Simulating *Channel Noise* in Conductance-based Model Neurons

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https://github.com/mgiugliano/Imperial2015

- Research interests
- Biophysical definition of channel noise
- Physiological impact on neuronal activity
- Markovian approximation for channel noise
- Langevin approach for channel noise
- Comparison and validation of the Langevin approach

Pointers to the literature

- **Linaro D, Giugliano M (2014) Markov models of ion channels. Springer Encyclopedia of Computational Neuroscience, http://dx.doi.org/10.1007/978-1-4614-7320-6_131-1**

- Faisal AA (2013) Noise in Neurons and Other Constraints, In: Le Novere (ed), Computational Systems Neurobiology, Springer.

- **Linaro D, Storace M, Giugliano M (2011) Accurate and fast simulation of channel noise in conductance-based model neurons by diffusion approximation. PLoS Comput Biol 7:e1001102**

- Goldwin J, Shea-Brown E (2011) The what and where of adding channel noise to the Hodgkin-Huxley equations. PLoS Comput Biol 7:e1002247

- Faisal AA (2009) Stochastic Simulation of Neurons, Axons, and Action Potentials, In: Laing & Lord (eds) Stochastic Methods in Neuroscience, Oxford University Press.

- Colquhoun D, Hawkes A (2009) The principles of the stochastic interpretation of ion-channel mechanisms. In: Sakmann B, Neher E (eds) Single-channel recording, ch. 18. Springer, pp 397–482.

- Faisal AA, White JA, Laughlin SB (2005) Ion-Channel Noise Places Limits on the Miniaturization of the Brain's Wiring, Current Biology 15; pp 1143-9.

- Mino H, Rubinstein JT, White JA (2002) Comparison of algorithms for the simulation of action potentials with stochastic sodium channels. Ann Biomed Eng 30:578–87

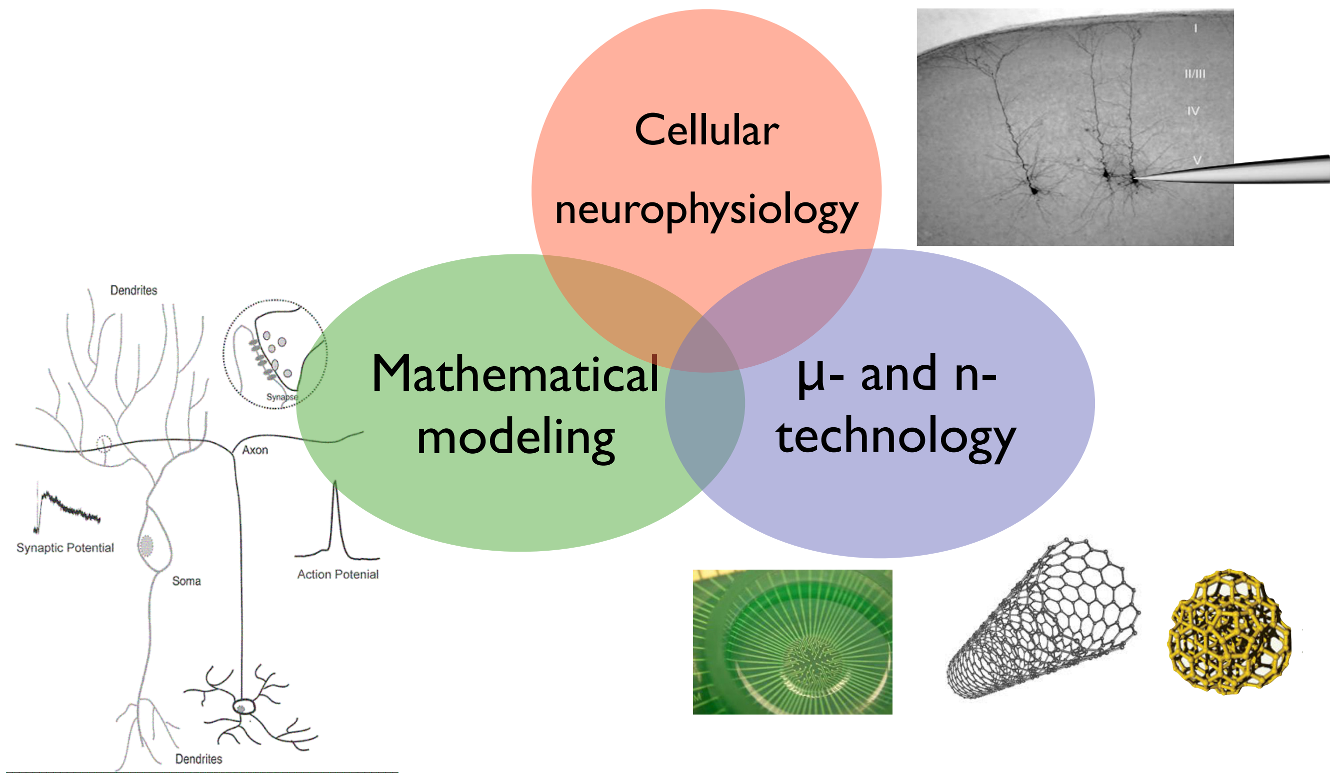
- **Fox R (1997) Stochastic versions of the Hodgkin-Huxley equations. Biophys J 72:2068–74**

- Clay J, DeFelice L (1983) Relationship between membrane excitability and single channel open-close kinetics. Biophys J 42:151-7

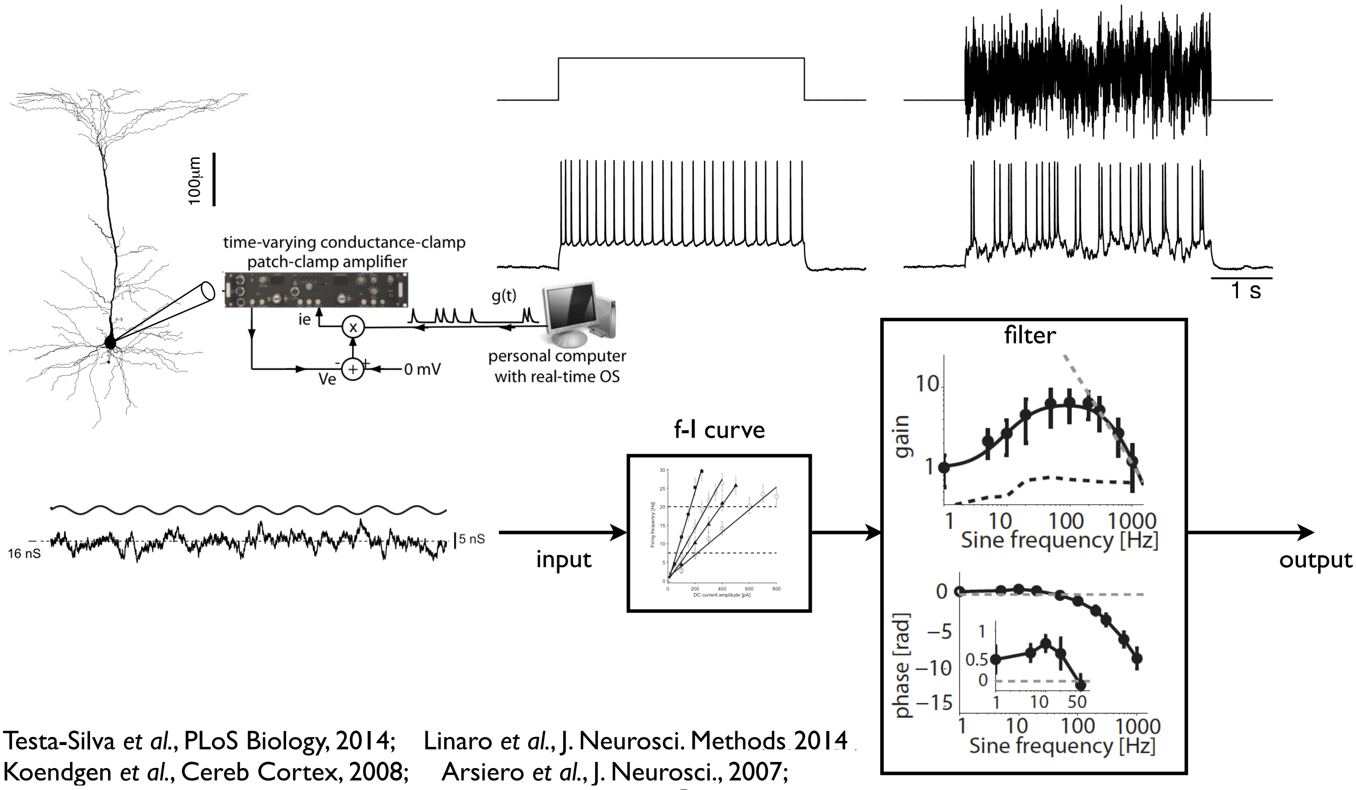
- Conti F, Wanke E (1975) Channel noise in nerve membranes and lipid bilayers. Q Rev Biophys 8:451–506

https://www.dropbox.com/sh/9h8ltdblp47bct0/AABDlO7rsSFmcufSNsYFxa-Za?dl=0

In vitro electrophysiology & Neuroengineering

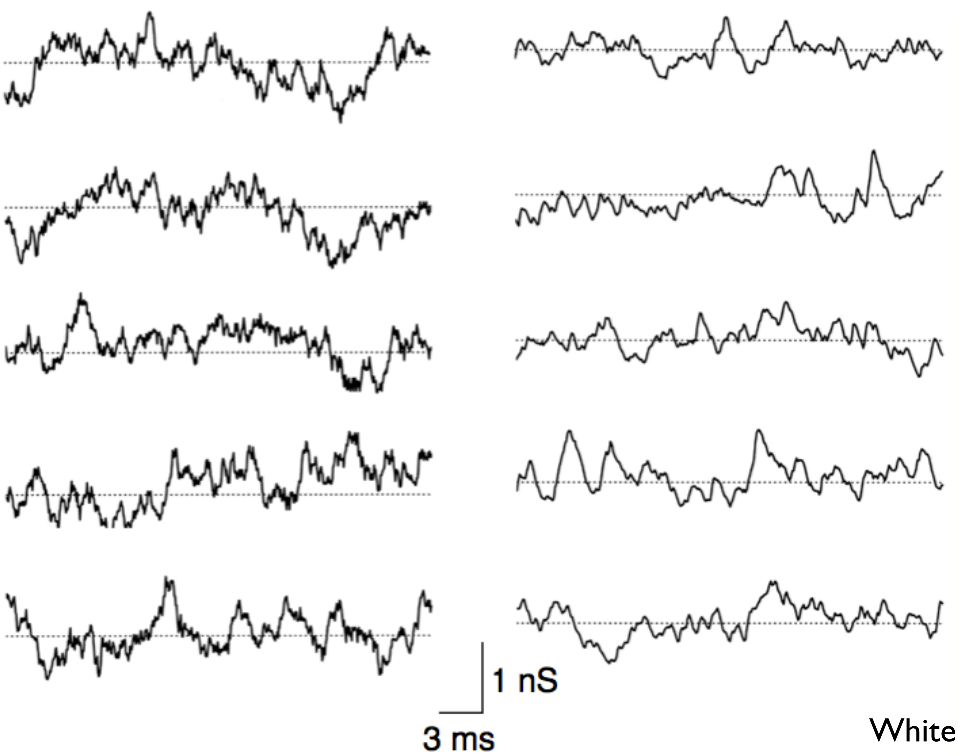


Neuronal dynamics and response properties under recreated background synaptic "noise"



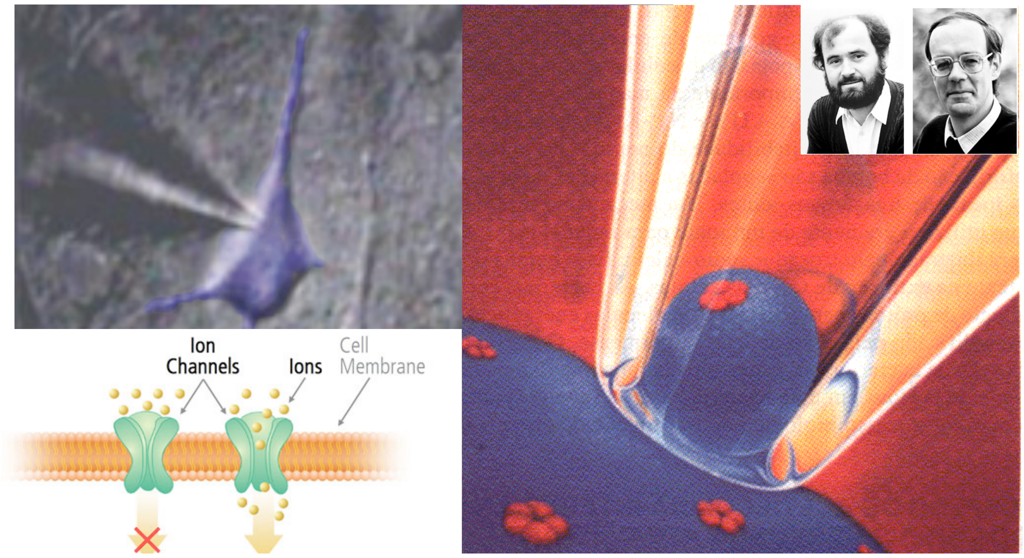
Testa-Silva *et al.*, PLoS Biology, 2014; Linaro *et al.*, J. Neurosci. Methods 2014
Koendgen *et al.*, Cereb Cortex, 2008; Arsiero *et al.*, J. Neurosci., 2007;

"Noisy" electrical activity (conductance)



White *et al.*, 2000

Membrane ionic permeability is <u>discrete</u> and <u>microscopic</u>

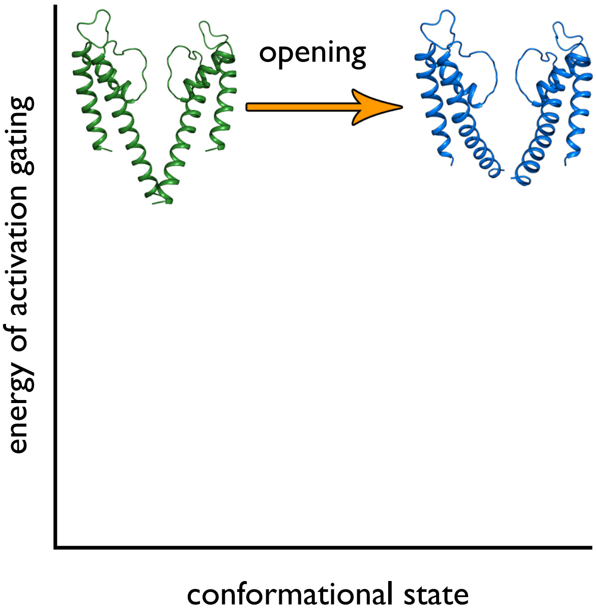


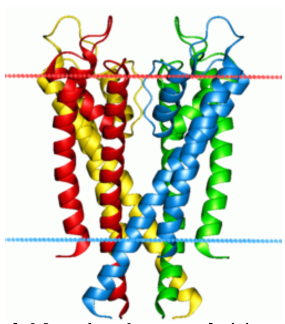
(Nobel p., 1991)

Neher & Sakmann, 1976

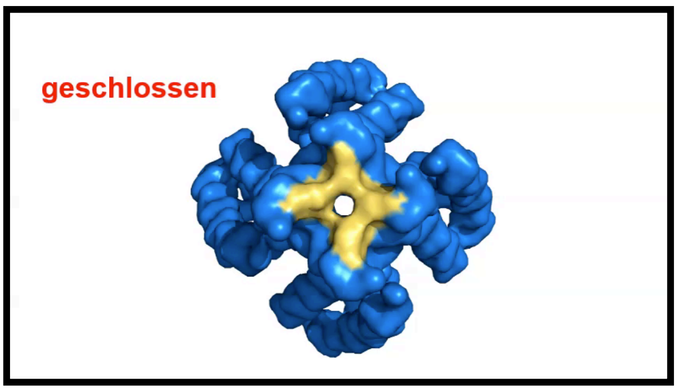
(trace from Berg *et al.*, 2002)

Membrane ionic permeability is <u>discrete</u> and <u>microscopic</u>



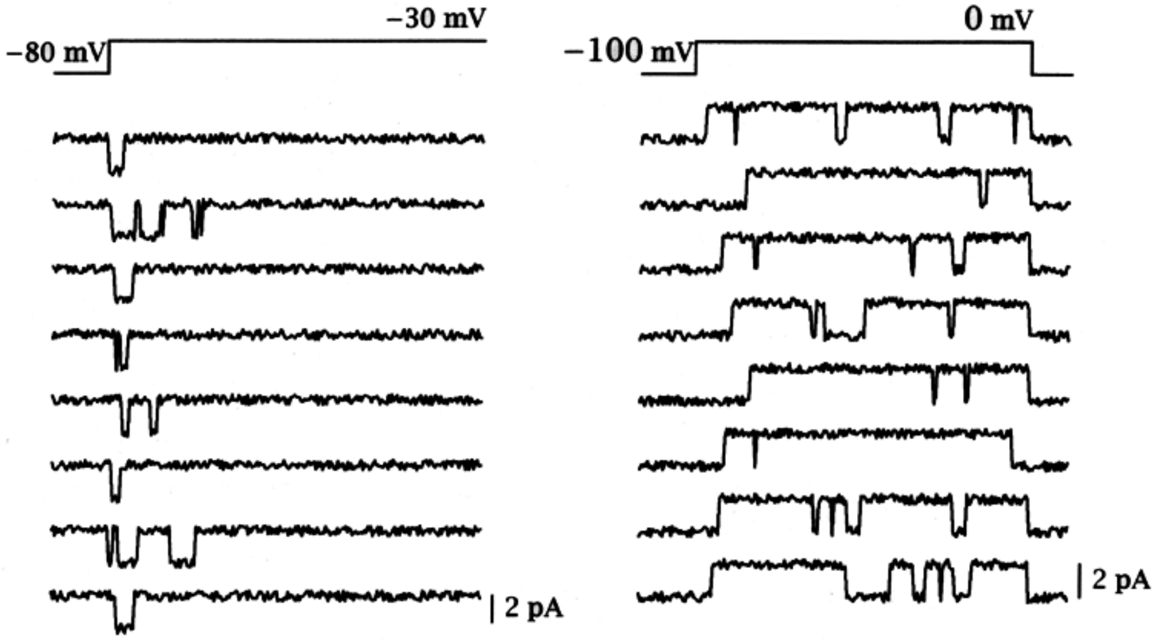


bacterial KcsA channel (4 subunits)



Linder *et al.*, 2013

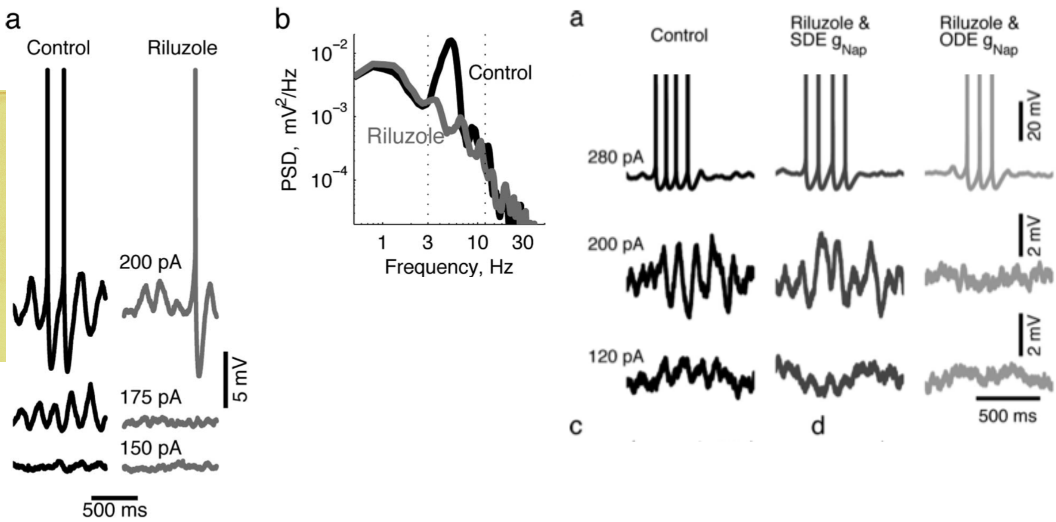
Single ion-channels undergo random transitions between conformational states



Hille, 2001

Stellate neurons, enthorinal cortex subthreshold membrane potential slow oscillations

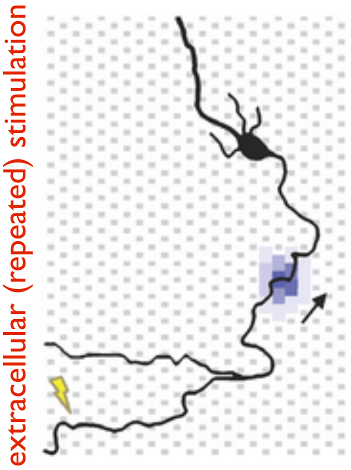
M. Economo

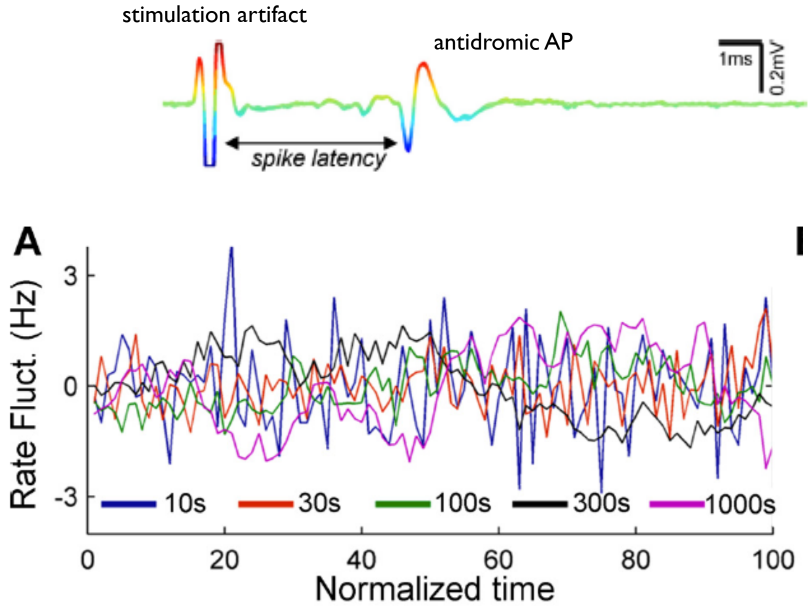


(Persistent Na-)Channel noise is necessary for the emergence of the oscillations!

Dorval *et al.*, 2005

Cortical neurons
excitability as a scale-free stochastic process

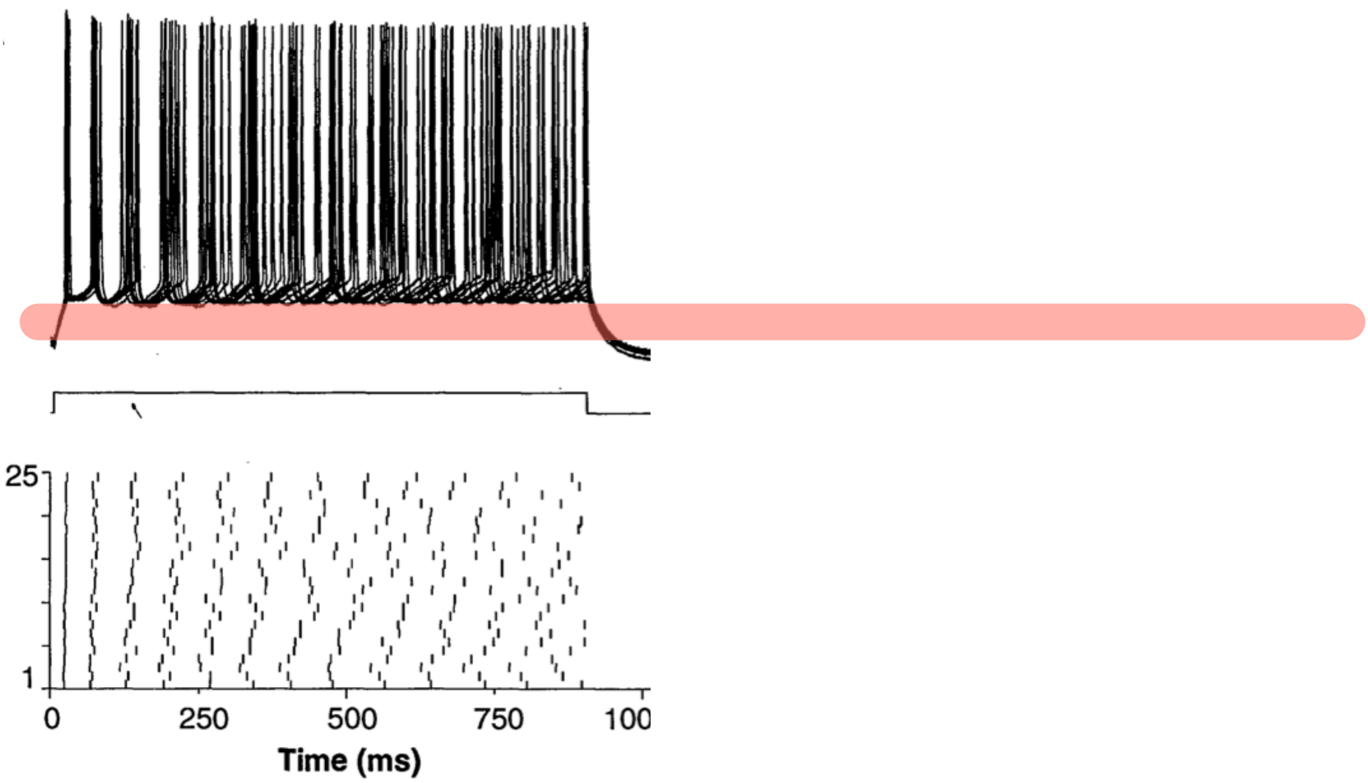




Spike latency and spike failures are indirect measures of excitability and of the excitability threshold, appearing to be a scale-free process!

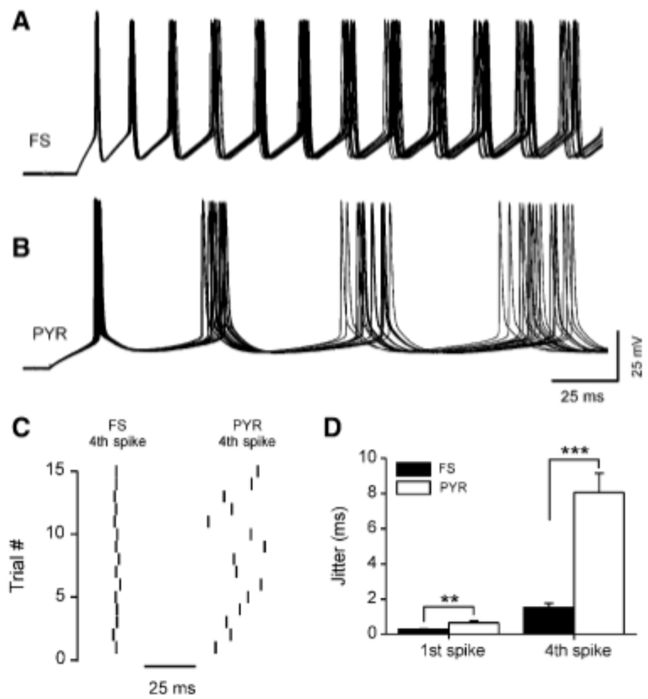
Gal et al., 2010; Soudry & Meir, 2012; Soudry & Meir, 2014

Pyramidal cortical neurons
spike-timing reliability



Mainen & Sejnowski, 1995

Fast-spiking cortical inter-neurons increased spike-timing reliability



Bacci & Huguenard, 2006

<u>Channel noise</u>: random "flickering" of the ion channels, as a source of <u>intrinsic</u> noise

- Induces **fluctuations** in the membrane potential;
- Contributes to the emergence of subthreshold **oscillations**;
- Determines fluctuations of the excitability **threshold**;
- Limits spike-timing **reliability & precision**;
- Induces **spontaneous APs** in thin axons;
- Affects synaptic release **variability**;
- Increases neuronal **excitability**;
- Allows broader electrical **behaviour repertoire**;

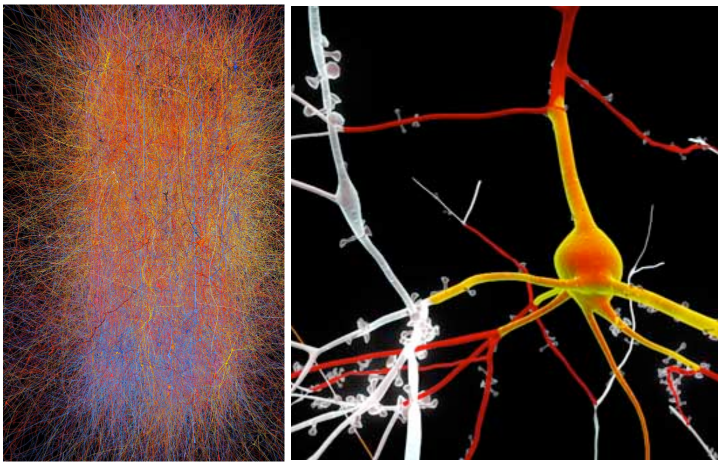
Neishabouri & Faisal 2014; Faisal *et al.*, 2005; Mainen & Sejnowski, 1995; White *et al.*, 1998; Schneidman *et al.*, 1998; Chow & White, 1996

(re)Introducing channel-noise *in silico*

Capture, model, and further explore the functional consequences of response variability and intrinsic noise, underlying neuronal excitability (at the level of neuronal networks).

Retaining the advantages of existing neuron models (single/multi compartmental):

- biophysical realism
- electrotonic properties
- large-scale models



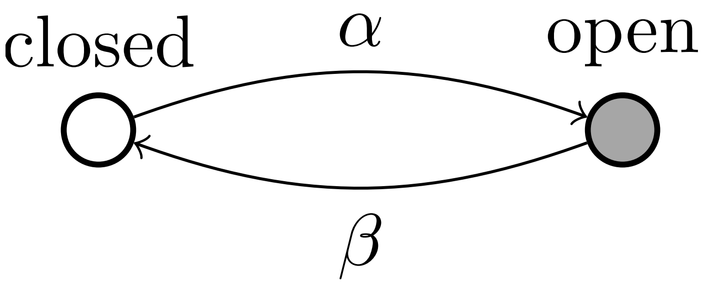
courtesy of H. Markram

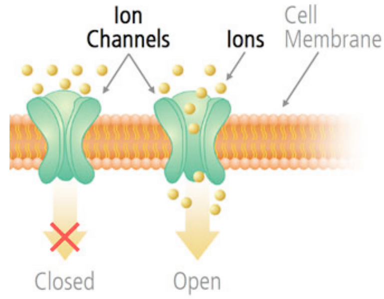
(re)Introducing channel-noise *in silico*

- Markovian formulation (i.e. microscopic, exact)

- Langevin formulation (i.e. effective, approximate)

Continuous-time Markov chain (M = 2 states)



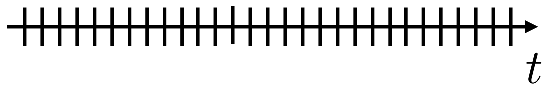


$$Prob\{\text{"}open \rightarrow closed\text{"}\ \ in\ [t; t+dt)\ \ /\ open\ at\ t\} \ = \ \beta dt$$

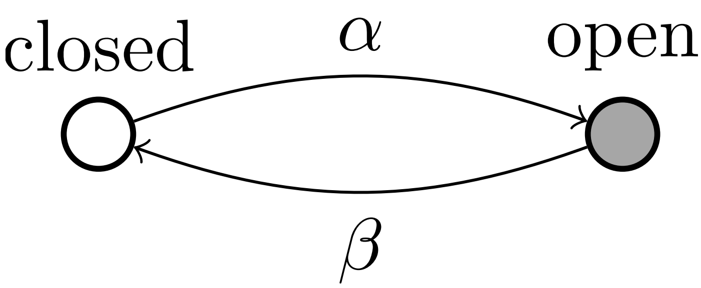
$$Prob\{\text{"}closed \rightarrow open\text{"}\ \ in\ [t; t+dt)\ \ /\ closed\ at\ t\} \ = \ \alpha dt$$

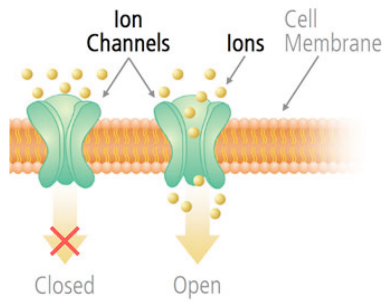
$$Prob\{no\ transition\ in\ [t; t+T)\ \ /\ closed\ at\ t\} \ = \ (1-\alpha dt)^{T/dt}$$

$$f_{T_C}(T)dt = (1-\alpha dt)^{T/dt}\alpha dt = \alpha e^{T/dt\ ln(1-\alpha dt)}dt \simeq \alpha e^{-\alpha T}dt$$



Analytical solution





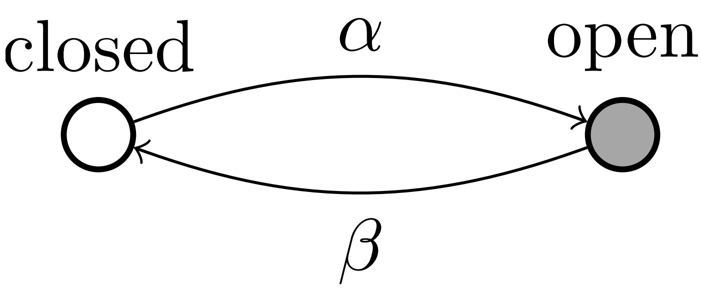
$$p_o(t\ +\Delta t) \ = \ p_o(t)(1-\beta\Delta t) \ + \ (1-p_o(t))\alpha\Delta t$$

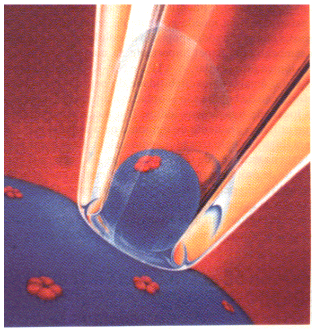
$$p_o(t\ +\Delta t) \ - \ p_o(t) \ = \ -(\alpha+\beta)\Delta t\ p_o(t) \ + \ \alpha\Delta t$$

$$\lim_{\Delta t \rightarrow 0} \frac{p_o(t\ +\Delta t) \ - \ p_o(t)}{\Delta t} \ = \ -(\alpha+\beta)\ p_o(t) \ + \ \alpha$$

$$\boxed{\frac{dp_o(t)}{dt} \ = \ -(\alpha+\beta)\ p_o(t) \ + \ \alpha} \qquad \boxed{\frac{dn(t)}{dt} \ = \ -(\alpha+\beta)\ n(t) \ + \ \alpha}$$

Simulating a Markov chain (M = 2 states)



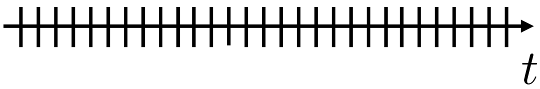


$$I = g(t)\,(E - V_m)$$

$$g(t) = \bar{g}_s\;\xi(t)$$

$$\xi(t) = \begin{cases} 1 & when\;\; open \\ 0 & otherwise \end{cases}$$

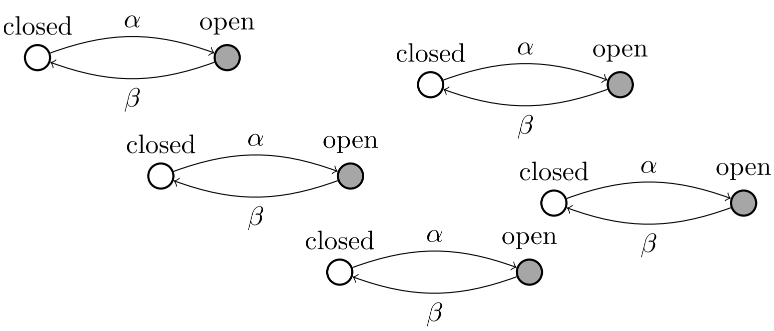
uniform time-step update

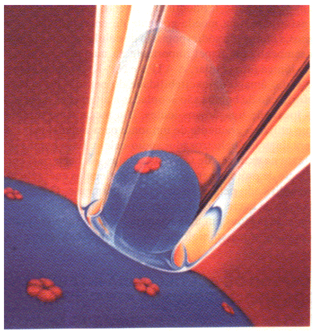



```
if xi == 0
    xi = (1 - xi) * (rand < alpha * dt);
else % xi == 1
    xi = (1 - xi) * (rand < beta  * dt);
end
```

0/1

Simulating "N" Markov chains (M = 2 states)



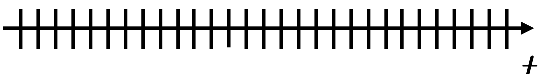


$$I = g(t)\,(E - V_m)$$

$$g(t) = \bar{g}_s\;\sum_{k=1}^{N} \xi_k(t)$$

$$\xi(t) = \begin{cases} 1 & when\;\; open \\ 0 & otherwise \end{cases}$$

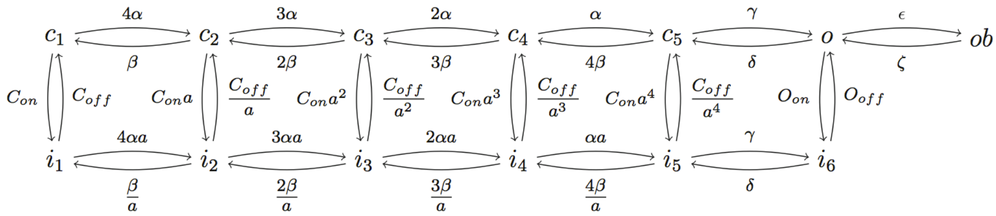
uniform time-step update

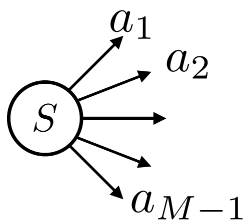



```
for k=1:N
 if xi(k) == 0
    xi(k) = (1 - xi(k)) * (rand < alpha * dt);
 else % xi(k) == 1
    xi(k) = (1 - xi(k)) * (rand < beta  * dt);
 end
end
```

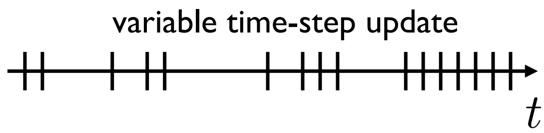
0/1	0/1	0/1	...	0/1

Faster simulation technique (Gillespie's algorithm)





$$\alpha = \left(\sum_{i=1}^{M-1} a_i\right)$$



1) For each channel track the state of the channel

0/1	0/1	0/1	…	0/1

2) Occupancy life-time for each state is a RV with pdf: $f_{T_S}(T) = \alpha e^{-\alpha T}$

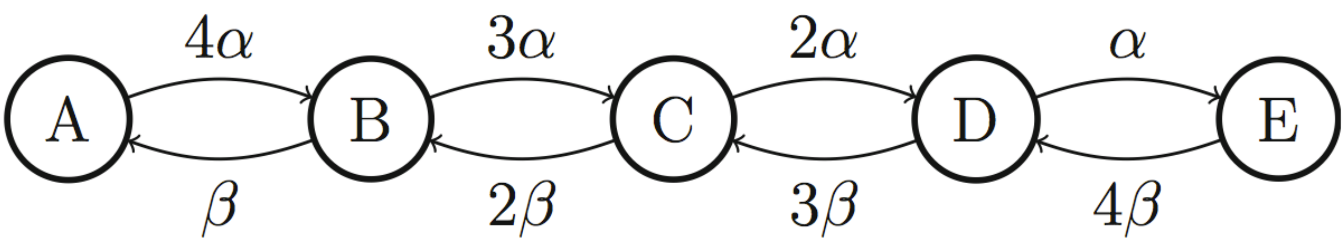
3) For each state, generate one realisation…

```
T = -(1./alpha) * log(rand);
```

4) Take the minimum, T_{min} and update V: $V_m(t + T_{min}) \;=\; ...V_m(t)$

5) For the corresponding channel, simulate the random transition event…

Example, stationary transition matrix Q

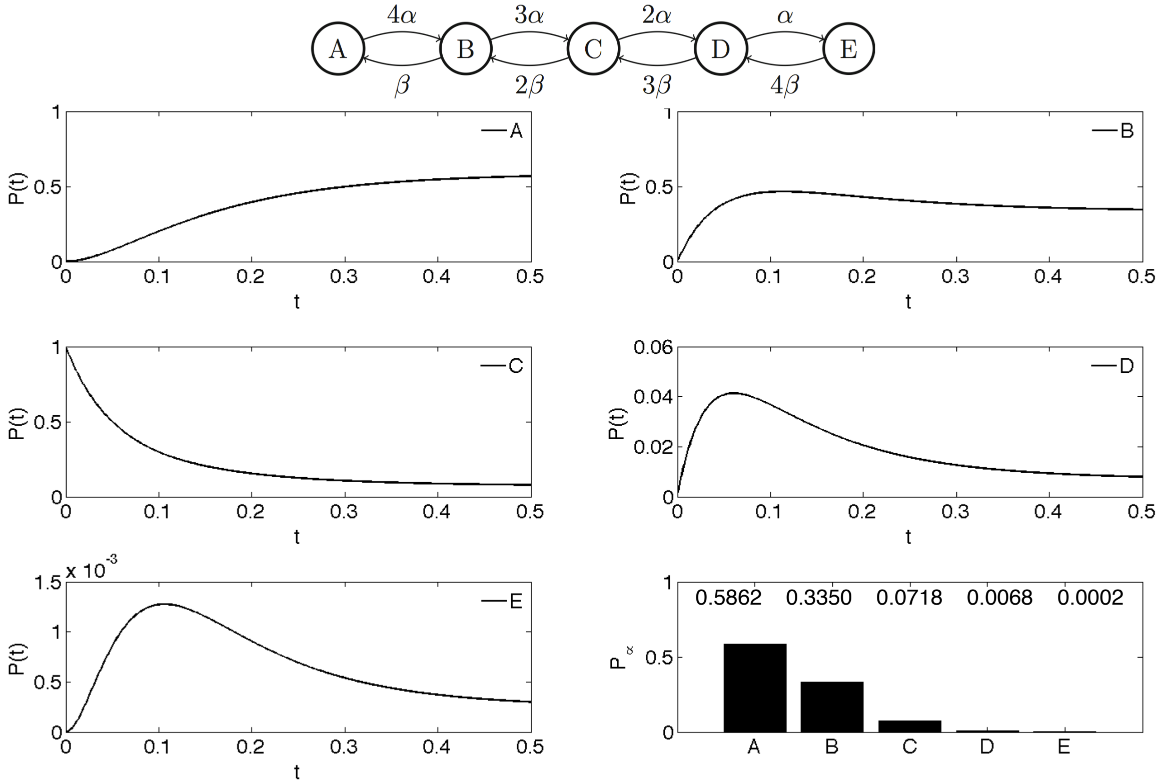


$$\mathbf{P} = \begin{pmatrix} P_\mathbf{A} \\ P_\mathbf{B} \\ P_\mathbf{C} \\ P_\mathbf{D} \\ P_\mathbf{E} \end{pmatrix} \qquad \mathrm{Q} = \begin{pmatrix} -4\alpha & \beta & 0 & 0 & 0 \\ 4\alpha & -(3\alpha+\beta) & 2\beta & 0 & 0 \\ 0 & 3\alpha & -(2\alpha+2\beta) & 3\beta & 0 \\ 0 & 0 & 2\alpha & -(\alpha+3\beta) & 4\beta \\ 0 & 0 & 0 & \alpha & -4\beta \end{pmatrix}$$

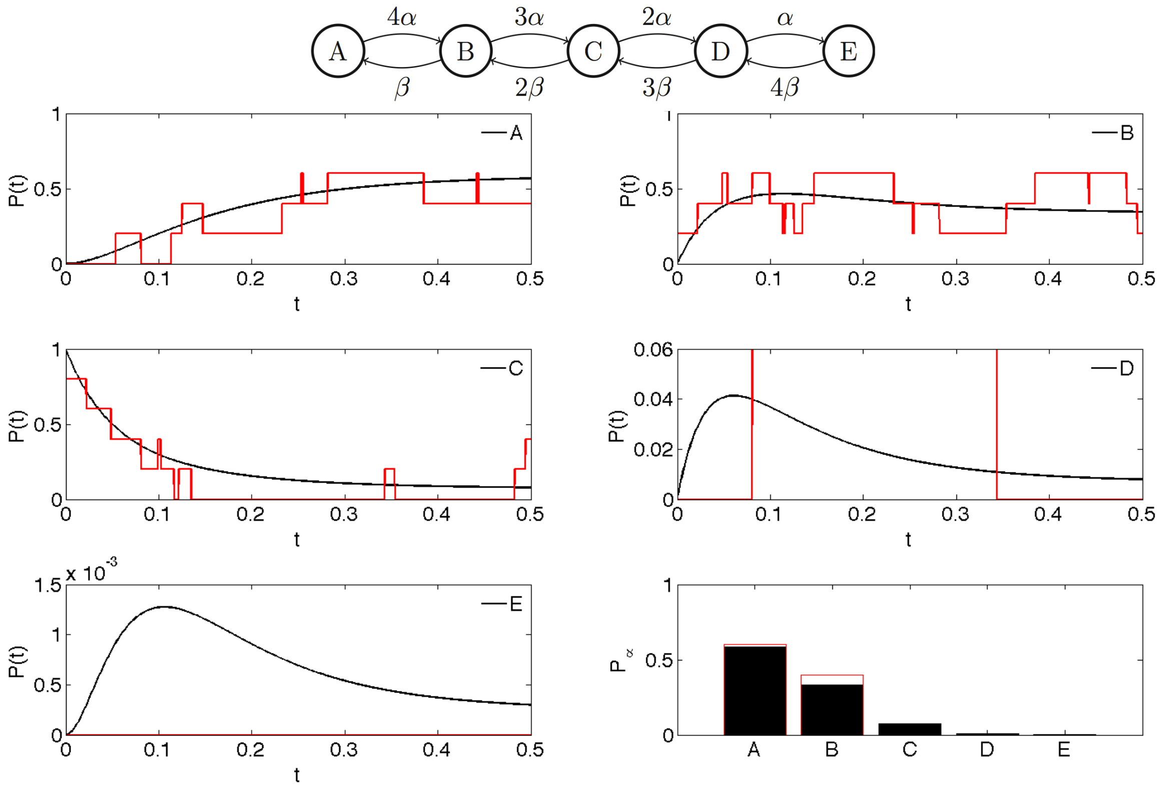
$$\frac{d}{dt}\mathbf{P} = \mathbf{QP} \qquad \alpha = 1, \quad \beta = 7$$

e.g., reviewed in Linaro & Giugliano, 2014

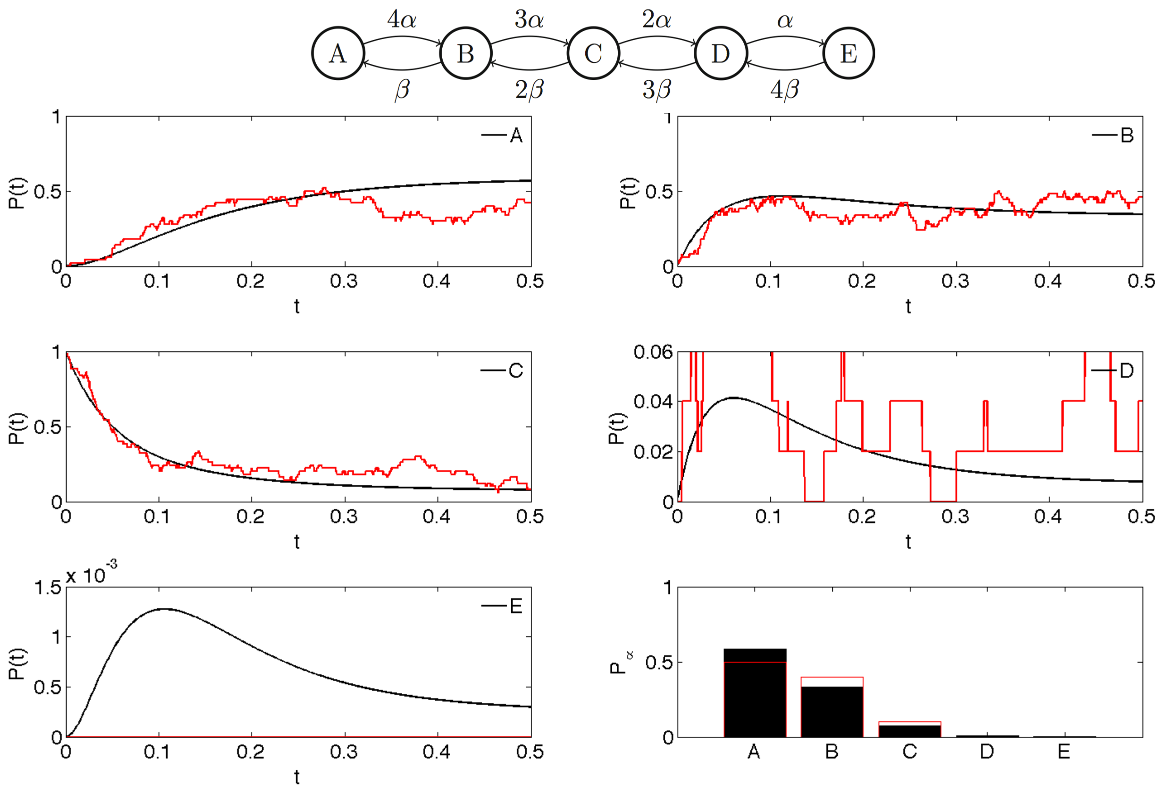
Example, stationary transition matrix Q analytical solution



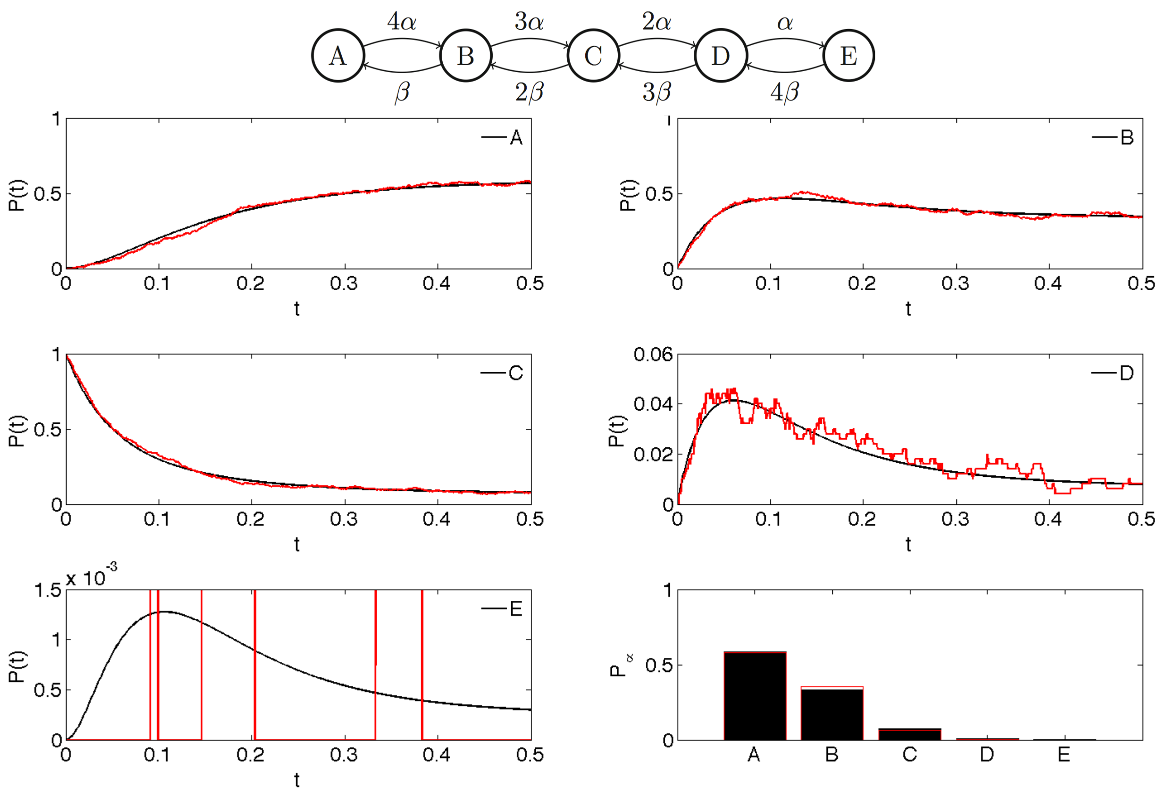
Example, stationary transition matrix Q numerical simulation (variable time-step, N=5)



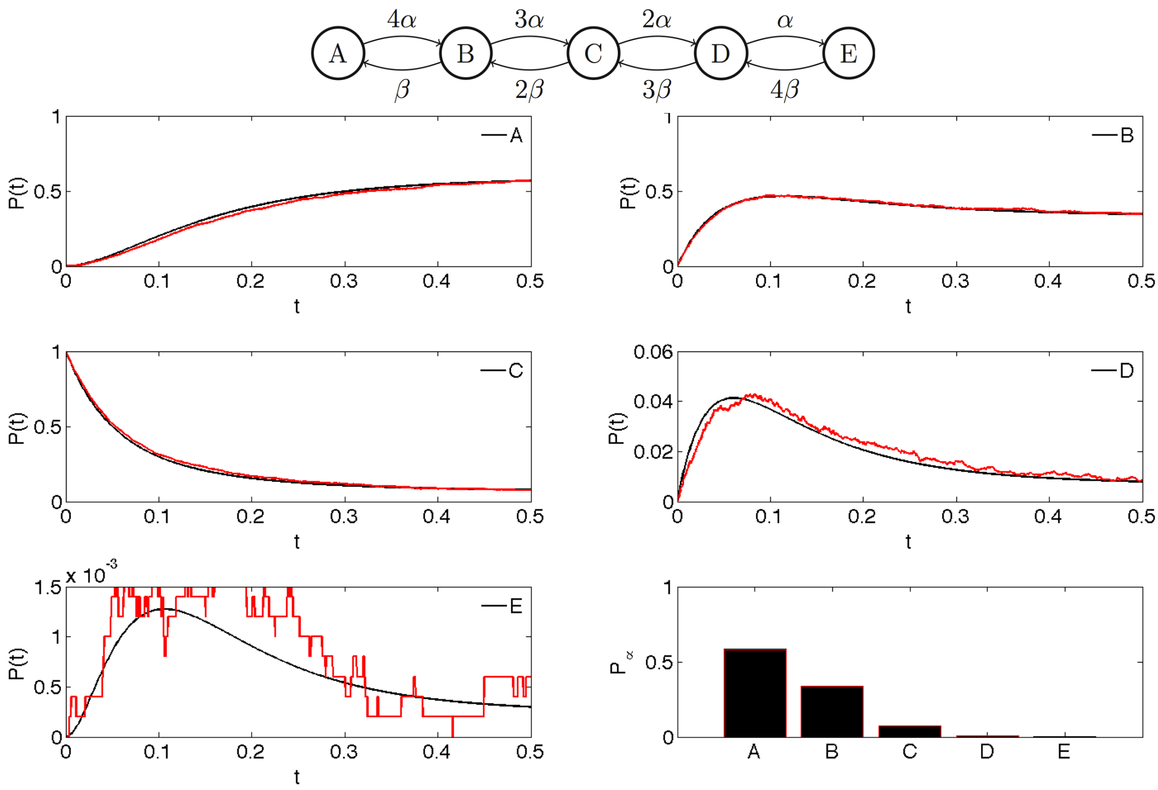
Example, stationary transition matrix Q numerical simulation (variable time-step, N=50)



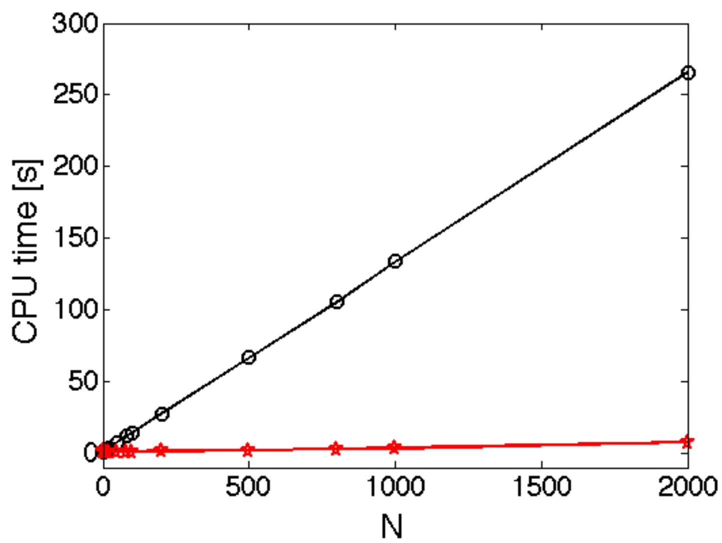
Example, stationary transition matrix Q numerical simulation (var. time-step, N=500)



Example, stationary transition matrix Q numerical simulation (var. time-step, N=5000)



Same (exact) statistical performances, different computational loads



Markovian formulation

PROS

- Biological realism
- Exact chan. fluctuations
- Basic building blocks

CONS

- <u>SLOW</u>
- Simulation times increase with N
- Inadequate for simulating large networks of interacting neurons

Langevin-like formulation

where and how does one "plug" an effective channel-noise term, into the usual (deterministic) conductance-based equations ?!?

1) *<u>gaussian current noise</u>* (simplest; heuristic; combined effect)
no method available to *design* the noise intensity, or its dep. on *V*

$$C\frac{dV}{dt} + \sum_k I_k + I_L + \boxed{\xi_V(t)} = I_{ext}$$

Rowat, 2007
Gerstein & Mandelbrot, 1964; Tuckwell, 1988; Brunel and collaborators

2) *<u>gaussian subunit-noise</u>* (subunits-limited; may not reduce to deterministic case; gaussianity!)

$$\frac{dx}{dt} = \frac{x_\infty - x}{\tau_x} + \boxed{\xi_x(t)}$$

Goldwyn & Shea-Brown, 2010, 2011
Fox *et al.*, *Phys. Rev. E* (1994) and Fox, *Biophys J.* (1997)... **<u>and >60 papers</u>**

Assumptions of a *diffusion* approximation

1) Each of the *N* channels is <u>identical</u> and statistically <u>independent</u>

2) single-channel kinetics is described by a Markov process

3) only one state is associated to a non-zero conductance

4) *N* is known and it is 'large' (hp: DeMoivre-Laplace theorem)
(360 K+, 1200 Na+)

5) biophysical variables that "gate" the channels (e.g. V(t), $[Ca^{++}]_{in}(t)$, T(t), ...) change slowly in time, compared to channel kinetics

Linaro *et al.*, PLoS Comp. Biology 2011

Langevin-like formulation

where and how does one "plug" an effective channel-noise term, into the usual (deterministic) conductance-based equations ?!?

3) *gaussian conductance-noise* (rigorous derivation; accurate; general)

$$I = \bar{g}\ [x^p(t) y^q(t)\ +\ \xi(t)]\ (V\ -\ E)$$

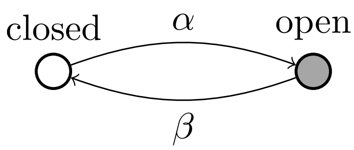
Linaro *et al.*, 2011
Steinmetz *et al.*, 2000
Conti & Wanke, 1975

1. Determine analytically the stochastic properties (mean and co-variance) of the the fraction of open channels as emulated by Markov models.

2. Use a continuous (i.e., diffusion) stochastic process to approximate the fraction of open channels as a superposition of independent Ornstein Uhlenbeck stochastic processes.

Langevin-like formulation

population of 2-state channels



Assume to have *N* channels: we want to determine the statistical properties of the fraction of open channels n_o.

The time-varying conductance is:

$$g(t) = \bar{g}\, n_o(t) = \frac{1}{N}\sum_i^N s_i$$

$$s_i = \begin{cases} 1, & p_o \\ 0, & 1-p_o \end{cases}$$

$$\tau_o\, \dot{p}_o = p_\infty - p_o$$

$$\boxed{\tau_o\, \dot{\bar{n}} = p_\infty - \bar{n}}$$

Conti & Wanke, 1975

Linaro *et al.*, PLoS Comp. Biology 2011

Langevin-like formulation

population of 2-state channels

Mean:

$$\bar{n}_o = n_\infty = \frac{\alpha}{\alpha+\beta}$$

Covariance:

$$\Phi_{n_o}(\Delta) = \sigma^2 \exp(-|\Delta|/\tau)$$

where $\tau = \dfrac{1}{\alpha+\beta}$ and $\sigma^2 = \dfrac{1}{N} n_\infty (1 - n_\infty)$

Take a OU process:

$$\tau\, \dot{\eta}(t) = -\eta(t) + \sqrt{2\tau}\, \xi(t)$$

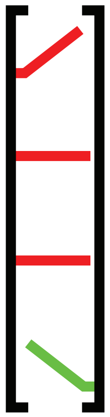
And express the time-varying conductance as:

$$g(t) = \bar{g}\left[\bar{n}_o(t) + \sigma\, \eta(t)\right]$$

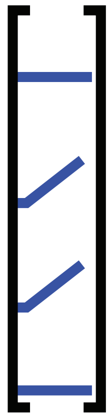
Linaro *et al.*, PLoS Comp. Biology 2011

population of M-state channels
(when they can be decomposed into multiple sets of identical subunits)

Example: sodium and potassium channels in the HH model.



$m^3 h$



n^4

Conti & Wanke, 1975

Linaro *et al.*, PLoS Comp. Biology 2011

Langevin-like versions of a stochastic conductance-based model

population of M-state channels (subunits)

Mean value:

$$\overline{x_p y_q}(t) = x^p(t)\ y^q(t)$$

Covariance function:

$$\Phi_{x_p y_q}(\Delta) = \frac{1}{N}[(\Phi_x(\Delta) + x_\infty^2)^p(\Phi_y(\Delta) + y_\infty^2)^q - x_\infty^{2p} y_\infty^{2q}]$$

where

$$\Phi_u(\Delta) = u_\infty(1 - u_\infty)\exp(-|\Delta|/\tau_u) \quad u = \{x, y\}$$

is the covariance of the simplest two-state chain.

Conti & Wanke, 1975

Linaro *et al.*, PLoS Comp. Biology 2011

Langevin-like versions of a stochastic conductance-based model

population of M-state channels (subunits)

The covariance function is made up of a sum of terms:

$$M = (p+1)(q+1) - 1$$

The expression of the conductance:

$$g_k(t) = \bar{g}_k \left[x^p(t) y^q(t) + \sum_{i=1}^{M} \sigma_i \; \eta_i(t) \right]$$

Each of the OU processes:

$$\tau_i \; \dot{\eta}_i(t) = -\eta_i(t) + \sqrt{2\tau_i} \; \xi(t)$$

Linaro *et al.*, PLoS Comp. Biology 2011

Given a deterministic model neuron,
composed of voltage-
and ligand-gated channels,...

...it can be turned into a
non-deterministic equivalent
by a simple method and minor computational loads!

Linaro *et al.*, 2011

Validation

tests outline

Let's consider the HH model

1) Steady-state (voltage-clamp) statistics

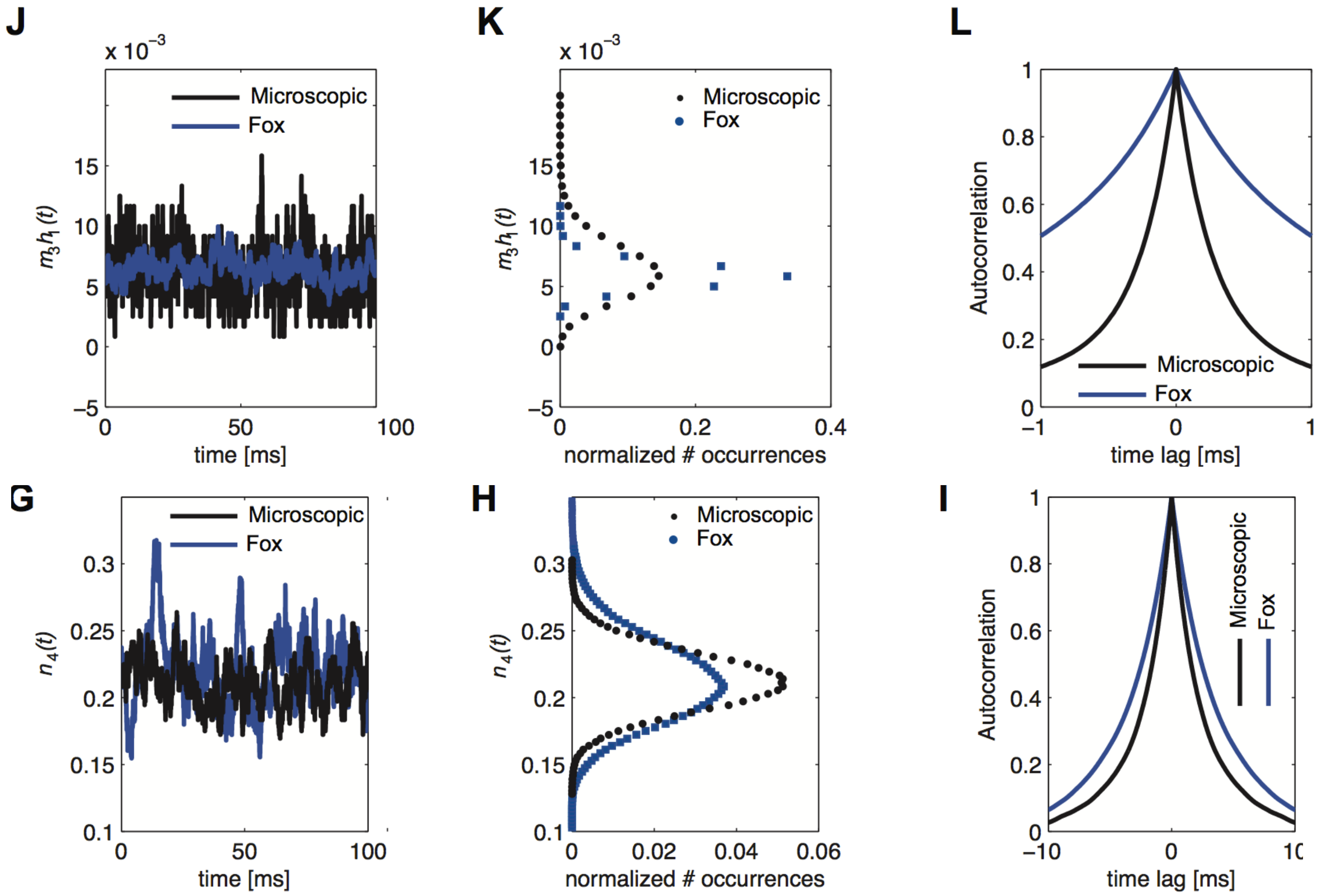
2) Dynamical Properties (suprathreshold)

3) Dynamical Properties (subthreshold)

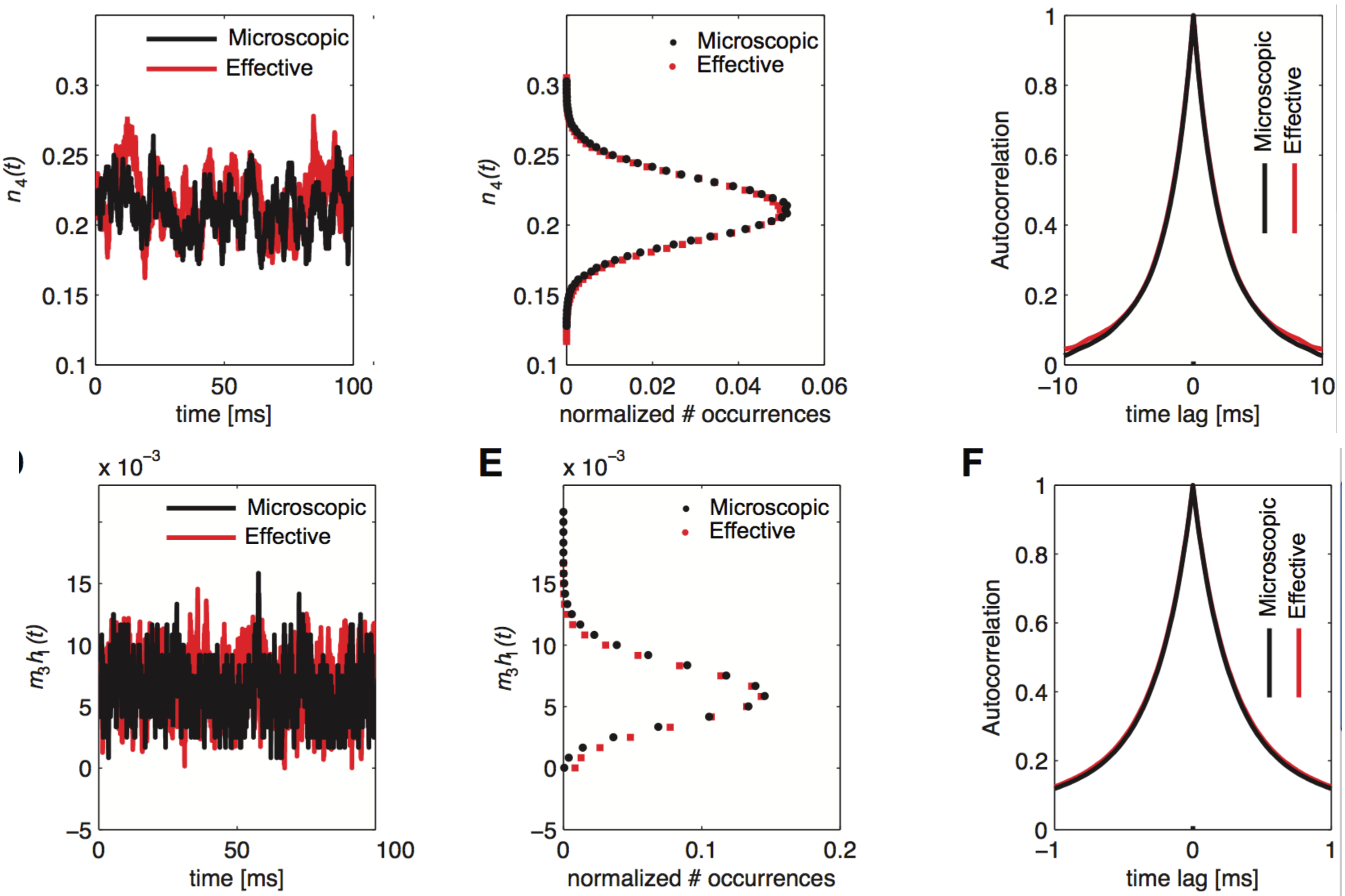
Direct comparison with the 'subunit-noise' approach, presented in Fox *et al.* (1994) and Fox (1997).

Linaro *et al.*, PLoS Comp. Biology 2011

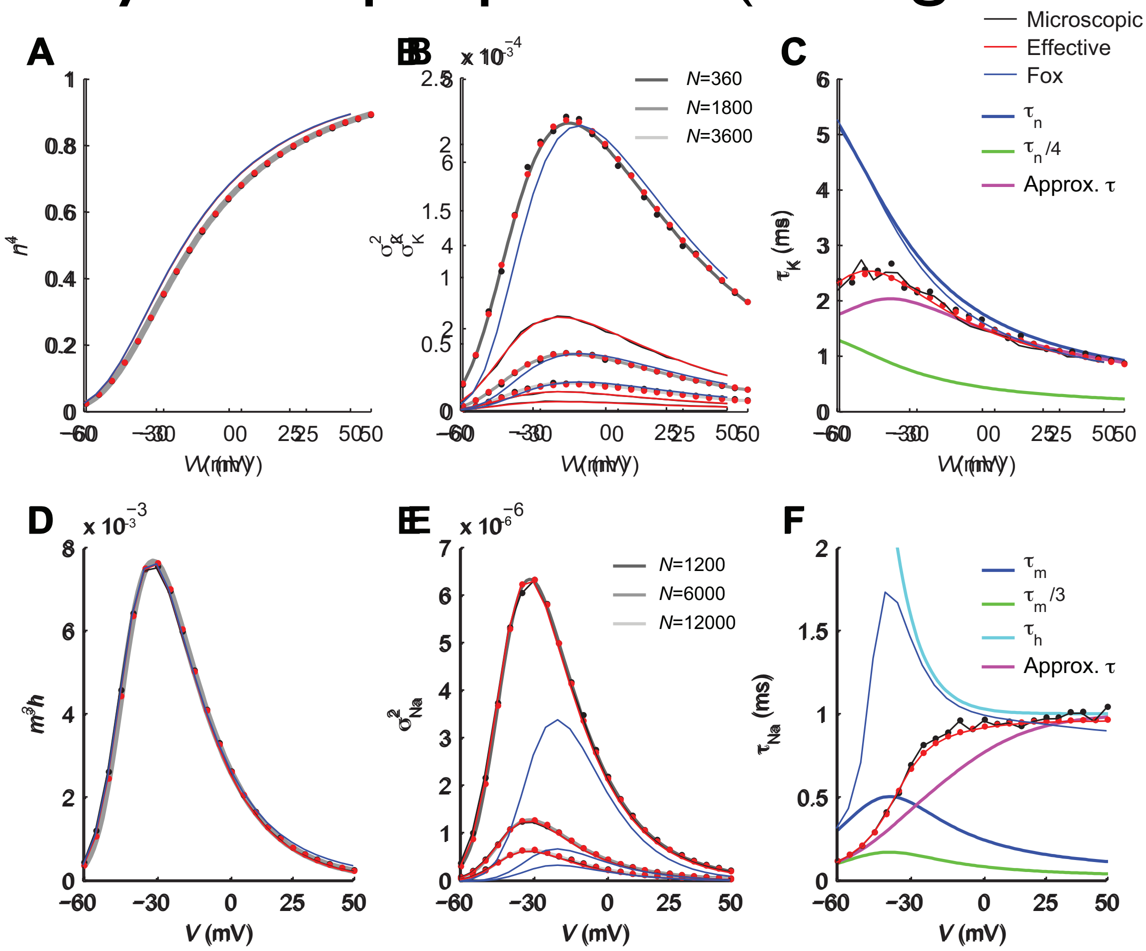
Steady-state properties (voltage-clamp)



Steady-state properties (voltage-clamp)



Steady-state properties (voltage-clamp)



dynamical PROPERTIES

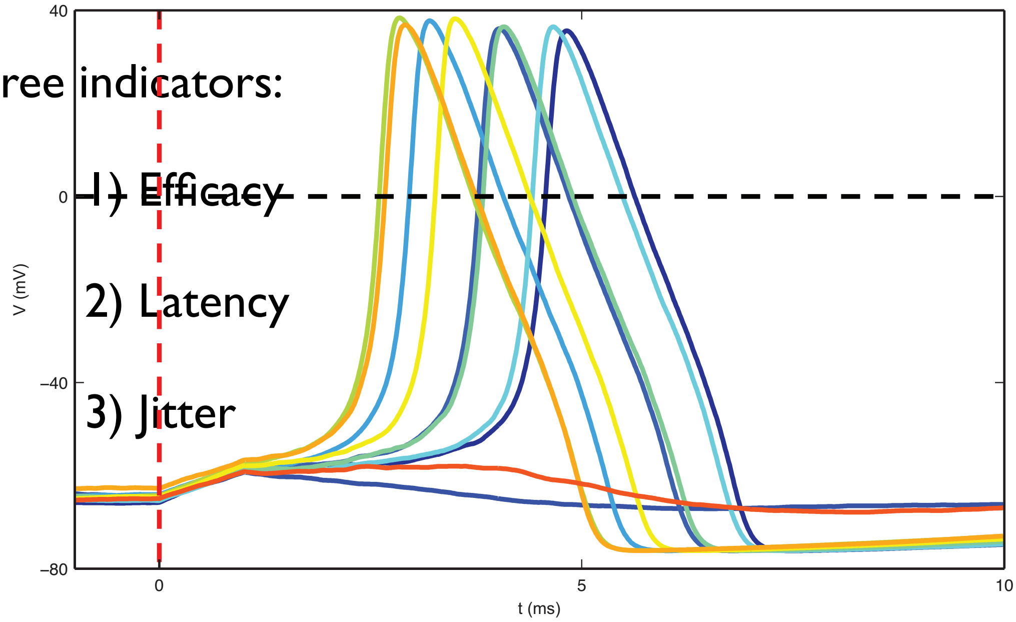
action potentials

Three indicators:

1) Efficacy

2) Latency

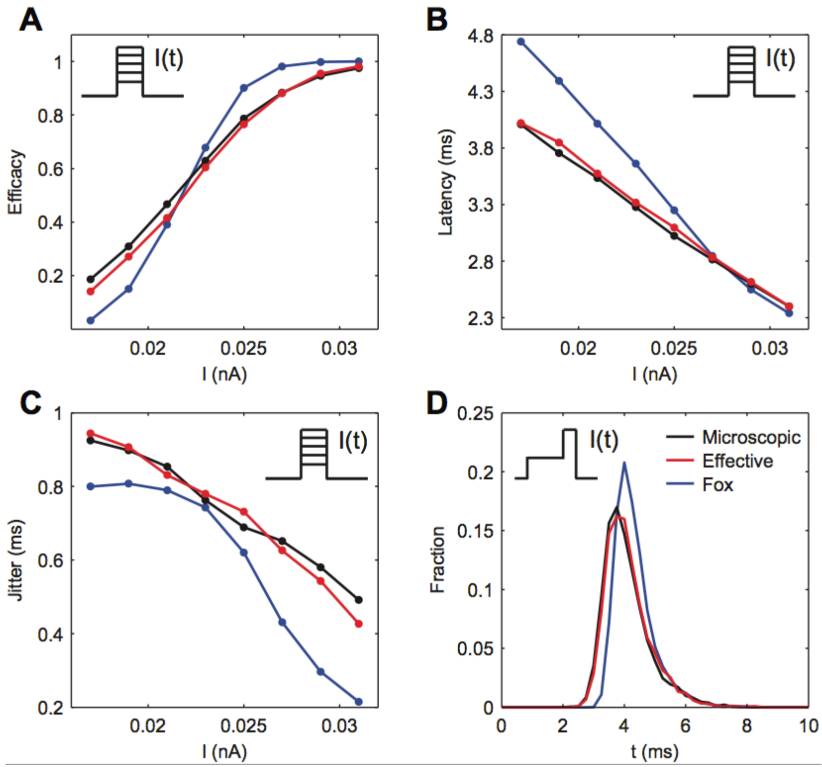
3) Jitter



Linaro *et al.*, 2011

dynamical PROPERTIES

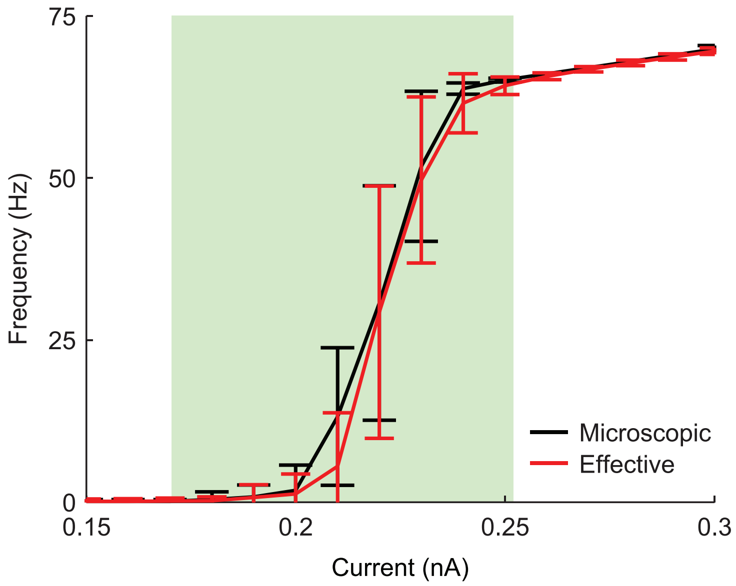
action potentials



Linaro *et al.*, 2011

dynamical PROPERTIES

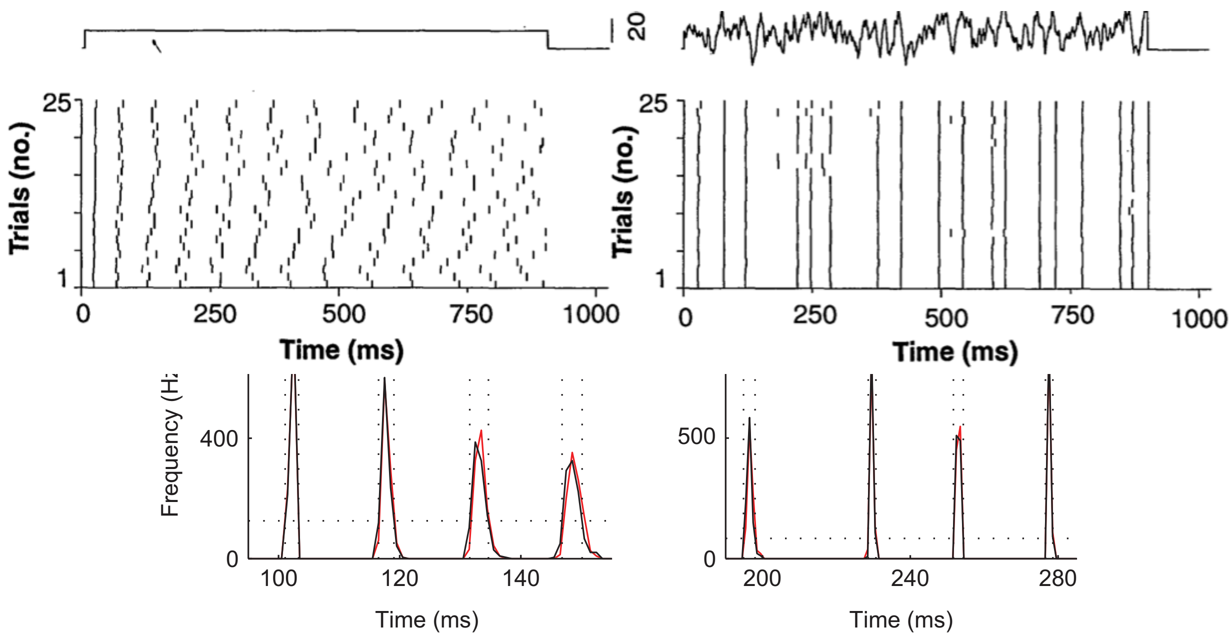
F-I curves



Linaro *et al.*, 2011

dynamical PROPERTIES

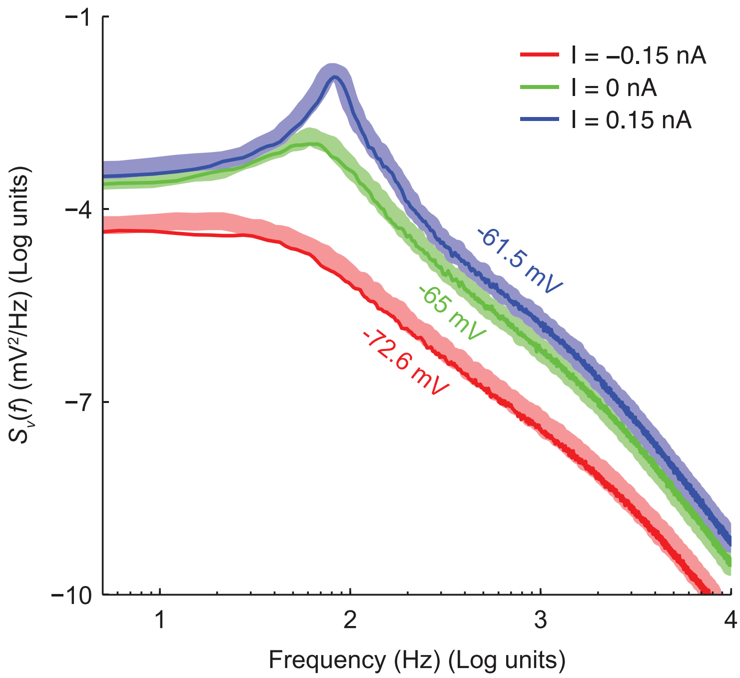
reliability



Linaro *et al.*, 2011

dynamical PROPERTIES

subthreshold voltage fluctuations, power-spectra



Linaro *et al.*, 2011

Conclusions (1/2)

RESULTS

It is possible to translate any deterministic conductance-based model into an effective stochastic model, which is

1) Precise

2) Reasonably fast (**4.5 faster** than the fastest µscopic algorithm),
(**1.5 slower** than Fox's, but with no inaccuracy)

3) General

4) Suitable for network simulations & dynamic-clamp

Conclusions (2/2)

VALIDATION

We have performed validation tests with our model:

1) Steady state properties

2) Dynamic properties

In all cases the results are comparable to Markov microscopic models and way superior to those that can be obtained with previous reference effective models (e.g., Fox).

Thanks for your attention!

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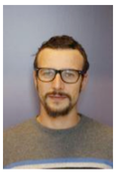
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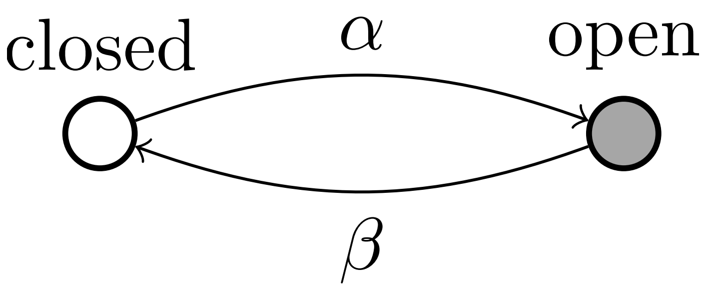
e-GAP2

Thanks for your attention!



$$p_o(t + \Delta t) = p_o(t)(1 - \beta \Delta t) + (1 - p_o(t))\alpha \Delta t$$

$$p_o(t + \Delta t) - p_o(t) = -(\alpha + \beta)\Delta t \, p_o(t) + \alpha \Delta t$$

$$\lim_{\Delta t \to 0} \frac{p_o(t + \Delta t) - p_o(t)}{\Delta t} = -(\alpha + \beta) \, p_o(t) + \alpha$$

$$\frac{dp_o(t)}{dt} = -(\alpha + \beta) \, p_o(t) + \alpha$$

$$\frac{dn(t)}{dt} = -(\alpha + \beta) \, n(t) + \alpha$$

$$g(t) = \bar{g}\, n_o(t) = \frac{1}{N}\sum_i^N s_i \qquad s_i = \begin{cases}1, & p_o \\ 0, & 1-p_o\end{cases}$$

$$< n_o(t) > = \frac{1}{N}\sum_i^N < s_i > \boxed{= p_o(t)}$$

$$< n_o(t)^2 > = \frac{1}{N^2} < \sum_i^N s_i \sum_j^N s_j > =$$

$$= \frac{1}{N^2}\sum_{i \neq j}^N < s_i > < s_j > + \frac{1}{N^2}\sum_j^N < s_j^2 > =$$

$$= \frac{1}{N^2} N(N-1) p_o(t)^2 + \frac{1}{N^2} N p_o(t) =$$

$$= \boxed{\frac{1}{N} p_o(t)\,(1 - p_o(t))} + p_o(t)^2$$

Powers of a gaussian random variable are NOT gaussian variables

$$f_x(X) = \frac{1}{\sqrt{2\pi\sigma^2}}\, e^{-\frac{(X-\mu)^2}{2\sigma^2}}$$

$$y = x^i, \quad i > 0$$

$$f_y(Y) = Y^{\frac{1-i}{i}} \frac{1}{i\,\sqrt{2\pi\sigma^2}}\, e^{-\frac{(Y^{1/i}-\mu)^2}{2\sigma^2}}$$

Papoulis and Pillail, 2002

Powers of a gaussian random variable are NOT gaussian variables

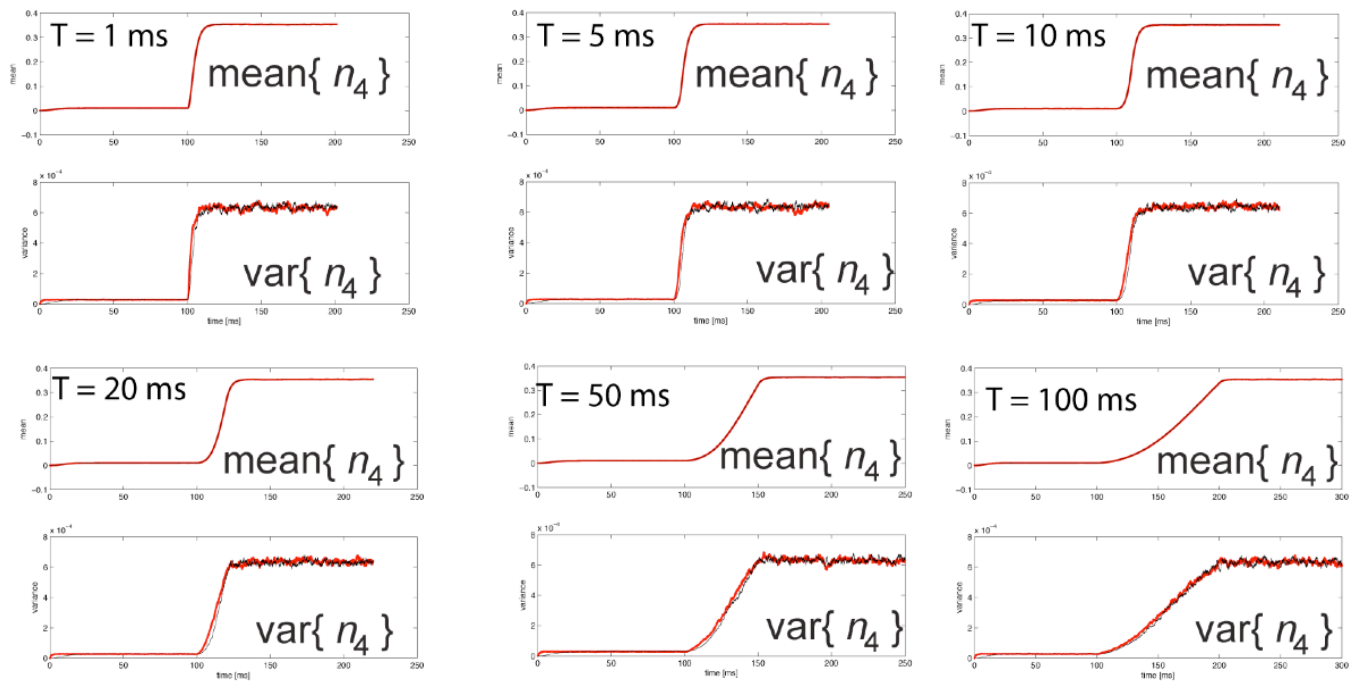
$$\mu_2 = \mu^2 + \sigma^2 \qquad \sigma_2^2 = 2\sigma^2 \left(\sigma^2 + 2\mu^2\right)$$

$$\mu_3 = \mu \left(\mu^2 + 3\sigma^2\right) \qquad \sigma_3^2 = 3\sigma^2 \left(3\mu^4 + 12\mu^2\sigma^2 + 5\sigma^4\right)$$

$$\mu_4 = \mu^4 + 6\mu^2\sigma^2 + 3\sigma^4$$

$$\sigma_4^2 = \sigma^2 \left(16\mu^6 + 168\mu^4\sigma^2 + 384\mu^2\sigma^4 + 97\sigma^6\right)$$

Speed of change of channel noise and quasi-stationary assumption



Speed of change of channel noise and quasi-stationary assumption