EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Stochastické aspekty početních neurověd

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Tato prezentace je spolufinancována Evropským sociálním fondem a státním rozpočtem České republiky.

Reference

- Tuckwell HC, Introduction to theoretical Neurobiology, CAMBRIDGE UNIV. PRESS, 1988, Two-volume set develops mathematical theories for the neurons.
- Gerstner W, Kistler WM, Spiking neuron models, CAMBRIDGE UNIV. PRESS, 2002, Introduction to spiking neurons models - advanced-level course in computational neuroscience.

Zde – krátký úvod, který je možný absolvovat s minimem matematických znalostí

Početní neurovědy

- Interdisciplinary field, theory: mathematics, biology, physics, computer science, information theory,...
- **The goal**:
  - To understand the way neural systems work
  - To implement new and effective: sensory systems, algorithms, computers, …

1. Using a computer to model neuron(s)

2. Studying neuron(s) as a computer

Početní neurovědy

- **1:** (“dynamics”)
  - Neuronal models:
    - Point (I-F), multicompartment, “realistic”
  - Population vs. single neurons, computationally intensive tasks, NEURON (software)
- **2:** (“coding”)
  - „The computer“: dynamical system → state represents information

coding+dynamics=comput. neurosci

Obsah

- Biologické základy, kódování
- Historické poznámky
- Matematické základy
- Stochastické modely neuronu
- Kódování, detekce signálu

BIOLOGICKÉ ZÁKLADY

Neurony

Neurony jsou základní jednotkou nervového systému.

S dalšími neurony vytvářejí sítě.

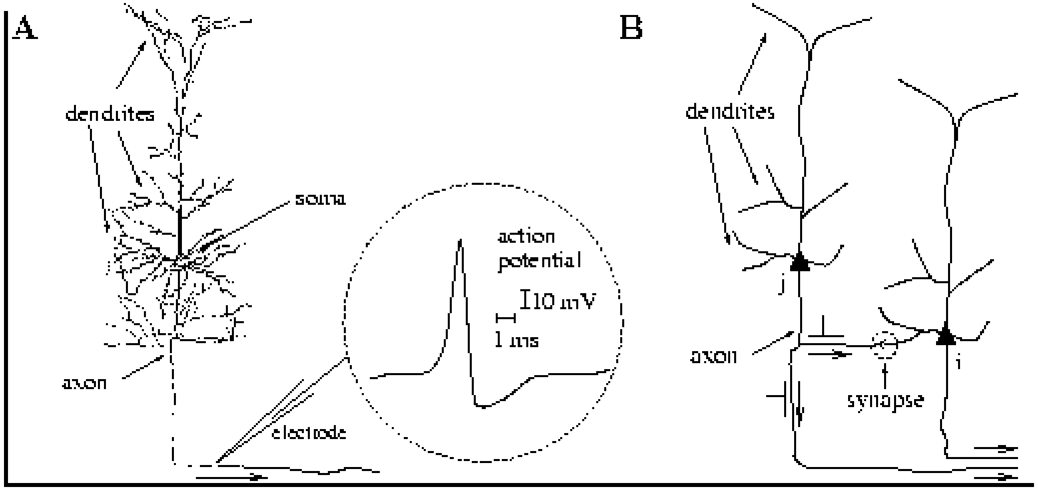
Signály se mezi neurony přenášejí pomocí synapsí.

Neurony jsou elektro-chemicky vzrušivé a tímto způsobem zpracovávají a ukládají informaci.

JAK?

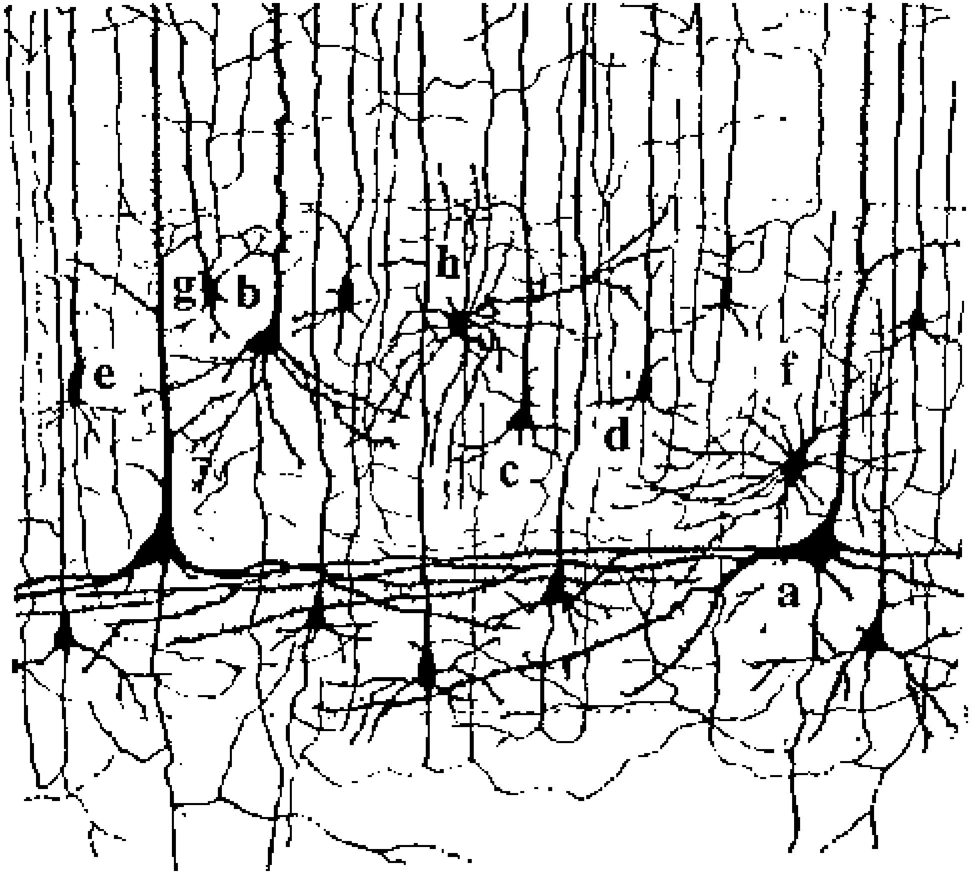
Neuron

- Soma, axon, dendrite, synapse
- Action potential – „the spike“ (up to 100mV),

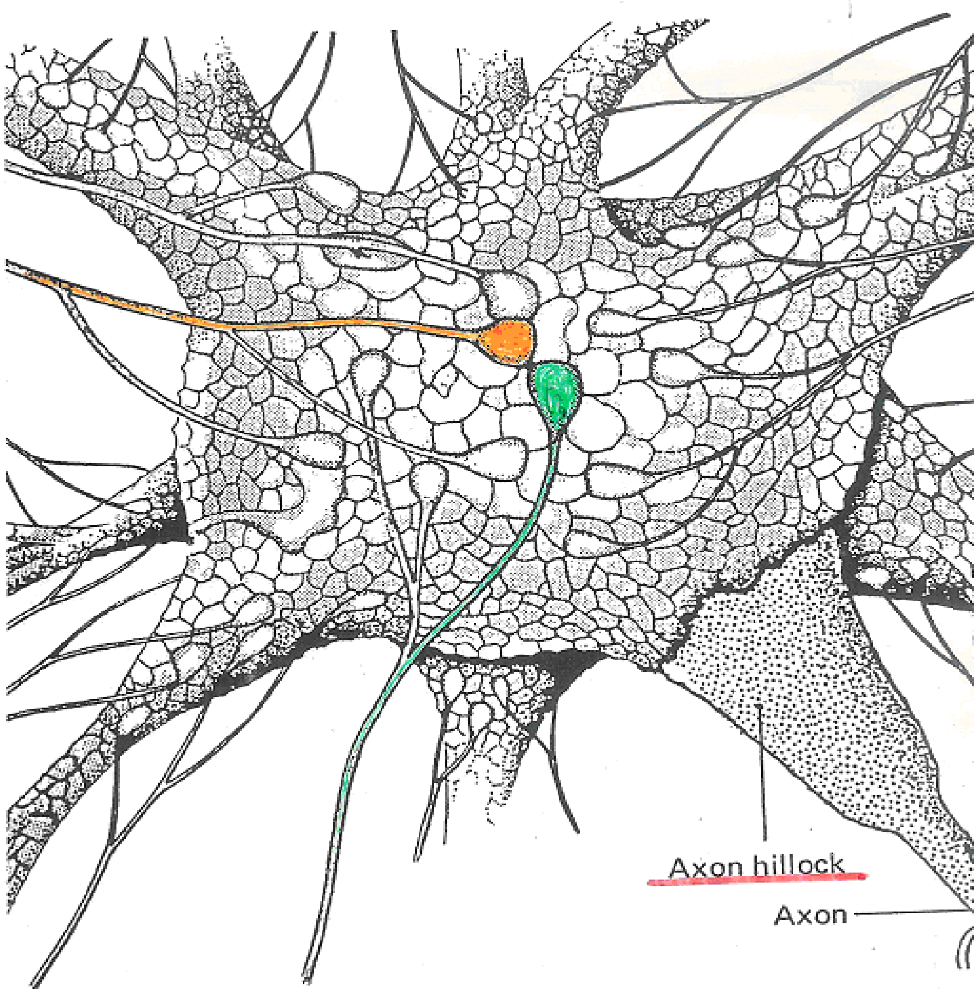


Nervová soustava

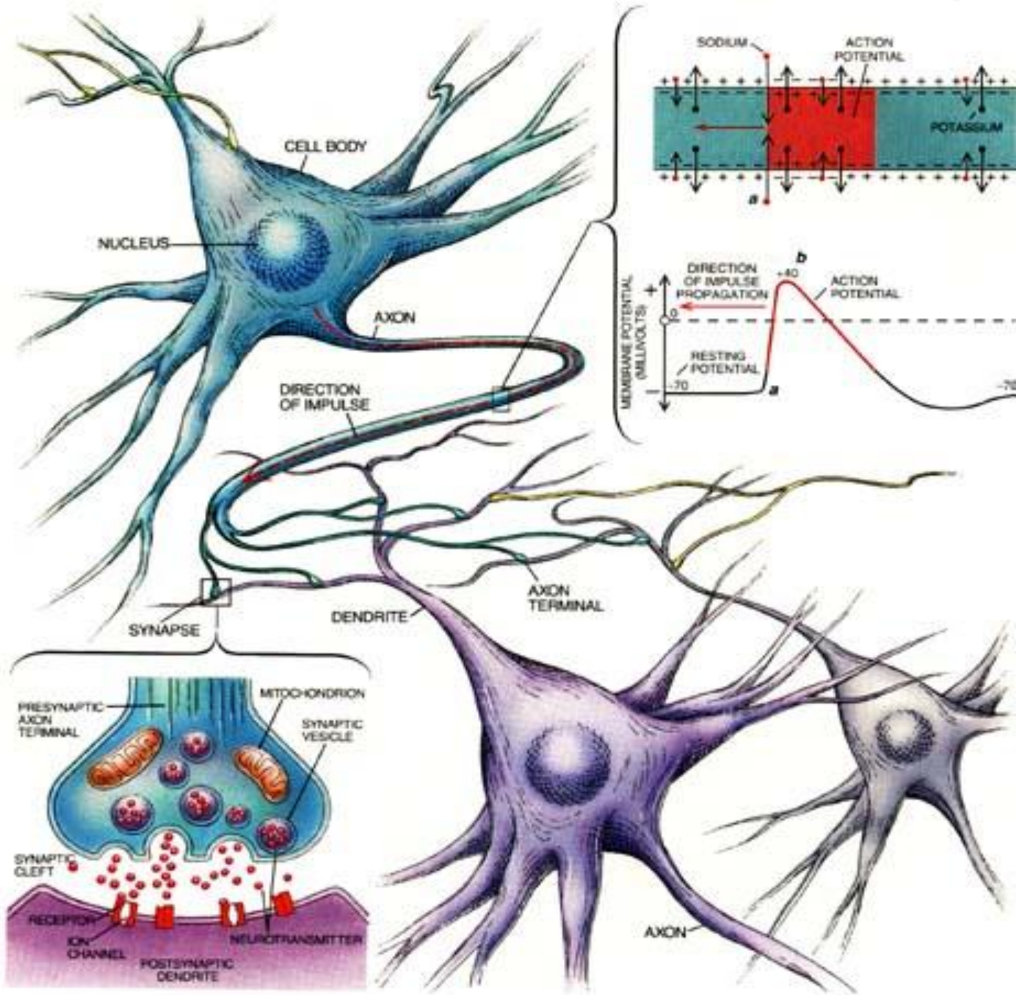
- Non-homogenous structure
- Vertebrates:
  - $1mm^3 \rightarrow 10^4$ neurons
  - $1mm^3 \rightarrow$ 3km of “wires”
  - 1 neuron $\rightarrow 10^4$ connections
- Sensory v. central systems
- Roles of neurons are very variable



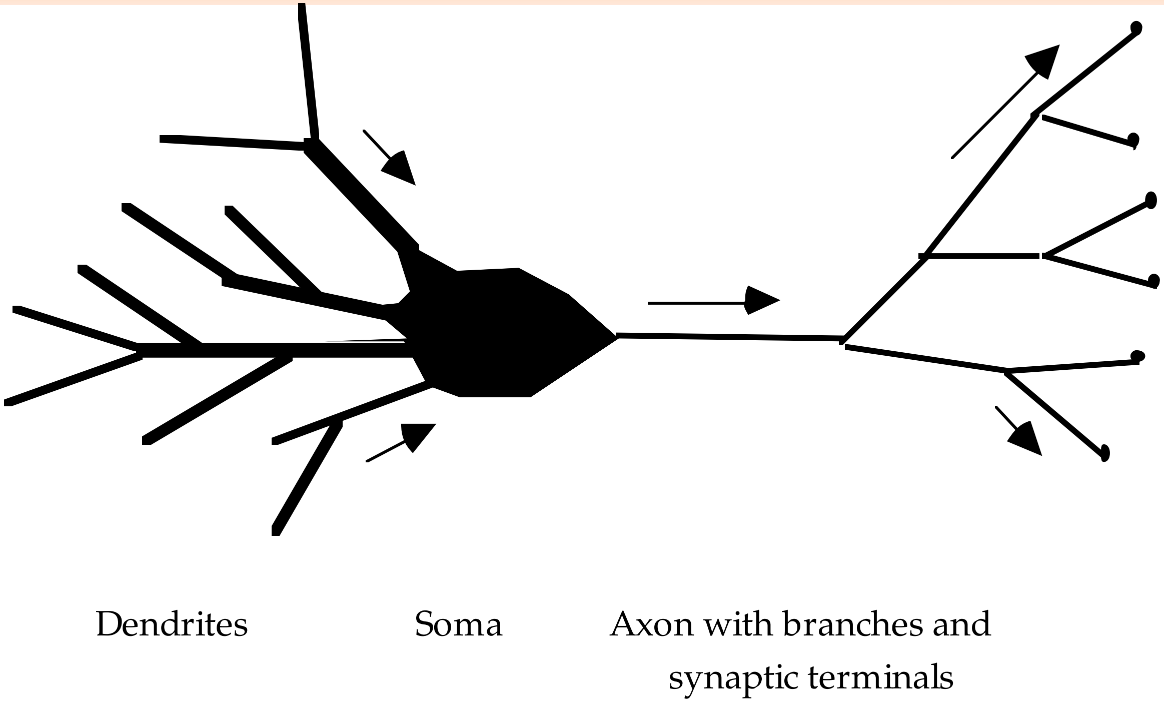
Neuron a Synapse



Neurony a Synapse



“Základní” neuron



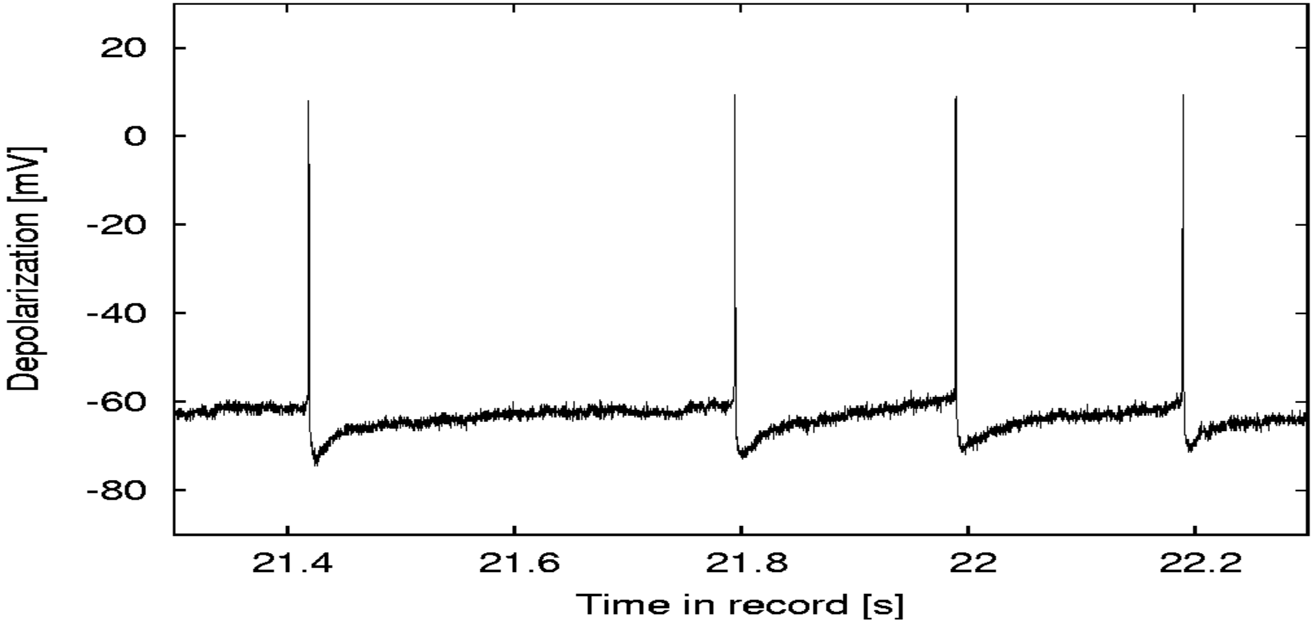
- The soma and dendrites act as the input; the axon carries the outputs.
- The tips of the branches of the axon form synapses upon other neurons or upon effectors (though synapses may occur along the branches of an axon as well as the ends). The arrows indicate the direction of "typical" information flow from inputs to outputs.

Sensorické neurony

- converting external stimuli from the environment into internal (electrical) representation, input is light, sound, chemical substance,...
- For example, in olfactory neurons sensory receptors located on the cell membrane are responsible for the conversion of stimuli into electrical impulses
- these are sent along axons to the olfactory bulb, where the smell is processed.

Intespikový interval – klíčový pojem

- The same stimulus produces a different spike train each time.



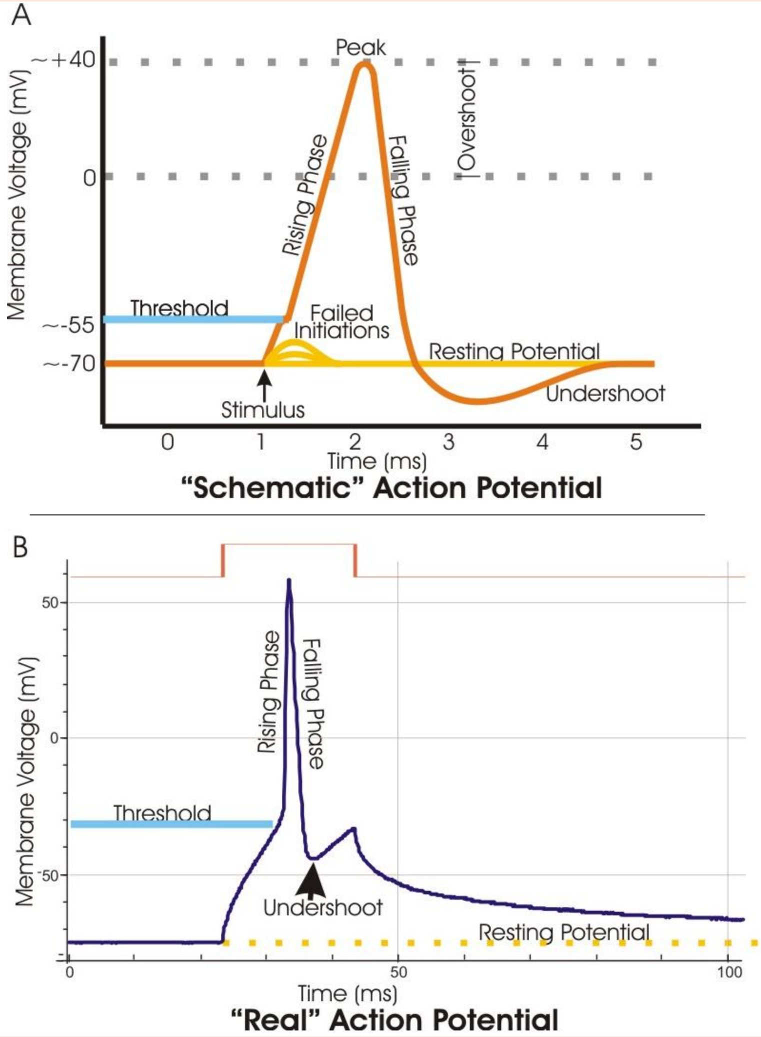
ISI je experimentálně dostupný

- Obvykle lze zaznamenávat pouze jeden nebo málo neuronů současně
- Ve skutečnosti masivně souběžné zpracovávání informace je nahrazeno délkou pokusu, nebo opakováním. To však představuje mnohá úskalí.
- Spontánní versus evokovaná aktivita, rozdíl je jasný pouze u senzorických neuronů
- dostupnost záznamu membránového potenciálu je obtížnější

Akční potenciál - spike

- Spike generation: non-linear operation integrating input with some memory
- Resting potential u_{rest}
- inputs to a *neuron* cause the membrane to *depolarize* or hyperpolarize;
- Threshold potential

  (20-30 mV above u_{rest})



"Schematic" Action Potential

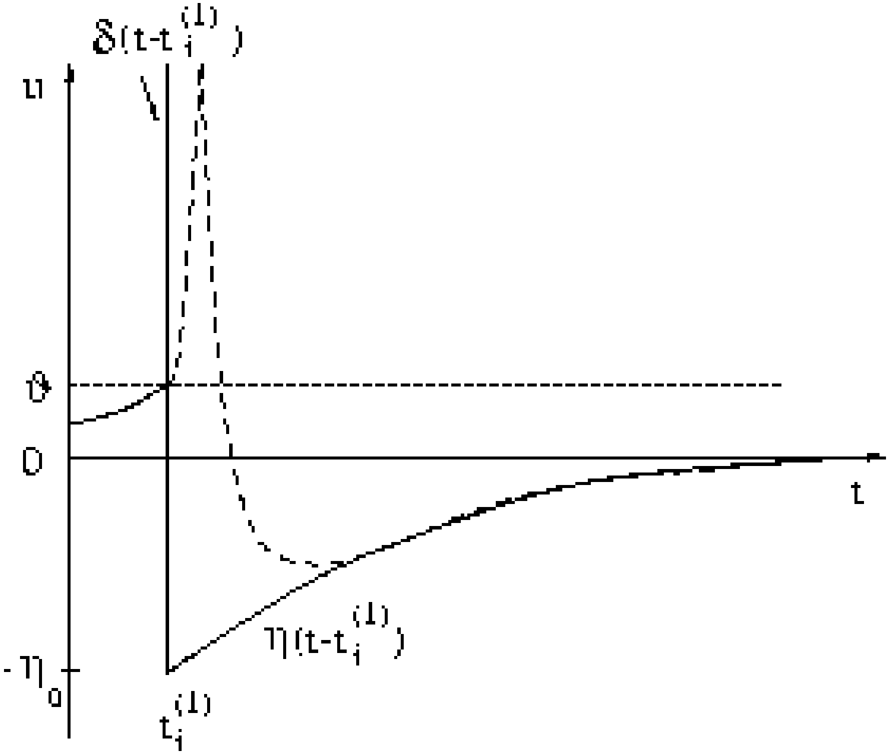
"Real" Action Potential

Spike podrobněji

- Tvar nehraje roli z pohledu neuronového kódování
- Absolutní/relativní refrakterní fáze, „the inner precision“, (1-4ms)
- Formalní model:

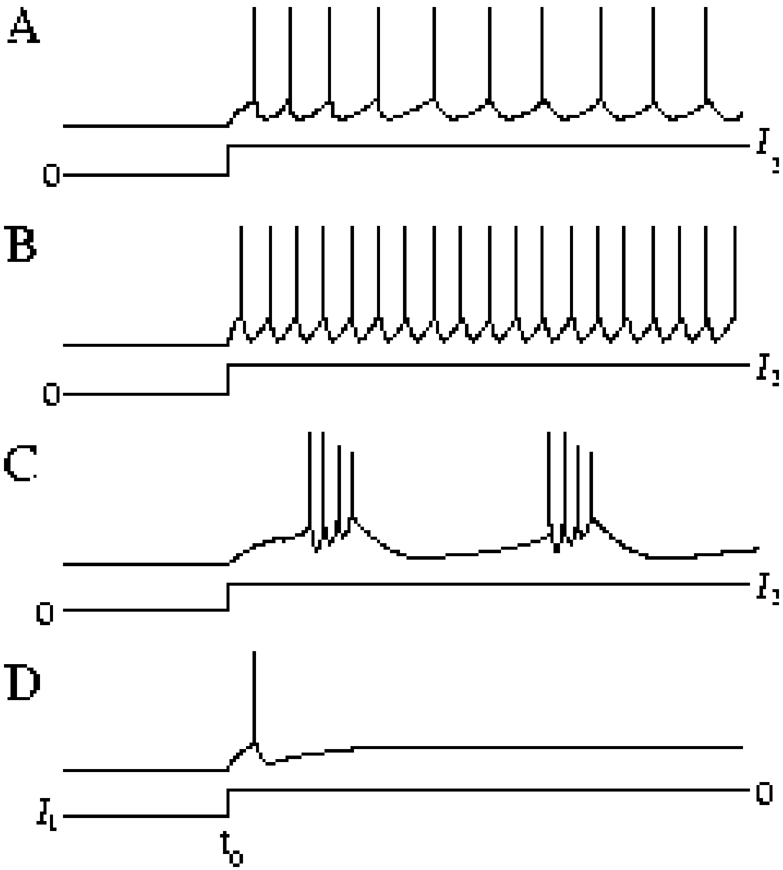
  spike = δ-funkce

  Refrakterní perioda – odhad posunutí



Posloupnost akčních potenciálů
The spike train (časová řada)

- Differ from cell to cell
- Differ for a single cell (e.g., stimulus onset)
- Some typical examples:
  - Adaptability (A)
  - Pacemaking (B)
  - Bursting (C)
  - Inhibition rebound (D)



Minimum biologických znalostí

- “our” neuron is a single point in space characterized by membrane potential. (Compartment models will be mentioned.) Neuron receives signals (sequence of pulses) which change the potential in positive and negative direction (excitation and inhibition).
- The incoming signal is “integrated” in time.
- Occasionally, when the membrane potential is high, the neuron generates spike (action potential) which is sent away. Then integration starts again.

KÓDOVÁNÍ

Frekvenční (rate) kódování

- Adrian ED & Zotterman Y. (1926). "The impulses produced by sensory nerve endings: Part II: The response of a single end organ.". *J Physiol (Lond.)* **61**: 151–171
- Váha působící na sval vyvolávala úměrný počet spiků
- 1932 Nobelova cena, společně s Ch. Sherringtonem

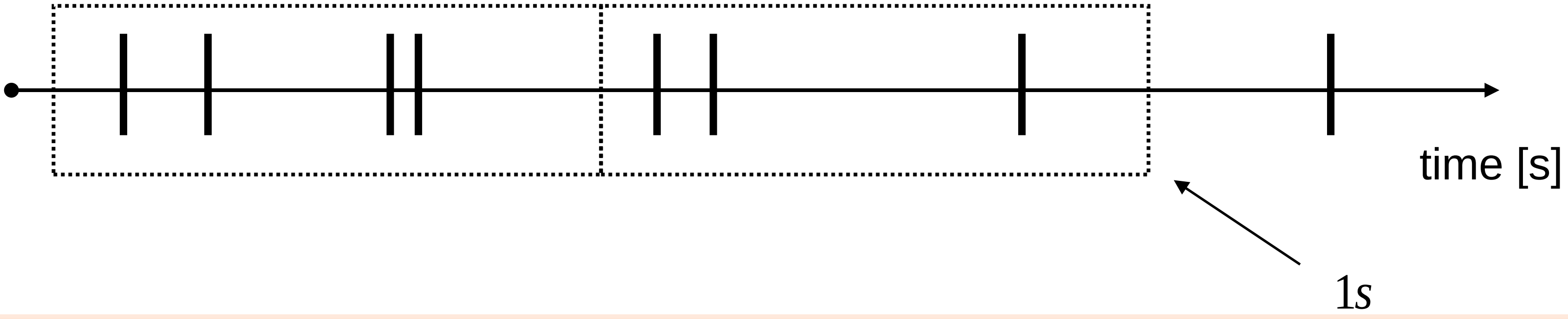
Frekvenční (rate) kódování

- Počet spiků v „daném“ okamžiku – populační kódování
- Jak hodnotit v experimentu ?

$$\upsilon(I)$$

$$\nu = \frac{4}{1} = 4s^{-1}$$

$$\nu = \frac{3}{1} = 3s^{-1}$$



Obecné otázky vyvolané konceptem frekvenčního kódování

- Které charakteristiky posloupnosti spiků jsou náhodný šum (proč existuje) a které jsou signálem ?
- Jaký signál nese populace neuronů a jaký aktivita jednoho ?
- Jaká je časová škála?

Časové kódování

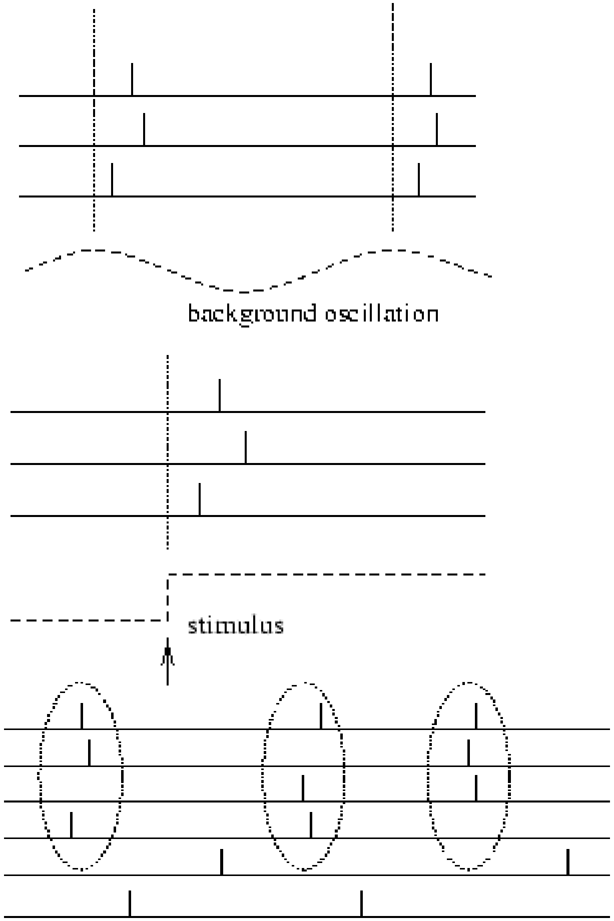
Latence – doba do spiku po stimulaci

Koincidence

Variabilita – v čase nahrazuje populační variabilitu

patterns

sparse coding



HISTORICKÉ POZNÁMKY

Historické poznámky

- Budeme se k nim vracet.
- Stejně jako biologické základy – osobní pohled
- Hardware, neuronové sítě a přístup pomocí teorie informace nejsou předmětem semináře

Louis Lapicque

- Lapicque L (1907). "Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarisation". *J. Physiol. Pathol. Gen.* **9**: 620–635
- Brunel N, Van Rossum MC (2007). "Lapicque's 1907 paper: from frogs to integrate-and-fire". *Biol. Cybern.* **97** (5-6): 337–339.

Lapicqueův model – Leaky integrator

$$\frac{dV}{dt} = -\frac{V}{\tau} + \mu, V(0) = v_0$$

V(t) is the membrane potential,

μ is the signal, can be time dependent

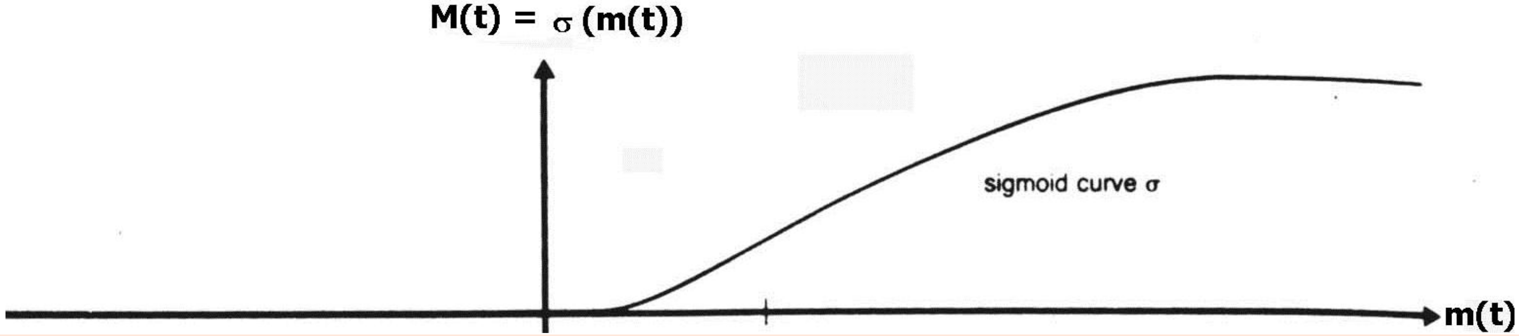
τ is time constant (memory of integration)

v_0 is the initial depolarization

$$V(t) = \mu\tau(1 - \exp(-t/\tau)) + v_0 \exp(-t/\tau)$$

Lapicqueův model – Leaky integrator

- The simplest "realistic" neuron model is a continuous time model.
- Firing rate as a continuously varying measure of the cell's activity
- The state of the neuron is described by a single variable, the membrane potential.
- The firing rate is approximated by a sigmoid, function of membrane potential.   THIS IS AN ALTERNATIVE



Lapicqueův model a spiky

- No intrinsic mechanism to generate spikes. Threshold is imposed, *S>0.*
- Time to the first crossing is identified with ISI (intrerspike interval), then there is reset.

$$\frac{dV}{dt} = -\frac{V}{\tau} + \mu, V(0) = 0,$$

$$V(t) = \mu\tau(1 - \exp(-t/\tau))$$

$$V(t_i) = S, t_i = \ldots$$

Lapicqueův model - časová konstanta

- Perfect integrator

$$\tau \to \infty$$

$$\frac{dV}{dt} = \mu, V(0) = 0,$$

$$V(t) = \mu t$$

$$t_i = S / \mu$$

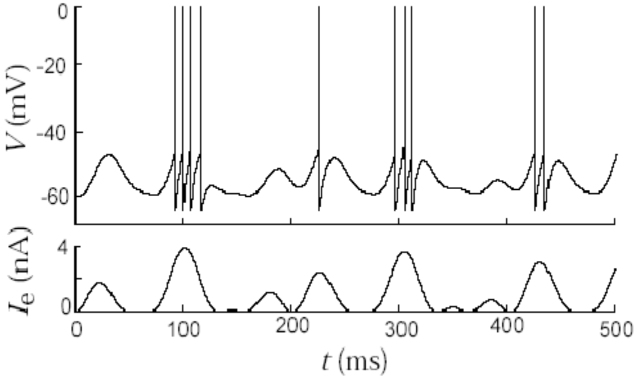
The standard I&F neuron

The standard I&F neuron

Assume that membrane is passive (RC circuit) in subthreshold range

$$C\frac{dV}{dt} + g(V - V_0) = I, \qquad V < \theta$$

When V reaches threshold, spike and reset at $V = V_r$



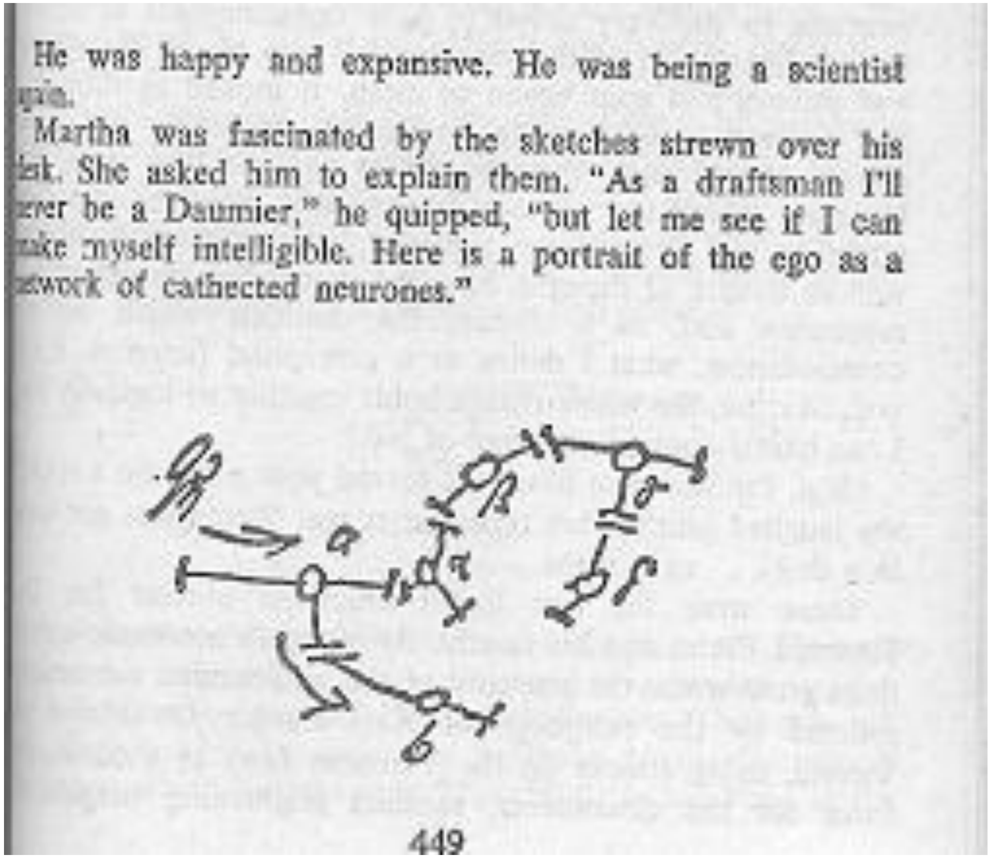
Leaky Integrator s PSP

- Excitatory input ($a > 0$) increases membrane potential
- Inhibitory input ($b < 0$) have the opposite effect.

$$\frac{dV}{dt} = -\frac{V}{\tau} + \mu + \sum_i a\delta(t - t_i) + \sum_j b\delta(t - t_j), V(0) = 0$$

- What are the instants of PSP (t_i and t_j)? For example constants, for periodically changing stimulation.

Irving Stone – The passions of the mind



He was happy and expansive. He was being a scientist gain.

Martha was fascinated by the sketches strewn over his esk. She asked him to explain them. "As a draftsman I'll ever be a Daumier," he quipped, "but let me see if I can ake myself intelligible. Here is a portrait of the ego as a etwork of cathected neurones."

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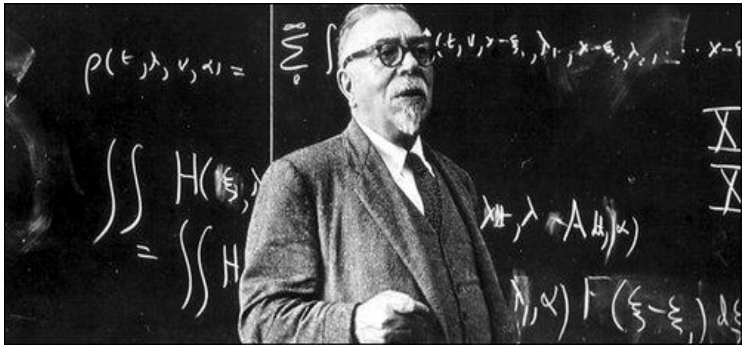
Kybernetika



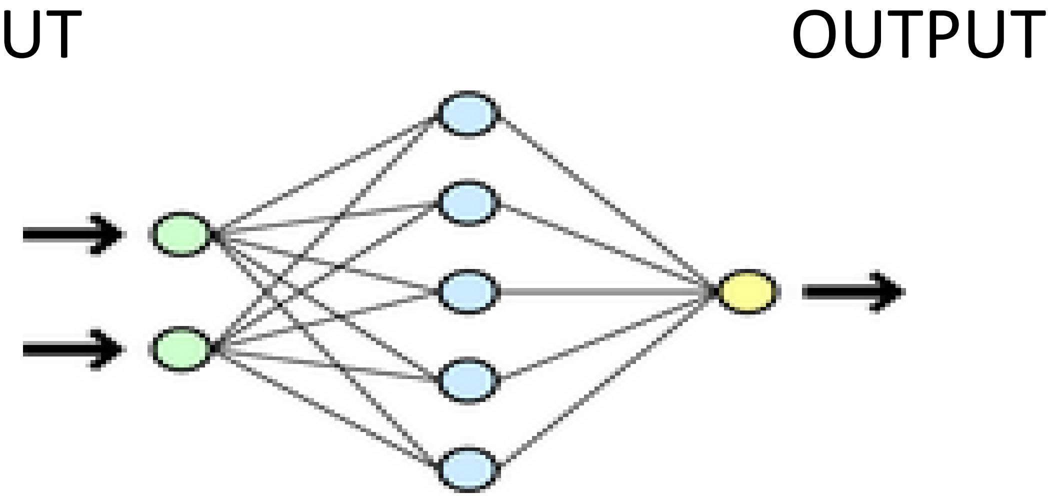
Norbert Wiener

Později BioCybernetics, název časopisu, který po dlouhá léta byl hlavním zdrojem informací v oboru.

Změna nastala v osmdesátých letech.

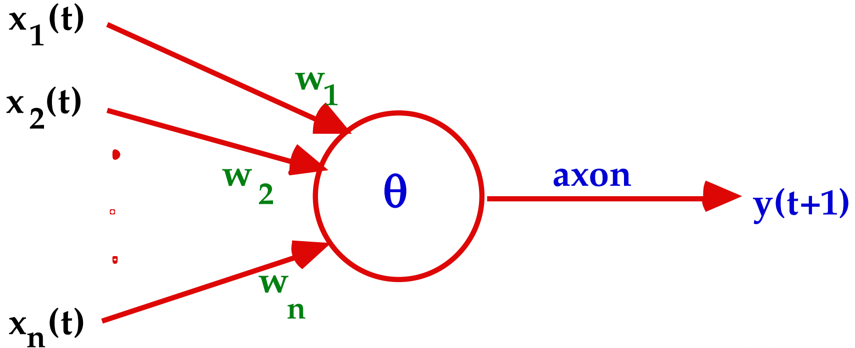
Waren McCulloch a Walter Pitts

Neuronové sítě



Warren McCulloch, Walter Pitts

- **A** McCulloch-Pitts neuron operates on a discrete time-scale, t = 0,1,2,3, ... with time tick equal to one refractory period



- At each time step, an input or output is *on* or *off* — 1 or 0, respectively.
- Each connection or synapse from the output of one neuron to the input of another, has an attached weight.

Excitační a inhibiční synapse

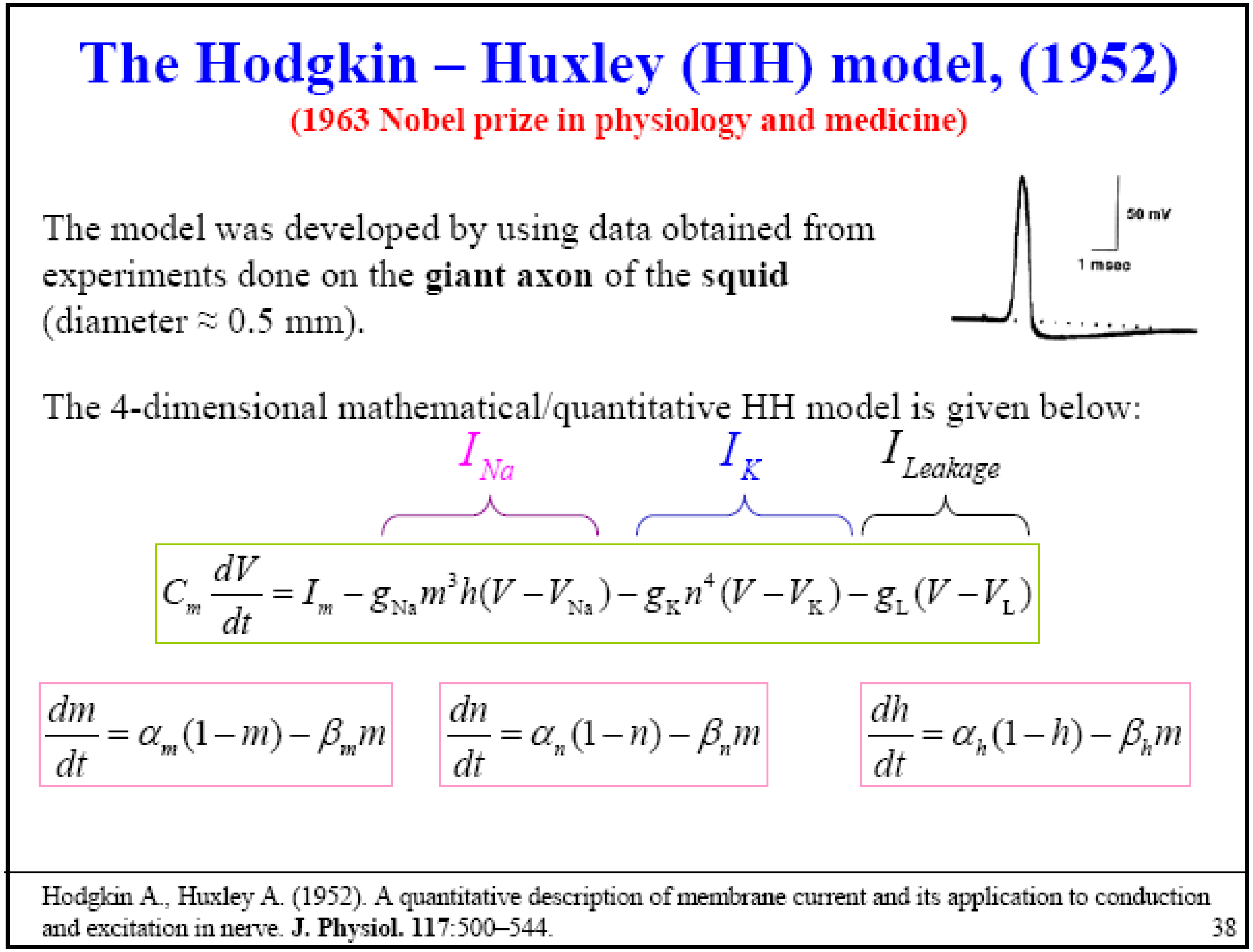
- We call a synapse
- excitatory if $w_i > 0$, and
- inhibitory if $w_i < 0$.
- We associate a threshold θ with a neuron
- A neuron fires (i.e., has value 1 on its output line) at time t+1 if the weighted sum of inputs at t reaches or passes θ:
  - $y(t+1) = 1$ if and only if $\Sigma\, w_i x_i(t) \geq \theta$.

Alan L. Hodgkin a Andrew Huxley

- **Hodgkin–Huxley model** popisuje generování akčního potenciál.

- Je to soustava nelineárních ODE, které aproximují electrické vlastnosti neuronu

- Nobelova cena ve fyziologii a lékařství 1963



The Hodgkin – Huxley (HH) model, (1952)

(1963 Nobel prize in physiology and medicine)

The model was developed by using data obtained from experiments done on the **giant axon** of the **squid** (diameter ≈ 0.5 mm).

The 4-dimensional mathematical/quantitative HH model is given below:

$$\boxed{C_m \frac{dV}{dt} = I_m \overbrace{- g_{\mathrm{Na}} m^3 h(V - V_{\mathrm{Na}})}^{I_{Na}} \overbrace{- g_{\mathrm{K}} n^4 (V - V_{\mathrm{K}})}^{I_K} \overbrace{- g_{\mathrm{L}} (V - V_{\mathrm{L}})}^{I_{Leakage}}}$$

$$\boxed{\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m} \qquad \boxed{\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n m} \qquad \boxed{\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h m}$$

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

G.L. Gerstein and B. Mandelbrot

- RANDOM WALK MODELS FOR THE SPIKE ACTIVITY OF A SINGLE NEURON, Biophys J. 4:41-68, 1964**.**
- Z abstraktu „a random walk towards an absorbing barrier, can describe a wide range of neuronal activity in terms of two parameters. These parameters are readily associated with known physiological mechanisms.“

Neural Coding workshops

- Perkel, D.H. and Bullock, T.H. (1968) Neural coding: A report based on an NRP work session. Neurosciences Research Program Bulletin, 6: 219-349.
- http://en.wikipedia.org/wiki/Neural_coding
- http://www.cnsorg.org/index.shtml
- http://www.neuroinf.org/
- http://www.cs.ucy.ac.cy/nc2010/

MATEMATICKÉ ZÁKLADY

Matematické základy

- ODE a PDE
- Markovské náhodné procesy
- Poissonův proces
- Náhodná procházka – difuzní aproximace
- Wienerův proces
- SDE
- FPT
- Statistické postupy, teorie odhadu

ODE

- Jedna nezávisle proměnná – čas.
- Jedna proto, že uvažujeme bodový neuron
- Neuron z více kompartmentů – soustava ODE.
- Nelinearita se dostaví s existencí prahu a „resetem“ počátečních podmínek po jeho dosažení.

$$\frac{dV}{dt} = -\frac{V}{\tau} + \mu, V(0) = 0,$$

$$S(t) = A + B\sin(\omega t)$$

$$V(t) = S \Rightarrow V(t^{+}) = 0$$

Cable equation - PDE

- Dvě nezávisle proměnné – čas a axon.
- Různé okrajové podmínky

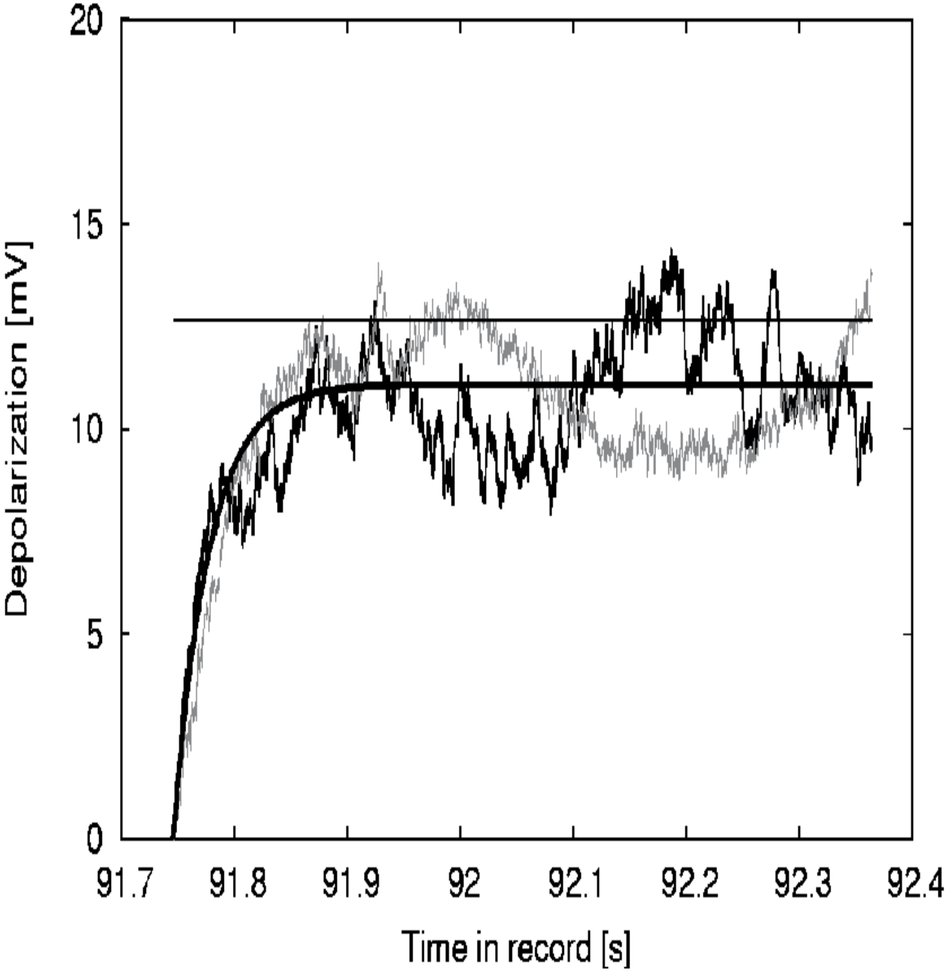
$$\lambda \frac{\partial^2 V}{\partial x^2} = \frac{\partial V}{\partial t} + V$$

Náhodný proces

- Náhodná funkce, v čase nabývá náhodné hodnoty
- Indexovaný systém náhodných veličin
- Index je v našem případě čas, většinou spojitý
- Markovský – budoucnost závisí pouze od současnosti, nikoliv od minulosti
- (pro popis membránového potenciálu)

$$P(X_{n+1} = x \mid X_1 = x_1, \dots, X_n = x_n) = P(X_{n+1} = x \mid X_n = x_n)$$

Stochastické versus deterministické



First-passage-time problem

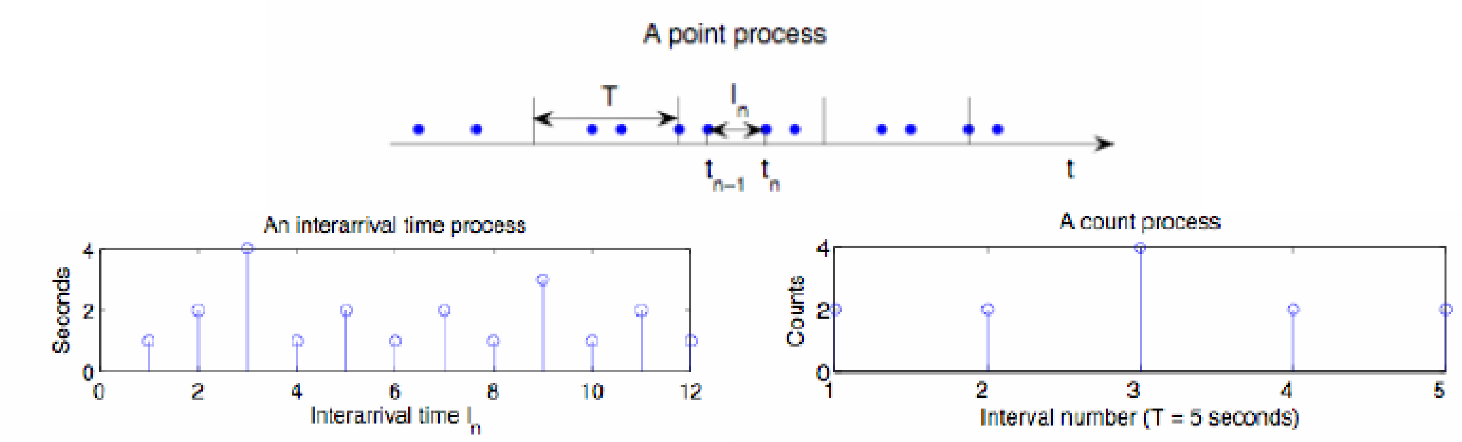
$$T = \inf\{t > 0, x(t) \geq S\}$$

with the interspike intervals

Stochastický bodový proces jako model řady událostí

- Poisson process, Renewal process, Intensity approach and estimation

- *Interarrivals*
- *Counts/Rates*



Dva přístupy k bodovým procesům

- 1) Sequence of intervals $\{T_i\}$
- 2) Counting process $N(t)$, number of spikes in time interval $<0,t)$.

Theoretically equivalent, but empirically not.

$$N(t) < k \Leftrightarrow \sum_{i=1}^{k} T_i > t$$

Renewal process, $\{T_i\}$ are i.i.d.

Poissonův proces

Pravděpodobnost události v krátkém časovém intervalu je úměrná délce tohoto intervalu a nezávisí na minulosti.

$N(0) = 0$

Model výskytu vzácných událostí bez ohledu na jejich kvalitu

$$\Pr(N_\Delta = 1) = \lambda\Delta$$
$$\Pr(N_\Delta = 0) = 1 - \lambda\Delta$$
$$\lambda > 0$$

Poissonův proces - vlastnosti

- Independent increments (the numbers of occurrences counted in disjoint intervals are independent from each other)
- Stationary increments (the probability distribution of the number of occurrences counted in any time interval only depends on the length of the interval)
- Consequences of the definition include:
- The probability distribution of $N(t)$ is a Poisson distribution.
- The probability distribution of the waiting time until the next occurrence is an exponential distribution.

Poissonův proces - vlastnosti

- Pure birth process – the birth intensity λ

In an infinitesimal time interval dt there may occur only one event. This happens with the probability

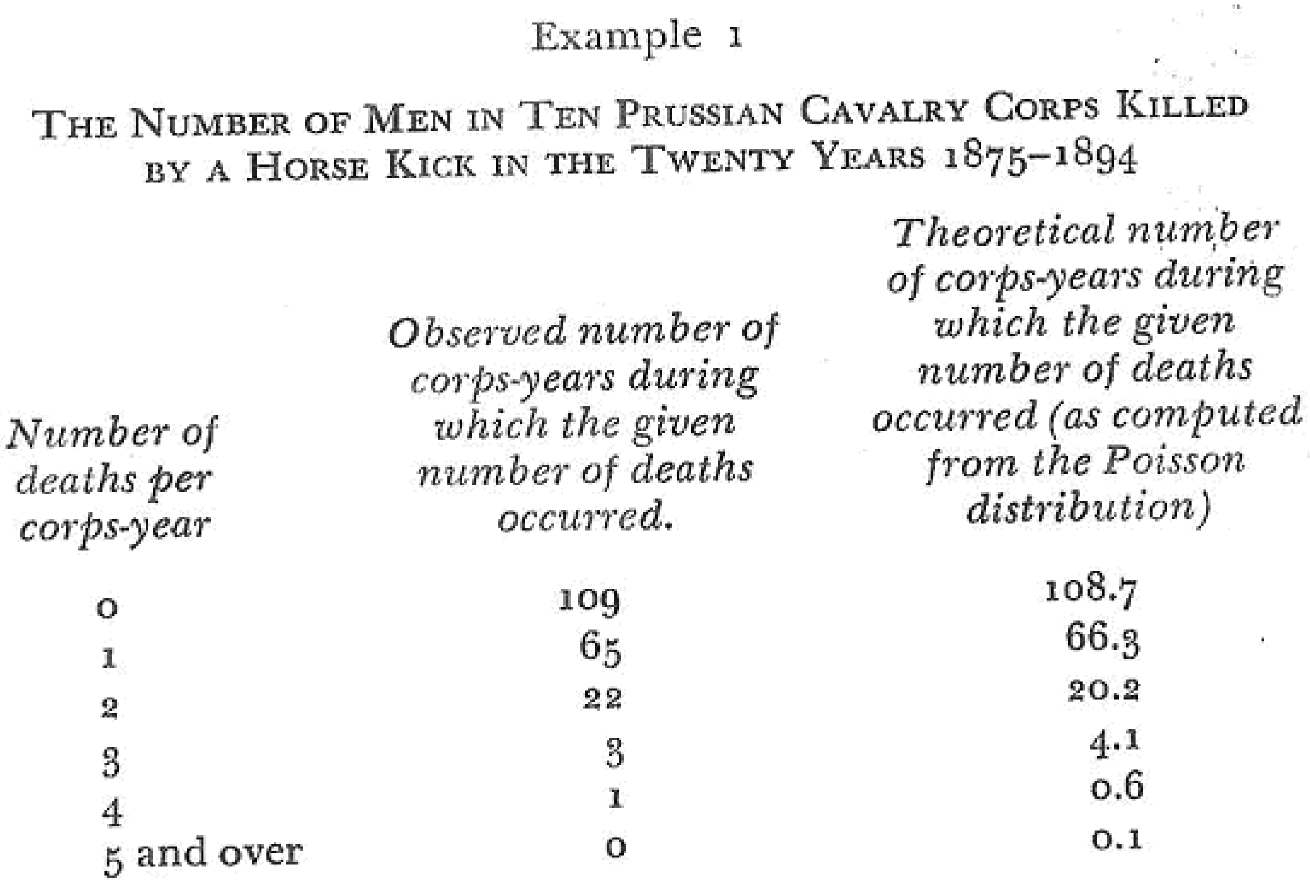
λdt independent of events outside the interval.

$$g(t) = \lambda \exp(-\lambda t)$$

$$E(T) = 1/\lambda$$

$$Var(T) = 1/\lambda^2$$

Poissonův proces - aplikace



Example 1

THE NUMBER OF MEN IN TEN PRUSSIAN CAVALRY CORPS KILLED BY A HORSE KICK IN THE TWENTY YEARS 1875–1894

Number of deaths per corps-year	*Observed number of corps-years during which the given number of deaths occurred.*	*Theoretical number of corps-years during which the given number of deaths occurred (as computed from the Poisson distribution)*
0	109	108.7
1	65	66.3
2	22	20.2
3	3	4.1
4	1	0.6
5 and over	0	0.1

Náhodná procházka

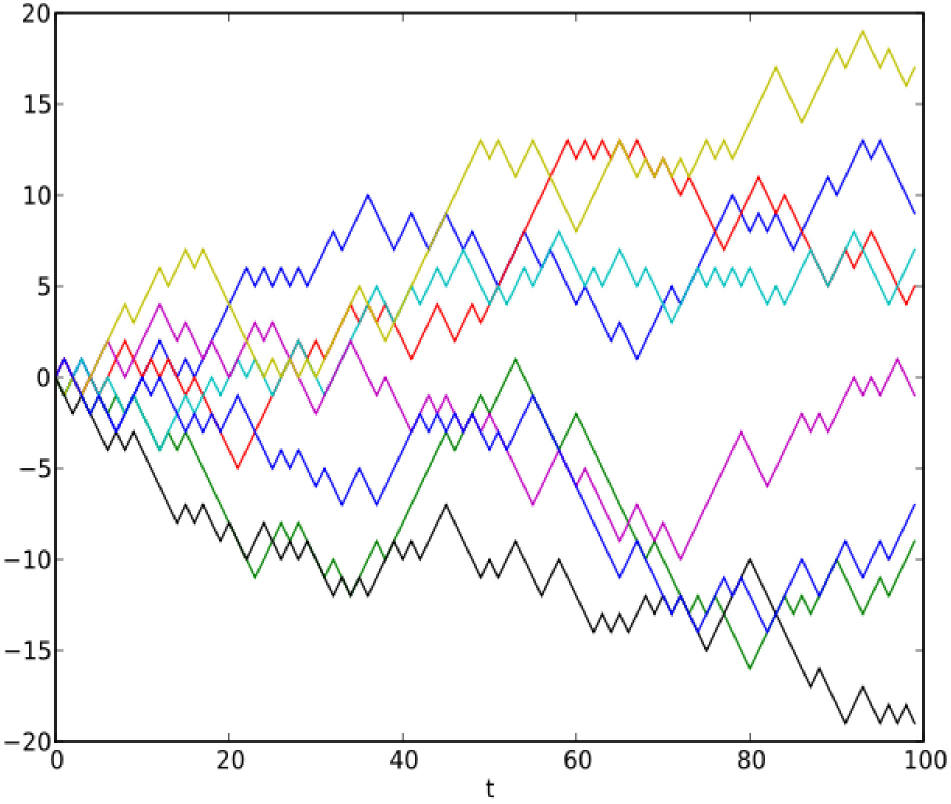
$$X_{n+1} = X_n + Z_n, X_0 =$$

$$X_{n+1} = \sum_{i=1}^{n+1} Z_i$$

$$\Pr(Z_n = 1) = p$$

$$\Pr(Z_n = -1) = 1 - p$$

„vše“ lze spočítat



Wienerův proces, Brownův pohyb

Louis Bachelier (1900) in his PhD thesis "The theory of speculation", supervised by Poincare presented a stochastic analysis of the stock and option markets. Albert Einstein (1905) and Marian Smoluchowski (1906) independently brought the solution of the problem.

Fokker-Planck equation

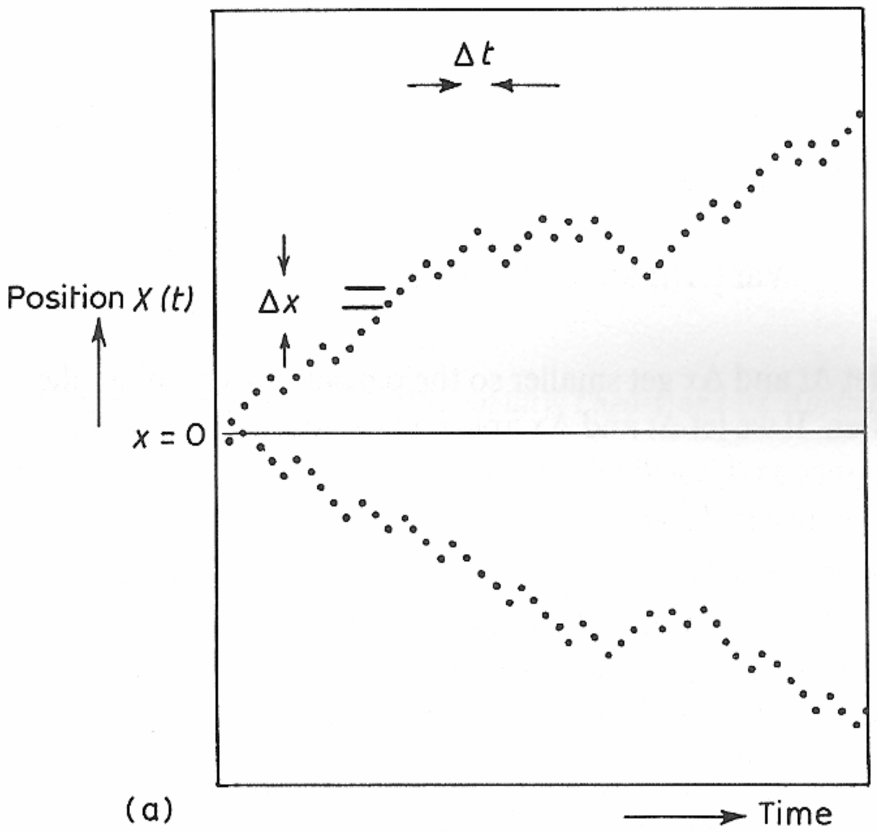
Langevin equation (speed of the Brownian motion),

Compare with Newton law, F(t) - friction

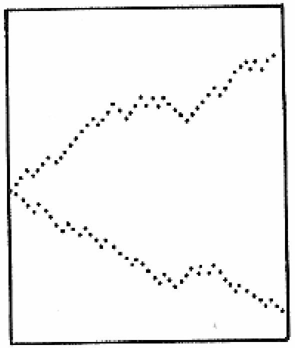
$$m\frac{\mathrm{d}v(t)}{\mathrm{d}t} = F(t)$$

$$\frac{\mathrm{d}v(t)}{\mathrm{d}t} = -\frac{\gamma}{m}v(t) + \frac{1}{m}\xi(t)$$

Difuzní aproximace náhodné procházky



(a)



(c)

(f)

Difuzní aproximace náhodné procházky

$$X(t;\Delta t,\Delta x)=\sum_{i=1}^{t/\Delta t} Z_i$$

$$\Pr(Z_i=\pm\Delta x)=1/2$$

$$E(Z_i)=0, Var(Z_i)=\Delta x^2$$

$$E(X(t;\Delta t,\Delta x)=0$$

$$Var(X(t;\Delta t,\Delta x)=\frac{t\Delta x^2}{\Delta t}$$

$$\Delta t\to 0, \Delta x\to 0, \Delta x=\sqrt{\Delta t}$$

$$X(t;\Delta t,\Delta x)\to W(t)$$

$$E(W(t))=0$$

$$Var(W(t)=t$$

W(t) je normální, „spojitý“ a má nezávislé přírůstky

Stochastické difuzní procesy

- Všechny podobné Wienerovu procesu
- drift a infinitezimální rozptyl
- časová homogenita
- dopředné a zpětné rovnice
- stacionární rozdělení

$$\Delta X(t) = X(t+\Delta t) - X(t)$$

$$\alpha(x,t) = \lim \frac{E(\Delta X(t) | X(t) = x)}{\Delta t}$$

$$\beta(x,t) = \lim \frac{Var(\Delta X(t) | X(t) = x)}{\Delta t}$$

$$p(y,t | x,s)$$

$$\frac{\partial p}{\partial t} = -\frac{\partial(\alpha p)}{\partial y} + \frac{1}{2}\frac{\partial^2(\beta p)}{\partial y^2}$$

Wienerův proces s driftem

- dualita zápisu
- Bílý šum, derivace Wienerova procesu, která neexistuje
- Rozdíl mezi šumem a signálem

$$X(t) = x_0 + \mu t + \sigma W(t)$$

$$dX(t) = \mu dt + \sigma dW(t)$$

$$X(0) = x_0$$

$$\frac{dX(t)}{dt} = \mu + \sigma \frac{dW(t)}{dt}$$

$$\frac{\partial p}{\partial t} = -\mu \frac{\partial p}{\partial y} + \frac{\sigma^2}{2} \frac{\partial^2 p}{\partial y^2}$$

SDE versus klasický popis

- Rovnice obsahující Wienerův proces – difuzní modely.
- Rovnice obsahující Poissonův proces – nespojité trajektorie
- Klasický popis pomocí hustot pravděpodobnosti přechodu je vhodný k hledání analytických výsledků
- SDE – transparentní a vhodné k simulaci !!!
- Výpočetní technika snižuje hodnotu analytických řešení?

SDE versus klasický popis

- Bez šumu – deterministický popis

$$dX(t) = f(X,t)dt + g(X,t)dW(t)$$

$$g \equiv 0 \rightarrow \frac{dx}{dt} = f(x,t)$$

$$X(t+\Delta) = X(t) + f(X(t),t)\Delta + g(X(t),t)\Delta W$$

Statistické postupy pro náhodné procesy

$$dX = \left(-\frac{X}{\tau} + \mu\right)dt + \sigma dW$$

- Například Ornstein-Uhlenbeckův process
- Jak odhadnout parametry v této SDE ?
- Rozdíl mezi lokálními vlastnostmi (šum) a globálními vlastnostmi (drift)
- jedna trajektorie versus opakovaní
- spojité versus diskrétní vzorkování

Doba prvního dosažení prahu

- pro náhodnou procházku, doba do ruinování hráče
- rovnice obnovy
- řada aplikací v jiných oborech
- masivní redukce informace o procesu

Fisherova informace

- It is not information
- Likelihood function (function of the original parameter with observation as a new parameter)

$$f(x;a)$$

- Unbiased estimate

$$E\{\hat{a}(X)-a\}=\int\{\hat{a}(x)-a\}f(x;a)dx=0$$

Cramer-Rao hranice

$$\frac{\partial}{\partial a}\int \{\hat{a}(x)-a\} f(x;a)dx = \int \{\hat{a}(x)-a\}\frac{\partial f}{\partial a}dx - \int f dx = 0$$

$$\int \{\hat{a}-a\}^2 f dx \int f (\frac{\partial \ln f}{\partial a})^2 dx \geq 1$$

$$\int \{\hat{a}-a\}^2 f dx = Var(\hat{a}) \geq \frac{1}{\int f (\frac{\partial \ln f}{\partial a})^2 dx}$$

Cramer-Rao hranice - příklad

$$Var(\hat{a}) \geq \frac{1}{\int f(\frac{\partial \ln f}{\partial a})^2 dx}$$

$$P(X=1) = p, P(X=0) = 1-p$$

$$J(p) \geq \int f(\frac{\partial \ln f}{\partial p})^2 dx =$$

$$= p(\frac{\ln(p)}{dp})^2 + (1-p)(\frac{\ln(1-p)}{dp})^2 =$$

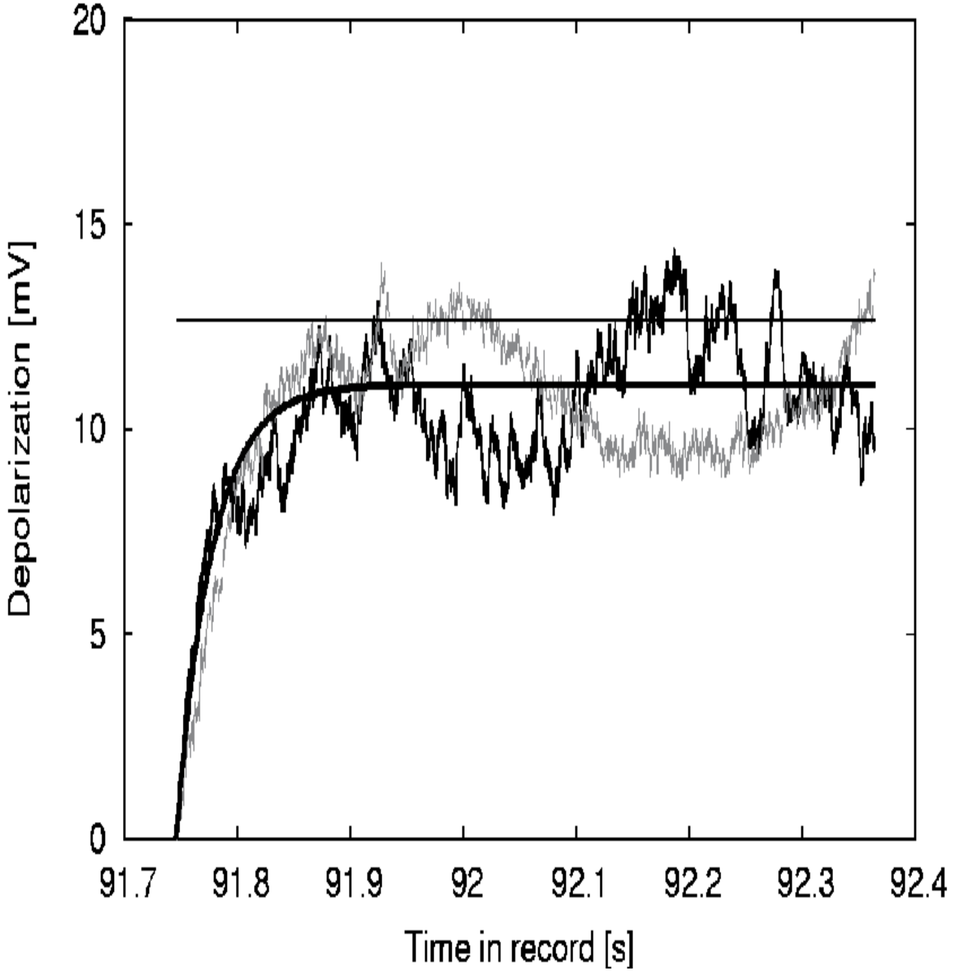
$$\frac{1}{p} + \frac{1}{1-p} = \frac{1}{p(1-p)}$$

STOCHASTICKÉ MODELY NEURONU

Předběžné poznámky

- Jednoduché modely jsou pouze obecně používané náhodné procesy (např. Poissonův proces). Vhodné ke statistickému porovnání
- Rozdíl mezi specifickým (biofyzikálním) a nespecifickým (statistickým) modelováním.
- „Přidání“ šumu k deterministickým modelům – nejasná úloha parametrů

Stochastický versus deterministický



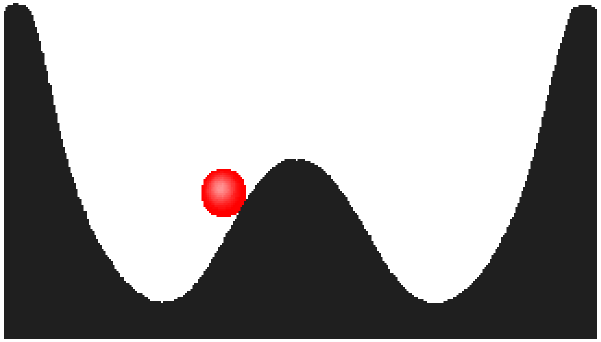
First-passage-time

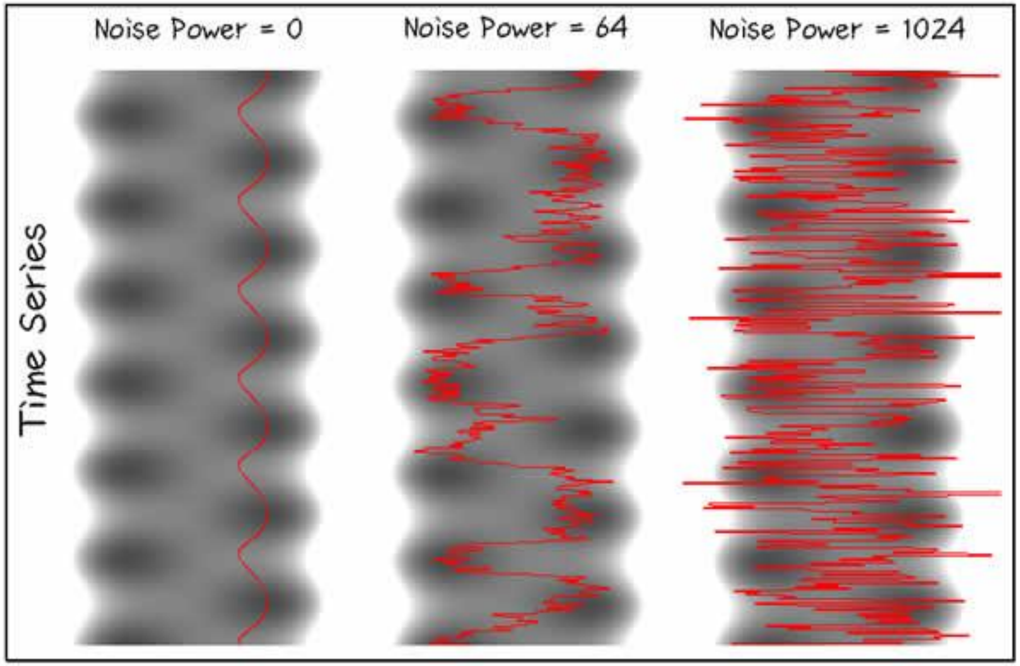
$$T = \inf\{t > 0, x(t) \geq S\}$$

is a random variable comparable with the interspike intervals

Stochastická rezonance

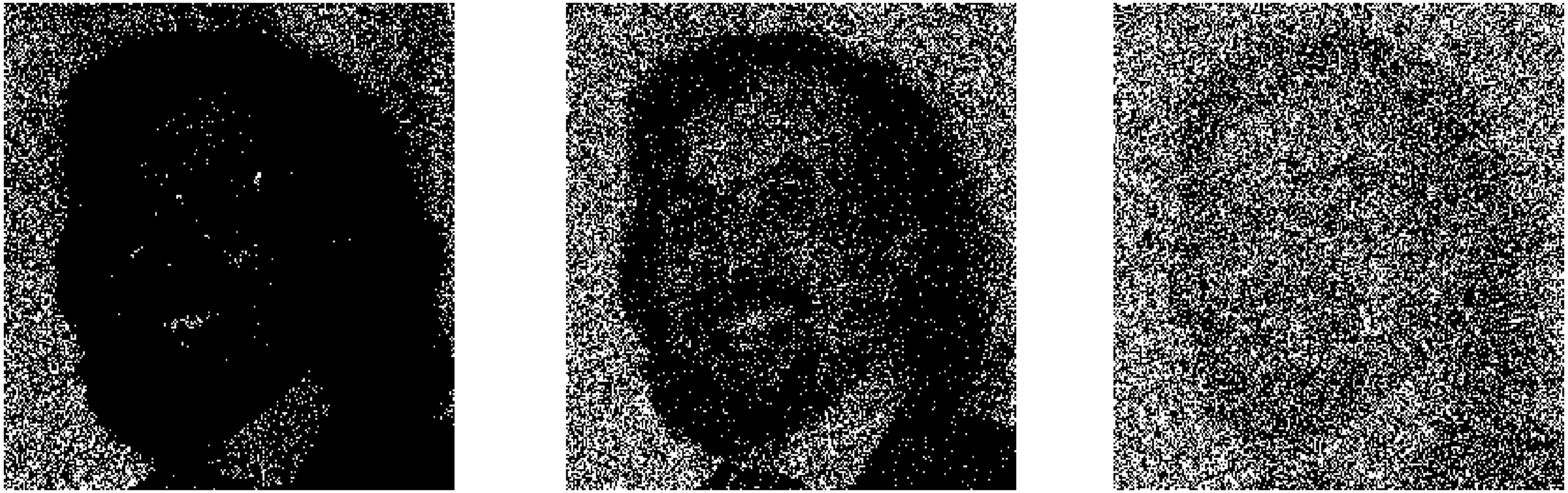
- Ball in double-potential well





- Noise !
- Weak – no effect
- Strong – no effect
- Optimum level

Šum přidaný k černobíle fotografii a filtrovaný prahem



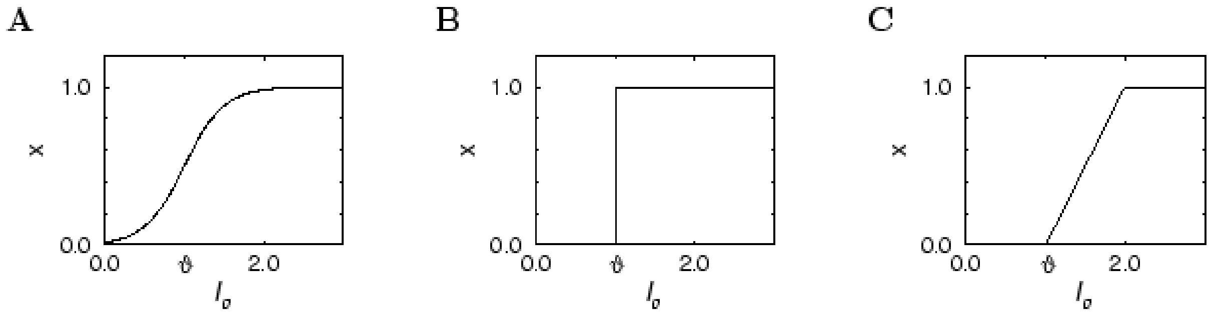
Slabý šum, většina signálu je pod prahem

Optimální šum

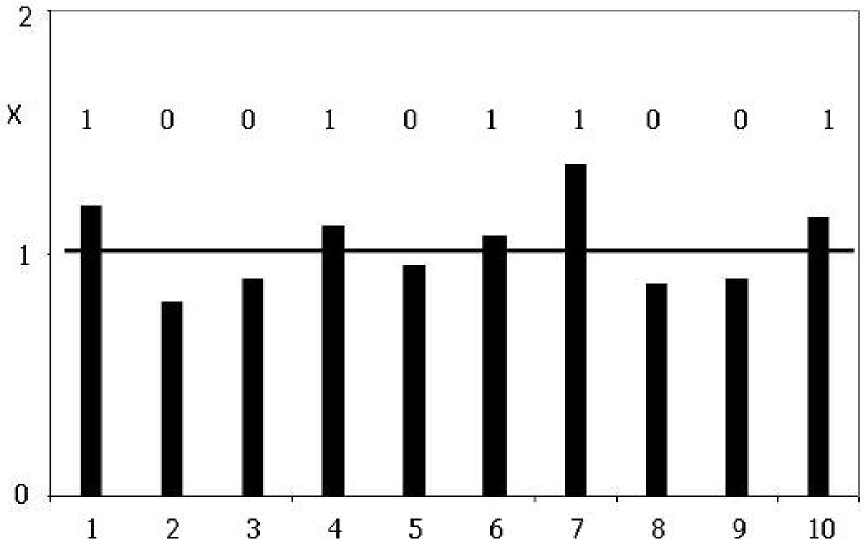
Silný šum, černá a bílá se střídá náhodně

Přenosová funkce

- A – sigmoida
- B – step
- C – lineární
- práh, coding range, saturation,.....



Jednoduchý prahový model



$$X_i^a = 1(s + \varepsilon_i > a), \qquad i = 1, \dots, n.$$

s - signal (constant),

ε - noise with cdf F,

a - threshold

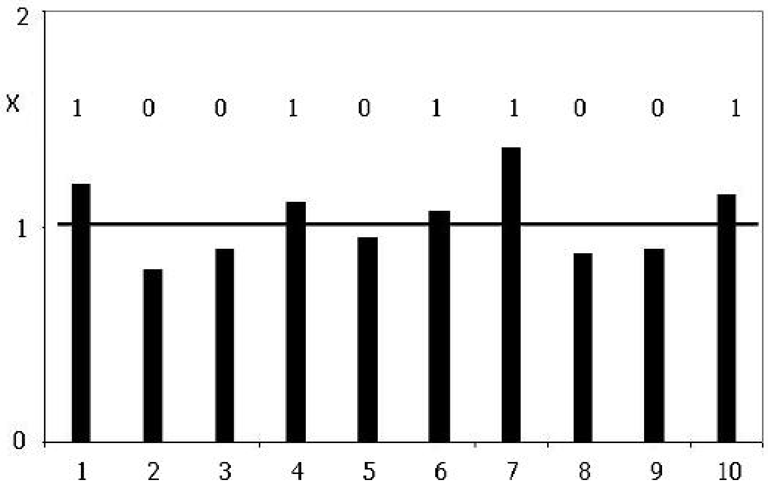
Bernoulli with probability p_s

$$p_s = P(X_i^a = 1) = P_s(a, \infty) = 1 - F(a - s).$$

$$\hat{s} = a - F^{-1}(1 - \hat{p}).$$

$$\hat{p} = \frac{1}{n} \sum_{i=1}^{n} X_i^a = \frac{\hat{n}}{n}$$

Jednoduchý prahový model



$$\hat{s} = a - F^{-1}(1 - \hat{p}).$$

How well can be *s* estimated from observations of 0 and 1 !

Noise enlarges the coding range

Superpozice bodových procesů

- Each incoming spike results as generated spike

- This model is simple, but neglects too many features of real neurons, for example

1) No inhibition
2) Too high firing frequency
3) No time integration

Selektivní interakce

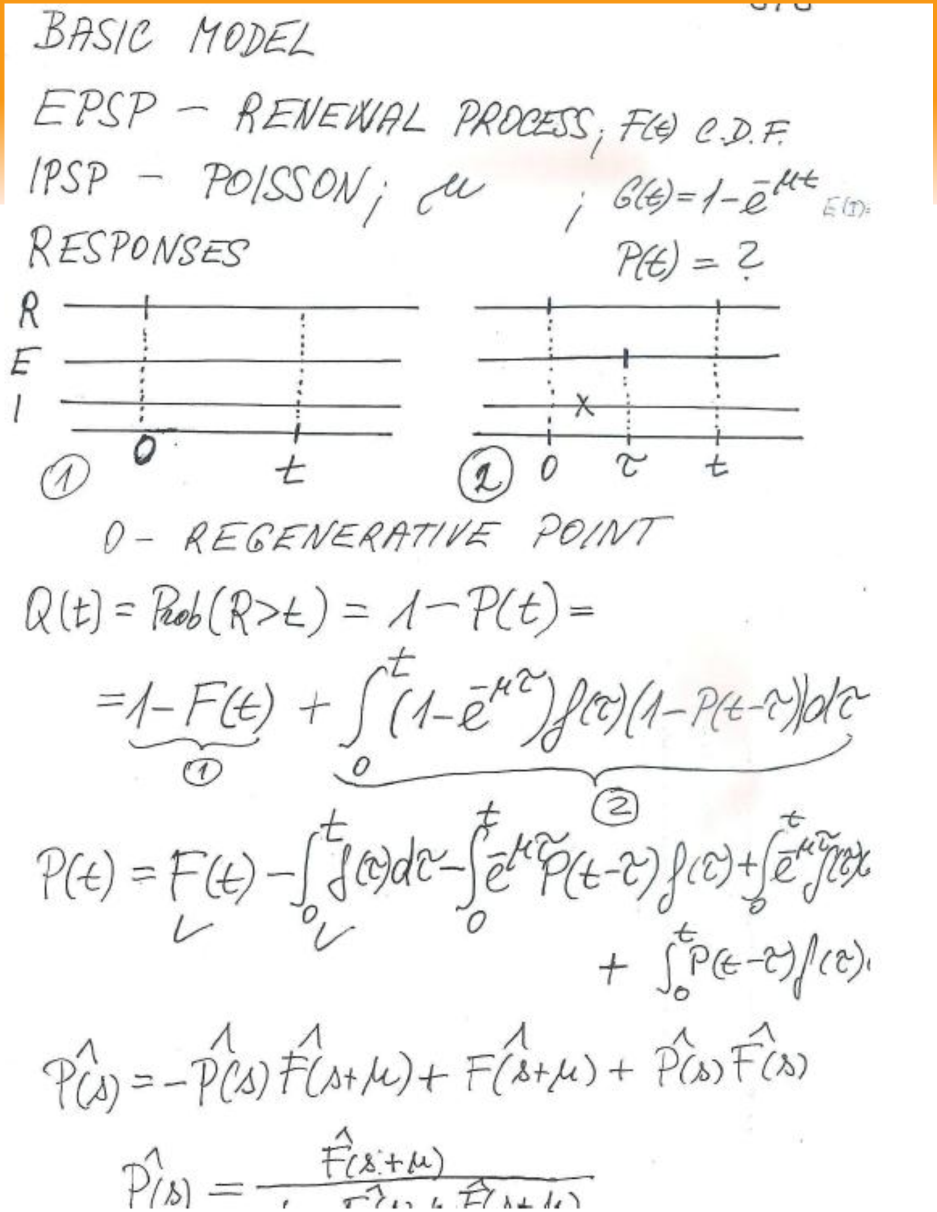
- Input – two independent point processes, one excitatory and one inhibitory
- Whenever one or more inhibitory pulses occur, the first consecutive excitatory pulse is eliminated
- Uneliminated excitatory pulses constitute output discharge
- Integrate-and-fire interpretation

Laplacova (Stieltjes) transformace

$$\varphi(s) = \int_0^\infty e^{-st}\,dF(t)$$

Platí běžná pravidla pro počítání s LT

$$EX^n = (-1)^n \varphi^{(n)}(0)$$



BASIC MODEL

EPSP – RENEWAL PROCESS; $F(t)$ C.D.F.

IPSP – POISSON; μ ; $G(t) = 1 - e^{-\mu t}$ $E(I)=$

RESPONSES $P(t) = ?$

R

E

I

① 0 t

② 0 x τ t

0 – REGENERATIVE POINT

$$Q(t) = \mathrm{Prob}(R > t) = 1 - P(t) =$$

$$= \underbrace{1 - F(t)}_{①} + \underbrace{\int_0^t (1 - e^{-\mu\tau}) f(\tau)(1 - P(t-\tau))\,d\tau}_{②}$$

$$P(t) = \underset{\checkmark}{F(t)} - \underset{\checkmark}{\int_0^t f(\tau)\,d\tau} - \int_0^t e^{-\mu\tau} P(t-\tau) f(\tau) + \int_0^t e^{-\mu\tau} f(\tau)\,d\tau$$

$$+ \int_0^t P(t-\tau) f(\tau)\,d\tau$$

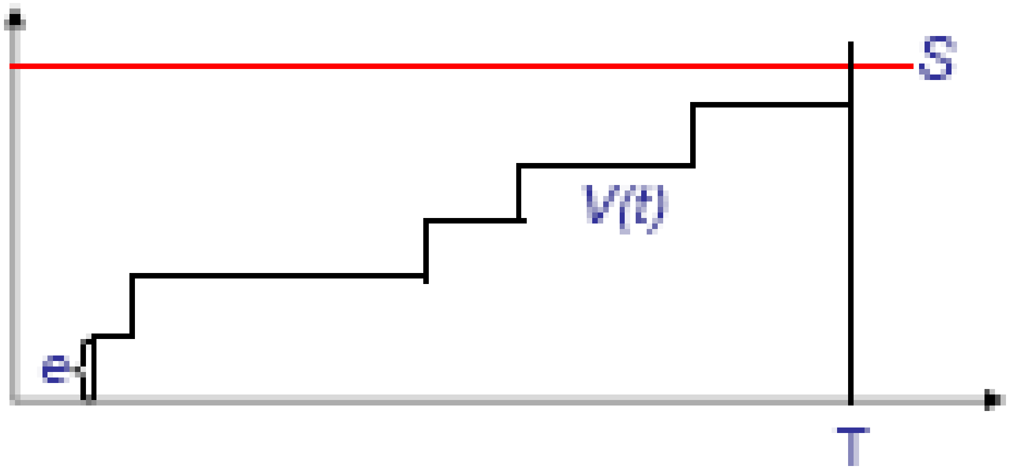
$$\hat{P}(s) = -\hat{P}(s)\hat{F}(s+\mu) + \hat{F}(s+\mu) + \hat{P}(s)\hat{F}(s)$$

$$\hat{P}(s) = \frac{\hat{F}(s+\mu)}{}$$

Poissonův proces s prahem

- Waiting time until the threshold is reached.
- Erlang distribution of ISI.

No inhibition, no decay

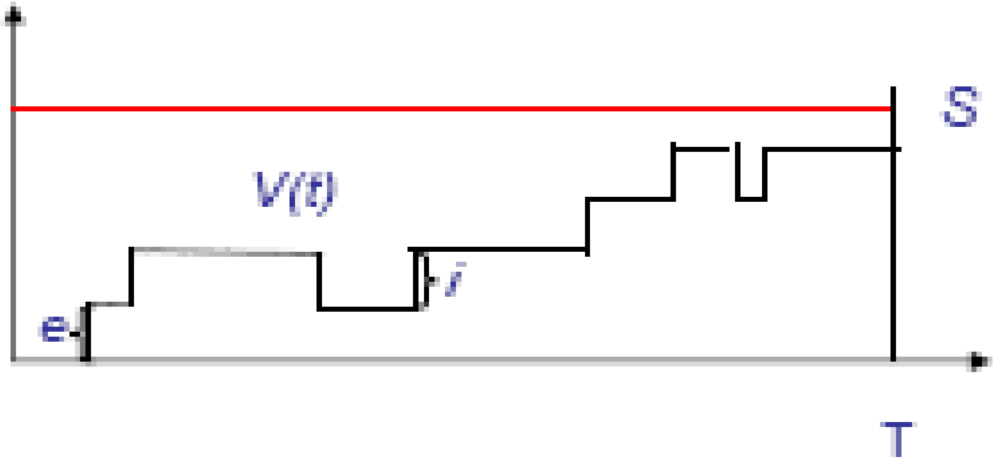


Znáhodněná náhodná procházka

Gerstein and Mandelbrot, 1964

inhibition is included

The problem of interspike interval distribution is solvable analytically



Historické poznámky

- Stein RB (1965) A theoretical analysis of neuronal variability. Biophys J 5:173-195.

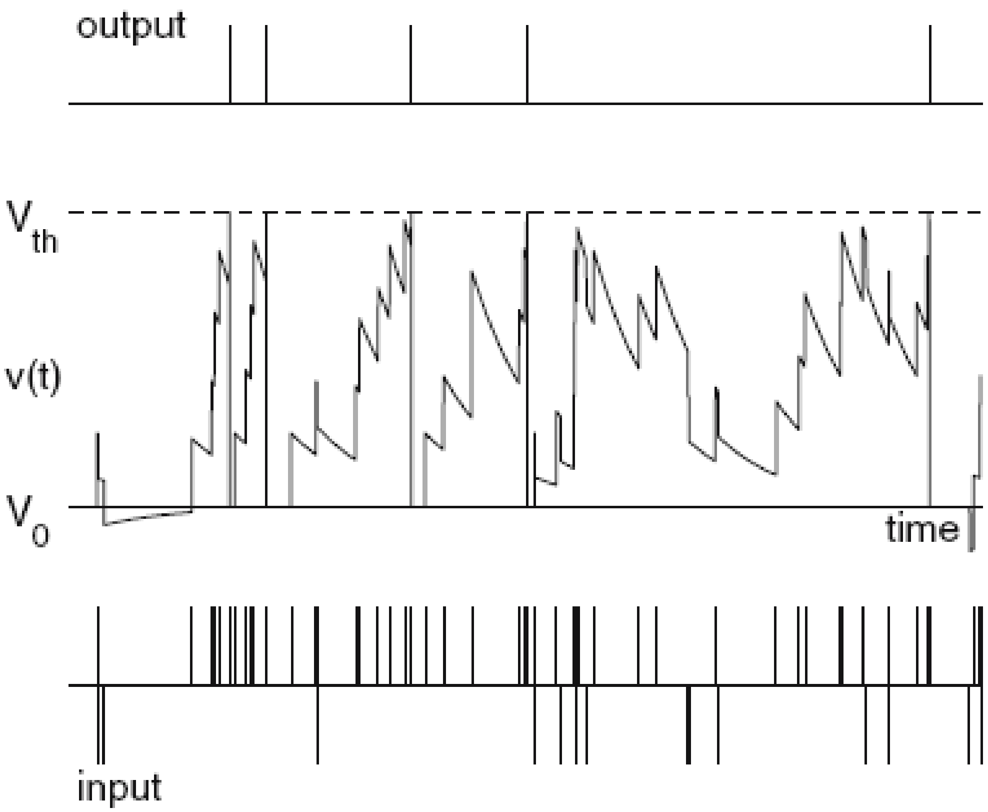
$$dX(t) = -\frac{X(t)}{\tau}dt + adP(t) + idN(t)$$

$a > 0, i < 0$ "amplitudes" of excitatory (inhibitory) postsynapic potentials

$P(t), N(t)$ point processes. Intensities λ and ω

τ membrane time constant

Leaky integrate-and-fire model



Difuzní aproximace

In some neurons postsynaptic potentials contribute little to depolarization at trigger zone (*a* and *i* are very small). There are many synapses, thus λ and ω are large.

$$\lambda a + \omega i \rightarrow \mu \neq 0$$

FREQUENCY CODING

$$\lambda a^2 + \omega i^2 \rightarrow \sigma^2$$

If the input intensities λ and ω are the signal, then in the diffusion model, μ and σ represent the signal.

Noise plays the role of the signal.

σ and μ are not independent

Stochastický Lapicqueův model

- Time to the first crossing is identified with ISI (intrerspike interval), then there is a reset.
- Now T is a random variable and its properties

charecterize the neuron (identical conditions – different interspike intervals)

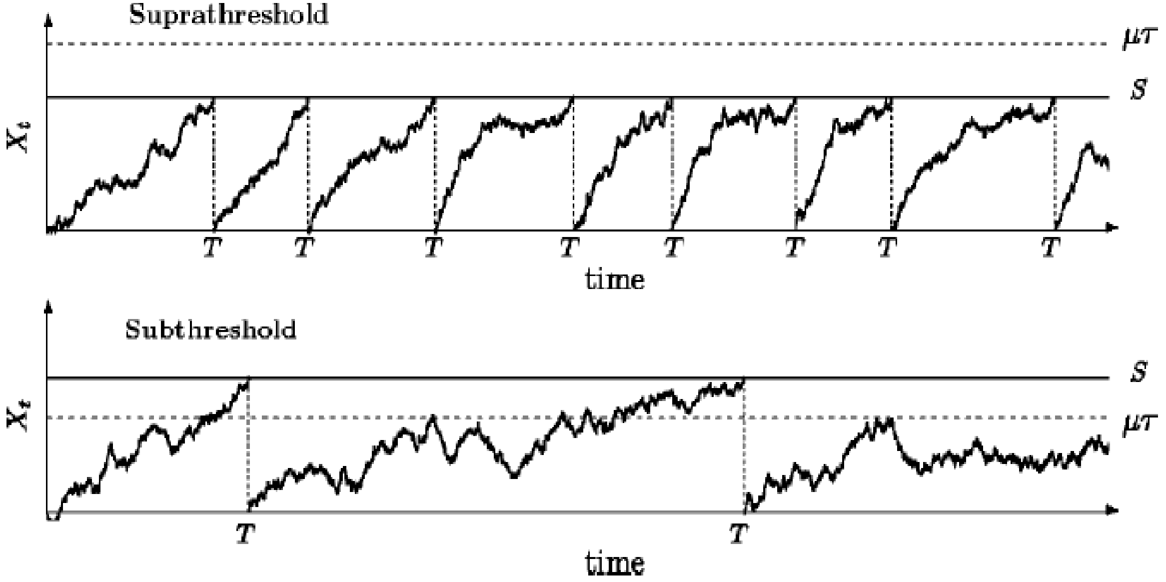
$$\frac{dV}{dt} = -\frac{V}{\tau} + \mu + \sigma\xi(t), V(0) = 0$$

$$T = \inf(t > 0, X(t) \geq S; X(0) < S)$$

Stochastický Lapicqueův model

- Time to the first crossing is identified with ISI (intrerspike interval), then there is a reset.

$$T = \inf(t > 0, X(t) \geq S; X(0) < S)$$



Signal dependent noise

Inspired by papers searching for an optimum or specific noise under stimulation by a given signal

$$\lambda a + \omega i \to \mu \neq 0, \lambda a^2 + \omega i^2 \to \sigma^2$$

In Stein’s model signal is formed by the intensities of the input streams of PSP, λ and ω. Thus μ determines σ and only an optimum signal exists.

Ornstein-Uhlenbeckův neuronový model

Stochastic differential equation describing membrane depolarization τ>0, σ>0, μ are constants.

$$dX(t) = \left(-\frac{X(t)}{\tau} + \mu\right)dt + \sigma dW(t), X(0) = 0$$

ISIs are identified with first-passage of X across boundary S

$$T = \inf(t > 0, X(t) > S; X(0) = 0 < S)$$

Transfer function has no saturation, μ is the signal

Obecný difuzní model

$$dX(t) = a(X,t)dt + b(X,t)dW$$

$$T = \inf(t > 0, X(t) > S; X(0) = 0 < S)$$

- First-passage time of a stochastic process, problem with many applications

Wienerův proces s driftem

- Fitting data to the model

$$dX = \mu dt + \sigma dW$$

$$T = \inf(t > 0, X(t) > S; X(0) = 0 < S)$$

- There are four parameters to be estimated
- Intrinsic – threshold *S*, initial depolarization *x(0)*,
- Input - μ, σ
- Parameter τ of the original model tends to infinity

Inverse Gaussian distribution

- Perfect integrator model, *a>0, b>0*

$$f(t) = \sqrt{\frac{a}{2\pi b t^3}} \exp\left[-\frac{1}{2b} \frac{(t-a)^2}{at} \right], \quad E(T) = a, \quad CV = \sqrt{b}$$

$$a = \frac{S - x(0)}{\mu}, \quad b = \frac{\sigma}{\mu(S - x(0))}$$

- IGD is never exponential

Fit of the data does not prove the model, thus this is more a statistical descriptor than a model.

Reversal potentials

$$dX(t) = -\frac{X(t) - x(0)}{\tau} dt + a(V_E - X)dP(t) + i(X - V_I)dN(t)$$

Reversal potentials restrict the state space.
When *X* gets closer to them, the jumps become smaller.

Diffusion approximation of this model is not unique

Fellerův model – Cox, Ingersoll, Ross

$$dX = \left(-\frac{X - x(0)}{\tau} + \mu\right)dt + \sigma\sqrt{X - V_I}\,dW$$

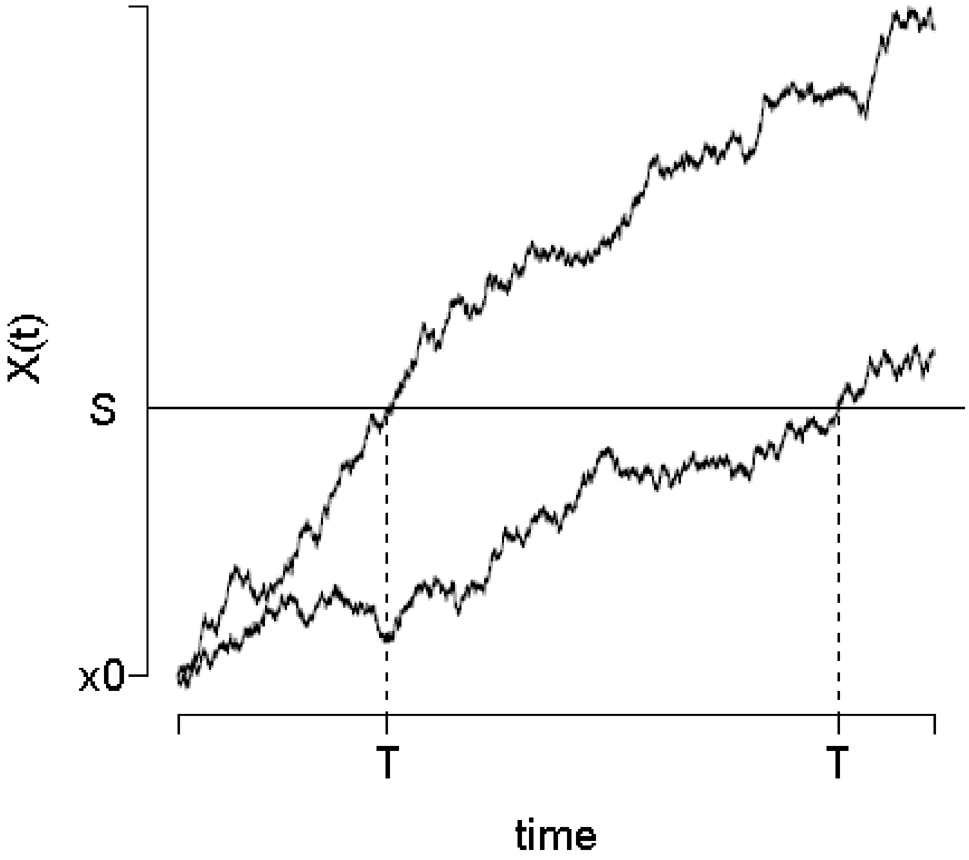
Inhibitory reversal potential restricts the state space from below. Upper bound is not so critical due to existence of the firing threshold

Additional parameter, the inhibitory reversal potential.

Identifikace parametrů

Two types of parameter
intrinsic (neuronal) and
external (signal).

Two types of data
membrane potential or
ISIs.



“Continuous” recording of *X(t)*

1) Transition probability density is Gaussian

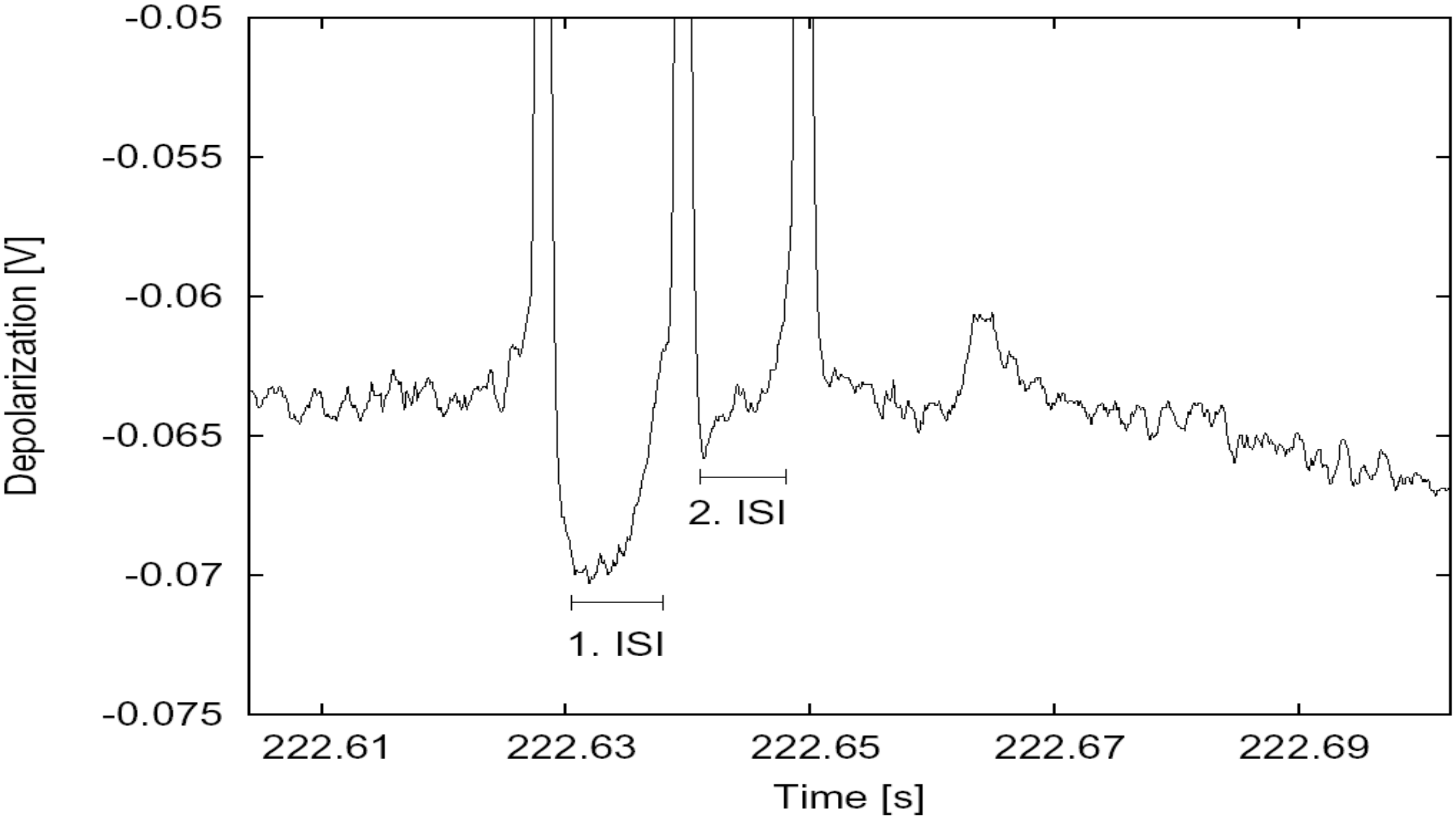
$$f(x, t_1 | y, t_0)$$

Independent increments, the likelihood function can be written

2) Mean value of *X(t)* can be used and regression method applied

$$E(X(t)) = \mu\tau(1 - \exp(-t/\tau)) + x_0 \exp(-t/\tau)$$

Example of experimental data during stimulation



Parametery Ornstein-Uhlenbeckova modelu

$$dX = \left(-\frac{X - x(0)}{\tau} + \mu\right)dt + \sigma dW$$

Interspike intervals are identified with the first crossing of a firing threshold *S*

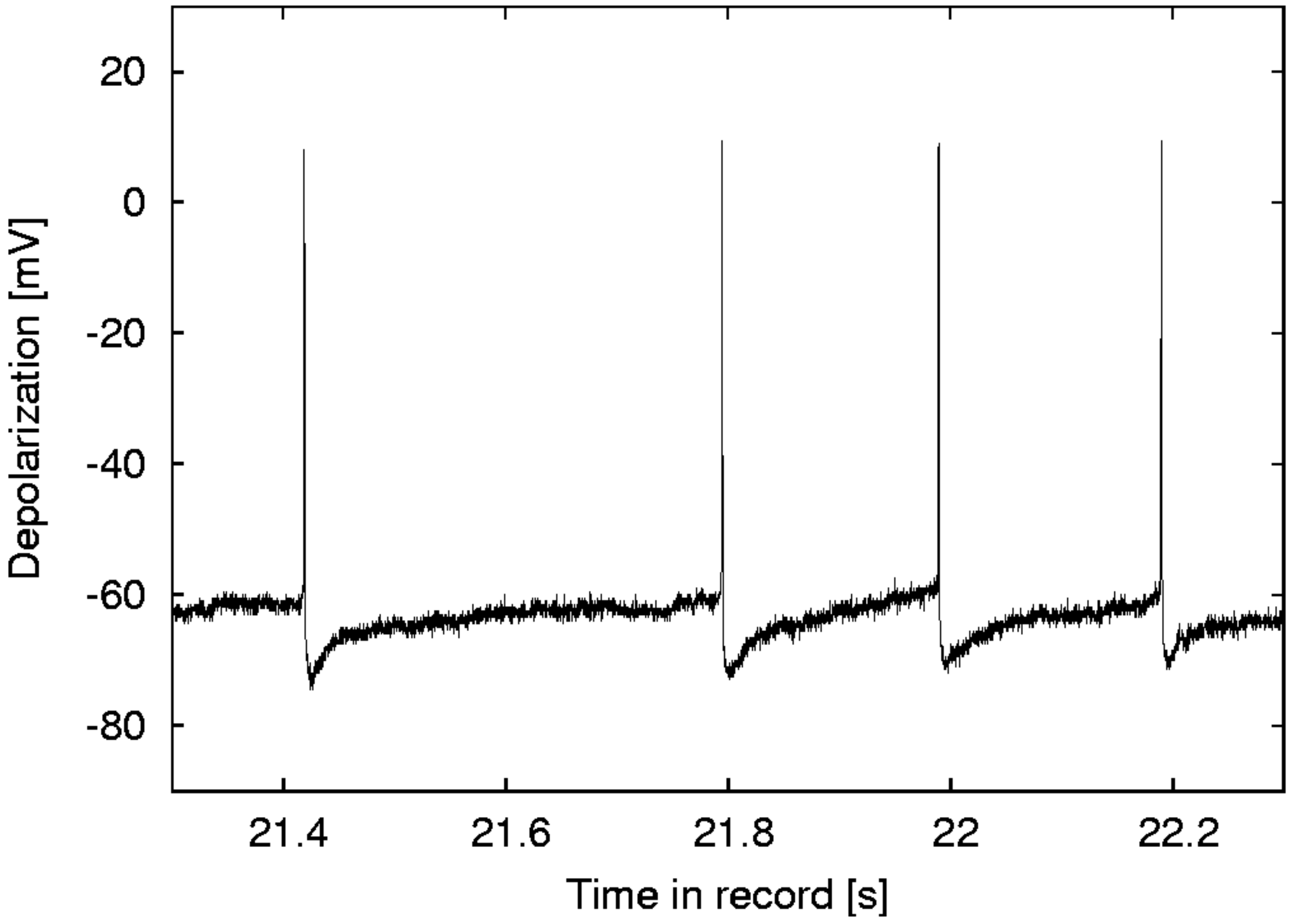
After firing, the potential is reset to a resting level *x(0)*

Membrane depolarization decays in absence of input to the resting level with time constant τ

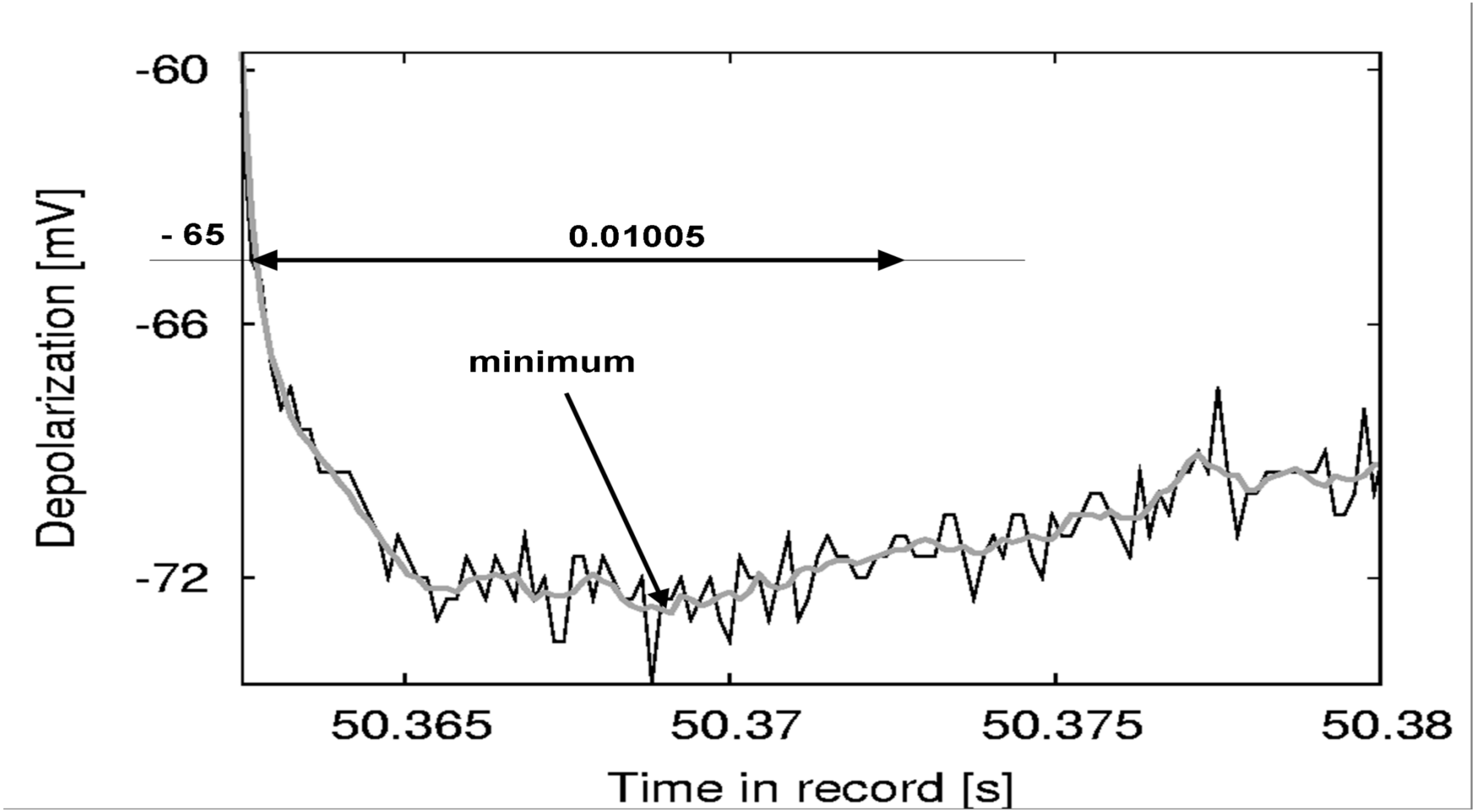
Input parameters μ and σ

First-passage-time problem is a “complicated” task.

Příklad dat

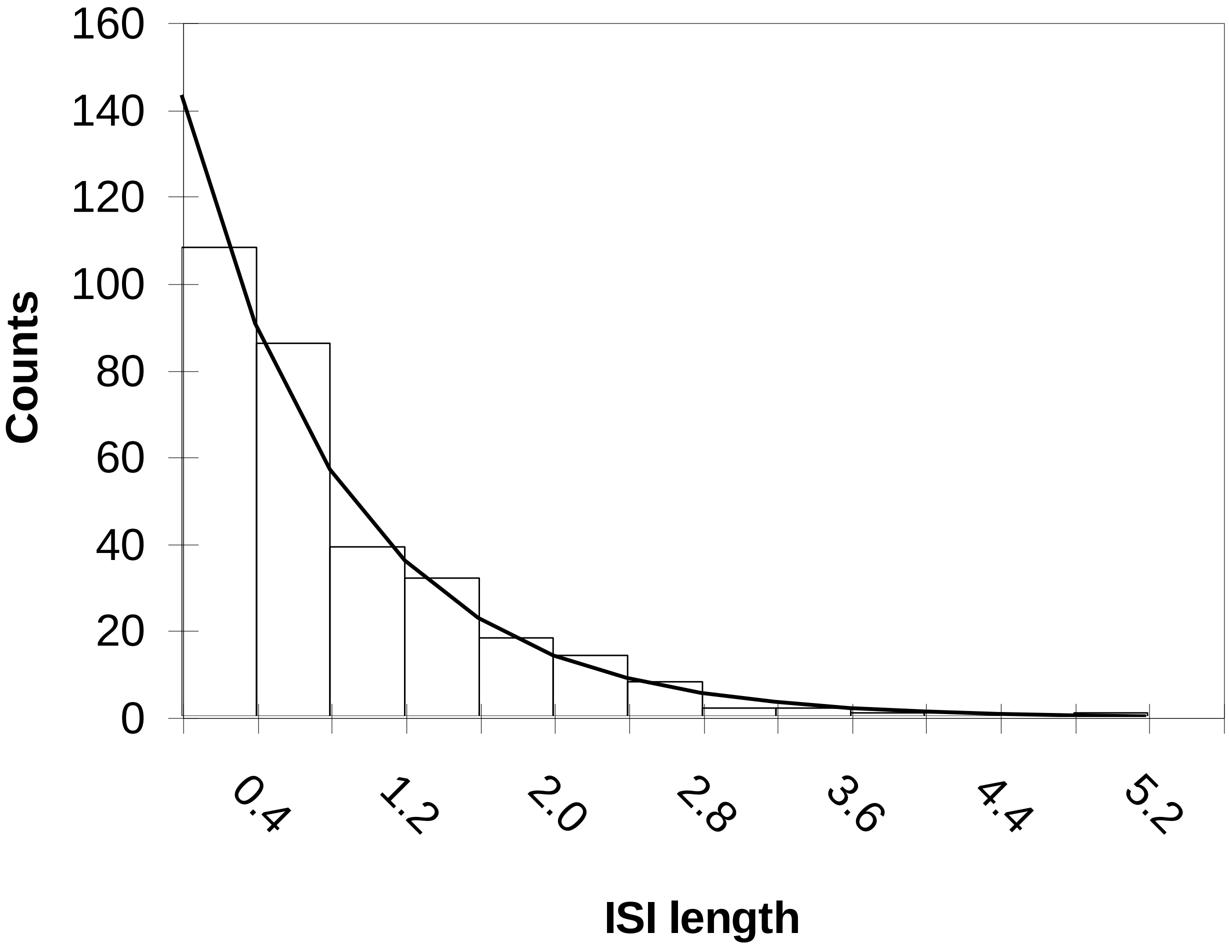

20
0
-20
-40
-60
-80
Depolarization [mV]
21.4
21.6
21.8
22
22.2
Time in record [s]

Odhad počáteční depolarizace

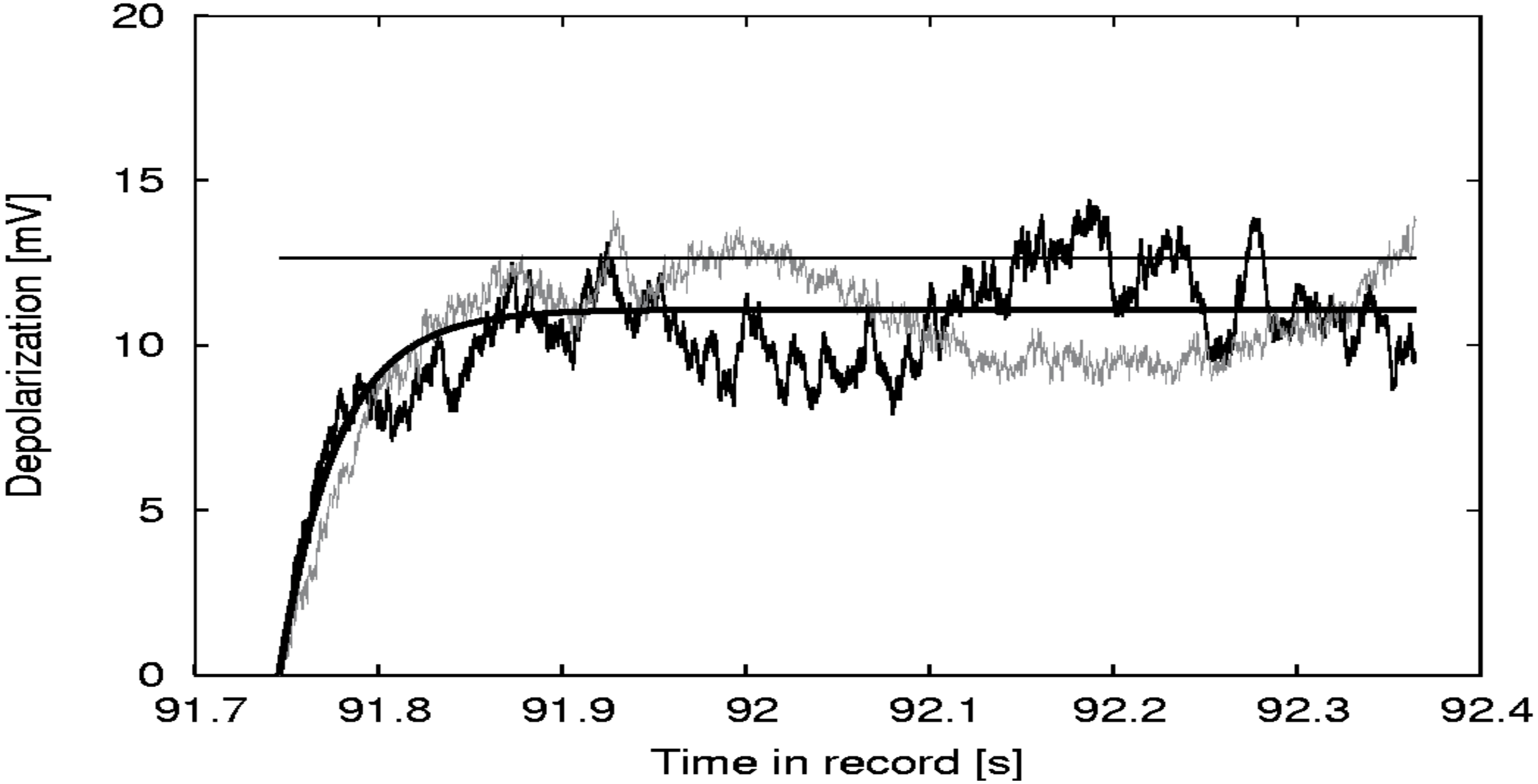


Histogram of ISIs

Corresponding density of exponential distribution normalized on the number of ISIs



gray - data; black - simulated model with parameters estimated by maximum likelihood method; smooth black - mean value (model without noise). The horizontal line represents the estimated threshold



Compartmentové modely

$$dX_d = \left(-\frac{X_d}{\tau} + \mu - \frac{X_d - X_s}{\tau_c}\right)dt + \sigma dW$$

$$dX_s = \left(-\frac{X_s}{\tau} + \frac{X_d - X_s}{\tau_c}\right)dt$$

Threshold is located at soma, and reset is only there.

Properties – correlated ISIs, „filtered behavior“

Olfaktorní neuron

- *R* – unbound
- *A* - odorant
- *C* – complex
- k_1 and k_{-1} are rates
- Stochastic variant – Birth-and-death process on {0, 1,…, N}.

$$\mathrm{A} + \mathrm{R} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{C} \;,$$

$$\lambda = k_1 A = k_1 \exp(s)$$

$$\mu = k_{-1}$$

KÓDOVÁNÍ, OPTIMALITA SIGNÁLU

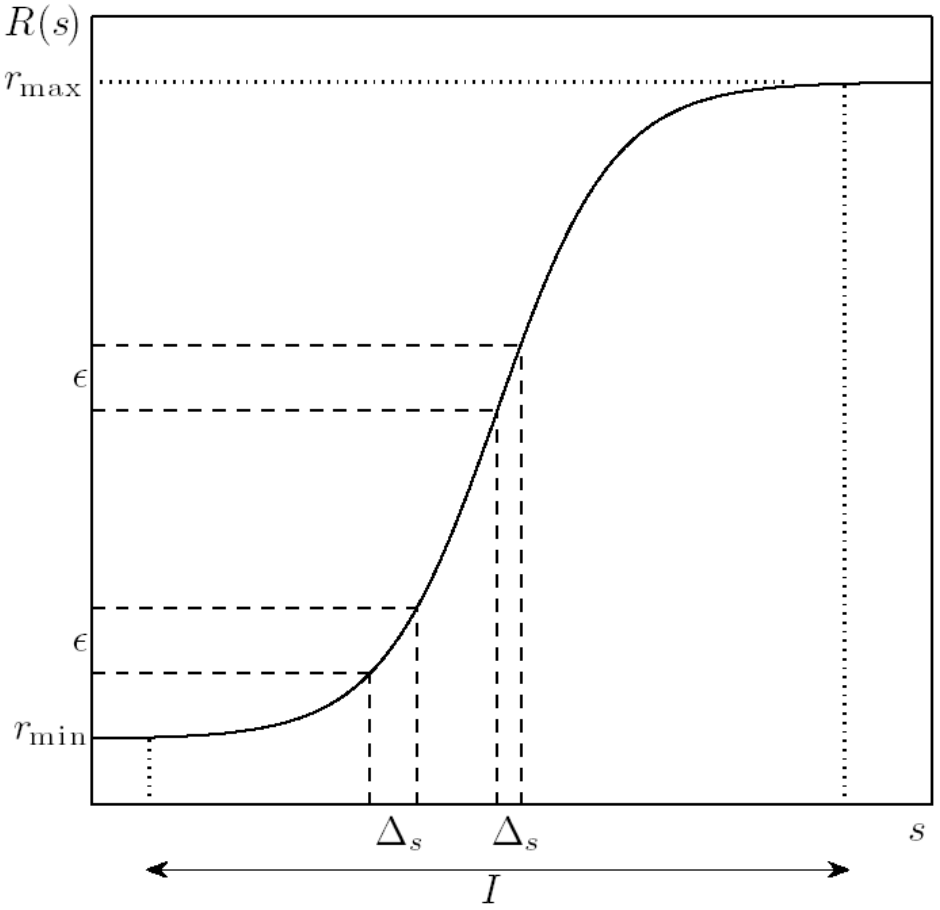
Neuronové kódování

- **The transfer** and the **encoding** of **information in the neuronal system**
- The problem of “parallel processing”
  - Homogenous neuronal populations
- Important differentiation:
  - **Sensory** neurons vs. **higher-order** neurons
  - The **olfactory system**

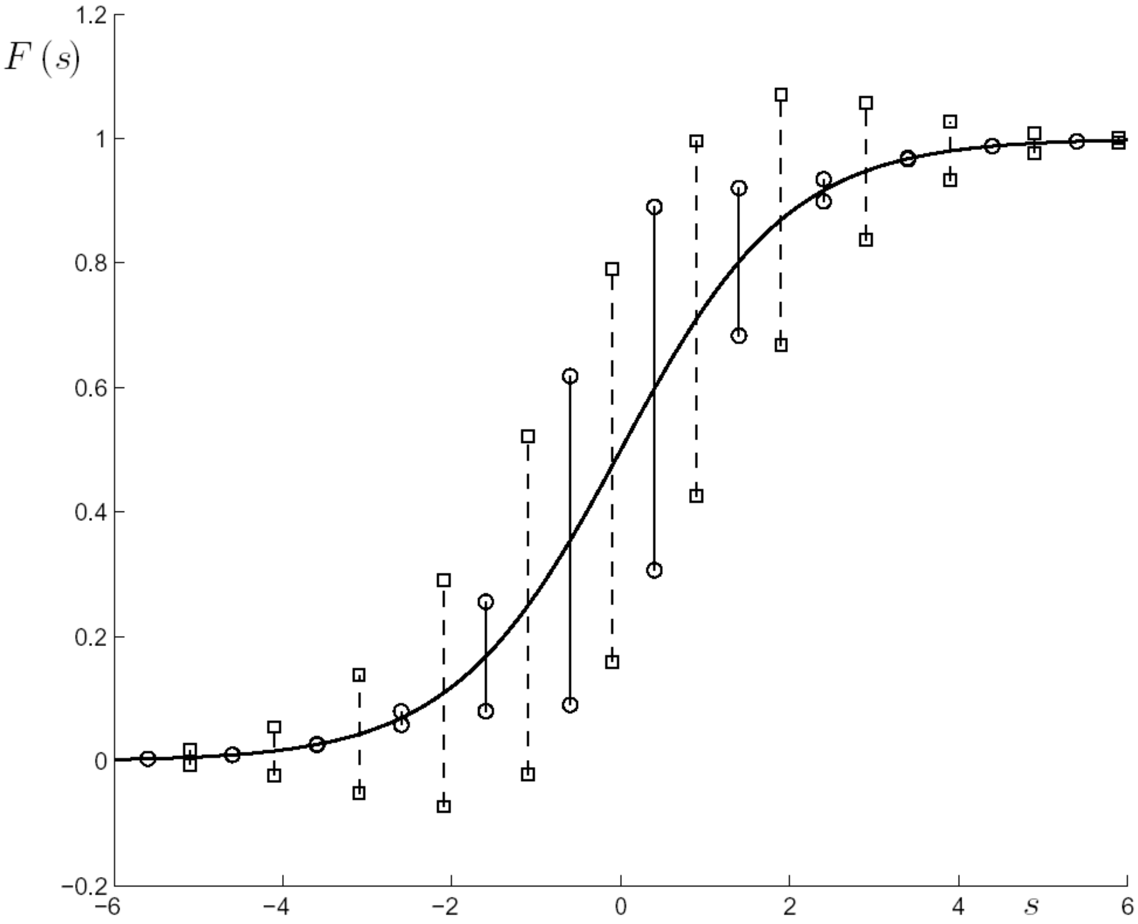
Neuronové kódování

- **The key assumptions**:
  - The spike is a point event (in time)
  - Spikes are mutually indistinguishable
  - The information is transferred/encoded by the temporal spike ordering
- **Interspike interval (ISI) - frequency, Latency,**
- **Number of spikes**
- **….**

Transfer function – just noticeable difference



Rate coding – noisy transfer function



Optimum signal – easily recognized

- Signal → Neuron → Response (internal representation)

Even if there is unique correspondence between signal and response, then which signal can be determined most precisely.

Response is realization of a random variable

- Statistical question, at which level of the parameter, this parameter can be deterimined at best.

Transfer functions

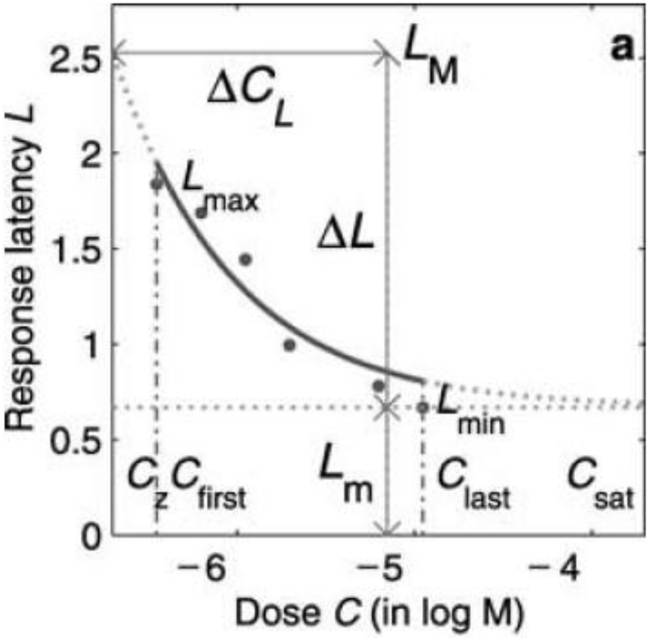
- IGD mean ISI and CV both are functions of the signal – μ, which is the parameter of the density.

$$E(T) = S/\mu, \quad CV = \sigma^2/\mu S$$

Problems

1) From observation or observations of *T* to determine μ
2) How well it can be done

Latency coding



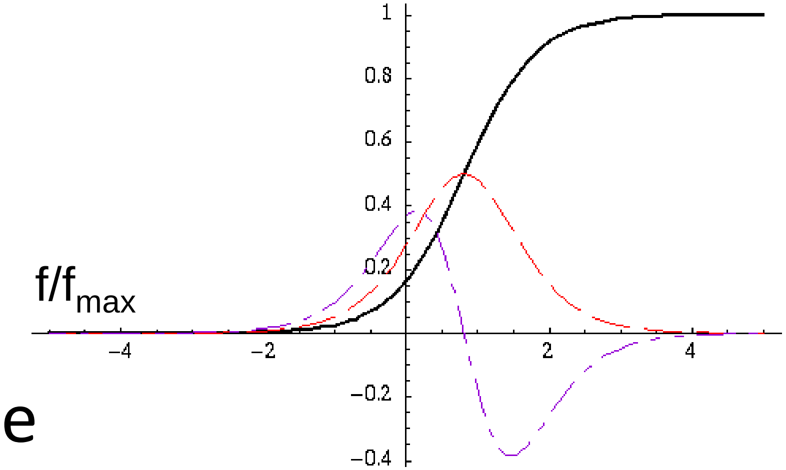
Rospars JP, Lansky P, Duchamp A, Duchamp-Viret P:
Relation between stimulus and response in frog olfactory receptor neurons in vivo.
European Journal of Neuroscience 18: 1135-1154, 2003.

Transfer function – frequency coding

$$E(T) = S/\mu, \quad CV = \sigma^2/\mu S$$

$E_s(t)$ -mean ISI, *$E_s(N(t))$* - mean of the counting process.

The logistic function is a typical transfer function. Best identification is where a small change in *s* implies a large change of the firing frequency. It means where the derivative of the transfer function is maximal.



Frequency coding - criterion

- Maximum of the derivative of the transfer function

$$f(s) = \frac{1}{E_s(T)}$$

example

$$f(s) = \frac{f_{\max}}{1 + \exp(-bs)}$$

Criterion

$$s_{opt} = \max\{-\frac{1}{E_s(T)^2}\left(\frac{\partial E_s(T)}{\partial s}\right)^2\}$$

$$s_{opt} = 0$$

Receiving neuron

- From observed frequency *f* the signal *s* is determined
- ISIs are random variables. It implies that for the same signal, different values of $E_s(T)$ are estimated. And therefore different firing frequency is observed
- Thus, we may ask how well the signal is determined. It depends, at least, on the variability of ISI for given signal level. For constant ISI – no problem arises

Specific Surprise

Optimum signal is such for which

$$I(R|s) = \int g(r|s) \ln \frac{g(r|s)}{g(r)} dr$$

reaches maximum. Distribution of responses is needed.

I=0 if distribution of responses does not depend on signal.

This is commonly used measure of signal optimality.

Fisher information

Random variable *T* has probability density function belonging to a parametric family *g(t;s).* The Fisher information with respect to the parameter is

$$J = \int \frac{1}{g}\left(\frac{\partial g}{\partial s}\right)^2 dt$$

Rao-Cramer inequality

$$Var(\hat{s}) \geq \frac{1}{J}$$

A lower bound for the Fisher information

From Cauchy-Schwartz inequality

$$J_2 = \frac{1}{Var_s(T)} \left(\frac{\partial E_s(T)}{\partial s} \right)^2 \qquad J_{norm} = \frac{J}{E_s(T)}$$

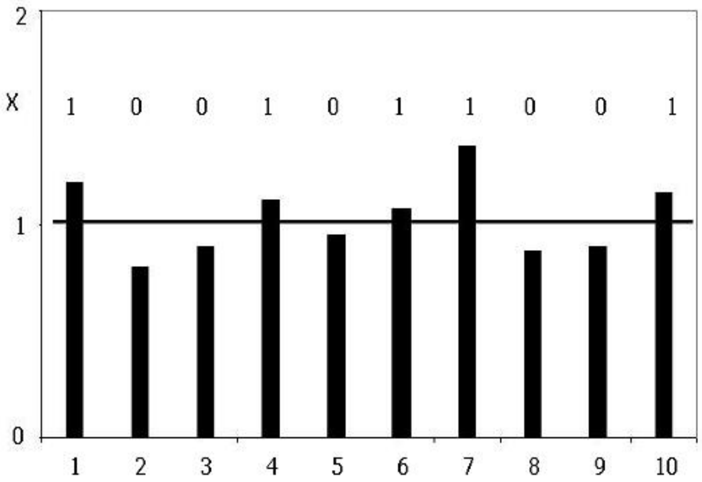
is a lower bound for J

Normalized Fisher Information

J gives FI in a single ISI. If *n* independent realizations are used, then *J* is replaced by *nJ*.

Measure of information obtained in (expected) natural time - dividing *J* by the expected value of the ISI.

Simple Threshold Model



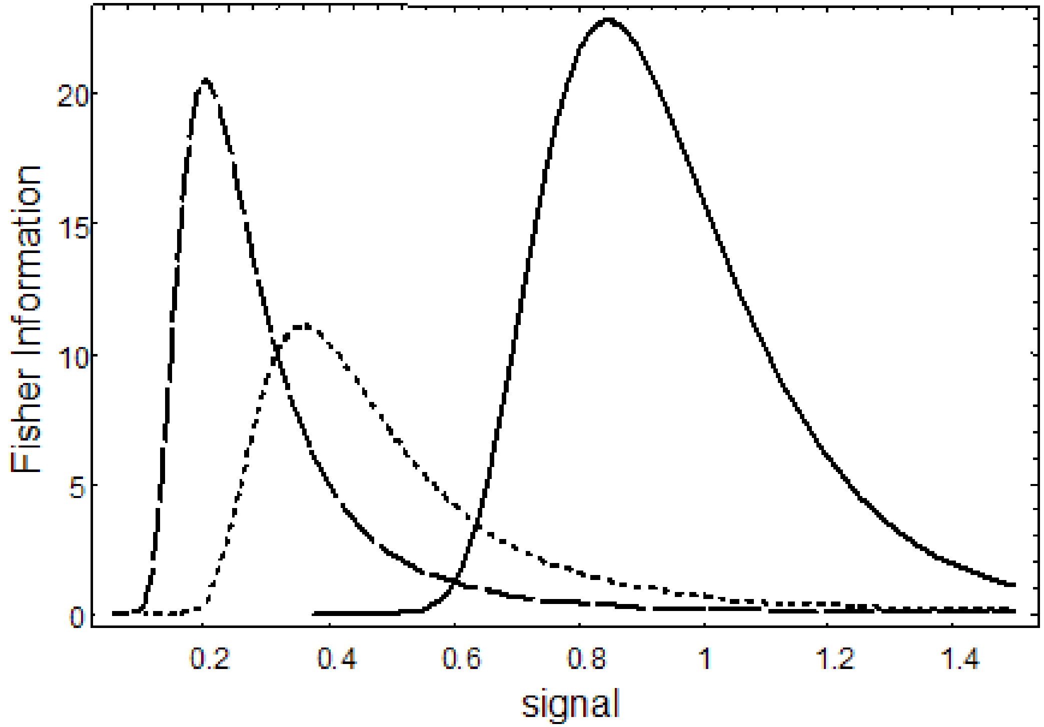
$$\hat{s} = a - F^{-1}(1 - \hat{p}).$$

$$J^X = \frac{\phi(\frac{a-s}{\sigma})^2}{\sigma^2 \Phi(\frac{a-s}{\sigma})(1 - \Phi(\frac{a-s}{\sigma}))}.$$

Fisher information – quality of estimation

Examples of FI.

Signal is functionally related to the noise, *σ=cs.*
Parameters: *a=1, c=0.2* (solid line), *c=1* (dotted line), *c=2* (dashed line)



Olfactory neuron

- R – unbound
- A - odorant
- C – complex
- k_1 and k_{-1} are rates
- Stochastic variant – Birth-and-death process on {0, 1,…, N}. Question – which concentration of odorant can be determined with the highest precision.

$$\mathrm{A} + \mathrm{R} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{C} \ ,$$

$$\lambda = k_1 A = k_1 \exp(s)$$

$$\mu = k_{-1}$$

Mean and SD of the process

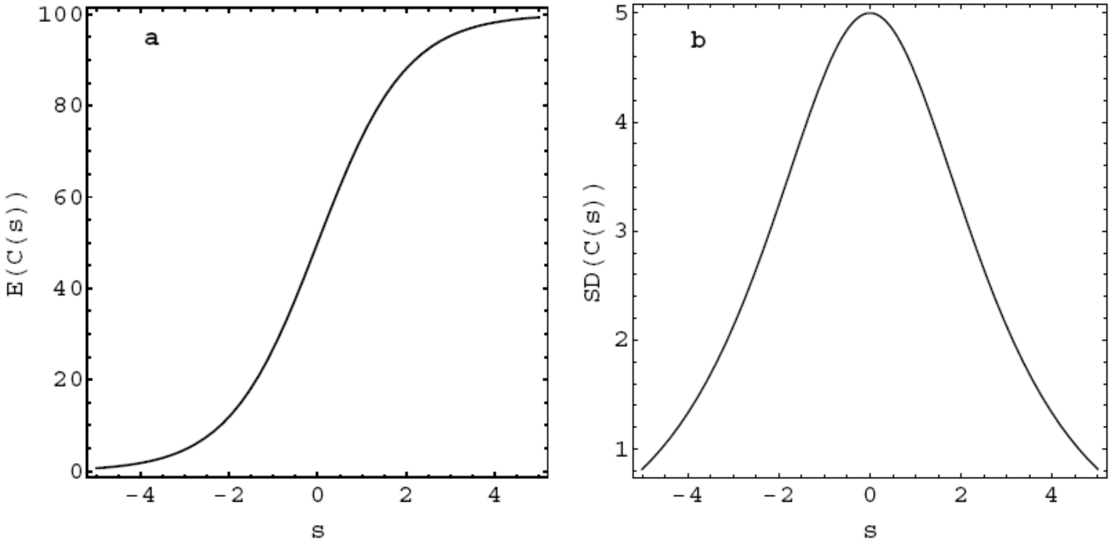
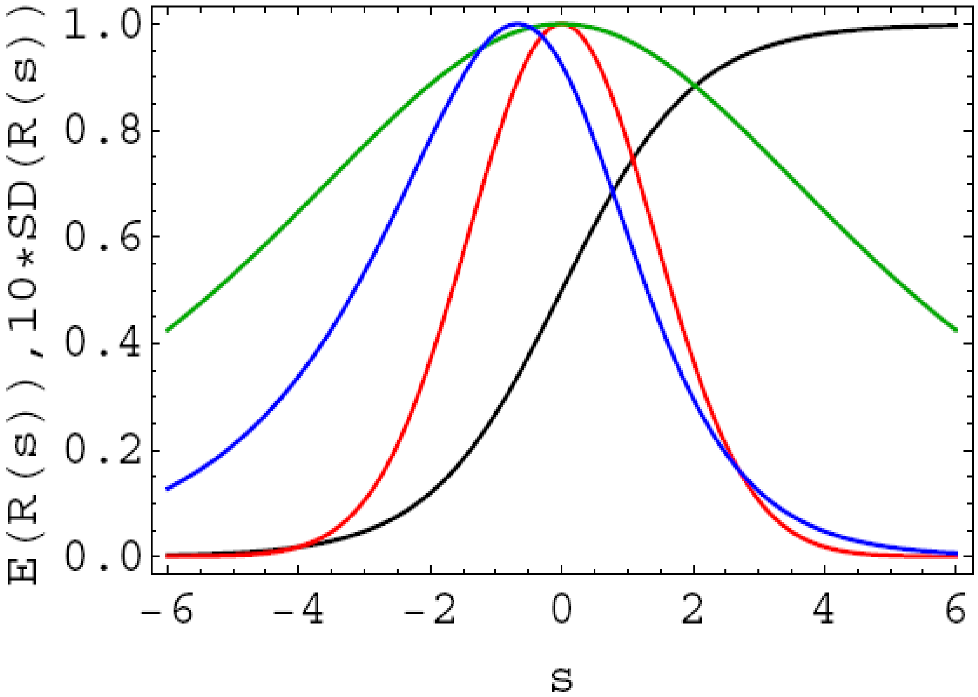


Fig. 2. (a) Mean $E(C(s))$ and (b) standard deviation $SD(C(s))$ of the number of activated receptors in the basic model, as functions of the odorant log-concentration, s, in perireceptor space. Parameters are $K_1 = 1$ and $N = 100$. Both the inflexion point of the curve of mean and the point of maximal standard deviation are located at $s = \log K_1 = 0$.

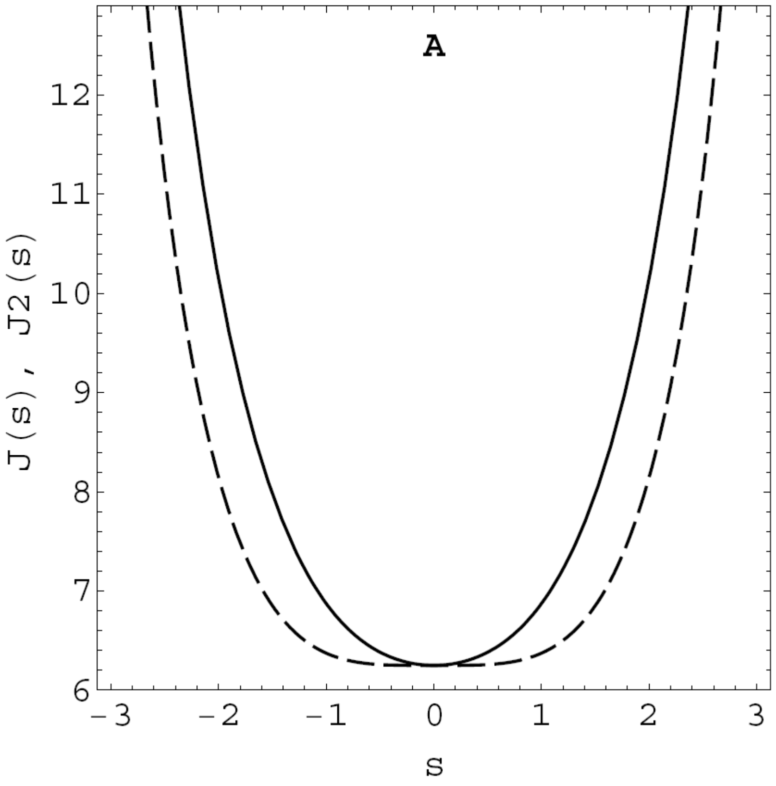
Transfer function and standard deviations

Mean transfer function *r*(*s*) (black line) and standard deviations
with quickly decreasing noise (red line),
slowly decreasing noise (green line) and example of asymmetry (blue line).

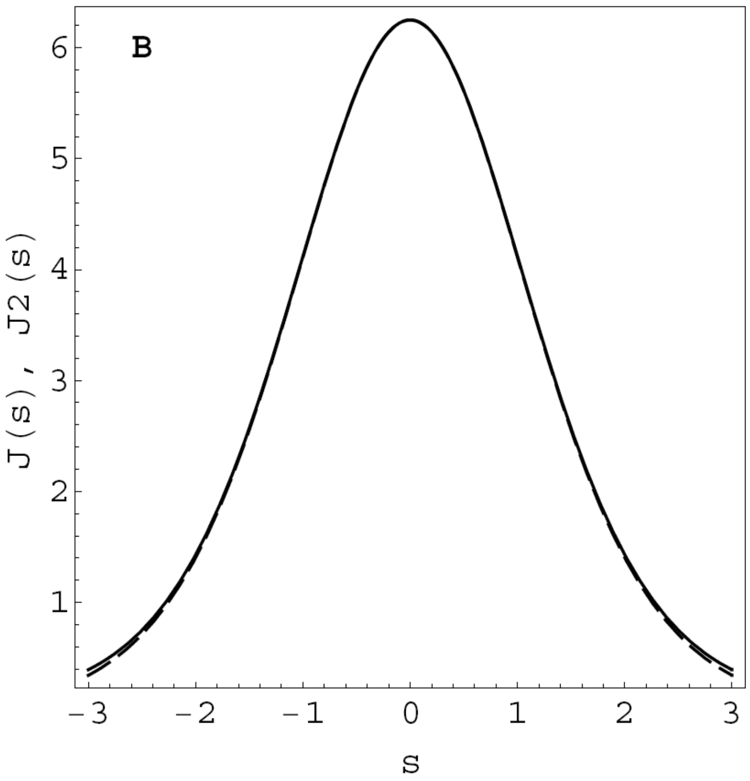


Examples

A - slowly decreasing noise

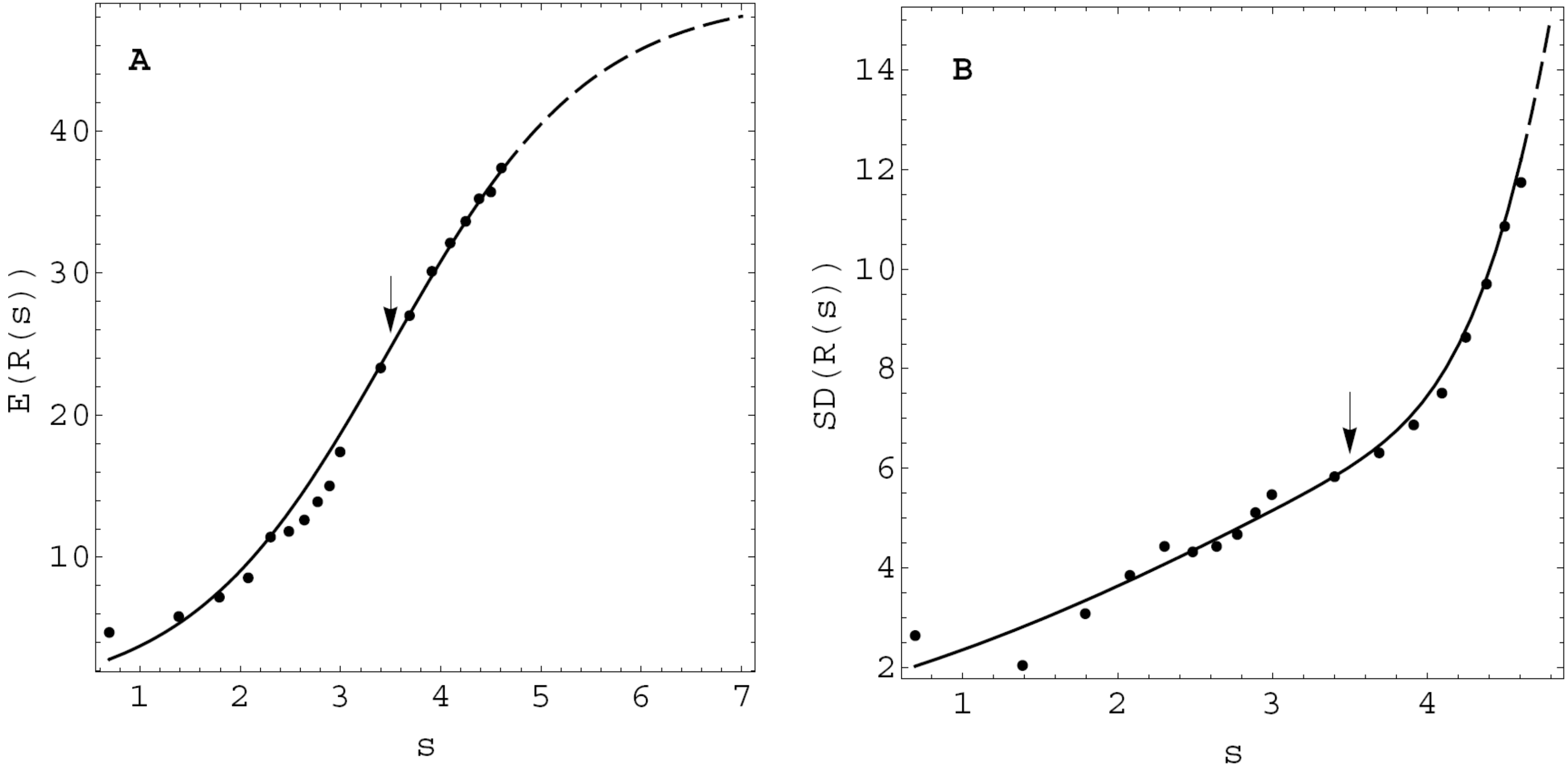


B - quickly decreasing noise



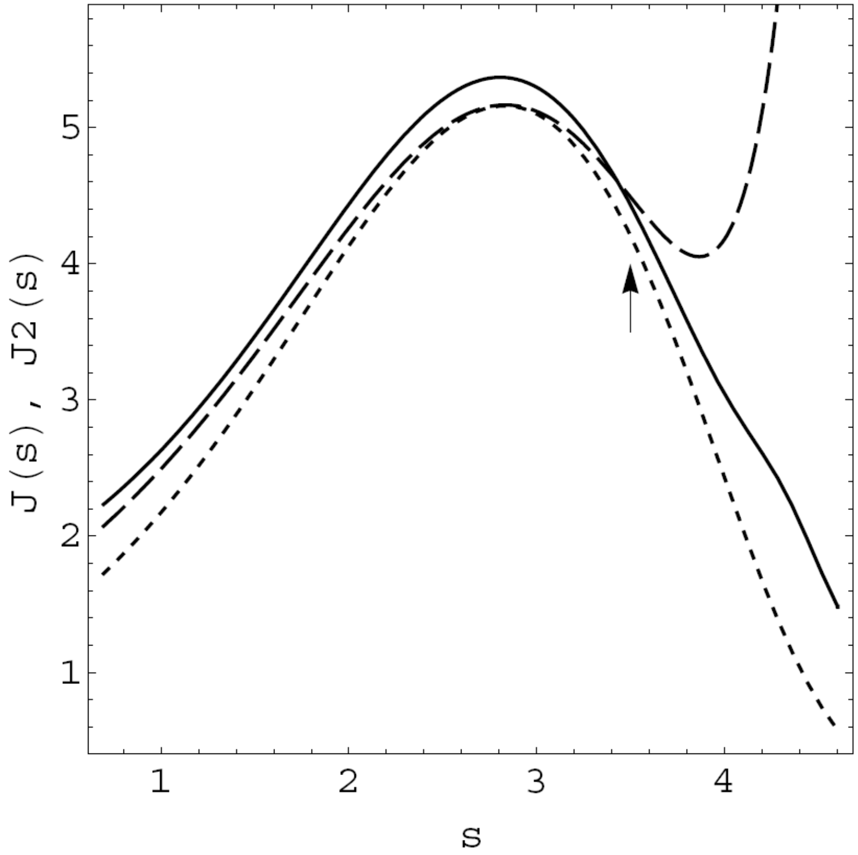
Empirical data (neuron firing frequency as a function of injected current)

Tomaru, A; Kurahashi, T (2005) [Mechanisms determining the dynamic range of the bullfrog olfactory receptor cell]() **J. NEUROPHYSIOL. 93: 1880-1888**



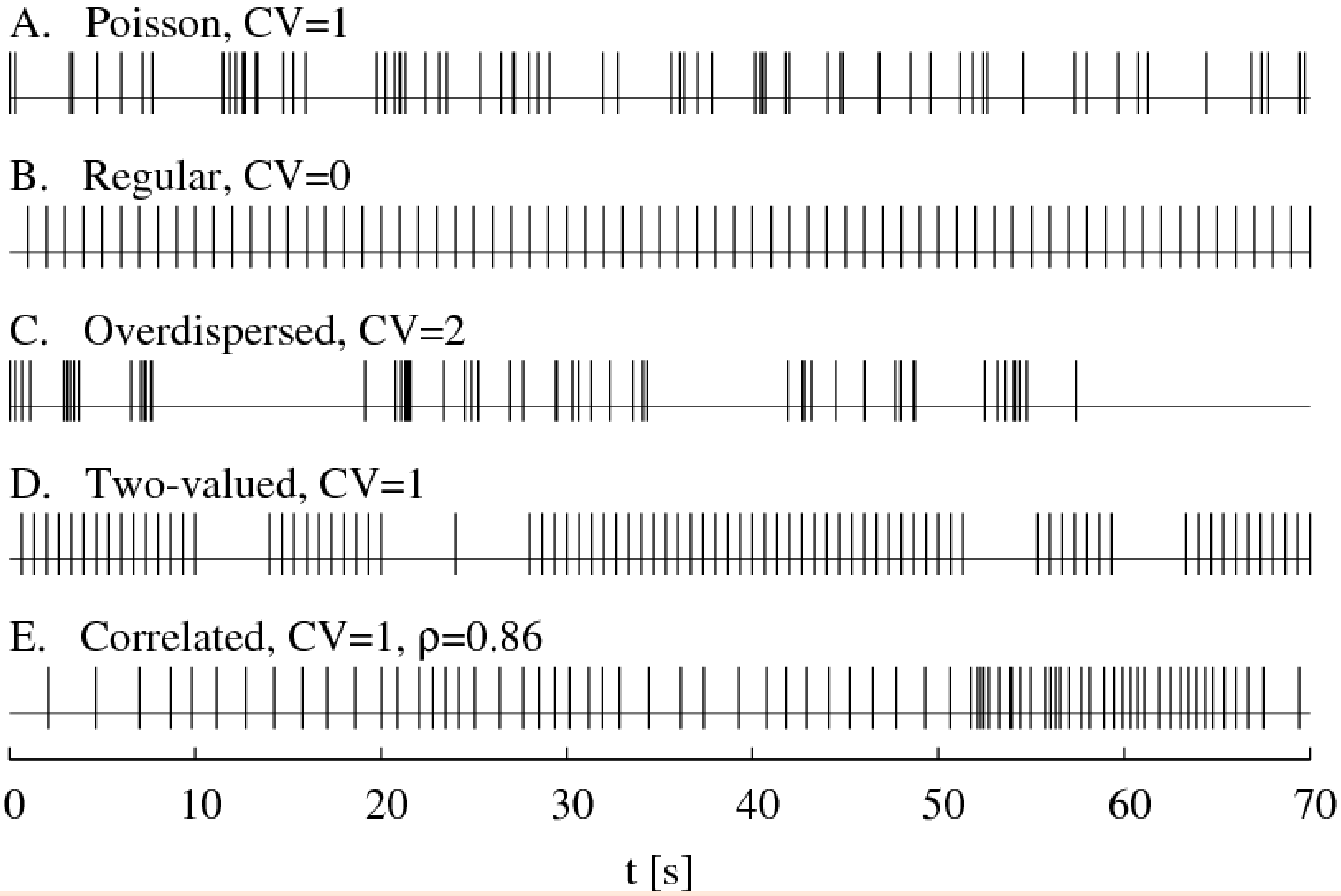
Fisher information for empirical data,

Gaussian distributed response (solid line), Beta distributed response (dashed line) and their lower bound *J*2(*s*) (dotted line). The arrow denotes the position of the inflection point of the mean response curve



Variability coding

- The same frequency – different variability



17.12.2010

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Measure of Variability

$$CV = \sqrt{Var(T)} / E(T)$$

Coefficient of variation

$$Y = T / E(T)$$

$$CV = \sqrt{Var(Y)}$$

Normalized standard deviation

$$FF = Var(N(t)) / E(N(t))$$

Fanno factor

Randomness

Variability and randomness is not the same

$$b(t) = \frac{f(t)}{1 - F(t)}$$

$f(t)$ density, $F(t)$ distribution function

Hazard rate is constant for Poisson process

Randomness coding

- The same frequency – different randomness

Most random is Poisson process !, but not most variable

Variability and randomness is not the same.

Is spontaneous activity Poissonian ?

In activity of hippocampal place cells,
additional information to the location is present

Poznámky o informaci

Amount (measure) of information

  - Unit: **bits**

- Entropy *H(X):* **minimal average length in bits** needed to describe random var. *X*

Information: the reduction in **uncertainty**:

{A, B, C, D} → {B}

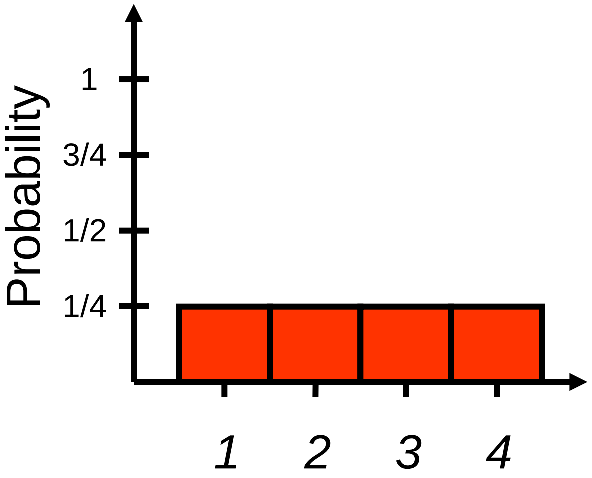
Information theory: entropy *H*

- Entropy *H(X):* **measures uncertainty** of a random var. *X*, resp. the amount of information "produced" by *X*, the choice
- **Discrete random variable** *X*: p_i, *i=1…n*
  - *H* is continuous in p_i
  - For all p_i equal (uniform dist.), *H* monotonously increases with *n*
  - Entropy is additive (separation into independent subsystems)

$$\boxed{H(X) = -\sum_{i=1}^{n} p_i \ln_2 p_i}$$

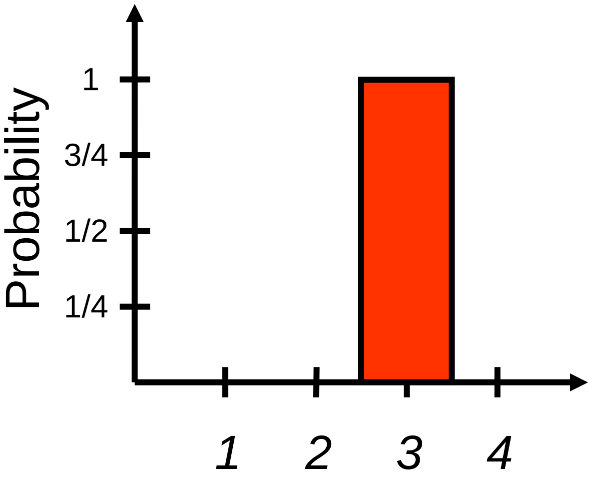
Entropy and information

- Case **A**



$$H(A) = -\sum_{i=1}^{4} p_i \ln_2 p_i =$$
$$= -4 \times \left(\tfrac{1}{4} \ln_2 \tfrac{1}{4}\right) = 2$$

- Case **B**



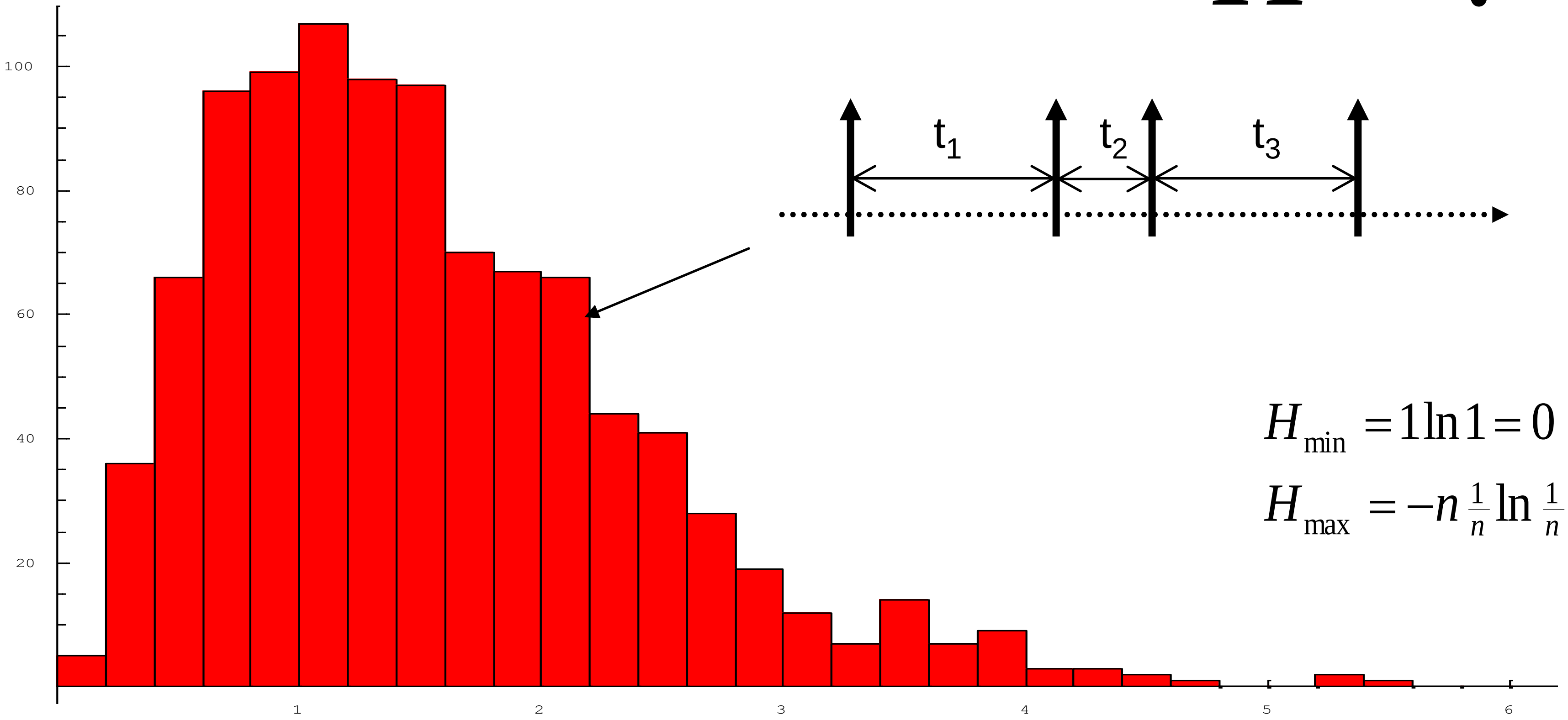
$$H(B) = -\sum_{i=1}^{4} p_i \ln_2 p_i =$$
$$= -\left(1 \ln_2 1\right) = 0$$

$$R = H(A) - H(B) = 2\,\text{bits}$$

ISI histogram and the entropy

- ISI is described by a **continuous random var. *T***

$$H = ?$$



$$H_{\min} = 1 \ln 1 = 0$$

$$H_{\max} = -n \tfrac{1}{n} \ln \tfrac{1}{n} = \ln n$$

Differential entropy *h*

- Continuous random variable *T* (ISI), described by PDF *f(t)*, D(f)=(0,∞)
- **Differential entropy** *h(f)*, the problem: *H(X)→h(X)*

$$h(f) = -\int_0^{\infty} f(t) \ln f(t) dt$$

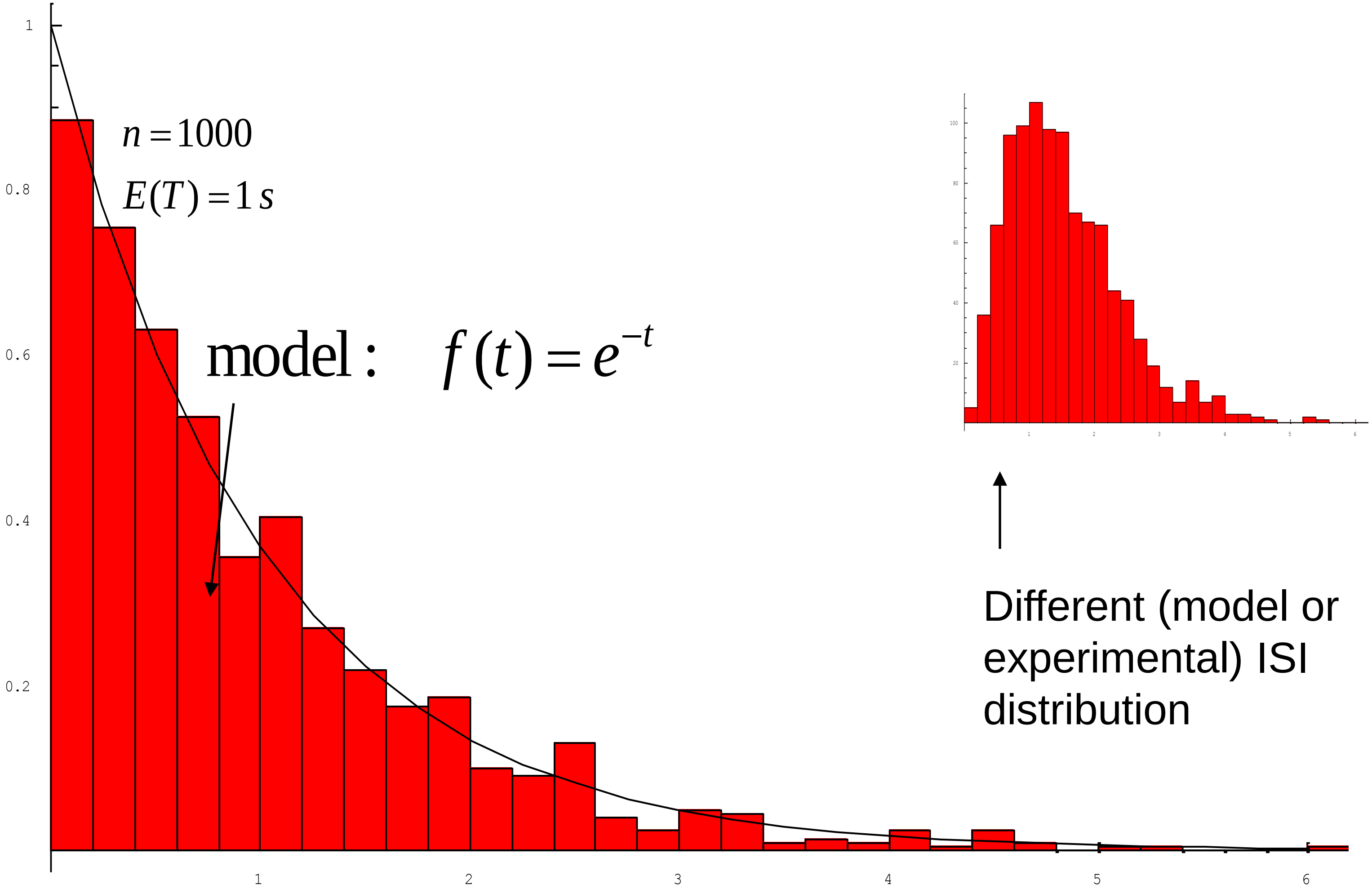
- Differences between *h* and *H:* interpretation, negativity, ∞
  - *h* is **not invariant** under variable transformations:

$$X \to Y: \quad h(Y) = -\int f(x) J_{X\to Y} \ln(f(x) J_{X\to Y}) dy$$

  - Example („**scaling**“):

$$X \to aX \equiv Y: \quad h(aX) = -\int \frac{1}{|a|} f(x) \ln\left[\frac{1}{|a|} f(x)\right] |a| dx = h(X) + \ln|a|$$

Exponential distribution of ISIs



$n = 1000$

$E(T) = 1\,s$

$\text{model}: \quad f(t) = e^{-t}$

Different (model or experimental) ISI distribution

KL distance from the exponential

- Choice of the exp. distribution *g(t)* as the reference state, then (mean value of *g(t)* is *1/a, f(t)→E(T)*):

$$\mathrm{KL}(f,g)=\int f\ln\tfrac{f}{g}=aE(T)-\ln a-h(f)$$

- If *E(T)=1/a*:

$$\boxed{\mathrm{KL}(f,g)=h(g)-h(f)=1+\ln E(T)-h(f)}$$

- Note:

$$\mathrm{KL}(f_B,g)-\mathrm{KL}(f_A,g)=h(f_A)-h(f_B)$$

Parameterization KL(*CV*)

- 2-parametric ISI models: ***f(t;a,b)*** → KL(f,g) is a function of 2 variables (equality of *E(T)*)
- „Scaling“ of *h* → KL is a function of only **one** var.
- Parameterization: KL(*CV*)
  - Quantification beyond the rate coding hypothesis (equality of *E(T)*)
  - The judgment of exponentiality compared to the *CV=1* indication:

$$(\mathrm{KL}(f, \exp.) = 0) \Leftrightarrow (f \equiv \exp.)$$

Gamma distribution

- Frequently used ISI model, *a>0, b>0; a=1→exp.*

$$f(t)=\frac{b^a t^{a-1} e^{-bt}}{\Gamma(a)}, \quad E(T)=\frac{a}{b}, \quad CV=\frac{1}{\sqrt{a}}$$

- Entropy

$$h(f)=a+(1-a)\Psi(a)-\ln b+\ln\Gamma(a), \quad \Psi(a)=\frac{d}{da}\ln\Gamma(a)$$

- Parameterization: KL*(CV)*

$$\mathrm{KL}(f,\exp)=1+\ln E(T)-h(f)$$

$$\mathrm{KL}(CV)=1-\ln CV^2-\ln\Gamma(CV^{-2})+\frac{\Psi(CV^{-2})-1}{CV^2}-\Psi(CV^{-2})$$

Inverse Gaussian distribution

- Interpretation: I-F neuronal model, *a>0, b>0*

$$f(t) = \sqrt{\frac{a}{2\pi b t^3}} \exp\left[-\frac{1}{2b} \frac{(t-a)^2}{at} \right], \quad E(T) = a, \quad CV = \sqrt{b}$$

- KL(CV) parameterization:

$$\mathrm{KL}(CV) = \frac{1}{2} \ln \frac{e}{2\pi} - \ln CV + \frac{3}{\sqrt{2\pi}} \frac{\exp CV^{-2}}{CV} K_{1/2}^{(1,0)}(CV^{-2})$$

- $K_{\upsilon}^{(1,0)}(z) = \frac{\partial}{\partial \upsilon} K_{\upsilon}(z)$ and $K_{\upsilon}(z)$ is the modified Bessel (2nd kind)
- Inv. Gaussian is never exponential, min. KL: KL(*CV*=1.173)

Lognormal distribution

- Lognorm. is not resulting from any “popular” neuron model
- If variable *T* is distributed normally, then ln*T* is lognormal => frequently used in data analysis, fitting

$$f(t) = \frac{1}{t\sigma\sqrt{2\pi}} \exp\left[-\frac{(\ln t - m)^2}{2\sigma^2} \right], \quad E(T) = e^{m+\sigma^2/2}, \quad CV = \sqrt{e^{\sigma^2} - 1}$$

$$\mathrm{KL}(CV) = \frac{1}{2}\left[\ln \frac{CV^2}{\ln(CV^2+1)} + \ln \frac{e}{2\pi} \right]$$

- Never exponential, min KL(CV): $\mathrm{KL}(CV = \sqrt{e-1}) \approx 1.311$

Posunuté exp. rozdělení

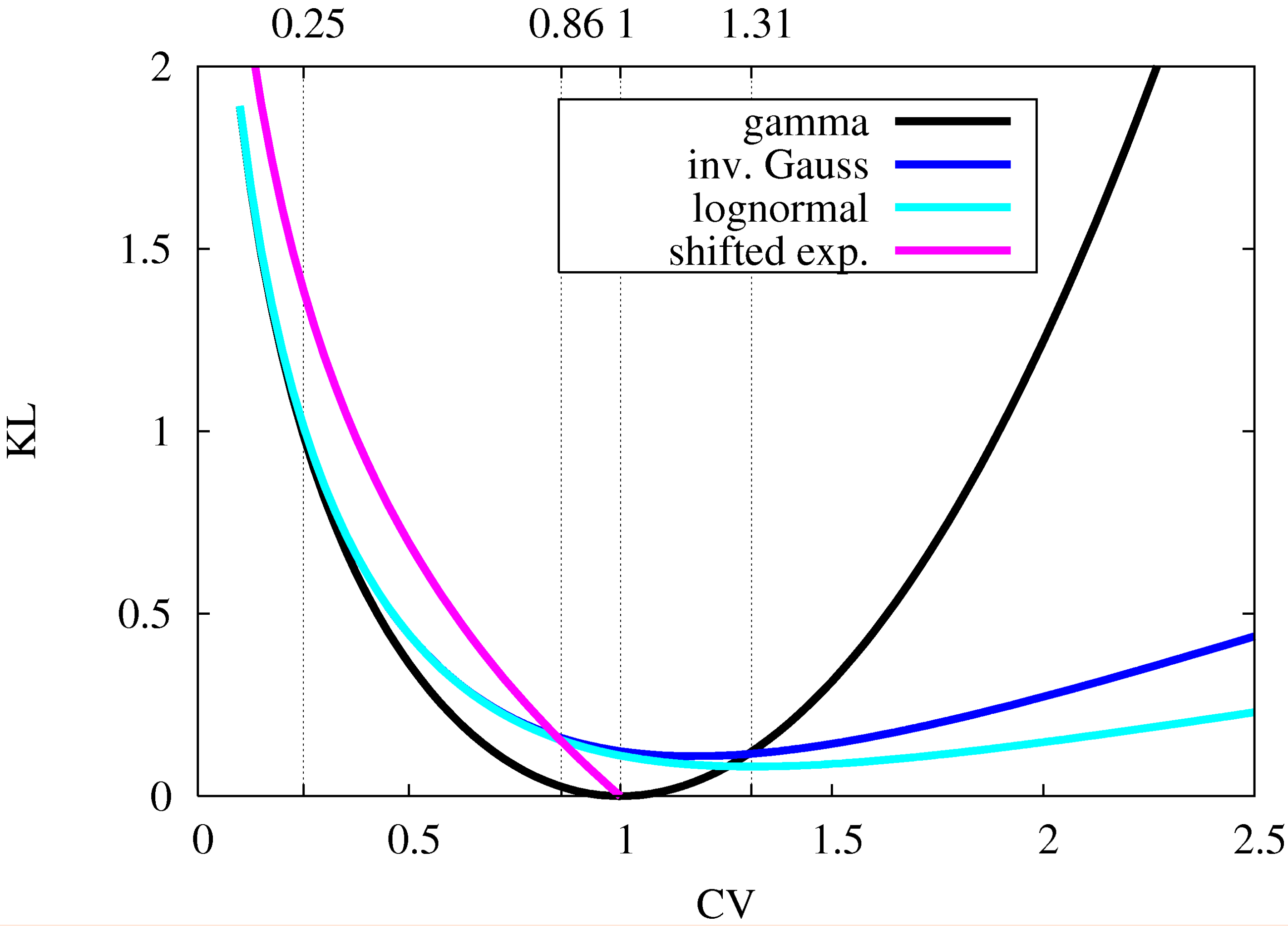
- A simple “refractory phase” model
- A comparison of exponential model with refr. phase to the template without refr. phase:

$$f(t) = \begin{cases} 0, & t \le \tau \\ ae^{-a(t-\tau)} & t > \tau \end{cases}, \quad E(T) = \frac{1+a\tau}{a}, \quad CV = \frac{1}{1+a\tau}$$

- Because *h(X+τ)=h(X):*

$$\mathrm{KL}(CV) = -\ln(CV), \quad CV < 1$$

KL(*CV*): the ISI models



KL(*CV*): the ISI models

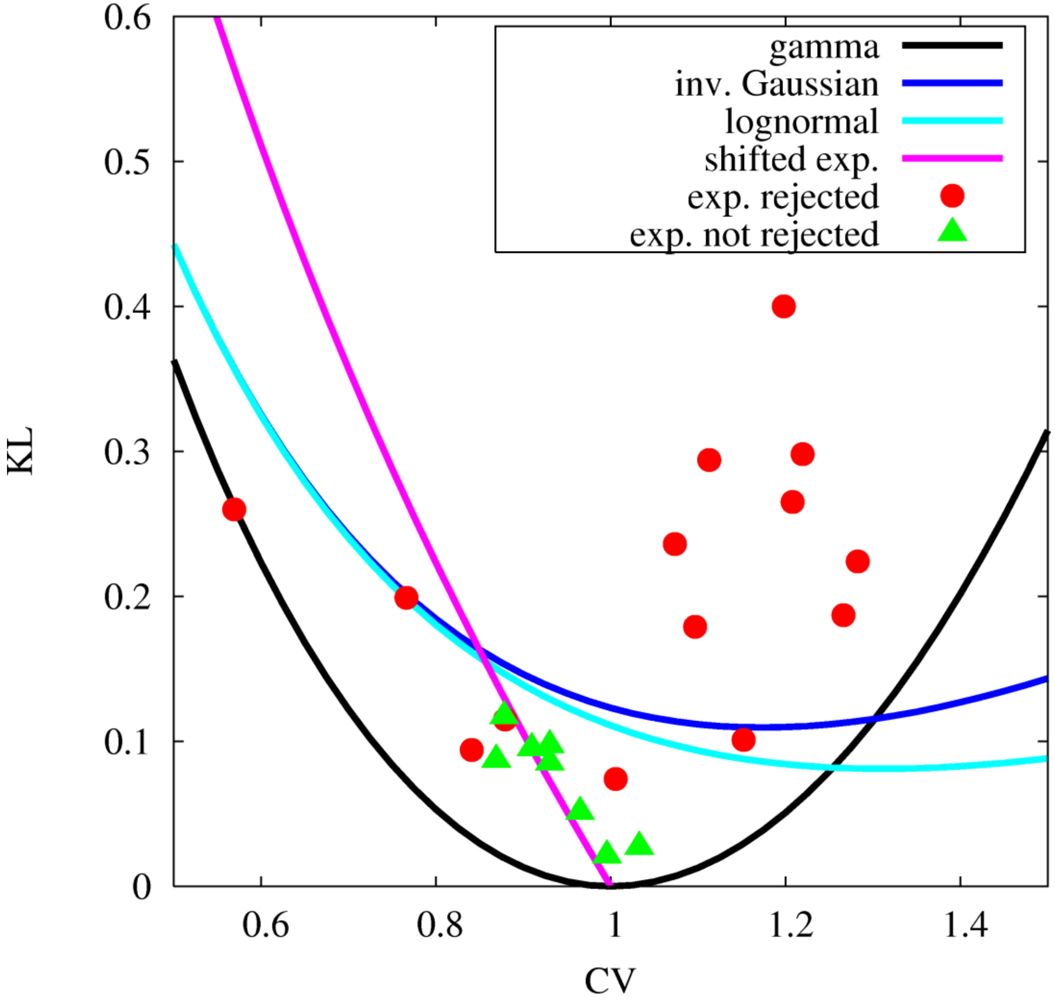
- CV<1: the curves hard to distinguish
- Equal KL dist. for two models ≠> their similarity
- CV=1 ≠> exponentiality (lognorm., iG)
- Different type of behavior for *CV*<1 and *CV*>1

Estimation of differential entropy

- Comparison of model and data: reduces to *h*(data) estimation
- Two different approaches (estimators):
  - „plug-in“: first estimate *f(t):* histograms, kernel estimates (difficulty with ISI=(0,∞))
  - Construction of *f(t)* not needed explicitly
- Vasicek’s estimator, *m(n): (n>200 → m=13)*

$$h(\text{data}) = \frac{1}{n}\sum_{i=1}^{n} \ln\left[\frac{n}{2m}\left(t_{[i+m]} - t_{[i-m]}\right)\right]$$

KL(CV): experimental data

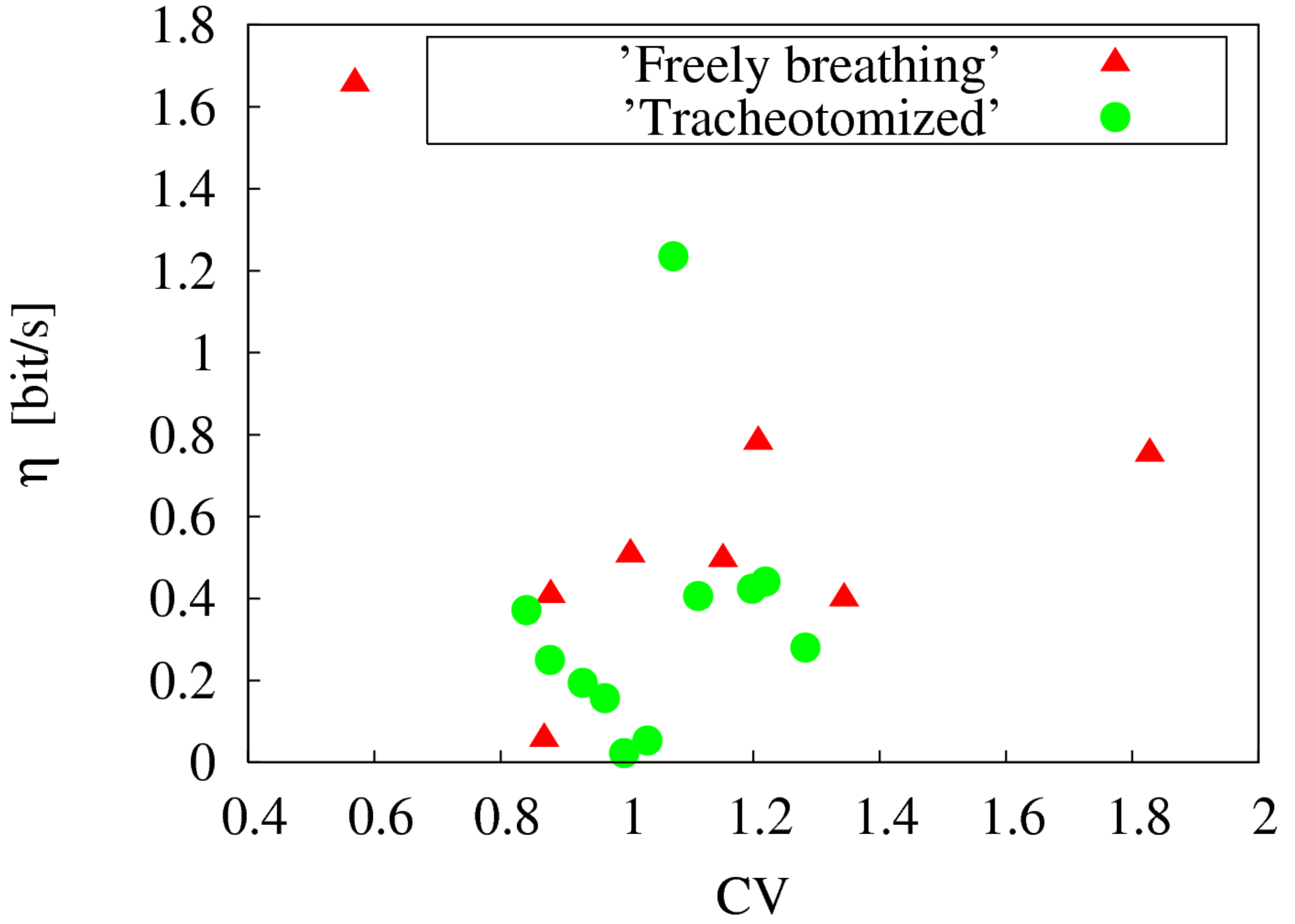


Experimental data, bursting

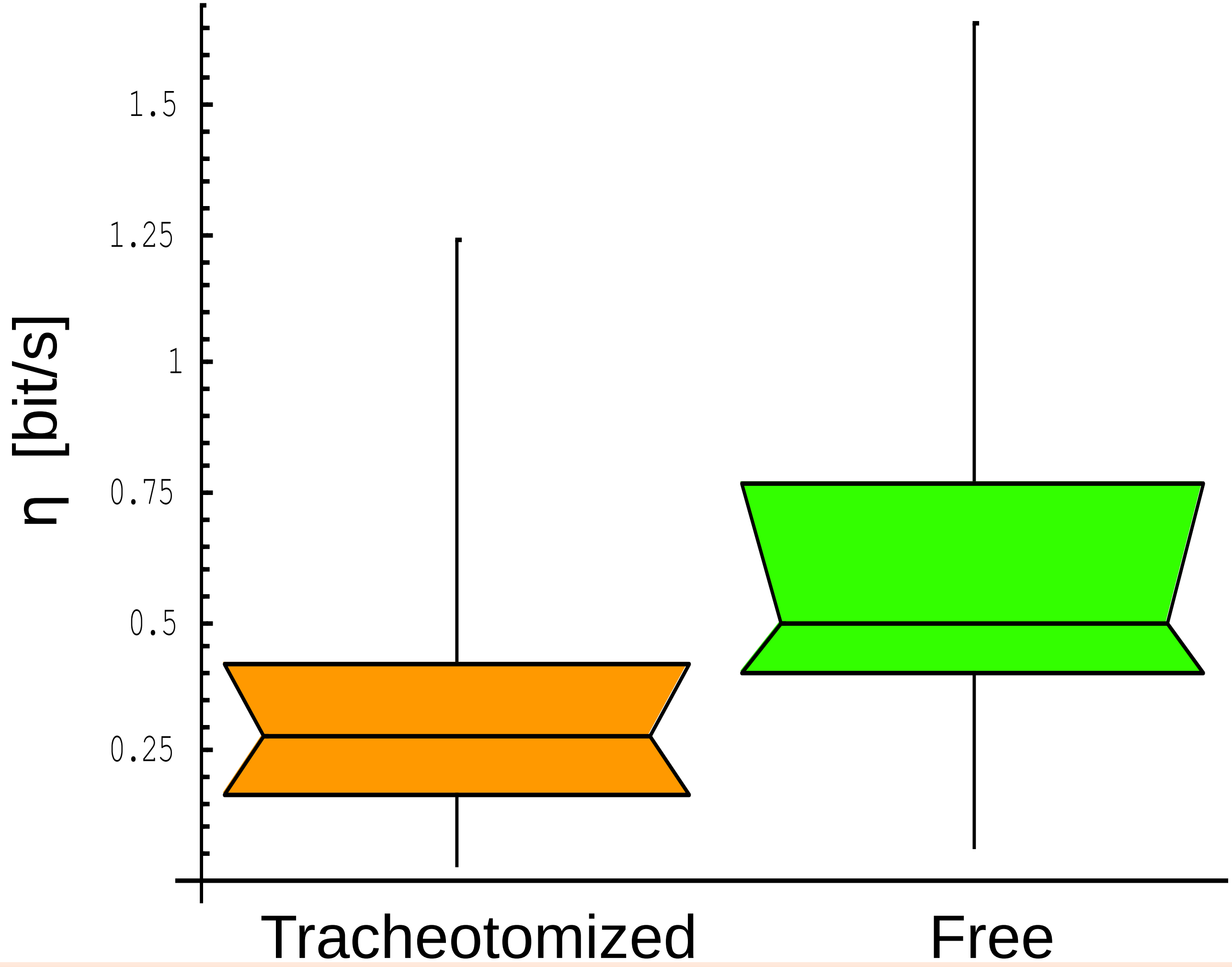
- The KL distance of some data is greater than that of the compared models
- Probably the kind of “bursting” activity
- Double-exponential distribution:
  - 3-parametric model
  - KL distance of the 2-exponential ≈ KL(data) ≠> 2-exp. Describes the data

$$f(t) = pae^{-ax} + (1-p)be^{-bx}, \quad p \in (0,1), \quad CV > 1$$

Experimental data



Experimental data (box & whisker plot)



Poděkování

- Dr. Ditlevsen – Kodaň
- Dr. Greenwood - ?
- Dr. Košťál - Praha
- Dr. Pokora – Brno
- Dr. Rospars – Versailles
- Dr. Sacerdote – Torino