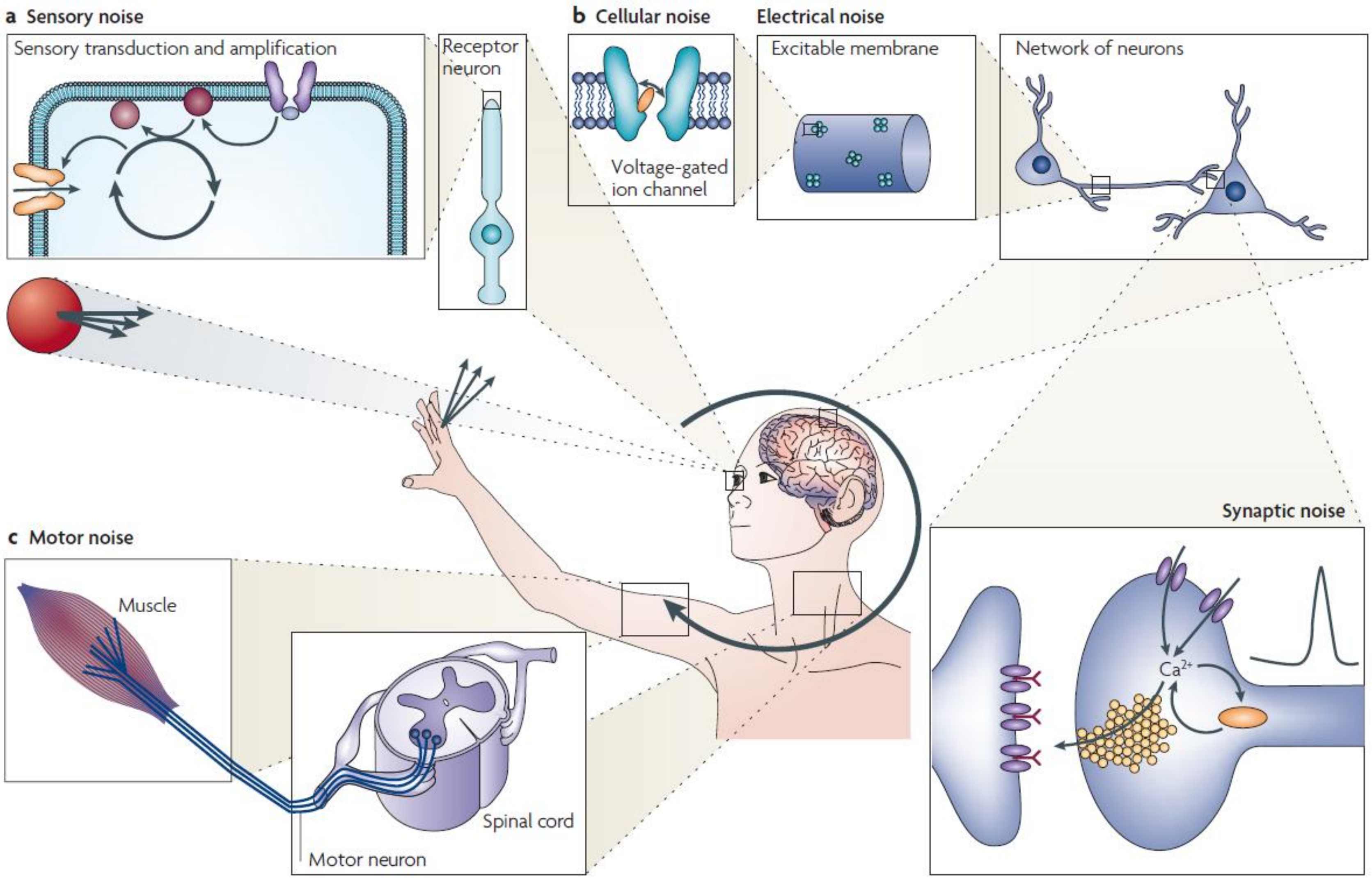
Understanding the Effects of Stochastic Ion Channel behavior through Modeling

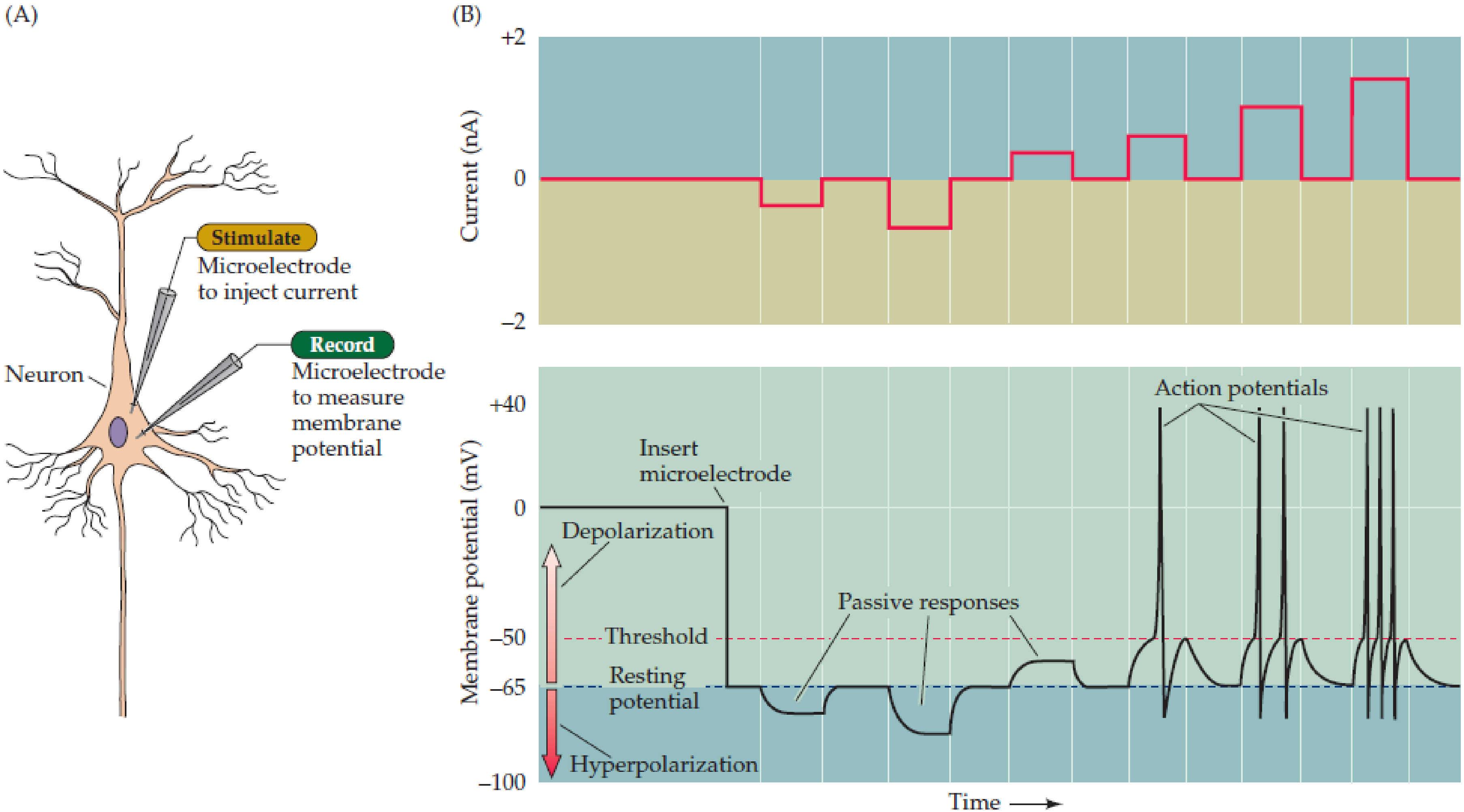
Patricio Orio Álvarez

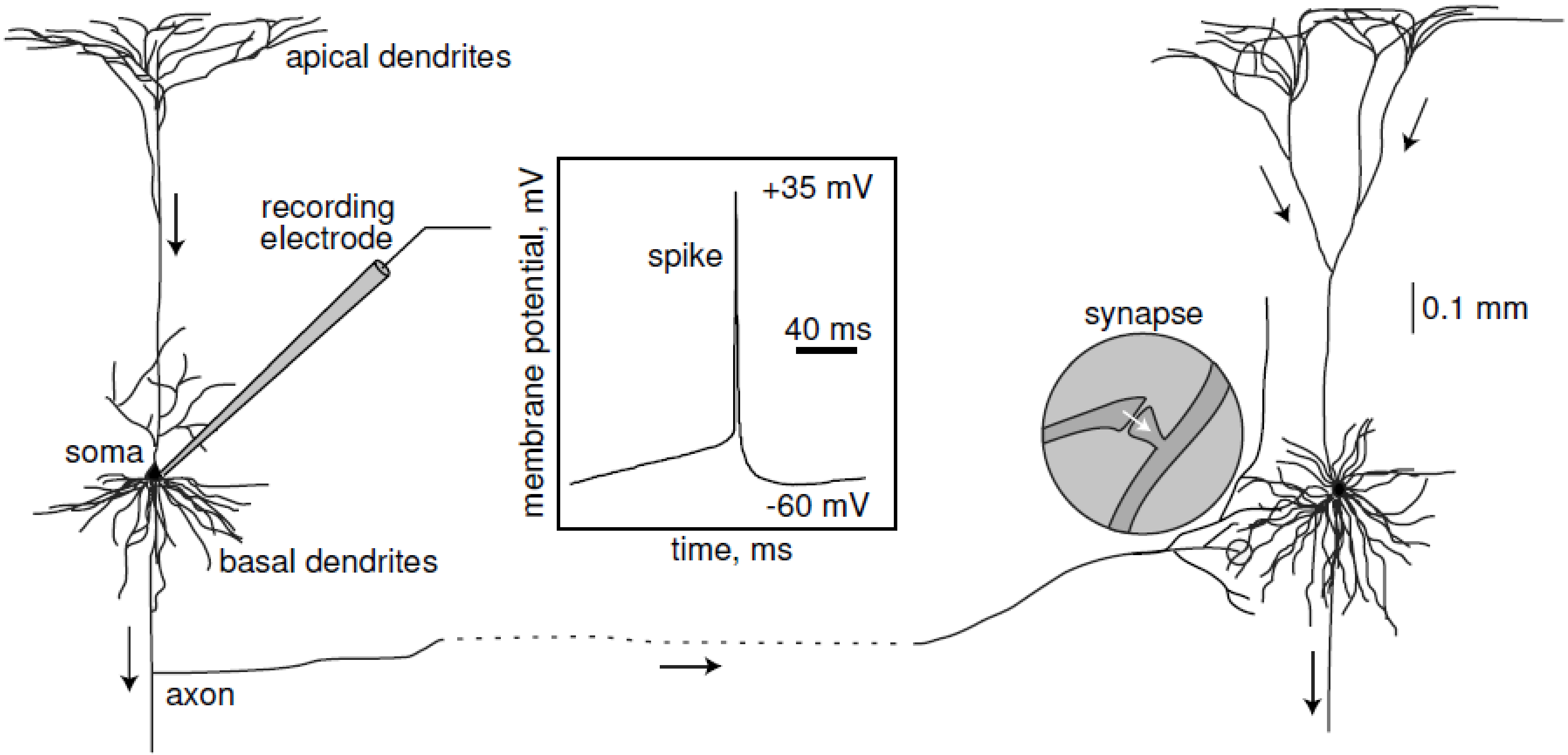
Centro Interdisciplinario de Neurociencia de Valparaíso



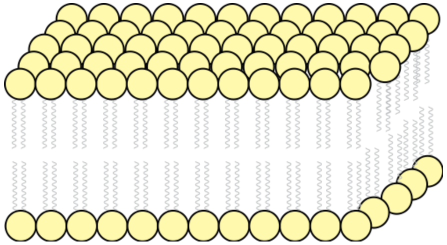
Faisal A.A., Selen L. & Wolpert D.M.(2008). Noise in the nervous system. *Nat Rev Neurosci* **9**:292-303

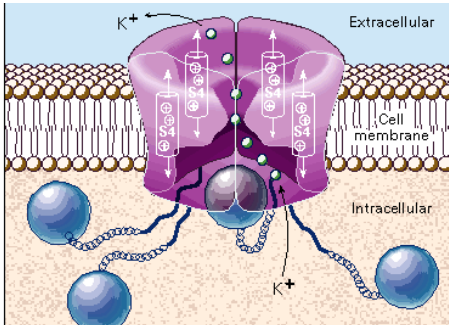
Neurons and Action Potentials

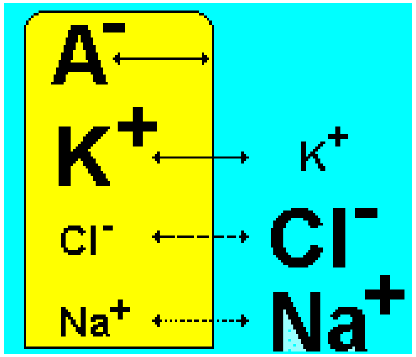



apical dendrites
recording
electrode
membrane potential, mV
+35 mV
spike
40 ms
-60 mV
time, ms
soma
basal dendrites
axon
synapse
0.1 mm

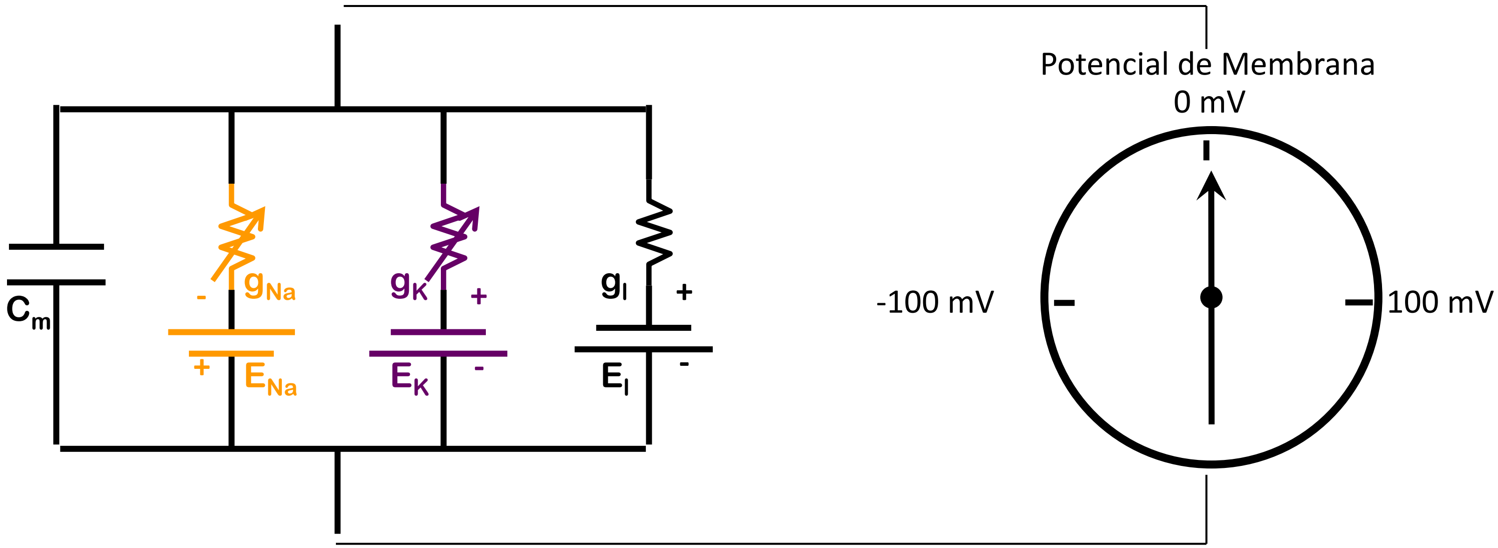
The cell membrane







Circuito Equivalente



$$I_m = C_m \frac{dV}{dt} + g_{Na}(V - E_{Na}) + g_K(V - E_K) + g_l(V - E_l)$$

$$V = \frac{g_K E_K + g_{Na} E_{Na} + g_l E_l}{g_K + g_{Na} + g_l}$$

$$E_i = \frac{RT}{F} \ln \frac{[i]_O}{[i]_i}$$

Hodgkin & Huxley (HH) equations

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n (1 - n) - \beta_n n,$$

$$dm/dt = \alpha_m (1 - m) - \beta_m m,$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h,$$

$$\alpha_n = 0{\cdot}01\ (V + 10) \Big/ \left(\exp \frac{V + 10}{10} - 1\right),$$

$$\beta_n = 0{\cdot}125 \exp (V/80),$$

$$\alpha_m = 0{\cdot}1\ (V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1\right),$$

$$\beta_m = 4 \exp (V/18),$$

$$\alpha_h = 0{\cdot}07 \exp (V/20),$$

$$\beta_h = 1 \Big/ \left(\exp \frac{V + 30}{10} + 1\right).$$

Hodgkin A.L., and Huxley A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**: 500-544

Hodgkin & Huxley (HH) equations

$$I = C_M \frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

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

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

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

$$C_M \frac{dV}{dt} = f(V, m, h, n)$$

$$\frac{dn}{dt} = g(V, n)$$

→ Voltage-dependent potassium channels

$$\frac{dm}{dt} = j(V, m)$$

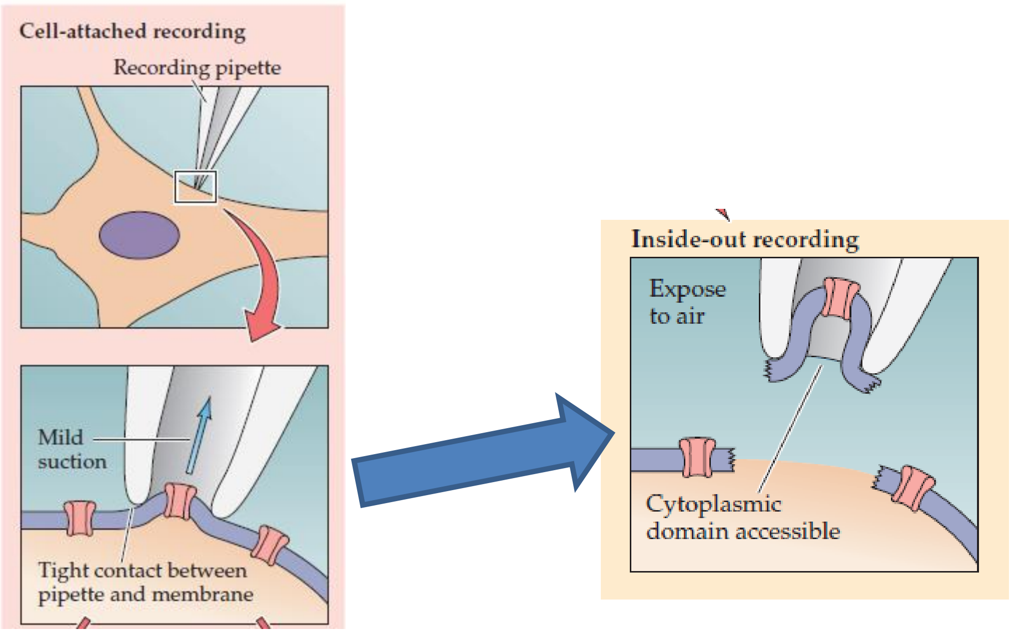
$$\frac{dh}{dt} = k(V, h)$$

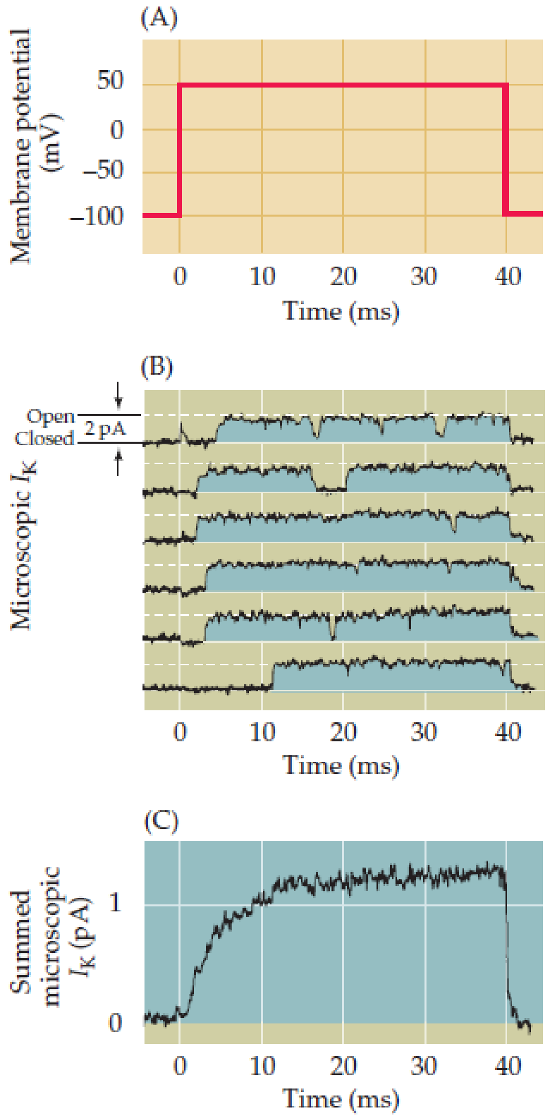
→ Voltage-dependent Sodium channels

Hodgkin A.L., and Huxley A.F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**: 500-544

Stochastic Nature of Ion channels

Stochastic Nature of Ion channels





Working with stochastic channels

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$N \qquad n_C \underset{\beta_n}{\overset{\alpha_n}{\rightleftarrows}} n_O \qquad n = \frac{n_O}{N}$$

$$M \qquad m_C \underset{\beta_m}{\overset{\alpha_m}{\rightleftarrows}} m_O \qquad m = \frac{m_O}{M}$$

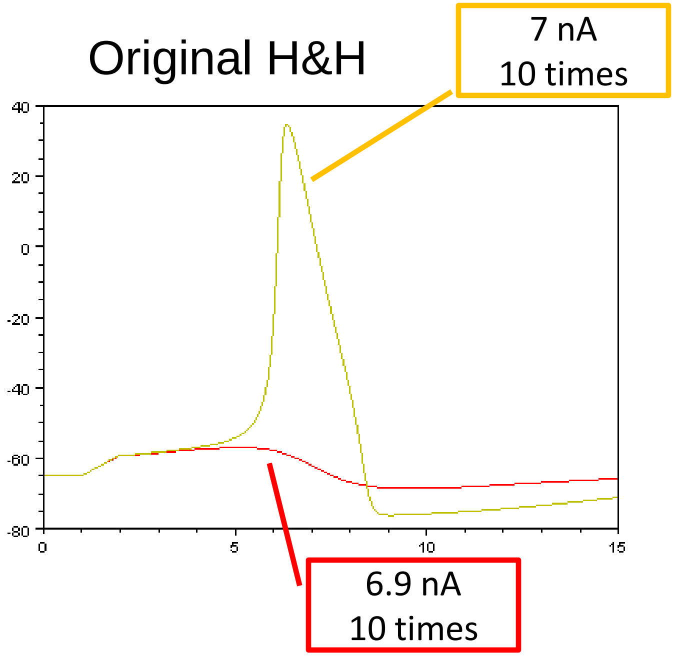
$$g_K = \bar{g}_K n = n_O g_K^u$$

$$\bar{g}_K = N g_K^u$$

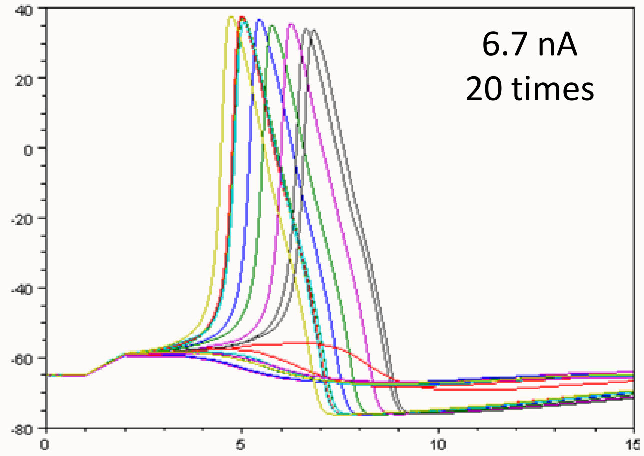
Conductancia *máxima* de potasio (n=1)

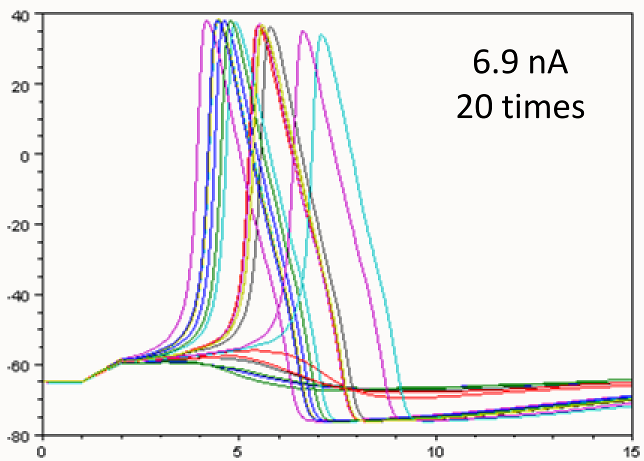
Conductancia de *un canal* de potasio

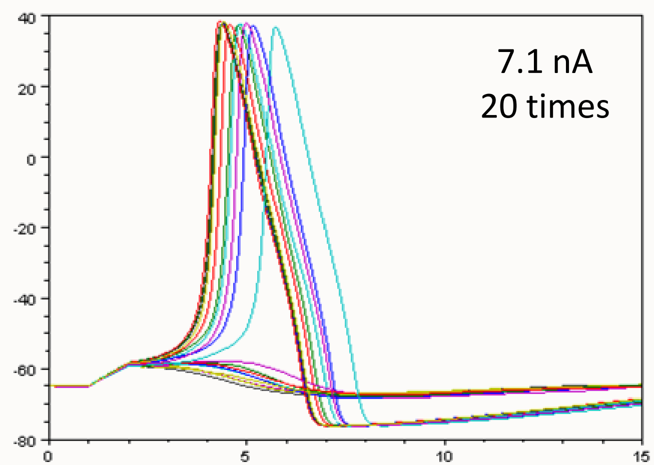
Original H&H



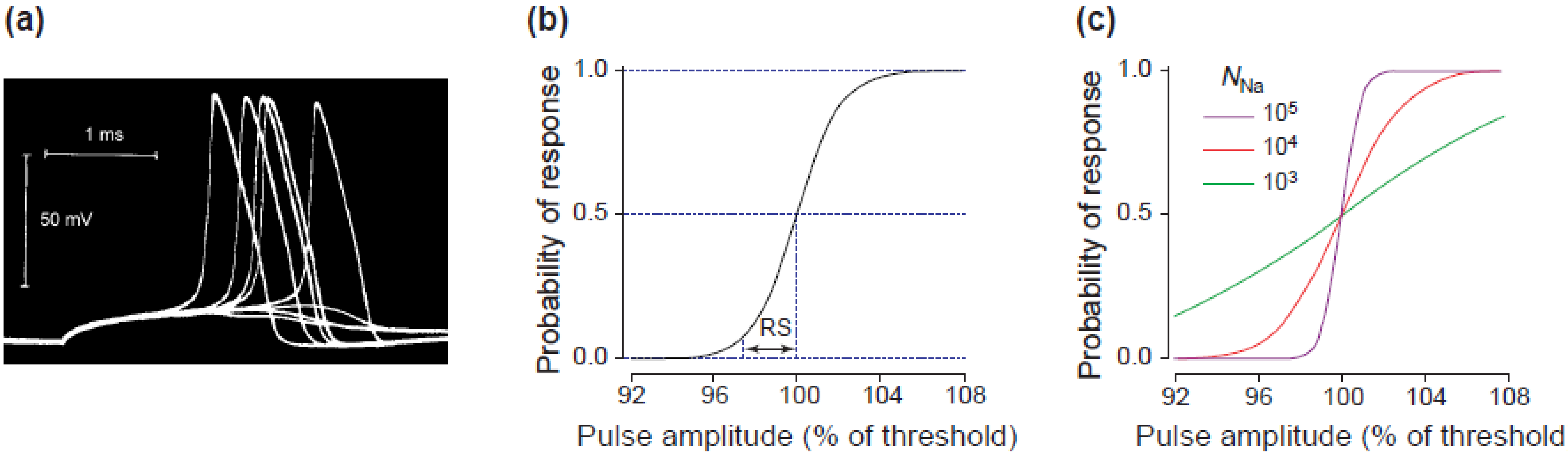
5000 sodium channels
1600 potassium channels

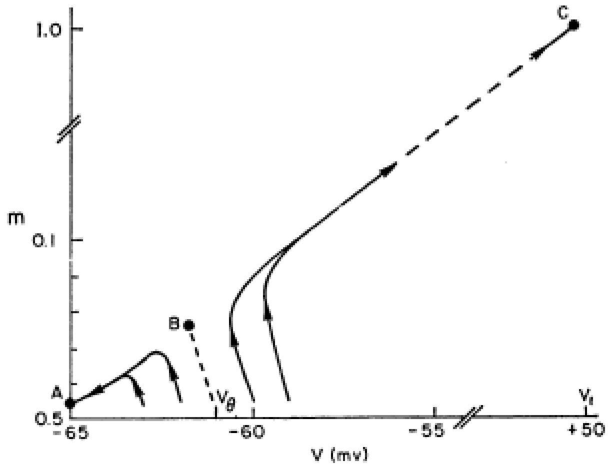






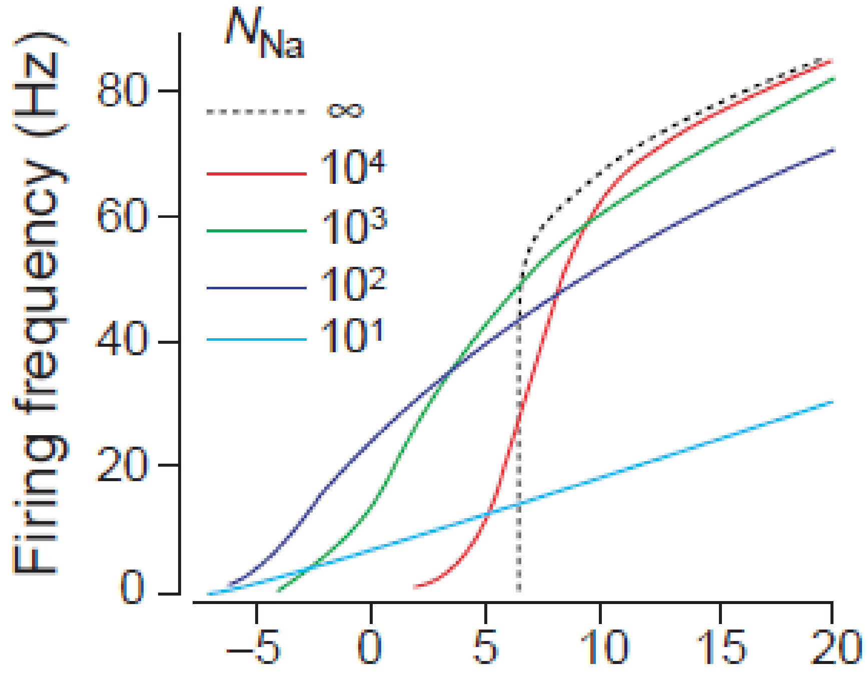
Firing Threshold



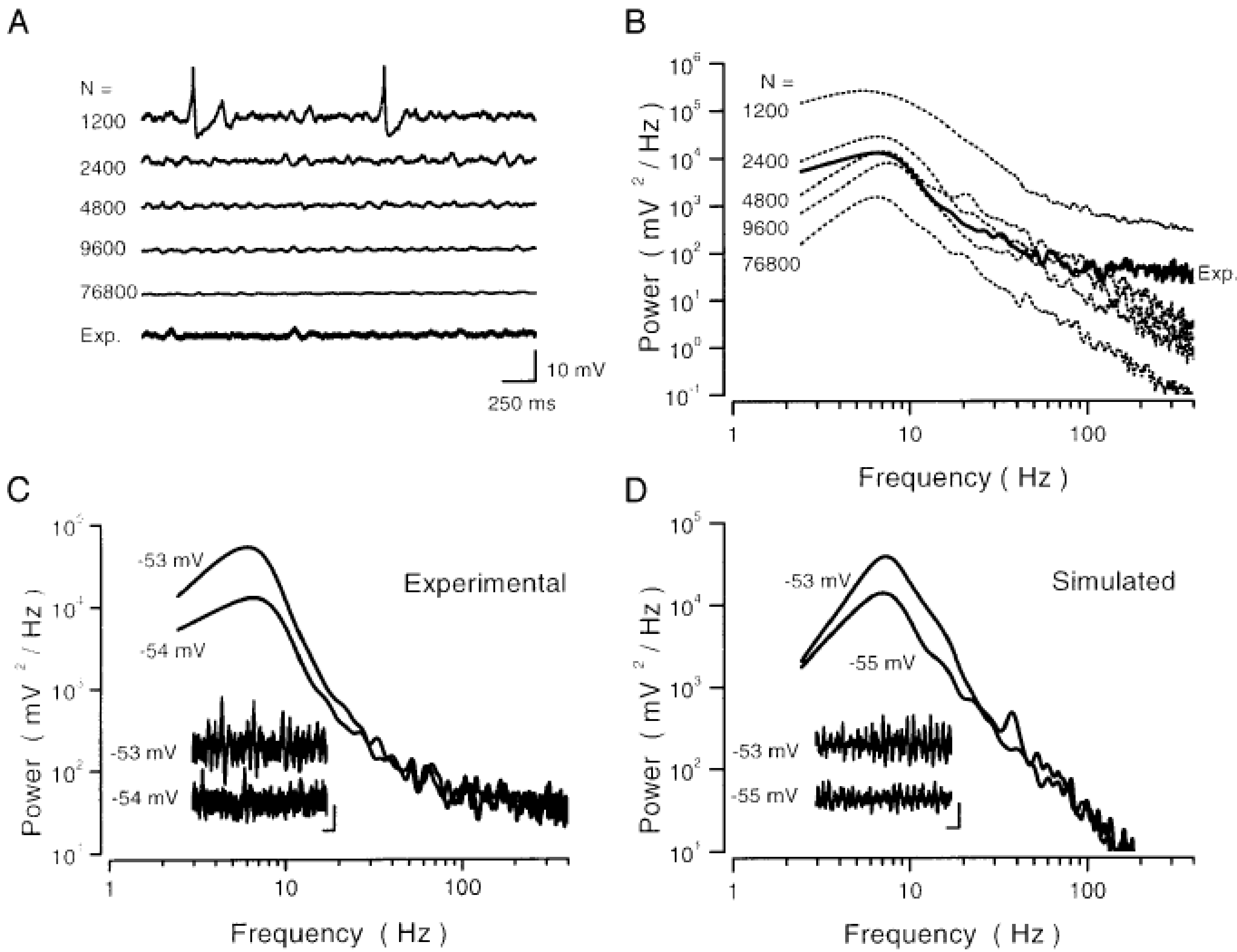


Lecar, H and Nossal, R. (1971) Theory of threshold fluctuations in nerves. *Biophys J.* **11**,1048-1067.

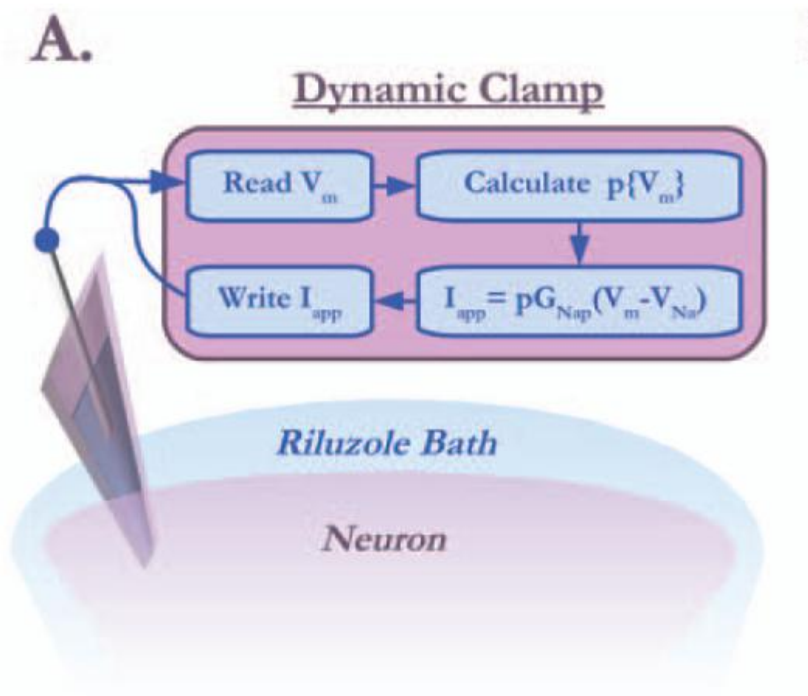
Better stimulus/response relationship

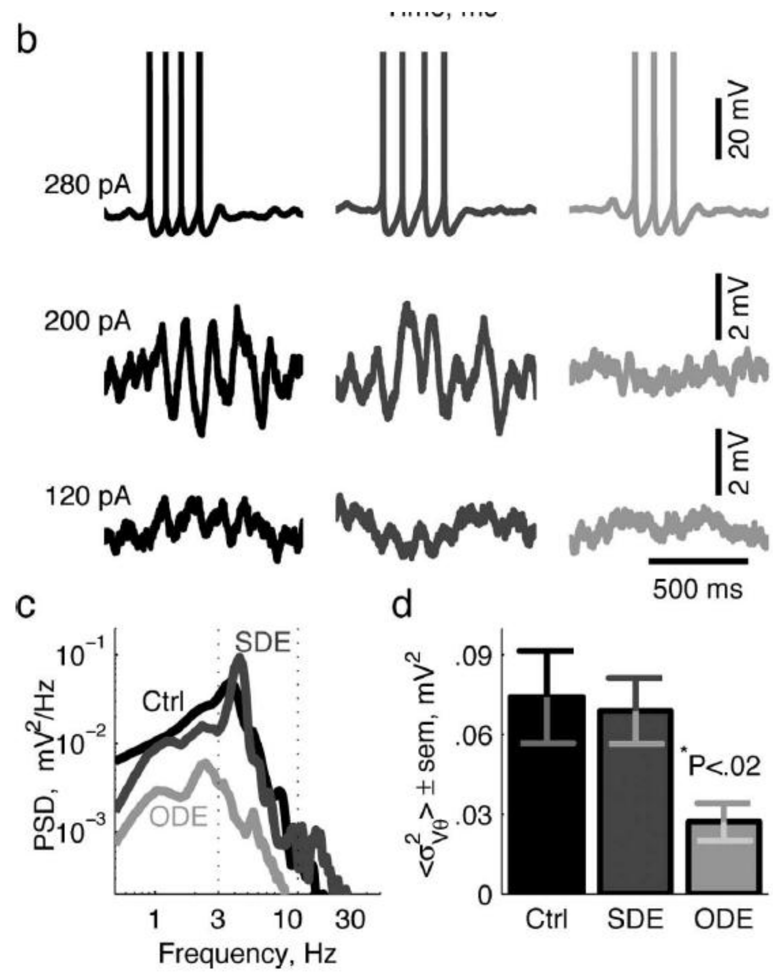


Dynamic properties induced by noise

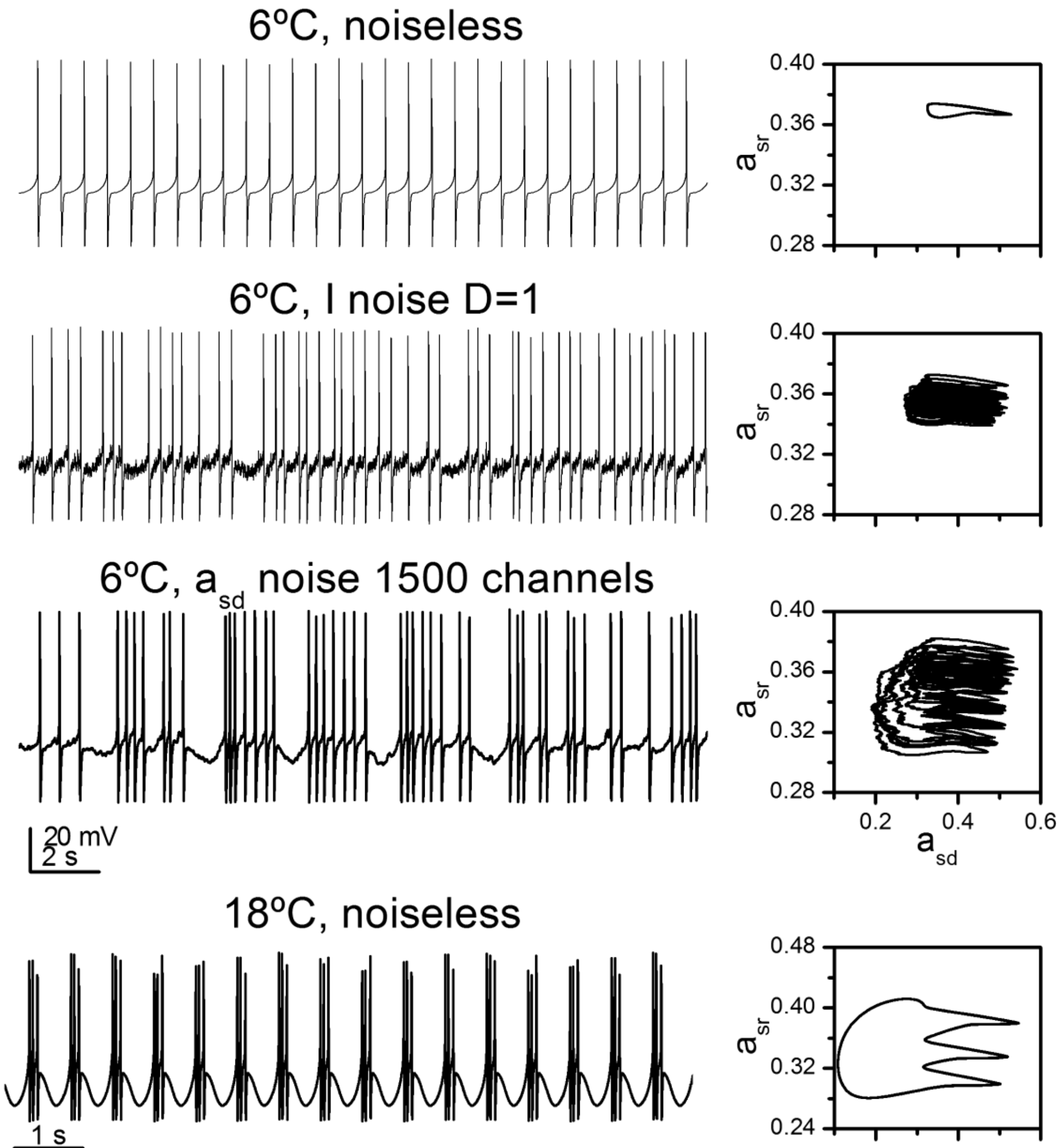


White J.A, Klink R., Alonso A. & Kay A.R. (1998) Noise From Voltage-Gated Ion Channels May Influence Neuronal Dynamics in the Entorhinal Cortex. *J Neurophysiol* **80**:262-269





Dorval, A.D. & White, J.A. (2005) Channel Noise is Essential for Perithreshold Oscillations in Entorhinal Stellate Neurons. *J Neurosci* **25**:10025-10028



6ºC, noiseless
6ºC, I noise D=1
6ºC, a sd noise 1500 channels
20 mV
2 s
18ºC, noiseless
1 s
0.40
0.36
0.32
0.28
0.48
0.24
a_{sr}
a_{sd}
0.2
0.4
0.6

Summary

- The electrical activity of neurons arise from ion channel function and their voltage-dependency.
- Opening and closing of ion channels is stochastic.
- Channel noise introduces new dynamics into the function of the CNS.

DO’S AND DON’TS OF MODELING STOCHASTIC ION CHANNELS

Making a Stochastic H&H

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$dn/dt = \alpha_n (1 - n) - \beta_n n,$$

$$dm/dt = \alpha_m (1 - m) - \beta_m m,$$

$$dh/dt = \alpha_h (1 - h) - \beta_h h,$$

$$\alpha_n = 0{\cdot}01\ (V + 10) \Big/ \left(\exp \frac{V + 10}{10} - 1 \right),$$

$$\beta_n = 0{\cdot}125\ \exp\ (V/80),$$

$$\alpha_m = 0{\cdot}1\ (V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1 \right),$$

$$\beta_m = 4\ \exp\ (V/18),$$

$$\alpha_h = 0{\cdot}07\ \exp\ (V/20),$$

$$\beta_h = 1 \Big/ \left(\exp \frac{V + 30}{10} + 1 \right).$$

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$$I = C_M \frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

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

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

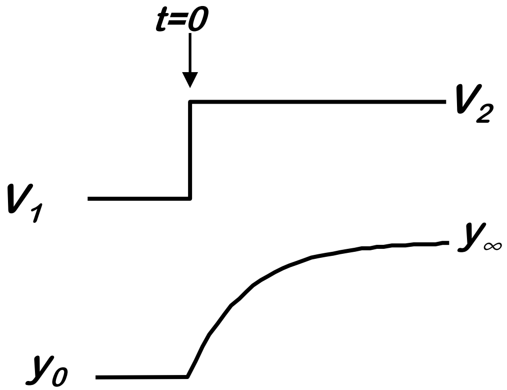
$$\alpha_i, \beta_i = f(V)$$

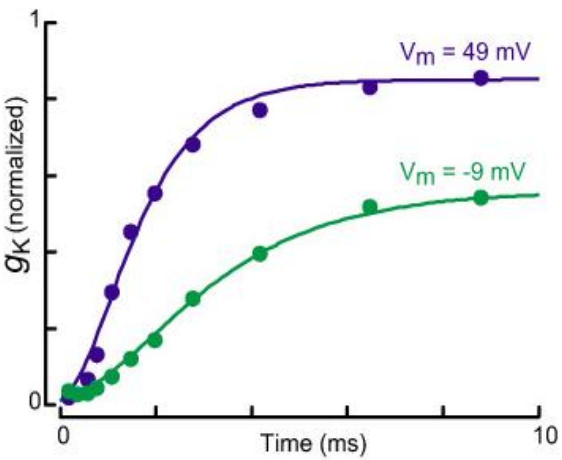
$$(i = m, n, h)$$

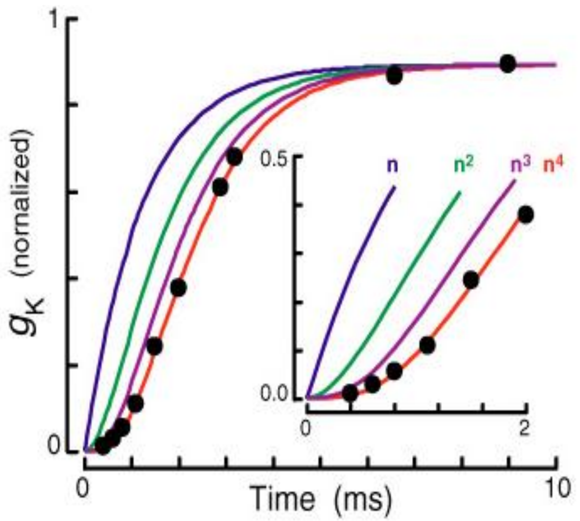
First-order kinetic model

$$\frac{dy}{dt} = \alpha_y(1-y) - \beta_y y \qquad y_\infty(V_m) = \frac{\alpha_y}{\alpha_y + \beta_y}$$

$$y(t) = y_\infty - (y_\infty - y_0)e^{-t/\tau_y} \qquad \tau_y = \frac{1}{\alpha_y + \beta_y}$$







Making a Stochastic H&H – Markov Chains

$$I = C_M \frac{\mathrm{d}V}{\mathrm{d}t} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$N_{Na} \qquad h_0 \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} h_1$$

$$3N_{Na} \qquad m_0 \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m_1$$

$$4N_K \qquad n_0 \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n_1$$

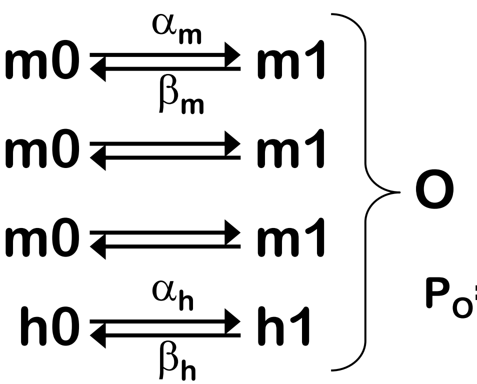
$$\alpha_i, \beta_i = f(V)$$

$$(i = m, n, h)$$

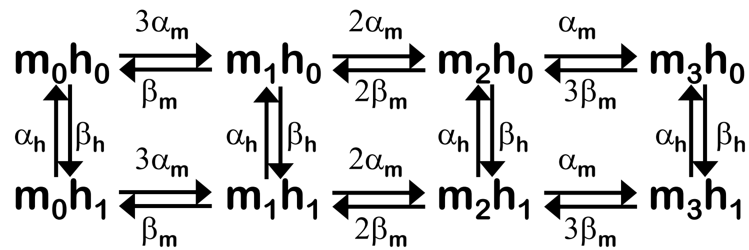
- The conductance is proportional to a probability raised to the fourth (or third) power.
- A simple interpretation is that in order to observe an increase in conductance, four (or three) i.i.d. events have to occur at the same time.

- 30 years afters, it was known that voltage-depenendent ion channels have 4 voltage sensors.

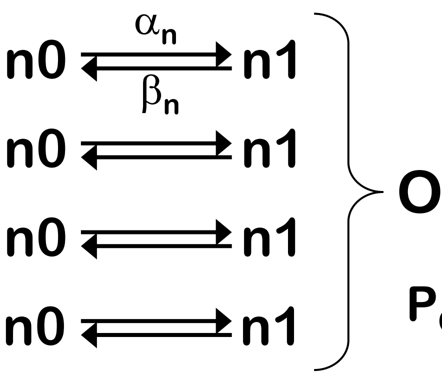
Making a Stochastic H&H –
Markov Chains II



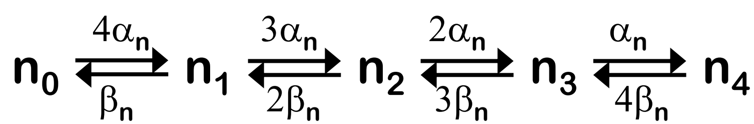
$P_O = P_{m1}^3 \times P_{h1}$



$P_O = P_{m3h1}$



$P_O = P_{n1}^4$



$P_O = P_{n4}$

Making a Stochastic H&H
Diffusion Approximation

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

N_{Na} $\quad h_0 \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} h_1$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h + \xi_h(t) \sqrt{\frac{\alpha_h (1-h) + \beta_h h}{N_{Na}}}$$

$3N_{Na}$ $\quad m_0 \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m_1$

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m + \xi_m(t) \sqrt{\frac{\alpha_m (1-m) + \beta_m m}{3N_{Na}}}$$

$4N_K$ $\quad n_0 \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n_1$

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n + \xi_n(t) \sqrt{\frac{\alpha_n (1-n) + \beta_n n}{4N_K}}$$

Deterministic

Random

Gaussian process
Zero mean
Unit variance

Standard deviation of the process

$$\alpha_i, \beta_i = f(V)$$
$$(i = m, n, h)$$

Fox and Lu, 1994; Fox 1997

How ‘approximate’ is the Diffusion Approximation?

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Comparison of Algorithms for the Simulation of Action Potentials with Stochastic Sodium Channels

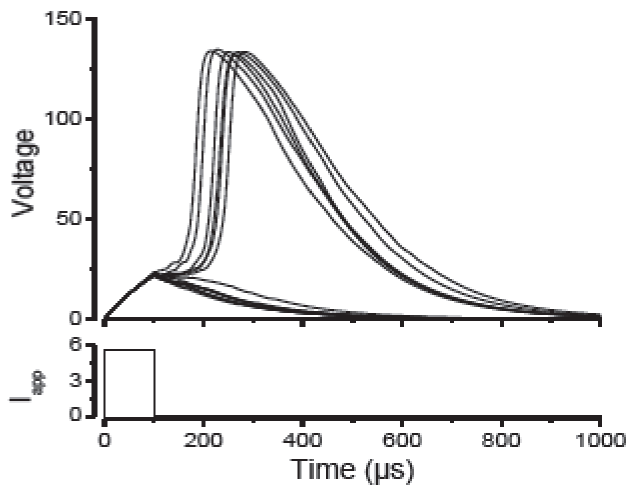
HIROYUKI MINO,[1] JAY T. RUBINSTEIN,[1,2] and JOHN A. WHITE[3]

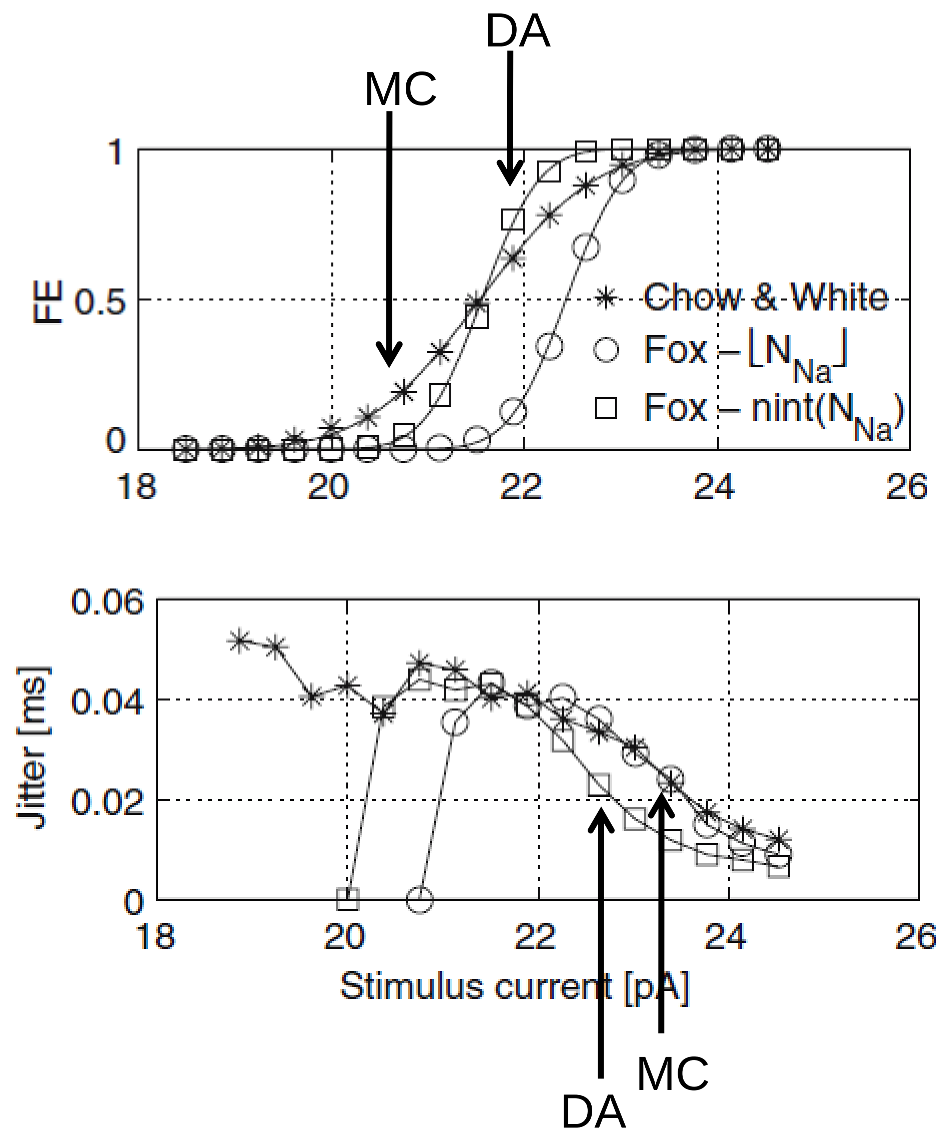
Annals of Biomedical Engineering, Vol. 35, No. 2, February 2007 (© 2006) pp. 315–318

Implementation Issues in Approximate Methods for Stochastic Hodgkin–Huxley Models

Ian C. Bruce

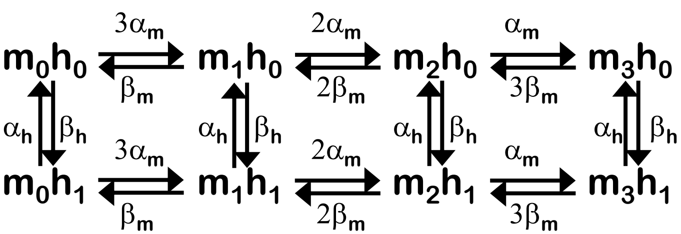
Mammalian Ranvier node model





Is it a fair comparison?

Markov Chain (MC) modeling



Particles are independent but 'packed' in groups of four

Correct DA?

Diffusion Approximation (DA)

$$I = C_M \frac{dV}{dt} + \bar{g}_K n^4 (V - V_K) + \bar{g}_{Na} m^3 h (V - V_{Na}) + \bar{g}_l (V - V_l),$$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h + \xi_h(t) \sqrt{\frac{\alpha_h (1-h) + \beta_h h}{N_{Na}}}$$

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_m m + \xi_m(t) \sqrt{\frac{\alpha_m (1-m) + \beta_m m}{3N_{Na}}}$$

Particles are independent and uncoupled

$$N_{Na} \qquad h_0 \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} h_1$$

$$3N_{Na} \qquad m_0 \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m_1$$

DA for a multi-state MC

$$\frac{d}{dt}y_{pr} = R_{pr}(\vec{y}) + S_{pr\,qs}\tilde{g}_{qs}(t),$$

The matrix $S_{pr\,qs}$ satisfies

$$(S^2)_{pr\,qs} = D_{pr\,qs},$$

$$\begin{aligned}
D_{pr\,qs}(\vec{y}) = \frac{1}{2N_{Na}A}&[\delta_{pq}\delta_{rs}\{(p\beta_m + (3-p)\alpha_m)y_{pr} \\
&+ (p+1)\beta_m y_{p+1\,r}(1-\delta_{p3}) \\
&+ (3-(p-1))\alpha_m y_{p-1\,r}(1-\delta_{p0}) \\
&+ (r\beta_h + (1-r)\alpha_h)y_{pr} + (r+1)\beta_h y_{p\,r+1} \\
&\cdot(1-\delta_{r1}) + (1-(r-1))\alpha_h y_{p\,r-1}(1-\delta_{r0})\} \\
&- \delta_{rs}\{p\beta_m\delta_{q\,p-1}(1-\delta_{q3})y_{pr} + (3-p)\alpha_m\delta_{q\,p+1} \\
&\cdot(1-\delta_{q0})y_{pr} + q\beta_m\delta_{p\,q-1}(1-\delta_{p3})y_{qs} \\
&+ (3-q)\alpha_m\delta_{p\,q+1}(1-\delta_{p0})y_{qs}\} \\
&- \delta_{pq}\{r\beta_h\delta_{s\,r-1}(1-\delta_{s1})y_{pr} \\
&+ (1-r)\alpha_h\delta_{s\,r+1}(1-\delta_{s0})y_{pr} + s\beta_h\delta_{r\,s-1} \\
&\cdot(1-\delta_{r1})y_{qs} + (1-s)\alpha_h\delta_{r\,s+1}(1-\delta_{r0})y_{qs}\}].
\end{aligned}$$

The complete Langevin treatment given above requires that at each time step the square root matrices, S, must be computed for both the potassium and the sodium terms.

computation. Recently we have shown that a faster approximate implementation is possible in which one numerically solves the simultaneous system of equations, Eqs. 1–8, but in which Eqs. 3–5 are made stochastic directly. They take the form

$$\frac{d}{dt}n = \alpha_n(1-n) - \beta_n n + \tilde{g}_n(t) \quad (30)$$

$$\frac{d}{dt}h = \alpha_h(1-h) - \beta_h h + \tilde{g}_h(t) \quad (31)$$

$$\frac{d}{dt}m = \alpha_m(1-m) - \beta_m m + \tilde{g}_m(t), \quad (32)$$

Fox and Lu, 1994; Fox 1997

Potassium channel

$$n_0 \underset{\beta_n}{\overset{4\alpha_n}{\rightleftharpoons}} n_1 \underset{2\beta_n}{\overset{3\alpha_n}{\rightleftharpoons}} n_2 \underset{3\beta_n}{\overset{2\alpha_n}{\rightleftharpoons}} n_3 \underset{4\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n_4$$

$$\mathbf{x} = \begin{bmatrix} x_0 & x_1 & x_2 & x_3 & x_4 \end{bmatrix}^T$$

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x} + S\xi \,,$$

$$A_K = \begin{bmatrix} -4\alpha_n & \beta_n & 0 & 0 & 0 \\ 4\alpha_n & -3\alpha_n - \beta_n & 2\beta_n & 0 & 0 \\ 0 & 3\alpha_n & -2\alpha_n - 2\beta_n & 3\beta_n & 0 \\ 0 & 0 & 2\alpha_n & -\alpha_n - 3\beta_n & 4\beta_n \\ 0 & 0 & 0 & \alpha_n & -4\beta_n \end{bmatrix}$$

$$SS^T = D$$

$$D_K = \frac{1}{N_K} \begin{bmatrix} 4\alpha n_0 + \beta n_1 & -4\alpha n_0 - \beta n_1 & 0 & 0 & 0 \\ -4\alpha n_0 - \beta n_1 & 4\alpha n_0 + \beta n_1 + 3\alpha n_1 + 2\beta n_2 & -3\alpha n_1 - 2\beta n_2 & 0 & 0 \\ 0 & -3\alpha n_1 - 2\beta n_2 & 3\alpha n_1 + 2\beta n_2 + 2\alpha n_2 + 3\beta n_3 & -2\alpha n_2 - 3\beta n_3 & 0 \\ 0 & 0 & -2\alpha n_2 - 3\beta n_3 & 2\alpha n_2 + 3\beta n_3 + \alpha n_3 + 4\beta n_4 & -\alpha n_3 - 4\beta n_4 \\ 0 & 0 & 0 & -\alpha n_3 - 4\beta n_4 & \alpha n_3 + 4\beta n_4 \end{bmatrix}$$

using Cholesky decomposition,

$$S_K = \frac{1}{\sqrt{N_K}} \begin{bmatrix} \sqrt{4an_0 + bn_1} & 0 & 0 & 0 & 0 \\ \sqrt{4an_0 + bn_1} & \sqrt{3an_1 + 2bn_2} & 0 & 0 & 0 \\ 0 & -\sqrt{3an_1 + 2bn_2} & \sqrt{2an_2 + 3bn_3} & 0 & 0 \\ 0 & 0 & -\sqrt{2an_2 + 3bn_3} & \sqrt{an_3 + 4bn_4} & 0 \\ 0 & 0 & 0 & -\sqrt{an_3 + 4bn_4} & 0 \end{bmatrix}$$

$$\frac{dn_0}{dt} = \left(-4a_n n_0 + b_n n_1\right) + x_1 \frac{1}{\sqrt{N_K}} \sqrt{4a_n n_0 + b_n n_1}$$

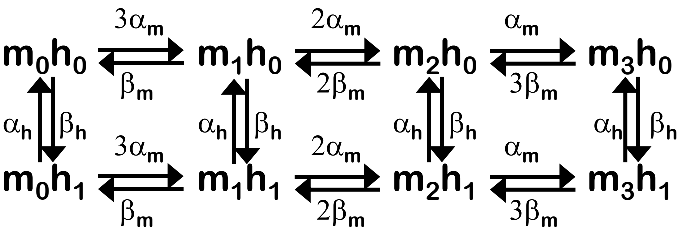
$$\frac{dn_1}{dt} = \left(4a_n n_0 - b_n n_1 - 3a_n n_1 + 2b_n n_2\right) - x_1 \frac{1}{\sqrt{N_K}} \sqrt{4a_n n_0 + b_n n_1} + x_2 \frac{1}{\sqrt{N_K}} \sqrt{3a_n n_1 + 2b_n n_2}$$

$$\frac{dn_2}{dt} = \left(3a_n n_1 - 2b_n n_2 - 2a_n n_2 + 3b_n n_3\right) - x_2 \frac{1}{\sqrt{N_K}} \sqrt{3a_n n_1 + 2b_n n_2} + x_3 \frac{1}{\sqrt{N_K}} \sqrt{2a_n n_2 + 3b_n n_3}$$

$$\frac{dn_3}{dt} = \left(2a_n n_2 - 3b_n n_3 - a_n n_3 + 4b_n n_4\right) - x_3 \frac{1}{\sqrt{N_K}} \sqrt{2a_n n_2 + 3b_n n_3} + x_4 \frac{1}{\sqrt{N_K}} \sqrt{a_n n_3 + 4b_n n_4}$$

$$\frac{dn_4}{dt} = \left(a_n n_3 - 4b_n n_4\right) - x_4 \frac{1}{\sqrt{N_K}} \sqrt{a_n n_3 + 4b_n n_4}$$

Sodium channel?



$$D_{\mathrm{Na}} = \frac{1}{N_{\mathrm{Na}}} \begin{bmatrix} d_1 & -2(\alpha_m \bar{y}_{10} + \beta_m \bar{y}_{20}) & 0 & 0 & -(\alpha_h \bar{y}_{10} + \beta_h \bar{y}_{11}) & 0 & 0 \\ -2(\alpha_m \bar{y}_{10} + \beta_m \bar{y}_{20}) & d_2 & -(\alpha_m \bar{y}_{20} + 3\beta_m \bar{y}_{30}) & 0 & 0 & -(\alpha_h \bar{y}_{20} + \beta_h \bar{y}_{21}) & 0 \\ 0 & -(\alpha_m \bar{y}_{20} + 3\beta_m \bar{y}_{30}) & d_3 & 0 & 0 & 0 & -(\alpha_h \bar{y}_{30} + \beta_h \bar{y}_{31}) \\ 0 & 0 & 0 & d_4 & -(3\alpha_m \bar{y}_{01} + \beta_m \bar{y}_{11}) & 0 & 0 \\ -(\alpha_h \bar{y}_{10} + \beta_h \bar{y}_{11}) & 0 & 0 & -(3\alpha_m \bar{y}_{01} + \beta_m \bar{y}_{11}) & d_5 & -2(\alpha_m \bar{y}_{11} + \beta_m \bar{y}_{21}) & 0 \\ 0 & -(\alpha_h \bar{y}_{20} + \beta_h \bar{y}_{21}) & 0 & 0 & -2(\alpha_m \bar{y}_{11} + \beta_m \bar{y}_{21}) & d_6 & -(\alpha_m \bar{y}_{21} + 3\beta_m \bar{y}_{31}) \\ 0 & 0 & -(\alpha_h \bar{y}_{30} + \beta_h \bar{y}_{31}) & 0 & 0 & -(\alpha_m \bar{y}_{21} + 3\beta_m \bar{y}_{31}) & d_7 \end{bmatrix}$$

$$\begin{aligned}
d_1 &= 3\alpha_m \bar{y}_{00} + (2\alpha_m + \beta_m + \alpha_h)\bar{y}_{10} + 2\beta_m \bar{y}_{20} + \beta_h \bar{y}_{11}, \\
d_2 &= 2\alpha_m \bar{y}_{10} + (\alpha_m + 2\beta_m + \alpha_h)\bar{y}_{20} + 3\beta_m \bar{y}_{30} + \beta_h \bar{y}_{21}, \\
d_3 &= \alpha_m \bar{y}_{20} + (3\beta_m + \alpha_h)\bar{y}_{30} + \beta_h \bar{y}_{31}, \\
d_4 &= \alpha_h \bar{y}_{00} + (3\alpha_m + \beta_h)\bar{y}_{01} + \beta_m \bar{y}_{11}, \\
d_5 &= \alpha_h \bar{y}_{10} + 3\alpha_m \bar{y}_{01} + (2\alpha_m + \beta_m + \beta_h)\bar{y}_{11} + 2\beta_m \bar{y}_{21}, \\
d_6 &= \alpha_h \bar{y}_{20} + 2\alpha_m \bar{y}_{11} + (\alpha_m + 2\beta_m + \beta_h)\bar{y}_{21} + 3\beta_m \bar{y}_{31}, \\
d_7 &= \alpha_h \bar{y}_{30} + \alpha_m \bar{y}_{21} + (3\beta_m + \beta_h)\bar{y}_{31}.
\end{aligned}$$

An alternative approach

Denote $X_i = Nx_i$, the number of channels in state i, and $\mathbf{X}$ to be the corresponding vector.

Assume that $\mathbf{X}\left(t\right)$ is known, and we wish to calculate $\mathbf{X}\left(t+dt\right)$.

For all $i \neq j$, we define the channel transition step

$$\Delta_{ij}(t) = \left\{ \begin{array}{l} \text{the number of channels switching} \\ \text{from state } j \text{ to state } i \text{ during } \left(t, t+dt\right) \end{array} \right\}.$$

$\Delta_{ij}(t)$ is a Random Variable (RV) composed of the sum of $n = X_j(t)$ independent events ("trials"), in which a channel either switched states, with probability of $p = A_{ij}dt$, or did not switch states, with probability $1 - A_{ij}dt$ (to first order in dt).

This entails that for all $i \neq j$, $\Delta_{ij}(t)$ are independent and binomially distributed with $n = X_j(t)$ and $p = A_{ij}dt$.

We use the properties of the binomial distribution and find the mean

$$\left\langle \mathrm{D}_{ij}(t) \right\rangle = np = X_j(t) A_{ij} dt \ , \tag{1}$$

And the variance

$$\mathrm{Var}\left(\mathrm{D}_{ij}(t)\right) = np\left(1-p\right) = X_j(t) A_{ij} dt \left(1 - A_{ij} dt\right) \ . \tag{2}$$

Since $\mathrm{D}_{ij}(t)$ are independent

$$\mathrm{Cov}\left(\mathrm{D}_{ij}(t), \mathrm{D}_{mk}(t)\right) = d_{im} d_{jk} \mathrm{Var}\left(\mathrm{D}_{ij}(t)\right) \ , \tag{3}$$

where $d_{ab} = 1$ if $a = b$, and 0 otherwise.

In the limit N ® ¥ $, dt$ ® 0:

n ® ¥ and p ® 0 for the binomial distribution of each $\mathrm{D}_{ij}(t)$.

This allows us to approximate $\mathrm{D}_{ij}(t)$ by a normal distribution with both mean and variance equal to $np = X_j A_{ij} dt$ (by the central limit theorem).

At each dt , X_i changes according to the sum of channels entering and leaving state i

$$dX_i\left(t\right) = X_i\left(t+dt\right) - X_i\left(t\right) = \sum_j \left(\mathrm{D}_{ij}\left(t\right) - \mathrm{D}_{ji}\left(t\right)\right) \quad . \tag{4}$$

Assuming $\mathrm{D}_{ij}(t)$ are all normal, then $d\mathbf{X}\left(t\right)$ (the of vector of $dX_i\left(t\right)$) is also normal, as a linear combination of independent normal RVs. Since the distribution of normal variables is entirely determined by their mean and covariance, we calculate them.

We use eq. (1) to find the mean of eq. (4)

$$\boldsymbol{m}_{d\mathbf{X}}\left(i\right) = \left\langle dX_i\left(t\right)\right\rangle = \sum_j \left(A_{ij}X_j(t) - A_{ji}X_i(t)\right)dt \quad .$$

Next, using eq. (3) we find the covariance

$$\begin{aligned}
&\mathrm{R}_{d\mathbf{X}}\left(i,j\right)=\mathrm{Cov}\left(dX_i\left(t\right),dX_j\left(t\right)\right)\\
&=\mathrm{Cov}\left(\sum_k\left(\mathrm{D}_{ik}(t)-\mathrm{D}_{ki}(t)\right),\sum_m\left(\mathrm{D}_{jm}(t)-\mathrm{D}_{mj}(t)\right)\right)\\
&=\mathrm{Cov}\left(\sum_k\mathrm{D}_{ik}(t),\sum_m\mathrm{D}_{jm}(t)\right)+\mathrm{Cov}\left(\sum_k\mathrm{D}_{ki}(t),\sum_m\mathrm{D}_{mj}(t)\right)\\
&-\mathrm{Cov}\left(\sum_k\mathrm{D}_{ik}(t),\sum_m\mathrm{D}_{mj}(t)\right)-\mathrm{Cov}\left(\sum_k\mathrm{D}_{ki}(t),\sum_m\mathrm{D}_{jm}(t)\right)\\
&=d_{ij}\sum_k\left(\mathrm{Cov}\left(\mathrm{D}_{ik}(t),\mathrm{D}_{ik}(t)\right)+\mathrm{Cov}\left(\mathrm{D}_{ki}(t),\mathrm{D}_{ki}(t)\right)\right)\\
&-\mathrm{Cov}\left(\mathrm{D}_{ji}(t),\mathrm{D}_{ji}(t)\right)-\mathrm{Cov}\left(\mathrm{D}_{ij}(t),\mathrm{D}_{ij}(t)\right)\\
&=d_{ij}\sum_k\left(\mathrm{Var}\left(\mathrm{D}_{ik}(t)\right)+\mathrm{Var}\left(\mathrm{D}_{ki}(t)\right)\right)-\mathrm{Var}\left(\mathrm{D}_{ji}(t)\right)-\mathrm{Var}\left(\mathrm{D}_{ij}(t)\right)
\end{aligned}$$

Using eq. (2), neglecting dt^2 terms and dividing by dt we obtain

$$\frac{1}{dt}\mathrm{R}_{d\mathbf{X}}\left(i,j\right)=\begin{cases}\sum_{k\neq i}\left(A_{ik}X_k(t)+A_{ki}X_i\left(t\right)\right), \text{if } i=j\\ -A_{ji}X_i(t)-A_{ij}X_j(t) \qquad ,\text{if } i\neq j\end{cases}. \tag{5}$$

Since we now know the mean of $d\mathbf{X}\left(t\right)$ and the covariance between all of its components, we can write

$$d\mathbf{X} = m_{d\mathbf{X}} + \sqrt{\mathrm{R}_{d\mathbf{X}}}\,\mathbf{Z},$$

where $\mathbf{Z}$ is a vector of independent Gaussian RVs with mean zero and unit variance.
To derive an SDE for $\mathbf{x} = \mathbf{X} / N$ we divide by N and take the limit of dt ® 0, yielding

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x} + S\boldsymbol{x} ,$$

with $S = \sqrt{D}$, where

$$D_{ij} = \frac{1}{N^2 dt}\mathrm{R}_{d\mathbf{X}}\left(i,j\right) = \frac{1}{N}\begin{cases} \sum_{k\neq i}\left(A_{ik}x_k(t) + A_{ki}x_i\left(t\right)\right), \text{if } i = j \\ -A_{ji}x_i(t) - A_{ij}x_j(t) \qquad , \text{if } i \neq j \end{cases} .$$

A simple example

$$1 \underset{A_{12}}{\overset{A_{21}}{\rightleftarrows}} 2 \underset{A_{32}}{\overset{A_{23}}{\rightleftarrows}} 3$$

we write

$$dX_1 = D_{12} - D_{21}$$
$$dX_2 = D_{21} - D_{12} + D_{23} - D_{32}$$
$$dX_3 = D_{32} - D_{23}$$

We can calculate the means, using $\langle D_{ij}(t) \rangle = X_j(t) A_{ij} dt$

$$\langle dX_1 \rangle = X_2 A_{12} dt - X_1 A_{21} dt$$
$$\langle dX_2 \rangle = - X_2 A_{12} dt + X_1 A_{21} dt - X_2 A_{32} dt + X_3 A_{23} dt \quad .$$
$$\langle dX_3 \rangle = X_2 A_{32} dt - X_3 A_{23} dt$$

$$1 \underset{A_{12}}{\overset{A_{21}}{\rightleftarrows}} 2 \underset{A_{32}}{\overset{A_{23}}{\rightleftarrows}} 3$$

Denoting $W_{ij} = \mathrm{D}_{ij} - \mathrm{D}_{ji}$ we notice that D_{ij} can be combined in opposing pairs

$$\begin{aligned} dX_1 &= W_{12} \\ dX_2 &= -W_{12} + W_{23} \\ dX_3 &= -W_{23} \end{aligned}$$

Denoting $Y_{ij}(t) = W_{ij}(t) - \langle W_{ij}(t) \rangle$, we obtain

$$\begin{aligned} dX_1 &= \langle dX_1 \rangle + Y_{12} \\ dX_2 &= \langle dX_2 \rangle - Y_{12} + Y_{23}\,, \\ dX_3 &= \langle dX_3 \rangle - Y_{23} \end{aligned}$$

where Y_{12}, Y_{23} are normal, independent, with zero mean and

$$\begin{aligned} \mathrm{Var}(Y_{12}) &= \mathrm{Var}(\mathrm{D}_{12}) + \mathrm{Var}(\mathrm{D}_{21}) = X_2 A_{12} dt + X_1 A_{21} dt \\ \mathrm{Var}(Y_{23}) &= \mathrm{Var}(\mathrm{D}_{23}) + \mathrm{Var}(\mathrm{D}_{32}) = X_3 A_{23} dt + X_2 A_{32} dt \end{aligned}$$

Now we can write

$$
\begin{aligned}
dX_1 &= X_2A_{12}dt - X_1A_{21}dt + Z_1\sqrt{X_2A_{12}dt + X_1A_{21}dt} \\
dX_2 &= -X_2A_{12}dt + X_1A_{21}dt - X_2A_{32}dt + X_3A_{23}dt \\
&\quad - Z_1\sqrt{X_2A_{12}dt + X_1A_{21}dt} + Z_2\sqrt{X_2A_{32}dt + X_3A_{23}dt} \\
dX_3 &= X_2A_{32}dt - X_3A_{23}dt - Z_2\sqrt{X_2A_{32}dt + X_3A_{23}dt}
\end{aligned}
$$

with Z_1, Z_2 are normal, independent, with zero mean and unit variance.

Dividing by N and taking the limit dt ® 0, we finally obtain the SDE

$$
\begin{aligned}
\frac{dx_1}{dt} &= x_2A_{12} - x_1A_{21} + \frac{1}{\sqrt{N}}x_1\sqrt{x_2A_{12} + x_1A_{21}} \\
\frac{dx_2}{dt} &= -x_2A_{12} + x_1A_{21} - x_2A_{32} + x_3A_{23} - \frac{1}{\sqrt{N}}x_1\sqrt{x_2A_{12} + x_1A_{21}} + \frac{1}{\sqrt{N}}x_2\sqrt{x_2A_{32} + x_3A_{23}} \\
\frac{dx_3}{dt} &= x_2A_{32} - x_3A_{23} - \frac{1}{\sqrt{N}}x_2\sqrt{x_2A_{32} + x_3A_{23}}
\end{aligned}
$$

$$1 \underset{A_{12}}{\overset{A_{21}}{\rightleftarrows}} 2 \underset{A_{32}}{\overset{A_{23}}{\rightleftarrows}} 3$$

$$dx_1 = \left(x_2 A_{12} - x_1 A_{21}\right)dt + \frac{1}{\sqrt{N}}\sqrt{x_2 A_{12} + x_1 A_{21}}\,dW_1$$

$$dx_2 = \left(- x_2 A_{12} + x_1 A_{21} - x_2 A_{32} + x_3 A_{23}\right)dt - \frac{1}{\sqrt{N}}\sqrt{x_2 A_{12} + x_1 A_{21}}\,dW_1 + \frac{1}{\sqrt{N}}\sqrt{x_2 A_{32} + x_3 A_{23}}\,dW_2$$

$$dx_3 = \left(x_2 A_{32} - x_3 A_{23}\right)dt - \frac{1}{\sqrt{N}}\sqrt{x_2 A_{32} + x_3 A_{23}}\,dW_2$$

each component of dW_n :

- is associated with a transition pair $i \; f \; j$
- multiplied by $\sqrt{\left(A_{ij} x_j + A_{ji} x_i\right) / N}$
- appears in the equations of dx_i and dx_j with opposite signs.

The variances in the SDE are ‘transition-centric’ and not ‘state-centric’

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The chemical Langevin equation

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Equation (22) thus implies the equivalent "white-noise form" Langevin equation

$$\frac{dX_i(t)}{dt} = \sum_{j=1}^{M} \nu_{ji} a_j(\mathbf{X}(t)) + \sum_{j=1}^{M} \nu_{ji} a_j^{1/2}(\mathbf{X}(t)) \Gamma_j(t)$$

$$(i = 1, \ldots, N), \qquad (23)$$

where the $\Gamma_j(t)$ are temporally uncorrelated, statistically independent Gaussian white noises.

Sum over the ji transitions

Potassium channel (again)

$$\mathbf{n_0} \underset{\beta_n}{\overset{4\alpha_n}{\rightleftarrows}} \mathbf{n_1} \underset{2\beta_n}{\overset{3\alpha_n}{\rightleftarrows}} \mathbf{n_2} \underset{3\beta_n}{\overset{2\alpha_n}{\rightleftarrows}} \mathbf{n_3} \underset{4\beta_n}{\overset{\alpha_n}{\rightleftarrows}} \mathbf{n_4}$$

$$\frac{dn_0}{dt} = \left(- 4a_n n_0 + b_n n_1\right) + x_1 \frac{1}{\sqrt{N_K}} \sqrt{4a_n n_0 + b_n n_1}$$

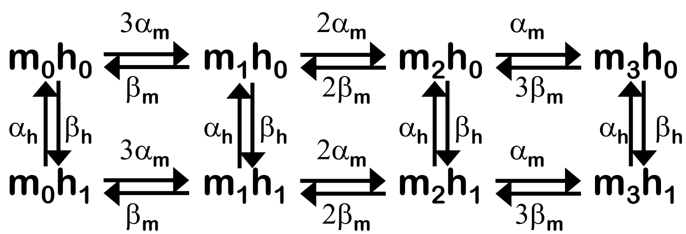
$$\frac{dn_1}{dt} = \left(4a_n n_0 - b_n n_1 - 3a_n n_1 + 2b_n n_2\right) - x_1 \frac{1}{\sqrt{N_K}} \sqrt{4a_n n_0 + b_n n_1} + x_2 \frac{1}{\sqrt{N_K}} \sqrt{3a_n n_1 + 2b_n n_2}$$

$$\frac{dn_2}{dt} = \left(3a_n n_1 - 2b_n n_2 - 2a_n n_2 + 3b_n n_3\right) - x_2 \frac{1}{\sqrt{N_K}} \sqrt{3a_n n_1 + 2b_n n_2} + x_3 \frac{1}{\sqrt{N_K}} \sqrt{2a_n n_2 + 3b_n n_3}$$

$$\frac{dn_3}{dt} = \left(2a_n n_2 - 3b_n n_3 - a_n n_3 + 4b_n n_4\right) - x_3 \frac{1}{\sqrt{N_K}} \sqrt{2a_n n_2 + 3b_n n_3} + x_4 \frac{1}{\sqrt{N_K}} \sqrt{a_n n_3 + 4b_n n_4}$$

$$\frac{dn_4}{dt} = \left(a_n n_3 - 4b_n n_4\right) - x_4 \frac{1}{\sqrt{N_K}} \sqrt{a_n n_3 + 4b_n n_4}$$

DA for a 8-state MC (Na channel)



$$\frac{dm_0h_0}{dt} = \left(-3\alpha_m m_0h_0 + \beta_m m_1h_0 - \alpha_h m_0h_0 + \beta_h m_0h_1\right) + \xi_1\sqrt{3\alpha_m m_0h_0 + \beta_m m_1h_0} + \xi_4\sqrt{\alpha_h m_0h_0 + \beta_h m_0h_1}$$

$$\frac{dm_1h_0}{dt} = \left(3\alpha_m m_0h_0 - \beta_m m_1h_0 - 2\alpha_m m_1h_0 + 2\beta_m m_2h_0 - \alpha_h m_1h_0 + \beta_h m_1h_1\right) - \xi_1\sqrt{3\alpha_m m_0h_0 + \beta_m m_1h_0} + \xi_2\sqrt{2\alpha_m m_1h_0 + 2\beta_m m_2h_0} + \xi_5\sqrt{\alpha_h m_1h_0 + \beta_h m_1h_1}$$

$$\frac{dm_2h_0}{dt} = \left(2\alpha_m m_1h_0 - 2\beta_m m_2h_0 - \alpha_m m_2h_0 + 3\beta_m m_3h_0 - \alpha_h m_2h_0 + \beta_h m_2h_1\right) - \xi_2\sqrt{2\alpha_m m_1h_0 + 2\beta_m m_2h_0} + \xi_3\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} + \xi_6\sqrt{\alpha_h m_2h_0 + \beta_h m_2h_1}$$

$$\frac{dm_3h_0}{dt} = \left(\alpha_m m_2h_0 - 3\beta_m m_3h_0 - \alpha_h m_3h_0 + \beta_h m_3h_1\right) - \xi_3\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} + \xi_7\sqrt{\alpha_h m_3h_0 + \beta_h m_3h_1}$$

$$\frac{dm_0h_1}{dt} = \left(-3\alpha_m m_0h_1 + \beta_m m_1h_1 + \alpha_h m_0h_0 - \beta_h m_0h_1\right) + \xi_8\sqrt{3\alpha_m m_0h_1 + \beta_m m_1h_1} - \xi_4\sqrt{\alpha_h m_0h_0 + \beta_h m_0h_1}$$

$$\frac{dm_1h_1}{dt} = \left(3\alpha_m m_0h_1 - \beta_m m_1h_1 - 2\alpha_m m_1h_1 + 2\beta_m m_2h_1 + \alpha_h m_1h_0 - \beta_h m_1h_1\right) - \xi_8\sqrt{3\alpha_m m_0h_1 + \beta_m m_1h_1} + \xi_9\sqrt{2\alpha_m m_1h_1 + 2\beta_m m_2h_1} - \xi_5\sqrt{\alpha_h m_1h_0 + \beta_h m_1h_1}$$

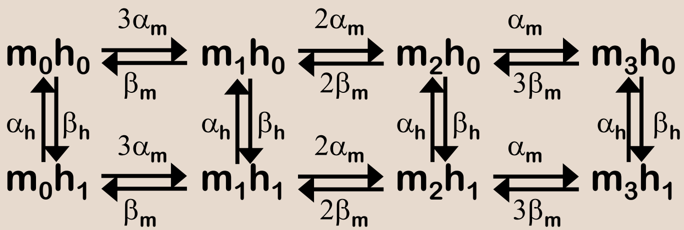
$$\frac{dm_2h_1}{dt} = \left(2\alpha_m m_1h_1 - 2\beta_m m_2h_1 - \alpha_m m_2h_1 + 3\beta_m m_3h_1 + \alpha_h m_2h_0 - \beta_h m_2h_1\right) - \xi_9\sqrt{2\alpha_m m_1h_1 + 2\beta_m m_2h_1} + \xi_{10}\sqrt{\alpha_m m_2h_1 + 3\beta_m m_3h_1} - \xi_6\sqrt{\alpha_h m_2h_0 + \beta_h m_2h_1}$$

$$\frac{dm_3h_1}{dt} = \left(\alpha_m m_2h_1 - 3\beta_m m_3h_1 + \alpha_h m_3h_0 - \beta_h m_3h_1\right) - \xi_{10}\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} - \xi_7\sqrt{\alpha_h m_3h_0 + \beta_h m_3h_1}$$

10 pairs of transitions → 10 stochastic terms

A fair comparison

Diffusion Approximation (DA)



$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h + \xi_h(t)\sqrt{\frac{\alpha_h(1-h)+\beta_h h}{N_{Na}}}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m + \xi_m(t)\sqrt{\frac{\alpha_m(1-m)+\beta_m m}{3N_{Na}}}$$

Coupled gating particles

Uncoupled gating particles

Markov Chain modeling (MC)

$$\frac{dm_0h_0}{dt} = \left(-3\alpha_m m_0h_0 + \beta_m m_1h_0 - \alpha_h m_0h_0 + \beta_h m_0h_1\right) + \xi_1\sqrt{3\alpha_m m_0h_0 + \beta_m m_1h_0} + \xi_4\sqrt{\alpha_h m_0h_0 + \beta_h m_0h_1}$$

$$\frac{dm_1h_0}{dt} = \left(3\alpha_m m_0h_0 - \beta_m m_1h_0 - 2\alpha_m m_1h_0 + 2\beta_m m_2h_0 - \alpha_h m_1h_0 + \beta_h m_1h_1\right) - \xi_1\sqrt{3\alpha_m m_0h_0 + \beta_m m_1h_0} + \xi_2\sqrt{2\alpha_m m_1h_0 + 2\beta_m m_2h_0} + \xi_5\sqrt{\alpha_h m_1h_0 + \beta_h m_1h_1}$$

$$\frac{dm_2h_0}{dt} = \left(2\alpha_m m_1h_0 - 2\beta_m m_2h_0 - \alpha_m m_2h_0 + 3\beta_m m_3h_0 - \alpha_h m_2h_0 + \beta_h m_2h_1\right) - \xi_2\sqrt{2\alpha_m m_1h_0 + 2\beta_m m_2h_0} + \xi_3\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} + \xi_6\sqrt{\alpha_h m_2h_0 + \beta_h m_2h_1}$$

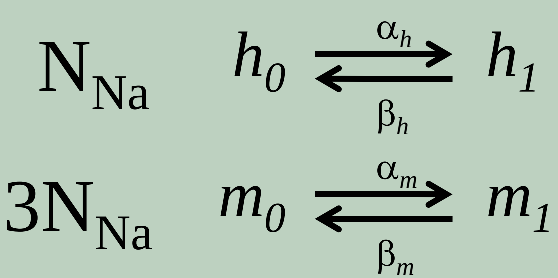
$$\frac{dm_3h_0}{dt} = \left(\alpha_m m_2h_0 - 3\beta_m m_3h_0 - \alpha_h m_3h_0 + \beta_h m_3h_1\right) - \xi_3\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} + \xi_7\sqrt{\alpha_h m_3h_0 + \beta_h m_3h_1}$$

$$\frac{dm_0h_1}{dt} = \left(-3\alpha_m m_0h_1 + \beta_m m_1h_1 + \alpha_h m_0h_0 - \beta_h m_0h_1\right) + \xi_8\sqrt{3\alpha_m m_0h_1 + \beta_m m_1h_1} - \xi_4\sqrt{\alpha_h m_0h_0 + \beta_h m_0h_1}$$

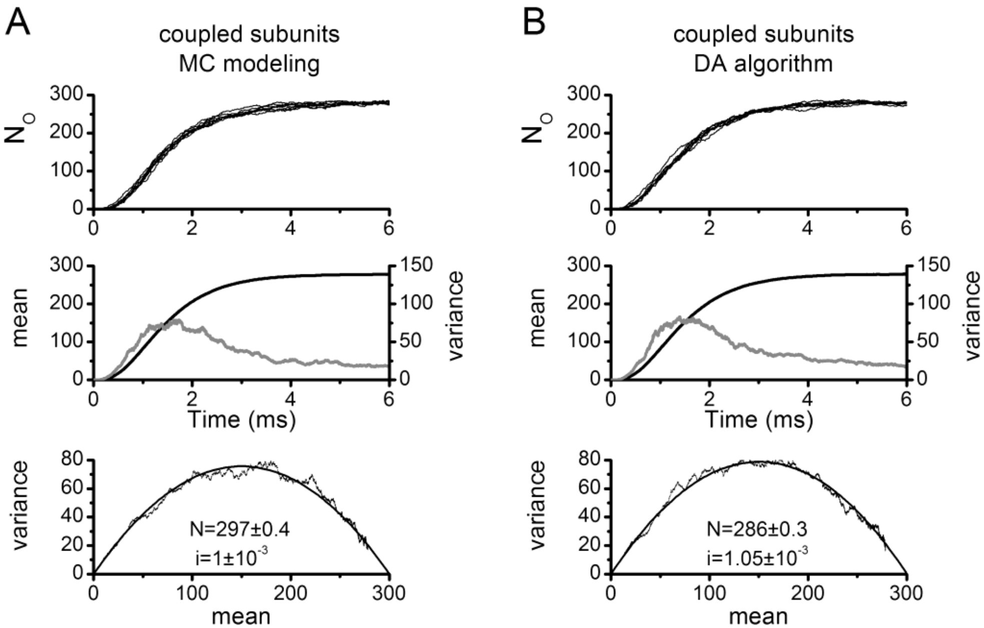
$$\frac{dm_1h_1}{dt} = \left(3\alpha_m m_0h_1 - \beta_m m_1h_1 - 2\alpha_m m_1h_1 + 2\beta_m m_2h_1 + \alpha_h m_1h_0 - \beta_h m_1h_1\right) - \xi_8\sqrt{3\alpha_m m_0h_1 + \beta_m m_1h_1} + \xi_9\sqrt{2\alpha_m m_1h_1 + 2\beta_m m_2h_1} - \xi_5\sqrt{\alpha_h m_1h_0 + \beta_h m_1h_1}$$

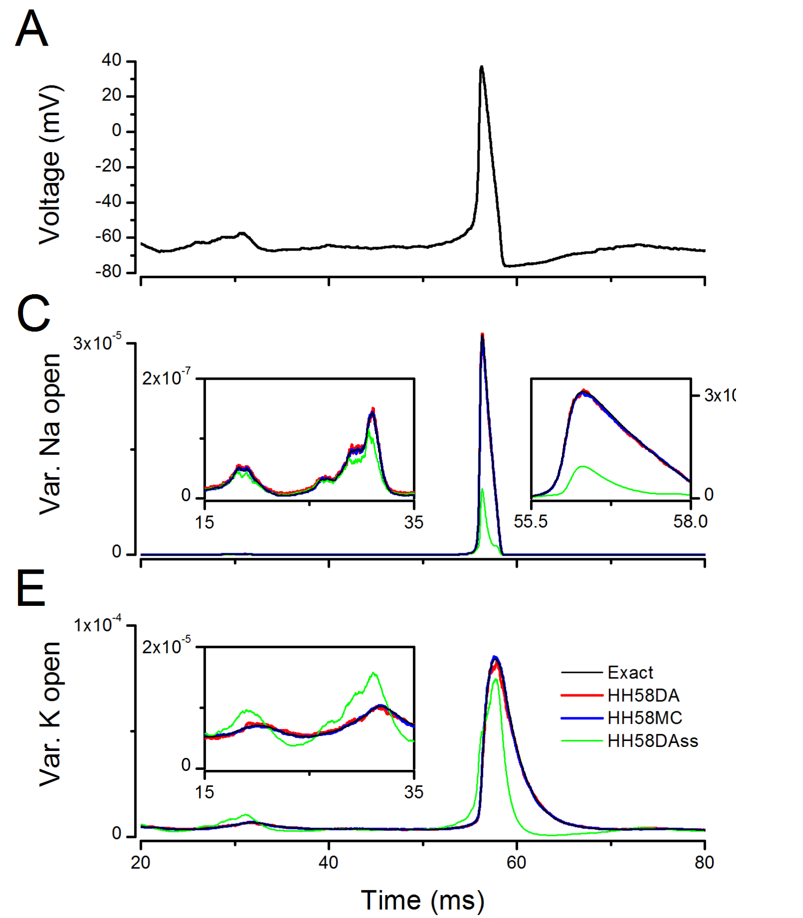
$$\frac{dm_2h_1}{dt} = \left(2\alpha_m m_1h_1 - 2\beta_m m_2h_1 - \alpha_m m_2h_1 + 3\beta_m m_3h_1 + \alpha_h m_2h_0 - \beta_h m_2h_1\right) - \xi_9\sqrt{2\alpha_m m_1h_1 + 2\beta_m m_2h_1} + \xi_{10}\sqrt{\alpha_m m_2h_1 + 3\beta_m m_3h_1} - \xi_6\sqrt{\alpha_h m_2h_0 + \beta_h m_2h_1}$$

$$\frac{dm_3h_1}{dt} = \left(\alpha_m m_2h_1 - 3\beta_m m_3h_1 + \alpha_h m_3h_0 - \beta_h m_3h_1\right) - \xi_{10}\sqrt{\alpha_m m_2h_0 + 3\beta_m m_3h_0} - \xi_7\sqrt{\alpha_h m_3h_0 + \beta_h m_3h_1}$$



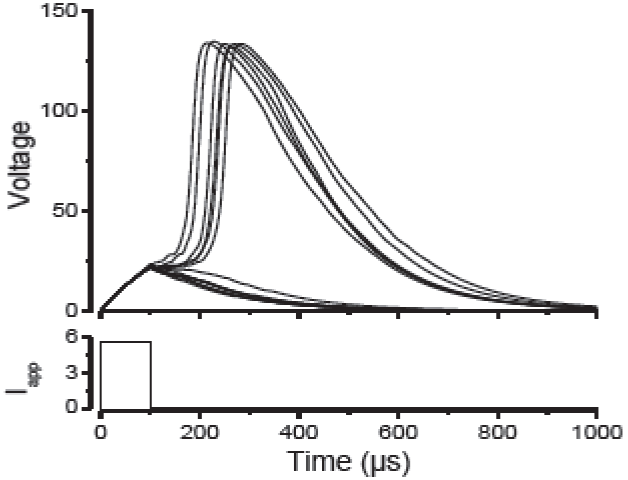
Test in ‘voltage clamp’

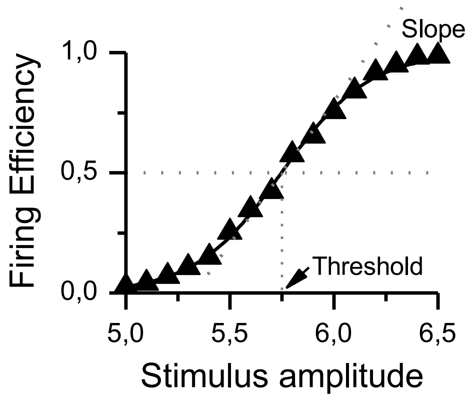




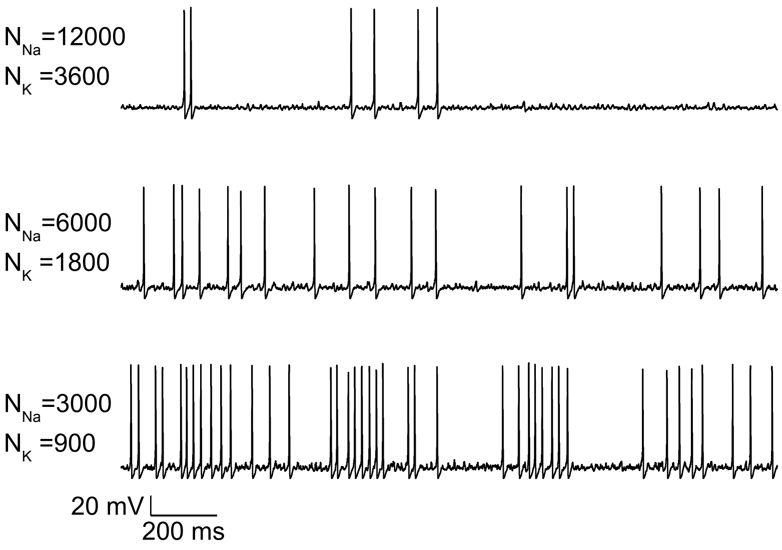
Test in ‘current clamp’

1 - Mammalian Ranvier node model (Rb)

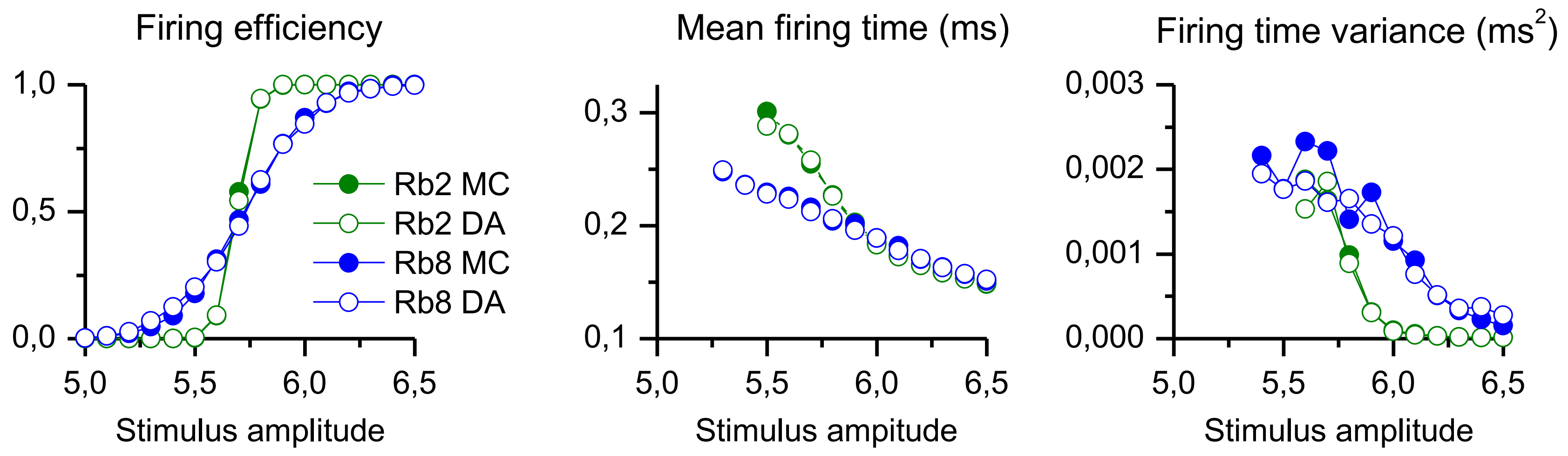




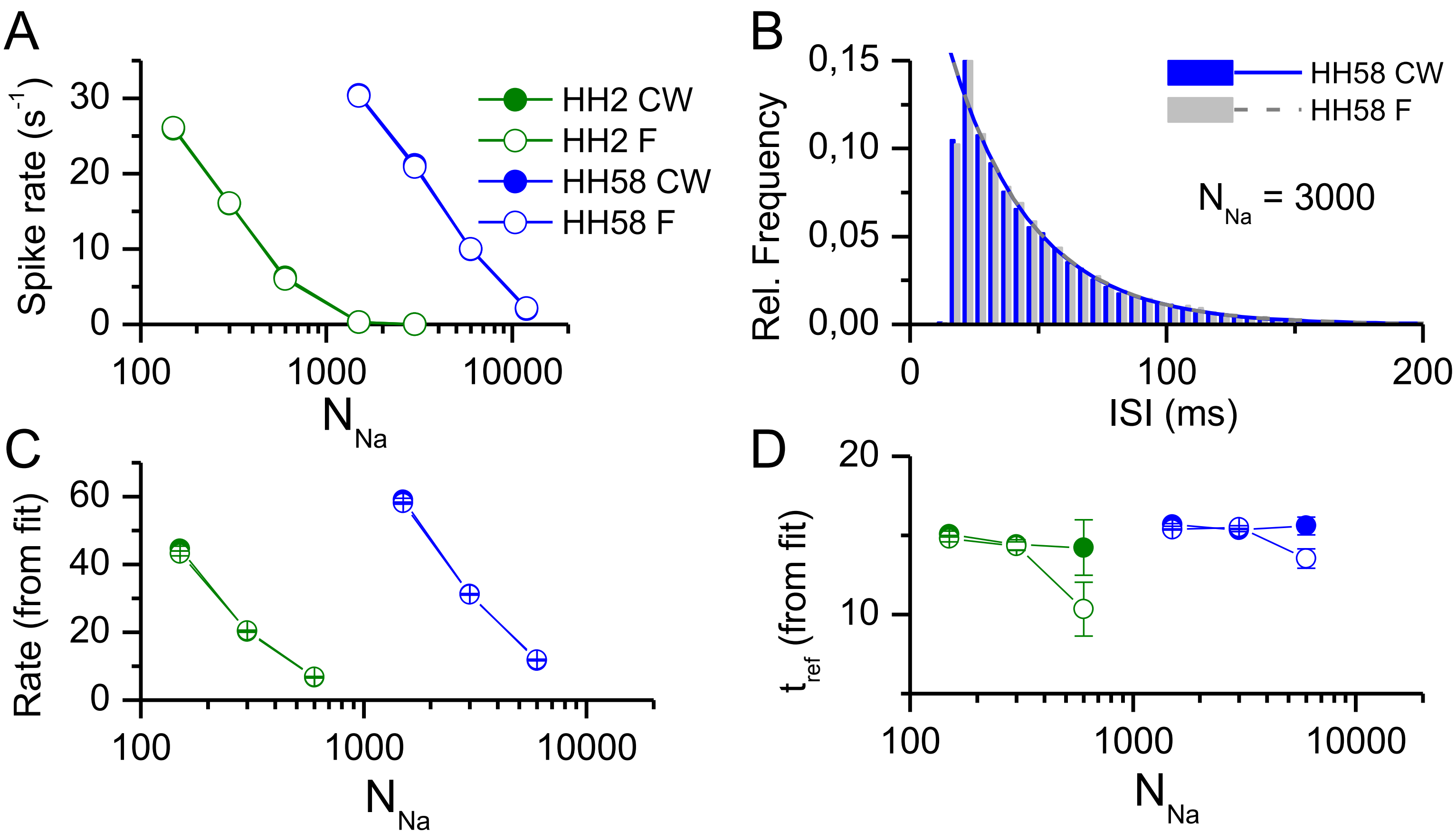
2 – H&H Model for Squid Axon



Results! – Model 1



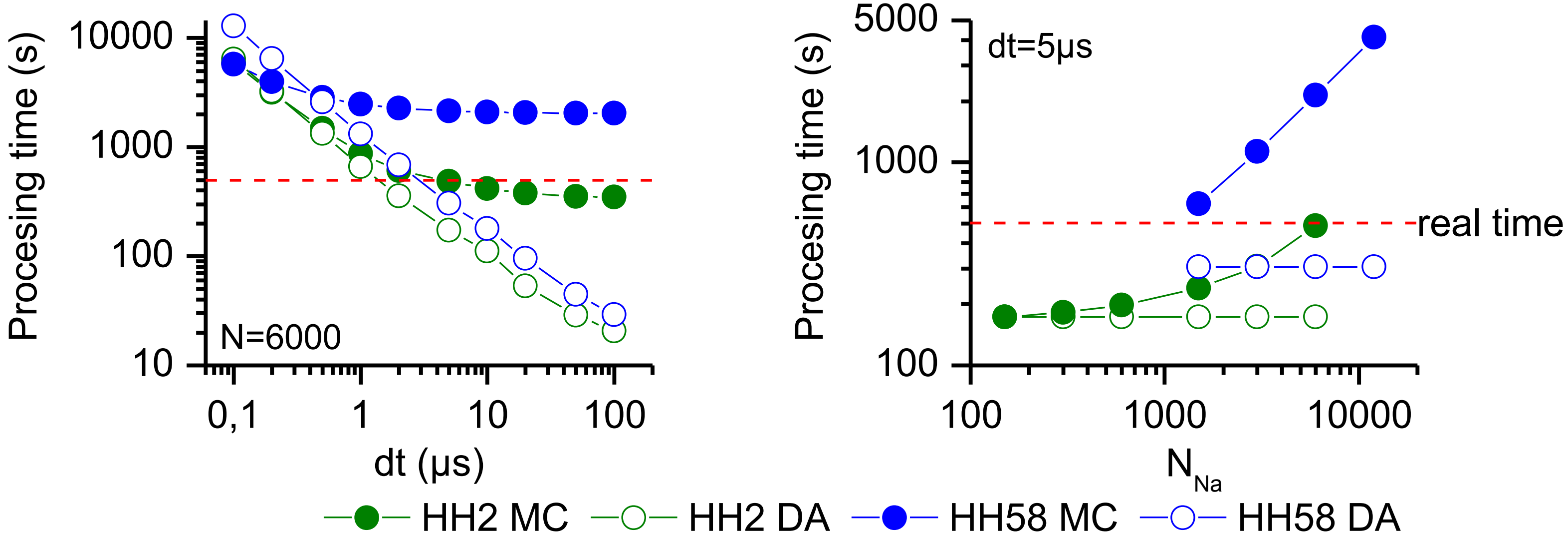
Results! – Model 2



What matters is the 'state representation' of the model, and not the simulation algorithm.

2-state representation is less noisy.

Computational Efficiency



Time to perform a 500 seconds simulation using the NEURON simulation environment under Linux in a Core i7 machine.

Conclusions II

- The Diffusion Approximation algorithm, when properly implemented, produces the same results as Markov Chain modeling
- A simple implementation of DA is presented, which reaches real time simulation speed allowing its application in dynamic clamp and complex neuronal models.
- The two-state representation introduces less variability than the full-state kinetic representation.
  - Studies using the two-state representation are underestimating channel noise.

Other Implementations

- Goldwyn & Shea-Brown 2011
  - Numerical calculation of matrix square root at each time step
  - First implementation used *steady state approximation*
- Linaro *et al.* 2011

$$\begin{cases} C_m \dot{V} = -I_L - I_{\mathrm{Na}} - I_{\mathrm{K}} + I_{app} \\ I_L = g_L(V - E_L) \\ I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}}(m^3 h + \sum_{i=1}^{7} \chi_i)(V - E_{\mathrm{Na}}) \\ I_{\mathrm{K}} = \bar{g}_{\mathrm{K}}(n^4 + \sum_{i=1}^{4} \zeta_i)(V - E_{\mathrm{K}}) \end{cases}$$

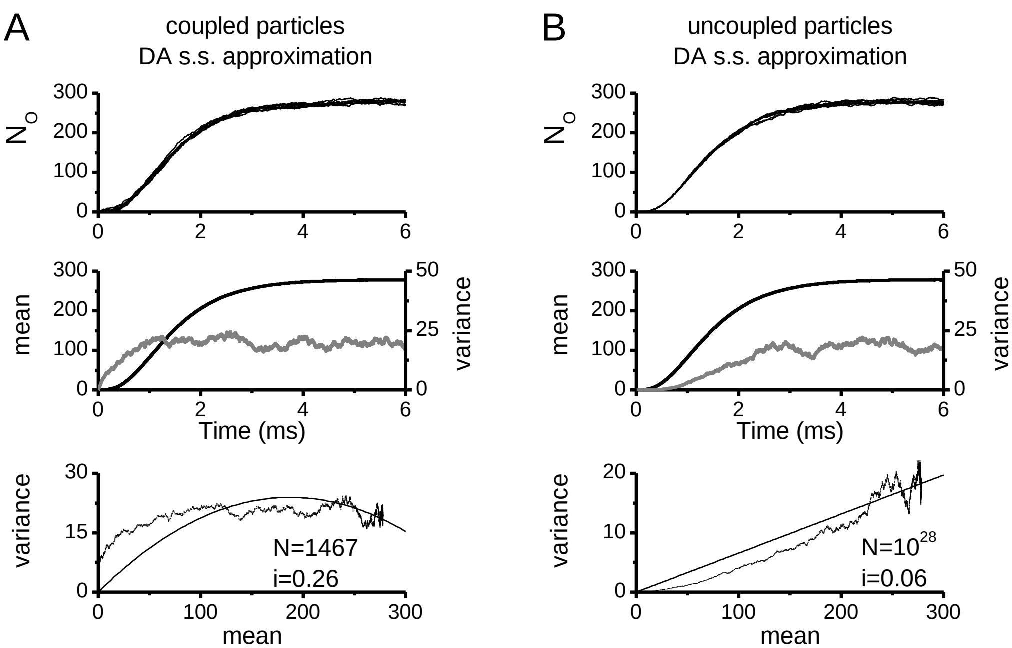
Coefficient	Sodium	Potassium	Time constant	Sodium	Potassium
σ_1^2	$\frac{1}{N}\bar{m}^6\bar{h}(1-\bar{h})$	$\frac{4}{N}\bar{n}^7(1-\bar{n})$	τ_1	τ_h	τ_n
σ_2^2	$\frac{3}{N}\bar{m}^5\bar{h}^2(1-\bar{m})$	$\frac{6}{N}\bar{n}^6(1-\bar{n})^2$	τ_2	τ_m	$\tau_n/2$
σ_3^2	$\frac{3}{N}\bar{m}^4\bar{h}^2(1-\bar{m})^2$	$\frac{4}{N}\bar{n}^5(1-\bar{n})^3$	τ_3	$\tau_m/2$	$\tau_n/3$
σ_4^2	$\frac{1}{N}\bar{m}^3\bar{h}^2(1-\bar{m})^3$	$\frac{1}{N}\bar{n}^4(1-\bar{n})^4$	τ_4	$\tau_m/3$	$\tau_n/4$
σ_5^2	$\frac{3}{N}\bar{m}^5\bar{h}(1-\bar{m})(1-\bar{h})$	–	τ_5	$\frac{\tau_m\tau_h}{\tau_m+\tau_h}$	–
σ_6^2	$\frac{3}{N}\bar{m}^4\bar{h}(1-\bar{m})^2(1-\bar{h})$	–	τ_6	$\frac{\tau_m\tau_h}{\tau_m+2\tau_h}$	–
σ_7^2	$\frac{1}{N}\bar{m}^3\bar{h}(1-\bar{m})^3(1-\bar{h})$	–	τ_7	$\frac{\tau_m\tau_h}{\tau_m+3\tau_h}$	–

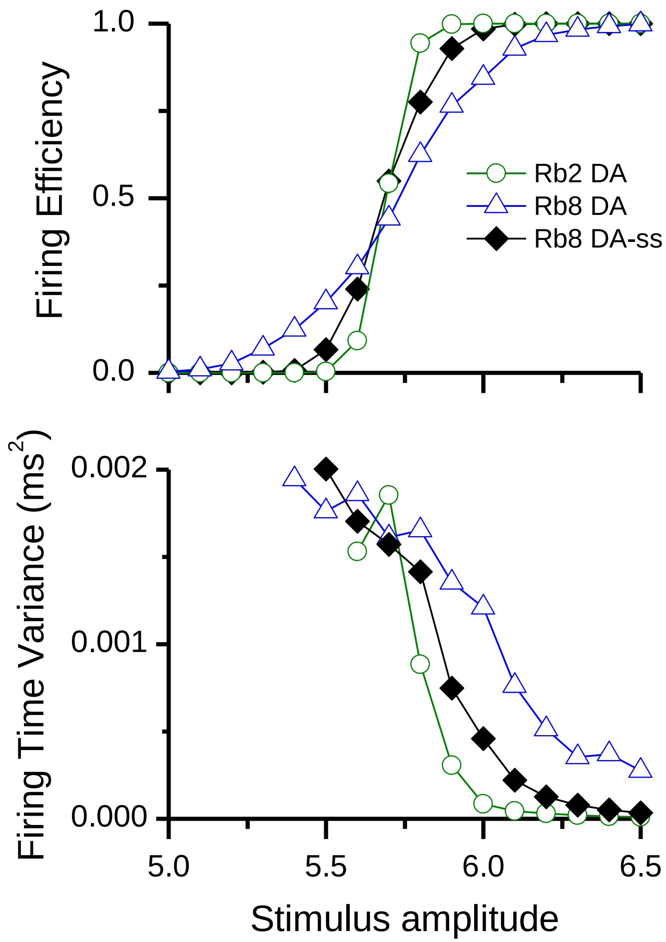
$$\begin{cases} \tau_{\mathrm{Na},i}\dot{\chi}_i(t) = -\chi_i(t) + \sigma_{\mathrm{Na},i}\sqrt{2\tau_{\mathrm{Na},i}}\,\xi_{\mathrm{Na},i}(t) \\ \tau_{\mathrm{K},i}\dot{\zeta}_i(t) = -\zeta_i(t) + \sigma_{\mathrm{K},i}\sqrt{2\tau_{\mathrm{K},i}}\,\xi_{\mathrm{K},i}(t) \end{cases}$$

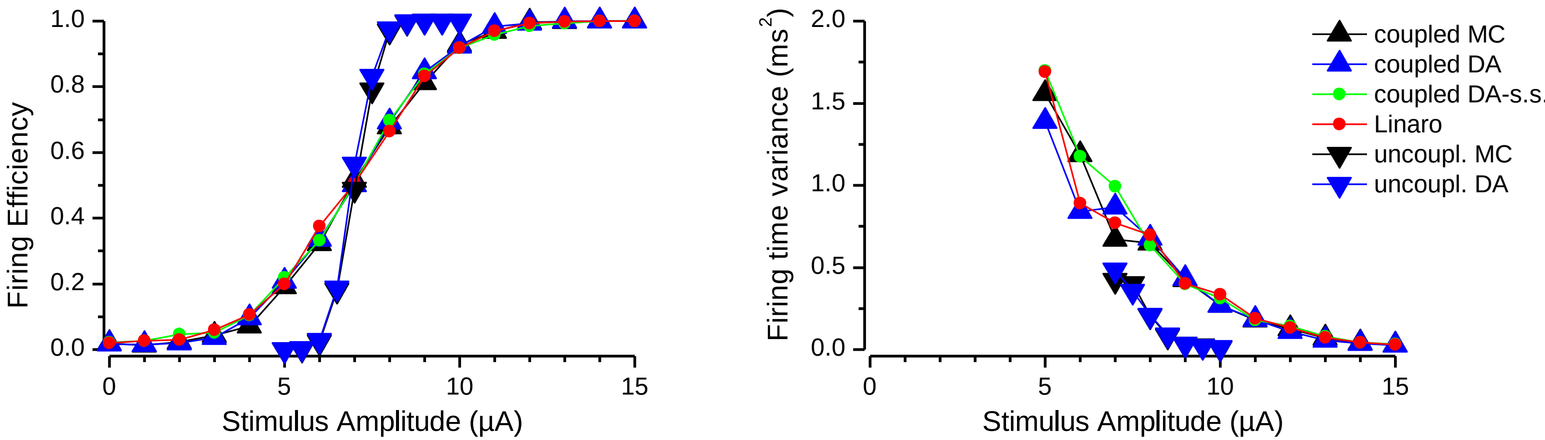
steady state approximation

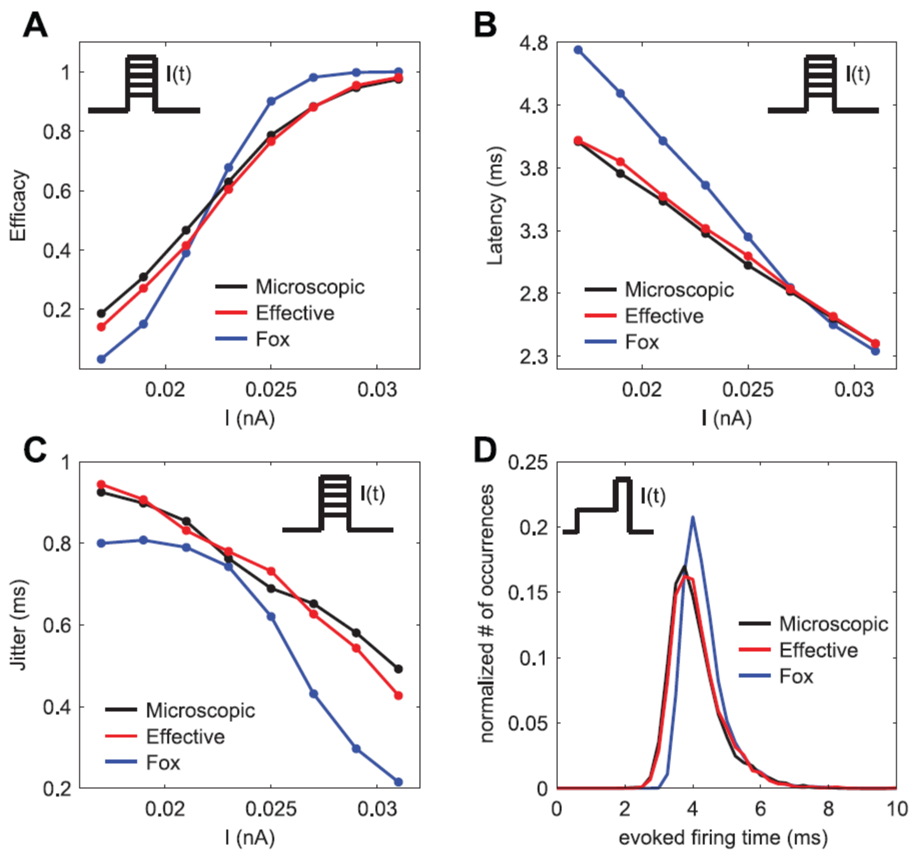
Steady-state aproximation

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m + \xi(t)\frac{1}{\sqrt{N}}\sqrt{\alpha_m(1 - m) + \beta_m m} \approx \ldots + \xi(t)\frac{1}{\sqrt{N}}\sqrt{\frac{2\alpha_m \beta_m}{\alpha_m + \beta_m}}$$






Firing Efficiency
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
Stimulus Amplitude (µA)
Firing time variance (ms²)
2.0
1.5
1.0
0.5
0.0
coupled MC
coupled DA
coupled DA-s.s.
Linaro
uncoupl. MC
uncoupl. DA


A
Efficacy
I(t)
Microscopic
Effective
Fox
I (nA)
0.02
0.025
0.03
B
Latency (ms)
4.8
4.3
3.8
3.3
2.8
2.3
C
Jitter (ms)
D
normalized # of occurrences
0.25
0.2
0.15
0.1
0.05
0
evoked firing time (ms)

Hodgkin&Huxley v/s Rubinstein

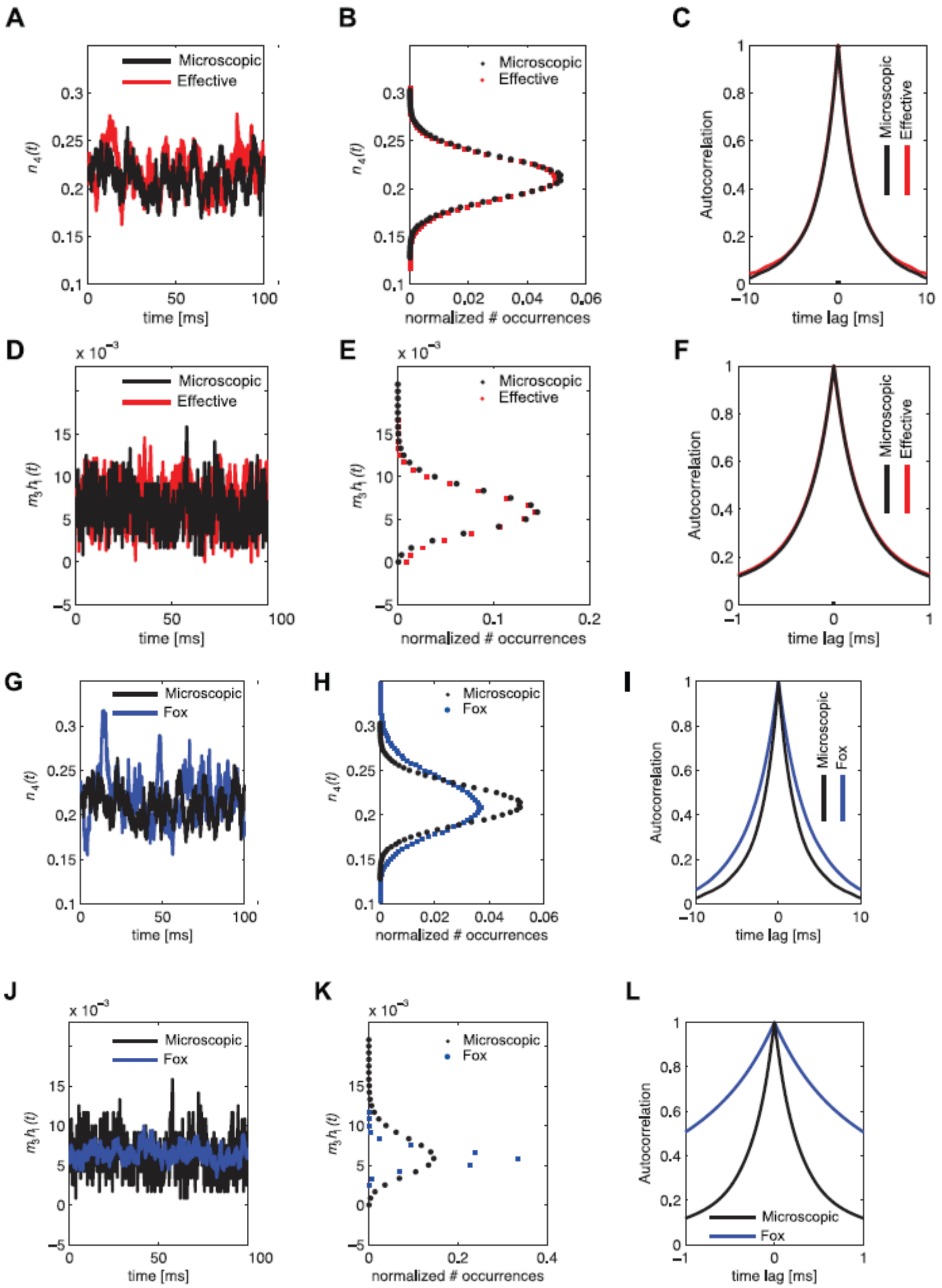
H&H Model

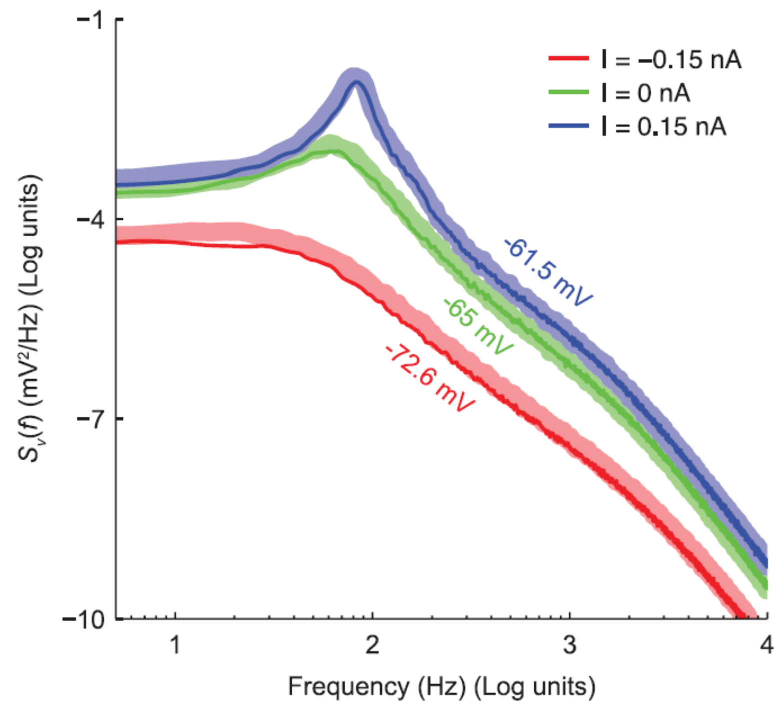
- Based on giant squid axon @6ºC
- Action potential: ~2 ms
- Channel time constans:
  - 0.2 – 0.5 ms (Na)
  - 1 – 6 ms (K)

Rb Model

- Based on mammalian Node of Ranvier @ 37ºC
- <1 ms
  - < 0.025 (Na)
  - 0.1 – 1 (Na inact)

Other benchmarks (Linaro 2011)





↑ voltage PSD

← Statistics of variable values in a trajectory

¡Gracias!