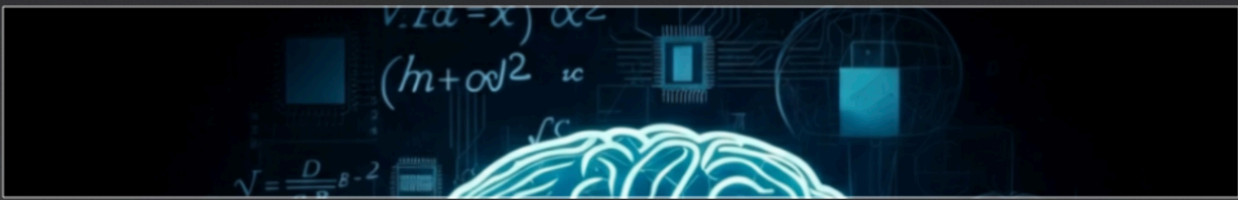
MODELLING NEURAL SYSTEMS



COMPUTATIONAL MODELLING OF NEURONS AND MICROCIRCUITS

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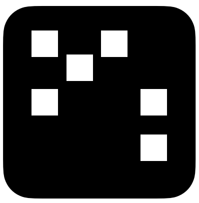
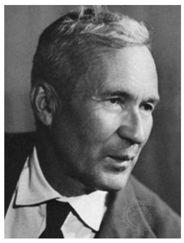
Stochastic processes

Probability Theory - *Experiment*

- The set Ω of **all possible outcomes of an experiment** is called the **sample space** for the experiment.
- e.g., *Tossing a coin:* Ω = { H , T }.
- e.g., *Tossing 2 coins:* Ω = { HH , HT , TH , TT}.
- An **event** A : **any collection of possible outcomes** of an exp.
  An event can be a subset of Ω, it can be Ω itself, it can be the null set ∅.
- *Tossing 2 coins:* e.g., A = { HH, HT } (i.e. *event* "*first coin is heads*").

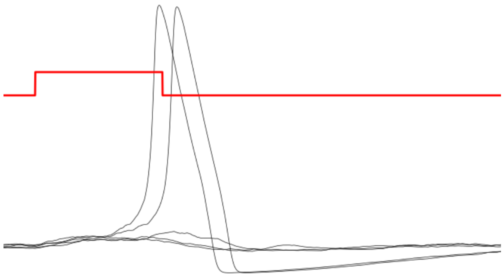
Ω 



A. Kolmogorov

Probability Theory - *Experiment*

- **Experiment:** I show very briefly a picture of a dog to a monkey, as a stimulus. Then, I observe - during and immediately after such a presentation - a specific neuron (in the IT cortex) and whether it responds with APs or remains silent.



Ω It fires | It stays at rest

- **Probability:** something I associate to an *event*.

Probability: relative frequency definition

$$P(A) \quad = \lim \frac{num\ of\ times\ A\ can\ occur}{total\ num\ of\ trials}$$

- **Def: probability** is the long-run *relative frequency* of an event, **after a very large number of (independent, repeated) trials.**
- **Calculation:** by dividing num. of times an event occurs by total num of trials.
- **Nature:** Empirical or *a posteriori*, as it is derived from experience.
- **Usefulness:** Practical for real-world problems, where probabilities need to be estimated from data (e.g. insurance company analysing car accidents).
- ***0*** means the event is almost impossible, and a probability of ***1*** almost certain
- **Problems with this definition:** An actual limiting value may not exist. Moreover, it relies on having *enough* data for a *reliable* estimate.

Probability: axiomatic definition

- **Def:** Probability is a **function** that assigns a number **p** to each possible event **A** in a sample space Ω. **p** satisfies three fundamental **axioms**:
  - Axiom 1 (*non-negativity*): $p(A) \geq 0$
  - Axiom 2 (*certainty*): $p(\Omega) = 1$
  - Axiom 3 (*additivity*): $p(A \cup B \cup C) = p(A) + p(B) + p(C)$

    (for any collection of mutually exclusive, i.e. disjoint, events)

- It follows that $P(\complement A) = 1 - A$ and that $P(\varnothing) = 0$
- e.g., *Tossing a coin:* $\Omega = \{ H , T \}$, $P(H) = 1/3$, $P(T) = 2/3$

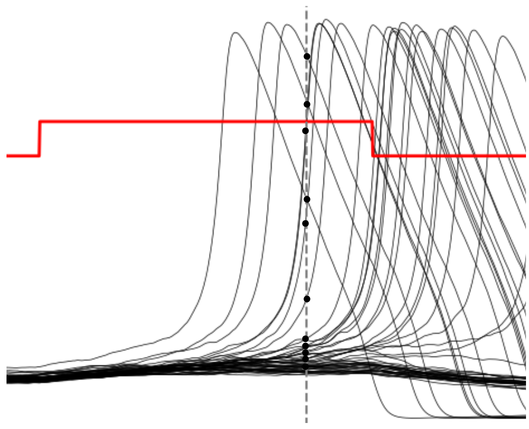
Random Variables (RV)

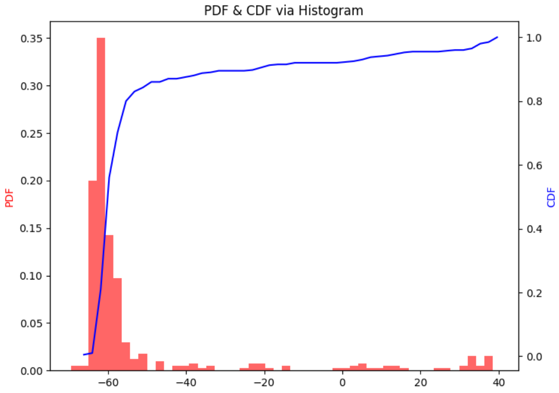
- a RV ***X*** : a **function** that for each element of Ω assigns a (real) number.
- It is a *numerical summary* of a random outcome of an experiment.
- **Notations:** we denote RVs by uppercase letters such as **X**, and use lowercase such as **x** for *potential* values and *realized* values.
- **Watch out!** a RV and its *realized* value are NOT the same thing.
  The former is a **function** (from outcomes to values).
  The latter is a **value**, associated with a specific outcome.
- For a RV ***X***, we define its **cumulative distribution function** (CDF) as

$$F_X(x) = p(X \leq x)$$

Random Variables (RV)

- **Experiment:** I show very briefly a picture of a dog to a monkey, as a stimulus. Then, I monitor during and immediately after such a presentation, a specific neuron (in the money's IT cortex) responds with APs or remains silent.

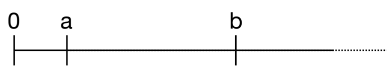




- **RV:** The numerical value of the membrane potential *4 ms* following the stimulus' onset.

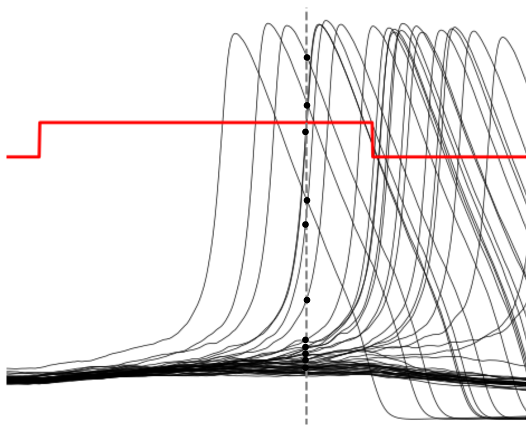
Random Variables (RV) - CDF

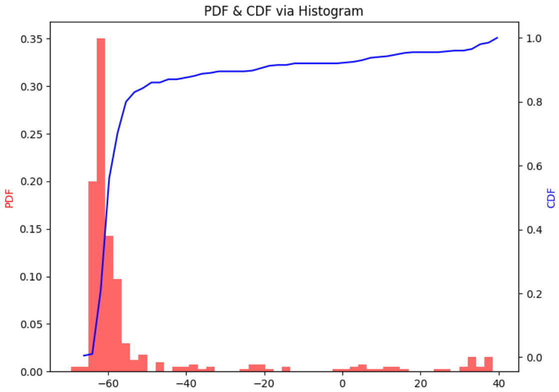
- $F_X(x) = p(\, X \leq x\,)$ **Cumulative distribution function**
- $0 \leq F_X(x) \leq 1$
- $\lim_{x \to -\infty} F_X(x) = 0 \qquad \lim_{x \to +\infty} F_X(x) = 1$



$$P(X \leq b) = P(X \leq a) + P(a < X \leq b)$$

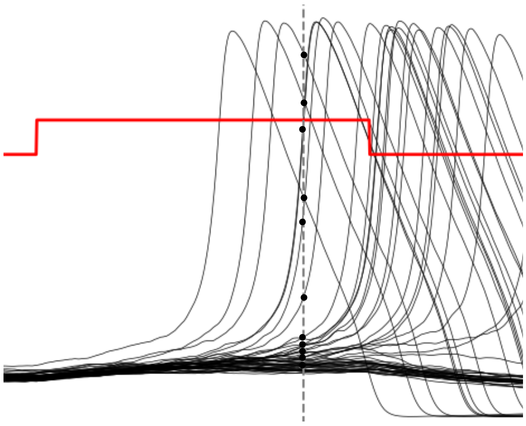
- $P(a < X \leq b) = F_X(b) - F_X(a)$

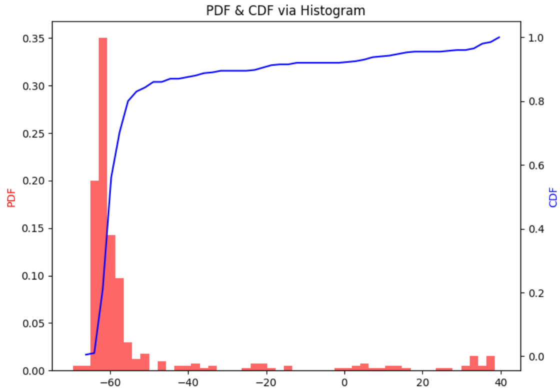




Random Variables (RV) - PDF

- $P(x < X \leq x + dx) = F_X(x + dx) - F_X(x)$
- $f_X(x) = \dfrac{dF_X(x)}{dx}$ **Probability (distribution) density function**
- $P(x < X \leq x + dx) = dx\, f_X(x)$
- $\int_{-\infty}^{+\infty} f_X(x)dx = 1 \qquad f_X(x) > 0$





Discrete-valued Random Variables

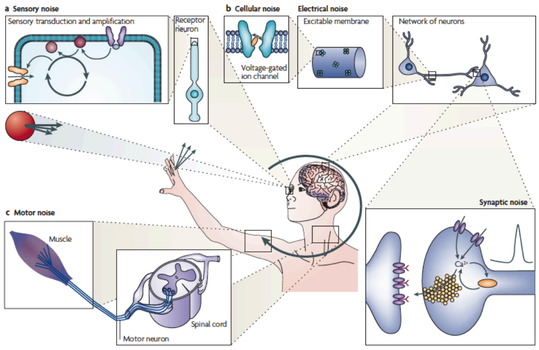
- a discrete-valued RV ***X*** : a **function** that take only finite (or countably many) values, $x_1, x_2, \ldots, x_N$ (N could be infinite, but it is NOT a continuum).
- probabilities takes the form

$$p(X = x_1) = p_1 \qquad p(X = x_2) = p_2 \qquad \ldots, p(X = x_N) = p_N$$

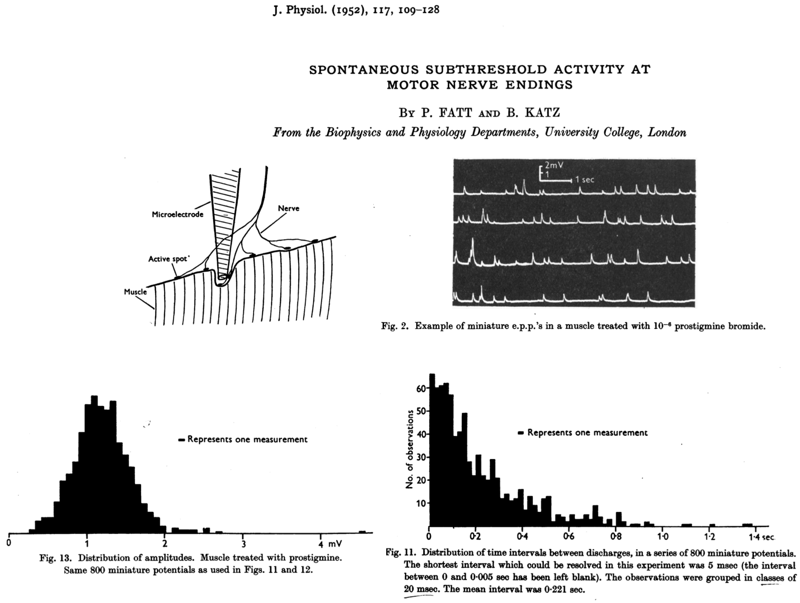
$$p_1 + p_2 + \ldots + p_N = 1$$

- For a discrete values RV ***X***, its **CDF** $F_X(x)$ is a **step (with values 0 or p_i)**

“Noise” and “*random* variables” in the brain

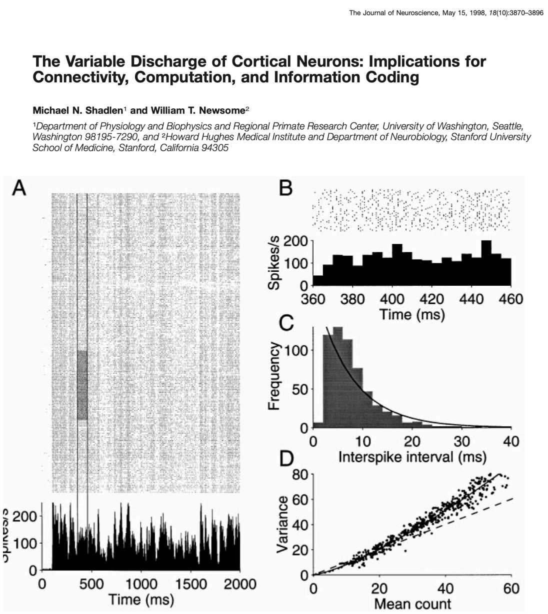


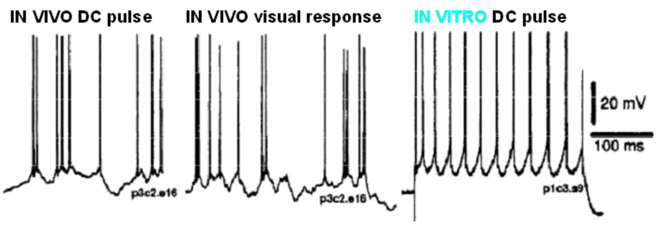
Faisal *et al.*, 2008



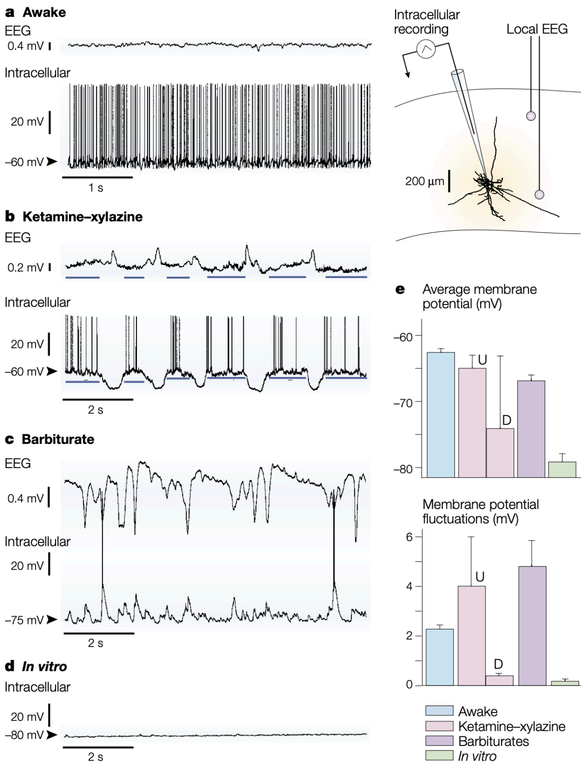
Fatt & Katz, 1952

Neuronal Firing appears to be irregular

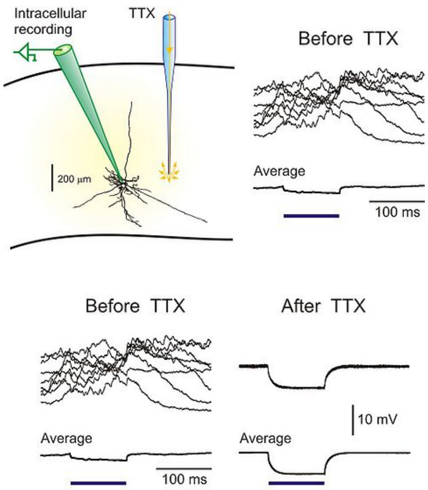




Holt, Softky, Koch, Douglas, J. Neurophysiol. 1996
Shadlen & Newsome, 1998



Synaptic inputs seems to be its culprit



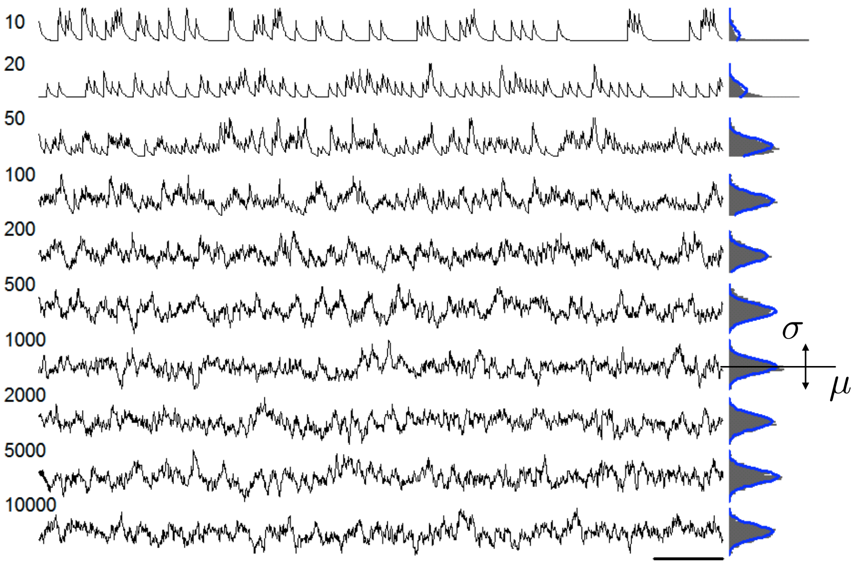
Destexhe et al., 2003

Plan for the day

- Refresher on stochastic processes
- Ornstein-Uhlenbeck's stochastic processes
- Stein's stochastic process
- Diffusion approximation

The *diffusion* approximation

$$\mu = J\ \lambda\tau$$
$$\sigma = J\ \sqrt{\lambda\tau/2}$$



Giugliano et al., 2008, Biological Cybernetics
Arsiero et al., 2007, J Neuroscience
Giugliano et al., 2004, J Neurophysiology

Probability Theory and Random Variables

- **Random Variable (RV):** A variable whose value is subject to variations due to chance (e.g., the mem. potential of a neuron at one moment in time).

- **Stochastic Process (of time)** $X(t)$: a collection of RVs, indexed **by time**.
  - At every (time) point t, $X(t)$ is a RV.

- **Trajectory (Realization):** One specific "run" of the experiment.

Gaussian *White* “noise” $\xi(t)$

- $\xi(t)$ is a continuous-time, continuous-valued stochastic process (of time)
- $\xi(t)$, at every t, is a RV whose prob. density function (PDF) is a Gaussian

$$f_\xi(Z) = \frac{1}{\sqrt{2\pi}} e^{-X^2/2}$$

mean is **zero**, variance is **unitary**

autocorrelation func. is a Dirac’s **delta**

- $\langle \xi(t) \rangle \; = \; 0, \qquad \langle \xi(t)^2 \rangle \; = \; 1, \qquad \langle \xi(t)\xi(t+T) \rangle \; = \; \delta(T)$

- **It does NOT exist in nature!** Real (biological) noise has a **finite** (auto-correlation) time scale (i.e., the "color" of noise). It is a building block.

Ornstein-Uhlenbeck process - (my) definition

- is a continuous-time, continuous-valued stochastic process (of time)
- I define it (abusing the mathematical notation of o.d.e.) as

$$\tau \frac{d}{dt} x(t) \; = \; \mu \; - \; x \; + \; \sigma\sqrt{2\tau} \; \xi(t)$$

with $x(t_0) = x_0$

(deterministically)

- It is an abuse because $\xi(t)$ is not a differentiable “function” (it not at all a function of time), but …hey, I am a bioengineer!

- Beware: there are slightly different definitions in the literature. You will understand in a moment why I like this one.

Ornstein-Uhlenbeck process - properties

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma\sqrt{2\tau}\;\xi(t)$$

- $m(t) \;=\; \langle x(t) \rangle \;=\; x_0\, e^{-(t-t_0)/\tau} \;+\; \mu\,(1 - e^{-(t-t_0)/\tau}) \;\rightarrow\; \mu,$
- $s(t)^2 \;=\; \langle [x(t) - m(t)]^2 \rangle \;=\; \sigma^2\,(1 - e^{-2(t-t_0)/\tau}) \;\rightarrow\; \sigma^2,$
- $Cov_x(t,T) \;=\; \langle [x(t) - m(t)][x(t+T) - m(t+T)] \rangle \;=$
  $= \sigma^2 e^{-|T|/\tau}\,(1 - e^{-2(t-t_0)/\tau}) \rightarrow \sigma^2 e^{-|T|/\tau}$

Ornstein-Uhlenbeck process
and …the Leaky Integrate-and-Fire?!???!?

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma\sqrt{2\tau}\;\xi(t)$$

$$C\;\frac{dV}{dt} \;=\; G\;(E - \;V) \;+\; I_{ext}$$

They look the same!

How do I... simulate it?

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma\sqrt{2\tau}\;\xi(t)$$

t

$\hat{x}(t) \quad \hat{x}(t+\Delta t) \quad \hat{x}(t+2\Delta t) \quad \hat{x}(t+3\Delta t) \;\ldots$

Ornstein-Uhlenbeck process - discrete time version

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma\sqrt{2\tau}\;\xi(t)$$

$$\hat{x}(t+\Delta t) = e^{-\Delta t/\tau}\;\hat{x}(t) \;+\; \mu(1-e^{-\Delta t/\tau}) \;+\; \sigma\sqrt{1-e^{-2\Delta t/\tau}}\;\Phi$$

- where $x(t)$ and $\hat{x}(t)$ have the same statistical properties (PDF, mean, var,…)
- where Φ is a (discrete sequence of) uncorrelated Gauss-distributed RVs, with zero-mean and unitary variance.
- Note: Δt is NOT required to be infinitesimal!

Ornstein-Uhlenbeck process - **wrong** discrete time ver.

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma \sqrt{2\tau}\; \xi(t)$$

$$\hat{x}(t + \Delta t) = e^{-\Delta t/\tau}\; \hat{x}(t) \;+\; \mu(1 - e^{-\Delta t/\tau}) \;+\; \sigma\sqrt{1 - e^{-2\Delta t/\tau}}\; \Phi$$

is **NOT** the Euler version of the o.d.e!!!

$$\cancel{\hat{x}(t + \Delta t) \approx \hat{x}(t) \;+\; \frac{\Delta t}{\tau}(\mu - \hat{x}(t)) \;+\; \frac{\Delta t}{\tau}\; \sigma\sqrt{2\;\tau}\; \Phi}$$

- With Euler, $x(t)$ and $\hat{x}(t)$ do **NOT** have the same statistical properties.
- Making Δt smaller and smaller, things should **NOT** change, right?
- With that Euler *abomination* things would depend on how you choose Δt !

Ornstein-Uhlenbeck process - discrete time version

$$\hat{x}(t + \Delta t) = e^{-\Delta t/\tau}\; \hat{x}(t) \;+\; \mu(1 - e^{-\Delta t/\tau}) \;+\; \sigma\sqrt{1 - e^{-2\Delta t/\tau}}\; \Phi$$

When Δt is set to be very small, by Taylor expansion… $e^{-\Delta t/\tau} \approx 1 \;-\; \frac{\Delta t}{\tau}$

$$\hat{x}(t + \Delta t) \approx \hat{x}(t) \;+\; \frac{\Delta t}{\tau}(\mu - \hat{x}(t)) \;+\; \sigma\sqrt{2\;\frac{\Delta t}{\tau}}\; \Phi$$

$$\hat{x}(t + \Delta t) \approx \hat{x}(t) \;+\; \frac{\Delta t}{\tau}(\mu - \hat{x}(t)) \;+\; \frac{\boxed{\sqrt{\Delta t}}}{\tau}\sigma\sqrt{2\;\tau}\; \Phi$$

$$\cancel{\hat{x}(t + \Delta t) \approx \hat{x}(t) \;+\; \frac{\Delta t}{\tau}(\mu - \hat{x}(t)) \;+\; \frac{\boxed{\Delta t}}{\tau}\; \sigma\sqrt{2\;\tau}\; \Phi}$$

Proof - O.U. process - properties

$$\tau \frac{d}{dt} x(t) \; = \; \mu \; - \; x \; + \; \sigma\sqrt{2\tau} \; \xi(t)$$

- write the analytical solution for $x(t)$, assuming that $\xi(t)$ is a normal function: sum of two terms… or the convolution integral… bla bla bla bla…)
- OR … follow this short-cut: multiply both sides by $e^{t/\tau}$ and then integrate both sides as $\int_0^t dt'$

$$\tau e^{t/\tau} \frac{d}{dt} x(t) \; = \; \mu \; e^{t/\tau} - \; x \; e^{t/\tau} + \; \sigma\sqrt{2\tau} \; e^{t/\tau}\xi(t)$$

$$\tau e^{t/\tau} \frac{d}{dt} x(t) \; + x \; e^{t/\tau} = \; \mu \; e^{t/\tau} \; + \; \sigma\sqrt{2\tau} \; e^{t/\tau}\xi(t)$$

$$\tau \frac{d}{dt} (e^{t/\tau} x(t)) = \; \mu \; e^{t/\tau} \; + \; \sigma\sqrt{2\tau} \; e^{t/\tau}\xi(t)$$

$$\tau (e^{t/\tau} x(t) - x_0) = \; \mu\tau \; (e^{t/\tau} - 1) \; + \; \sigma\sqrt{2\tau} \; \int_0^t e^{t'/\tau}\xi(t')dt'$$

Proof - O.U. process - properties

$$\tau (e^{t/\tau} x(t) - x_0) = \; \mu\tau \; (e^{t/\tau} - 1) \; + \; \sigma\sqrt{2\tau} \; \int_0^t e^{t'/\tau}\xi(t')dt'$$

$$x(t) \; = \; x_0 \; e^{-(t-t_0)/\tau} \; + \; \mu \; (1 - e^{-(t-t_0)/\tau}) \; + \; \sigma\sqrt{2\tau} \; \int_0^t e^{-(t-t')/\tau}\xi(t')dt'$$

- Now you can (simply!) use this expression for $x(t)$ to evaluate the mean, the variance, and the covariance.
- You remember that $\xi(t)$ has very specific statistical properties (mean, variance, covariance, PDF) and remember that $\langle \ldots \rangle$ is a *linear* operator and therefore you can swap it with the sing of integral and with the *product by a deterministic quantity.*

Stein process - definition

- is a continuous-time, continuous-valued stochastic process (of time)
- I define it, through an ordinary differential equation as

$$\tau \frac{d}{dt} y(t) \;=\; -\; y \;+\; \tau J \sum_k \delta(t - t_k) \qquad \text{with } y(t_0) = y_0$$

(deterministically)

- There is an (exponentially) decaying term and a *shot-noise* term (deja-vu?!)

- By using that specific definition, *around* t_k, the *jump* is $y(t_k^+) = y(t_k^-) + J$

Stein process - definition

- $\{t_k\}$ are sequences of RVs in time (called technically a **point process**).
- I require that *renewal* property is satisfied, i.e. the occurrence of an *event* is <u>independent</u> on the previous history:

$$Prob\{an\ event\ in[t; t + dt]\} = \lambda dt + O(dt)$$

λ as unit of 1/time, and it represents the *rate* of occurrence of the *events.*

- When λ does not change over time, then $\{t_k\}$ is called **homogeneous** Poisson Point process.
- The RVs defined as the *inter-event* intervals $\{T_k\}$, $T_k = t_k - t_{k-1}$ have a PDF that is an *exponential* function $\lambda e^{-\lambda T}$.

Stein process
and …the eq. for tot. synaptic currents?!???!?

$$\tau \frac{d}{dt} y(t) \;=-\; y \;+\; \tau J \;\sum_k \delta(t - t_k)$$

$$\frac{dI_{syn\ i}}{dt} \approx -\beta I_{syn\ i} \;+\; \sum_j C_{ij}\; W_{ij} \;\sum_{k_j} \delta\left(t - t_{k_j}\right)$$

They look the same!

Stein - Let's integrate both sides of the o.d.e

$$\tau \frac{d}{dt} y(t) \;=-\; y \;+\; \tau J \;\sum_k \delta(t - t_k)$$

$$\tau \int_0^t \frac{d}{dt} y(t) dt \;=-\; \int_0^t y\; dt + \;\tau J \;\int_0^t \sum_k \delta(s - t_k) ds$$

$$y(t) = \; y_0 \;-\; \frac{1}{\tau}\int_0^t y\; dt + \;J \;\boxed{\int_0^t \sum_k \delta(s - t_k) ds}$$

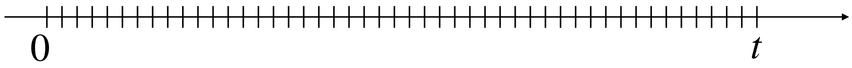
$$N(t) \;= \boxed{\int_0^t \sum_k \delta(s - t_k) ds}$$

At every moment in time, $N(t)$ is an integer number, a RV distributed according to a Poisson distribution. It counts how many *events* occurred since t = 0.

Let's study …the monster!

$$N(t) = \boxed{\int_0^t \sum_k \delta(s - t_k) ds}$$

$M = t/dt$ bins



$$Prob\{an\ event\ in[t; t + dt]\} = \lambda dt + O(dt)$$

$$Prob\{N\ events\ in[0; t), i.e.\ over\ M\ bins\} = \binom{M}{N} (\lambda dt)^N (1 - \lambda dt)^{M-N}$$

$$\binom{M}{N} = \frac{M!}{(M-N)!N!}$$

$$\langle N(t) \rangle = M\ \lambda dt = t\lambda$$

$$\langle N(t)^2 \rangle - (\langle N(t) \rangle)^2 = M\ \lambda dt (1 - \lambda dt) = t\lambda(1 - \lambda dt)$$

Note: We should anyway remember to go back to continuous time! We exploit the known fact that as $dt \to 0, M \to +\infty$, the Binomial distribution → Poisson. Now, Poisson →Gaussian, but only if $N \to +\infty$ (i.e. $\lambda \to +\infty$).

O.U. - Let's integrate both sides of the o.d.e

$$\tau \frac{d}{dt} x(t) = \mu - x + \sigma\sqrt{2\tau}\ \xi(t)$$

$$\tau \int_0^t \frac{d}{dt} x(t) dt = \int_0^t \mu\ dt - \int_0^t x dt + \sigma\sqrt{2\tau} \int_0^t \xi(s) ds$$

$$x(t) = x_0 - \frac{1}{\tau} \int_0^t x dt + \boxed{\frac{\mu}{\tau} t + \frac{\sigma}{\tau}\sqrt{2\tau} \boxed{\int_0^t \xi(s) ds}} \qquad a + bW(t)$$

$$y(t) = y_0 - \frac{1}{\tau} \int_0^t y\ dt + J \int_0^t \sum_k \delta(s - t_k) ds$$

$$W(t) = \boxed{\int_0^t \xi(s) ds}$$

At every moment in time, $W(t)$ is <u>**gaussian**</u> distributed continuous-time, continuous-valued process, called Wiener's process. It has *zero* mean and variance *t*.

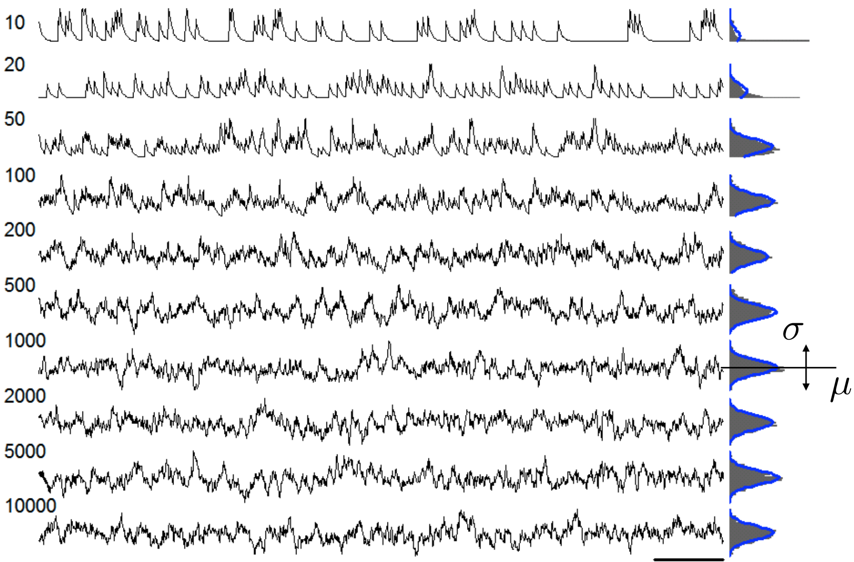
The *diffusion* approximation

$$\tau \frac{d}{dt} x(t) \;=\; \mu \;-\; x \;+\; \sigma\sqrt{2\tau}\;\xi(t)$$

$$\tau \frac{d}{dt} y(t) \;=\; -\; y \;+\; \tau J \;\sum_k \delta(t - t_k)$$

The *diffusion* approximation

$$\mu = J\ \lambda\tau$$
$$\sigma = J\ \sqrt{\lambda\tau/2}$$



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Stein vs O.U.

$$y(t_0) = y_0 = x_0 = x(t_0)$$

Poisson

$$y(t) = y_0 - \frac{1}{\tau}\int_0^t y\, dt + \boxed{J\, N(t)}$$

$J\, t\, \lambda$
mean

$J^2\, t\, \lambda$
variance

Weiner's process (Gaussian)

$$x(t) = x_0 - \frac{1}{\tau}\int_0^t x\, dt + \boxed{\frac{\mu}{\tau}\, t + \frac{\sigma}{\tau}\sqrt{2\tau}\, W(s)}$$

$\frac{\mu}{\tau}\, t$
mean

$2\frac{\sigma^2}{\tau} t$
variance

$$J\, \lambda = \frac{\mu}{\tau}$$

$$J^2\, \lambda = 2\frac{\sigma^2}{\tau}$$

$$\boxed{\mu = J\, \lambda\tau \qquad \sigma^2 = \frac{1}{2}J^2\, \lambda\tau}$$

Warning: This makes sense only when Poisson → Gaussian, but this is only if $N \to +\infty$ (i.e. $\lambda \to +\infty$).

Therefore only when $J \to 0$, the term $J\lambda$ remain finite.