Stochastic neuronal models

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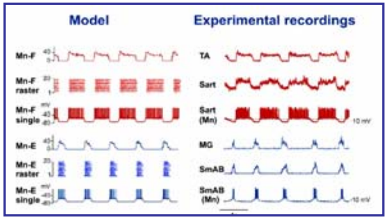

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Summary

- Basic Introduction to Neurosciences
  - Structure and function of the nervous system
  - Elements of Neuroanatomy
  - Neuronal signals
- Mathematical models for single units
  - Aims of models
    - First models
    - Hodgkin and Huxley type models
    - Stochastic models
- Mathematical methods and related problems
- Usefullness of single neuron activity models
- Models for assemblies of neurons
  - Aims of the models
    - Models of jump diffusion type
  - Mathematical methods and related problems
  - Alternative approaches and new researches topics

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Different mathematical approaches correspond to different models aims

- Focus on the membrane potential evolution,
- Focus on the neuronal coding properties
  - Most of the relavant information is contained in the mean firing rate

Interspike intervals as a code of the nervous system

Related problems:

Description of Interspikes Intervals
Measures of the Information contained in the ISIs
Statistical estimations of the most important model parameters

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Lapique model

- Deterministic theories
  - Equilibrium voltages

$$V_K = \frac{RT}{F}\ln\left(\frac{[K]_e}{[K]_i}\right) \qquad \text{Nernst law}$$

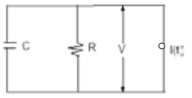
$$V = \frac{RT}{F}\ln\left(\frac{P_K[K]_e + P_{Na}[Na]_e + P_{Cl}[Cl]_e}{P_K[K]_i + P_{Na}[Na]_i + P_{Cl}[Cl]_i}\right)$$

P_Permeability

  - Lapique model (1907)

Describes the underthreshold membrane potential evolution.

$$C\frac{dV(t)}{dt} + \frac{V(t)}{R} = I(t)$$



1957: Eccles gives experimental values for C and R.

A threshold condition should be imposed

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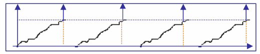
Lapique model

$$V(t) = e^{-t/RC}\left[\int_0^t \frac{I(s)}{C} e^{s/RC} ds + k\right]$$

- Lapique model: any initial value
V(0) decays exponentially

- Assuming R= ∞
  PERFECT INTEGRATOR MODEL

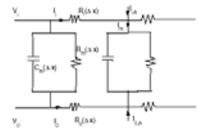
$$V(t) = V(0) + \frac{1}{C}\int_0^t I(s) ds.$$



Remarks:
1. It is a non linear model
2. The output train is completely described by the sequence t_i, times at which action potentials occur
1. It is a point model: the entire cell is lumped together into a representative circuit.
2. Mathematically: it implies the study of first order differential equations in correspondence of different input current stimula.
   - Suthreshold response to current steps or to repetitive excitation
   - Condition for firing under different stimulations, strengh-duration curve
   - Stability analysis and phase diagram

Linear cable models

- Lapique model: disregards the neuronal structure
- Synapses close to the soma are more effective compared to those with the same strengh on distal parts of the dendritic tree.
- Integration effect of various inputs may vary the neuron response
- **Linear cable models**: account for the geometry of the cell in subthreshold regime
  - Variou portions of the dendritic tree and of the axon are regarded as passive nerve cylinders and equations for the electrical potential are the partial differential equations of the cable theory



$$r_m c_m \frac{\partial V}{\partial t} = \frac{r_m}{r_i}\frac{\partial^2 V}{\partial x^2} - V + r_m I_A \qquad a \le x \le b, t > 0$$

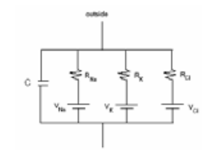
A theorem allows to solve only one equation in spite of several cable equations. Walsh and Tuckwell (1985)

Linear cable models

- Remarks
  1. It is necessary to perform a **selection of boundary conditions** between several choices (voltage clamp,killed end, current injection at the end,…)
  2. **Steady state solutions** describe the effect of a current applied for a sufficient long time
  3. The model holds only for **subthreshold respenses**. For stronger responses the membrane conductance changes too much to allow the hypothesys of passive nature of nerve cylinders. A threshold condition must be added.
  4. Mathematically:
     - **Second order linear differential equations** to describe steady- state response (current applied for a sufficiently long time): allow to get quick insights into the effect of various input patterns
     - **Solution of partial differential equations** to obtain time-dependent behaviors (Green function method)

Hodgkin Huxley type models

- The **Hodgkin-Huxley model** is a scientific model that describes how action potentials in neurons are initiated and propagated. It is a *set of nonlinear ordinary differential equations* that approximates the electrical characteristics of excitable cells



- The major achivement in the experiments perfomed by Hodgkin Huxley and Kats (1952) was the division of the current into the components capacitive and ionic currents, so that for asmall patch of membrane the total current is

$$I = C\frac{dV}{dt} + I_i \qquad I_i = I_k + I_{Na} + I_l$$

Leakeage current carried by other ions

Hodgkin Huxley type models

- Replacing the RC circuits in the cable model representing patches of membrane by the HH type circuits we obtain the **full Hodgkin Huxley system**

$$
\begin{aligned}
C_m \frac{\partial V}{\partial t} &= \frac{a}{2\rho_i}\frac{\partial^2 V}{\partial x^2} + \overline{g}_K n^4 (V_K - V) + \overline{g}_{Na} m^3 h (V_{Na} - V) + g_l (V_l - V) + I,\\
\frac{\partial n}{\partial t} &= \alpha_n (1-n) - \beta_n n,\\
\frac{\partial m}{\partial t} &= \alpha_m (1-m) - \beta_m m,\\
\frac{\partial h}{\partial t} &= \alpha_h (1-h) - \beta_h h,
\end{aligned}
$$

Describes both suprathreshold and subthreshold dynamics

C_m : membrane capacitance per unit area
$g_{Na}\, g_K,\, g_l$: conductances
m: sodium activation
h: sodium inactivation
ρ_i : intracellular resistivity
I: applied current per unit area
n: potassium activation
a: fiber radius

Mathematically: their study is very difficult due to nonlinearities and to the high number of involved variables

Stochastic models for neuronal activity

Basic assumptions:

- the input current I is a random process, i.e. $\{I_t, t \geq 0\}$ is a family of r.v. parametrized by the index t, then V_t is a random process too, related to I
- The action potential occur when V_t exceeds a threshold S=S(t).
- Usually after an action potential follows an absolute refractory period of duration t_R, and after the membrane potential is reset to V_0.
- The first interspike interval corresponds to the first passage time r.v.

$$T=\inf\{t \geq 0:\ V_t \geq S(t)\}.$$

- The r.v. $T_1, \ldots, T_n$ are i.i.d. (i.e. the process is a renewal process)
- Different hypotheses about the process V_t and the boundary S give different models

Aim of these models

- Theoretically describe input-output relationships
  - For neurons under spontaneous activity
  - For neurons stimulated by specific inputs
  - Investigate neuronal coding rules (in a model the input can be specified while in experiments is often unknown or noisy)
    - Information transmission mechanisms
    - Reliability of the transmission
    - Phenomena involved in an optimization of the transmission

Poisson process and input events

- We can mimic the input-output relationships exhibited by certain biological neurons under suitable assumptions on the input process
  - It is customary to assume Poisson processes as approximation of the input event sequences when the number of synapses involved in the transmission is high enough

Motivation for the Poisson hypothesis:

- The membrane potential is continuos in time even during the action potential but if we believe that the information is carried by the time of the spike we can extract the sequence of interspike times (a spike is read as an event)
- If there are n_E excitatory channels and n_i inhibitory channels the total input sequence is a superposition of $n = n_E + n_I$ point processes that we approximate with a Poisson process thanks to the following theorem

…A theorem

Theorem 0.2 (Franken(1963), Grigelionis(1963), Cinlar(1972)) *Let $(M_i)_{i=1}^{\infty}$ a sequence of point processes such that*

i) *$\forall k$, $M_{i_1}, \dots, M_{i_k}$ are mutually independent;*

ii) *for any bounded B*

$$\lim_{k\to\infty} \sup_{1\le i\le k} \mathbb{P}(M_i(B) \ge 1) = 0.$$

Then the superposition process $S_k = M_1 + \dots + M_k$ converges weakly (finite dimensional distributions convergence) for $k \to \infty$ to a Poisson process with mean measure μ if and only if for any bounded B

$$\lim_{k\to\infty} \sum_{i=1}^{k} \mathbb{P}(M_i(B) = 1) = \mu(B)$$

$$\lim_{k\to\infty} \sum_{i=1}^{k} \mathbb{P}(M_i(B) \ge 2) = 0.$$

$\rightsquigarrow$ we can appeal Theorem (0.2) to justify the use of Poisson processes to approximate the arrival times of synaptic inputs.

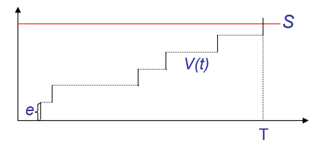
Stochastic models: Perfect Integrator

Simplest model: Perfect Integrator without inhibition

input process

$$\{N(t), t > 0\} \sim \text{Poisson}(\lambda)$$

$$N(0) = 0 \qquad V(t) = eN(t)$$



$$g_T(t) = \begin{cases} 0 & t < t_R \\ \frac{\lambda(\lambda(t-t_R))^{n-1}}{(n-1)!} e^{-\lambda(t-t_R)} & t > t_R \end{cases} \qquad n = \lceil S/e \rceil$$

Spontaneous decay and inhibitory inputs are disregarded

Stochastic models: randomized random walk 1/2

Gerstein (1962) and Gerstein and Mandelbrot (1964)

Very simple model: it allows to determine analytical results (birth and death process)

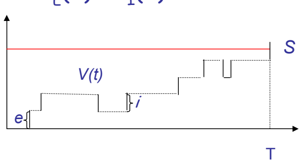
- Consider both inhibitory and excitatory Poisson time distributed inputs of parameters λ_E and λ_I respectively:

  $V(t)=N_E(t)-N_I(t)$; $\qquad N_E(0)= N_I(0)=0$

e=-i=1 in absence of boundary:

$$p_m(t) = \left(\frac{\lambda_E}{\lambda_I}\right)^{m/2} e^{-(\lambda_E+\lambda_I)t} I_m\left(2t\sqrt{\lambda_E\lambda_I}\right)$$

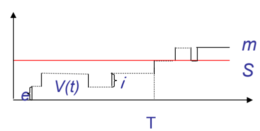
Modified Bessel functions



Stochastic models: randomized random walk 2/2

Gerstein (1962) and Gerstein and Mandelbrot (1964)

Renewal equation



$$p_m(t) = \int_0^t g_T(\tau)\, p_{m-S}(t-\tau)\, d\tau \qquad 0 < S < m$$

1. Solution (through Laplace transform)

$$g_T(t) = S\left(\frac{\lambda_E}{\lambda_I}\right)^{S/2} \frac{e^{-(\lambda_E+\lambda_I)t}}{t} I_S\left(2t\sqrt{\lambda_E\lambda_I}\right)$$

2, Moments

$$\mathbb{E}(T) = \frac{S}{\lambda_E - \lambda_I}, \qquad \text{Var}(T) = \frac{S(\lambda_E+\lambda_I)}{(\lambda_E-\lambda_I)^3} \qquad \lambda_E > \lambda_I$$

3. Probability to elicite a spike

$$\mathbb{P}(T < \infty) = \begin{cases} 1 & \lambda_E \ge \lambda_I \\ (\lambda_E/\lambda_I)^S & \lambda_E < \lambda_I \end{cases}$$

Stein's model 1/2

(Stein 1965)

Extends the randomized random walk to include the spontaneous decay of the membrane potential

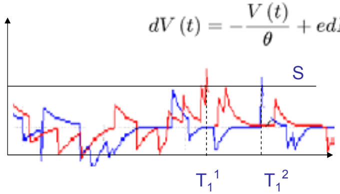
$$V(t) = V(t_0)\exp\left(\frac{t-t_0}{\theta}\right)$$

Underthreshold dynamic:

$$V(t) \longrightarrow V(t)+e$$
$$V(t) \longrightarrow V(t)+i$$

$$dV(t) = -\frac{V(t)}{\theta} + edN_E(t) + idN_I(t)$$

T= inf {t: X_t>S}



After each spike the membrane potential is reset to V_0:
Renewal process

Stein's model 2/2

(Stein 1965)

- Analytical results:
  - In **absence of threshold** it is possible to calculate mean depolarization and its variance

$$\begin{aligned}\mathbb{E}(V_t) &= V_0 e^{-t} + (e\lambda_E + i\lambda_I)(1-e^{-t}) \\ \mathrm{Var}(V_t) &= 1/2\,(e^2\lambda_E + i^2\lambda_I)(1-e^{-2t})\end{aligned}$$

    - As t → ∞ mean and variance approach steady state values in absence of a threshold
  - In presence of threshold
    - No closed form expression for the first passage time distribution is available (only available approach: simulations);
    - If $\lambda_E>0$ and e>0 the probability to attain the threshold in a finite time can be proven to be one;
    - In the case of pure excitation with ad hoc procedures one can compute ET and Var T.

Diffusion approximations

- Stein model: mathematically difficult due to the presence of discontinuities in the samples
  - Brownian motion: many closed form results. Mathematically more manageable than its discontinuos counterpart, the random walk
  - Idea: to determine a continuos approximation of the Stein model, i.e. a diffusion process for the process V_t

    We perform the following limit for n→ ∞, increasing the rates of the Poisson processes while the size of the jumps decrease:

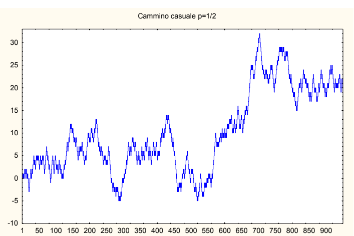
    $e_n \to 0$ $i_n \to 0$ $\lambda_n^E \to \infty$ $\lambda_n^I \to \infty$ in such a way to get:

    $\mu_n = e_n\,\lambda_n^E + i_n\,\lambda_n^I \to \mu < +\infty$ $\sigma_n^2 = e_n^2\,\lambda_n^E + i_n^2\,\lambda_n^I \to \sigma^2 < +\infty$

Diffusion limit: the Ornstein Uhlenbeck process

$$dV(t) = -\frac{V(t)}{\theta} + edN_E(t) + idN_I(t)$$

Stein model



Diffusion limit

- Convergence Kolmogorov eq.
  - Roy Smith, 1969
  - Capocelli Ricciardi, 1971
  - Tuckwell Cope, 1980
- Weak convergence
  - Lansky 1984
  - Lansky Lanska 1987
  - Kallianpur Wolpert, 1987

$$\begin{aligned} dV_t &= \left(-\frac{V_t}{\theta} + \mu\right) dt + \sigma dW_t \\ V_0 &= 0 \end{aligned}$$

Ornstein-Uhlenbeck process

Diffusion type models

the boundary is not naturally implied in the model

Underthreshold membrane potential time evolution

- Wiener process (Perfect Integrator)

$$\frac{\partial f}{\partial t}+\mu\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}\frac{\partial^2 f}{\partial x^2}=0 \Leftrightarrow dV_t=\mu dt+\sigma dW_t$$

- Ornstein- Uhlenbeck process (Leaky Integrate and Fire)

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}\frac{\partial^2 f}{\partial x^2}=0 \Leftrightarrow dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma dW_t$$

- Feller process (Leaky Integrate and Fire with inferior reversal potential)

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}(x-V_I)\frac{\partial^2 f}{\partial x^2}=0 \Leftrightarrow dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma\sqrt{X_t-V_I}dW_t$$

- Reversal potentials Leaky Integrate and Fire

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}(x-V_I)(x-V_E)\frac{\partial^2 f}{\partial x^2}=0 \Leftrightarrow dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma\sqrt{V_t-V_I}\sqrt{V_t-V_E}dW_t$$

Diffusion models (Wiener Process) 1/5

Consider the underthreshold membrane potential evolution

- due to the arrival of inhibitory (i<0) and excitatory (e>0) contributions the membrane potential can be described by a random walk with continuos time. Let $f(x,t|y,\tau)$ be the transition probability density, we have

$f(x,t+\Delta t\ |y,t) = [1-(\lambda_E+\lambda_I)\Delta t]\delta(x-y)+\lambda_E\Delta t\delta(x-(y+e))+\lambda_I\Delta t\delta(x-(y+i))$

Probability to have an excitatory input in $(t,t+\Delta t)$

Probability to have an excitatory input in $(t,t+\Delta t)$

Diffusion models (Wiener Process) 2/5

- It holds Smolukowsky equation (Markov process)

$$f(x,t+\Delta t\,|x_0,t_0)=\int f(x,t+\Delta t\,|y,t)\,f(y,t\,|x_0,t_0)\,dy$$

That in our case becomes

$$\begin{aligned} f(x,t+\Delta t\,|x_0,t_0) &= [1-(\lambda_E+\lambda_I)\Delta t]\int f(y,t\,|x_0,t_0)\,\delta(x-y)\,dy+ \\ &\lambda_E\Delta t\int f(y,t\,|x_0,t_0)\,\delta(x-(y+e))\,dy+ \\ &\lambda_I\Delta t\int f(y,t\,|x_0,t_0)\,\delta(x-(y+i))\,dy \end{aligned}$$

⇓

$$f(x,t+\Delta t\,|x_0,t_0)=[1-(\lambda_E+\lambda_I)\Delta t]\,f(x,t\,|x_0,t_0)+\lambda_E\Delta t f(x-e,t\,|x_0,t_0)+\lambda_I\Delta t f(x-i,t\,|x_0,t_0)$$

Diffusion models (Wiener Process) 3/5

- Subtract in the last equation $f(x,t|x_0)$ and divide by Δt, we get

$$\begin{aligned} \frac{f(x,t+\Delta t\,|x_0,t_0)-f(x,t\,|x_0,t_0)}{\Delta t} = &\lambda_E[f(x-e,t\,|x_0,t_0)-f(x,t\,|x_0,t_0)]+ \\ &\lambda_I[f(x-i,t\,|x_0,t_0)-f(x,t\,|x_0,t_0)] \end{aligned}$$

- In the limit $\Delta t\to 0$ and developing the square brackets inTaylor series:

$$\frac{\partial f}{\partial t} = \sum_{n=1}^{\infty}\frac{(-1)^n}{n!}[\lambda_E e^n-\lambda_I i^n]\frac{\partial^n f}{\partial x^n}$$

with

$$A_n = \lim_{\Delta t\to 0}\frac{1}{\Delta t}\int (x-y)\,f(x,t+\Delta t\,|y,t)\,dt=[\lambda_E e^n-\lambda_I i^n]$$

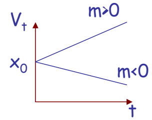
Diffusion models (Wiener Process) 4/5

- Different assumptions can be done in the limit $\Delta t \to 0$:

a. $e \to 0 \quad i \to 0 \Rightarrow \frac{\partial f}{\partial t} = 0$

b $A_1 = \lambda_E e - \lambda_I i = m \Rightarrow \frac{\partial f}{\partial t} = -m \frac{\partial f}{\partial x}$

$$\frac{dt}{1} = -\frac{dx}{m} = \frac{df}{0} \Rightarrow \begin{cases} x - mt = c_1 \\ f = c_2 \end{cases} \Rightarrow \begin{cases} c_2 = H(c_1) \\ f = H(x - mt) \end{cases}$$



+ Condiz. iniziale $f(x, t | x_0, t_0) = \delta(x - (x_0 - m(t - t_0)))$

c $\begin{cases} e = \lim_{\rho \to 0} k_e \rho \quad i = \lim_{\rho \to 0} k_i \rho \\ \lambda_E = \lim_{\rho \to 0} \frac{c_e}{\rho} \quad \lambda_I = \lim_{\rho \to 0} \frac{c_i}{\rho} \end{cases} \quad \lambda_E e = \lambda_I i; \; k_e = \frac{c_i}{c_e} |k_i|$

$A_1 = 0 \; A_2 = \sigma^2 \; A_j = 0 \quad j = 3, 4, \ldots \Rightarrow$

$$\frac{\partial f}{\partial t} = \sigma^2 \frac{\partial^2 f}{\partial x^2}$$

Diffusion models (Wiener Process) 5/5

- Alternative choices for the parameter relationships give:

$$\frac{\partial f}{\partial t} = \sigma^2 \frac{\partial^2 f}{\partial x^2} + \mu \frac{\partial f}{\partial x};$$
$$\lim_{\Delta t \to 0} f(x, t + \Delta t | y, t) = \delta(x - y)$$

Kolmogorov equation for the Wiener Process with drift μ

- While inserting the membrane potential spontaneous exponential decay in absence of external input one gets the Ornstein-Uhlenbeck process

$$\frac{\partial f}{\partial t} = \sigma^2 \frac{\partial^2 f}{\partial x^2} + \left(-\frac{x}{\theta} + \mu\right) \frac{\partial f}{\partial x};$$
$$\lim_{\Delta t \to 0} f(x, t + \Delta t | y, t) = \delta(x - y)$$

Randomized random walk 1/2

Let
$$N(t) = N_E(t) + N_I(t) \sim Poisson(\lambda)$$
and indicate
$$p_m(t) = P(V(t) = m | V(0) = 0) \; . \; m = 0, \pm 1, \ldots.$$
We have:
$$P(V(t + \Delta t) - V(t) = 1 | N(t + \Delta t) - N(t) = 1) = \frac{\lambda_E}{\lambda} + o(\Delta t) \doteq p$$
$$P(V(t + \Delta t) - V(t) = -1 | N(t + \Delta t) - N(t) = 1) = \frac{\lambda_I}{\lambda} + o(\Delta t) \doteq q.$$
with $p + q = 1$ and

Randomized Random Walk 2/2

Hence we have:

$$P(V(t) = m | n \text{ events in } (0, t]) = \binom{n}{n_1} p^{n_1} q^{n - n_1} = \binom{n}{(m+n)/2} p^{(m+n)/2} q^{(n-m)/2}$$

Applying the law of total probability we get:

$$p_m = P(V(t) = m) = \sum_{n \geq m} P(V(t) = m | n \text{ events in } (0, t]) P(n \text{ events in } (0, t]) =$$
$$= e^{-\lambda t} \sum_{n=m}^{\infty} \binom{n}{(m+n)/2} p^{(m+n)/2} q^{(n-m)/2} \frac{(\lambda t)^n}{n!} \binom{n}{(m+n)/2} p^{(m+n)/2} q^{(n-m)/2} =$$

where the sum is other either even or odd n. Since $n = m, m+2, ..$implies $n_2 = 0, 1, 2, ..,$ recalling the definition of the modified Bessel functions

$$I_k(x) = \sum_{j=0}^{\infty} \frac{1}{k! \Gamma(k + j + 1)} \left(\frac{x}{2}\right)^{2j+k}$$

we have

$$p_m = \left(\frac{\lambda_E}{\lambda_I}\right)^{m/2} I_m\left(2t\sqrt{\lambda_E \lambda_I}\right)$$