Freie Universität Berlin

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Neuroinformatics and Theoretical Neuroscience
Institute of Biology – Neurobiology

Bernstein Center for
Computational Neuroscience

Estimating Variability in Neural Spike Trains – Theory and Practice

Martin P. Nawrot

2nd G-Node Winter Course in Neural Data Analysis
Munich, Mar 02, 2010

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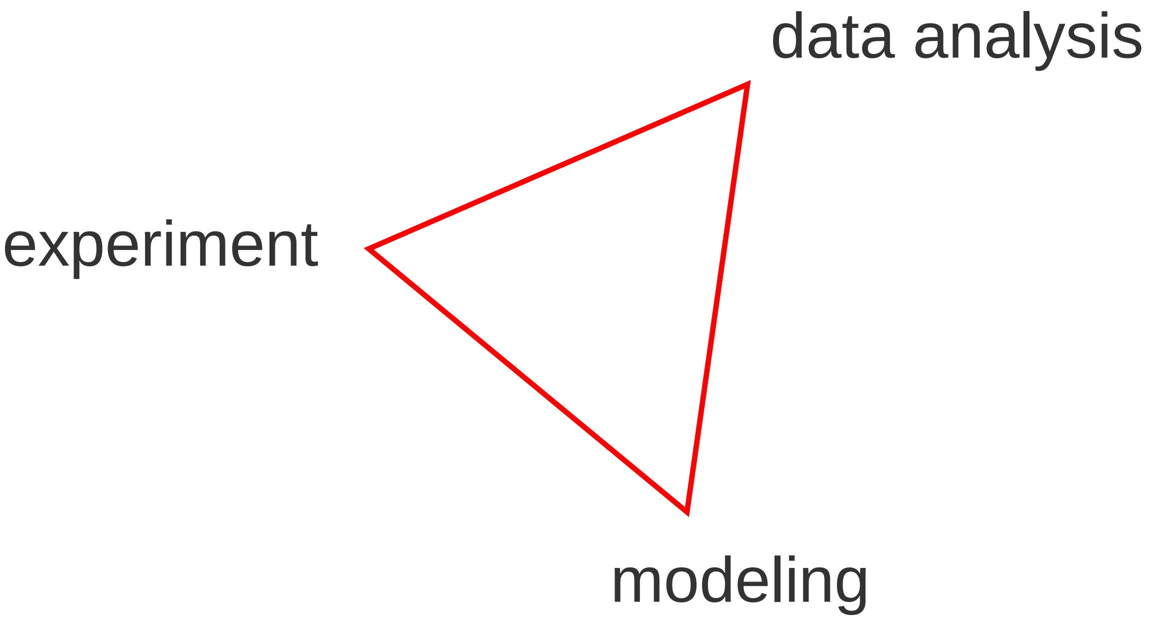


GOALS for today

- motivation: precision and variability in neural systems
- practical experience with spike train data
- ‘howto’ estimate variability of intervals and counts
- insight into the relation of interval and count statistics
- usefulness of point process theory

Introductory reading:

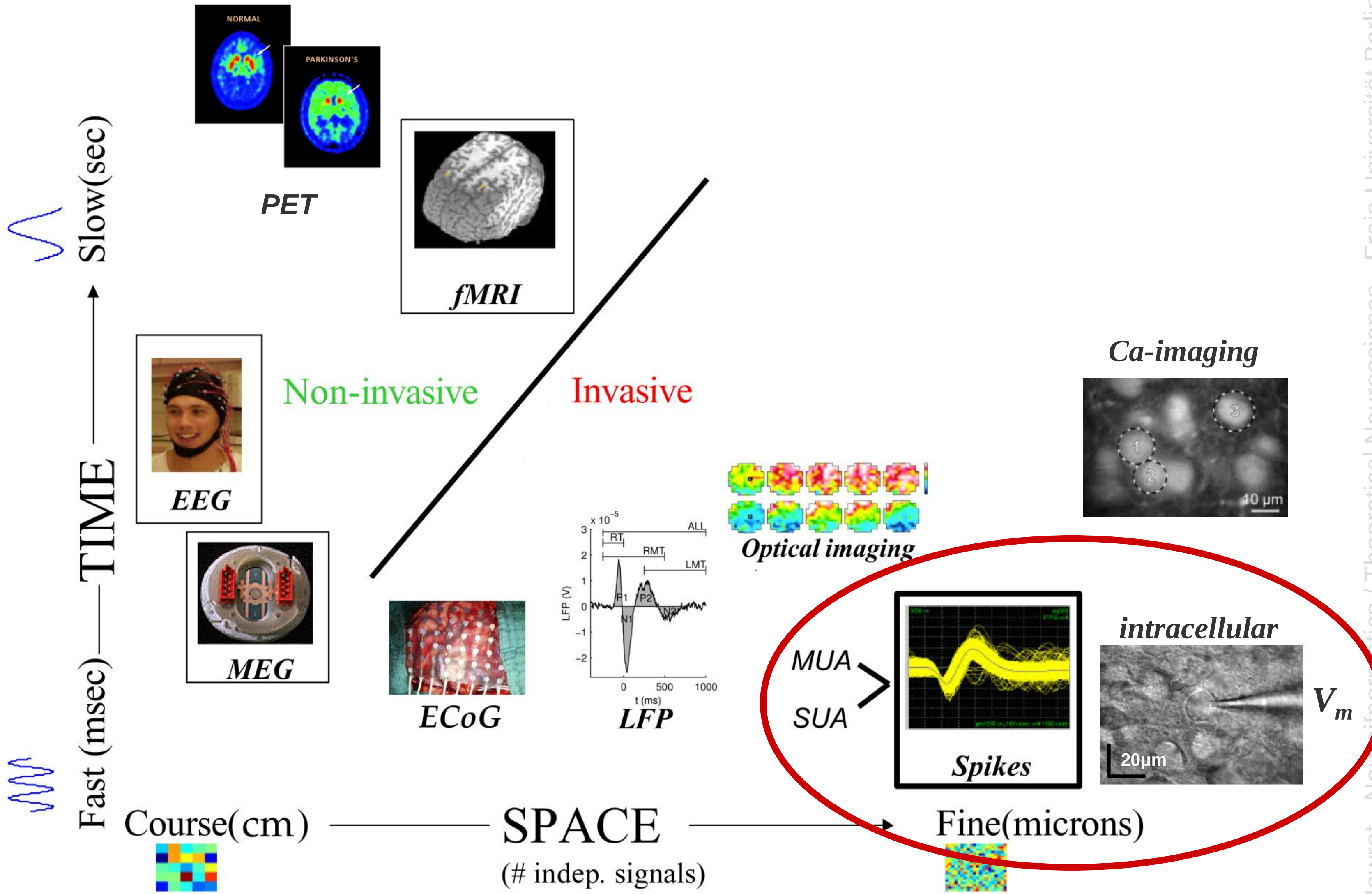
Nawrot MP (2010) Analysis and Interpretation of Interval and Count Variability in Neural Spike Trains. In: Analysis of Parallel Spike Trains, Grün S, Rotter S (Eds.), Springer, New York

1. Experimental spike trains
2. Introduction
3. Theory: Point process models
4. Practice: Empiric interval / count statistics
5. Course Data

1. Experimental Spike Trains

- intracellular recording
- extracellular recording
- spike sorting
- spike train representation

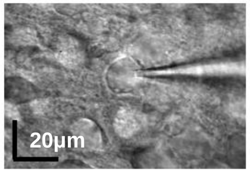
Recording Techniques | spatial vs. temporal resolution



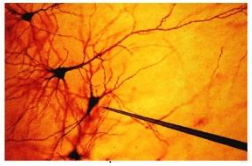
(adapted from Matt Fellows)

electrophysiology

- direct measurement of neuronal signals



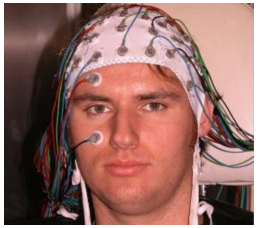
intracellular recording from
- single neurons / dendrites



extracellular recording of
- action potentials (SUA/MUA) *and*
- local field potential (LFP, indirect)

- measurement of electric mass signals

electrocorticography (ECoG)
- epicortical field potentials

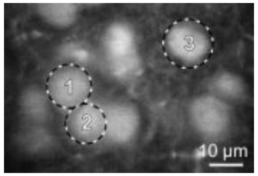


electroencephalography (EEG)

magnetoencephalography (MEG)

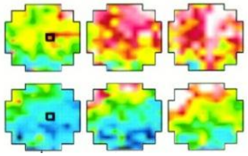
imaging

- visualization of single neuron activity

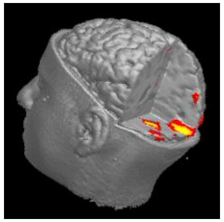


optical imaging of intracellular Ca activity
- *in vitro* / *in vivo*
- 2D / 3D

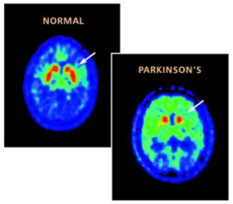
- visualization of average activity



optical imaging with voltage sensitive dyes



functional magnetic resonance imaging (fMRI)



positron emission tomography (PET)

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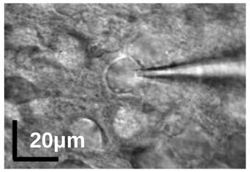
electrophysiology

■ direct measurement of neuronal signals



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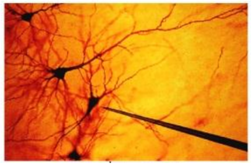

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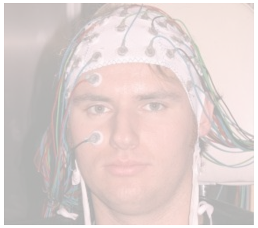

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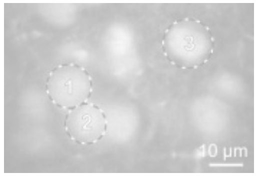
■ visualization of single neuron activity



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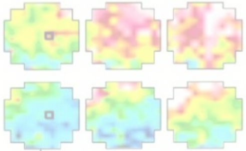

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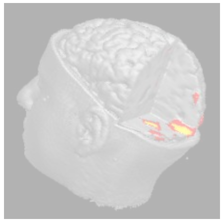

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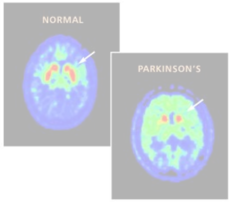
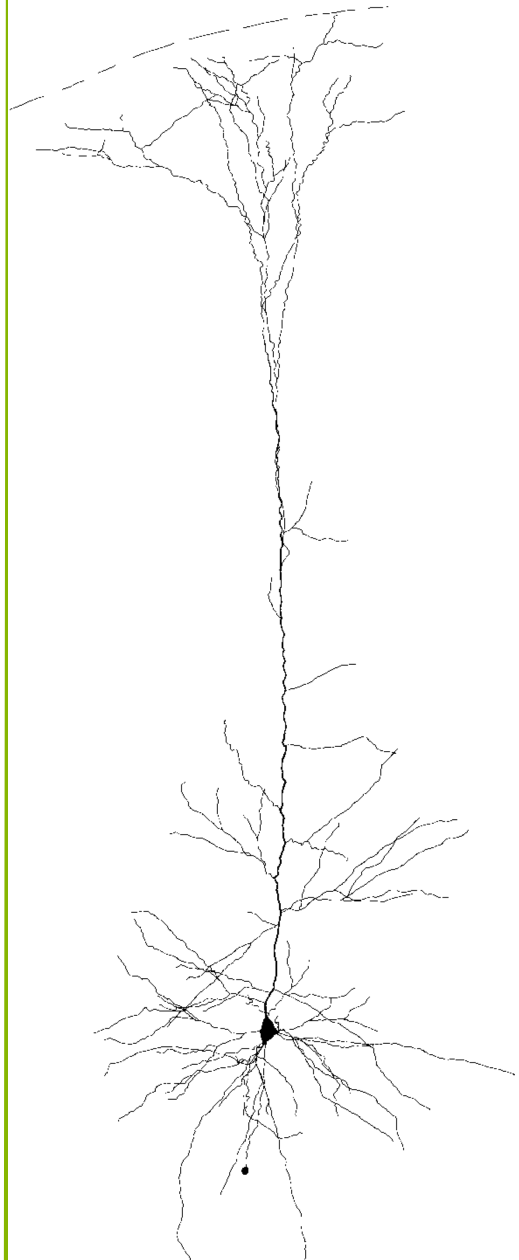
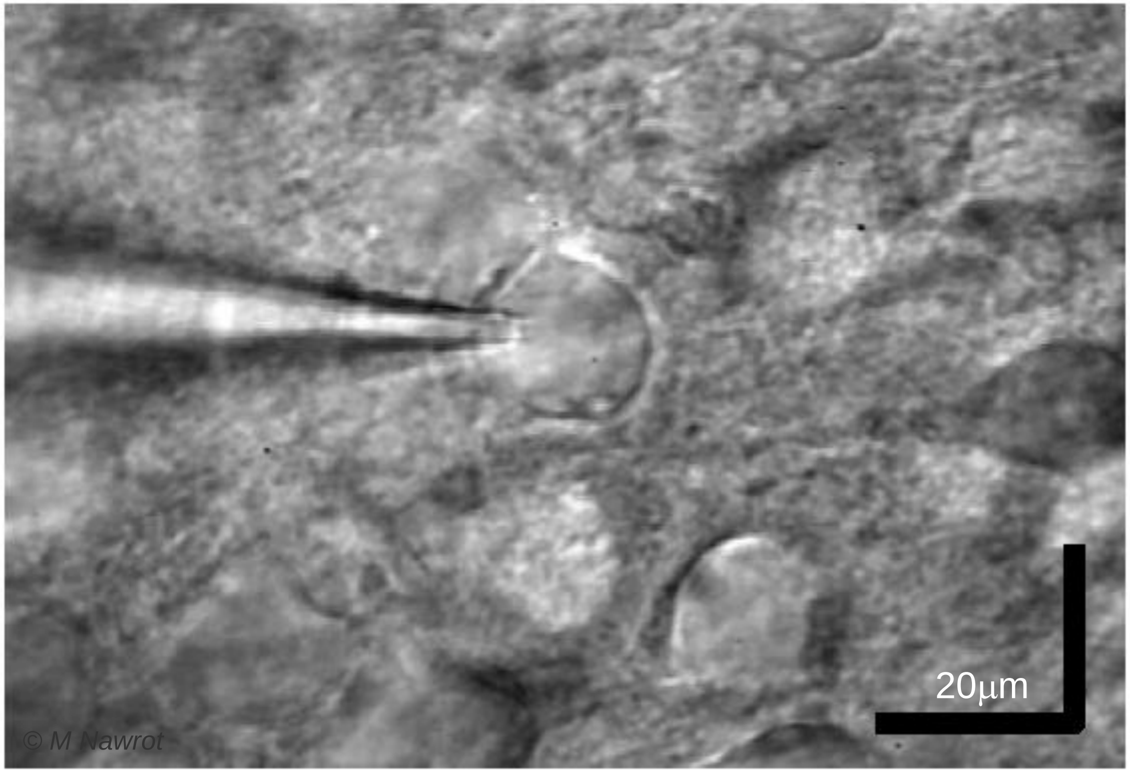


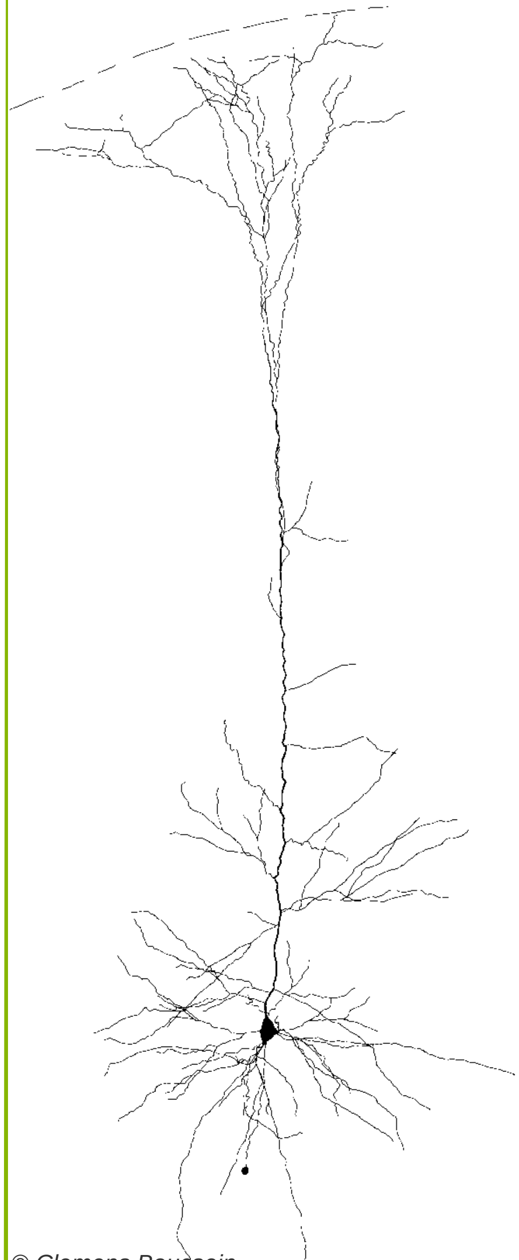
positron emission tomography (PET)

Intracellular Recording



- in vitro | in vivo
- sharp recording | patch recording
- whole-cell patch | dendritic patch
- infrared microscopy





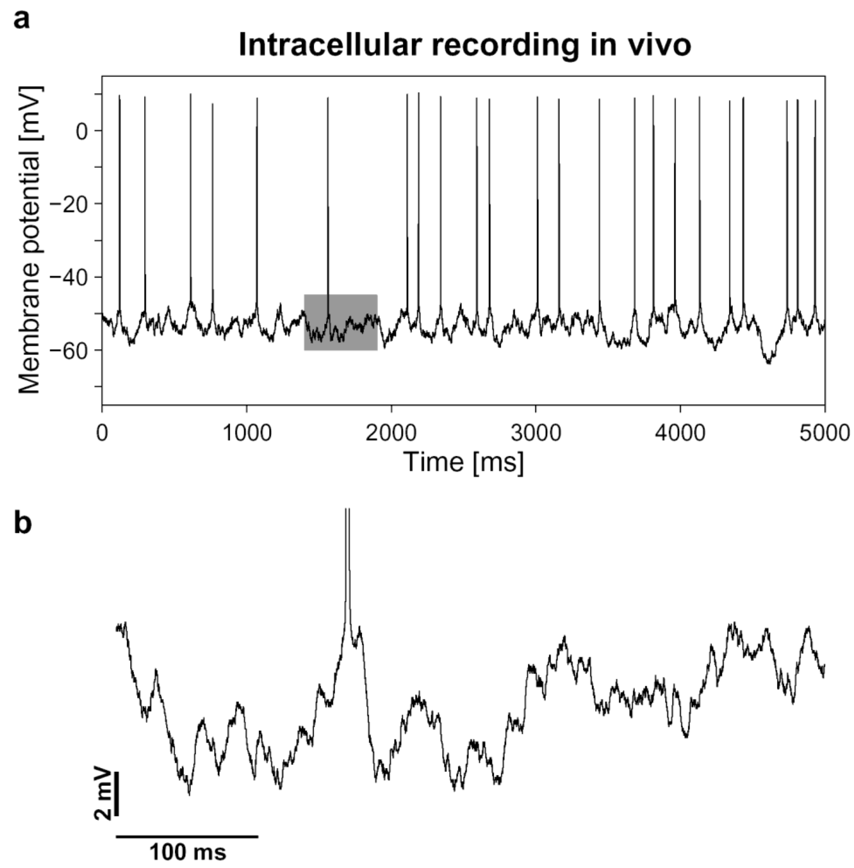
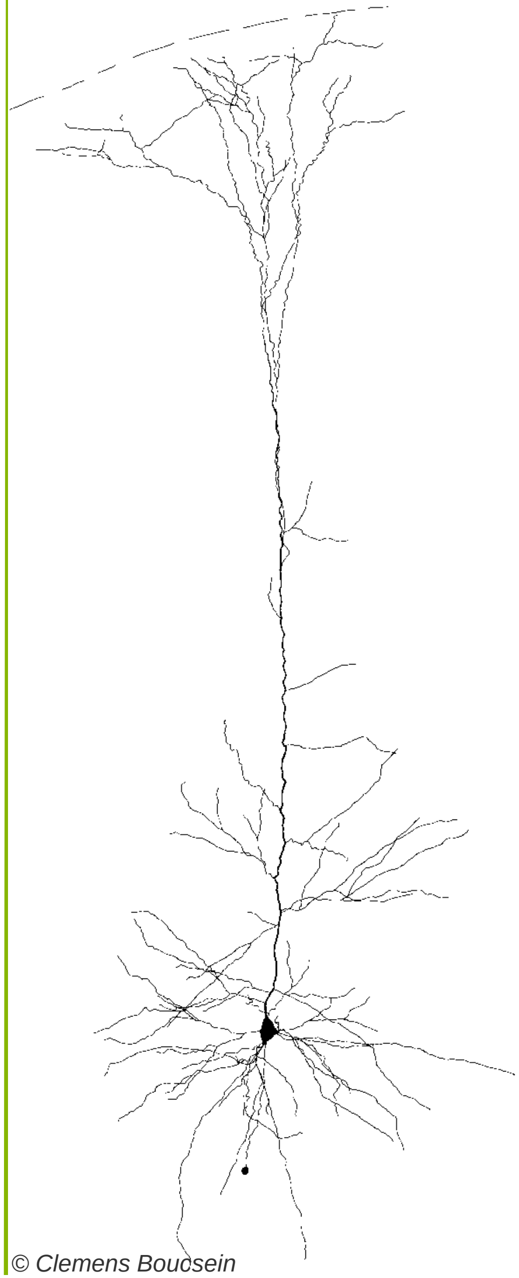
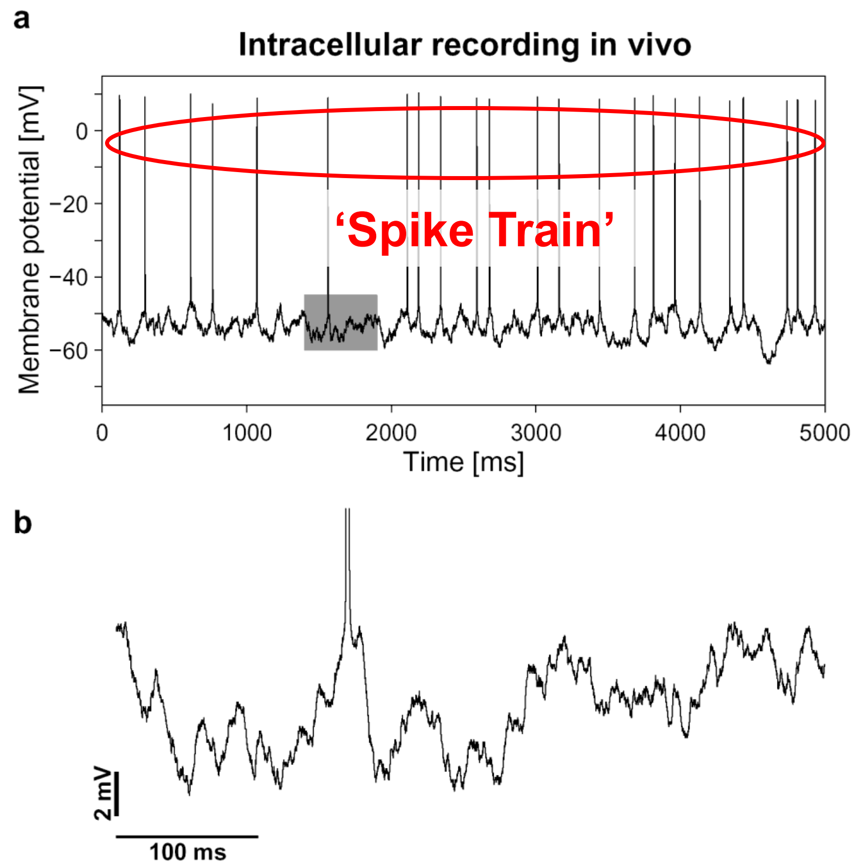


Figure 1. Permanent background input *in vivo* causes dynamic fluctuations of the membrane potential and drives the neuron to spontaneous spiking activity. (A) Membrane potential recorded intracellularly in the frontal cortex of the anesthetized rat. Presynaptic inputs from several hundreds or thousand of presynaptic neurons cause depolarization of the cell to a resting potential of about -50 mV and salient fluctuations of the membrane potential. (B) The enlarged cut-out from A reveals the fine structure of the signal that results form the superposition of many single EPSPs and IPSPs and gives an impression of the time scale on which these fluctuations take place. Data by courtesy of Detlef Heck (Léger, Stern, Aertsen, & Heck, 2003).

Intracellular Recording | spontaneous activity in vivo





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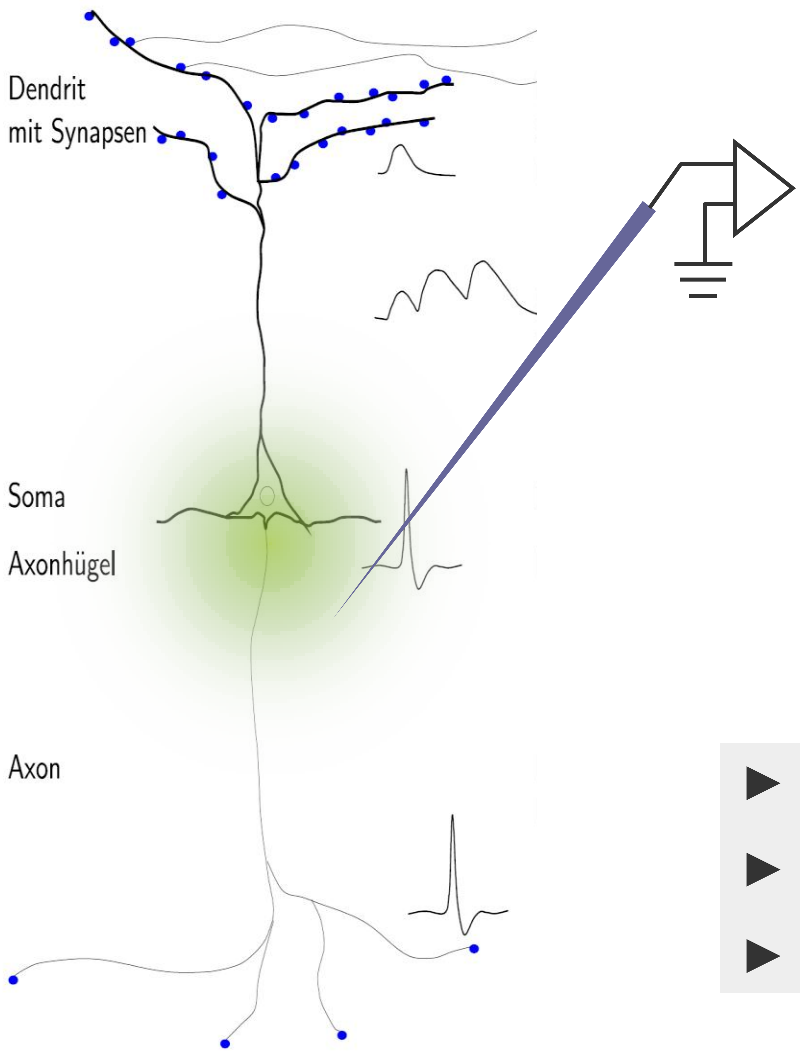
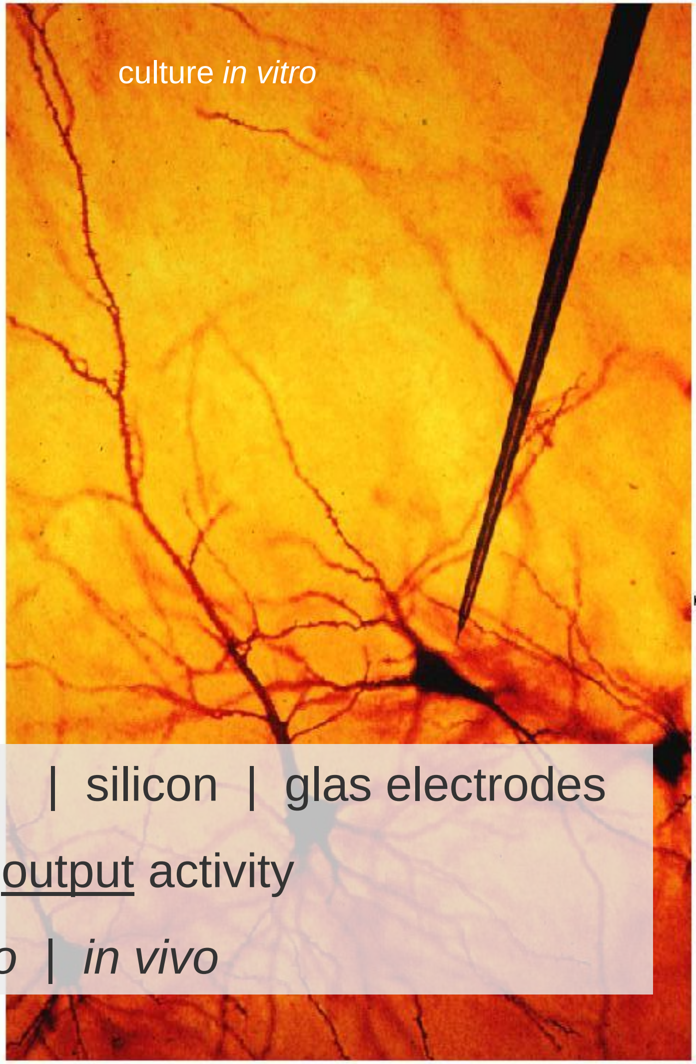
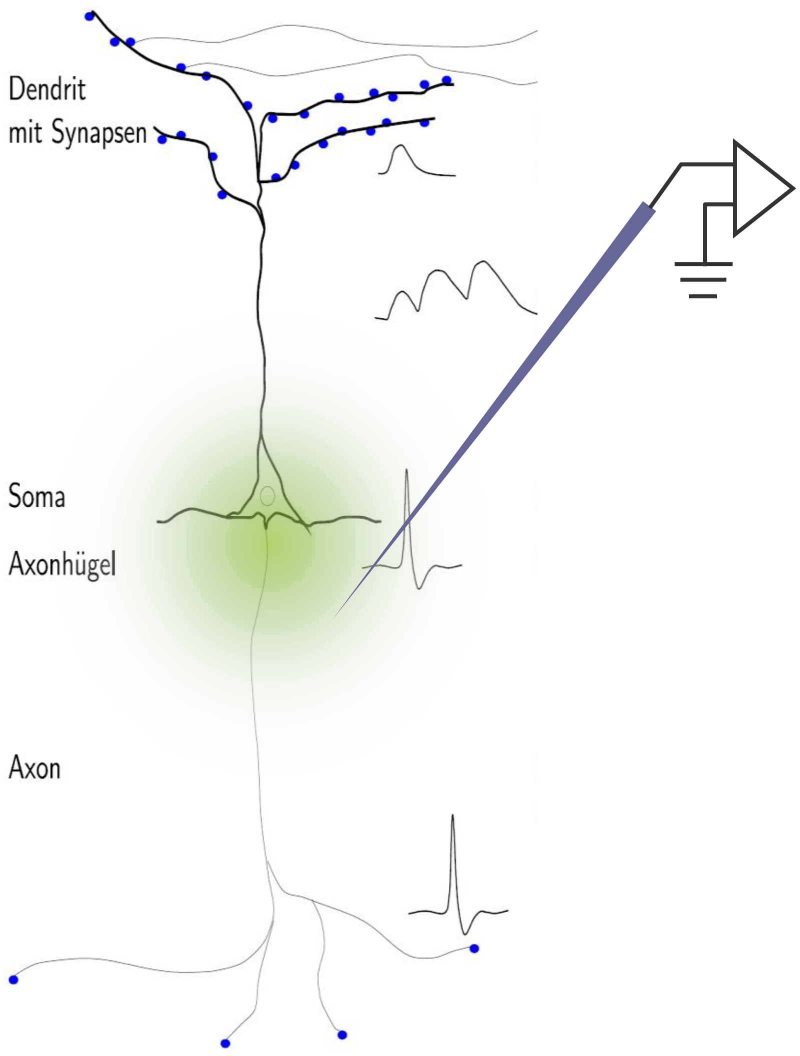
Extracellular Recording

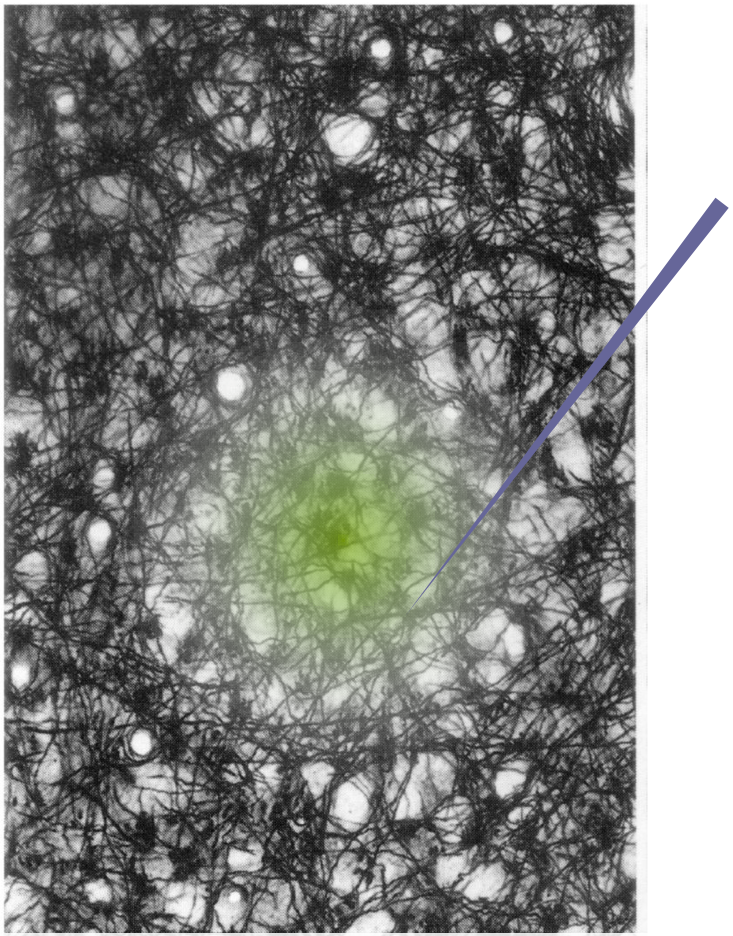




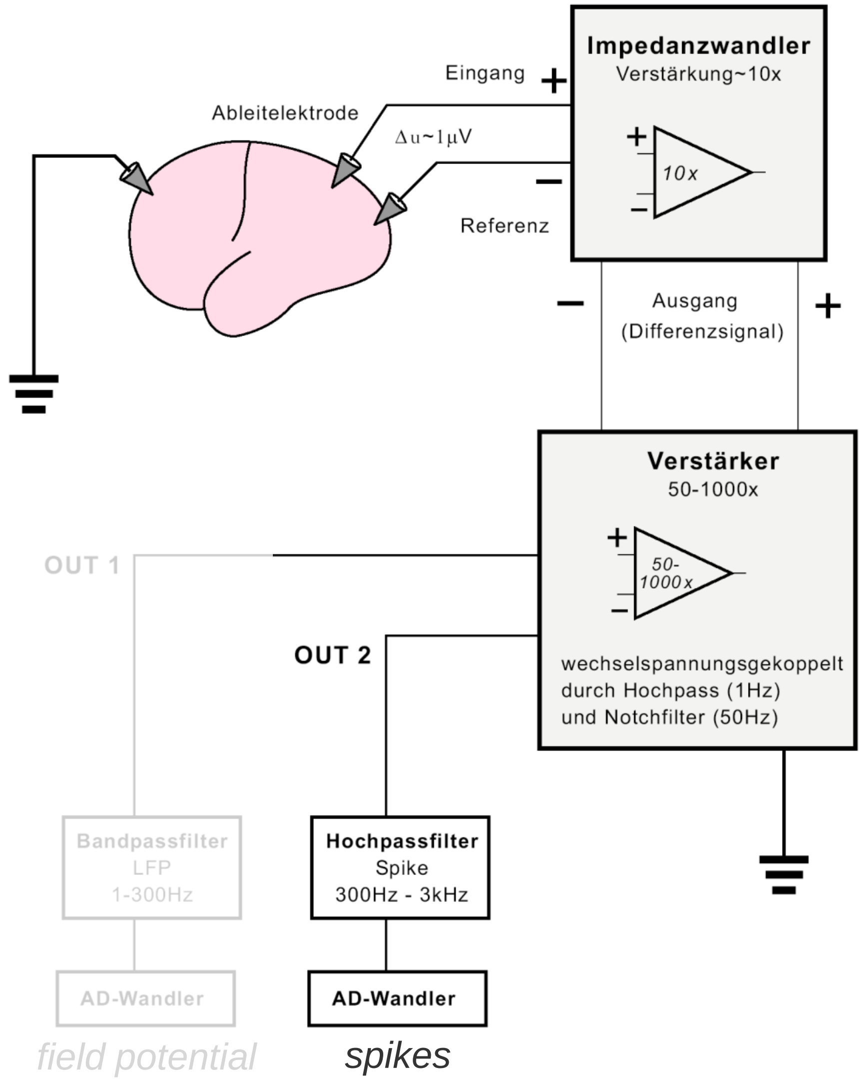
- ► metal | silicon | glas electrodes
- ► spike <u>output</u> activity
- ► *in vitro* | *in vivo*

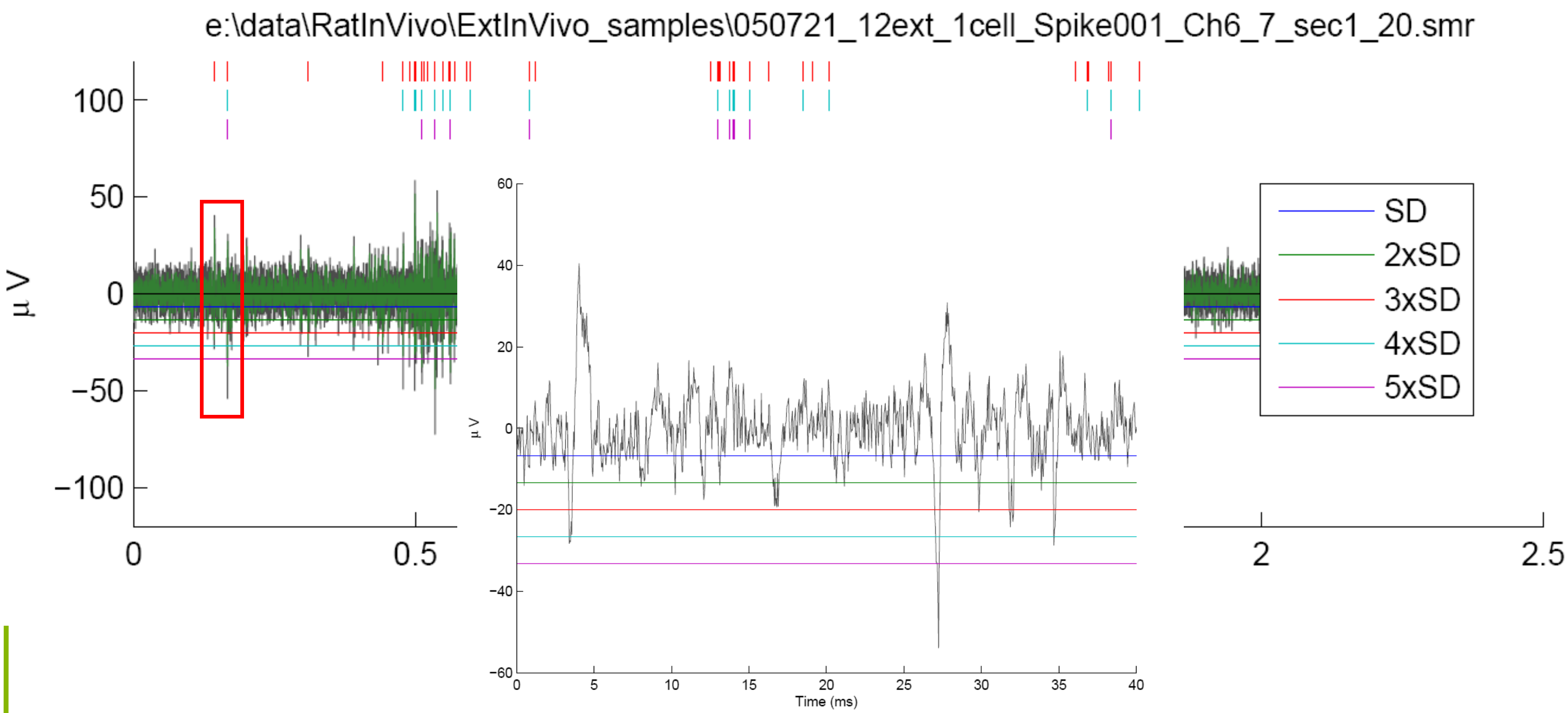


Cortex

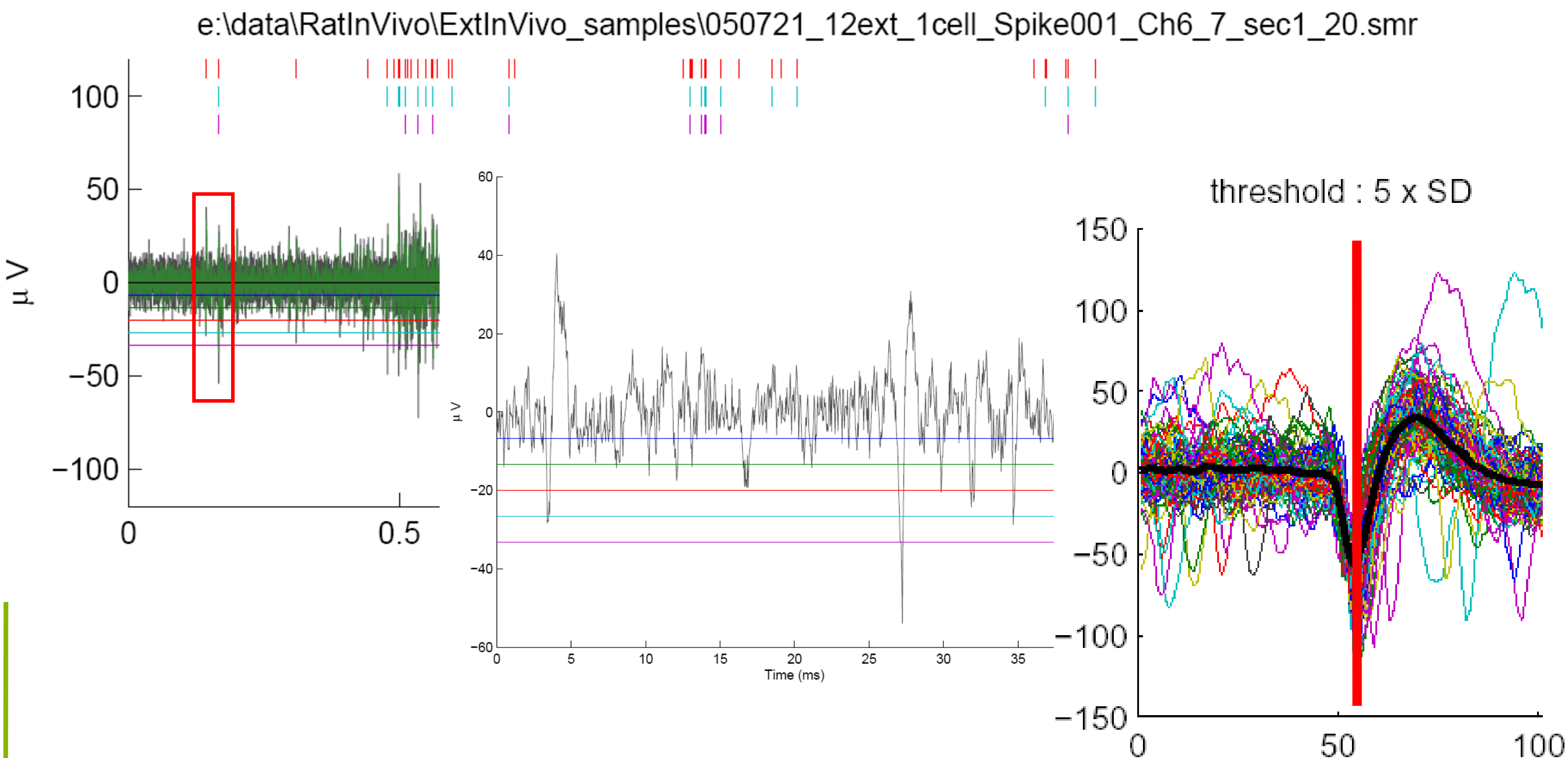


Valentino Braitenberg & Almut Schüz
Cortex: Statistics and Geometry of Neuronal Connectivity
Springer, Berlin, 1998 (Second Edition)


Impedanzwandler
Verstärkung~10x
Eingang
Ableitelektrode
Δu~1μV
10x
Referenz
Ausgang
(Differenzsignal)
Verstärker
50-1000x
50-
1000x
OUT 1
OUT 2
wechselspannungsgekoppelt
durch Hochpass (1Hz)
und Notchfilter (50Hz)
Bandpassfilter
LFP
1-300Hz
Hochpassfilter
Spike
300Hz - 3kHz
AD-Wandler
AD-Wandler
field potential
spikes



Extrazelluläre Aufnahmen im somatosensorischen Kortex der Ratte. Spontanaktivität unter Anästhesie.
Data Curtsey: Clemens Boucsein und Dymphie Suchanek, Neurobiologie & Biophysik, Universität Freiburg



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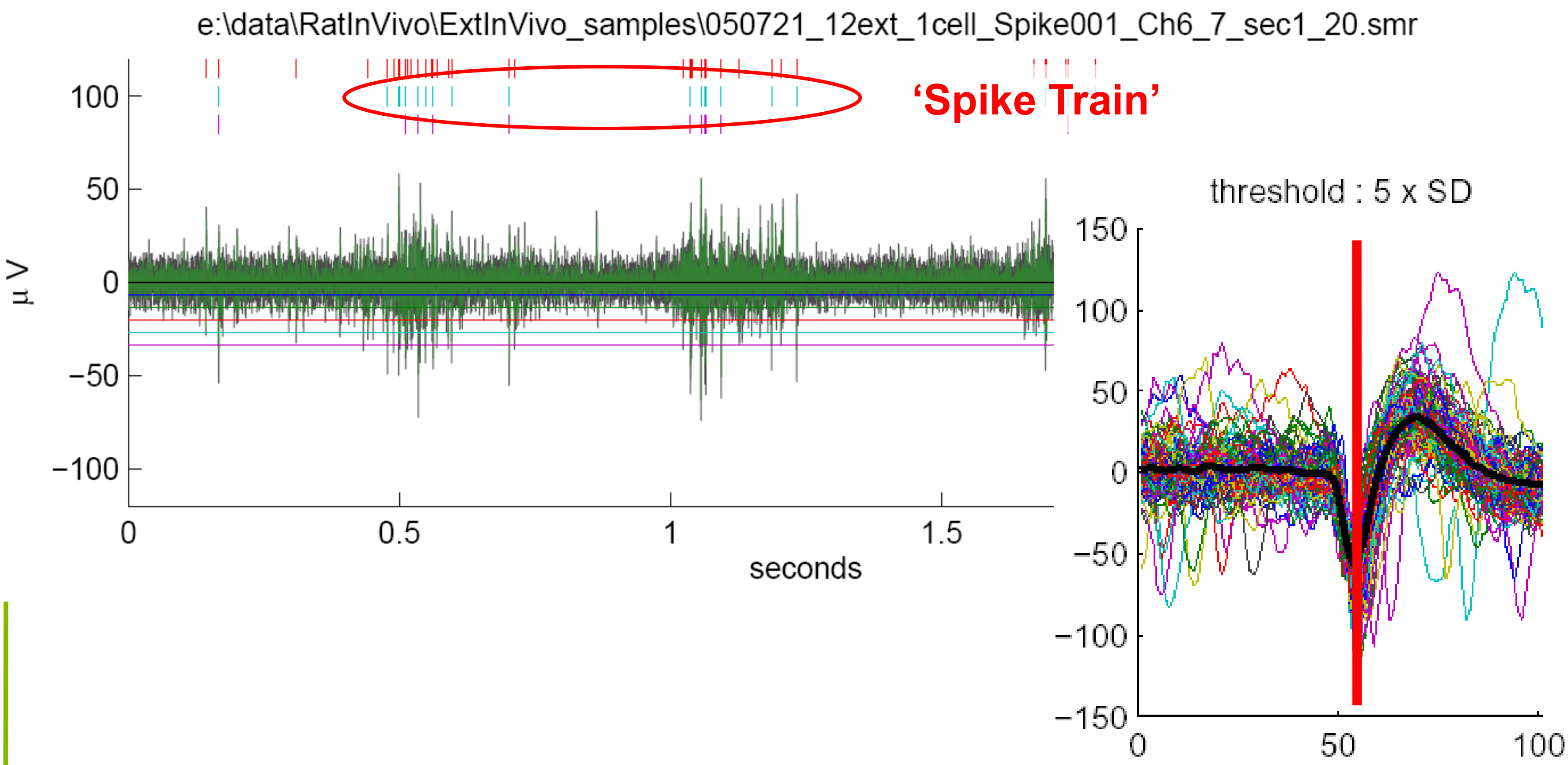

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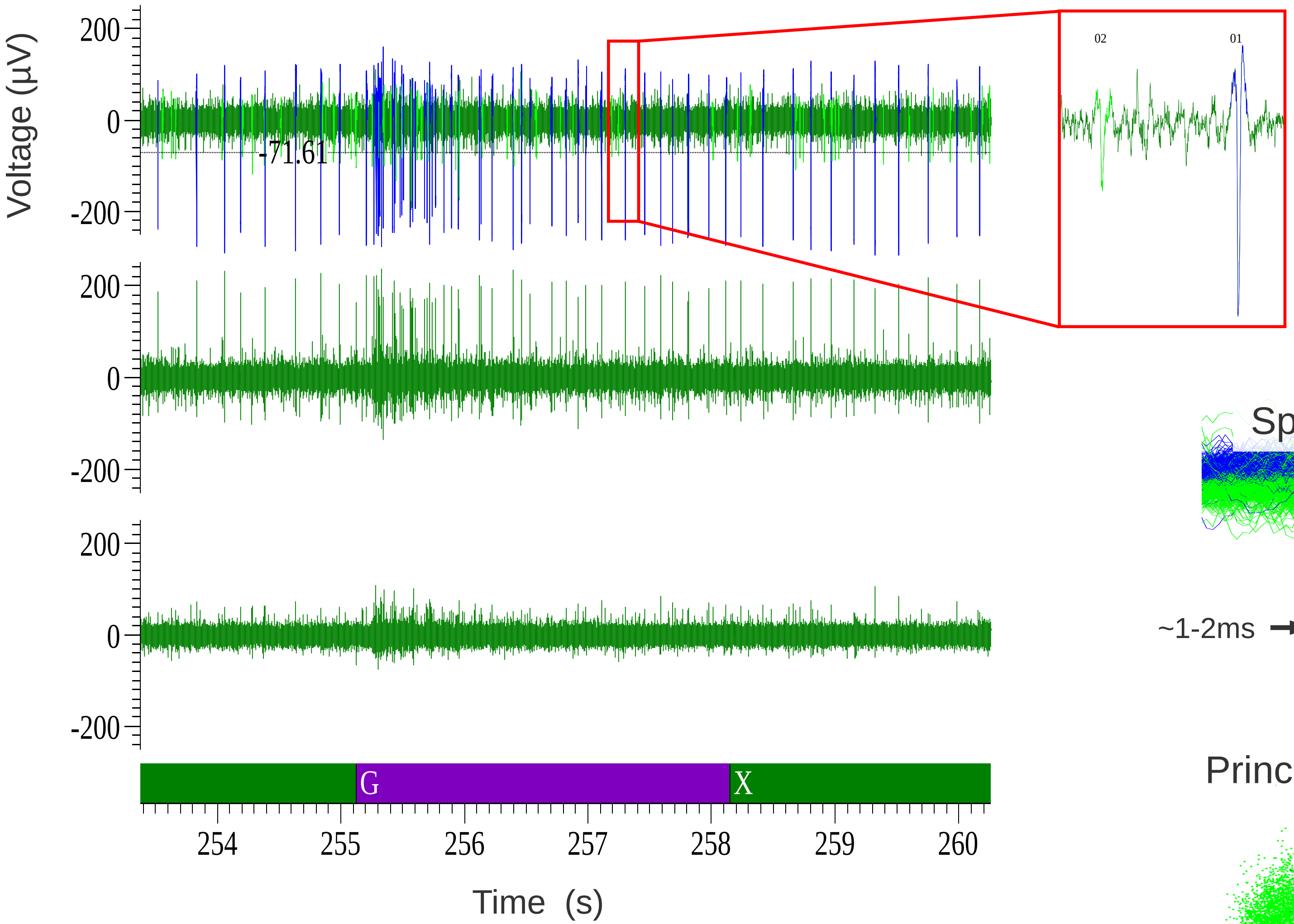
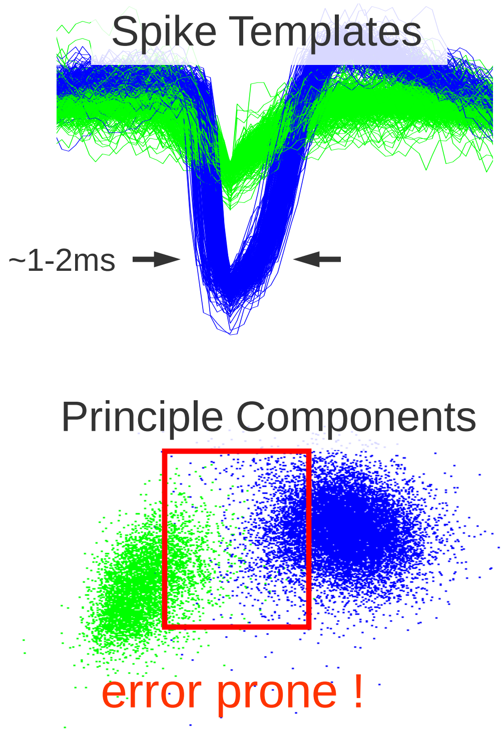
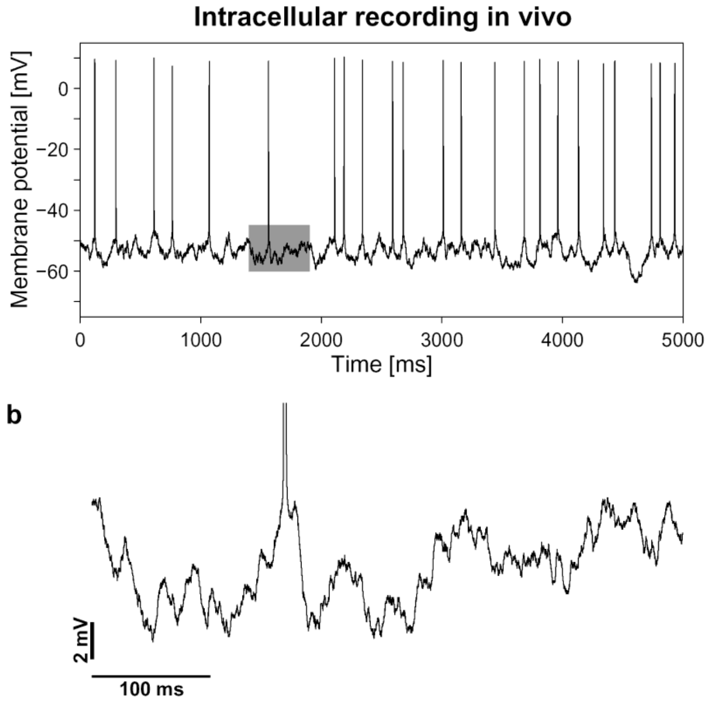




Extrazelluläre Aufnahmen von α-extrinsischen Neuronen im Bienengehirn. Antwort auf Duftreiz.
Data Curtsey: Dr. Martin Strube, Neurobiologie, Freie Universität Berlin

2. Introduction

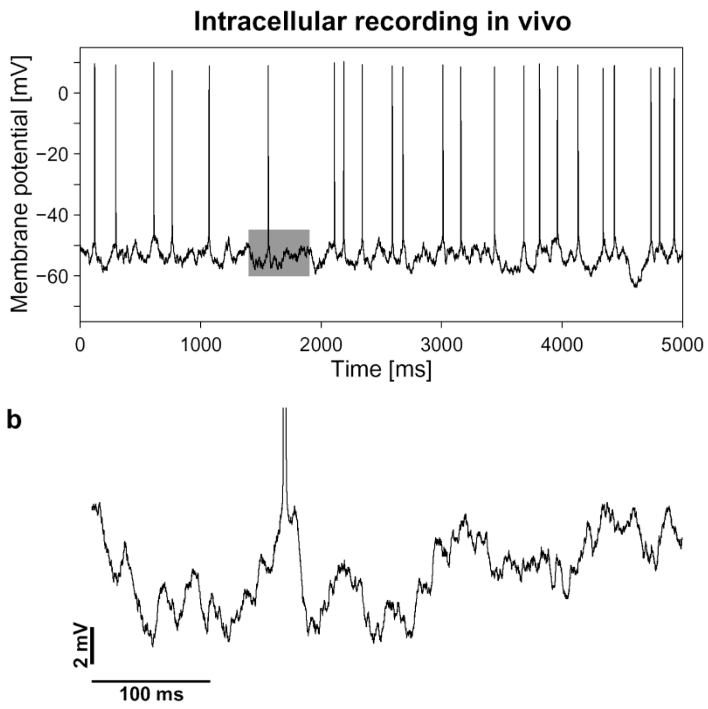
neocortex *in vivo* is **permanently active**



Leger, Stern, Aertsen, Heck (2004) J Neurophysiol 93

neocortex *in vivo* is **permanently active**

spike trains of single neurons are **irregular** in time

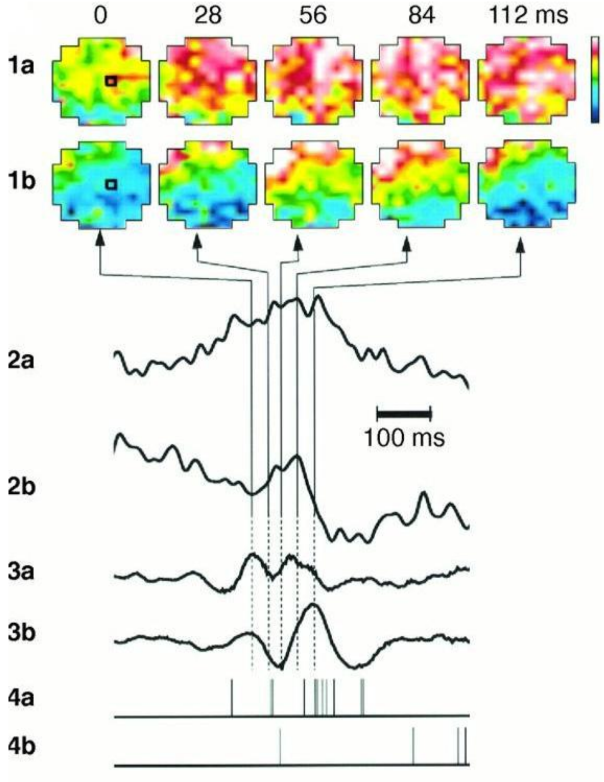


Leger, Stern, Aertsen, Heck (2004) J Neurophysiol 93

neocortex *in vivo* is **permanently active**

spike trains of single neurons are **irregular** in time

highly **variable responses** upon repeated stimulation



Arieli, Sterkin, Grinvald, Aertsen (1996) Science 273

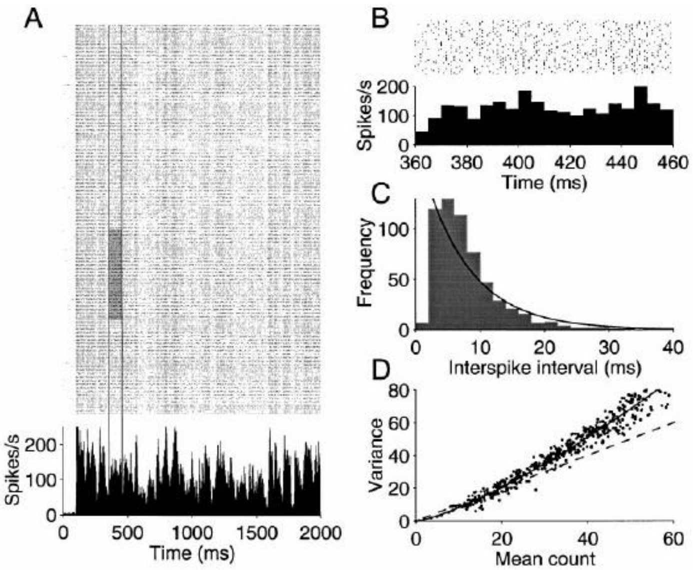
The Variable Discharge of Cortical Neurons: Implications for Connectivity, Computation, and Information Coding

Michael N. Shadlen[1] and William T. Newsome[2]

3872 J. Neurosci., May 15, 1998, *18*(10):3870–3896

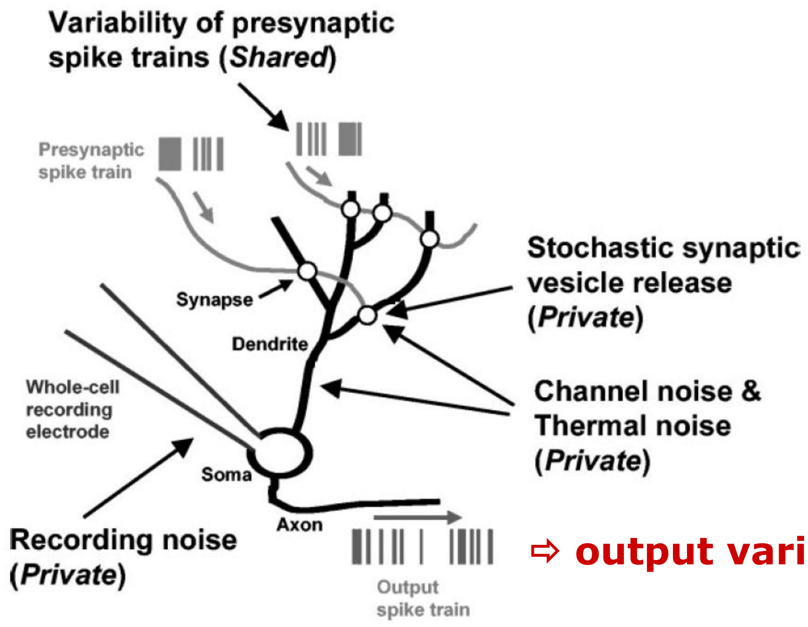
Table 1. Properties of statistical homogeneity for cortical neurons

Response property	Approximate value
Dynamic range of response	0–200 spikes/sec
Distribution of interspike intervals	Approximately exponential ~ Poisson
Spike count variance	Variance ~1–1.5 times the mean count FF > 1
Spike rate modulation	Expected rate can vary in ~1 ISI, 5–10 msec



⇨ spiking process **more variable than the Poisson process ! (?)**

What are the sources of cortical single neuron variability *in vivo*?



⇨ **output variability**

DeWeese & Zador (2004) J Neurophysiol 92

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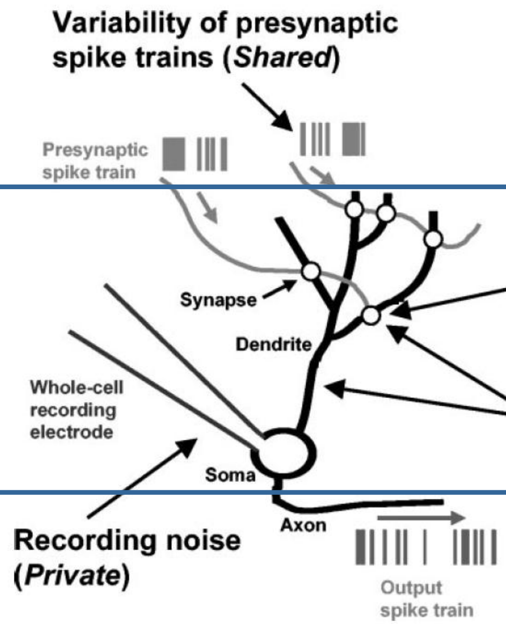

⇦ **intrinsic sources** ⇦

⇨ **output variability**

DeWeese & Zador (2004) J Neurophysiol 92

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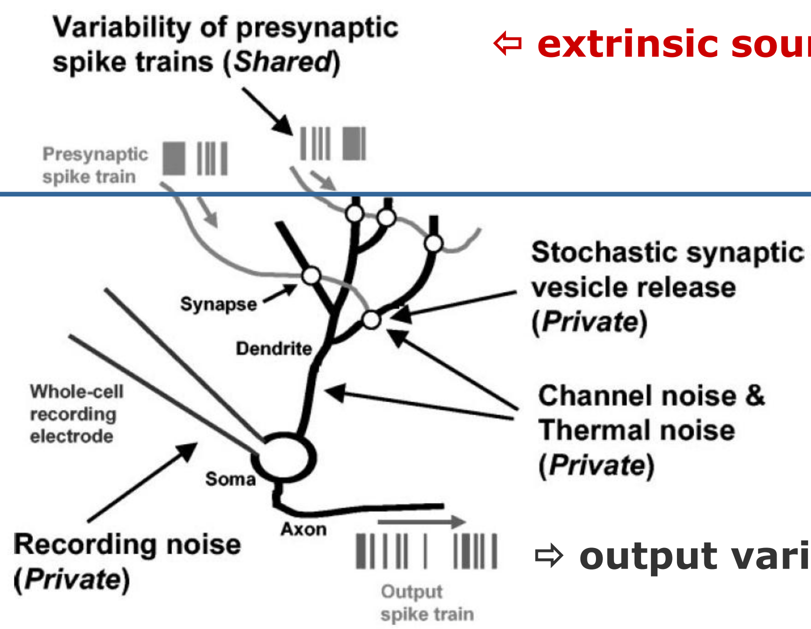
What are the sources of cortical single neuron variability *in vivo*?



⇦ **extrinsic sources**

⇦

intrinsic sources

⇦

⇨ **output variability**

DeWeese & Zador (2004) J Neurophysiol 92

3. Theory: Stochastic Point Processes

- interval and count random variables
- Poisson process
- renewal process
- nonhomogenous Poisson process
- non-renewal processes

A ***point*** is a discrete event that occurs in continuous time (or space). We regard action potentials as point events ignoring their amplitude and duration.

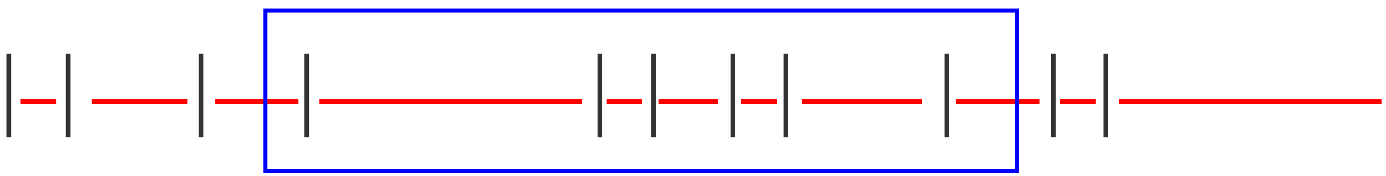
A ***point process*** is a mathematical description of a process that generates points in time (or space) according to defined stochastic rules (probability distribution).

Only a ***finite number of events*** are generated within a *finite time observation interval* (true for neural spike train).

In computational neuroscience point processes are used *to simulate* single neuron activity and *to predict* the statistical measures of spiking activity.

2 basic **random variables** :

- inter-event intervals *X* (continuous random variable)
- number of spikes *N* (discrete random variable) in interval of length T



Any point process definition uniquely determines its interval and count stochastic, and both random variables are related.

1010000100010000000000101001010000010001010000000001

binary representation

One possibility to define a point process is the **complete intensity function**.

Consider a point process as defined on the complete time axis (−∞,+∞). Let H_t denote the **history of the process**, i.e. a specification of the position of all points in (−∞, t]. Then a general description of this process maybe formulated in terms of the probabilities of observing a single event at an arbitrary time t

$$P(N(t,t+\delta t)=1|H_t\}$$

Definition

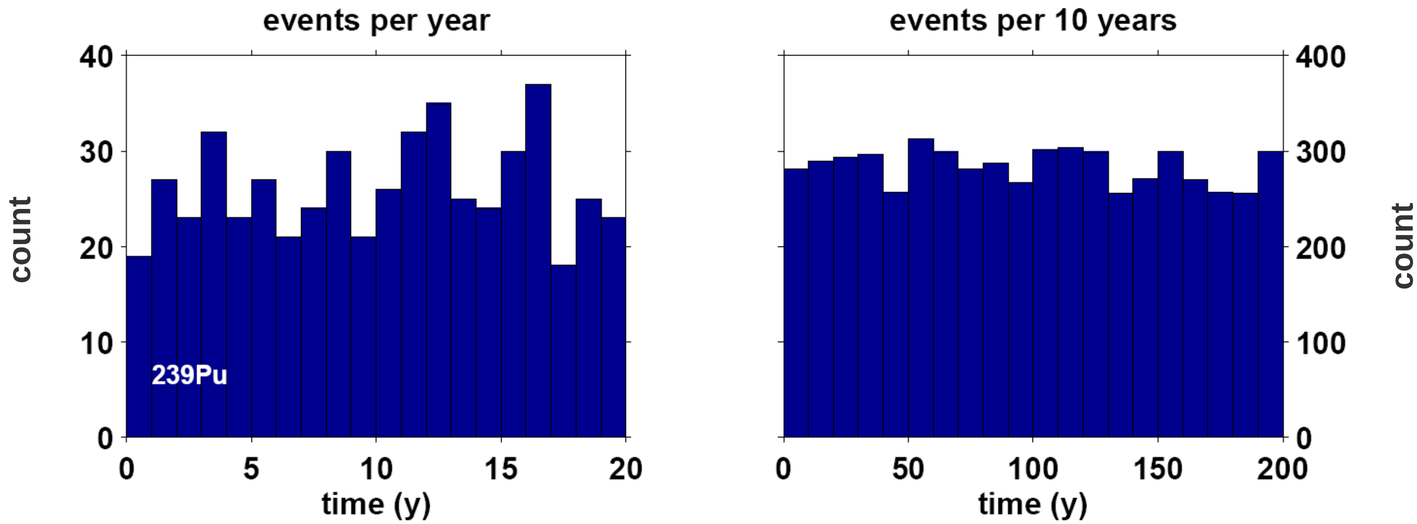
The **Poisson process** of intensity λ is defined by the requirements that for all t and for $\delta \to 0+$

$$P\{N(t,t+\delta t)=1|H_t\}=\lambda\delta+o(\delta)$$

- the only process for which all events are completely independent
- ‘simple process’, often used for the description of neural spiking
- the Bernoulli process approximates the Poisson process for $\Delta t \to 0$.

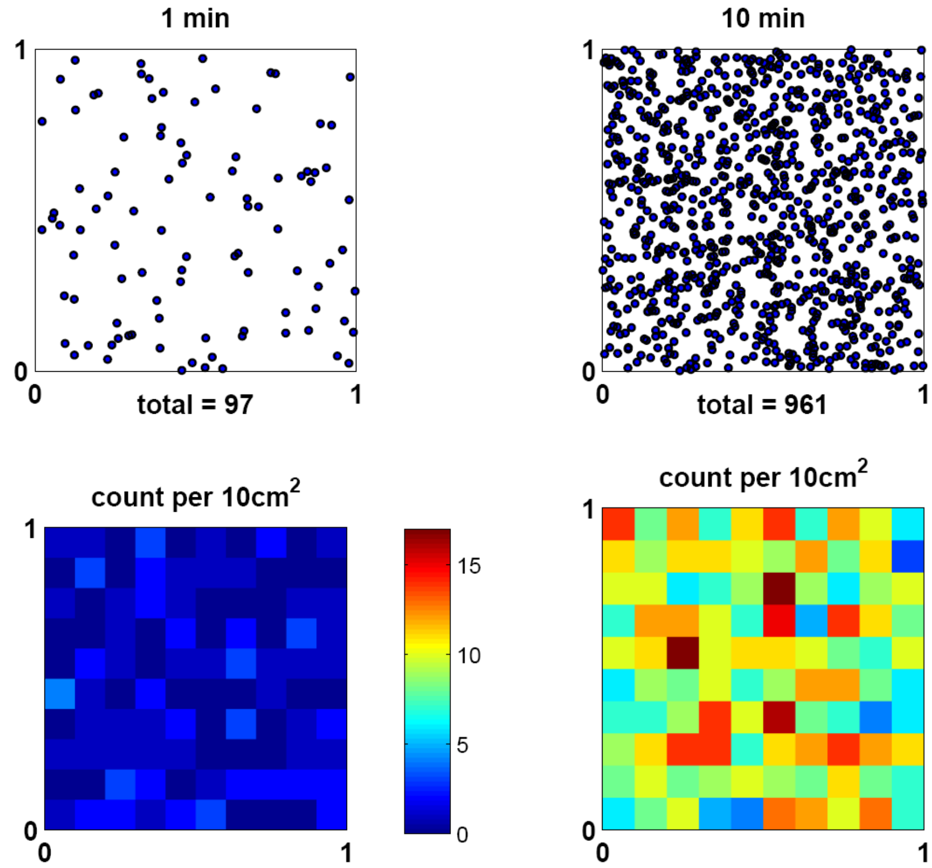
Example 1: radioactive decay of 239Pu (half-life : 4110 years).

- continuous time intervals
- discrete event count



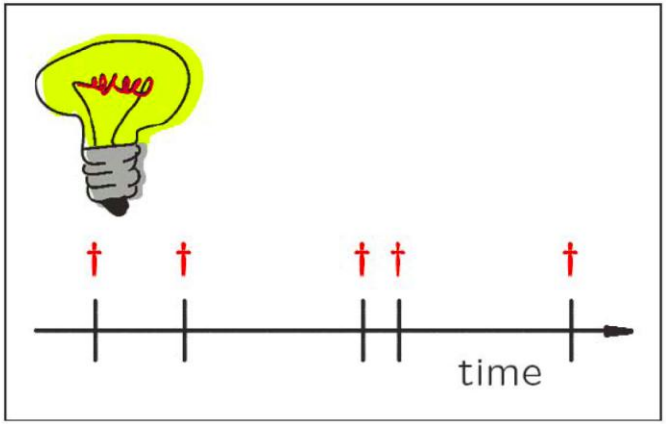
Example 2: rain drops

- continuous space intervals
- discrete event count



Definition

inter-event intervals are **independent** and **identically distributed** (iid)



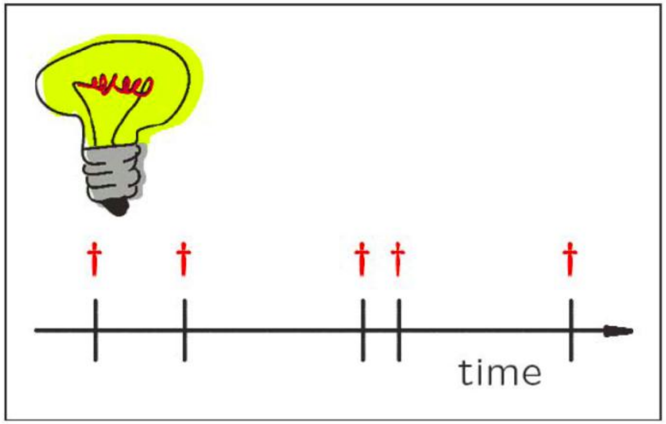
† = replacement from a homogeneous population

Definition

inter-event intervals are **independent** and **identically distributed** (iid)

Thus

• individual intervals are serially independent
• process history extends only up to the previous event
• the intervals between successive points are mutually independent
• the Poisson process is a renewal process



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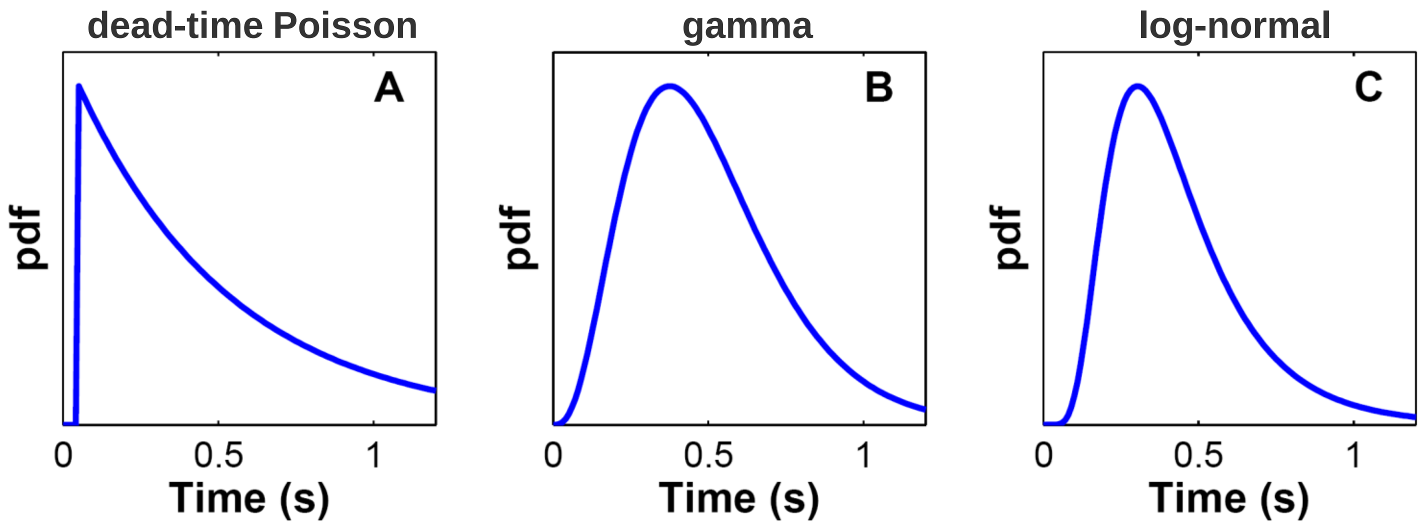

dead-time Poisson
A
pdf
0
0.5
1
Time (s)
gamma
B
pdf
0
0.5
1
Time (s)
log-normal
C
pdf
0
0.5
1
Time (s)

Model classes

constant intensity λ

dynamic intensity λ(t)

Poisson

- exponential interval distribution
- Poisson count distribution
- events are uniformly distributed in time
- special case of gamma process

non-homogenous Poisson

Renewal

- iid interval distribution
- FF = CV^2

Rate modulated Renewal

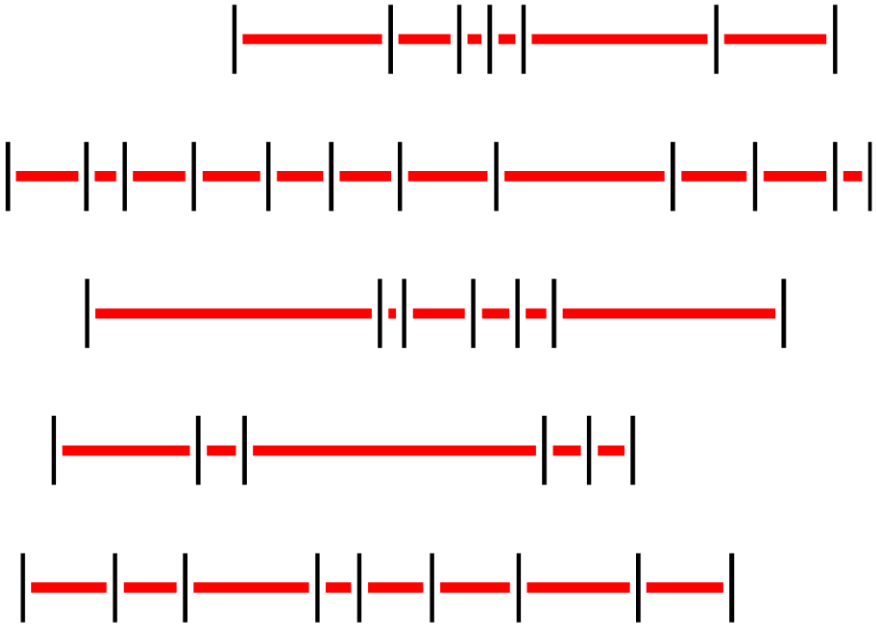
stationary non-Renewal

- constant intensity parameter
- non-trivial history dependence
- serial interval correlations

increasing importance of process history

4. Practice: Empiric Interval and Count Statistics

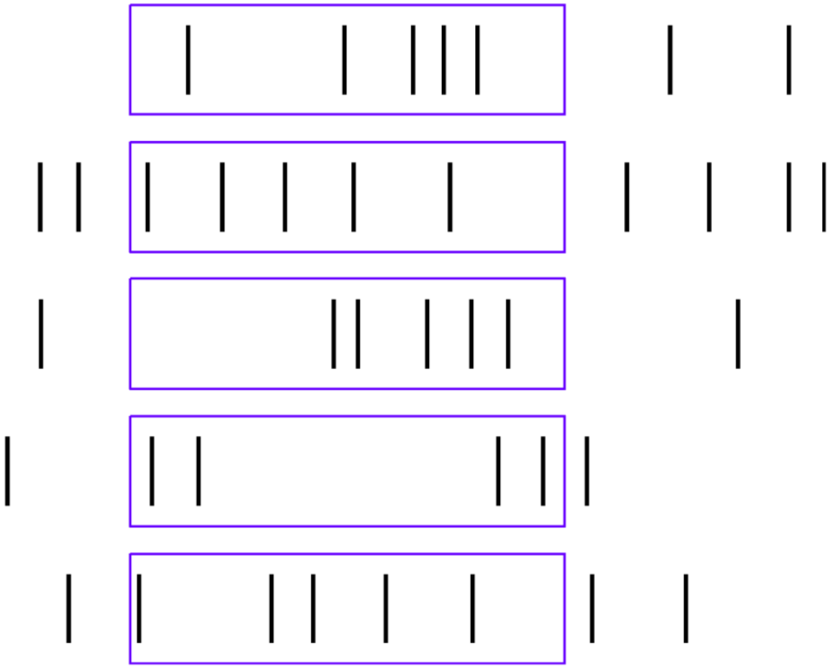
Inter-spike intervals



inter-spike intervals

continuous data

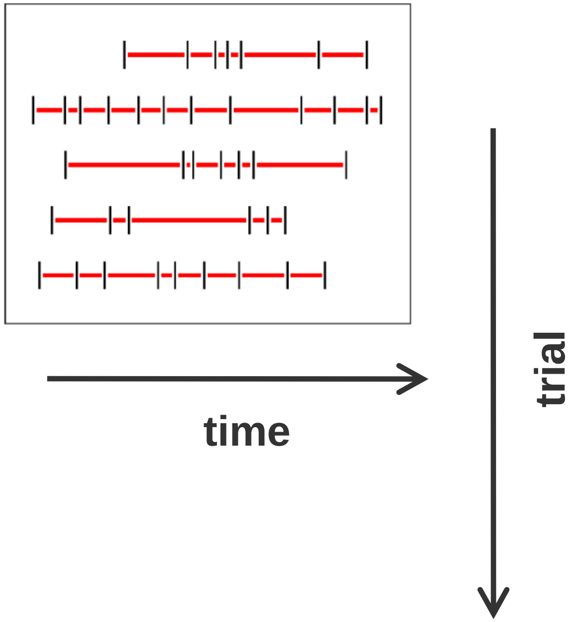
Spike count



spike count
discrete data

Coefficient of variation (interval variability)

$$CV^2 = \frac{Var(ISI)}{mean^2(ISI)}$$

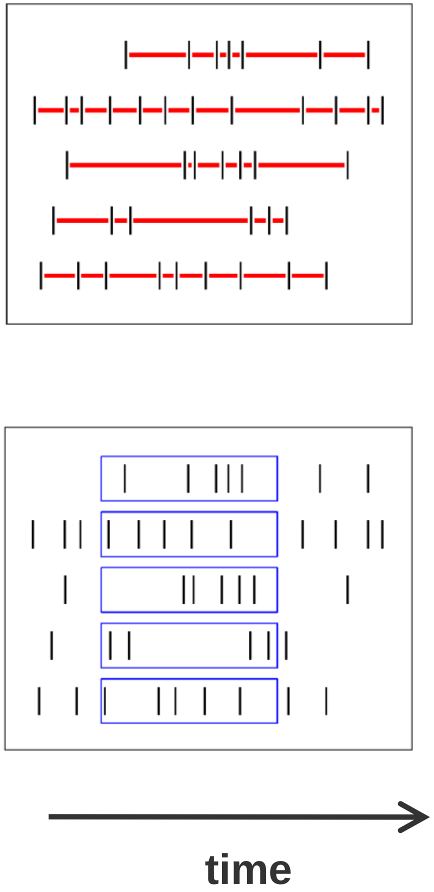


Coefficient of variation (interval variability)

$$CV^2 = \frac{Var(ISI)}{mean^2(ISI)}$$

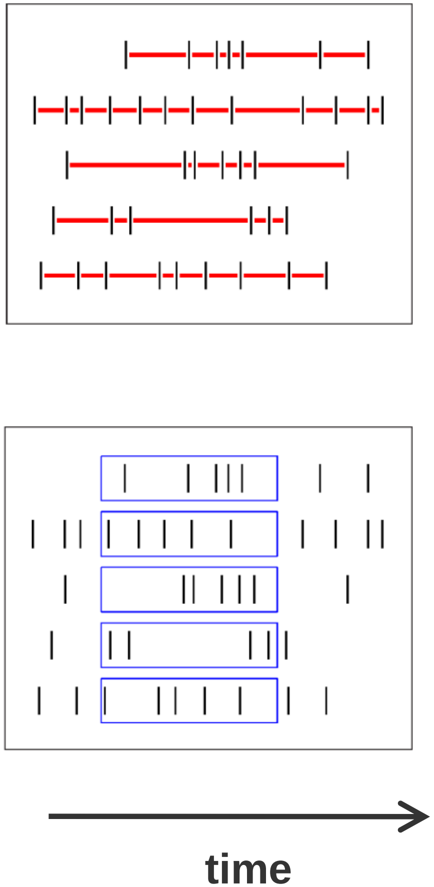
Fano factor (count variability)

$$FF = \frac{Var(count)}{mean(count)}$$



Coefficient of variation (interval variability)

$$CV^2 = \frac{Var(ISI)}{mean^2(ISI)}$$



Fano factor (count variability)

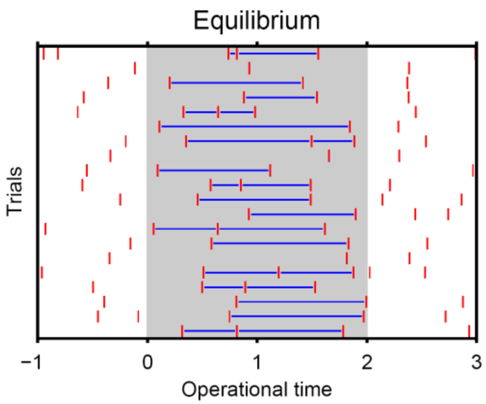
$$FF = \frac{Var(count)}{mean(count)}$$

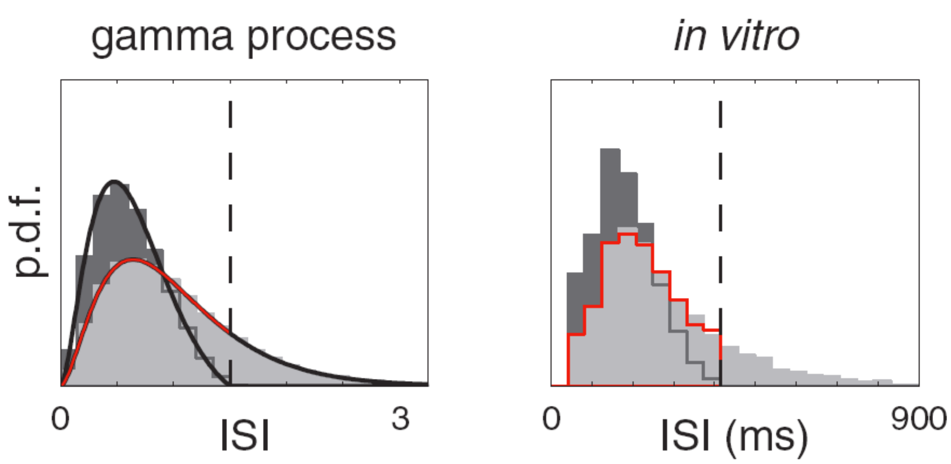
theoretic relation for **renewal process**

$$\boxed{FF = CV^2}$$

Caution : Estimation bias CV

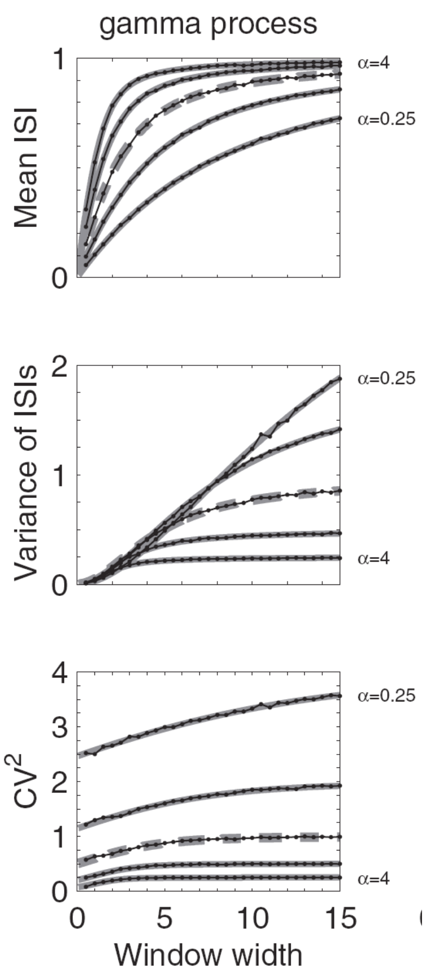
We observe intervals in **finite** time interval !

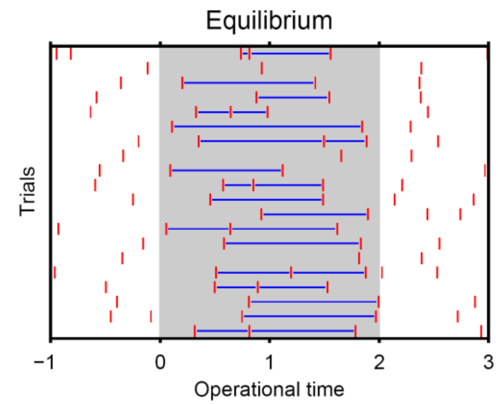




Nawrot et al. (2008) J Neurosci Meth 169: 374:390
Nawrot (2003) PhD Thesis

Caution : Estimation bias CV



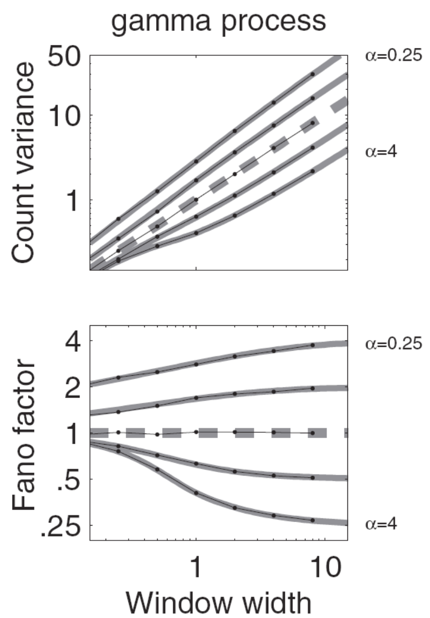


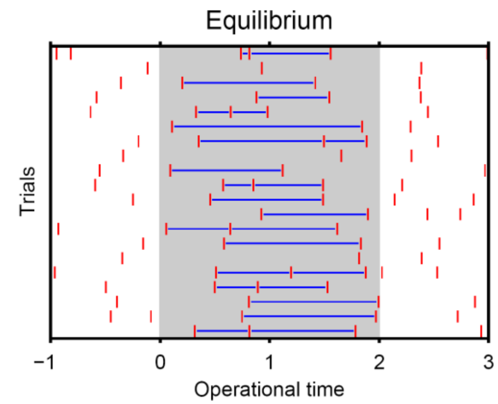
⇨ **1.3 TASK A 6 - 9**

► CV is underestimated for a low count number

Nawrot et al. (2008) J Neurosci Meth 169: 374:390
Nawrot (2003) PhD Thesis

Caution : Estimation bias FF

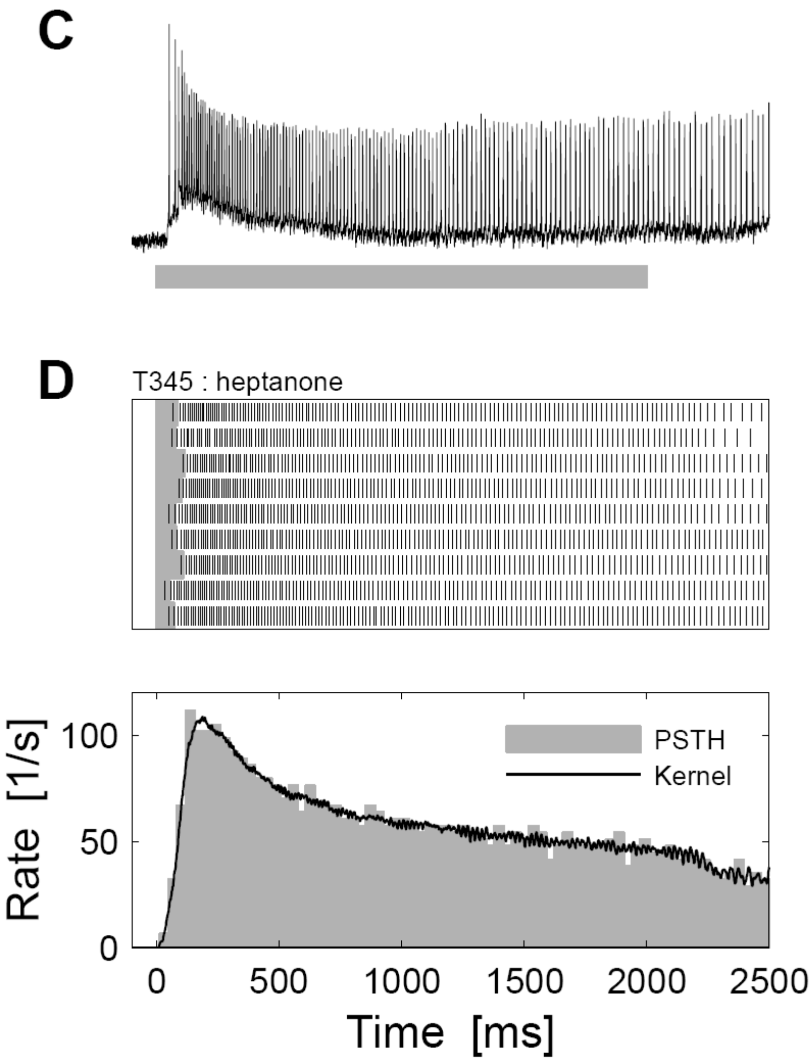




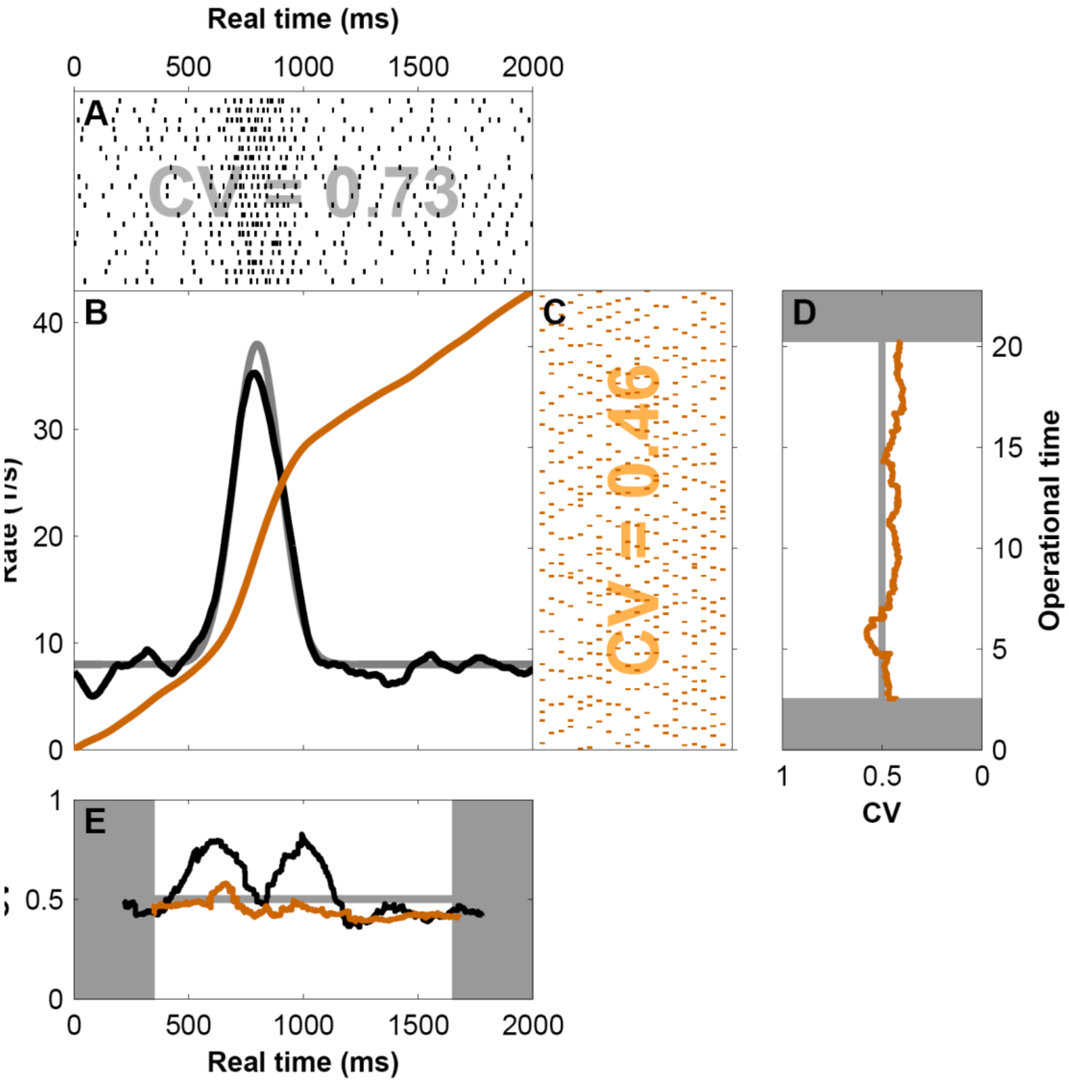
► FF approaches unity for a decreasing count number

Nawrot et al. (2008) J Neurosci Meth 169: 374:390
Nawrot (2003) PhD Thesis

Problem for CV measurement : rate modulation



Krofczik S, Menzel R, Nawrot MP (2008) Front Comp Neurosci 2:9



Nawrot et al. (2008) J Neurosci Meth 169: 374:390

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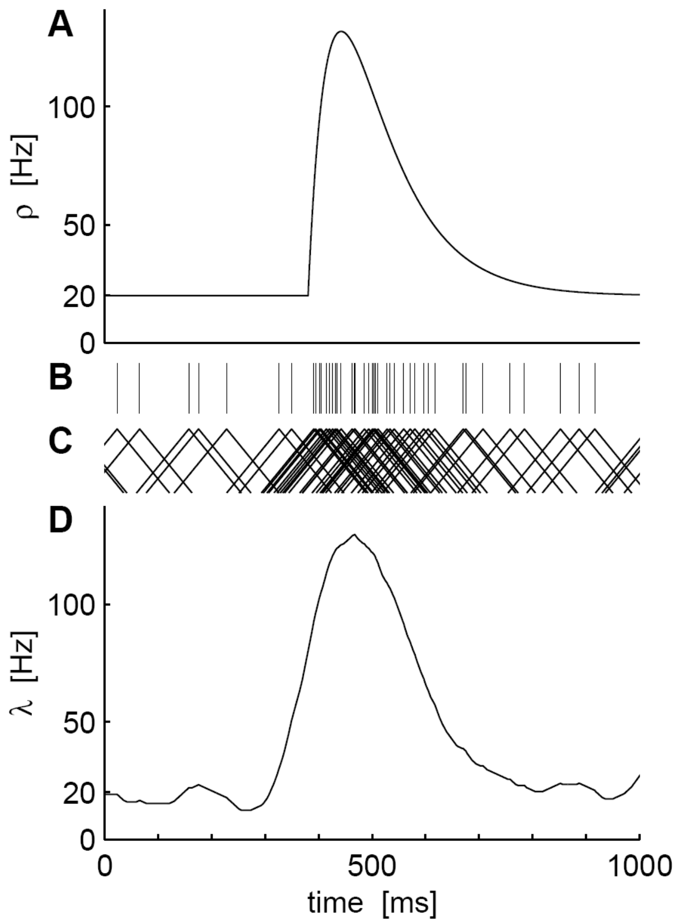


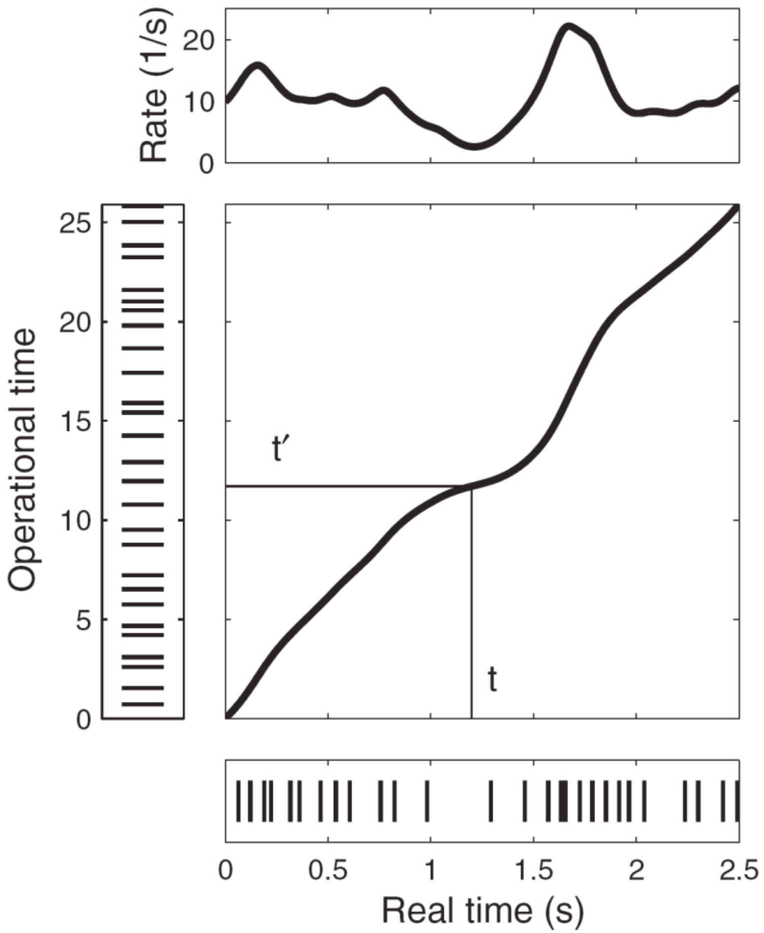
$$\lambda(t) := \sum_{i=1}^{n} K(t - t_i)$$

Table 1
Tested kernel functions[a]

Kernel	$K(t, \sigma)$	Support
Boxcar	$\frac{1}{2\sqrt{3}\sigma}$	$[-\sqrt{3}\sigma, \sqrt{3}\sigma]$
Triangle	$\frac{1}{6\sigma^2}(\sqrt{6}\sigma - \lvert t \rvert)$	$[-\sqrt{6}\sigma, \sqrt{6}\sigma]$
Epanechnikov	$\frac{3}{4\sqrt{5}\sigma}\left(1 - \frac{t^2}{5\sigma^2}\right)$	$[-\sqrt{5}\sigma, \sqrt{5}\sigma]$
Gauss	$\frac{1}{\sqrt{2\pi}\sigma}\exp\left(-\frac{t^2}{2\sigma^2}\right)$	$[-\infty, +\infty]$

⇨ 1.3 TASK B 12 - 13

Nawrot, Aertsen, Rotter (1999) J Neurosci Meth 94: 81-92



$$t' = \Lambda(t) = \int_0^t \lambda(s)\,\mathrm{d}s$$

‘unwarp’ spike train !

Nawrot et al. (2008) J Neurosci Meth 169: 374:390
Meier, Egert, Aertsen, Nawrot (2008) Neural Networks 21:1085-1093

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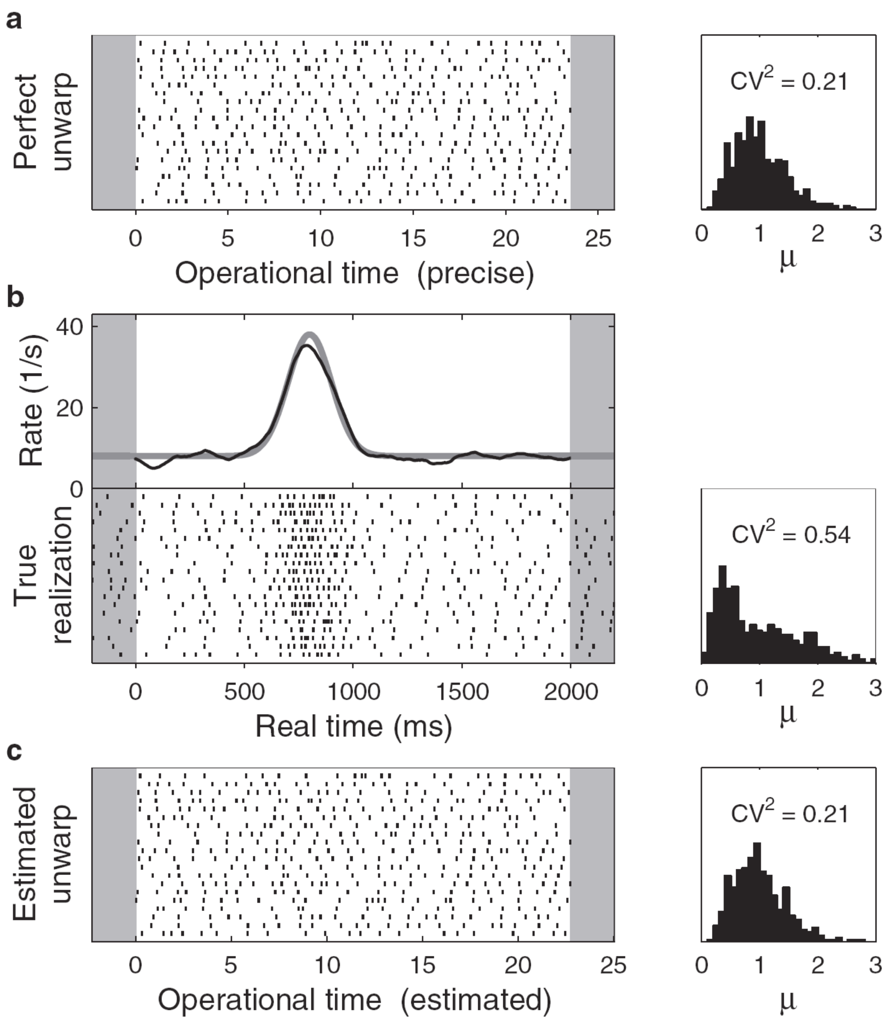

⇨ 1.3 TASK B 14 - 15

Nawrot et al. (2008) J Neurosci Meth 169: 374:390

5. Course Data

- intracellular in vivo : A1
- intracellular in vitro : A2, B1
- extracellular mushroom body honeybee : B2
- point process simulation : C1/C2/C3

A1 : Spontaneous activity ***in vivo***

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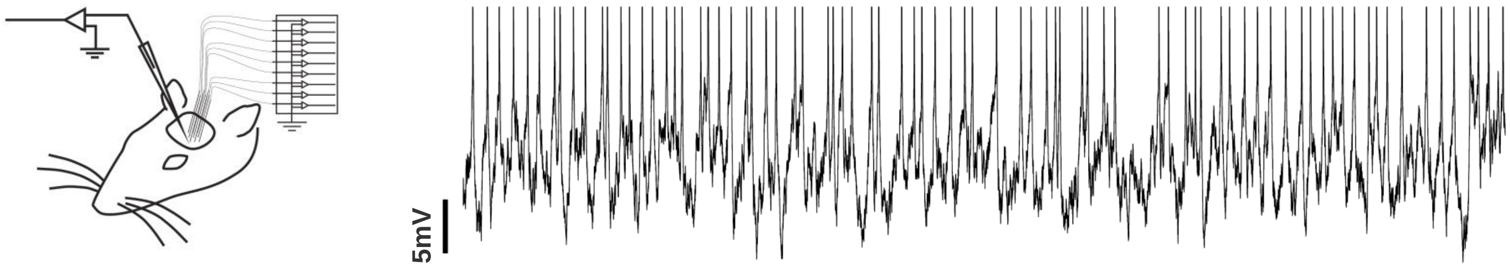
Experiments *by Clemens Boucsein and Yamina Seamari, Uni Freiburg*

- *In vivo* **intracellular** recordings from *cortical neurons* in anesthetized rat
- **spontaneous activity** (no stimulation)



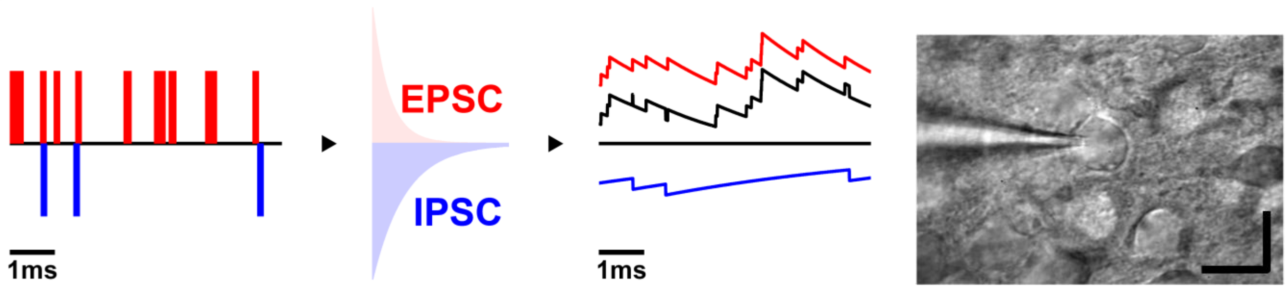
A1_data_set_040528_boucsein

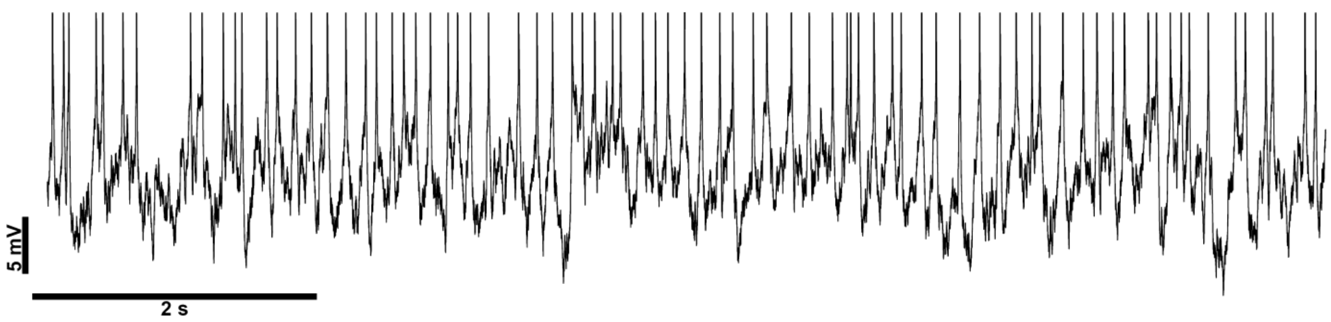
Nawrot et al. (2007) Neurocomputing 70: 1717-1722

A2/B1 : Stationary noise current injection ***in vitro***

Experiments *with Clemens Boucsein and Victor Rodriguez, Uni Freiburg*

- *In vitro* patch clamp recordings from pyramidal cells (acute slice)
- **stationary noise current** injection (5-20min)

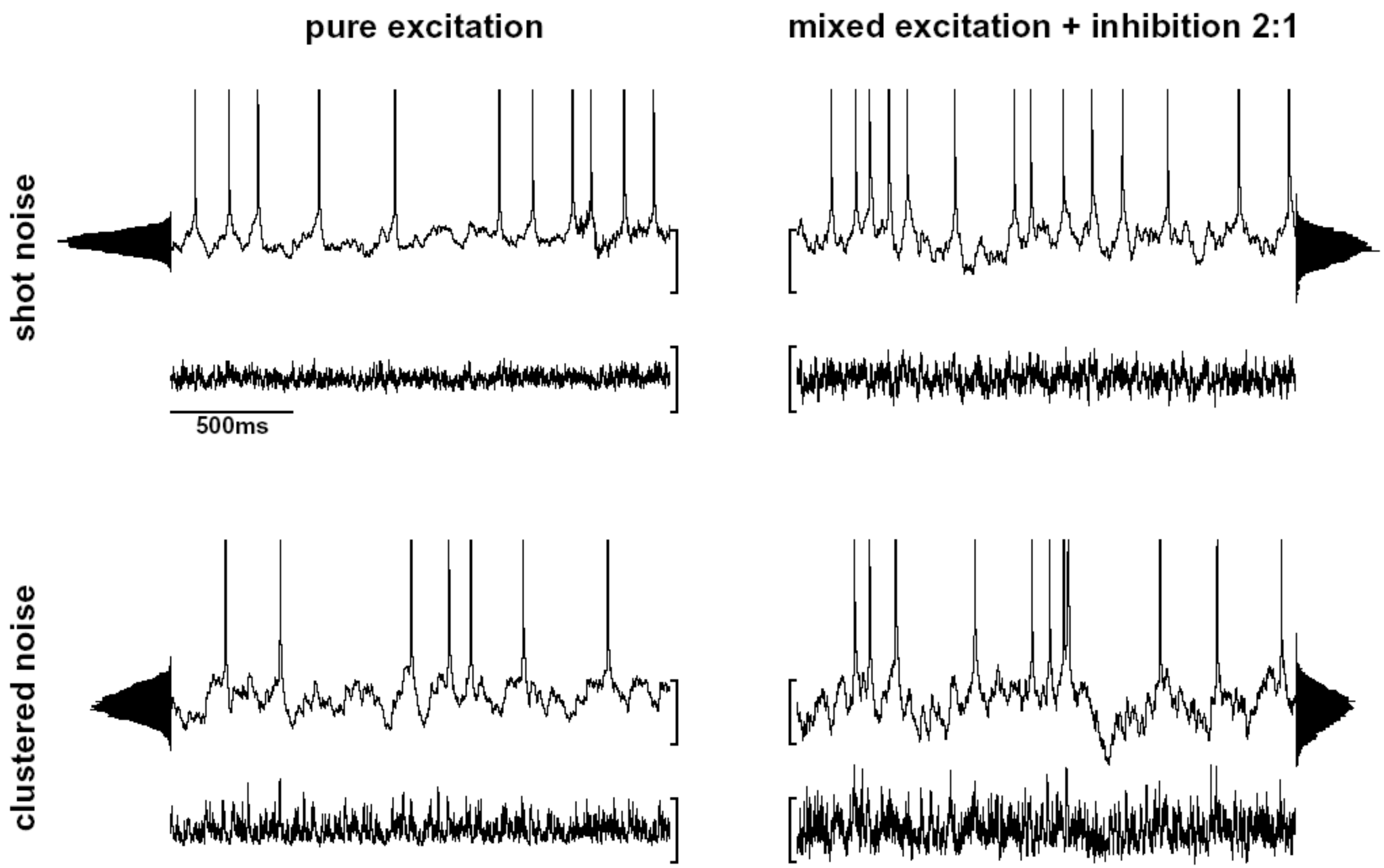




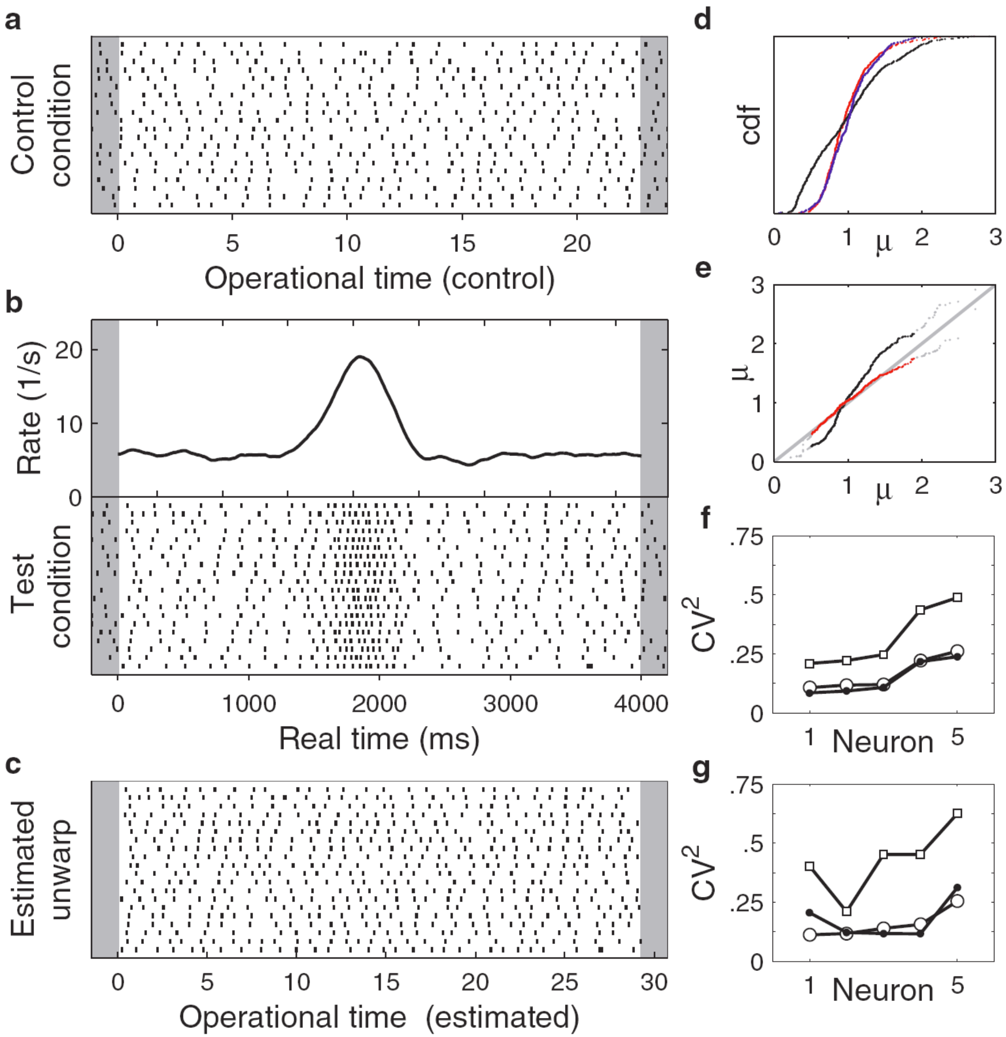
A2_data_set_2003_rodriguez_nawrot
B1_DCS_041020_cortex1_2cell008

Nawrot et al. (2008) J Neurosci Meth 169: 374 - 390

A2 : Stationary noise current injection ***in vitro***



Nawrot et al. (2008) J Neurosci Meth 169: 374 - 390



⇨ 1.3 TASK B 14 - 15

Nawrot et al. (2008) J Neurosci Meth 169: 374:390

Autoregressive model approach

We propose the following process to model inter-event intervals

$$\Delta_s = \exp(X_s) = \exp(\beta X_{s-1} + \varepsilon_s) \qquad (|\ \beta\ | < 1)$$

When we choose ***ε_s* normal distributed** with mean μ and variance σ^2 then ***Δ_s* is log-normal** distributed.

β=0 : no correlation = renewal model

β<0 : *negative* serial correlation

β>0 : *positive* serial correlation

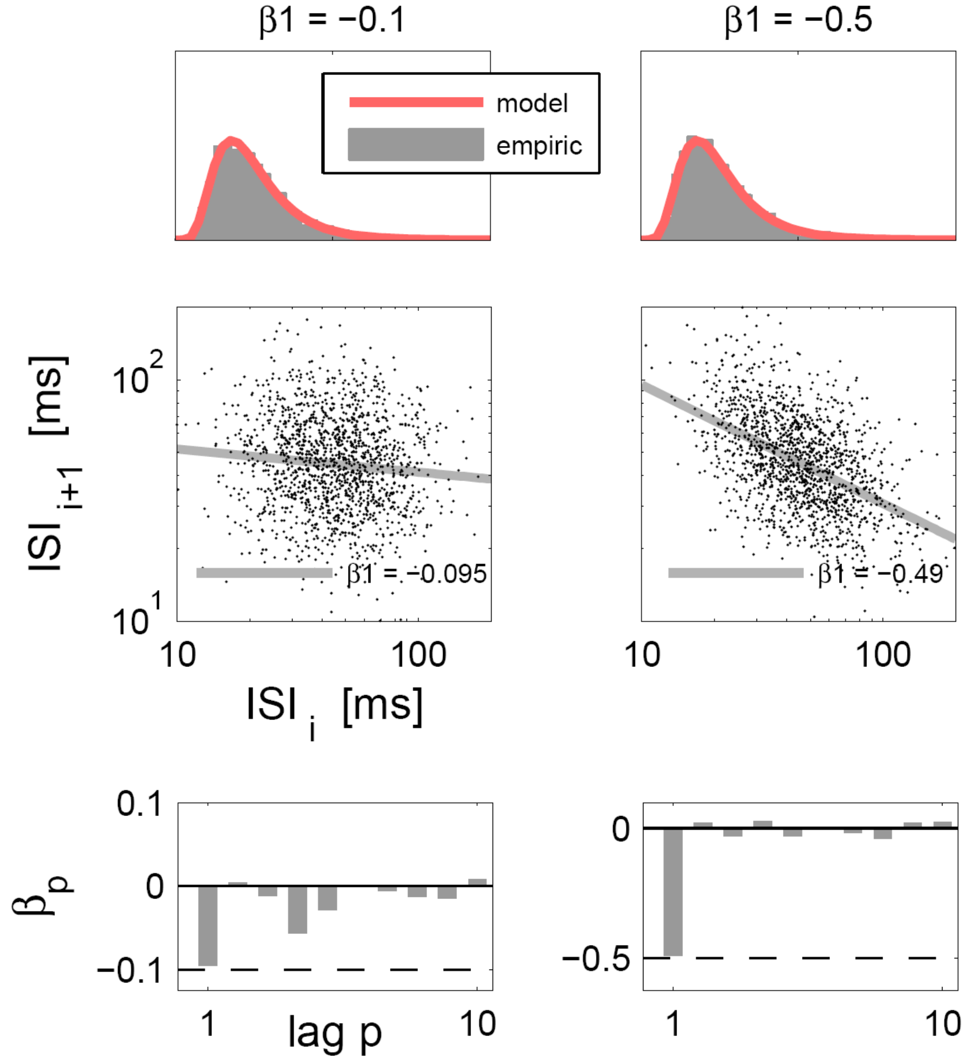
C1_Simulation | C2_Simulation | C3_Simulation

Farkhooi, Strube-Bloss, Nawrot (2009) Phys Rev E 79

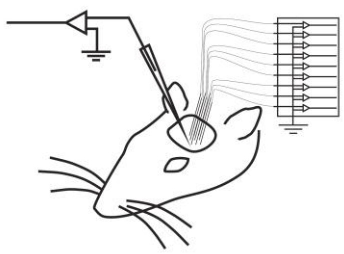
Numeric Simulation

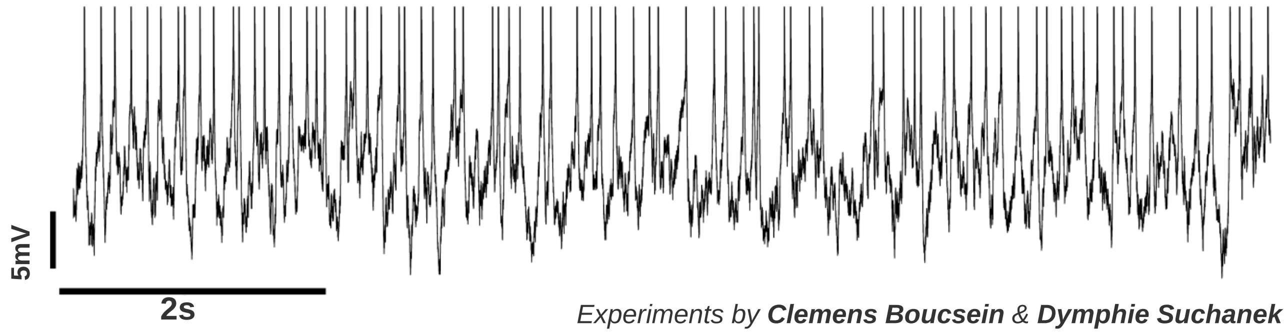
log-normal

CV = 0.5



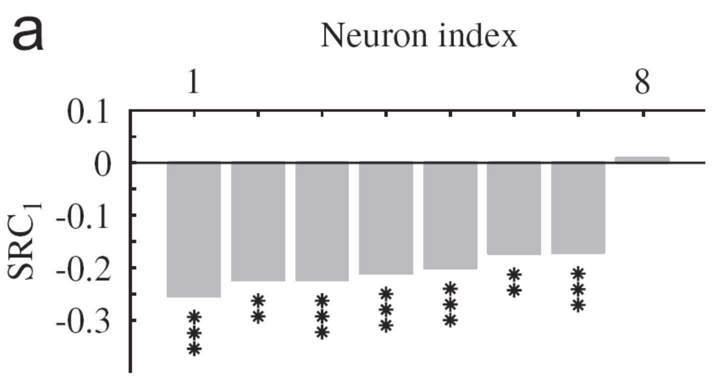
Farkhooi, Strube-Bloss, Nawrot (2009) Phys Rev E 79





*Experiments by **Clemens Boucsein** & **Dymphie Suchanek***

University of Freiburg, Germany



X_1	X_2
X_2	X_3
X_3	X_4
:	:
X_i	X_{i+1}

Nawrot et al. (2007) Neurocomputing 70: 1717-1722

GOALS for today

- motivation: precision and variability in neural systems
- practical experience with spike train data
- ‘howto’ estimate variability of intervals and counts
- insight into the relation of interval and count statistics
- usefulness of point process theory

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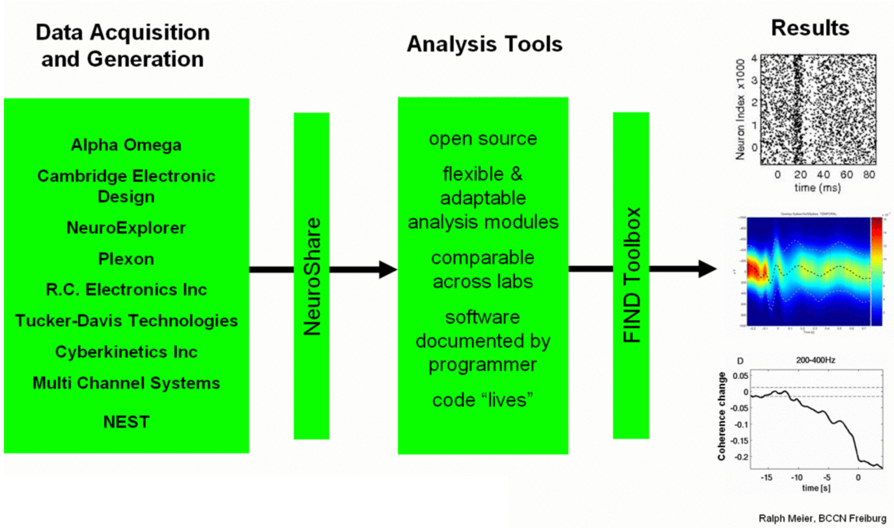
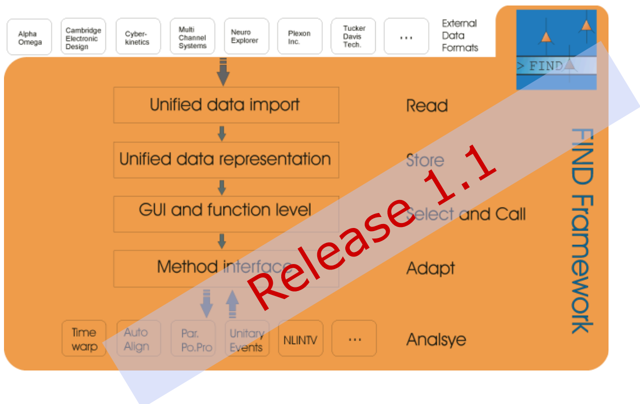
Open source tools for neural data analysis in MATLAB





http://find.bccn.uni-freiburg.de

Meier R, Egert U, Aertsen A, Nawrot MP (2008) Neural Networks 21

FIN