Workshop: *Dynamical Complex Systems*
INTECIN -- Facultad de Ingeniería (U.B.A.)
December 17th, 2009 -- 3rd floor, EGRIET's room

Solving the inverse problem: deducing a kinetic model from electrophysiology data

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Direct problem

- We have an ion channel kinetic model (transitions probabilities between states)
- We know the experimental conditions

→

We deduce the expected electrophysiology data

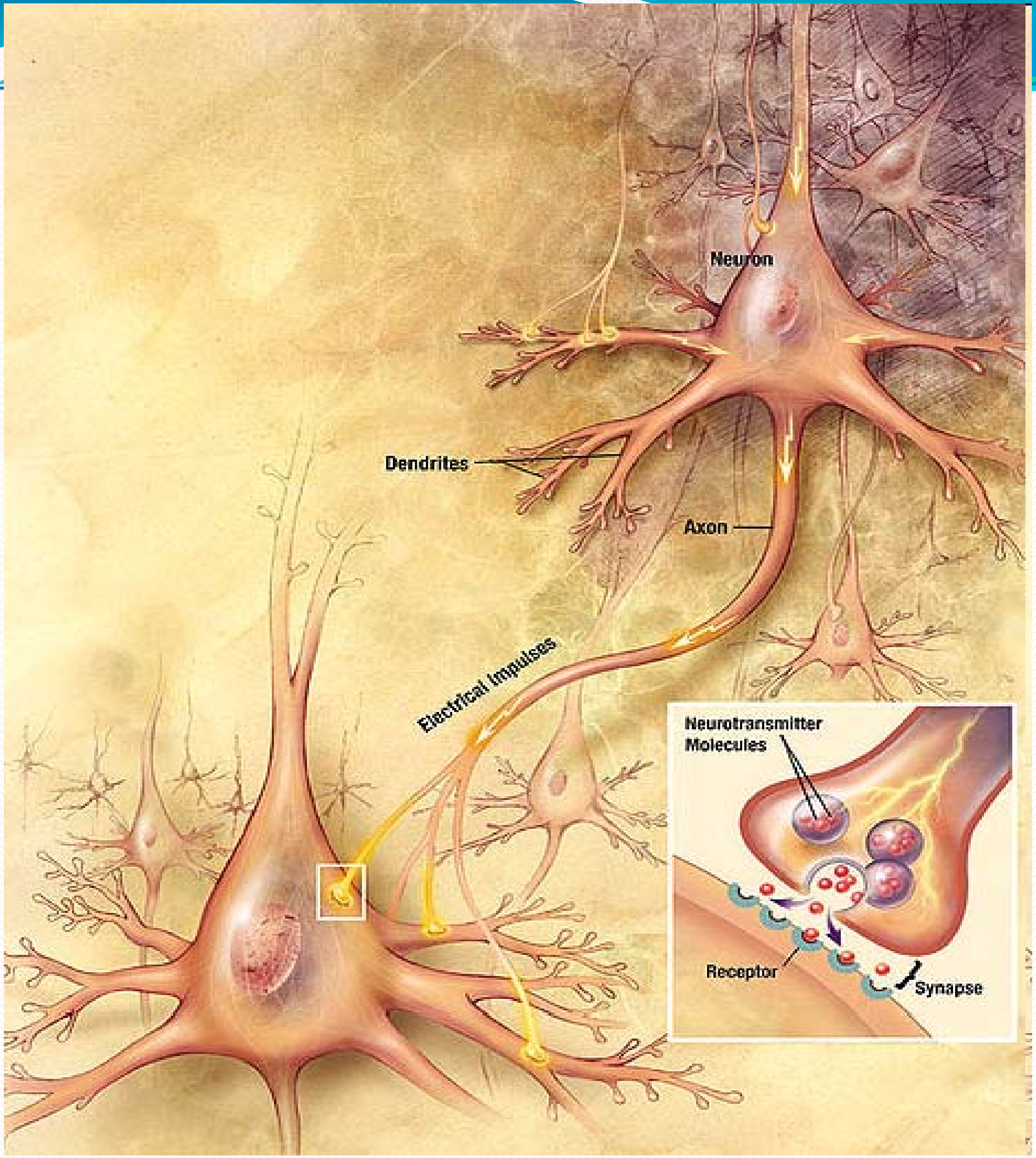
Inverse problem

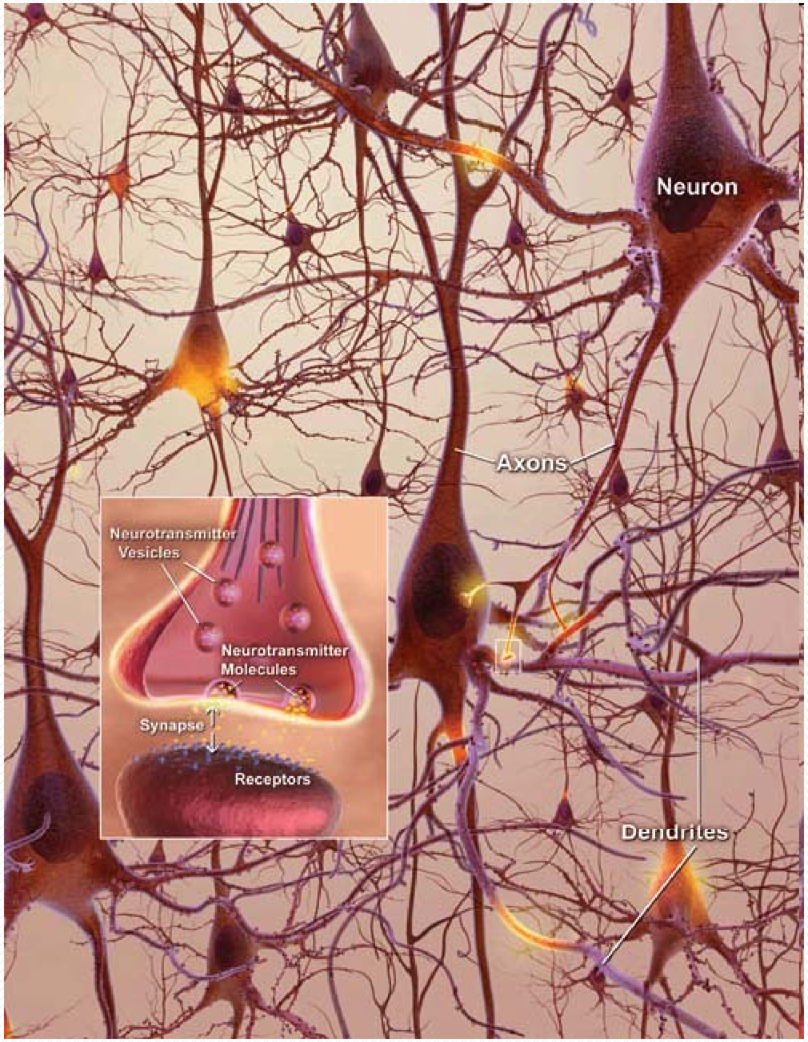
- We have the electrophysiology data
- We have the experimental conditions

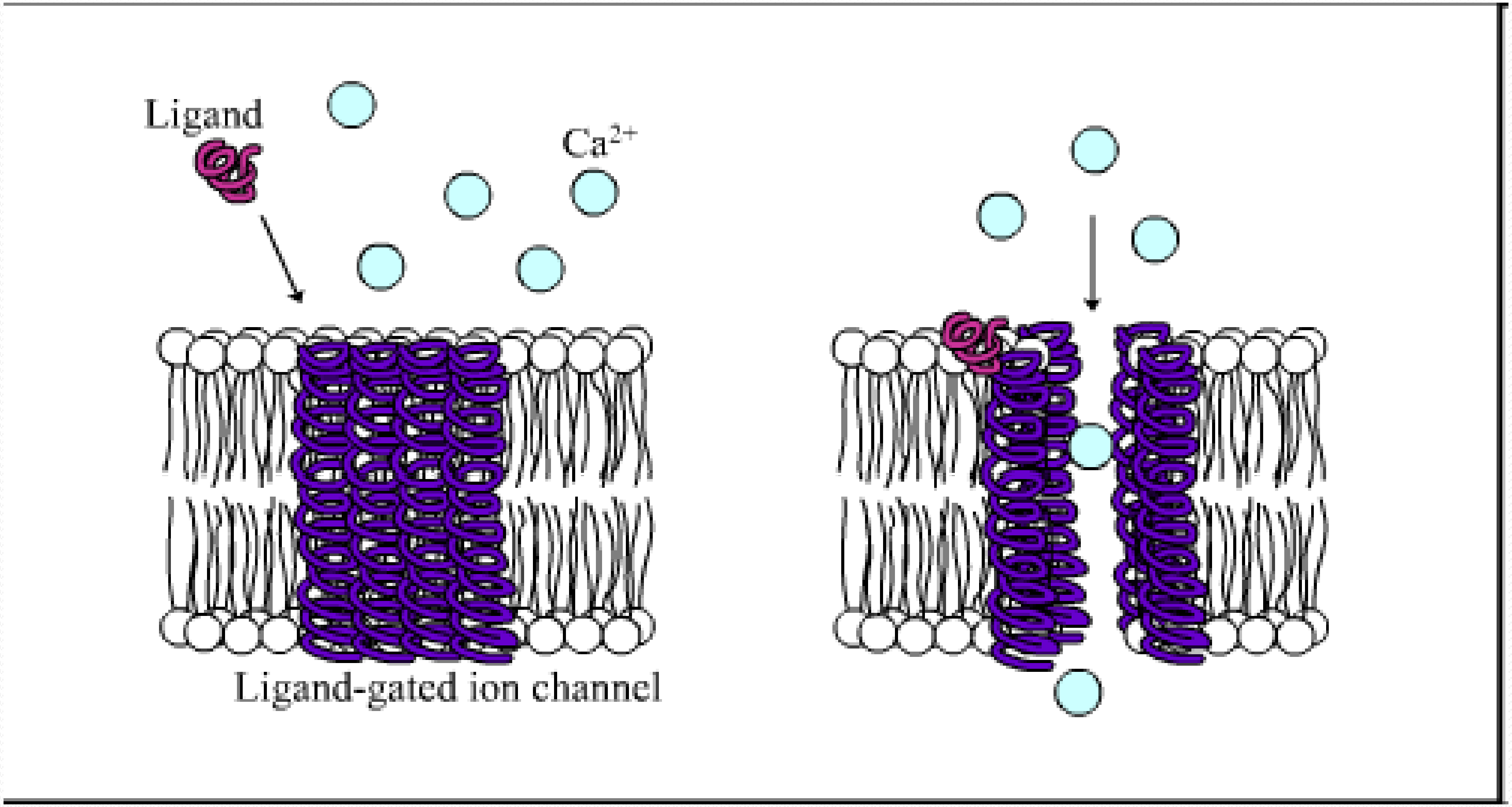
→→→

We deduce the kinetic model

Some background information

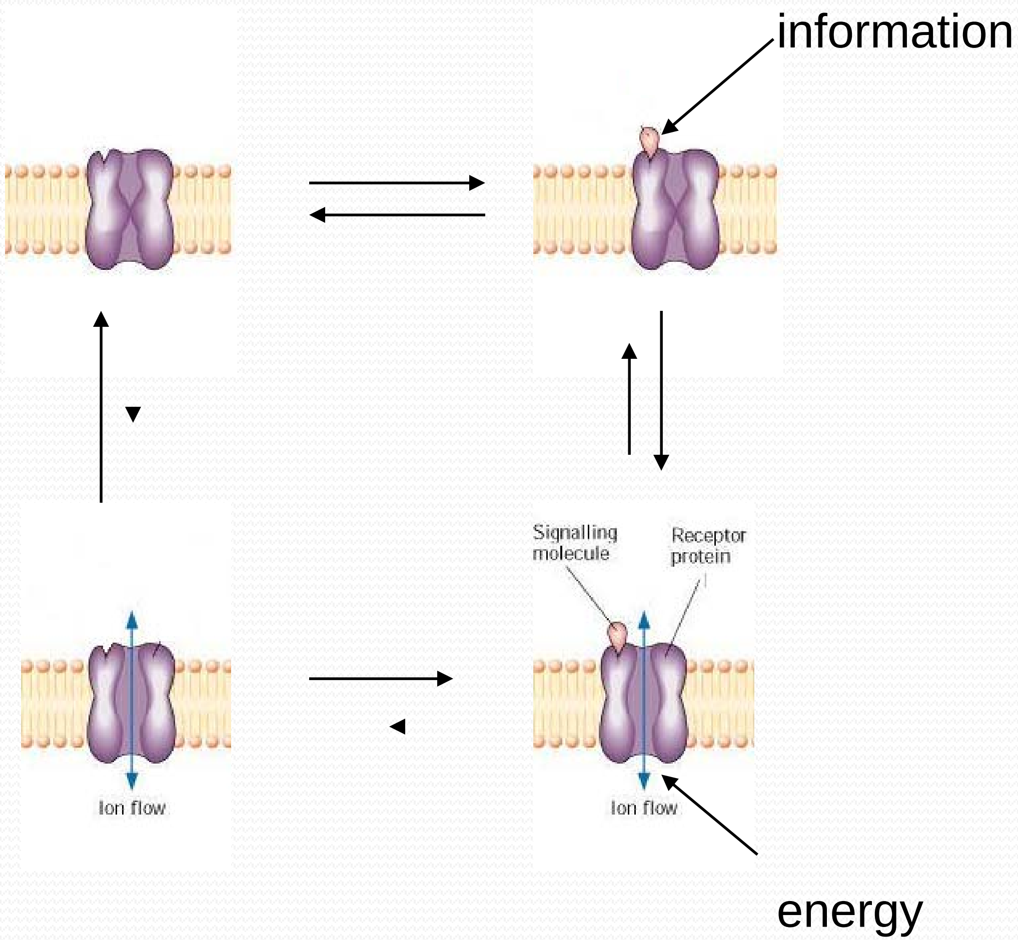

Neuron
Dendrites
Axon
Electrical impulses
Neurotransmitter
Molecules
Receptor
Synapse


Neuron
Axons
Neurotransmitter
Vesicles
Neurotransmitter
Molecules
Synapse
Receptors
Dendrites

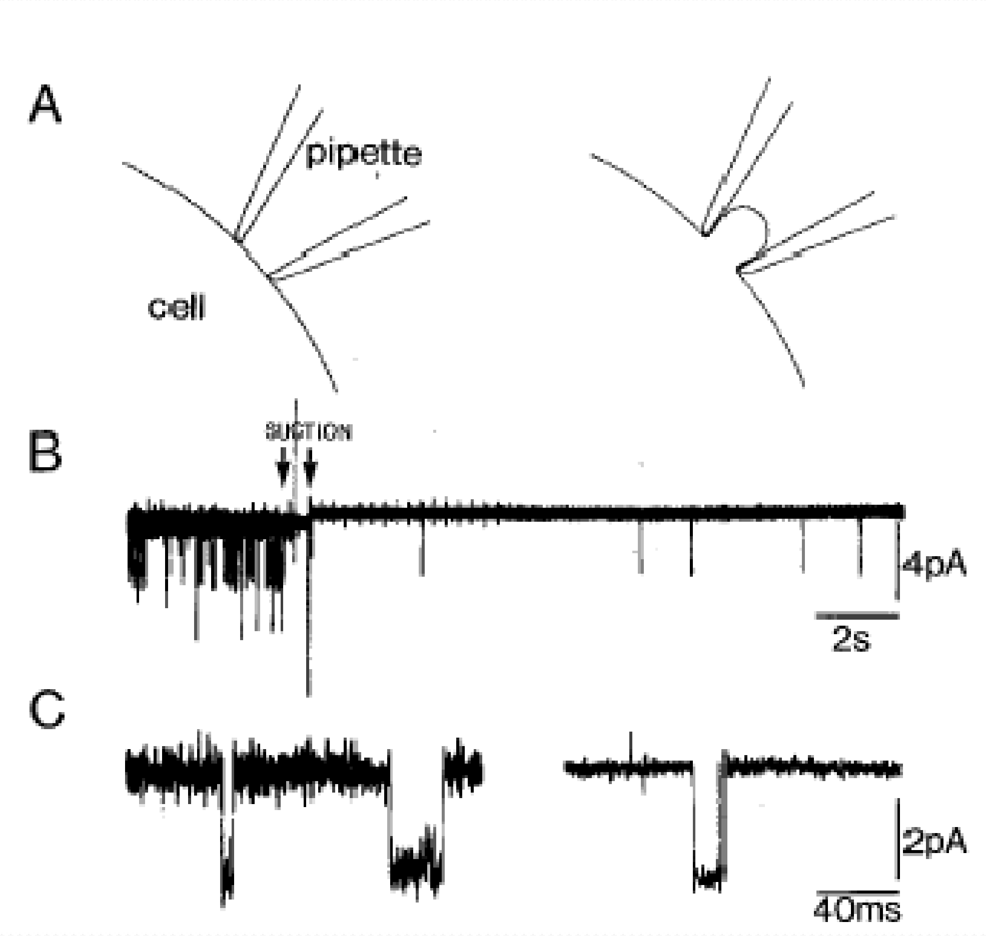


Ligand
Ca2+
Ligand-gated ion channel

Alosteric coupling

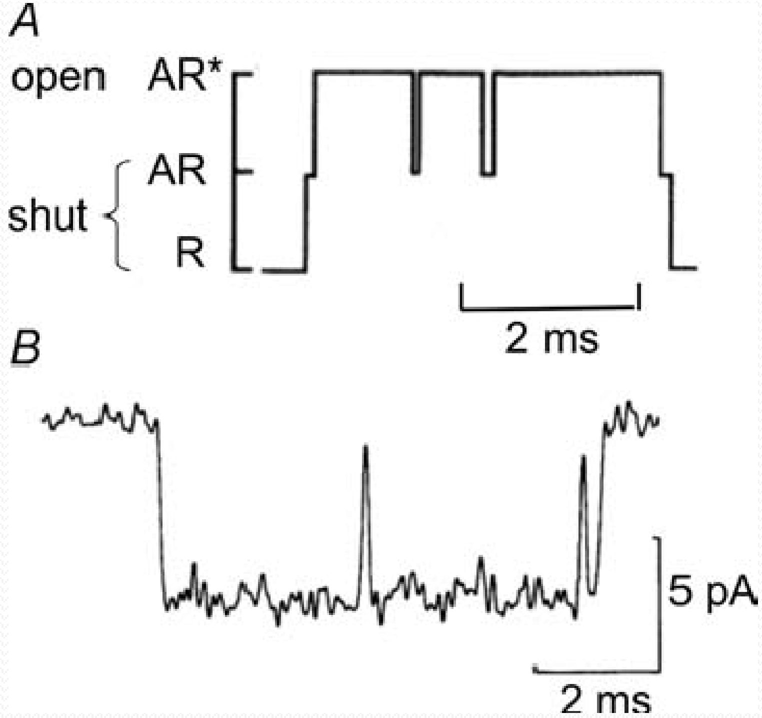


Patch clamp technique



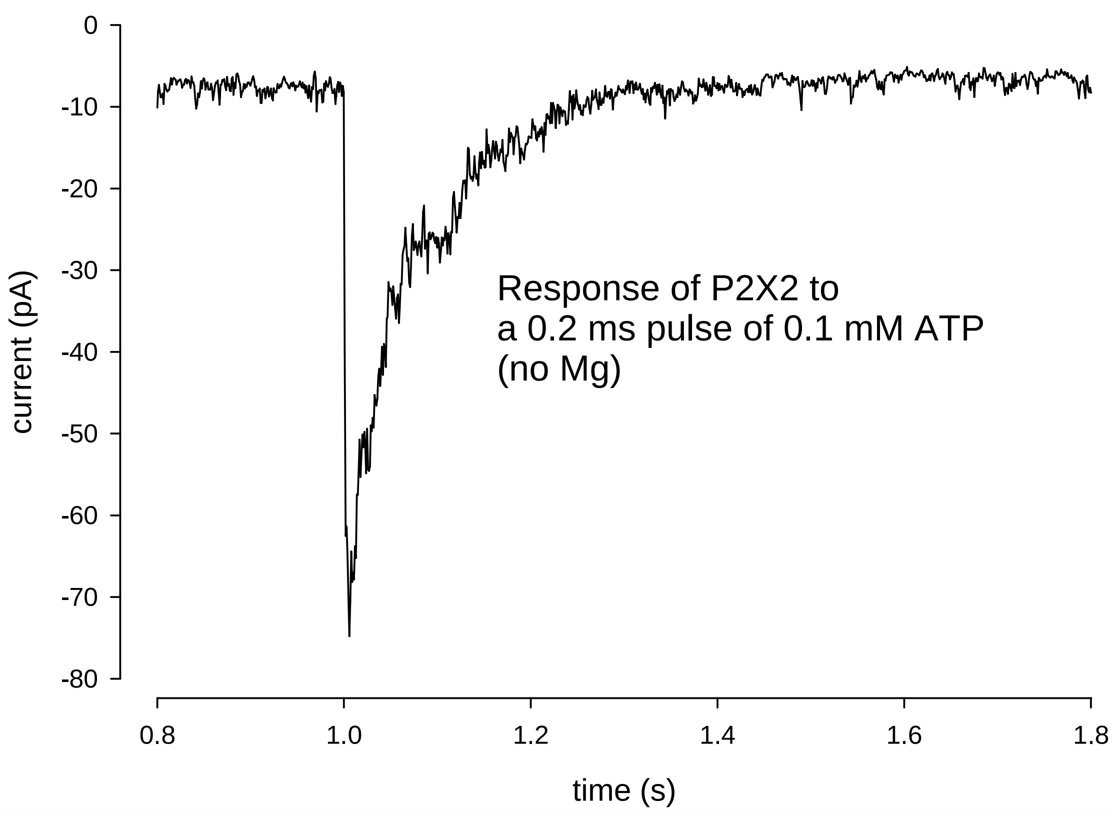
O. P. Hamill, A. Marty, E. Neher, B. Sakmann, and F. J. Sigworth
Pflügers Arch (1981) 39: :85 – 100

Ligand gated channels

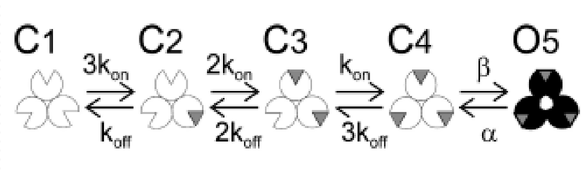


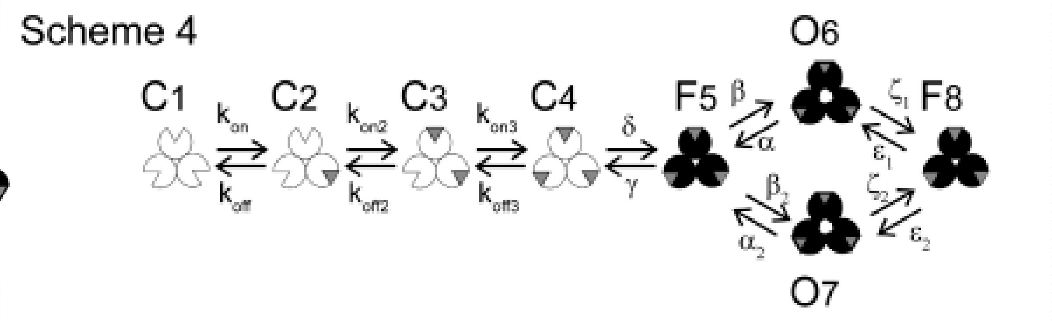
- Closed without agonist
- On agonist presence, ion channels open and close at random

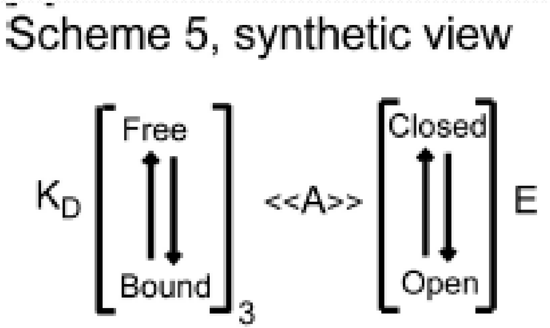
Macroscopic currents

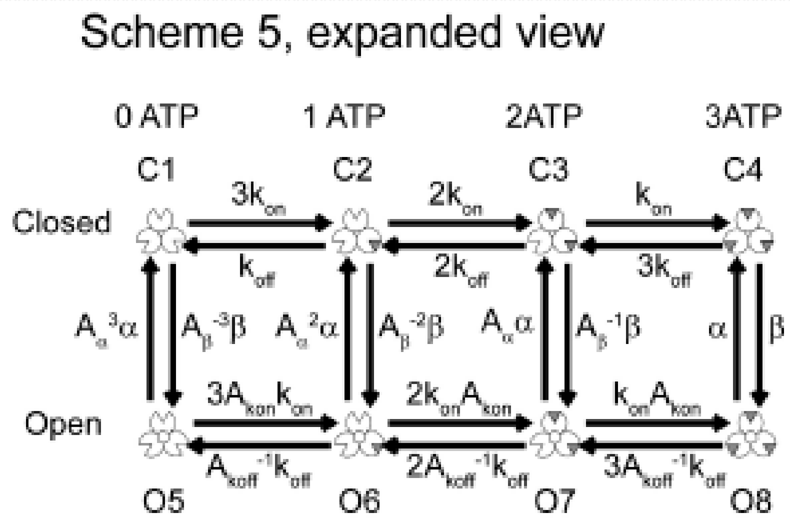


Kinetic models









Direct problem

- Markov process master equation

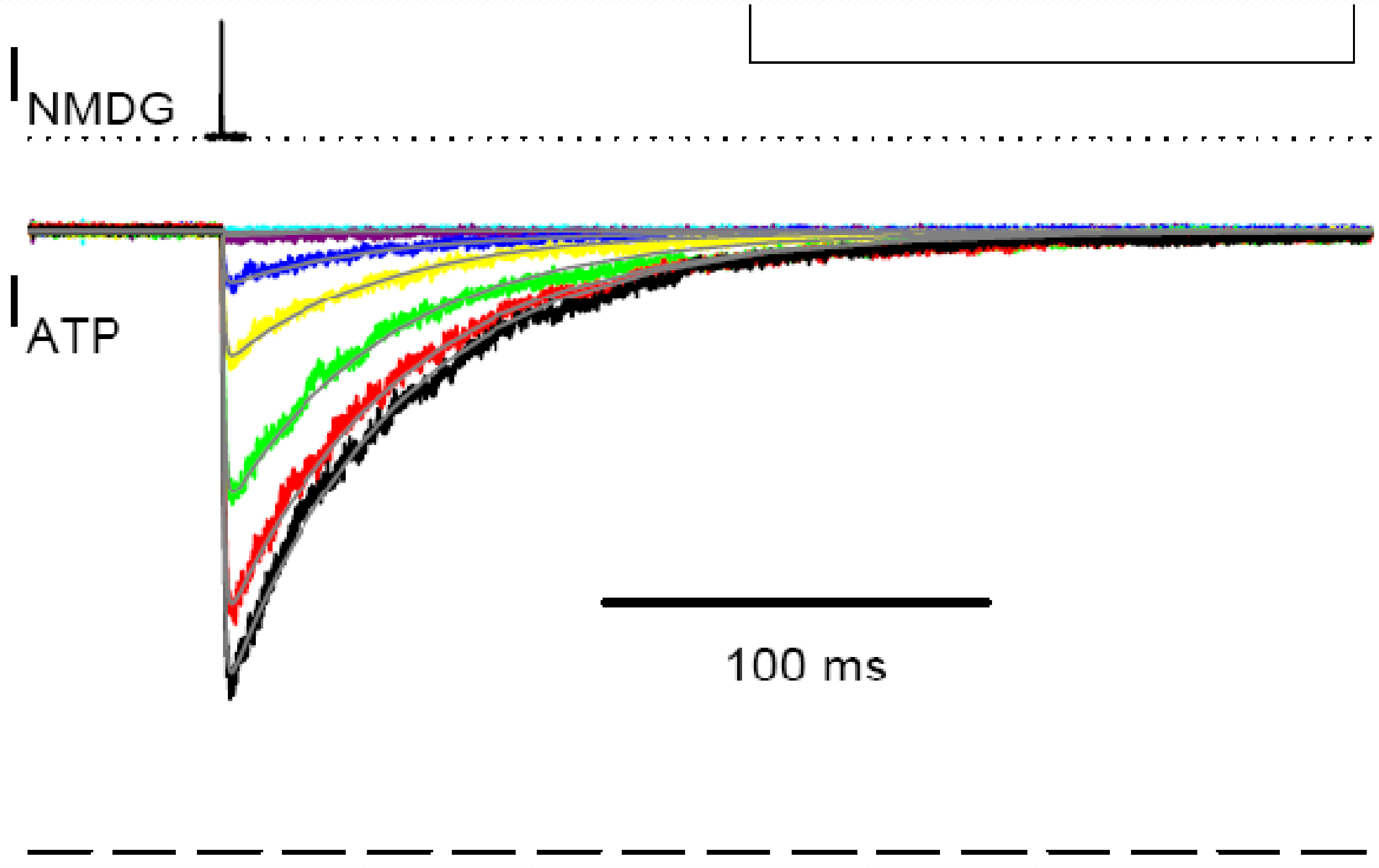
$$\dot{p}(t) = p(t) \cdot \mathbf{Q}(t)$$

$$p(t + \Delta t) = p(t) \cdot \exp\left(\mathbf{Q} \cdot \Delta t\right).$$

$$\mathbf{Q}(t) = \left(\mathbf{Q_0} + \mathbf{Q_a} \cdot ATP(t)\right).$$

$$y(t) = p(t) \cdot g$$

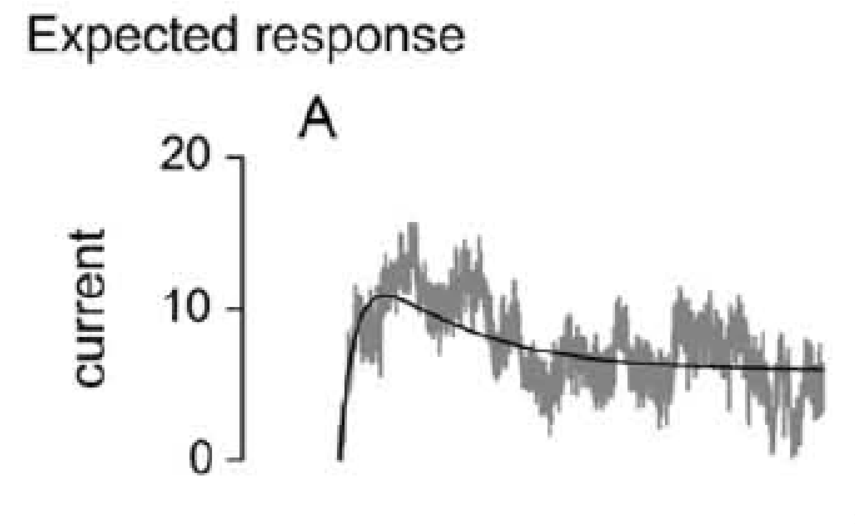
Inverse problem



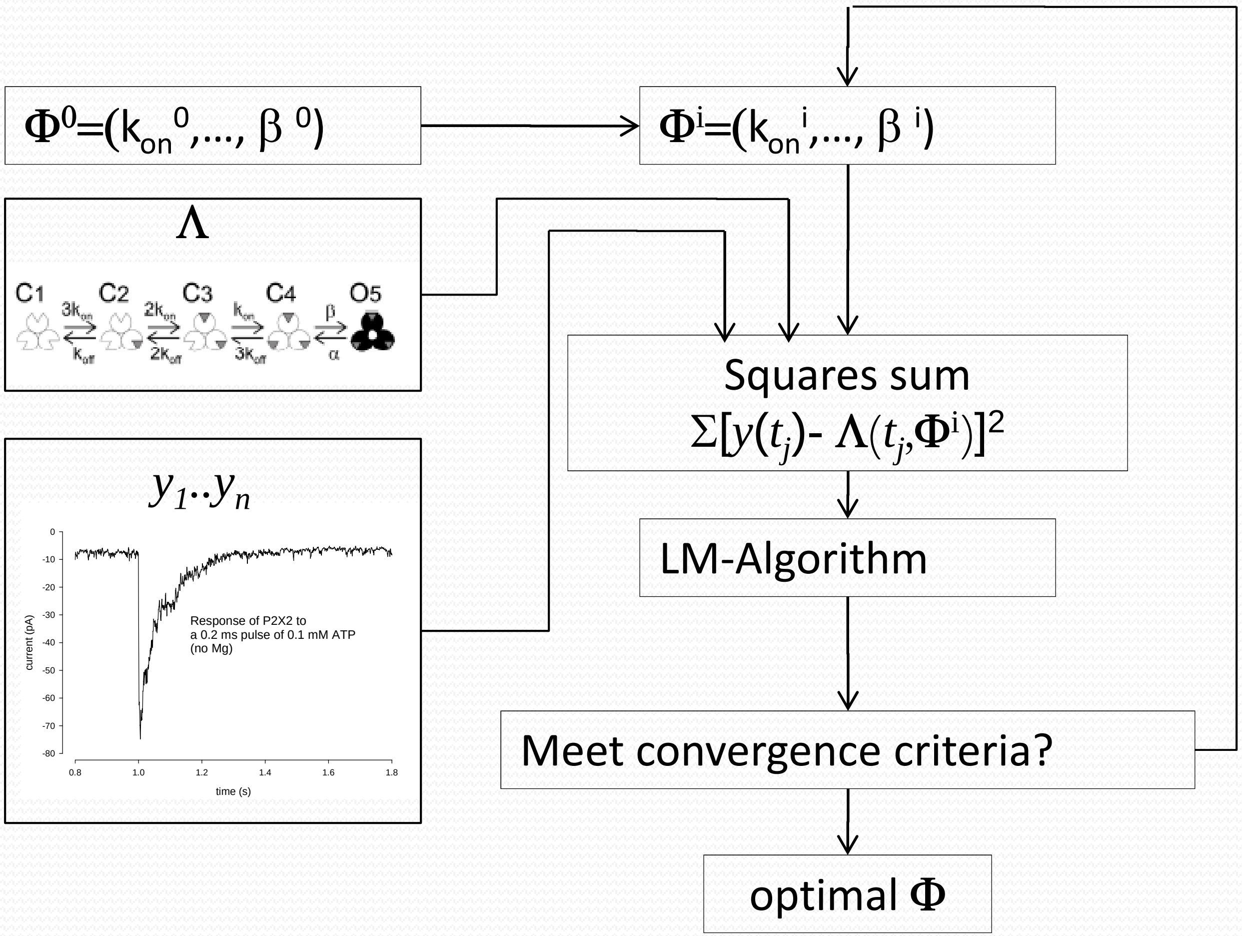
Moffatt & Hume JGP 2007

Least squares approach

- Given a kinetic model, make an initial guess of the kinetic constants and minimize the squared difference between expected and measured.

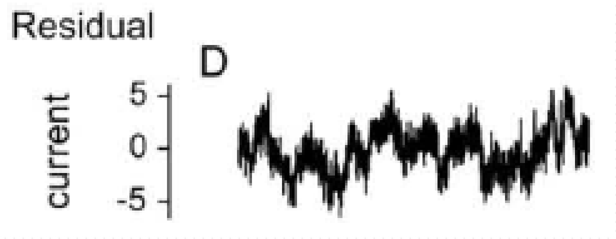


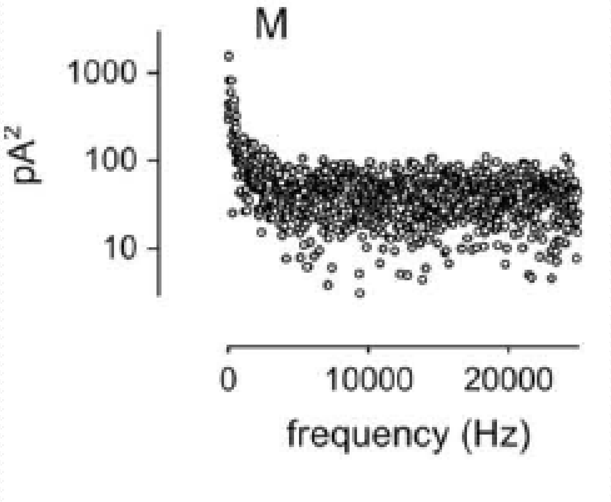
Least squares estimation



Problems with this approach

- Time correlation on the residuals-> NO VALID STATISTICAL ANALYSIS

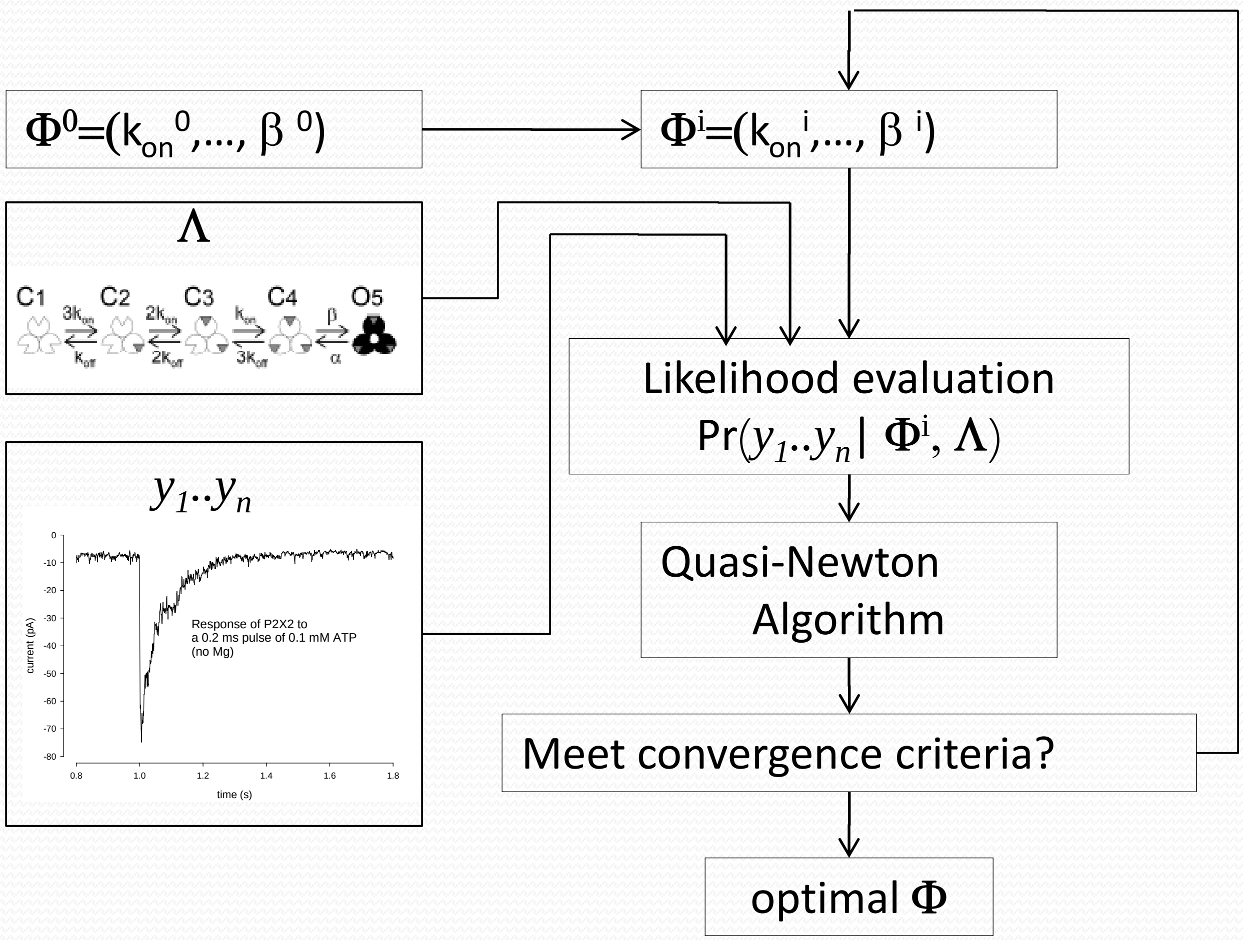




A possible solution

- Maximize the likelihood.

Maximum likelihood estimation



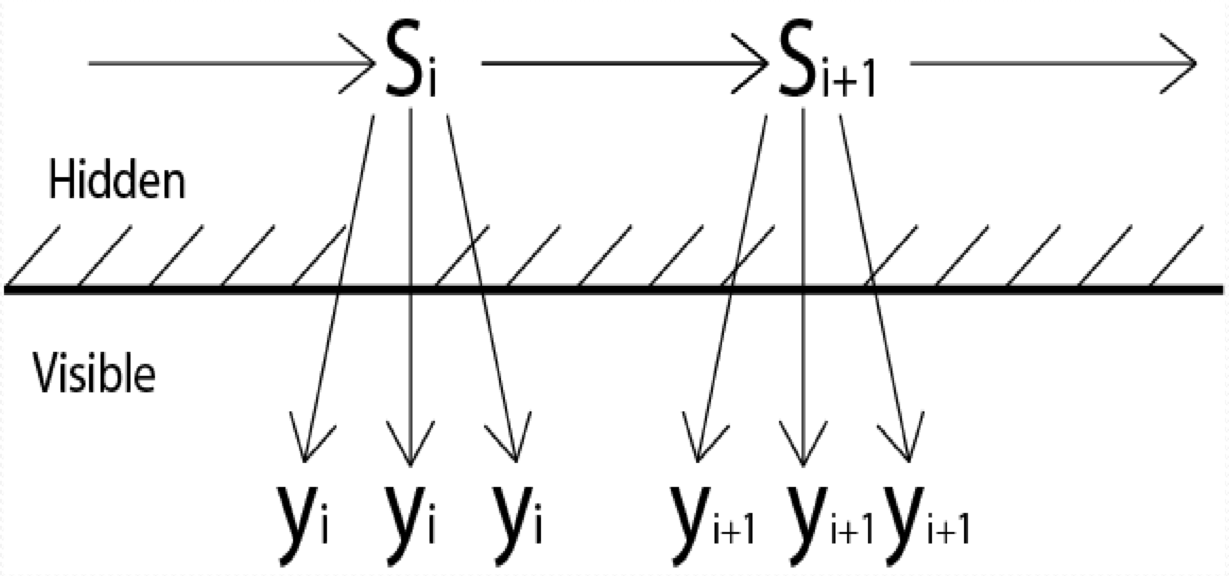
Using the incremental likelihood

$$\ell_T = \ell(\Theta | y_1 \dots y_T) = \prod_{t=1}^{T} \ell'_t,$$

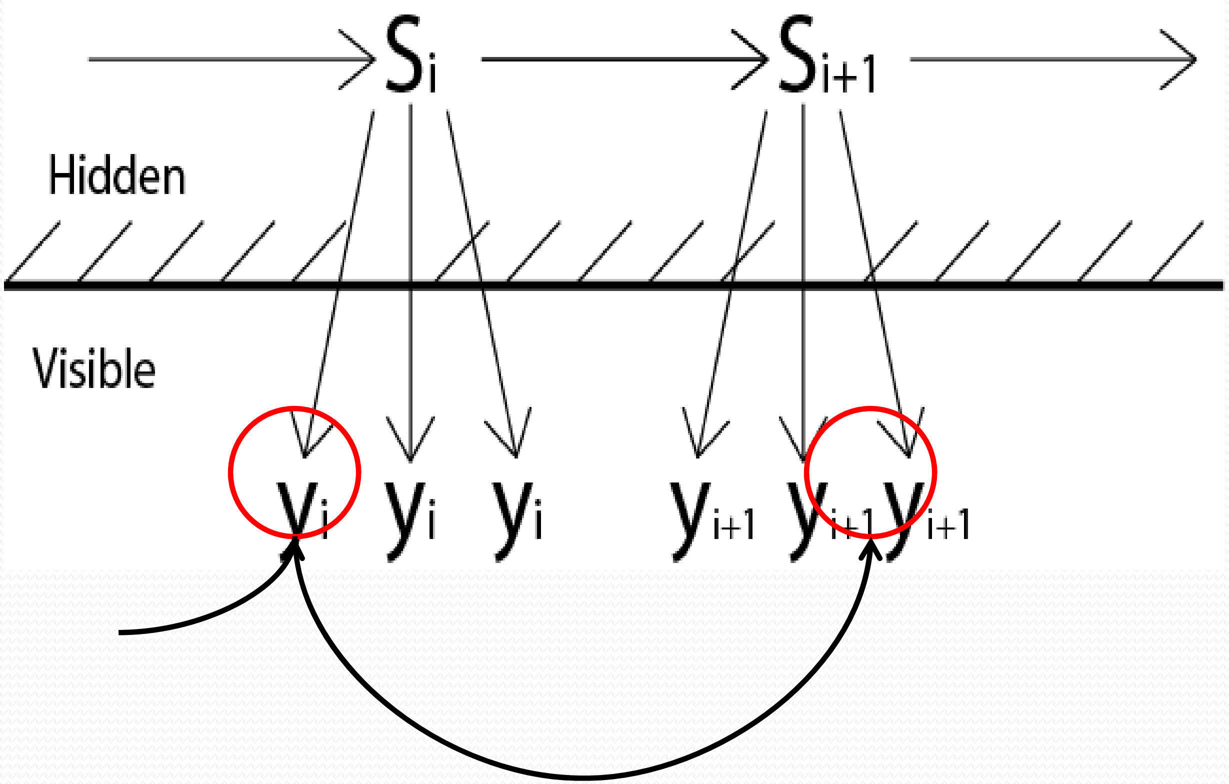
$$\ell'_t = Pr(y_t | y_1 \dots y_{t-1}, \Theta).$$

- It decomposes the likelihood of the joint measurement on a product of the partial likelihoods of each measurement, given the previous ones.

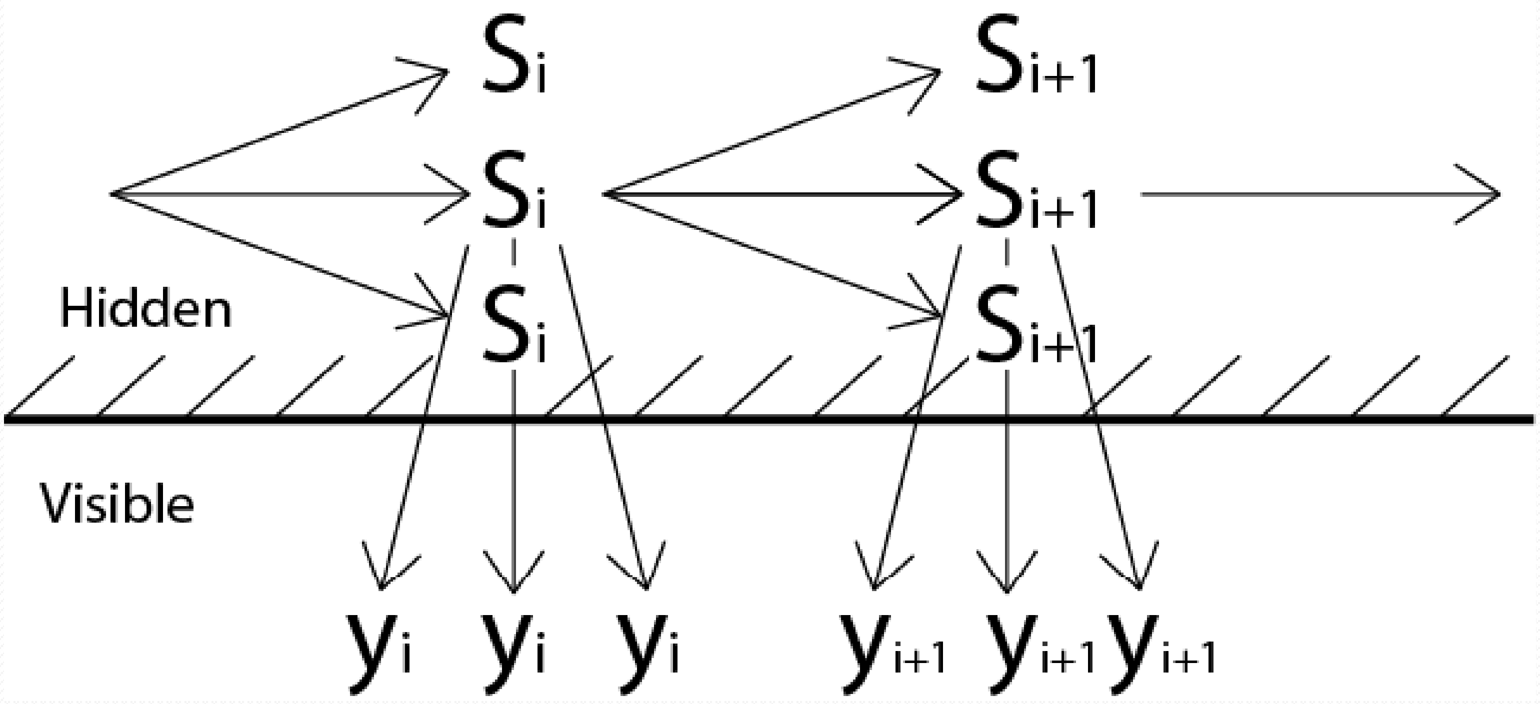
Deterministic models



Deterministic models



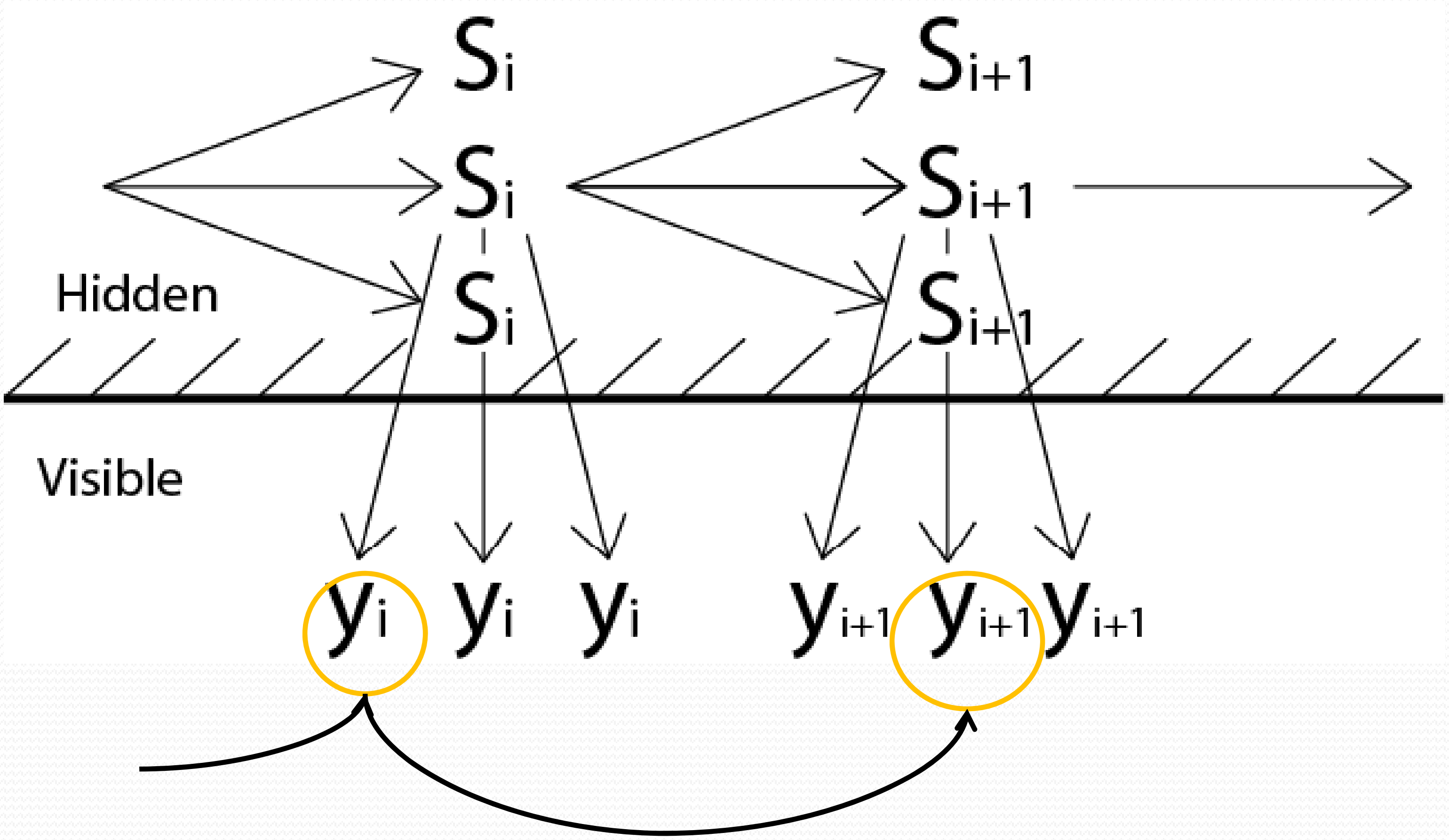
Stochastic models



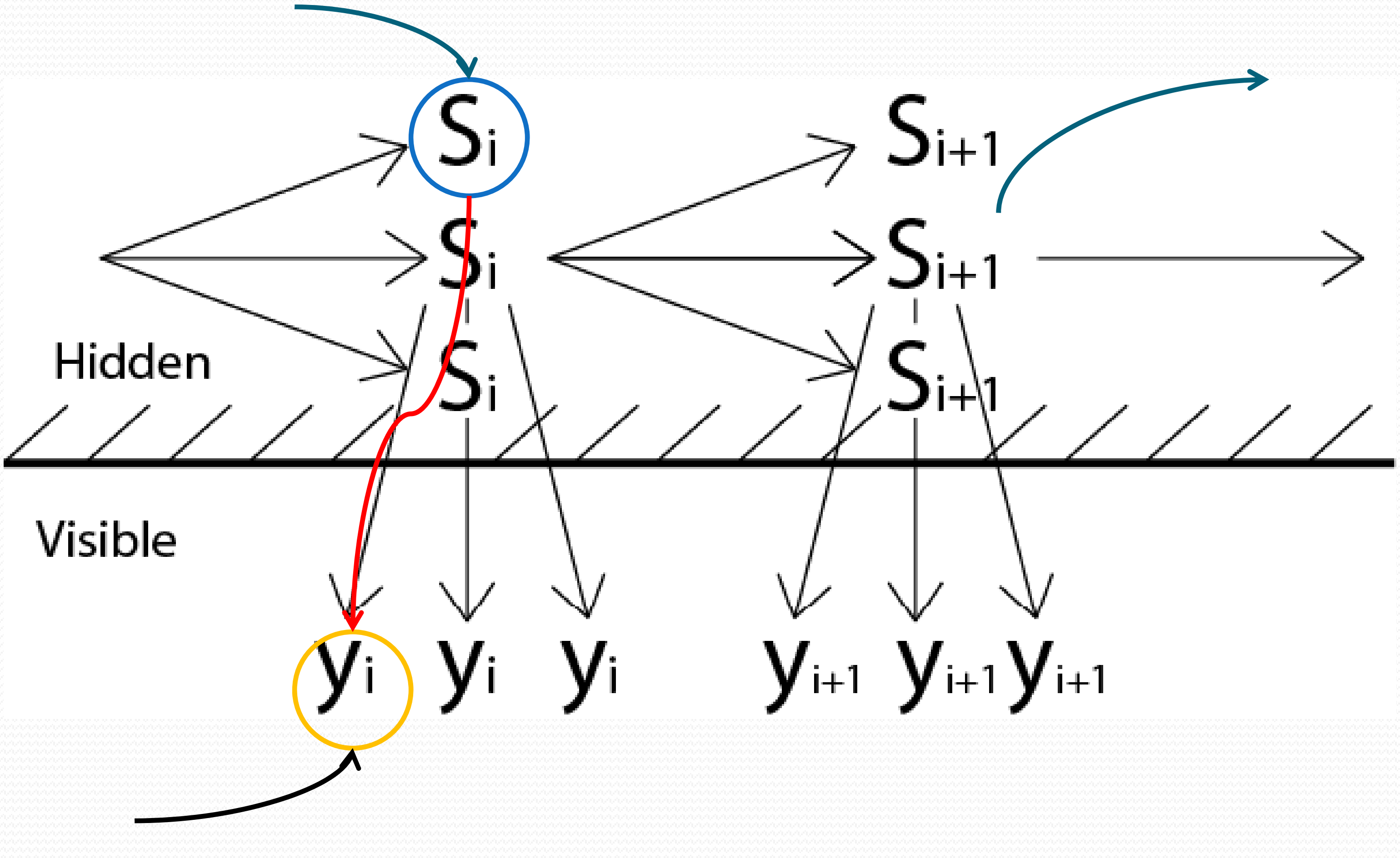
Classical Hidden Markov Modeling

- Markov model: rules of change of the hidden system
- Observational model: the relationship between the hidden and the observed
- The sequence of hidden states
- The sequence of observations

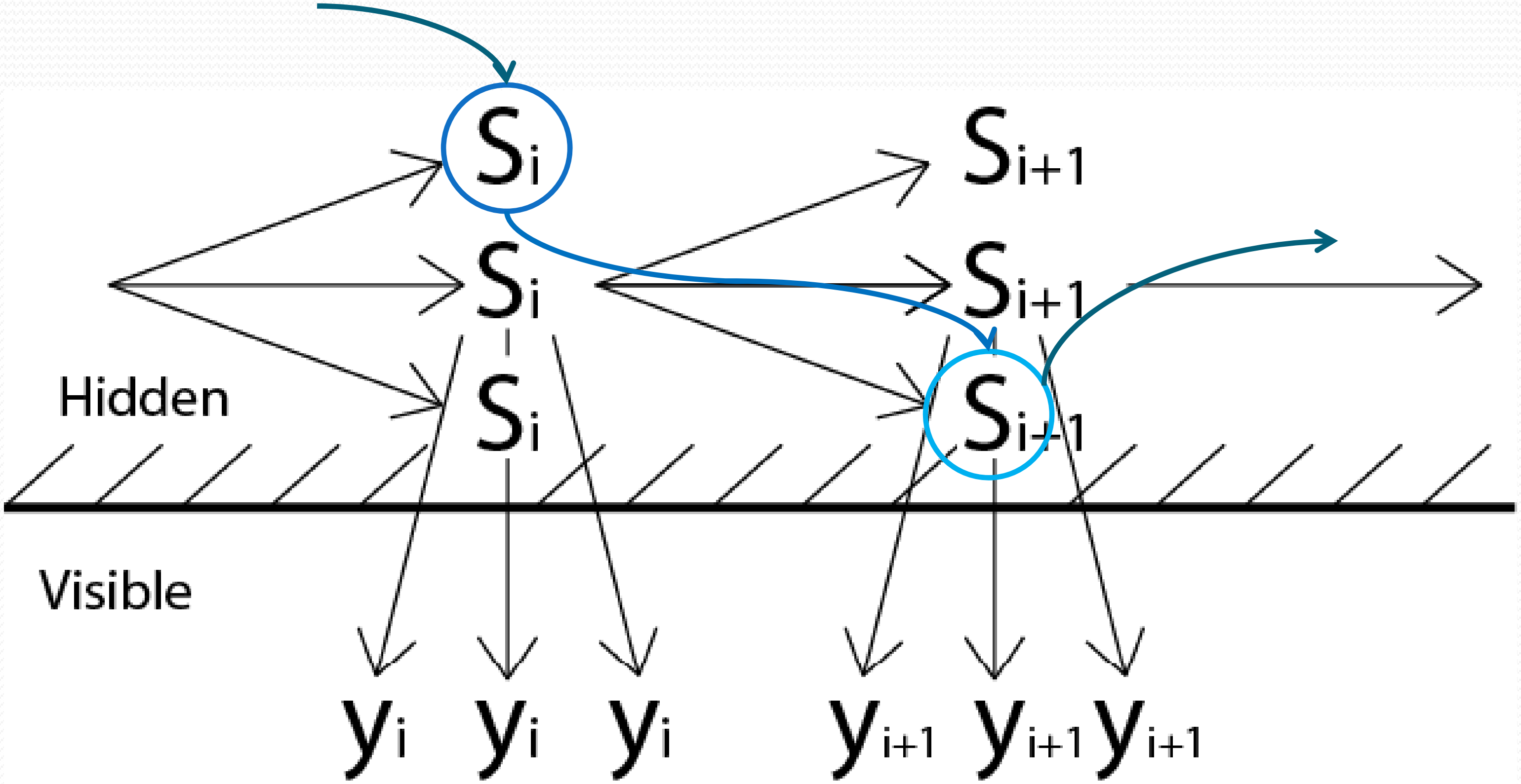
Observations



Observational model



Markov model



Bayesian statistics

- Probability is the measure of the plausibility of something given a series of hypothesis and data.
- Bayes theorem

$$\Pr(H_i|D, X) = \Pr(H_i|X)\frac{\Pr(D|H_i, X)}{\Pr(D|X)}$$

Hi-> Series of alternative Hypothesis
D-> new data
X-> old data

Bayes theorem to HMM

- Incremental Likelihood from Observational model

$$\Pr\left(y_n | y_{1..n-1}, \Theta\right) = \sum_j \Pr\left(y_n | s_j(t_n), y_{1..n-1}, \Theta\right) \Pr\left(s_i(t_n) | y_{1..n-1}, \Theta\right)$$

- Posterior

$$\Pr\left(s_i(t_n) | y_{1...n}, \Theta\right) = \Pr\left(s_i(t_n) | y_{1...n}, \Theta\right) \frac{\Pr\left(y_n | s_i(t_n), y_{1..n-1}, \Theta\right)}{\Pr\left(y_n | y_{1..n-1}, \Theta\right)}$$

Markov chain rule

- Markov model

$$\Pr\left(s_i(t_{n+1}) | s_j(t_n)\right) = a_{i,j}$$

$$a_{i,j} = \exp\left(\mathbf{Q} \cdot (t_{n+1} - t_n)\right)$$

- Next prior

$$\Pr\left(s_j(t_{n+1}) | y_{1 \ldots n}, \Theta\right) = \sum_j a_{i,j} \Pr\left(s_i(t_n) | y_{1 \ldots n}, \Theta\right)$$

Approaches to many channels

Definition of the “meta state”

Microscopic approach

- It lists all the possible
  M $= \binom{N+k-1}{N}$ combination of states:
  N,0,0,0,…,0
  N-1,1,0,…,0
  N-1,0,1,…,0
  0,0,0,…N

- The knowledge we have about the state of the system is a M-vector

Microscopic recursive

- It uses the same equations of single channel applied to the M-state.

Macroscopic approach

$$Pr(\mathbf{r}_t) = N\left(\mathbf{r} - \boldsymbol{\mu}_t, \frac{1}{N}\boldsymbol{\Sigma}_t\right) = N^{k/2}(2\pi)^{-k/2}|\boldsymbol{\Sigma}_t|^{-1/2}$$

$$\exp\left(-\frac{N}{2}(\mathbf{r} - \boldsymbol{\mu}_t) \cdot \boldsymbol{\Sigma}_t^{-1} \cdot (\mathbf{r} - \boldsymbol{\mu}_t)^{T}\right),$$

- The knowledge about the state of the channels (i.e., **r**) is provided by a continuous multinormal distribution.
- Two parameters define the distribution: the mean μ and covariance Σ

Incremental Likelihood

$$\ell'_t = \int_s Pr(y_t | s_t = \mathbf{r}, \varepsilon^2) \cdot p^*_t(\mathbf{r}) \cdot \mathbf{dr}.$$

$$\ell'_t = \int_s N(y_t - N\mathbf{r}_t \cdot \boldsymbol{\gamma}, \varepsilon^2) N\left(\mathbf{r}_t - \boldsymbol{\mu}^*_t, \frac{1}{N}\boldsymbol{\Sigma}^*_t\right) \mathbf{dr}_t,$$

$$\ell'_t = N(y_t - y^*_t, \sigma^2_t),$$

$$y^*_t = N\boldsymbol{\mu}^*_t \cdot \boldsymbol{\gamma},$$

$$\sigma^2_t = \varepsilon^2 + N\boldsymbol{\gamma}^{\mathbf{T}} \cdot \boldsymbol{\Sigma}^*_t \cdot \boldsymbol{\gamma}.$$

- We integrate the product of the measurement probability by the prior

Posterior

$$p_t(\mathbf{r}) = \frac{N(y_t - N\mathbf{r}_t \cdot \boldsymbol{\gamma}, \varepsilon^2)}{\ell'_t} N\left(\mathbf{r}_t - \boldsymbol{\mu}_t^*, \frac{1}{N}\boldsymbol{\Sigma}_t^*\right).$$

$$p_t(\mathbf{r}) = N\left(\mathbf{r}_t - \boldsymbol{\mu}_t, \frac{1}{N}\boldsymbol{\Sigma}_t\right),$$

$$\boldsymbol{\mu}_t = \boldsymbol{\mu}_t^* + \frac{(y_t - y_t^*)}{\sigma_t^2} \cdot \boldsymbol{\gamma}^{\mathrm{T}} \cdot \boldsymbol{\Sigma}_t^*,$$

$$\boldsymbol{\Sigma}_t = \boldsymbol{\Sigma}_t^* - \frac{N}{\sigma_t^2}\boldsymbol{\Sigma}_t^* \cdot \boldsymbol{\gamma} \cdot \boldsymbol{\gamma}^{\mathrm{T}} \cdot \boldsymbol{\Sigma}_t^*.$$

- We normalize the priors by the measurement probabilities.
- We just update the value of the mean and covariance

Completing the loop

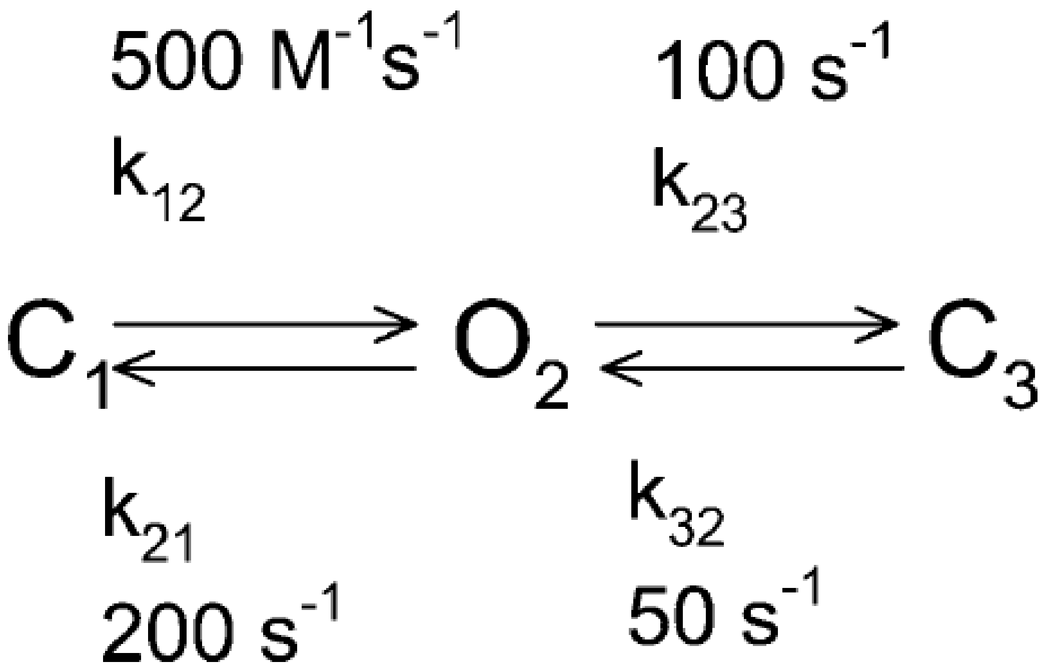
$$\boldsymbol{\mu}^{*}_{t+\Delta t} = \boldsymbol{\mu}_{t} \cdot \mathbf{A},$$

$$\boldsymbol{\Sigma}^{*}_{t+\Delta t} = (\boldsymbol{\mu}_{t} \cdot \mathbf{A})^{\mathbf{D}} - \mathbf{A}^{\mathrm{T}} \cdot \boldsymbol{\mu}^{\mathbf{D}}_{t} \cdot \mathbf{A} + \mathbf{A}^{\mathrm{T}} \cdot \boldsymbol{\Sigma}_{t} \cdot \mathbf{A}.$$

- The mean is updated with the usual formula for single channels

Simulations

Pet model



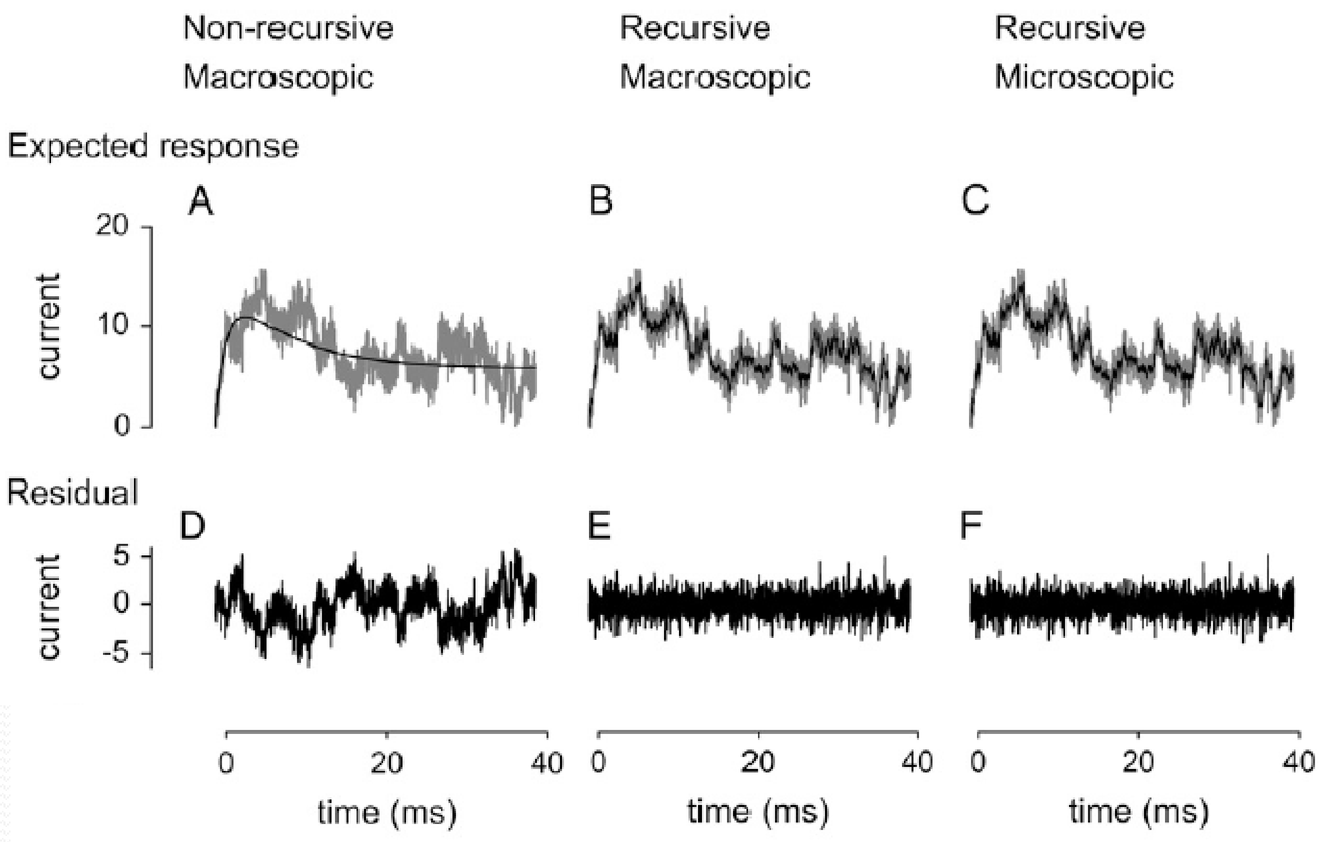
ε=1 pA; γ=1pA; sample time=0.02ms

Algorithms

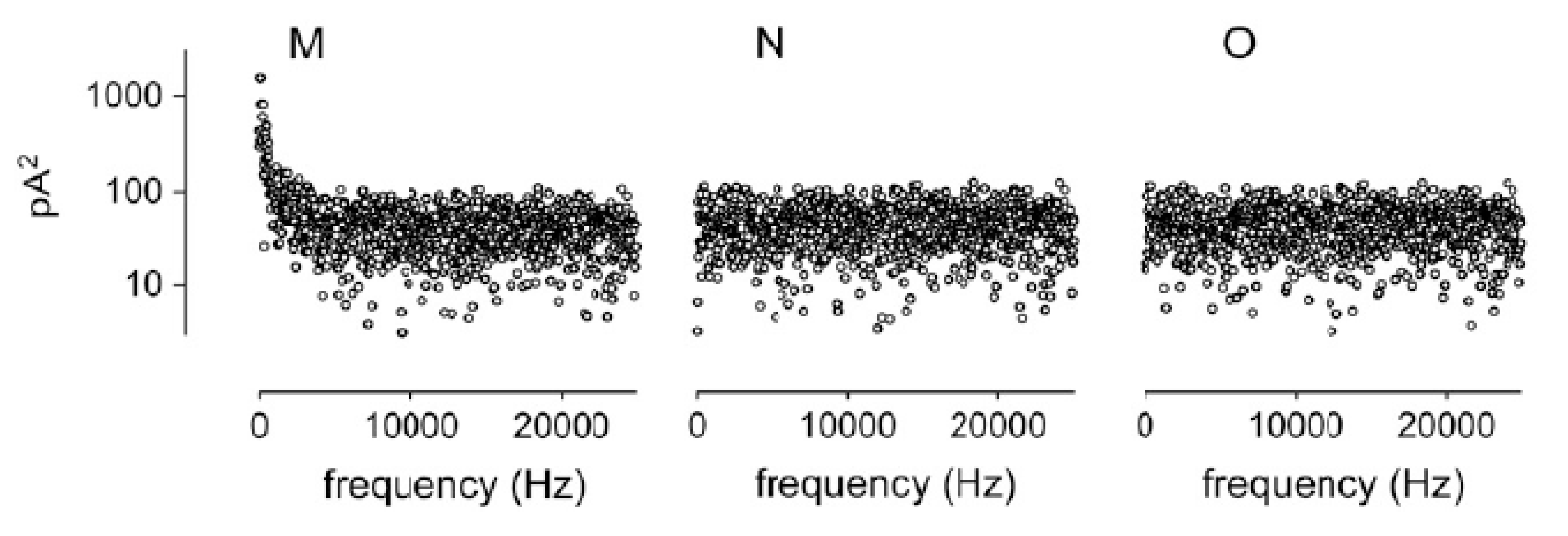
- Microscopic Recursive
- Macroscopic Recursive
- Macroscopic Non Recursive

Non-stationary conditions

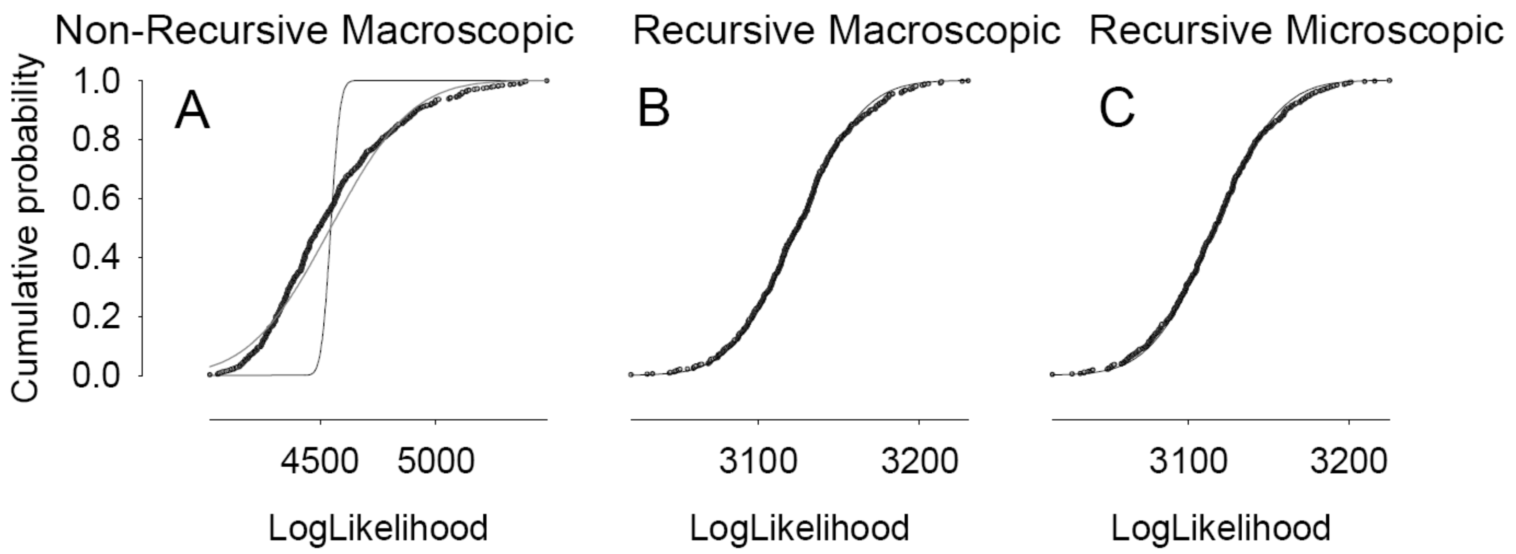
Prediction of the response



FFT of the residuals



Likelihood distribution



- The expected variance of the loglikelihood of a normal is ½, therefore the whole loglikelihood has a $\sigma^2 = 1/2\ n_{samples}$

Prior probability evolution

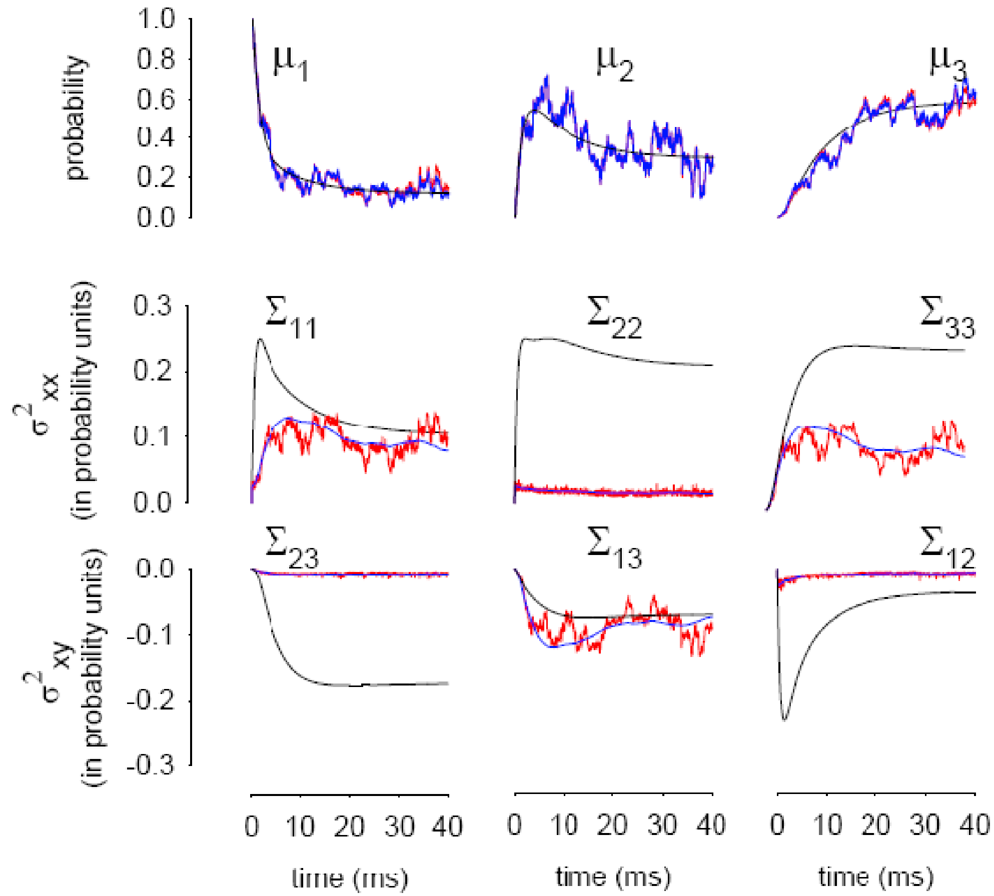
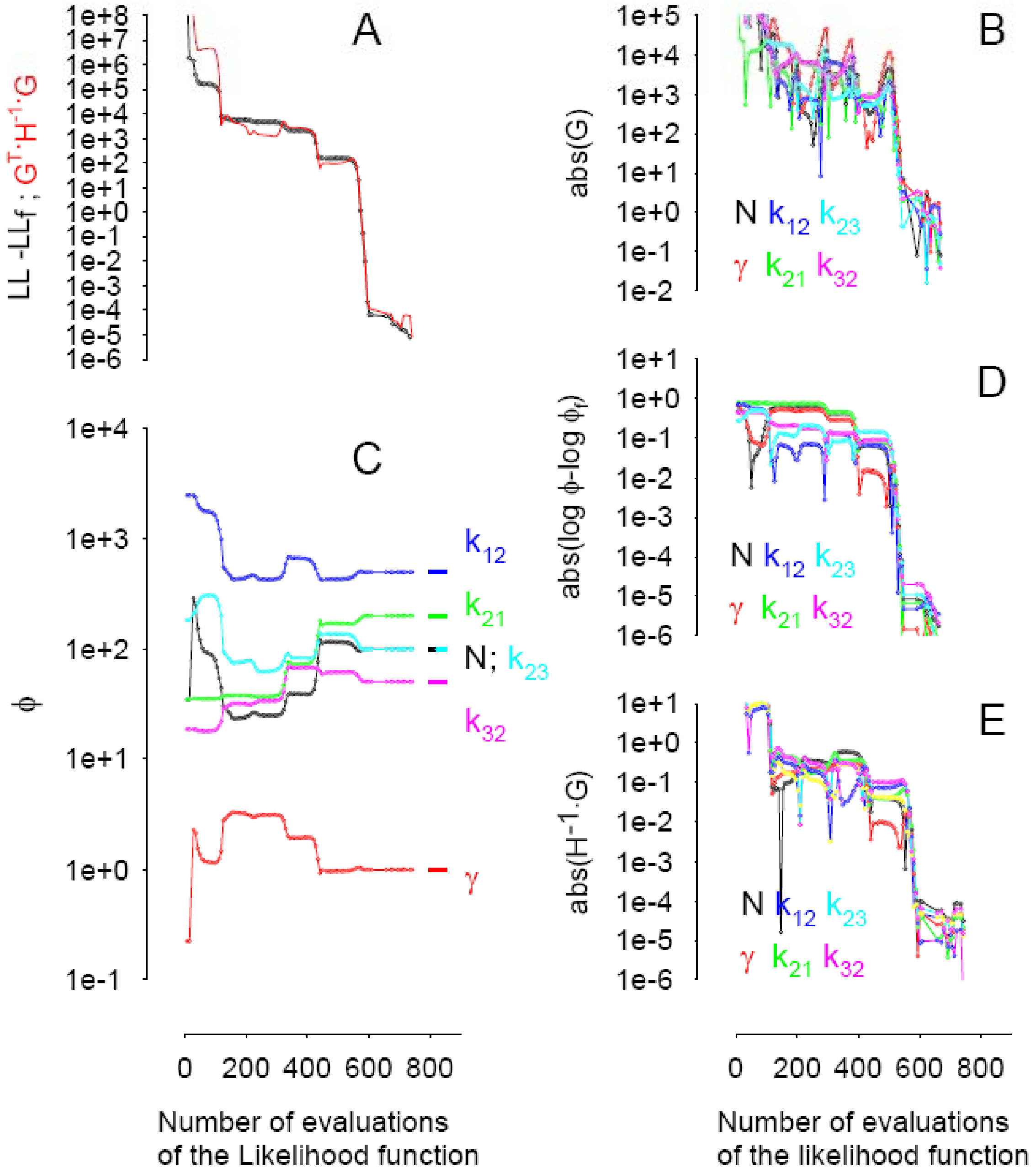


Figure 3

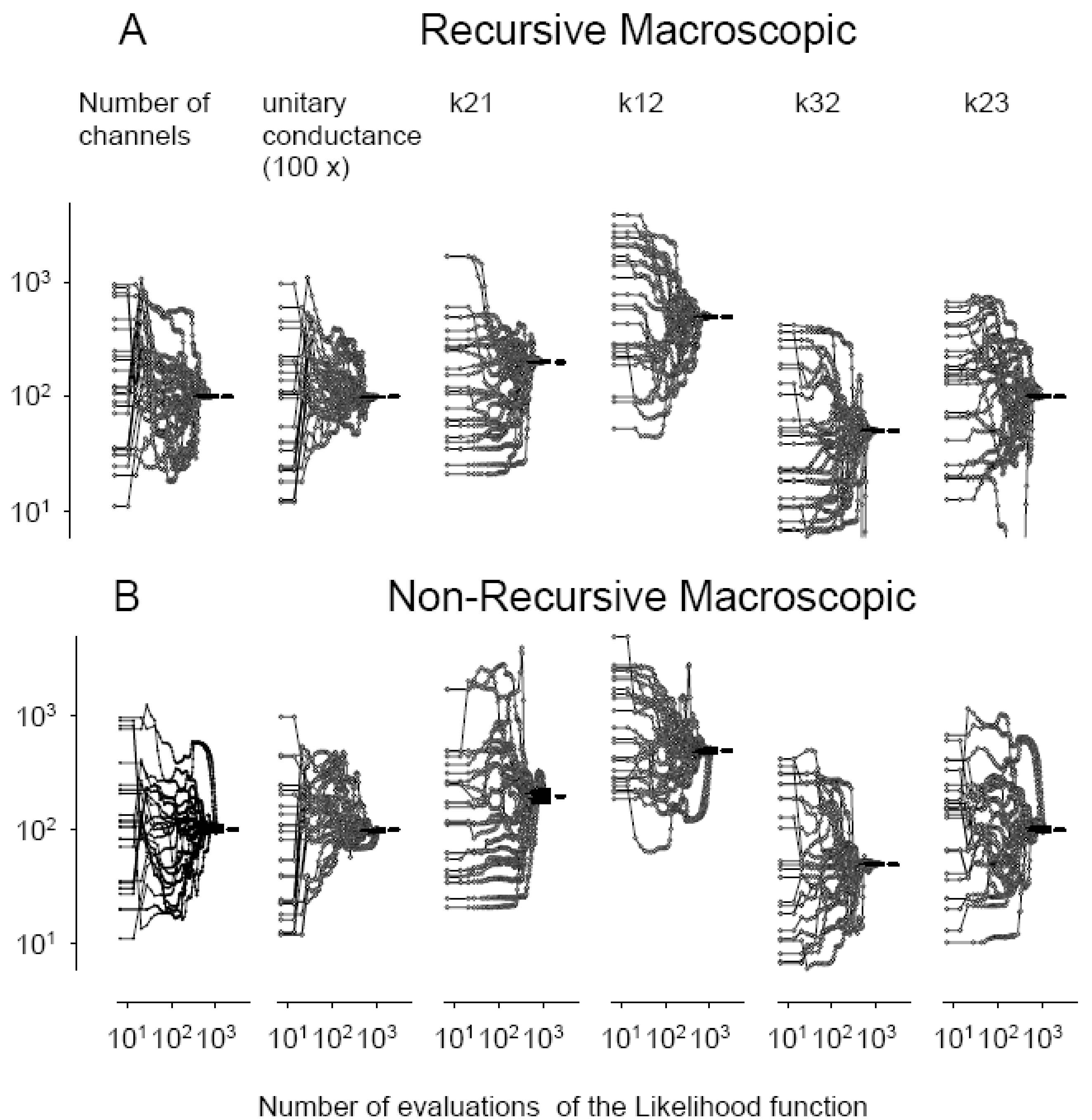
Micro R red

Macro R blue

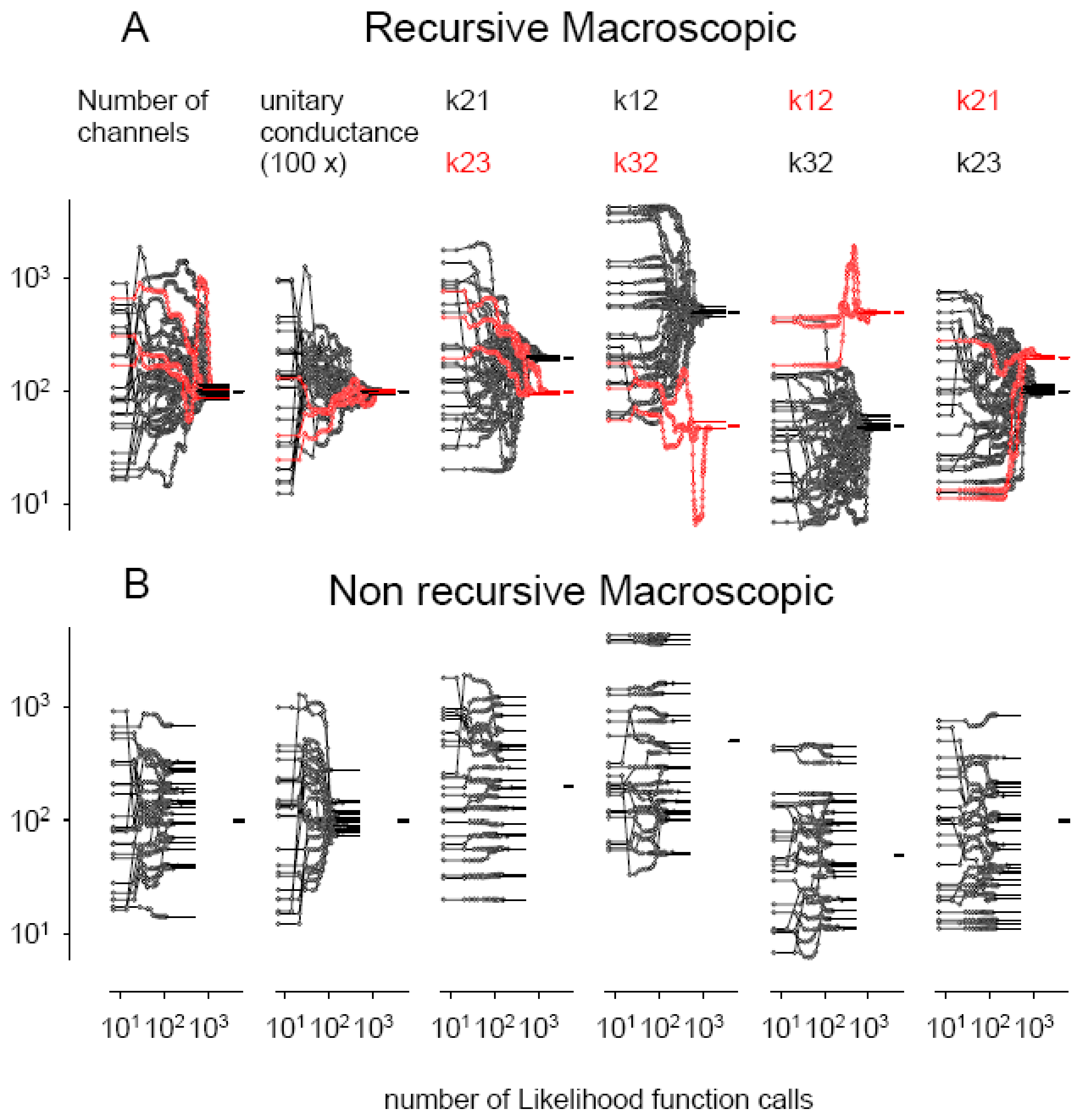
Macro NR black



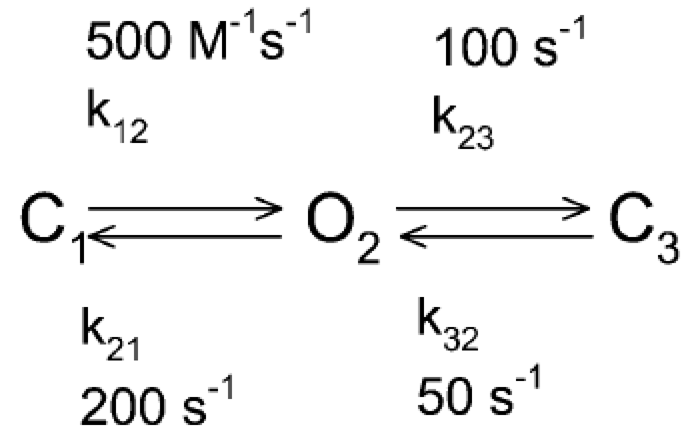
A
B
C
D
E
LL -LLf ; G^T·H^-1·G
abs(G)
abs(log φ-log φf)
abs(H-1.G)
φ
N k12 k23
γ k21 k32
k12
k21
N; k23
k32
γ
Number of evaluations of the Likelihood function
Number of evaluations of the likelihood function


A
Recursive Macroscopic
Number of channels
unitary conductance (100 x)
k21
k12
k32
k23
10^3
10^2
10^1
B
Non-Recursive Macroscopic
10^1 10^2 10^3
Number of evaluations of the Likelihood function

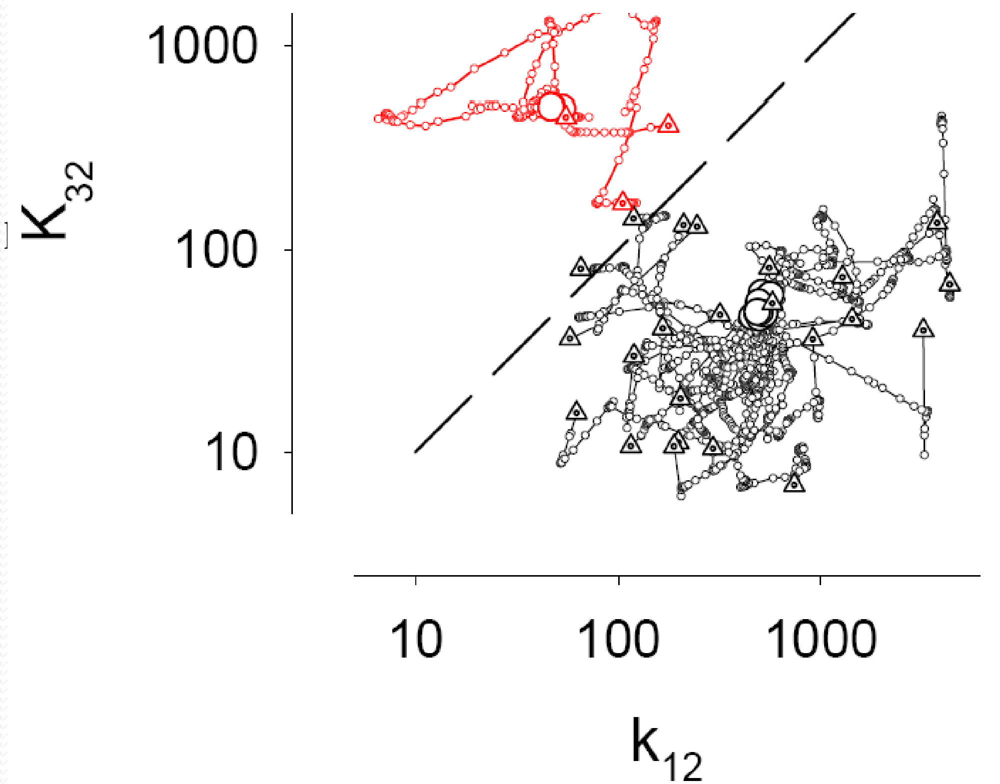
Stationary conditions

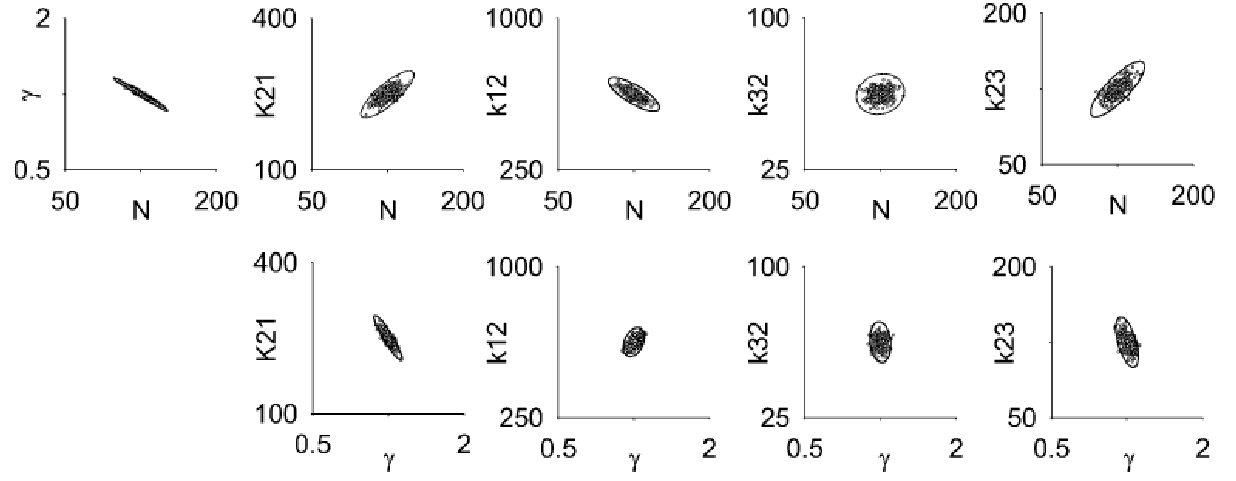

A
Recursive Macroscopic
Number of channels
unitary conductance (100 x)
k21
k23
k12
k32
k12
k32
k21
k23
10³
10²
10¹
B
Non recursive Macroscopic
10³
10²
10¹
10¹ 10² 10³
number of Likelihood function calls

When does the algorithm flipped?

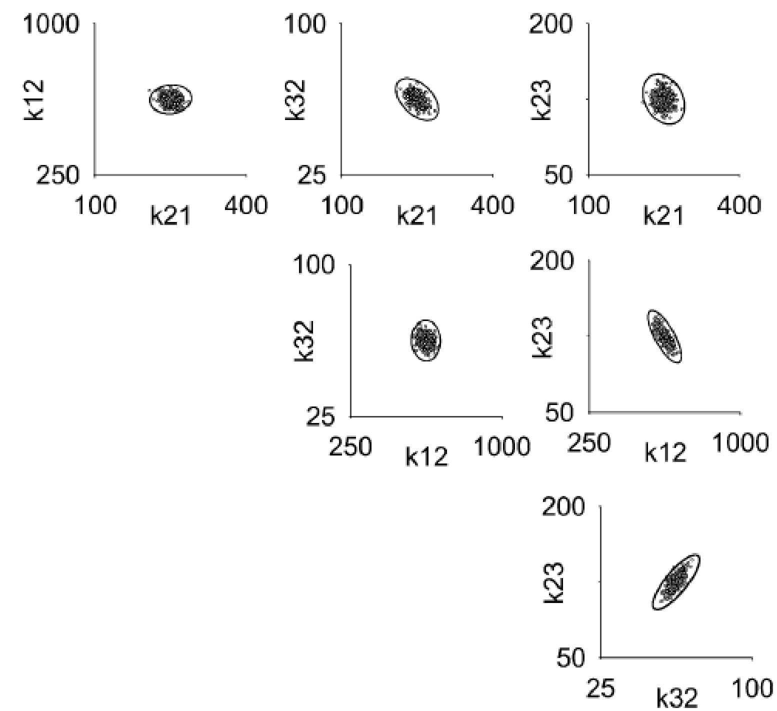


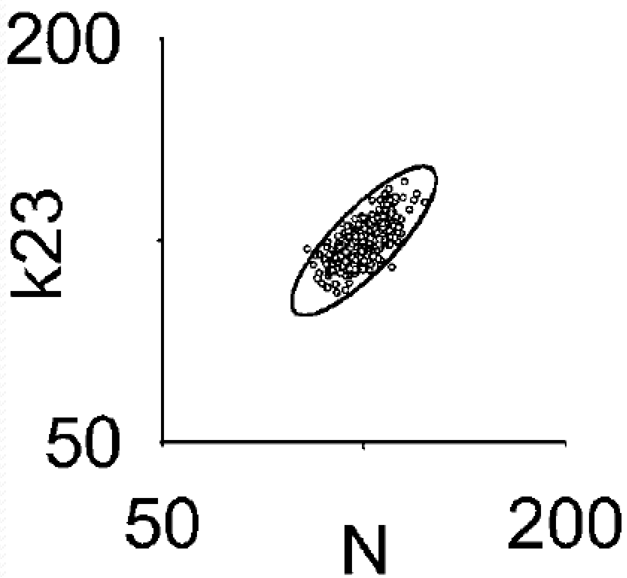
When the starting value of k32 is l
than the starting value of k12.



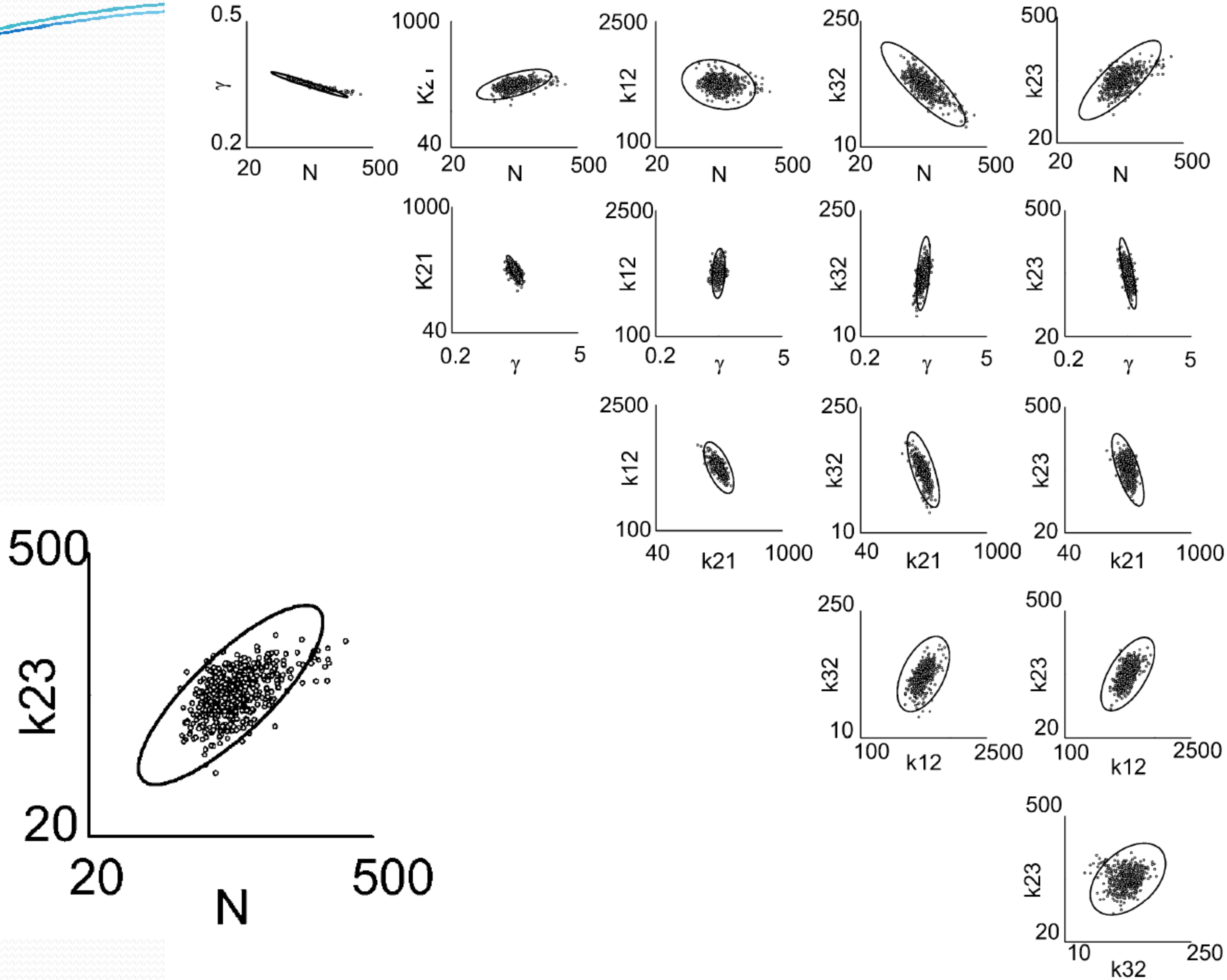


2
γ
0.5
50
N
200
400
K21
100
1000
k12
250
100
k32
25
200
k23
50
0.5
2
100
400
k21
250
1000
k12
25
k32

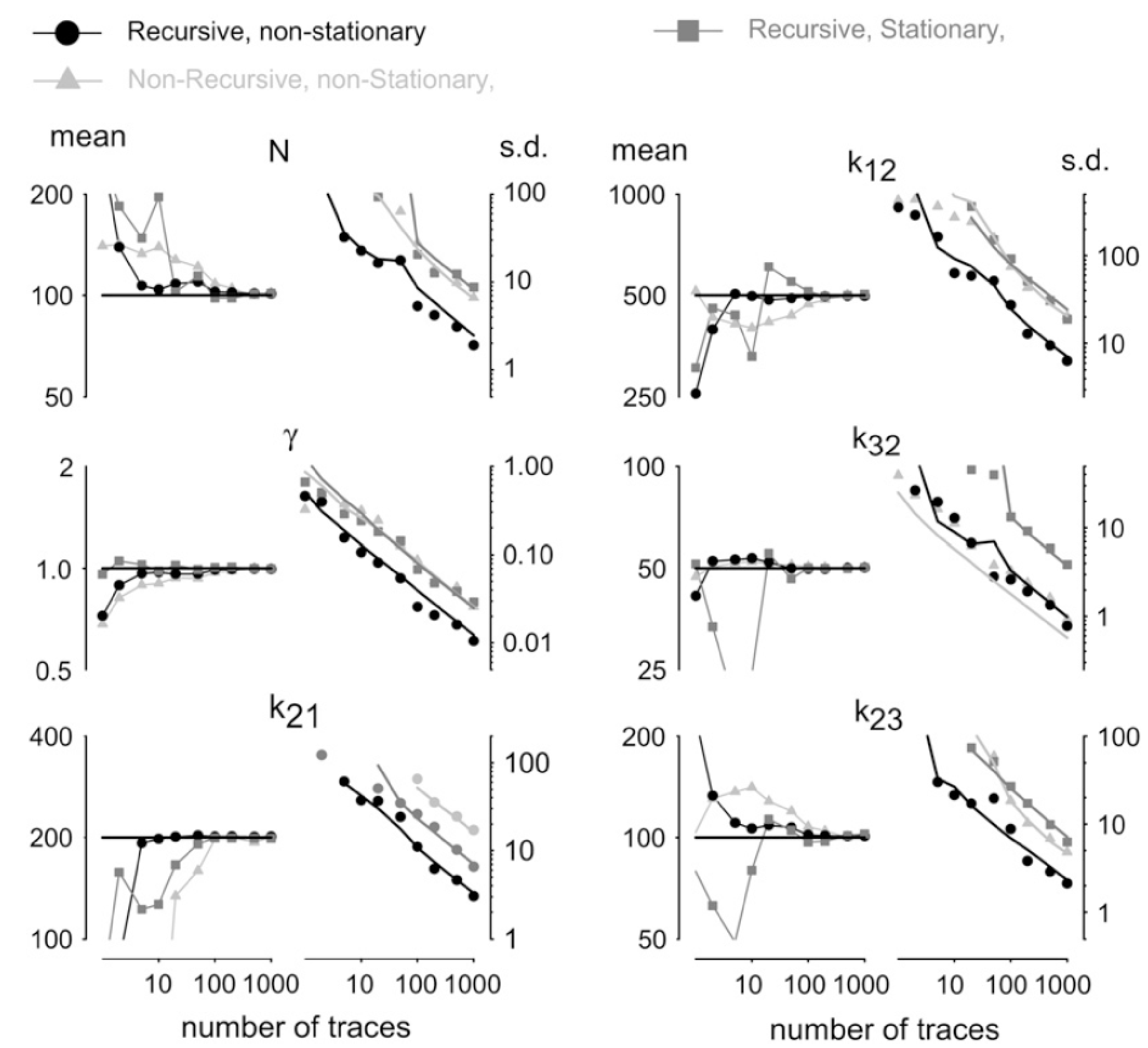




200
k23
50
50
N
200



γ
N
K21
k21
k12
k32
k23
0.5
0.2
20
500
1000
40
2500
100
250
10
5



Recursive, non-stationary
Recursive, Stationary,
Non-Recursive, non-Stationary,
mean
N
s.d.
mean
k12
s.d.
200
100
50
100
10
1
1000
500
250
100
10
γ
2
1.0
0.5
1.00
0.10
0.01
k32
100
50
25
10
1
k21
400
200
100
100
10
1
k23
200
100
50
100
10
1
10
100
1000
number of traces
number of traces

Present research

- MacroR-TA, time averaged version of MacroR
- Developing a GPL library than implements MacroR-TA in C++
- Working on electrophysiology experiments with pulses of 20 microseconds.