UCL quadrangle, 20 March 2003

Single Ion Channels: Receptor and Synaptic Mechanisms

Professor David Colquhoun, FRS

I apologise for my failure to turn up at the meeting of the Institute of Pure and Applied Mathematics, UCLA, where I was to talk about "Single ion channels: theory and practice of the analysis of a single molecule", on May 25.

In the light of recent events, I have decided that I simply cannot bring myself to visit the USA again, for the time being. [Why?]

"Those abusive actions do not appear to be aberrant conduct by individuals, but part of a conscious method of extracting information."
Senator Carl Levin (Senate Armed Services Committee) (BBC News)

"The roots of the Abu Ghraib prison scandal lie not in the criminal inclinations of a few Army reservists but in a decision, approved last year by Secretary of Defense Donald Rumsfeld, to expand a highly secret operation, which had been focussed on the hunt for Al Qaeda, to the interrogation of prisoners in Iraq."
[Seymour Hersh , New Yorker]

US claps British tourists in irons [Sunday Times]

More links.

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Dr Marco Beato
Dr Philippe Béhé
Dr Sergio Elenes

Spring has sprung, 2004

Click HERE for DC Analysis Programs

NEW!
HJCFIT 21 Aug 03

Latest science : glycine receptor

Latest CAM: give your view!

Latest politics : Abu Ghraib unveiled

Quackery (in Universities)

Photo pages + Galapagos

Jurassic theology Oxford Union talk

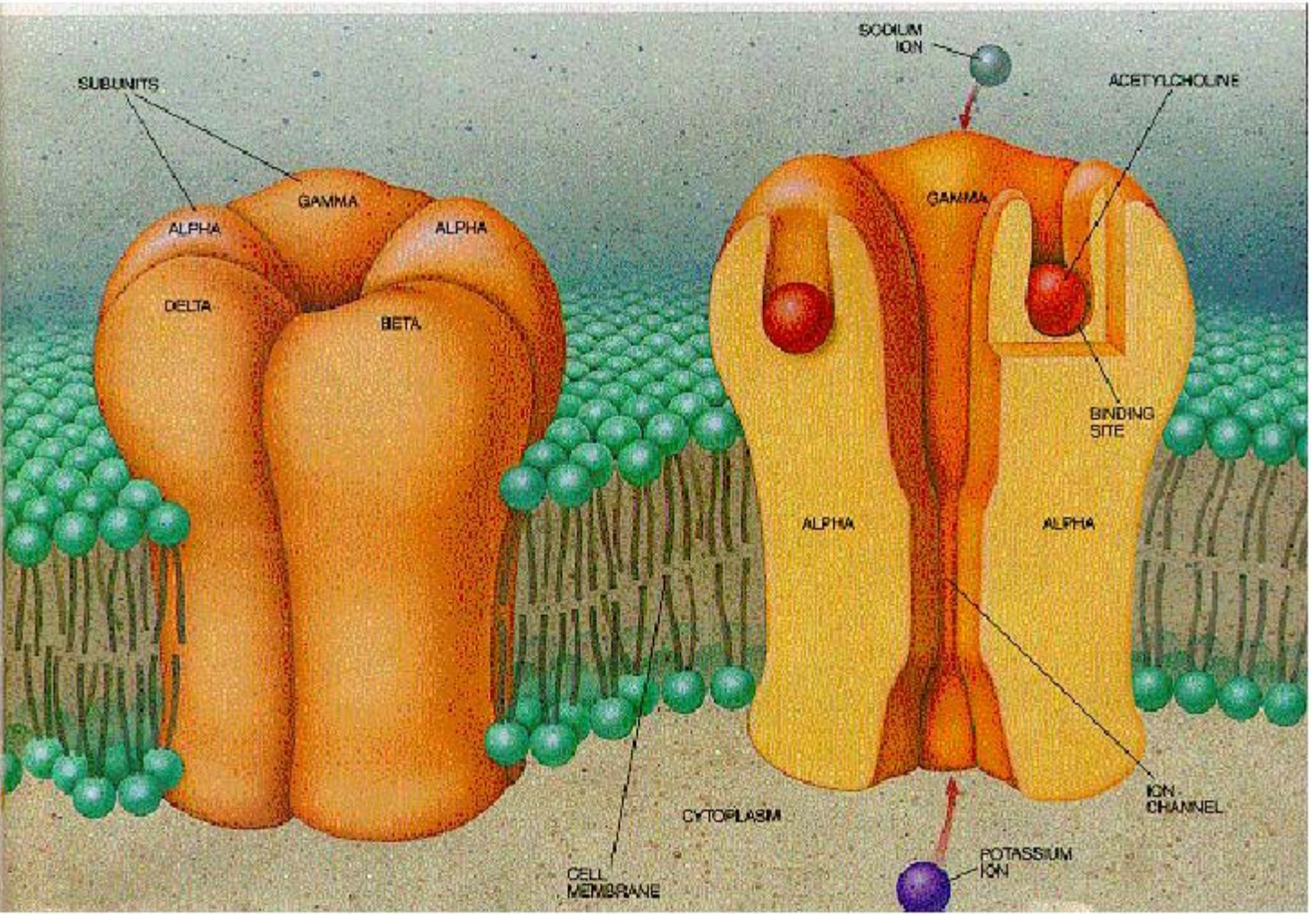
Creationist speaks

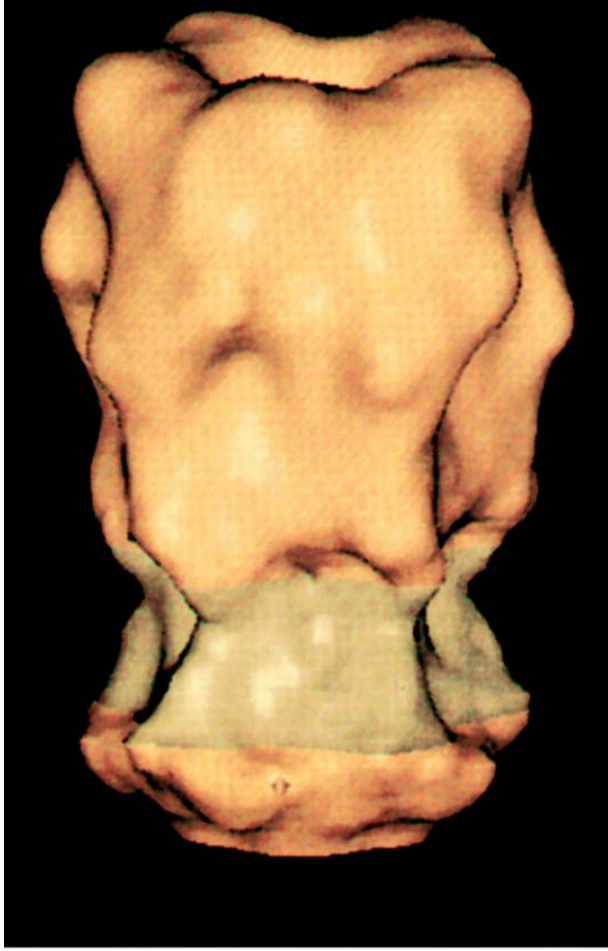
Tribute to a great American

Graduate School 2004; see (picture)

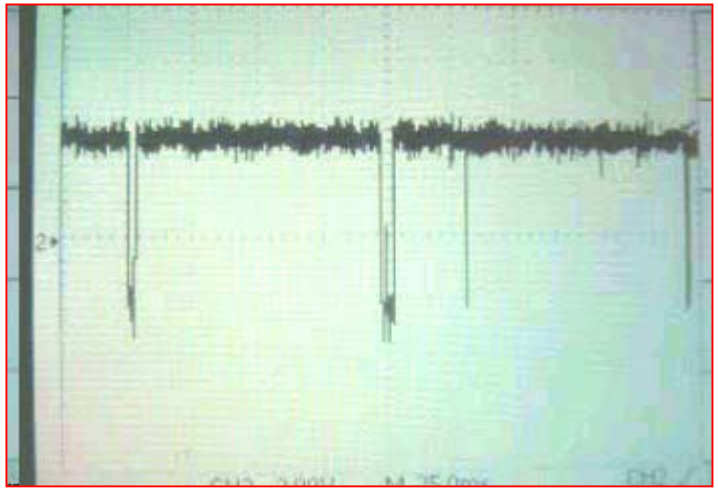
Committee for UCL

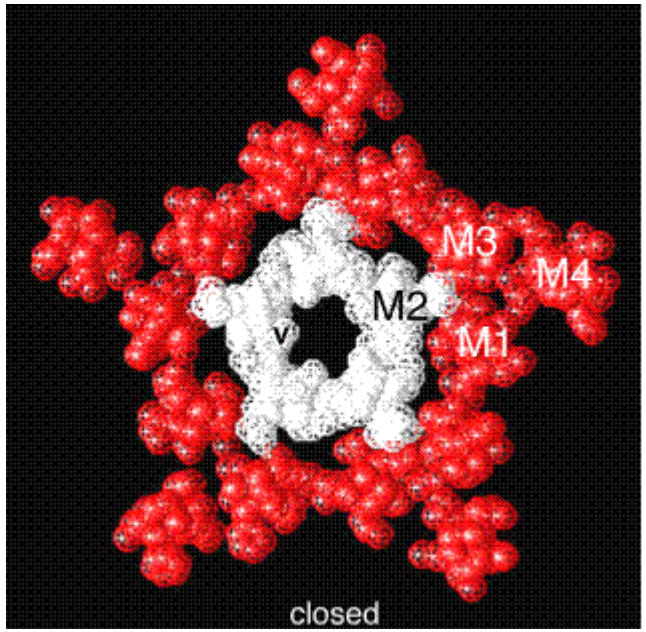
A cartoon version of the nicotinic acetylcholine receptor of the type found at the neuromuscular junction or in *Torpedo* electric organ





Sources: Changeux, Unwin





Channels opened by a low concentration of acetylcholine

Human recombinant muscle type nicotinic receptor ($\alpha_2\beta\varepsilon\delta$), expressed in HEK cell, Openings are downward deflections, and have amplitude of about 6 pA at –100 mV.

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Rate constants interpreted as probabilities $\mathrm{R} \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \mathrm{AR} \underset{\alpha}{\overset{\beta}{\rightleftharpoons}} \mathrm{AR}^*$

Prob(open channel shuts during Δt) $= \alpha\, \Delta t + o(\Delta t)$

Prob(channel shuts between t and $t + \Delta t$ | open at $t = 0$) $= \alpha\, \Delta t + o(\Delta t)$

so the law of mass action rate constant is

$$\alpha = \lim_{\Delta t \to 0} [\ \text{Prob(channel shuts between } t \text{ and } t + \Delta t \mid \text{open at } t = 0) / \Delta t\ ]$$

The *Q* matrix

In the general treatment, the rates for transition from state *i* to state *j* (q_{ij} say) are tabulated in the ***Q*** matrix. The diagonal elements are defined so that the sum of each row is zero.

$$\boldsymbol{Q} = \begin{bmatrix} -(q_{12}+q_{13}) & q_{12} & q_{13} \\ q_{21} & -(q_{21}+q_{23}) & q_{23} \\ q_{31} & q_{32} & -(q_{31}+q_{32}) \end{bmatrix}$$

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Macroscopic (deterministic) behaviour

Define $\boldsymbol{p}(t)$ as a row vector ($1 \times k$) that contains the occupancy of each state at time t :

$$\boldsymbol{p}(t) = [p_1 \quad p_2 \quad p_3 \ldots \ldots p_k]$$

$$\frac{\mathrm{d}\boldsymbol{p}(t)}{\mathrm{d}t} = \boldsymbol{p}(t)\boldsymbol{Q}$$

When $\boldsymbol{Q}$ is constant, the solution is just like the simple scalar case

$$\boldsymbol{p}(t) = \boldsymbol{p}(0)\exp(\boldsymbol{Q}t)$$

This is all there is to say about macroscopic kinetics!

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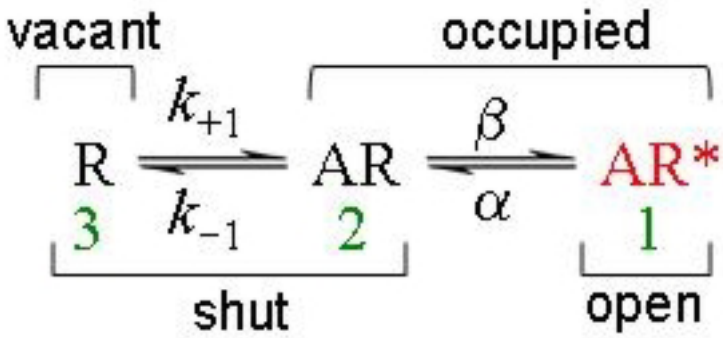
Partitioned matrices

Any matrix can be divided up into rectangular subsections, each of which is itself a matrix. We shall often want to divide the k states in a mechanism into k_A open states (set A) and k_F shut states (set F) ($k = k_A + k_F$). By convention the open states are given the lowest numbers so they appear in the upper left hand part of the ***Q*** matrix.

For the del Castillo-Katz mechanism we have $k = 3$ states, divided into $k_A = 1$ open state and $k_F = 2$ shut states



$$\boldsymbol{Q} = \left[\begin{array}{c|cc} -\alpha & \alpha & 0 \\ \hline \beta & -(\beta + k_{-1}) & k_{-1} \\ 0 & k_{+1}x & -k_{+1}x \end{array}\right]$$

AA AF FA FF

This can be written as

$$\boldsymbol{Q} = \begin{bmatrix} \boldsymbol{Q}_{AA} & \boldsymbol{Q}_{AF} \\ \boldsymbol{Q}_{FA} & \boldsymbol{Q}_{FF} \end{bmatrix}$$

where the submatrices are

$$\boldsymbol{Q}_{AA} = [-\alpha] \qquad \boldsymbol{Q}_{FF} = \begin{bmatrix} -(\beta + k_{-1}) & k_{-1} \\ k_{+1}x & -k_{+1}x \end{bmatrix} \qquad \boldsymbol{Q}_{FA} = \begin{bmatrix} \beta \\ 0 \end{bmatrix} \qquad \boldsymbol{Q}_{AF} = [\alpha \quad 0]$$

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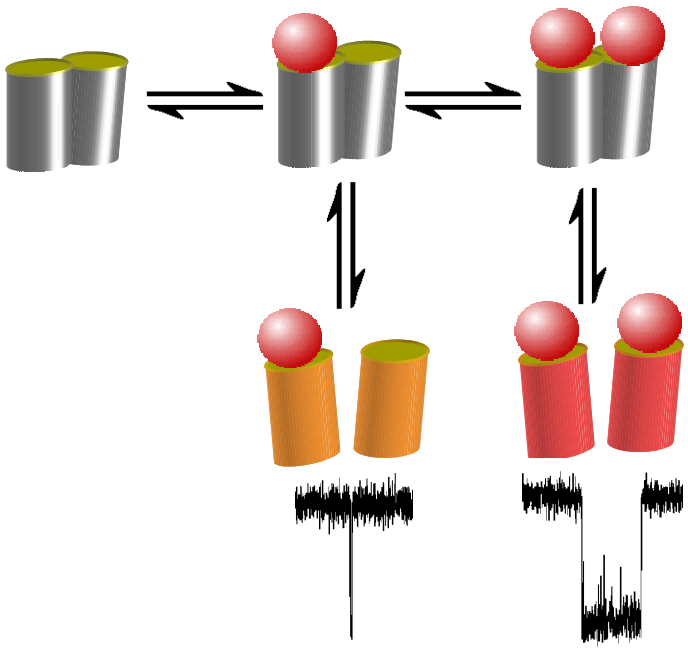
An example from muscle nicotinic receptors



$$\begin{array}{ccccc} 5 & & 4 & & 3 \\ \mathrm{R} & \underset{k_{-1}}{\overset{2k_{+1}}{\rightleftharpoons}} & \mathrm{AR} & \underset{2k_{-2}}{\overset{k_{+2}}{\rightleftharpoons}} & \mathrm{A_2R} \\ & & \beta_1 \rightleftharpoons \alpha_1 & & \beta_2 \rightleftharpoons \alpha_2 \\ & & \mathrm{AR^*} & \rightleftharpoons & \mathrm{A_2R^*} \\ & & 1 & & 2 \end{array}$$

shut

open

$$\boldsymbol{Q} = \left[\begin{array}{cc:cc:c} -(\alpha_1 + k^*_{+2}x_A) & k^*_{+2}x_A & 0 & \alpha_1 & 0 \\ k^*_{-2} & -(\alpha_2 + k^*_{-2}) & \alpha_2 & 0 & 0 \\ \hdashline 0 & \beta_2 & -(\beta_2 + 2k_{-2}) & 2k_{-2} & 0 \\ \beta_1 & 0 & k_{+2}x_A & -(\beta_1 + k_{-1} + k_{+2}x_A) & k_{-1} \\ 0 & 0 & 0 & 2k_{+1}x_A & -2k_{+1}x_A \end{array}\right]$$

AA AF FA FF

Colquhoun & Sakmann, 1985

What is $\boldsymbol{P}_{AA}(t)$?

For the purposes of macroscopic currents we are interested only in the state (open or shut) at time *t*, and it does not matter what happens between 0 and *t*, so we start with probabilities defined thus

$$p_{ij}(t) = \text{Prob}[\text{in state } j \text{ at } t \,|\, \text{in state } i \text{ at } t = 0]$$

But for the purposes of single channels it *does* matter what happens between 0 and *t*, so to find the lifetime of the open state (length of time spent *continuously* in set A, the open states, we define

$${}^{A}p_{ij}(t) = \text{Prob}[\text{remains within set A throughout 0 to } t, \text{ and in state } j \text{ at time } t \,|\, \text{in state } i \text{ at } t = 0]$$

$$i, j \in \text{A}$$

If the ${}^{A}p_{ij}$ are the elements of a matrix $\boldsymbol{P}_{AA}(t)$ (value in *i*th row and *j*th column), then, when the transition rates are constant,

$$\boldsymbol{P}_{AA}(t) = \exp(\boldsymbol{Q}_{AA}t)$$

Chapman-Kolmogorov equation

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What is G_{AB}? (1)

Next we need to define a density that describes the probability of staying open (within the subset of states, A) for a time *t*, and then leaving A for a state outside A, in subset B say.

Probabilities in $\boldsymbol{P}_{AA}(t)$

Probabilities from $\boldsymbol{Q}_{AB}\,\Delta t$

$$g_{ij}(t) = \lim_{\Delta t \to 0}[\text{Prob}(\text{stay in A from time 0 to } t \textbf{ and leave A for state } j \text{ between } t \text{ and } t+\Delta t \mid \text{in state } i \text{ at } t=0)/\Delta t\,] \qquad i \in \text{A},\ j \in B$$

If the $g_{ij}(t)$ are elements of a matrix $\boldsymbol{G}_{AB}(t)$, this is given (see C&H82 p10 for details) by

$$\boldsymbol{G}_{AB}(t) = \boldsymbol{P}_{AA}(t)\,\boldsymbol{Q}_{AB} = \exp(\boldsymbol{Q}_{AA}t)\,\boldsymbol{Q}_{AB}$$

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What is $\boldsymbol{G}^*_{AB}(s)$?

The Laplace transform of these matrices is what is actually used in most of the derivations

The Laplace transform of an ordinary exponential is $$\mathrm{L}[\exp(-\alpha t)] = \frac{1}{\alpha + s}$$

The Laplace transform of a matrix exponential is $$\mathrm{L}[\exp(-\boldsymbol{Q}_{\mathrm{AA}} t)] = (s\boldsymbol{I} - \boldsymbol{Q}_{\mathrm{AA}})^{-1}$$

Since $$\boldsymbol{G}_{\mathrm{AB}}(t) = \exp(\boldsymbol{Q}_{\mathrm{AA}} t)\, \boldsymbol{Q}_{\mathrm{AB}}$$

its transform is

$$\boldsymbol{G}^*_{\mathrm{AB}}(s) = (s\boldsymbol{I} - \boldsymbol{Q}_{\mathrm{AA}})^{-1}\, \boldsymbol{Q}_{\mathrm{AB}}$$

If we are interested only in the probabilities of particular transitions, regardless of how long they take to occur, simply set $s = 0$:

$\boldsymbol{G}^*_{\mathrm{AB}}(0) = -\boldsymbol{Q}_{\mathrm{AA}}^{-1}\, \boldsymbol{Q}_{\mathrm{AB}}$, which, for brevity, we write as $\boldsymbol{G}_{\mathrm{AB}}$

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The distribution of the open time

Call the set of *all shut states* F (= B∪C). The matrix $\boldsymbol{G}_{AF}(t)$ describes the time from the start of an opening, through any number of transitions *within* open states (set A), until eventual exit to any of the shut states (set F), so the pdf is

$$f(t) = \boldsymbol{\varphi}_o \boldsymbol{G}_{AF}(t)\, \boldsymbol{u}_F \quad = \boldsymbol{\varphi}_o \exp(\boldsymbol{Q}_{AA} t)\, \boldsymbol{Q}_{AF}\, \boldsymbol{u}_F$$

or $$f(t) = \boldsymbol{\varphi}_o \exp(\boldsymbol{Q}_{AA} t)(-\boldsymbol{Q}_{AA})\, \boldsymbol{u}_A$$

compare $f(t) = \exp(-\lambda t)\, \lambda$ (simple exponential pdf: one open state)

[Here, $\boldsymbol{\varphi}_o$ is a 1 x k_A row vector that contains the probabilities that an opening starts in each of the k_A open states, and $\boldsymbol{u}_A$ is a k_A x 1 unit vector.]

The mean open time can be found by using the Laplace transform

$$\mu = \left[-\frac{df^*(s)}{ds} \right]_{s=0} = \boldsymbol{\varphi}_o (-\boldsymbol{Q}_{AA}^{-1}) \boldsymbol{u}_A$$

(compare $\mu = \lambda^{-1}$ in simple case)

$$f^*(s) = \boldsymbol{\varphi}_o (s\boldsymbol{I} - \boldsymbol{Q}_{AA})^{-1} (-\boldsymbol{Q}_{AA}) \boldsymbol{u}_A$$

(NB $\boldsymbol{Q}_{AA}\boldsymbol{u}_A + \boldsymbol{Q}_{AF}\boldsymbol{u}_F = 0$ because rows sum to zero)

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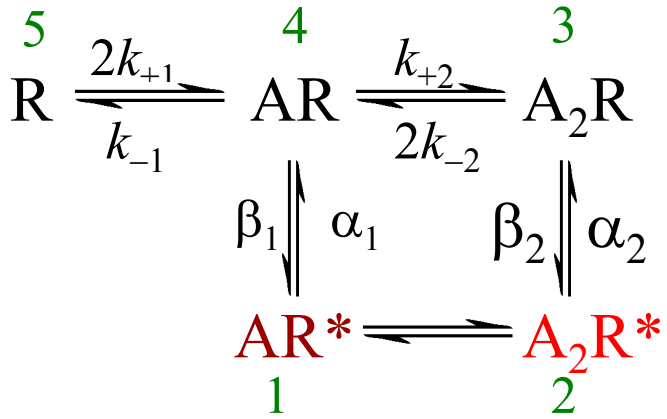
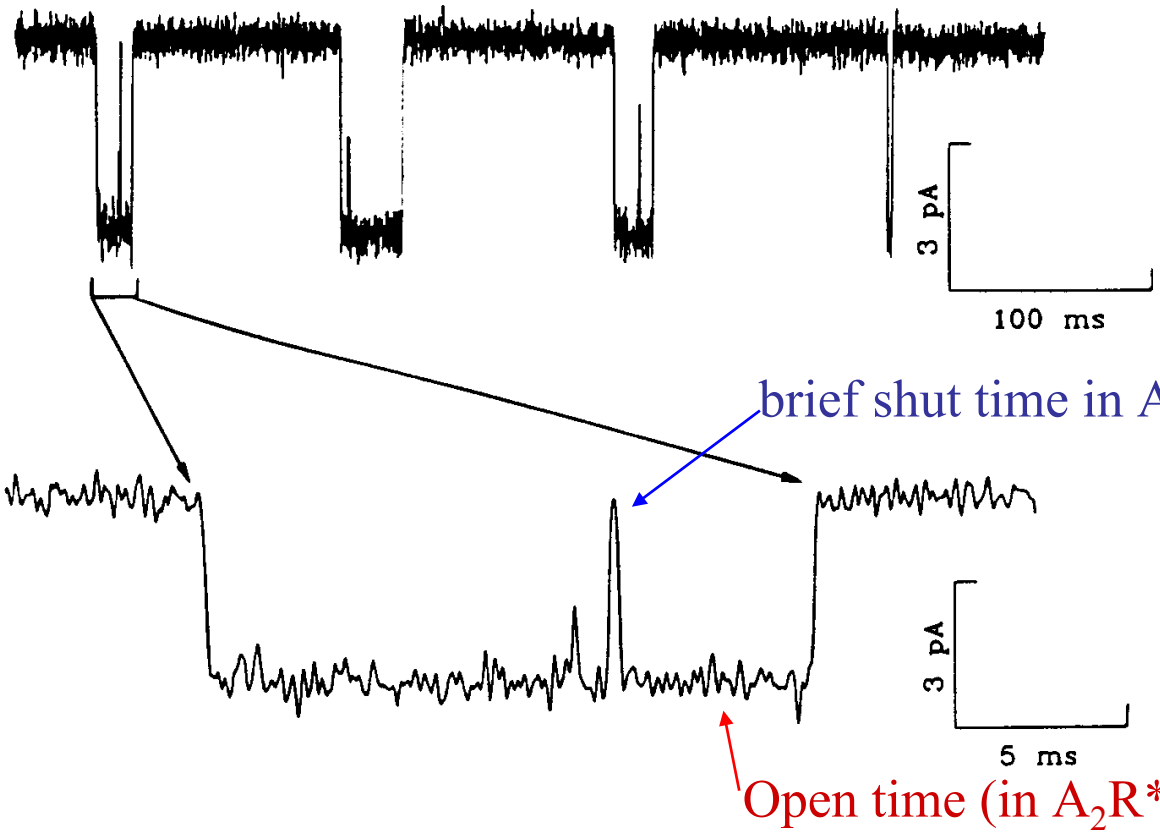
Channel openings usually occur in ‘bursts’

Bursts are interesting for two reasons

(1) From the ‘physiological’ point of view they are the effective channel openings, and they provide the connection between the single molecule behaviour and the macroscopic currents that flow in synapses.

(2) The fine structure of bursts provides information about the channel opening mechanism. It allows the separation of effects on binding and gating and the estimation of rate constants.





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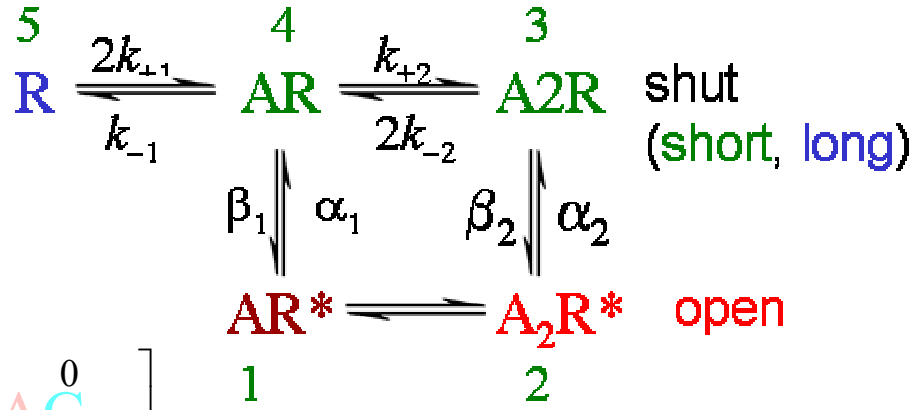
An example in which the burst contains two open states and two short-lived shut states



The ***Q*** matrix, is again partitioned into A (open states), B (brief shut states) and C (long shut states)

$$\boldsymbol{Q} = \left[\begin{array}{cc:cc:c} -(\alpha_1 + k^*_{+2}x_A) & k^*_{+2}x_A & 0 & \alpha_1 & 0 \\ k^*_{-2} & -(\alpha_2 + k^*_{-2}) & \alpha_2 & 0 & 0 \\ \hdashline 0 & \beta_2 & -(\beta_2 + 2k_{-2}) & 2k_{-2} & 0 \\ \beta_1 & 0 & k_{+2}x_A & -(\beta_1 + k_{-1} + k_{+2}x_A) & k_{-1} \\ \hdashline 0 & 0 & 0 & 2k_{+1}x_A & -2k_{+1}x_A \end{array}\right]$$

AA AB AC BA BB BC CA CB CC

For example, the top left hand sub-matrix is

$$\boldsymbol{Q}_{AA} = \begin{bmatrix} -(\alpha_1 + k^*_{+2}[A]) & k^*_{+2}[A] \\ 2k^*_{-2} & -(\alpha_2 + 2k^*_{-2}) \end{bmatrix}$$

Bursts of openings are spent in states A∪B = E ('burst states')

$$\boldsymbol{Q} = \left[\begin{array}{cccc:c} -(\alpha_1 + k^*_{+2}x_A) & k^*_{+2}x_A & 0 & \alpha_1 & 0 \\ k^*_{-2} & -(\alpha_2 + k^*_{-2}) & \alpha_2 & 0 & 0 \\ 0 & \beta_2 & -(\beta_2 + 2k_{-2}) & 2k_{-2} & 0 \\ \beta_1 & 0 & k_{+2}x_A & -(\beta_1 + k_{-1} + k_{+2}x_A) & k_{-1} \\ \hdashline 0 & 0 & 0 & 2k_{+1}x_A & -2k_{+1}x_A \end{array}\right]$$

EE EC CE CC

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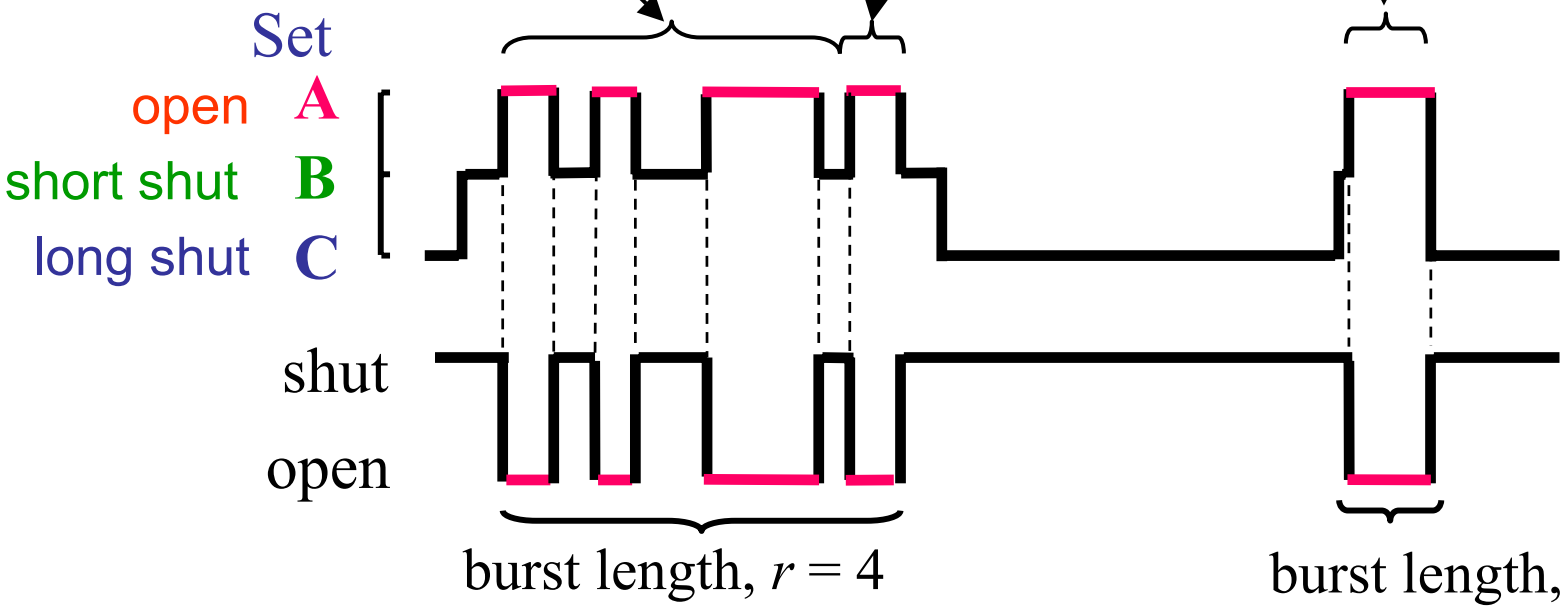
The distribution of the burst length (1)

A burst will contain a random number of openings, the probability of getting *r* openings in a burst, regardless of their duration, being $P(r) = \boldsymbol{\varphi}_{\mathrm{b}} (\boldsymbol{G}_{\mathrm{AB}} \boldsymbol{G}_{\mathrm{BA}})^{r-1} (\boldsymbol{I} - \boldsymbol{G}_{\mathrm{AB}} \boldsymbol{G}_{\mathrm{BA}}) \boldsymbol{u}_{\mathrm{A}}$

The distribution of the burst length is found by convolving the distributions of the intervals that constitute the burst.

$$f^*(s) = \boldsymbol{\varphi}_{\mathrm{b}} \sum_{r=1}^{\infty} [\boldsymbol{G}^*_{\mathrm{AB}}(s)\boldsymbol{G}^*_{\mathrm{BA}}(s)]^{r-1} [\boldsymbol{G}^*_{\mathrm{AB}}(s)\boldsymbol{G}_{\mathrm{BC}} + \boldsymbol{G}^*_{\mathrm{AC}}(s)\,]\, \boldsymbol{u}_{\mathrm{C}}$$

$[\boldsymbol{G}^*_{\mathrm{AB}}(s)\boldsymbol{G}^*_{\mathrm{BA}}(s)]^3$ $\quad \boldsymbol{G}^*_{\mathrm{AB}}(s)\boldsymbol{G}_{\mathrm{BC}}$ $\quad \boldsymbol{G}^*_{\mathrm{AC}}(s)$



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The distribution of the burst length (2)

We now have the Laplace transform of the pdf as

$$f^*(s) = \varphi_b \sum_{r=1}^{\infty} [\boldsymbol{G}^*_{AB}(s)\boldsymbol{G}^*_{BA}(s)]^{r-1}[\boldsymbol{G}^*_{AB}(s)\boldsymbol{G}_{BC} + \boldsymbol{G}^*_{AC}(s)]u_C$$

$$= \varphi_b [\boldsymbol{I} - \boldsymbol{G}^*_{AB}(s)\boldsymbol{G}^*_{BA}(s)]^{-1}[\boldsymbol{G}^*_{AB}(s)\boldsymbol{G}_{BC} + \boldsymbol{G}^*_{AC}(s)]u_C$$

It is not obvious how to invert this, because s occurs in four different places, and in fact it is one of the trickier inversions. The method is described in appendix 1 of C&H 1982. The result is, however, simple and elegant,

$$f(t) = \boldsymbol{\varphi}_b [\exp(\boldsymbol{Q}_{EE}t)]_{AA}(-\boldsymbol{Q}_{AA})(\boldsymbol{I} - \boldsymbol{G}_{AB}\boldsymbol{G}_{BA})\,\boldsymbol{u}_A$$

time spent in the burst states (E)

starting and ending in open state (A)

burst fails to continue

c.f scalar case $P(r) = \pi_{21}^{r-1}(1-\pi_{21})$

Note: $\exp(\boldsymbol{Q}_{EE})$ is a $k_E \times k_E$ matrix so the result will be a mixture of k_E exponentials

Note: we need only the AA subsection of $\exp(\boldsymbol{Q}_{EE})$, i.e. the upper $k_A \times k_A$ part.

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The spectral expansion of $\boldsymbol{Q}$

When $\boldsymbol{Q}$ is a $k \times k$ matrix, with k eigenvalues, we can also calculate, from the eigenvectors of $\boldsymbol{Q}$, the k matrices, $\boldsymbol{A}_m$,

$$\boldsymbol{A}_m \boldsymbol{A}_n = 0, \quad m \neq n \quad , \quad \text{but} \quad \boldsymbol{A}_m^r = \boldsymbol{A}_m \qquad \text{and} \qquad \sum_{m=1}^{k} \boldsymbol{A}_m = \boldsymbol{I}$$

Once the $\boldsymbol{A}$ matrices have been found they can be used to define any analytic function of a matrix, $\boldsymbol{Q}$, as that function of the *eigenvalues* of $\boldsymbol{Q}$ (also OK with repeated eigenvalues if Q is diagonalisable, i.e. process is reversible).

$$f(\boldsymbol{Q}) = \sum_{m=1}^{k} f(\lambda_m) \boldsymbol{A}_m$$

Sylvester's theorem

In particular, in our case, we find the ubiquitous matrix exponential as

$$\exp(\boldsymbol{Q}) = \sum_{m=1}^{k} \exp(\lambda_m) \boldsymbol{A}_m$$

This allows all the distributions to be expressed in scalar form as a linear combination of exponentials with exponents that are the eigenvalues of the matrix, $\exp(\lambda_m t)$.

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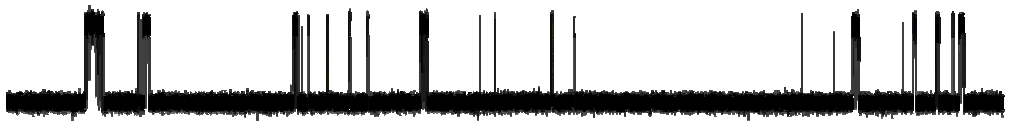


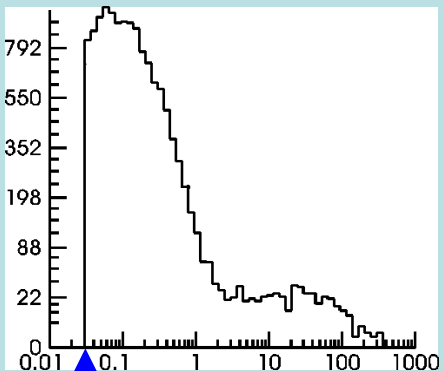
A first look at single channel data: empirical fits

(1) Idealise: make list of open and shut times

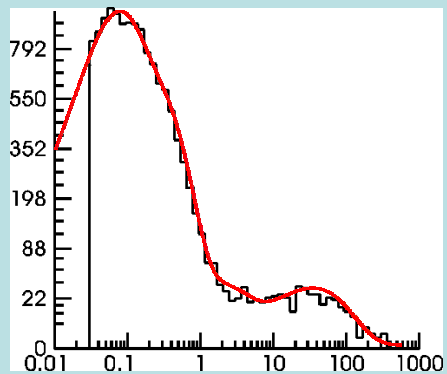
Gly 10 μM

#	ms	pA
1	3.045	0
2	0.064	2.43
3	0.035	0
4	….	…

(2) Display data as distributions: open times, shut times, burst lengths, correlations..



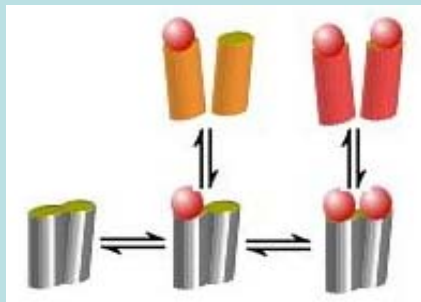
Note –resolution 30 μs



(3) Fit exponentials to DISTRIBUTIONS

Minimum number of shut and open states, time constants, connectivity…

(4) Build a plausible mechanism



(5) Attempt to estimate physical rate constants retrospectively from the distributions

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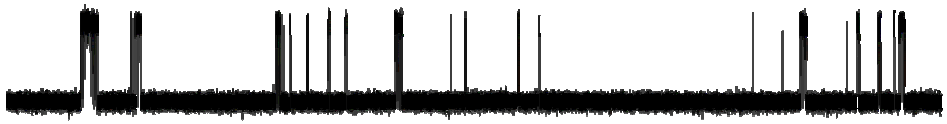


A better way: direct fit of a mechanism to data

(1) Idealise

resolution = 30 μs

Gly 10 μM

#	ms	pA
1	3.045	0
2	0.064	2.43
3	0.035	0
4	....	...

Gly 300 μM

#	ms	pA
1	9.325	0
2	2.562	2.51
3	0.050	0
4	....	...

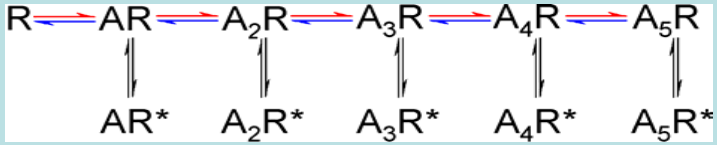
Gly 100 μM

#	ms	pA
1	5.120	0
2	1.312	2.48
3	0.044	0
4	....	...

Gly 1000 μM

#	ms	pA
1	2.215	0
2	5.327	2.47
3	0.539	0
4	....	...

(2) Postulate a plausible mechanism



(3) Choose rate constants to maximise likelihood HJCFIT

(with exact missed event method)

(4) Rate constants

$\alpha_2 = 1250 \pm 120$

$\beta_2 = 1250 \pm 120$

$k_{+2} = ...$

(5) Do these rates, with the mechanism, describe the data accurately?

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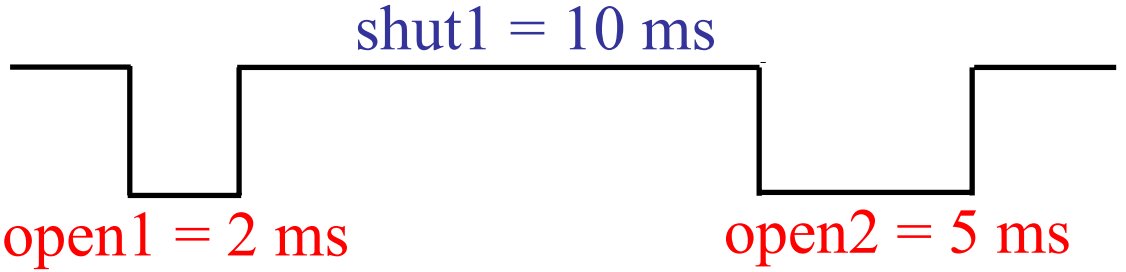
Maximum likelihood fitting to a sequence



Likelihood of this sequence = Prob[open1 = 2 ms]
× Prob[shut1 = 10 ms *given* open1=2 ms]
× Prob[open2 = 5 ms *given* (shut1 = 10 ms *and* open1=2 ms)]

These probabilities depend on the values for the rate constants in the mechanism *and* on the resolution of the observations, from which they are calculated, by the method of Hawkes, Jalali & Colquhoun (1990, 1992). The values of the rate constants are adjusted until the likelihood is maximised.

To infer, for example, whether a mutation affects the binding site, we need values for the underlying rate constants. This method fits what we want directly to the observations, so avoiding entirely the difficult step between fitting exponentials to distributions, and inference of values for the underlying rate constants.

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The equation for the likelihood can be evaluated from the known resolution and the $\boldsymbol{Q}$ matrix, which specifies the mechanism, and the values of the rate constants in it. The parameters are not now the τ_1, τ_2, a_1, etc for arbitrary exponentials, but are the elements the $\boldsymbol{Q}$ matrix, *i.e* the rate constants in the mechanism.

$\boldsymbol{\phi}_A$ is a $(1 \times k_A)$ vector that gives the probability that an opening starts in each of the open states at equilibrium, and when the next factor in eq. 6.1 is included, $\boldsymbol{\phi}_A \, {}^e\boldsymbol{G}_{AF}(t_{o1})$ is a $(1 \times k_F)$ vector that gives the probability that the next shut period starts in each of the shut states *following an opening of length* t_{o1}; and $\boldsymbol{\phi}_A \, {}^e\boldsymbol{G}_{AF}(t_{o1}) \, {}^e\boldsymbol{G}_{FA}(t_{s1})$ is again a $(1 \times k_A)$ vector that gives the probability that the next opening starts in each of the open states following an opening of length t_{01} *and* a shutting of length t_{s1}, and so on, up to the end of the data

$$\boldsymbol{\phi}_A \, {}^e\boldsymbol{G}_{AF}(t_{o1}) \quad {}^e\boldsymbol{G}_{FA}(t_{s1}) \quad {}^e\boldsymbol{G}_{AF}(t_{o2}) \quad {}^e\boldsymbol{G}_{FA}(t_{s2}) \quad {}^e\boldsymbol{G}_{AF}(t_{o3}) \quad \ldots \boldsymbol{u}_F = \boldsymbol{L}$$

$1 \times k_A$ $\quad$ $k_F \times 1$ $\quad$ 1×1

$1 \times k_F$

$1 \times k_A$

$1 \times k_F$

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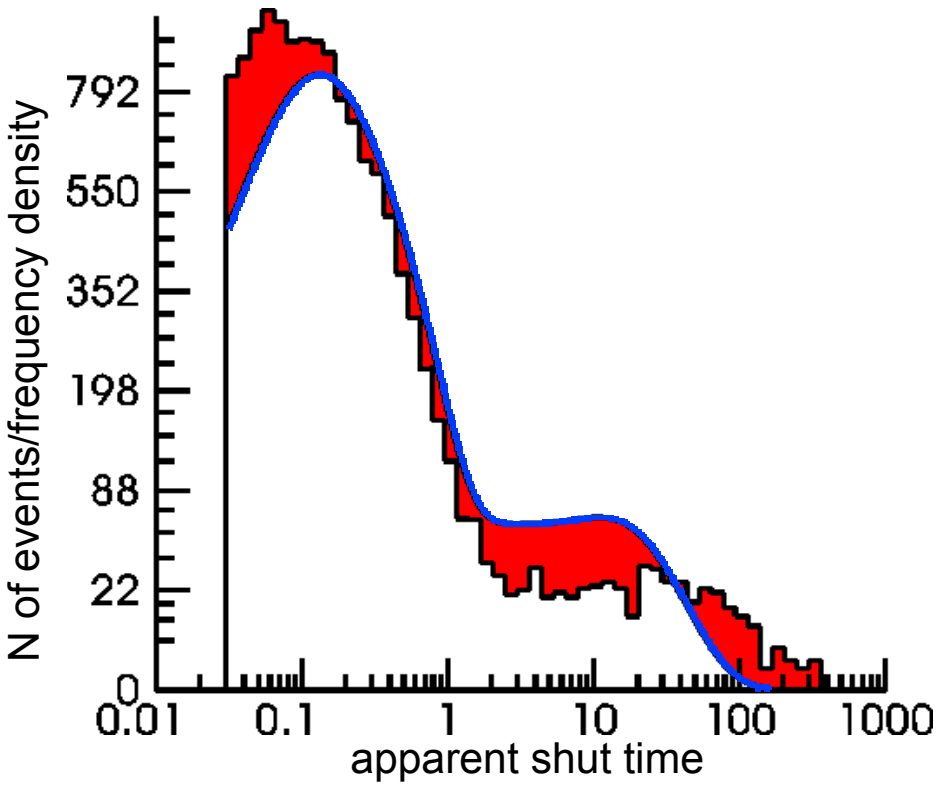
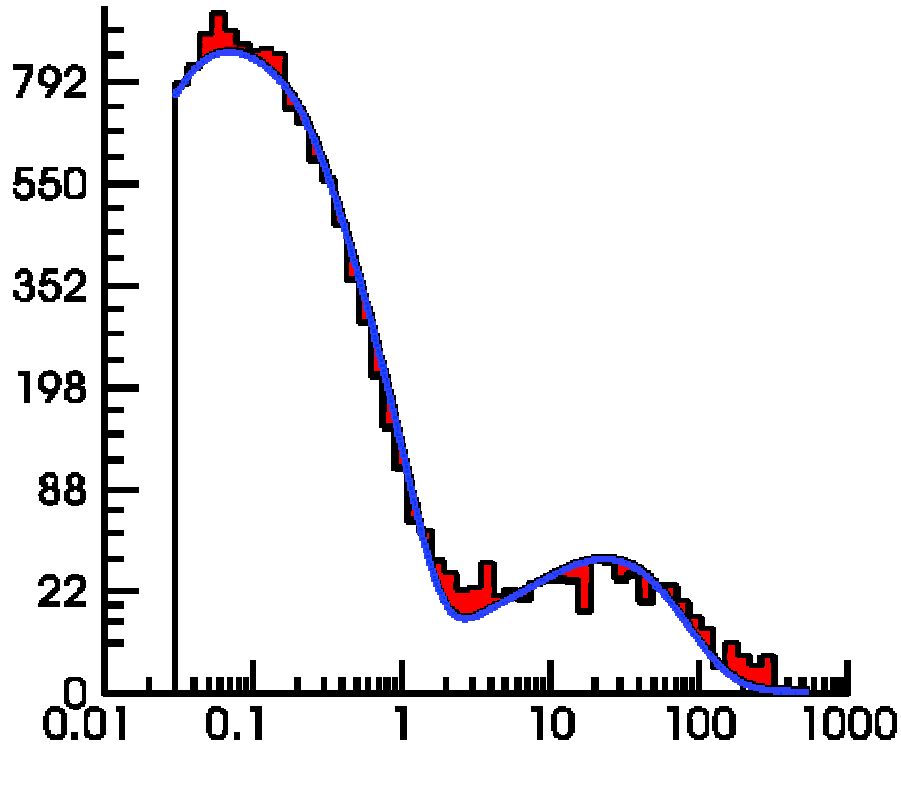
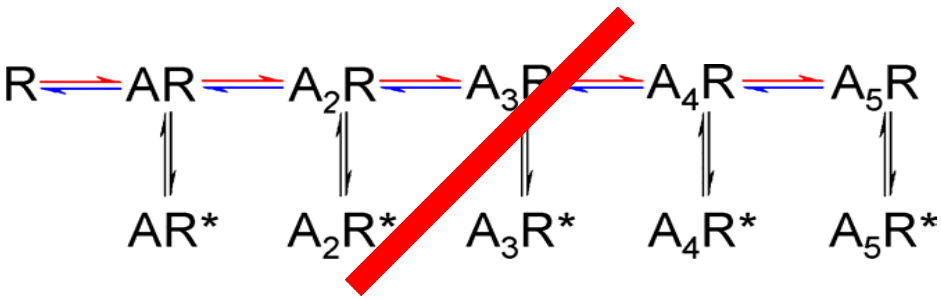
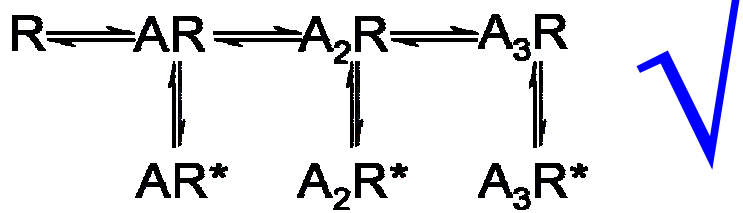
Testing the quality of the fit









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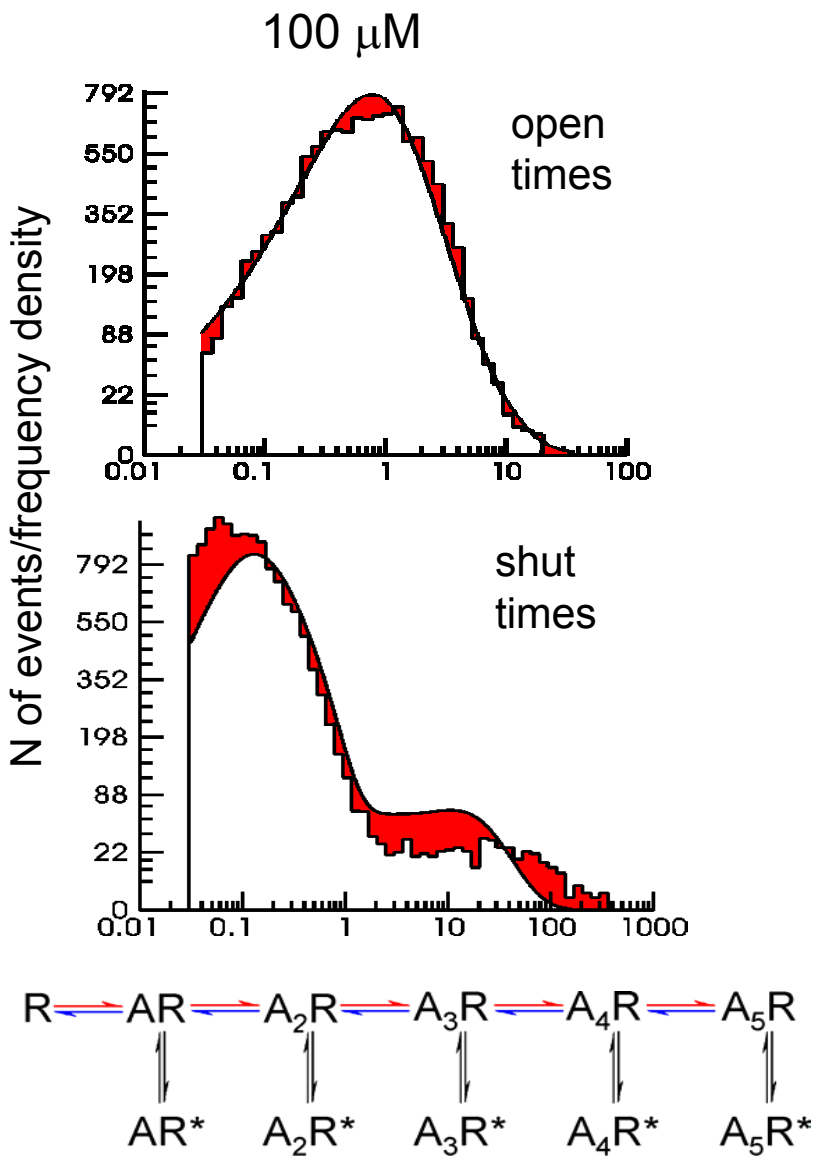
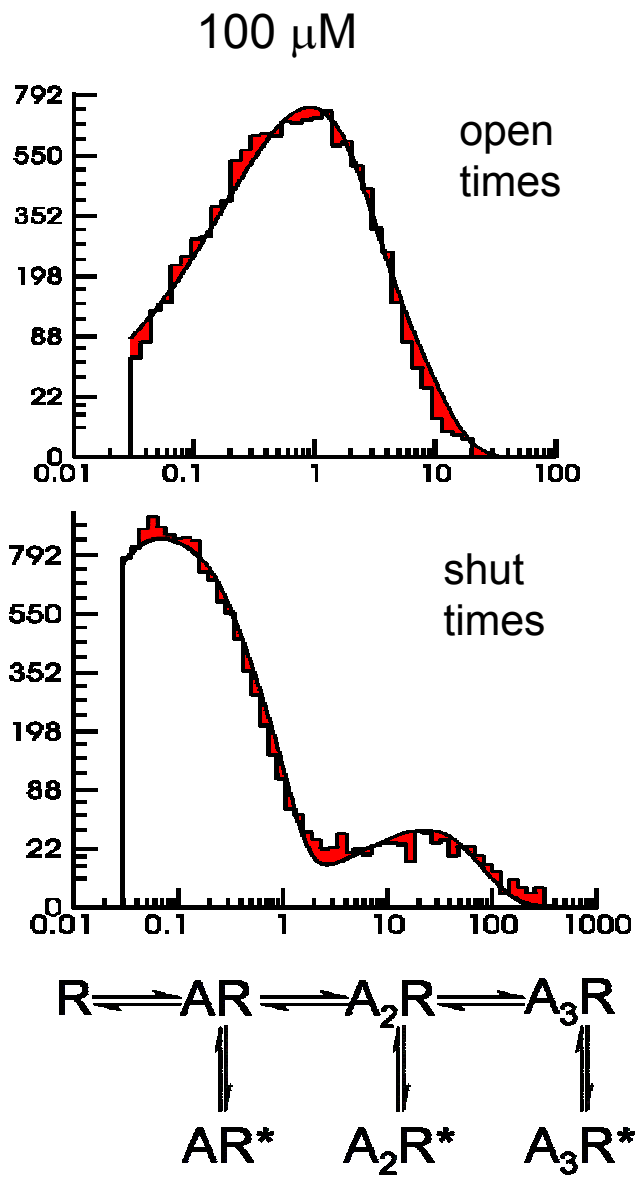
Several types of distribution at a range of concentrations





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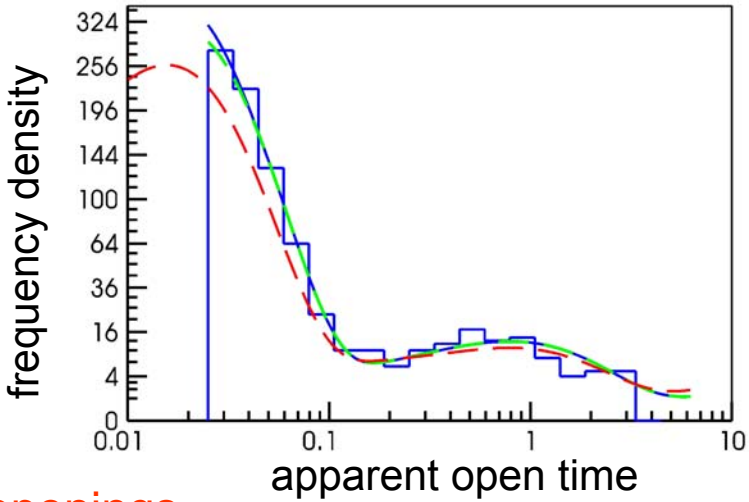
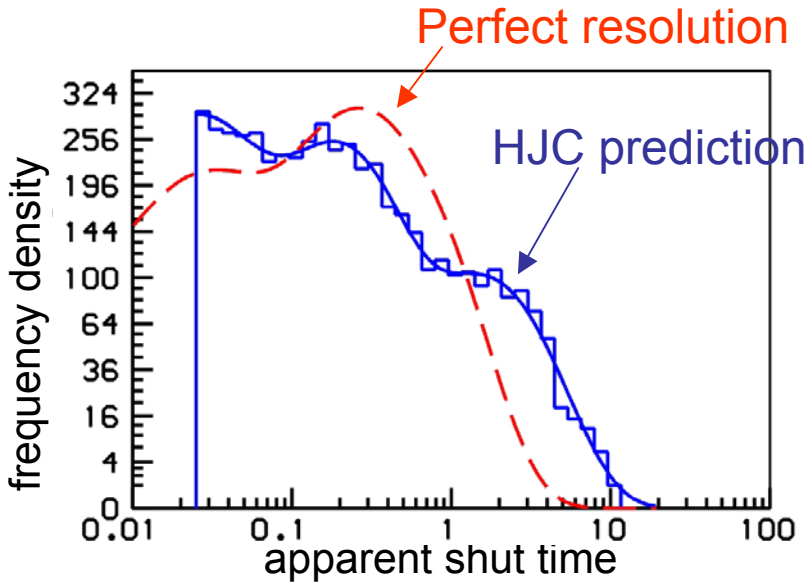
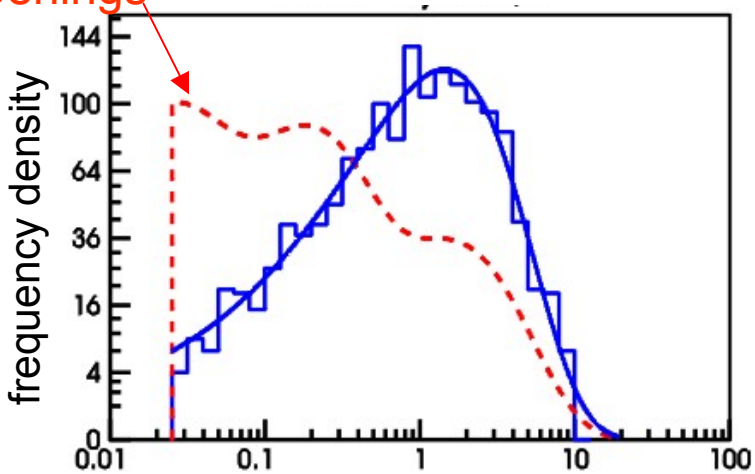
Testing whether the fitted rate constants describe the data accurately

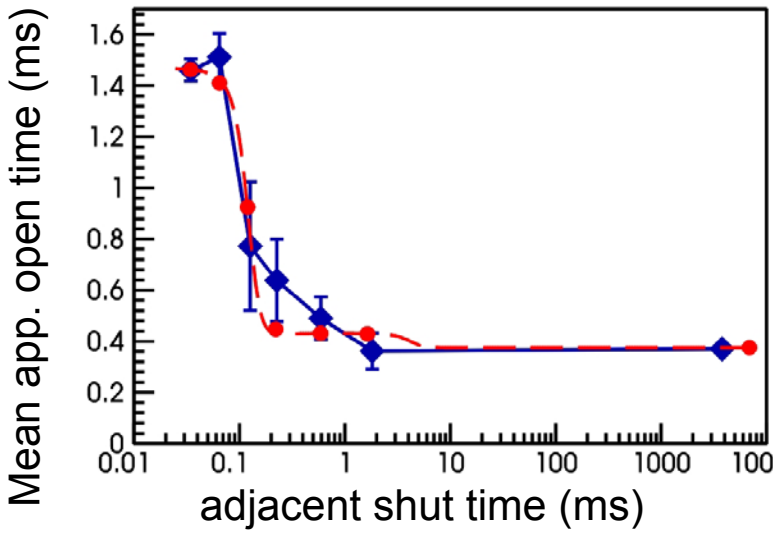




All openings



conditional open time (openings adjacent to apparent shut times shorter than 100 μs)



Blue: observed mean open time

Red: HJC predictions from fit

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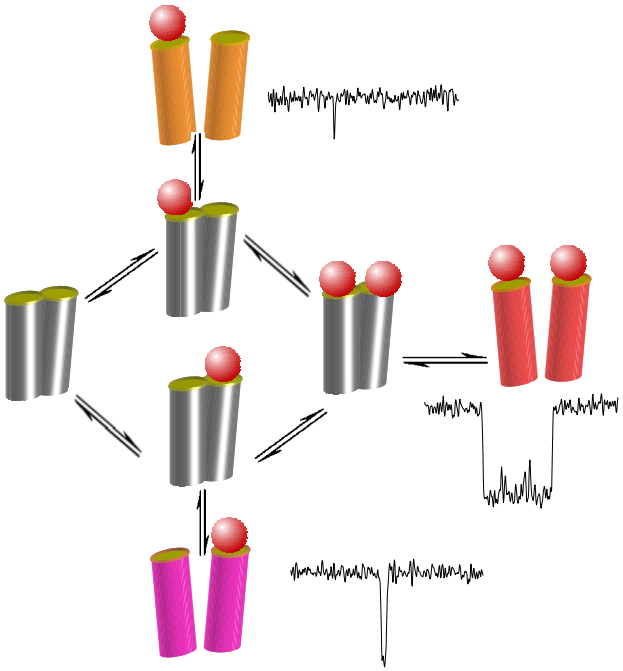
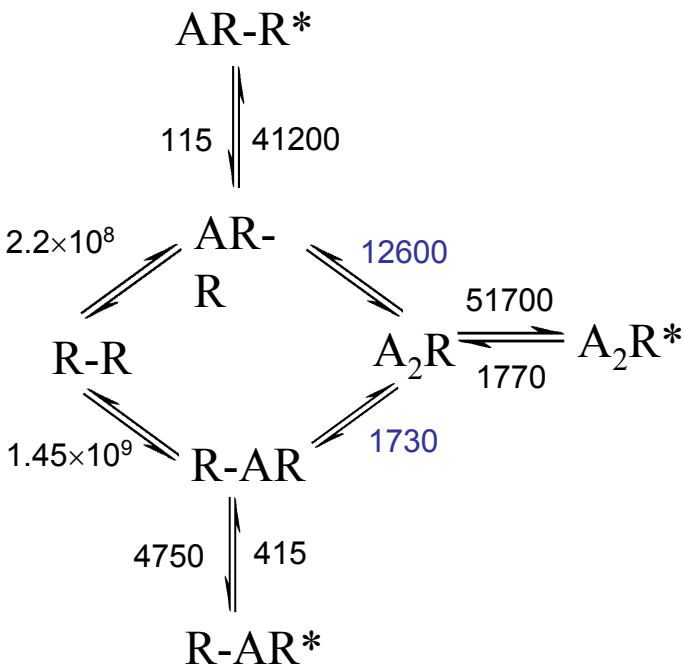
HJCsim Figure 6
sim39b

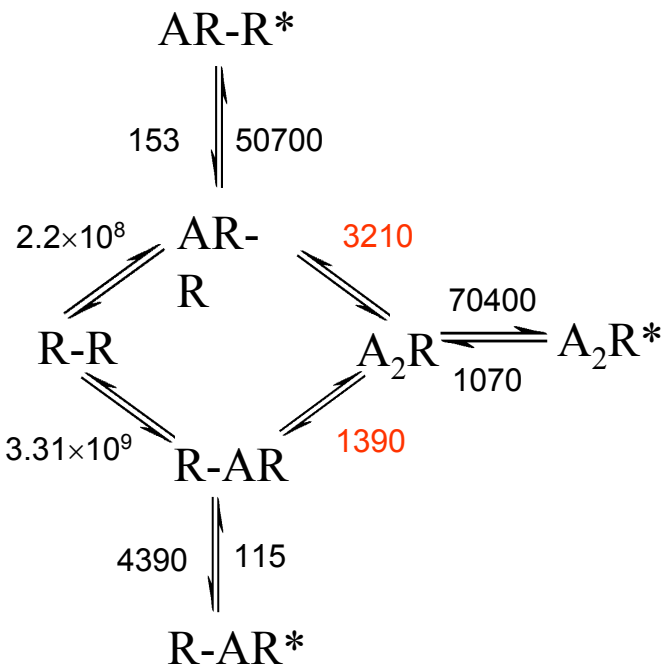
The mechanism



Wild type



εL221F



For the doubly-occupied receptor (mean of 5 patches in each case):

total dissociation rate	14300 ± 1640 s^{-1}	4600 ± 741 s^{-1}
opening rate (β)	51700 ± 2300 s^{-1}	70400 ± 2170 s^{-1}
shutting rate (α)	1770 ± 113 s^{-1}	1070 ± 119 s^{-1}

Thus the main effect of the mutation is to slow agonist dissociation from the shut state, and so to prolong the burst of openings (channel activation)

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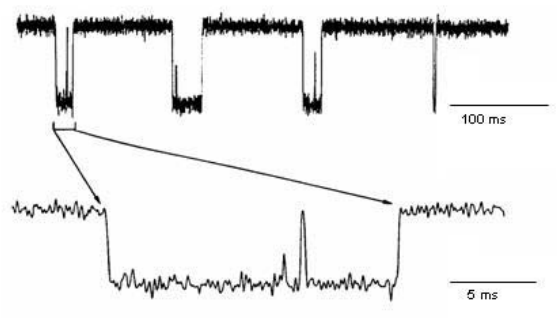
Come to our course (14th-18th June 2004)

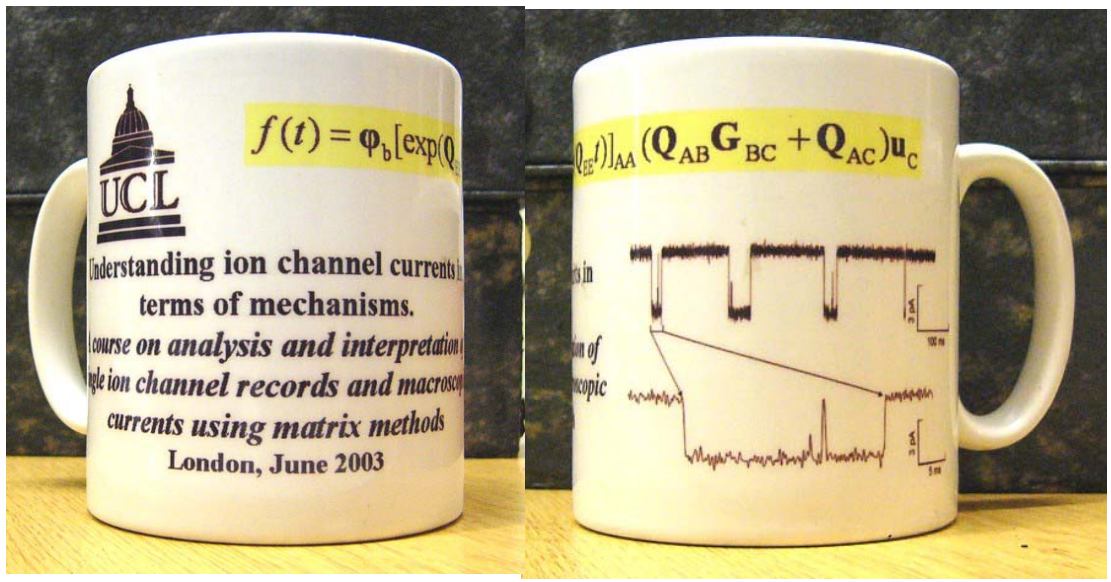
$$f_{bst}(t) = \varphi_b [\exp(Q_{EE} t)]_{AA} (Q_{AB} G_{BC} + Q_{AC}) u_C$$

Understanding ion channel currents in terms of mechanisms.

A course on analysis and interpretation of single ion channel records and macroscopic currents using matrix methods

London, June 2003





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