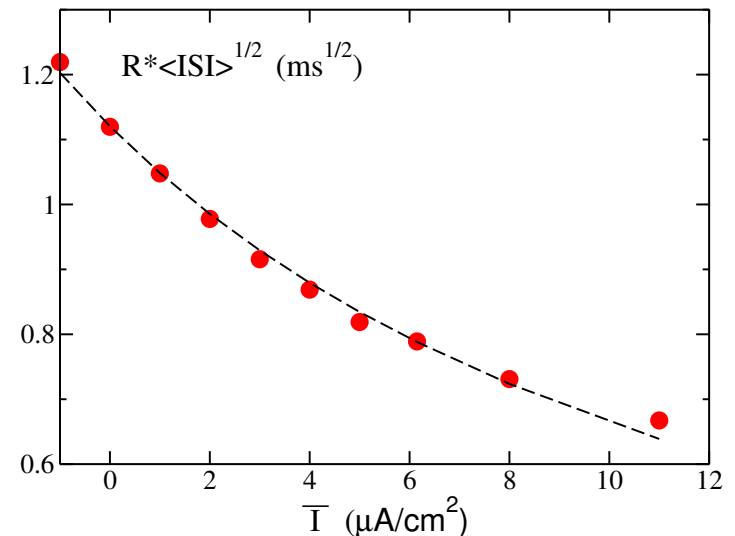
- a constant current  $\bar{I}$  driving the system;
- a stochastic term with zero average.

The dynamics of  $V(t)$  can therefore be described in terms of a Langevin process with a drift and the distribution of the first passage times is given by the inverse Gaussian distribution:

$$f(t) = \frac{\alpha}{\sqrt{2\pi\beta t^3}} e^{-\frac{(t-\alpha)^2}{2\beta t}}$$

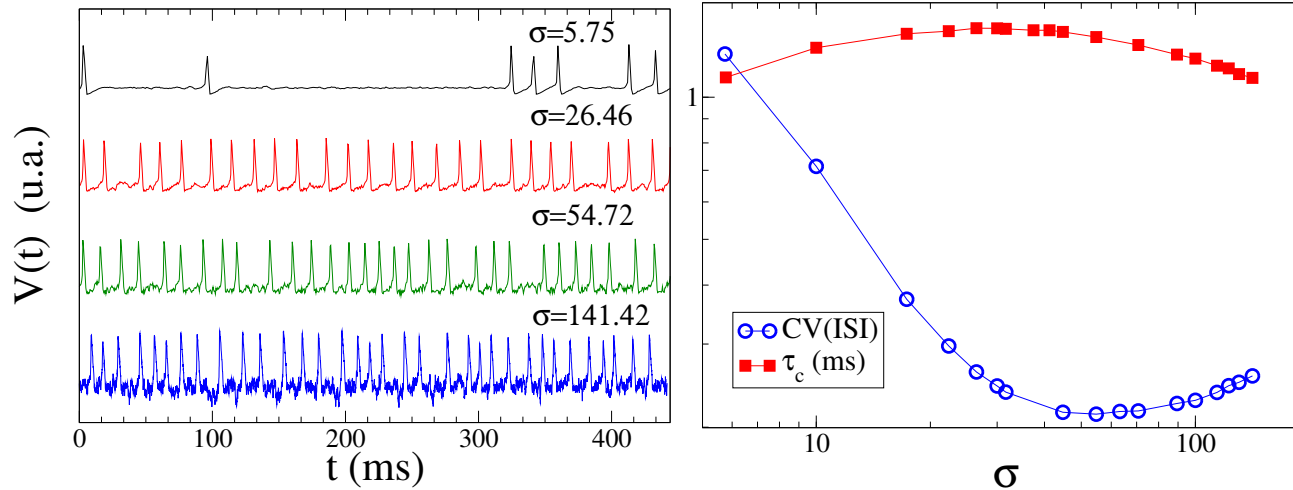
In this case the coefficient of variation should be given by

$$CV \propto \frac{\sigma}{(\bar{I} + I_0)\sqrt{\langle ISI \rangle}}$$



# Coherence resonance

## Coherence of the emitted spike trains



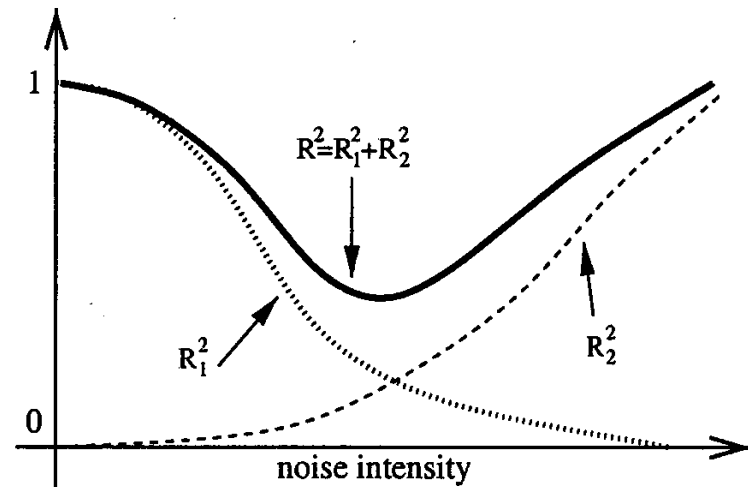
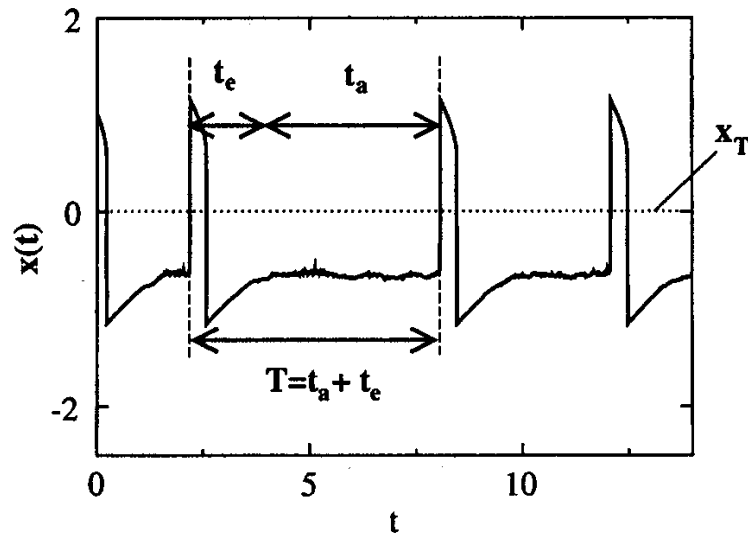
In the silent and bistable regime ( $I < 8\mu A/cm^2$ ):

- in the beginning the HH neuron response becomes more regular for increasing  $\sigma$ ;
- the maximal coherence is reached for a finite  $\sigma$ -value;
- for higher noise amplitudes the response becomes again more irregular.

A. Pikovsky & J. Kurths, PRL 78, 775 (1997)



# Coherence resonance



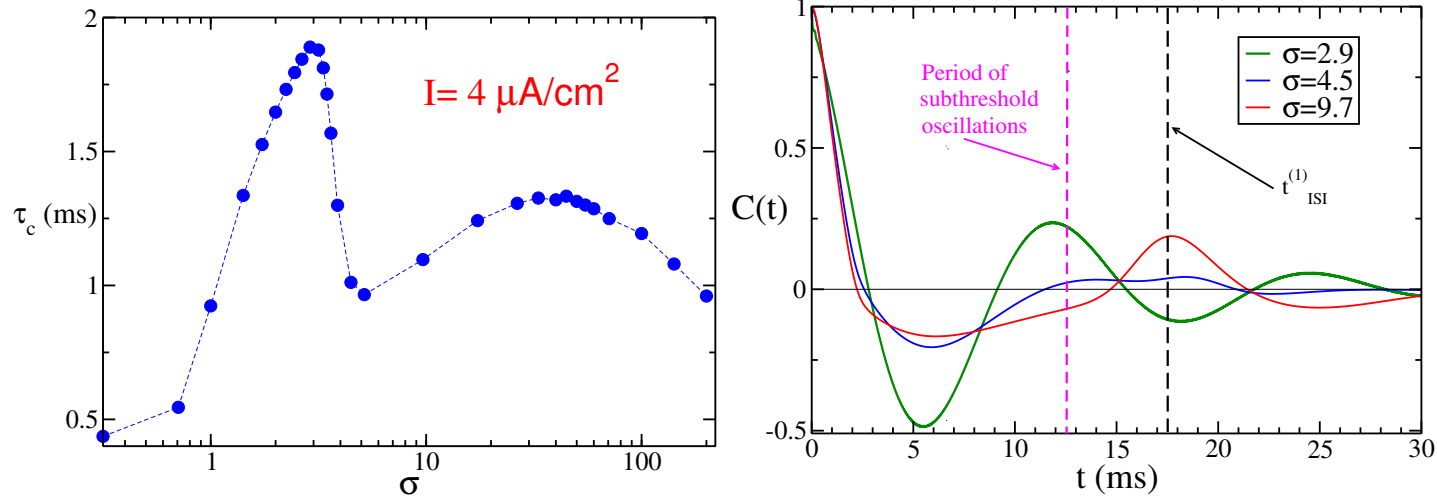
- The system is characterized by **two characteristic times**  $\rightarrow ISI \equiv T = t_a + t_e$  :
  - $t_a$  = **activation time**  $\rightarrow$  time needed to excite the system;
  - $t_e$  = **excursion time**  $\rightarrow$  duration of the spike (excited state).
- The competition of the two effects leads to an intermediate regime of coherence:

$$CV(ISI)^2 = CV(t_a)^2 \frac{\langle t_a \rangle^2}{\langle T \rangle^2} + CV(t_e)^2 \frac{\langle t_e \rangle^2}{\langle T \rangle^2} = R_1^2(t_a) + R_2^2(t_e)$$

$R_1^2(t_a)$  **decreases** with  $\sigma$ , while  $R_2^2(t_e)$  **increases**  $\rightarrow$  **minimum** in  $R(ISI)$

# Coherence resonance

## Coherence of the subthreshold oscillations



A second coherence resonance is revealed by analyzing the correlations of the potential:

- for  $\sigma < 3$  almost no spikes are emitted, but the increase of noise leads to more and more regular subthreshold oscillations;
- for  $\sigma > 3$  the statistics of the emitted spikes is no more negligible and this decorrelates the signal;
- for  $\sigma > 10$  the dynamics is dominated by sequences of spikes and a second peak occurs related to the regularization of the spike trains.

# Response to correlated inputs

## Correlations generated via common drive

In order to generate  $N_E$  correlated ( $\rho$ ) Poissonian spike trains (with rate  $\nu_0$ ) :

- firstly a long sequence of  $M$  ISI's is extracted from a Poissonian distribution with rate  $\nu_0/\rho$ ;
- secondly from this common pool  $N_{sp} = M\rho$  ISI's are randomly extracted  $N_E$  times;
- the superposition of the  $N_E$  correlated trains gives rise to a sequence of kicks of variable amplitude (with average  $\rho N_E \Delta V$ ) and with ISIs Poissonian distributed with rate  $\nu_0/\rho$ .

The correlation between two input spike trains originating from neuron  $i$  and  $j$  is measured in terms of the Pearson correlation coefficient :

$$\rho = \frac{\langle (n_i - \langle n_i \rangle)(n_j - \langle n_j \rangle) \rangle}{s^2}$$

where  $n$  is the number of spikes in a time window  $\Delta T$  and  $s^2$  its variance.

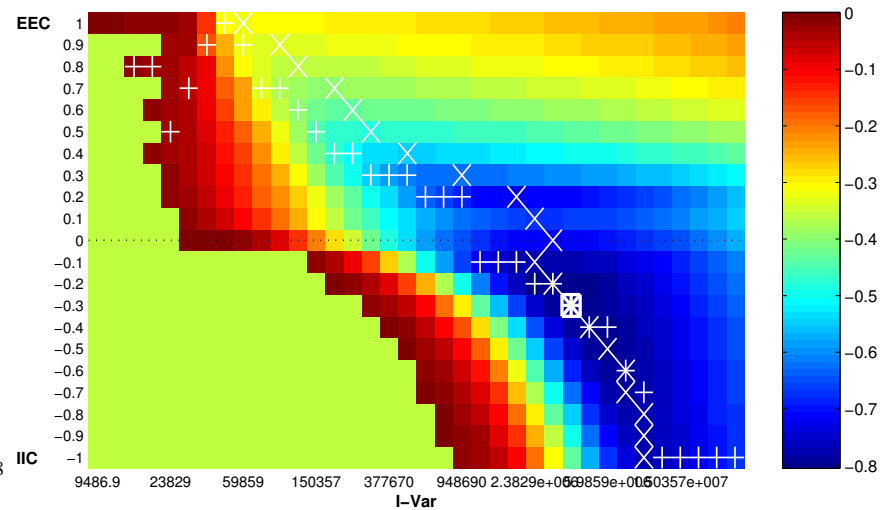
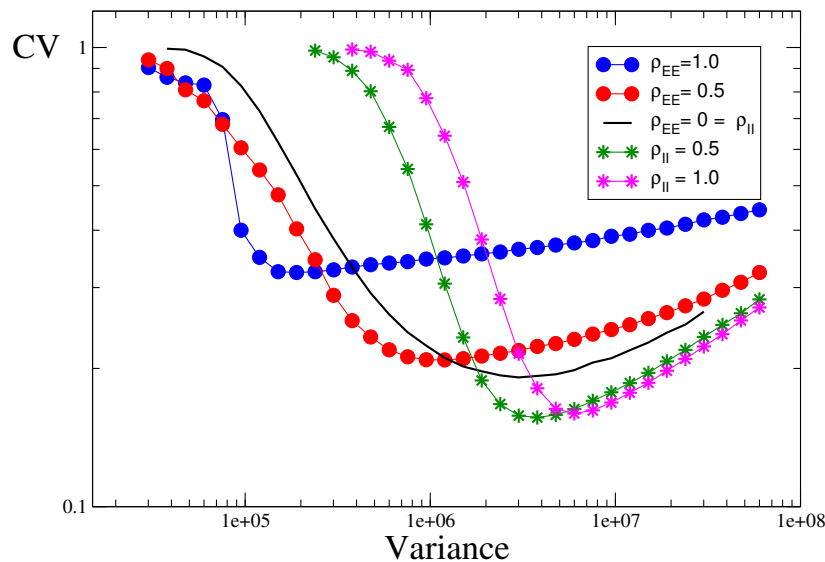
M.N. Shadlen & W.T. Newsome (1998) – E. Salinas & J. Sejnowski (2000)



# Response to correlated inputs

We have studied the response of the (balanced  $N_E = N_I$ ) Fitz-Hugh Nagumo model in the silent regime for excitatory (resp. inhibitory) correlated inputs at constant correlation  $\rho$  by varying the noise variance. The increase of the variance leads to an increase of the average amplitude for the correlated kicks, while their frequency remains constant.

- Coherence resonance is observed for any excitatory (resp. inhibitory) correlation at finite noise amplitude.
- An absolute resonance with respect to noise and correlation can be identified.



# Response to correlated inputs

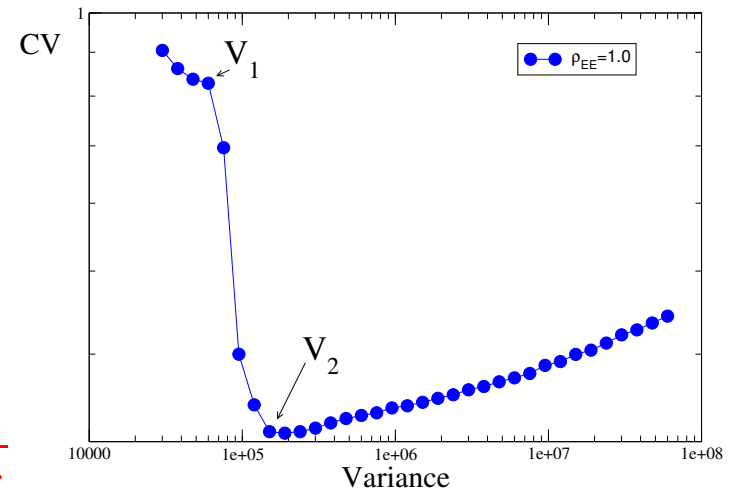
## Strong excitatory correlation

The coherence phenomenon is now determined only by the **kick amplitude** and not by the properties of the asymptotic stochastic processes, since in the present case the output can be always described as a **Poissonian process with a refractory time**.

For increasing variance the amplitude of the correlated kicks increases.

- for  $Variance < V_1 \rightarrow$  **Activation Process**
- for  $V_1 < Variance < V_2$   
**One kick is sufficient to induce a spike emission**
- for  $V_2 < Variance$   
**One kick elicits always a spike -  $T_{ref}$  decreases**

$$CV = \frac{T}{T + T_{ref}}$$



For  $Variance > V_2 \rightarrow T = 1/\nu_0$ , we have a 1 : 1 correspondence between input and output (apart from the refractory period).

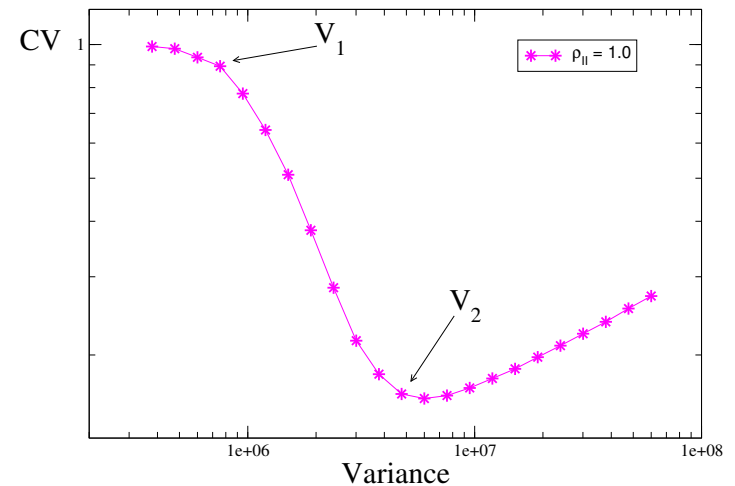


# Response to correlated inputs

## Strong inhibitory correlation

At large variances the dynamics is again ruled by the the **kick amplitude** of the correlated kicks, but at lowervariances the correlated kicks are quite rare and their amplitude is not sufficient to influence the dynamics.

- for  $Variance < V_1$   
Activation Process -  $CV \simeq 1$
- for  $V_1 < Variance < V_2$   
Dynamics dominated by uncorrelated excitatory kicks leading the system in the repetitive firing regime
- for  $Variance > V_2$   
Each kick induces a certain delay in the spike time of the neuron - A multimodal structure appears in the ISI distribution



Frequency of the correlated kicks ( $\nu_0$ )  $\ll$  Frequency of the uncorrelated kicks ( $N\nu_0$ )



# Summary and perspectives

- Uncorrelated stochastic inputs
  - The response of a **HH neuron** depends only on the **average** and the **variance** of the input, at least in the high input regime;
  - at  $I < I_{SN}$  the neuronal firing, induced by the stochastic inputs, can be expressed as an **activation process** at low variances ( $\sigma^2$ ), while for large  $\sigma^2$  this process becomes essentially **diffusive**;
  - at low noise, beside of the exponential tail, the ISI distributions reveal a **multimodal structure** due to spiking triggered by **relaxation oscillations** towards the rest state;
  - **coherence resonance** can be observed in a large interval of currents in the silent and bistable regime;
  - a second **coherence resonance** (associated to **subthreshold oscillations**) coexists with the usual one;
- Correlated stochastic inputs
  - new mechanisms for the **coherence resonance** have been reported at high excitatory and inhibitory correlations;
  - coherence effects can be induced by varying only the correlation.



# Summary and perspectives

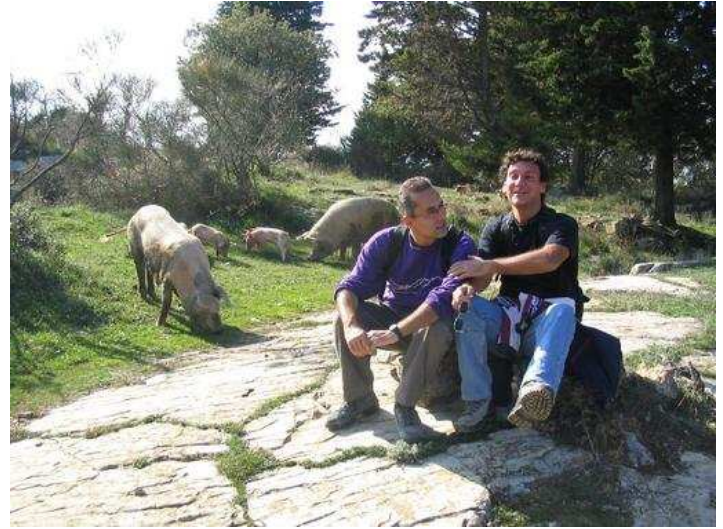
## What to do next ?

- Experiments
  - Is it possible to reveal both kinds of CR with dynamic clamp measurements of Stellate Cells ?
  - Due to the high degree of **erraticity** in the response of the Stellate Cells, maybe CR could be observed without injecting noise in the system, but just varying the DC current.
- Networks
  - A single HH neuron can fire at different frequencies (when stochastically stimulated) therefore a network of coupled HH neurons should exhibit coherent and correlated activities over different time scales. (**several rhythms**)
  - How CR will influence network dynamics ?



# Credits

- **Stefano Luccioli** - Msc in Physics (2004-2005)
- Dynamics of realistic single neuronal models

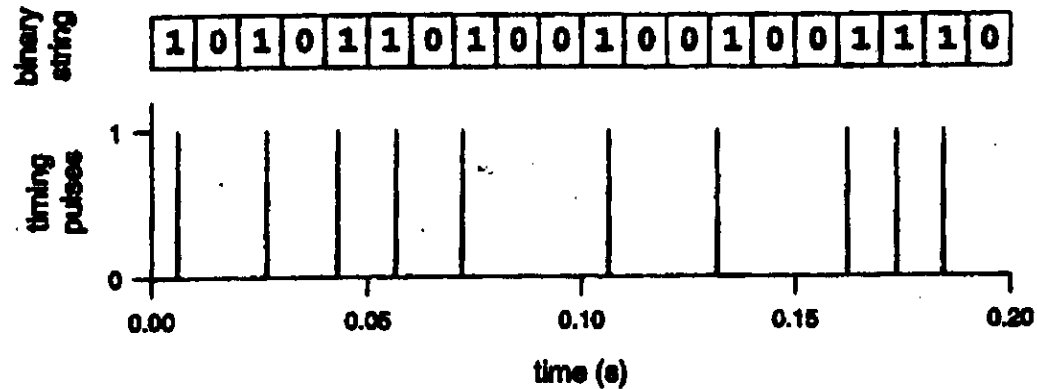


- **Thomas Kreuz** - Marie Curie Fellow (2005-2006)
- Dynamical Entropies in Assemblies of Neurons



<http://www.ino.it/torcini/neurores.html>

# Entropie condizionali



- $\Delta t$ ="finestra" temporale  $\rightarrow$  *codifica binaria* ("1"/"0") del potenziale di membrana;
- $C_N = (1, 0, 1, \dots) \rightarrow$  "parola" (o "stato") di lunghezza  $N$ ;
- $H(N) = - \sum_{\{C_N\}} P(C_N) \log_2 P(C_N)$ , "entropia del blocco  $N$ ";
- $h(N) = H(N + 1) - H(N)$ , "entropia condizionale"  $\rightarrow$  regolarità, prevedibilità:

$$(1, 0, 0, 1, 0, 1, ?, \dots) \quad h(N + 1) \leq h(N)$$

$$h_{max}(N) = \log_2 2 = 1.$$