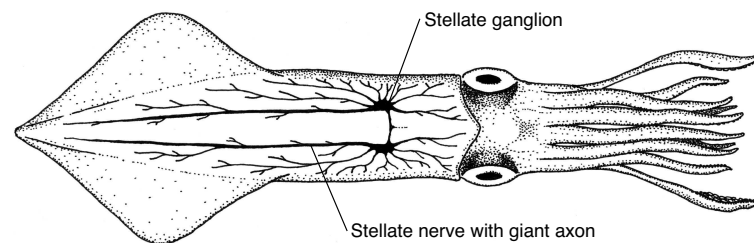


# Response of single neuronal models to uncorrelated and correlated stochastic inputs

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# Linee di ricerca

- Studi di dinamica di reti neuronali, effetti del disordine e del ritardo
  - dr. Rüdiger Zillmer (Post-Doc – INFN)
  - prof. Roberto Livi (Dip. Fisica)
  - dr. Antonio Politi (Dir. Ricerca - ISC)
- Risposta di singolo neurone sottoposto a stimoli stocastici
  - dr. Thomas Kreuz (Marie-Curie Fellow - ISC)
  - Stefano Luccioli (Dottorando - Dip. Sistemi e Informatica)
- Analisi dati sperimentali di neuroni sottoposti a stimoli complessi
  - dr. Thomas Kreuz (Marie-Curie Fellow - ISC)
  - prof. H.D. Abarbanel e dr. J. Haas (UCSD - La Jolla - San Diego - USA)
  - dr. Antonio Politi (Dir. Ricerca – ISC)
- Caratterizzazione della transizione da “spiking” a “bursting” caotico
  - Giacomo Innocenti e prof. Roberto Genesio (Dip. Sistemi e Informatica)
  - dr. Alice Morelli (Phd in Dinamica Nonlineare e Sistemi Complessi)

<http://www.fi.isc.cnr.it/users/alessandro.torcini/neurores.html>



# Main motivations

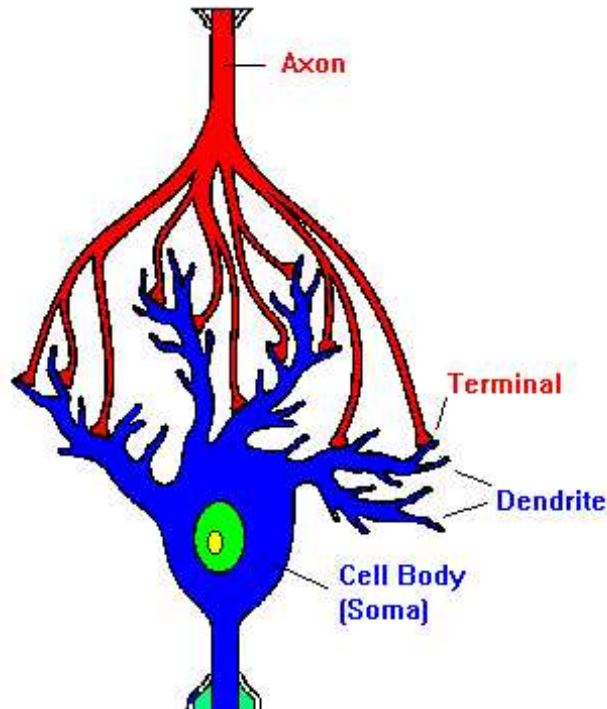
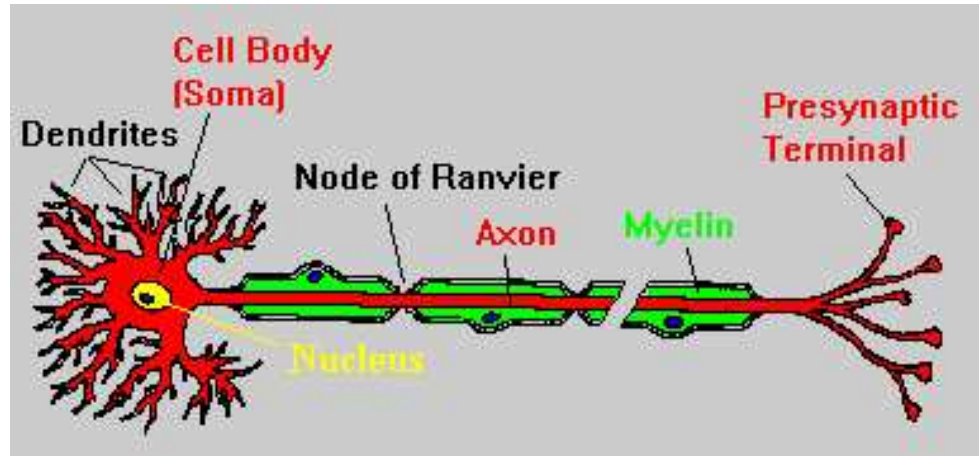
- A neuron in the brain cortex is subject to a continuous synaptic bombardment of inputs, resembling a background noise  
(A. Destexhe, M. Rudolph, D. Paré - Nature Reviews - Neuroscience - 2003)
- Inputs are mainly originating from the cortex itself, the statistical properties of the neural response (input) can be (roughly) summarized as
  - Frequency range 0 – 200 Hz;
  - Distribution of interspike interval : approximately Poissonian;
  - Spike rate modulations (5 – 10 msec)(M.N. Shadlen & W.T. Newsome, J. Neuroscience - 1998)
- Neurons in the cortex, due to the high connectivity, can receive inputs from the same axon: **correlation via common drive**; correlations are important for information processing. (E. Salinas & T.J. Sejnowski, J. Neuroscience - 2000)

How do noise and correlated inputs influence the response of single neurons ?

# 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

# The neuron in brief



A neuron in the brain cortex has many ( $\sim 5,000 - 60,000$ ) 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



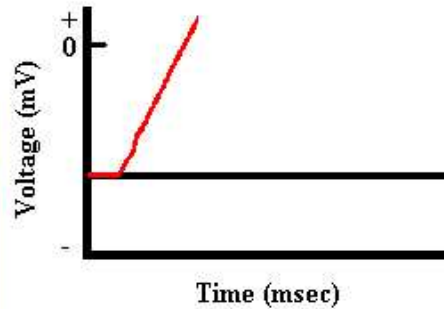
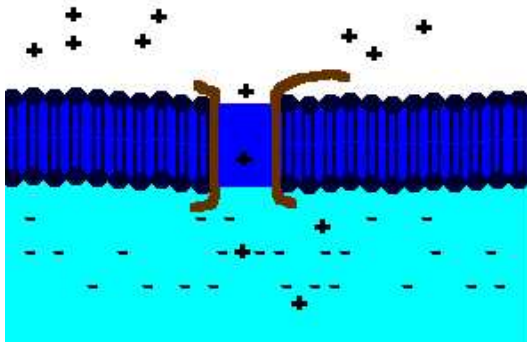
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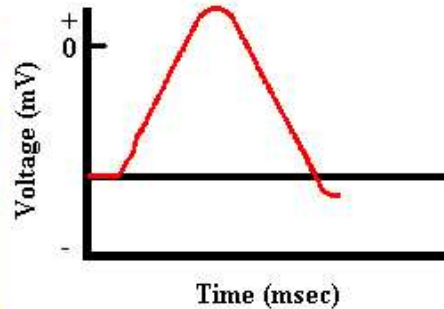
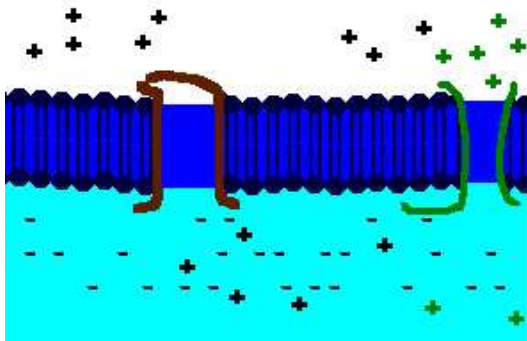
Huxley

## Membrane Depolarization



$Na^+$  enters inside the cell

## Membrane Repolarization



$K^+$  leaves the cell

# The Hodgkin-Huxley model

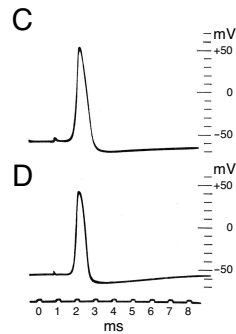
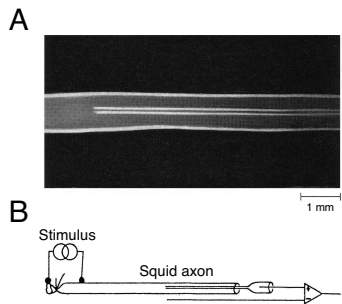


Hodgkin

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Huxley



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

$V$  - Membrane Potential ( $mV$ )

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

$g_j$  - Maximal ionic conductances ( $mS/cm^2$ )

$V_j$  - Ionic reversal potentials ( $mV$ )

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

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

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



# The Hodgkin-Huxley model



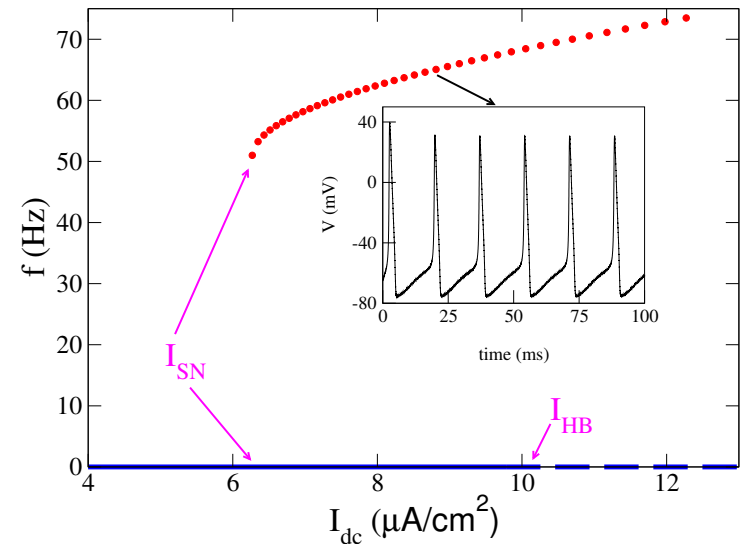
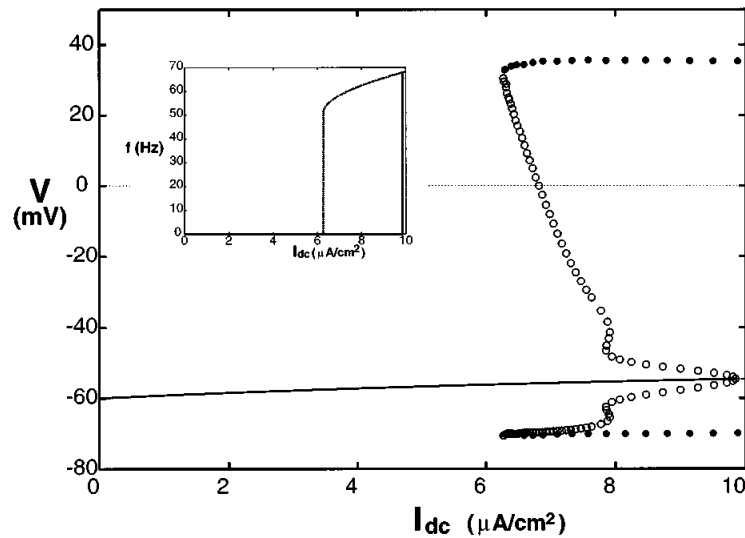
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Huxley

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.

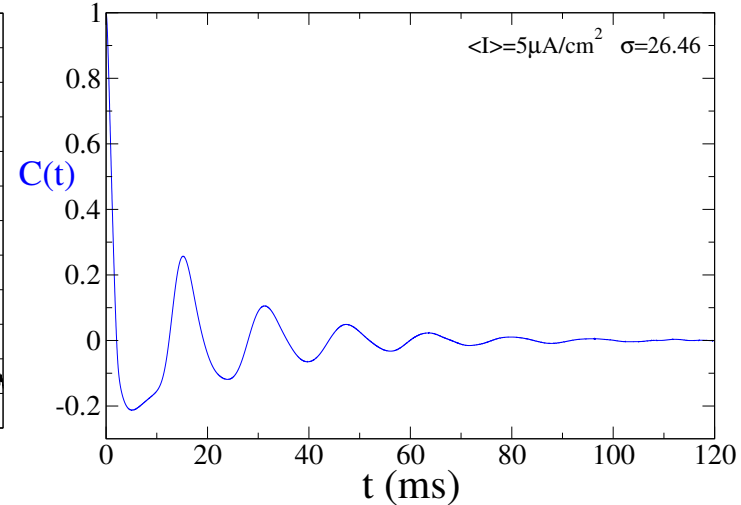
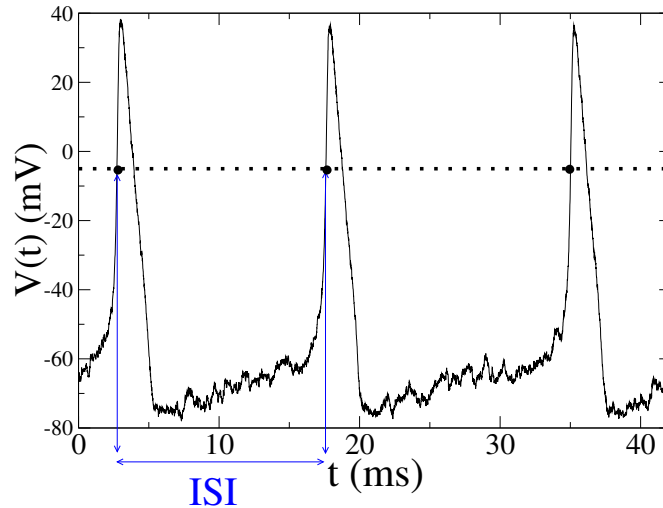
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At these frequencies the **net input spike count** within a temporal window  $\Delta T$  ( $\geq 1 \text{ msec}$ ) is essentially **Gaussian distributed** and it can be characterized by its average  $\mu = \nu(N_E - N_I)\Delta T$  and variance  $V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

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:

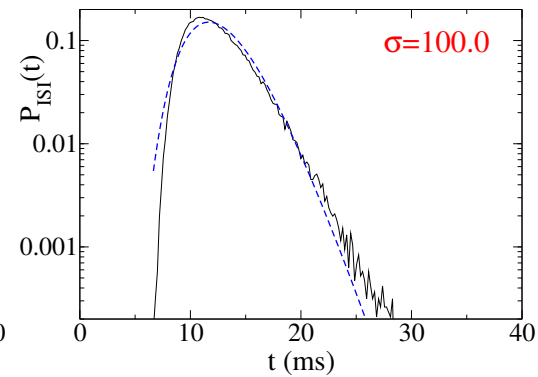
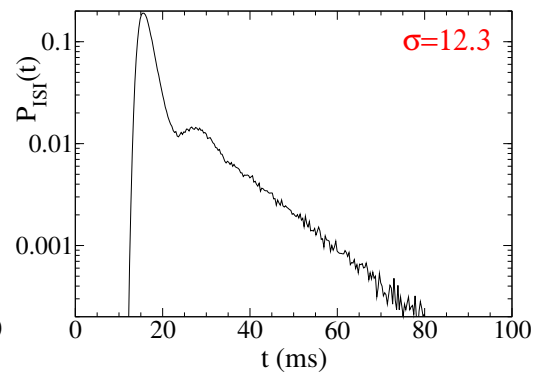
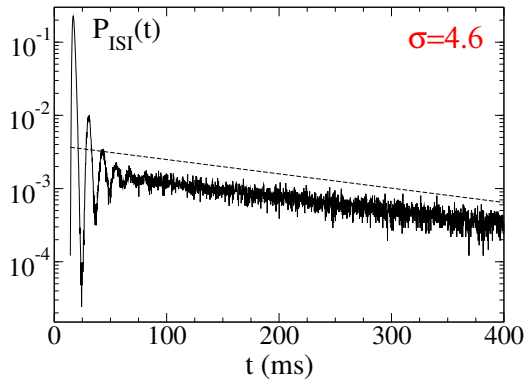
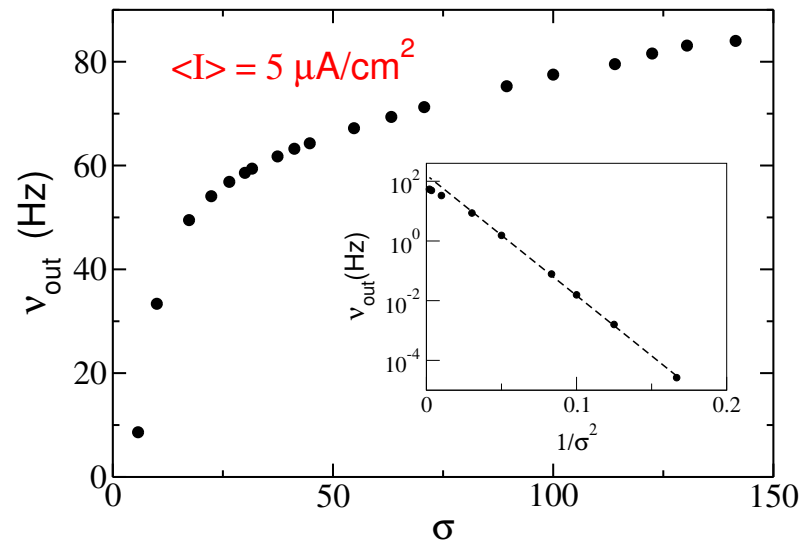
Poisson distribution  $\rightarrow CV = 1$  \*\*\* regular sequence  $\rightarrow CV = 0$ ;

●  $\tau_c = \int_0^\infty C^2(t) dt$   $\rightarrow$  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

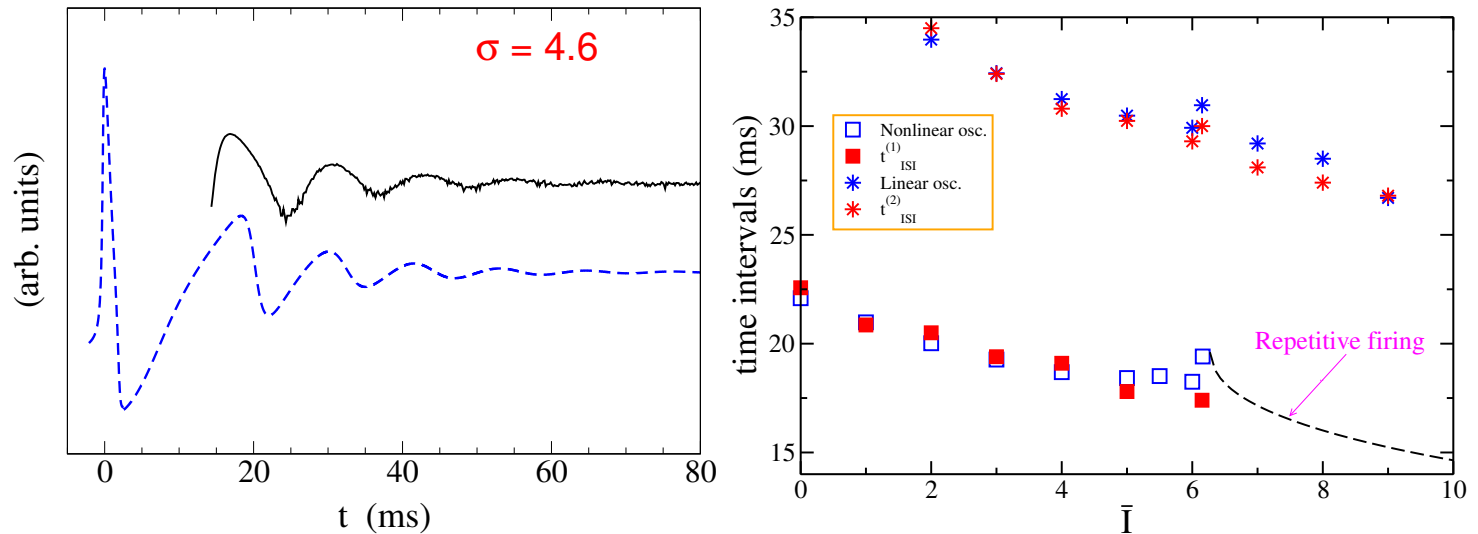
The HH neuron is in the silent state, i.e. the average input current  $\bar{I}$  is smaller than  $I_{SN}$ .





# 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:

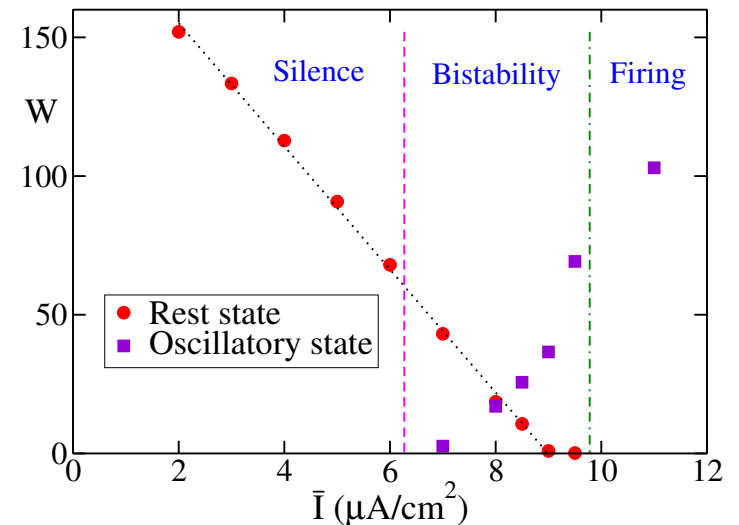
- the HH dynamics tends to relax towards the rest state;
- noise fluctuations lead the system towards an excitation threshold.

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:

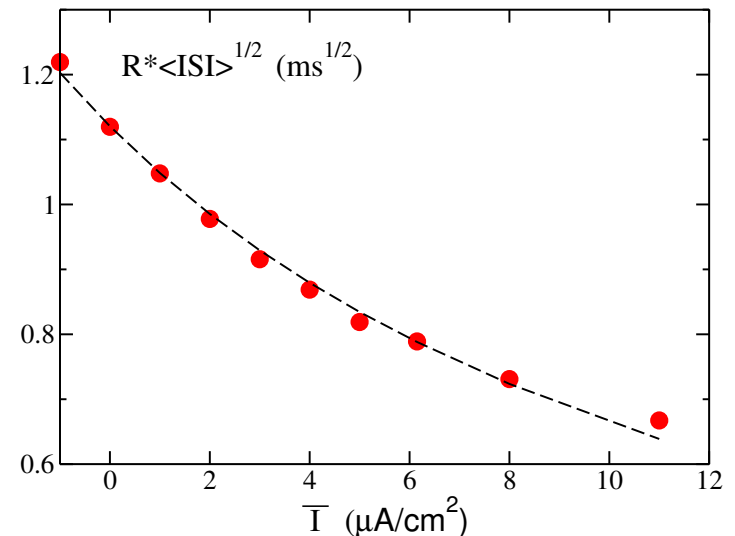
- a constant current  $\bar{I}$  driving the system;
- a stochastic term with zero average.

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:

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

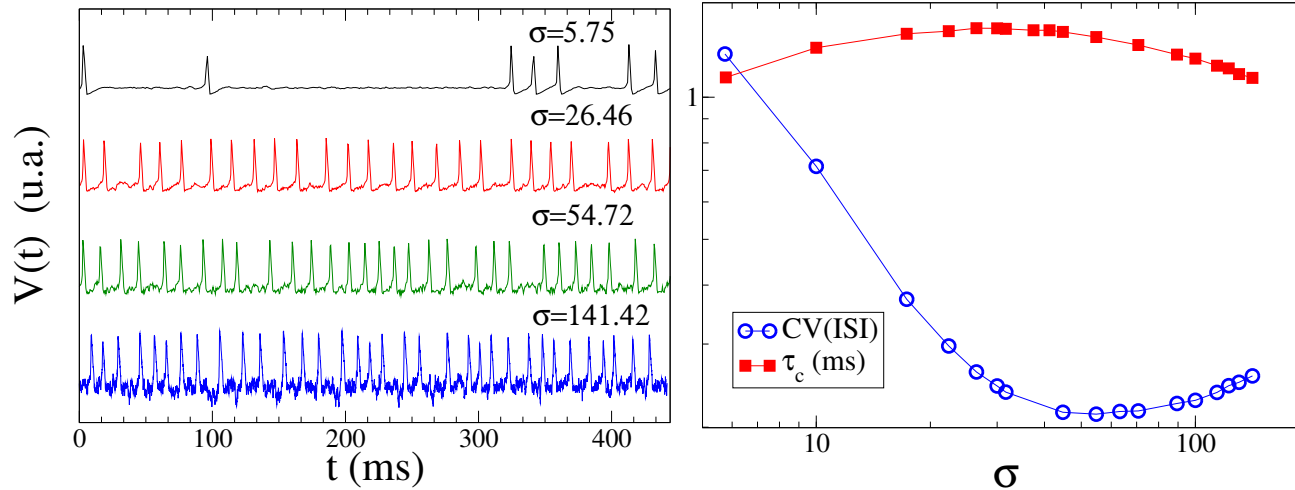
In this case the coefficient of variation should be given by

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



# Coherence resonance

## Coherence of the emitted spike trains



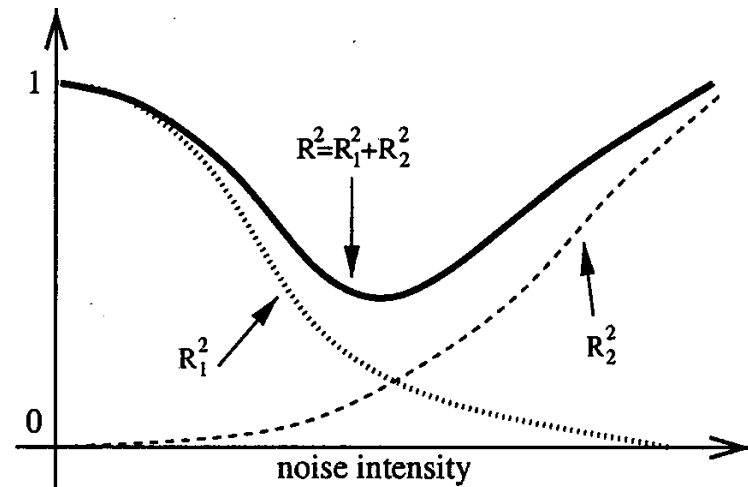
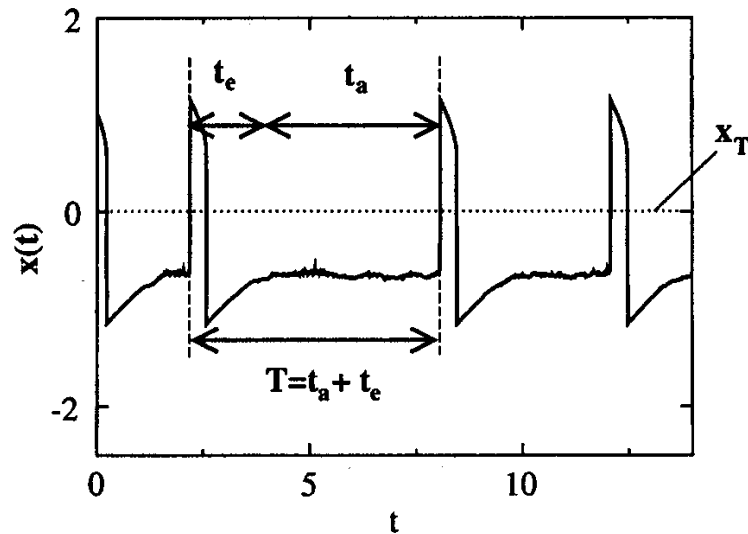
In the silent and bistable regime ( $I < 8\mu\text{A}/\text{cm}^2$ ):

- by increasing  $\sigma$  the firing rate increases, the spike train becomes more regular (**Activation Process**);
- the maximal coherence is reached for an optimal  $\sigma$ -value;
- for higher noise amplitudes the noise influence even the duration of the single spike, the response becomes again more irregular (**Brownian motion + drift**).

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).

- $CV(T)$  can be splitted in two contributions

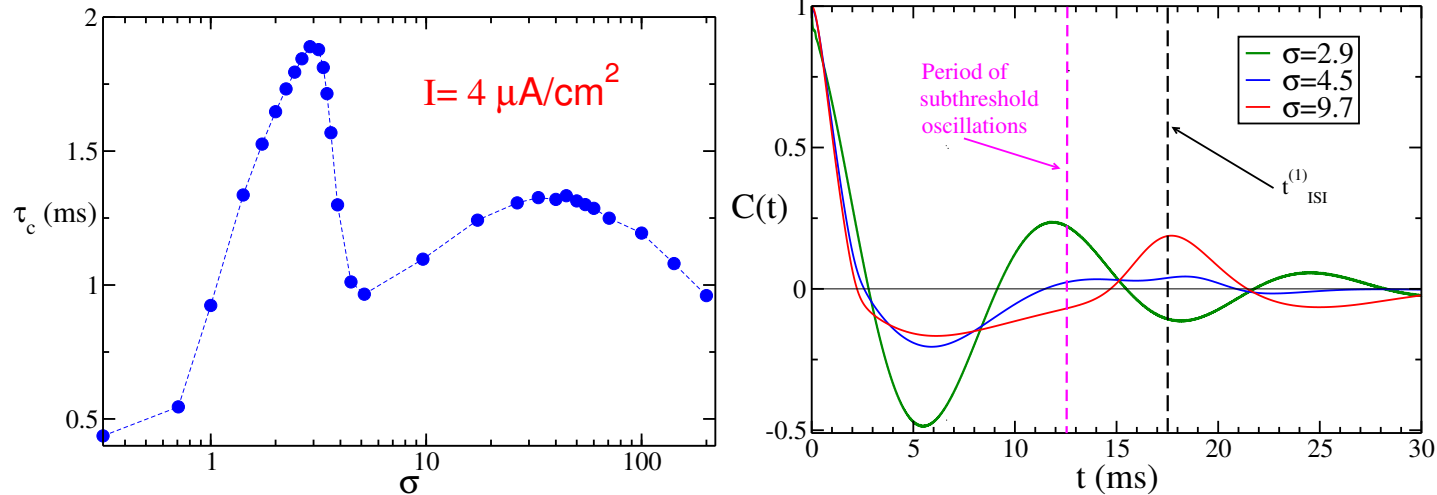
$$CV(T)^2 = CV(t_a)^2 \frac{\langle t_a \rangle^2}{\langle T \rangle^2} + CV(t_e)^2 \frac{\langle t_e \rangle^2}{\langle T \rangle^2} = R_1^2(t_a) + R_2^2(t_e)$$

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

B. Lindner *et al.*, Phys Rep. 392 (2004) 321-424

# 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.

S. Luccioli, T. Kreuz, A.T. Phys. Rev. E (2006)



# The FitzHugh-Nagumo Model

The FitzHugh-Nagumo (FHN) model is a two dimensional "simplification" of the HH model:

$$\begin{aligned}\dot{V} &= \phi\left(V - \frac{V^3}{3} - W\right) \quad ; \\ \dot{W} &= V + a - I(t)\end{aligned}$$

where  $V$  is a voltage-like variable,  $W$  is a recovery variable and  $a$  is the bifurcation parameter.

For  $\phi = 100$  the **silent regime** is observed for  $a < 1$ , while at  $a > 1$  one has **periodic firing**.

$$I(t) = \Delta W_0 \left[ \sum_{k=1}^{N_e} \sum_l \delta(t - t_k^l) - \sum_{m=1}^{N_i} \sum_n \delta(t - t_m^n) \right]$$

We examine the FHN model subject to  $N_E$  (resp.  $N_I$ ) trains of excitatory (resp. inhibitory) post-synaptic potentials, in the **balanced** case (i.e. for  $N_E = N_I \equiv N$ ) where  $\langle I \rangle \equiv 0$  for  $a = 1.05$  and  $\Delta W_0 = 0.0014$ .



# Correlations via common drive

- The FitzHugh-Nagumo Model and correlations **only** among **excitatory** or **inhibitory** inputs are considered in the **balanced case**  $N_E = N_I \equiv N$ ;



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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.

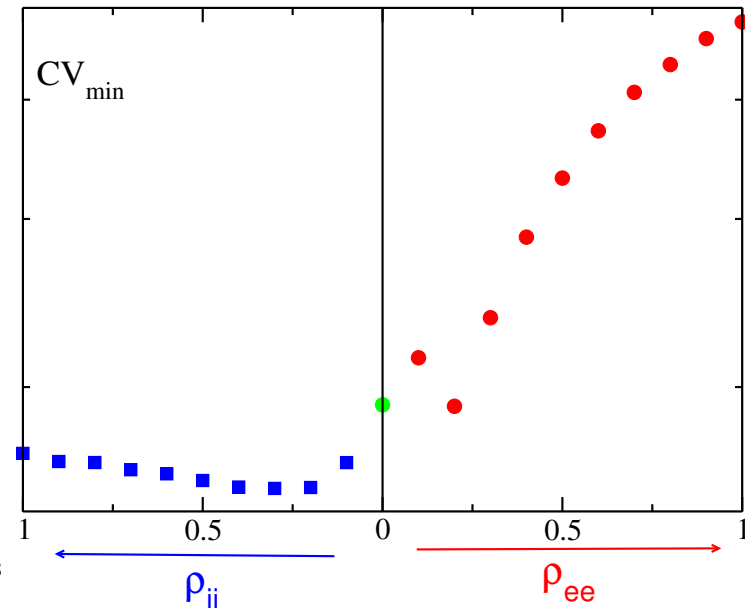
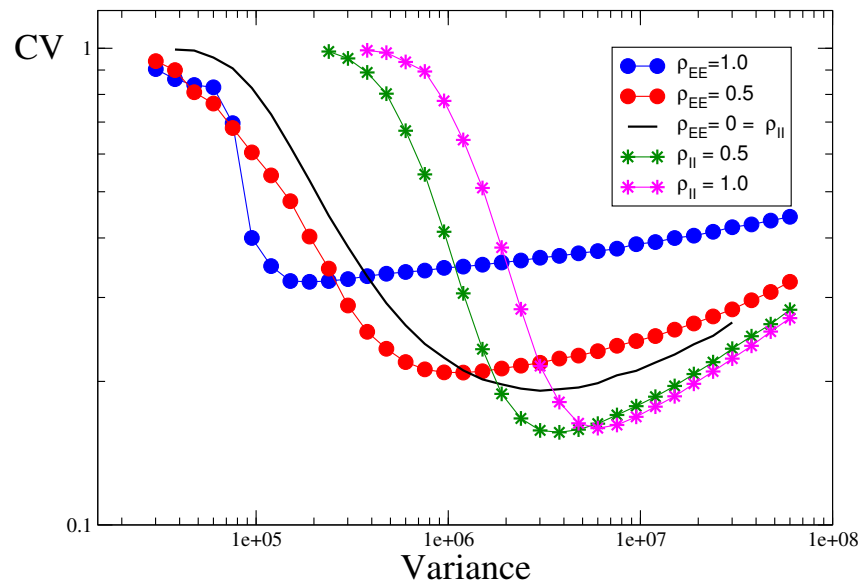
M.N. Shadlen & W.T. Newsome (1998) – E. Salinas & J. Sejnowski (2000)



# 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**.

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



# Response to correlated inputs

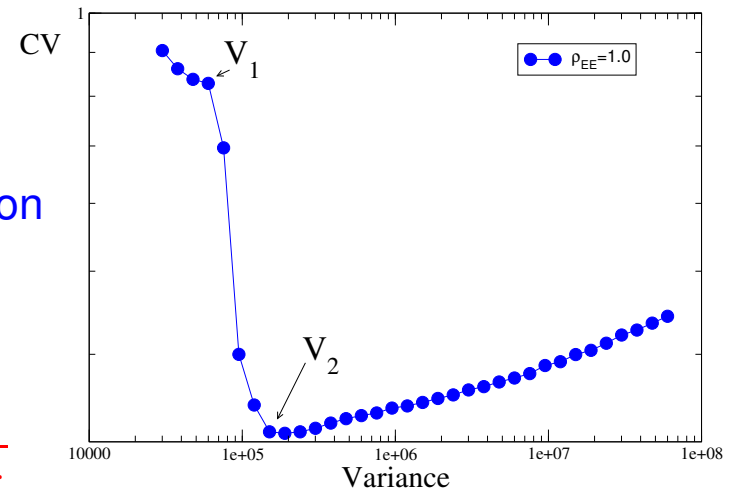
## Strong excitatory correlation

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 ( $N$ ) the amplitude of the correlated kicks increases. and due to the uncorrelated (inhibitory) input the systems is more and more silent.

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

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



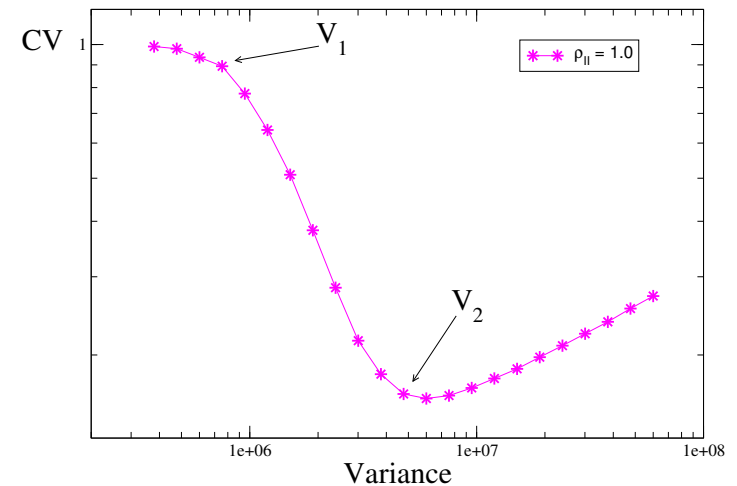
For  $Variance > V_2 \rightarrow T = 1/\nu_0$ , we have a **1 : 1 synchronization** between input and output (apart from the refractory period).

# Response to correlated inputs

## Strong inhibitory correlation

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

- for  $Variance < V_1$   
Silent regime - Activation Process -  $CV \simeq 1$
- for  $V_1 < Variance < V_2$   
Dynamics dominated by uncorrelated excitatory input leading the system in the repetitive firing regime
- for  $Variance > V_2$   
Each inhibitory 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 ( $N\nu_0$ )



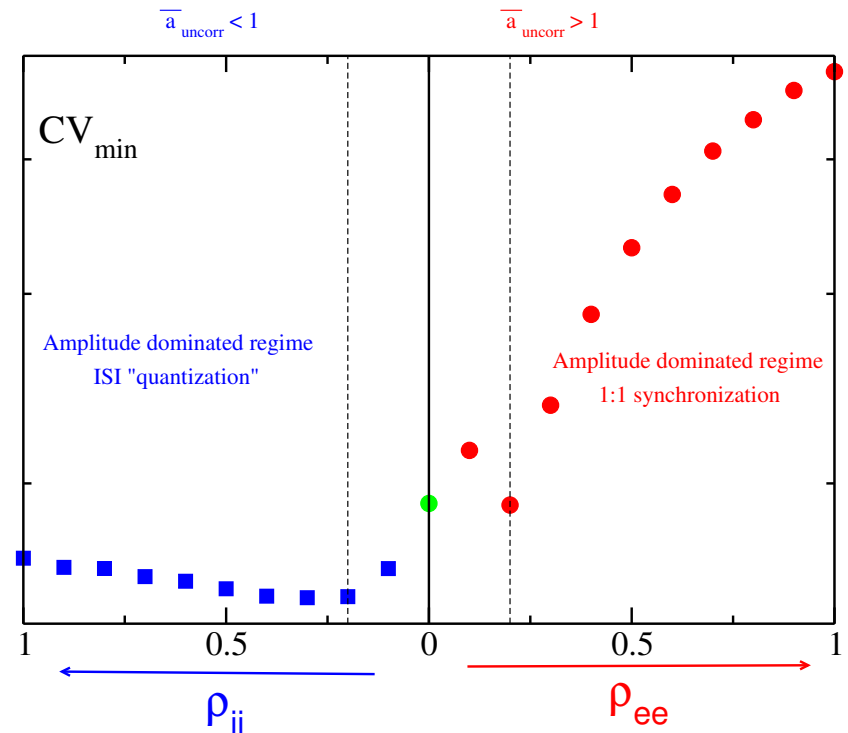
# Response to correlated inputs

## Maximal Coherence

Absolute minima of CV corresponding to maximal coherence are observed at **finite noise and correlation** for both **inhibitory** and **excitatory** case.

The extrema of  $CV_{min}$  indicate the change in the mechanisms inducing CR, from amplitude dominated to **usual mechanisms** related to the crossover from activated to (biased) diffusive processes.

The  $CV_{min}$  associated to **inhibitory correlations** are **lower** since the system is driven in the repetitive firing regime by the uncorrelated input.



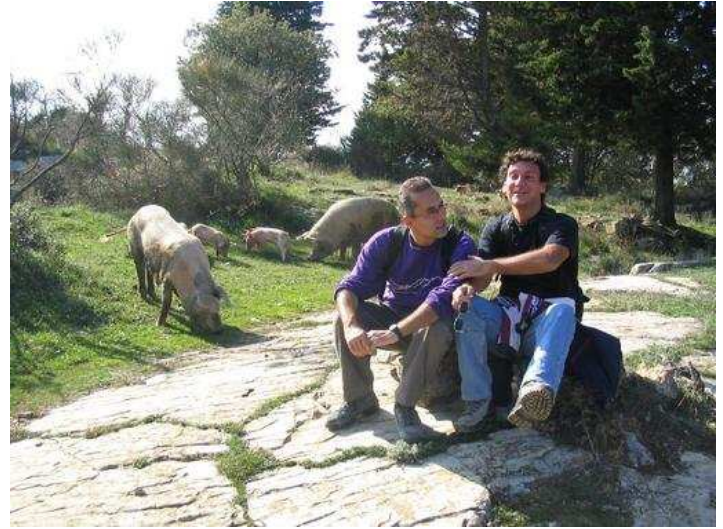
# Conclusions

- 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 whenever  $W_S > W_O$ ;
  - 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;
  - **maximal coherence** can be induced by an optimal combination of noise and correlation



# Credits

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

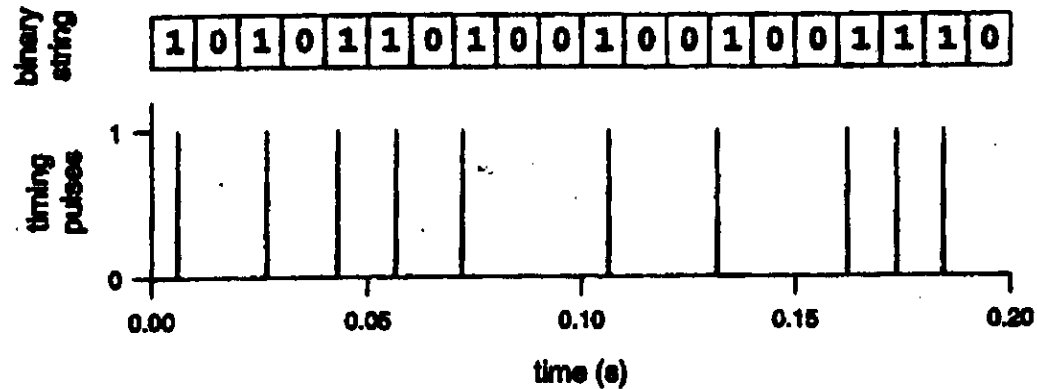


- **Thomas Kreuz** - Marie Curie Fellow (2005-2006)
- Dynamical Entropies in Assemblies of Neurons



<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:

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

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