
Molecular Na–channel excitability from statistical physics

L. RAMÍREZ–PISCINA¹ and J.M. SANCHO²

¹ *Departament de Física Aplicada, Universitat Politècnica de Catalunya
Avinguda Doctor Marañón, 44. E-08028 Barcelona. Spain*

² *Universitat de Barcelona, Departament d'Estructura i Constituents de la Matèria
Martí i Franqués, 1. E-08028 Barcelona. Spain*

PACS 05.10.Gg – Stochastic analysis methods
PACS 87.16.Vy – Ion channels
PACS 87.15.A- – Theory, modeling, and computer simulation

Abstract – The excitable properties of the neural cell membrane is the driving mechanism of the neural pulses. Coordinated ionic fluxes across Na and K channels are the devices responsible of this function. Here we present a simple microscopic physical scenario which accounts for this phenomenology. The main elements are ions and channel doors that obey standard formulation of statistical physics (overdamped Langevin equations) with appropriate nonlinear interacting potentials. From these equations we obtain the ionic flux and the dynamics of the membrane potential. We show that the excitable properties of the membrane are present in a single and simple Na channel. From this framework, additional microscopic information can be obtained, such as statistics of single channels dynamics or the energetics of action potential events.

Introduction. – Experimental understanding of biological electrical processes in the cell membrane during the action potential has much progressed during the last 60 years, mainly fostered by the seminal works by Hodgkin and Huxley [1]. They performed extensive experiments on the giant squid axon, and constructed a mathematical model that has constituted since then the basis for the interpretation of the behaviour of nerve and cardiac cells. According to the Hodgkin-Huxley [HH] model, action potential is produced by coordinated ionic fluxes crossing the cell membrane, which acts as a capacitor. Then the excitable characteristics of the membrane action potential is the result of a dynamical coupling between the ionic flux, the membrane conductance and the electrostatic potential [1].

It is now also well known that ions flow along some biochemical molecules (channels) embedded in the cell membrane. These channels present two main structural conformations (open and closed), with transitions between these two states controlled by the membrane potential. Action potential is then known to be the result of the synchronized dynamics of a large number of ionic channels [2]. Moreover much quantitative physical information is also known on the dynamics of the distinct states of single ionic channels [3–6]. In particular experiments on single channels show very strong fluctuations in the intensity (pA,

i.e. a few charges in a microsecond) crossing the channel. As a result the observed stochastic behavior has become a active topic in recent studies.

Several theoretical scenarios have been used to address this stochastic phenomenology. Most of these approaches incorporate fluctuations in some of the elements of the HH theory, for instance by using Langevin [7–10] or master equations [11] for the conductance equations or noise terms in the equation for the membrane charge [12]. A more microscopic approach used Langevin equations for the ions with Poisson equation for the potential membrane [13] in order to obtain the effects of fluctuations on the membrane conductivity.

A microscopic modeling of the excitable dynamics of the action potential, treating channels and ions as physical objects, merits attention. This approach would allow for studying single channel excitable events, and to obtain additional information of some aspects of the action potential dynamics, such as energetic balances. It would also provide the influence of changes of different physical parameters (concentrations, temperature, etc) on the whole process, without the need of additional parameter fittings. Then one could address questions such as the minimum elements necessary to produce the action potential or whether the cooperative coupling of a large number of channels is necessary for excitability.

Our aim in this work is thus to place the action potential spikes within the framework of statistical physics to explain these phenomena at the microscopic level. We will propose a minimum model presenting the desired excitable behavior, and accordingly we will not try to get quantitative agreements with any particular cell type. As a result we expect our simplified model to be close to a very primitive channel, presumably much simpler than in modern organisms and containing the minimum set of elements that permit a *bona fide* excitability behavior.

In this paper we proceed first with the description of the Na channel and the physical elements that constitute our model. Next we present the numerical results for the excitable behavior of a single Na channel, and relate the excitable properties of the model to the physical mechanisms implicit in the classical HH theory. We will show that the minimum scenario to explain the excitable properties is a single gated Na channel in the presence of a leakage of K ions. We end with some conclusions and perspectives.

Microscopic physical approach and modelization.

Our approach consists of treating ions as Brownian particles, and channels as physical pores with mechanical doors that have two steady states (open and closed). All of them are driven by the membrane potential which also depends on the ionic flux. We will focus on the dynamics of a Na channel with two doors, whose states are defined by the variables Y_1 and Y_2 , that will evolve according to their respective dynamics controlled by the membrane potential ΔV . Our approach is then closely related with that of Ref. [13] but within a more simple scenario. The leak of K ions through the membrane will be modeled as an additional channel with effective parameters without doors.

Other relevant point for a microscopic description is that fluctuations should be relevant locally due to the very small number of charges involved and the fact that, although they move deterministically under the electrostatic force, they diffuse also by thermal noise. Following standard formulations of nonequilibrium statistical mechanics, the main variables of the model follow overdamped Langevin equations with their corresponding potential energies and thermal noises. The system is autonomous, and the only source of energy is the Gibbs energy associated with the ionic concentrations and the membrane potential. In this way the model is also able to give information about the energetics of any excitable event. In this formulation, the model parameters and other characteristics can be related to biological experimental information.

To make explicit our microscopic approach we will formulate our approach following the following assumptions:

(i) The first assumption is the use of the capacitor equation for the membrane potential ΔV ,

$$-C_M \frac{d\Delta V}{dt} = I_{Na} + I_K + I_0, \quad (1)$$

where C_M is the membrane capacity assumed to be con-

stant and adjusted to a single Na channel. The intensities I_{Na} , and I_K correspond to the flux of Na and the leak of K ions. I_0 is a perturbative current pulse that will trigger the spike. This equation will be integrated as

$$\Delta V(t + \Delta t) = \Delta V(t) - \frac{\Delta Q(Na^+) + \Delta Q(K^+)}{2C_M}, \quad (2)$$

where $\Delta Q(Na^+)$ and $\Delta Q(K^+)$ are the balance of charges crossing any of the channel boundaries during the interval of time Δt which are obtained from the trajectories of ions. The divisor “2” takes into account that charges cross both boundaries of the channel (then being counted twice) when crossing the membrane from one side to the other one.

(ii) The second assumption has to do with the calculation of the ionic flux. Ions inside the channel are described by point-like particles with electrical charge $+q$ moving in one dimension. Their positions $x_i(t)$ obey overdamped Langevin equations, $\gamma_i \dot{x}_i = -\partial_{x_i} U + \xi_i(t)$, where γ_i is the effective friction and $\xi_i(t)$ is a thermal noise of zero mean and intensity $\gamma_i k_B T$. The interaction potential U is the addition of the interactions with the doors (see below) and the electrostatic membrane potential $V_e(x_i, \Delta V)$,

$$V_e(x_i, \Delta V) = q \frac{\Delta V}{L} (x_i - L), \quad 0 < x_i < L. \quad (3)$$

This Langevin equation has to be complemented with boundary conditions of concentration values $\rho_0 = A c_{in}$ at $x = 0$ and $\rho_2 = A c_{out}$ at $x = L$, being A the effective section of the channel and $c_{in/out}$ the bulk ion concentration, interior and exterior to the cell respectively (note that any ion affinity of the pore could be accounted for by changing the value of A in these relations). Boundary conditions are implemented in the following way: ions disappear when hopping out of the channel due to their Brownian motion, and they appear into the channel according with a probability depending on the concentration at this boundary. There is no need of any explicit assumption about the form of the conductances, but nevertheless the fact that it is formulated consistently with statistical mechanics guarantees that this model evolves towards the correct steady state membrane potential without further parameters or fine tuning. That is, it provides the Nernst potential when a single ion species can cross the membrane, and the Goldman–Hodgkin–Katz theoretical prediction [14] when different ions compete. Note also that we are explicitly neglecting any ion-ion interaction inside the channel. This is justified by the small number of ions simultaneously present in the system and the screening of the aqueous medium.

(iii) The dynamical equations for the channel doors are the kernel of our approach. There is strong experimental evidence that the Na channel has two active doors or barriers [2], and that they open and close stochastically according to the value of the electrostatic membrane potential and thermal fluctuations [6]. This hypothesis

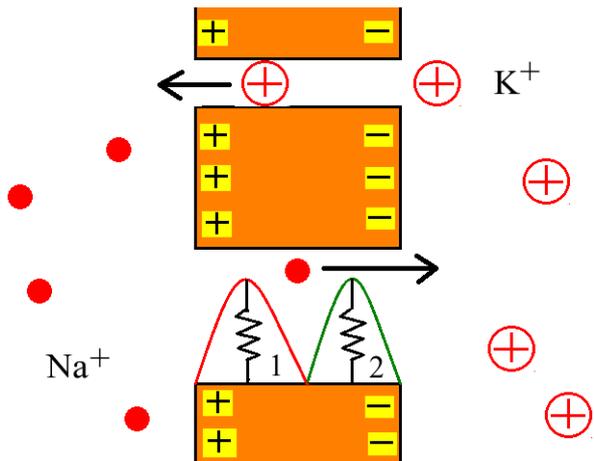


Fig. 1: Na channel model (bottom) with two doors (1,2) and the K pore (top). Arrows indicate the ion flux when the channels are open.

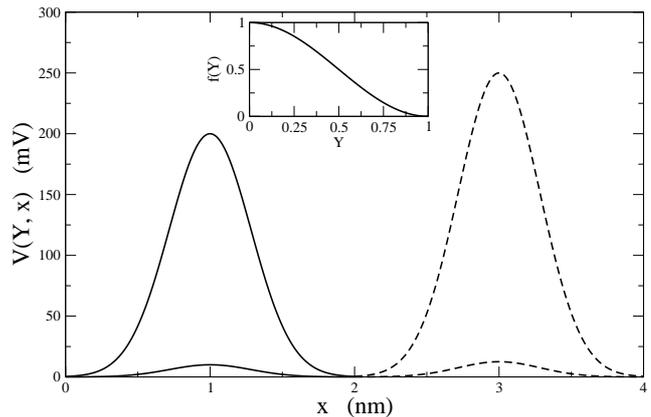


Fig. 2: Doors' energy barriers $V_I(Y_i, x)$ and positions. The maximum height is controlled by variable Y . Left: Door 1 at values $Y = 1$ and $Y = 0.05$ (small barrier). Right: Door 2 for the same Y -values. Inset: Envelope function $f(Y)$ (6).

145 and the use of Langevin equations are the original parts
 146 of our approach. Then we describe a channel door as a
 147 physical barrier controlled by the dimensionless variable
 148 Y which behaves as a nonlinear spring with two steady
 149 states: $Y \sim 0$ (closed) and $Y \sim 1$ (open). These door
 150 states are controlled by the elastic potential $V_j(Y_j, \Delta V)$
 151 ($j = 1, 2$), given by

$$V_j(Y_j, \Delta V) = V_0 [-a \ln(Y_j(1 - Y_j)) - b(Y_j - 0.5)^2] + Q_j(\Delta V - \phi_{ref})Y_j, \quad (4)$$

152 where Q_j is the charge of each door sensor and ϕ_{ref} is
 153 a reference potential. Their values are specific of each
 154 door, $Q_1 = 12 e$, $Q_2 = -8 e$, whereas we take common
 155 values for the other parameters: $V_0 = 7k_B T$, $a = 0.2$,
 156 $b = 9$, and $\phi_{ref} = -40$ mV. his potential presents two
 157 minima near $Y_i \sim 0, 1$ corresponding to the closed and
 158 open states respectively. These minima interchange their
 159 relative metastability by changing the value of ΔV . For
 160 smaller voltages the door 1 (2) is in the closed $Y_1 \sim 0$ (open
 161 $Y_2 \sim 1$) state, and for larger voltages we have the oposite
 162 behavior. At $\Delta V = -40$ mV both states are equally prob-
 163 able in both doors.

Since barriers are physical entities, when ions interact
 with them they interchange momentum and energy. Thus
 variables Y and x_i have to obey physical laws expressed
 in terms of dynamical (Langevin) equations constructed
 from a common potential. With this requirement the po-
 tential $V_I(Y, x_i)$ corresponding to the interaction between
 particles and internal barriers is modeled as

$$V_I(Y, x_i) = V_d f(Y) \exp\left(-\frac{(x_i - x_c)^2}{2\sigma^2}\right), \quad (5)$$

164 where V_d is the barrier height, x_c is the position of the
 165 barrier center inside the channel and σ is its width (see
 166 Fig. 2). The function $f(Y)$ modules the aperture of the
 167 doors according to the Y_j variables. The parameter values

for the two doors have been taken as $V_d(1) = 200$ meV,
 $V_d(2) = 250$ meV, $x_c(1) = 1$ nm, $x_c(2) = 3$ nm, and $\sigma =$
 0.283 nm.

For the modulated function $f(Y)$ in Eq. (5) we have
 taken the function,

$$f(Y) = \frac{1}{2}(1 + \cos \pi Y), \quad (6)$$

which has the values $f(0) = 1$ for the closed state, and
 $f(1) = 0$ for the open state, and has relative extrema at
 these points. This property reduces the sensitivity against
 thermal fluctuations of Y around the steady states.

Regarding the K leakage through the membrane, we
 consider the motion of K ions as equivalent to moving in
 an additional (K-selective) channel without any door, and
 with effective parameters. This provides a charge leakage
 that restores the membrane potential at the end of the ac-
 tion potential. Then we have not considered for K a gated
 channel in the spirit of the HH-theory (see below), since
 we are seeking a minimal model and as we will show such
 a gate is not necessary for excitability.

According to the former assumptions our approach has
 a set of equations that need to be numerically simulated.
 Our variables are the position x_i of the ions (Na and K)
 inside the channel, the Na channel doors Y_1 and Y_2 and
 the membrane electrostatic potential ΔV .

The whole system can be characterized by the potential
 energy,

$$U(x_i, \Delta V, Y_1, Y_2) = \sum_i V_e(x_i, \Delta V) + \sum_{i,j} V_I(Y_j, x_i) + \sum_j V(Y_j, \Delta V), \quad (7)$$

and accordingly the set of Langevin dynamical for our
 mechanical variables are,

$$\gamma_i \dot{x}_i = -\partial_{x_i} U(x_i, \Delta V, Y_1, Y_2) + \xi_i(t), \quad (8)$$

$$\gamma_{Y_1} \dot{Y}_1 = -\partial_{Y_1} U(x_i, \Delta V, Y_1, Y_2) + \xi_{Y_1}(t), \quad (9)$$

$$\gamma_{Y_2} \dot{Y}_2 = -\partial_{Y_2} U(x_i, \Delta V, Y_1, Y_2) + \xi_{Y_2}(t), \quad (10)$$

where thermal noises fulfill,

$$\langle \xi_a(t)\xi_b(t') \rangle = 2\gamma_a k_B T \delta_{a,b} \delta(t-t'). \quad (11)$$

193 Note that the first Langevin equation is for all ions:
194 both Na and K. The simulation of these equations deter-
195 mines the state of the doors and the trajectories of the
196 ions. The numbers of particles entering into and leaving
197 the channels through each boundary are used to evaluate
198 the potential ΔV through Eq. (2). The final output is
199 $\Delta V(t)$ which has to be compared with the known experi-
200 mental results.

γ_{Na^+} particle friction	$2 \mu s \text{ meV}/\text{nm}^2$
γ_{Y_1} door 1 friction	$1000 \mu s \text{ meV}/\text{nm}$
γ_{Y_2} door 2 friction	$4000 \mu s \text{ meV}/\text{nm}$
$K_B T$	25 meV
L channel length	4 nm
ρ_0^{Na}, ρ_1^{Na}	$0.01, 1.2 \text{ charges}/\text{nm}$
C_{eff} effective capacity	$1.25 \text{ charges}/\text{mV}$

Table 1: Physical parameter values used in the simulations for a single Na channel.

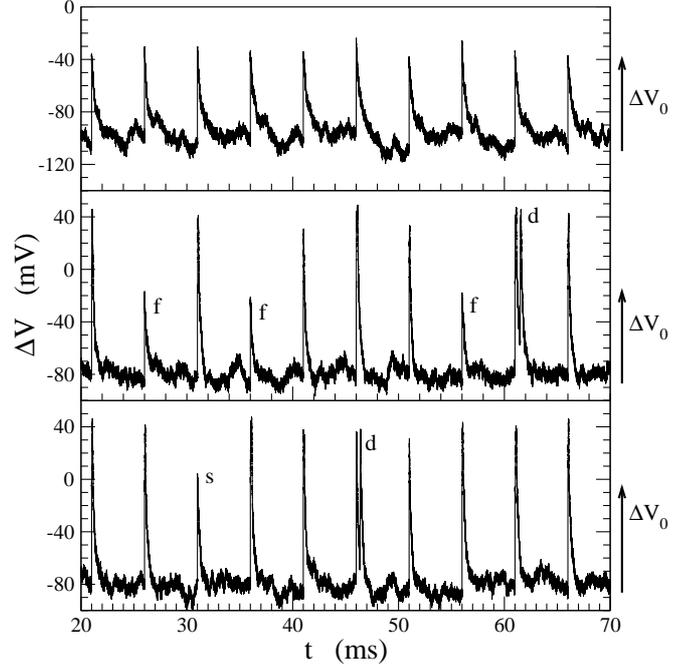


Fig. 3: Top: As an example we show the membrane potential when a set of small periodic depolarizing perturbations $\Delta V_0 = +70 \text{ mV}$ are applied on the membrane without the Na channel, as discussed in the text. Middle and bottom figures: membrane potential as a function of time, when pulses of $+70 \text{ mV}$ (middle) and $+80 \text{ mV}$ (bottom) are applied to the membrane with a single Na channel and the K leakage. Parameters values in Table I. Magnitude of ΔV_0 indicated in the plots.

201 **The excitable Na-K system.** – We have consid-
202 ered a single Na channel and the leak of K ions, and we
203 have simulated the whole system of equations (2) and (8)-
204 (11). The parameter values of the Na channel in Table
205 1 have been selected to fulfill the experimental observa-
206 tions [6]. For the K leakage the effective parameter val-
207 ues are: $\gamma_{K^+} = 200 \mu s \text{ meV}/\text{nm}^2$, and $\rho_0^K, \rho_1^K = 20, 0.36$
208 charges/nm, respectively.

209 More specifically, as in a real experiment, we follow
210 the dynamical evolution of the membrane potential when
211 small and instantaneous discharges ΔQ of positive ions,
212 corresponding to depolarizing voltage perturbations ΔV_0
213 of $+80$ or $+70 \text{ mV}$, are applied to the membrane with
214 a period of 5 ms . In Fig. 3 we show a typical time in-
215 terval with 10 of these perturbation events. In order to
216 show the characteristics of the perturbations, we show, on
217 top of this figure, how these pulses are seen when they
218 are applied to the membrane without the presence of the
219 Na channel, i.e. with only the K leakage. We see the ex-
220 pected response of the system as a sudden increase of ΔV_0
221 followed by a slow relaxation towards the steady value of
222 the membrane potential. We can also appreciate the size
223 of the voltage stochastic fluctuations.

224 In the middle and bottom figures we show the response
225 of the system under these perturbations. The middle
226 graph of the figure corresponds to perturbations equiv-
227 alent to instantaneous increases of ΔV of $+70 \text{ mV}$, and
228 the bottom graph to increases of $+80 \text{ mV}$. At each pertur-
229 bation event the value of the potential membrane $\Delta V(t)$
230 presents narrow and larger excursions towards positive val-
231 ues. This high increase is due to the fast flux of Na ions
232 into the cell when both channel doors are opened. Then

233 the door 2 of this channel closes suddenly and the out-
234 ward K-flux starts to restore the initial steady state of the
235 membrane potential but in a larger time scale. Although
236 most of the peaks are real excitable events (their height
237 are around two times larger than the perturbation), a few
238 of them have some imperfections. In the middle figure we
239 see some failed (f) or missing events when the Na channel
240 door Y_1 does not open, and double peaks (d) when door
241 2 opens again before the closing of door 1. Also at the
242 bottom graph we see small (s) pulses, in which the door
243 2 closes very fast and the channel has been active a very
244 short time. One appreciate that for pulses of $+70 \text{ mV}$
245 (middle graph) the number of errors is larger.

246 To describe more explicitly the dynamics of the model
247 during the action potential, we show in Fig. 4 a detailed
248 view of a single pulse (the 9th pulse in Fig. 3-bottom) with
249 numerical results for other observables. The top frame in
250 this figure is an amplification of the membrane potential,
251 the middle frame is the plot of the ionic intensities dur-
252 ing the same pulse, and in the bottom part we find the
253 evolution of the two Na channel doors, Y_1 and Y_2 . In
254 these frames we have marked five different times: t_0 is the
255 perturbative trigger time, where the potential is instan-
256 taneously increased in an amount $\Delta V_0 = 80 \text{ mV}$. This is
257 followed by the opening of door Y_1 at t_1 . Then at t_2 the
258 door Y_2 closes. In the interval (t_1, t_2) both Na channel

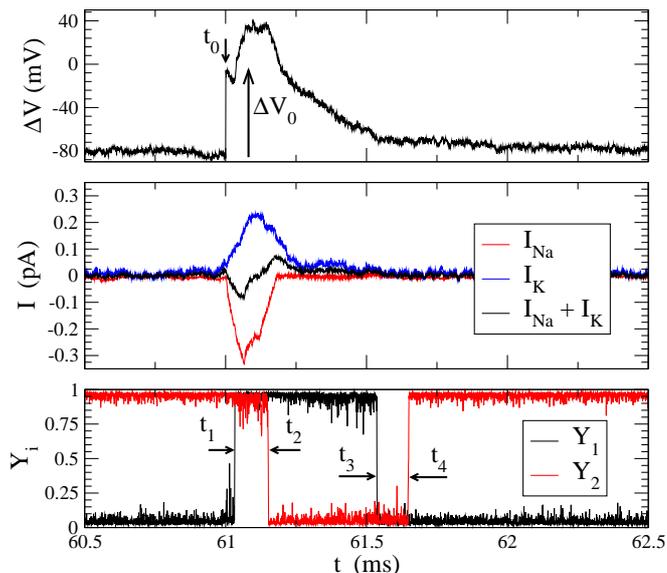


Fig. 4: Top: Detailed view of the 9th pulse of Fig. 3-bottom. Middle: Intensities across the membrane for Na and K channels. Bottom: Time evolution of the two doors Y_1 and Y_2 of the Na channel.

doors are open and Na ions enter into the cell producing the rise of the ΔV pulse. This is manifest in the middle figure where we see the corresponding inward (negative) Na intensity. This interval corresponds to the so-called open state [2]. After t_2 the Na flux is stopped, due to the closing of Y_2 , which corresponds to what is known as the inactivated state of the channel. Here an eventual additional perturbation would not induce any channel opening. Now K leak starts to dominate tending to restore the initial or standby state by an outward (positive) K intensity, as seen in the middle frame. Then at t_3 the Y_1 closes and at t_4 the Y_2 opens. The refractory time corresponds to the interval (t_2, t_4) when Y_2 remains closed. After t_4 the channel recovers the steady (excitable) closed state. In this figure we can also see the fluctuations of the door variables and their almost instantaneous transitions following the membrane potential. In the middle frame data of ion intensities have been filtered by using an averaging filter with a window of $62.5 \mu\text{s}$ to improve the signal from the sea of statistical fluctuations.

Thus our model exhibits some of the fluctuations and imperfections observed in experiments. These figures could be refined by further adjustment of the system parameters to a specific experiment, or by introducing a second kind of K-channel with a door, but the excitability properties of the model are clearly manifest.

It is interesting to relate the assumptions of this model to the main elements of the classical Hodgkin-Huxley theory. In this theory the crossing of ions through the membrane is described by time-dependent currents, representing the total of a large number of channels. These currents produce changes in the membrane potential according to

the capacitor equation. Our first assumption Eq. 1 is exactly this, but applied to discrete charges (ions) instead to currents. Moreover, according to HH, the charge intensity crossing many Na channels depends on the membrane potential according to a generic law,

$$I_{Na} = g_{Na}(t)(\Delta V - V_{Na}), \quad (12)$$

where V_{Na} is the Na Nernst potential and $g_{Na}(t)$ is the ionic conductance. Membrane conductances represent thus the average of the states of a large number of channels, each of them either open or closed. We have substituted this Ohm-type law by the Langevin dynamics of ions along a single channel. Nernst potential is not a parameter of our model, but instead it is reached automatically (in a single ion species situation) since it corresponds to the equilibrium state of our model. Analogously Goldman-Hodgkin-Katz law is verified in the steady state corresponding to more general situations.

Moreover in Eq. (12) the membrane conductance depends on other variables subjected to dynamical equations [1]. Namely this conductance depends on so called activation and deactivation functions m and h ,

$$g_{Na}(t) = \bar{g}_{Na} m^3(t) h(t), \quad (13)$$

where \bar{g}_{Na} is a constant. Activation and deactivation functions are interpreted in the context of our model as the average state of each of the two channel doors, *i.e.* of our variables Y_1 and Y_2 , for a large number of channels. The way these functions m and h are built is the kernel of the HH theory. They obey deterministic linear differential equations, chosen in such a way that each variables m , h have a single steady state that, depending on the value of ΔV , ranges continuously from 1 (all doors open) to 0 (all doors closed). On the contrary our variables Y_i , representing the doors of a single channel, present two steady state (open and closed) in such a way that a stochastic dynamics permits transitions between both states

The HH-theory includes K-channels with a different conductance (with a single door) and a ionic leakage. In our model we have only implemented the leak. The K-channel with door could be implemented in our model straightforwardly, but it has not been necessary for obtaining excitability.

As a result, both in the HH-theory and in our model, the coupling between potential and the channels state trigger a well synchronized temporal sequence of events, resulting in a sudden discharge of Na ions, the appearance of the spike and the K flux restoring the potential.

Conclusions and perspectives. – We have presented a microscopic physical approach to the excitable properties seen in neuronal cell membranes. The main points of our approach are: ions obey classical statistical equations of motion, channels are pores with doors whose dynamics are controlled by elastic nonlinear potentials, and the electrostatic potential of the cell

327 membrane follows the capacitor equation. Moreover,
 328 since it is constructed incorporating fluctuations accord-
 329 ing to fundamental statistical physics (namely according
 330 to fluctuation-dissipation theorem), it provides the correct
 331 statistical fluctuations of the diverse variables. This model
 332 can then be used to study the dynamics of a small num-
 333 ber of channels, and in particular it appears as specially
 334 suitable for analyzing single channel experiments. Note
 335 that in global measurements of real neural spikes a large
 336 number of channels are involved, and fluctuations will be
 337 smoothed out.

338 We have shown that a single Na channel in the presence
 339 of K leakage constitute an excitable system producing the
 340 characteristic spikes in the action potential. Our objective
 341 here was not to reproduce the exact form of the action
 342 potential for some specific channels or neurons but rather
 343 to formulate in terms of fundamental statistical mechanic
 344 laws the underlined physical mechanisms in this biomolec-
 345 ular process.

346 It is worth to comment about the model parameters
 347 and their specific values. All of them have a clear physical
 348 meaning. Ionic concentrations per length are fixed by the
 349 experimental densities and the estimated channel areas.
 350 Friction parameters are estimated from experimental time
 351 scales, and barrier heights are of order of a few $k_B T$ as
 352 it is expected in the biomolecular scale. Parameters of
 353 the doors and the function in Eq. (6) have been chosen
 354 to fix the door's steady states (open and closed) and their
 355 location inside the channel. Other parameters such Q_j
 356 and ϕ_{ref} are adjusted to enter in the experimental scale.
 357 Since their physical meaning is clear and they are used in
 358 physical dynamical equations the whole model lies within
 359 the framework of well founded physics.

360 This approach presents several perspectives worth to be
 361 explored:

- All model elements are described by standard phys-
 ical equations based on a single energy functional, and
 accordingly it is possible to address the energetics of an
 excitable event. Before and after a pulse the system is in
 the same thermodynamic state but several (few) charges
 have changed of reservoir: Δq_{Na} influx of Na and Δq_K
 outflow of K. Thus it is easy to estimate their loss of Gibbs
 energy,

$$\Delta G = \Delta q_{Na} g(Na) + \Delta q_K g(K), \quad (14)$$

362 where $g(Na), g(K)$ are the Gibbs energy per particle of
 363 Na and K ions.

364 - The approach allows for other channels and doors mod-
 365 elizations which could be related to different biochemical
 366 structures of the channel proteins. Each door would have
 367 specific effective parameters that can be estimated from
 368 appropriate experiments.

369 - The role of the ionic concentrations on the channel
 370 states has not been receiving so far enough experimental
 371 attention, but we have observed, in our simulations, im-
 372 portant sensitivity due to the ion-door collisions (in this
 373 regard see for instance Fig. 5 in Ref. [15]).

374 - Our approach allows to a new view, from statistical
 375 physics, of the well established Hodgkin-Huxley theory
 376 and other models based in it.

377 Finally, it is worth to remark that we have employed
 378 the minimum set of elements that results in the excitable
 379 dynamics observed in biological membranes. In this re-
 380 gard, it could also be seen as a modelization of hypothet-
 381 ical primitive channels, which presumably would be much
 382 simpler than present biological structures, which are the
 383 result of a long evolution and likely much more sophis-
 384 ticated. Thus our approach opens a complementary sce-
 385 nario to study ionic channel phenomenology from funda-
 386 mental physics.

387 This work was supported by the Spanish DGICYT
 388 Projects No. FIS2012-37655 and by the Generalitat de
 389 Catalunya Projects 2009SGR14 and 2009SGR921. We
 390 acknowledge fruitful discussions with Profs. J. García-
 391 Ojalvo, F. Giraldez and R. Vicente from Universitat Pom-
 392 peu Fabra.

REFERENCES

- 393
- [1] HODGKIN A.L., and HUXLEY A.F., *J. Physiol (Lond.)*, **117** 394
(1952) 500. 395
 - [2] ALBERTS B. and ET AL., *Molecular Biology of the Cell*, 4th 396
ed. (Garland Science, New York) 2002. 397
 - [3] SAKMANN B. and NEHER E., *Single-Channel Recording*, 398
2nd ed. (Plenum Press) 1995. 399
 - [4] HILLE B., *Ion Channels of Excitable Cells*, 3rd ed. (Sin- 400
auer) 2001. 401
 - [5] LEUCHTAG H. R., *Voltage-Sensitive Ion Channels: Bio- 402
physics of Molecular Excitability* (Springer) 2008. 403
 - [6] HAMMOND C., *Cellular and Molecular Neurophysiology*, 404
3th ed. (Academic Press) 2008. 405
 - [7] SCHMID G. and GOYCHUK I. and HÄNGGI P., *EPL*, **56** 406
(2001) 22. 407
 - [8] JUNG P. and SHUAI J. W., *EPL*, **56** (2001) 29. 408
 - [9] OZER M. and PERC M. and UZUNTARLA M., *EPL*, **86** 409
(2009) 40008. 410
 - [10] HUANG Y. and RÜDIGER S. and SHUAI J., *Phys. Rev. E*, 411
87 (2013) 012716 412
 - [11] GOLDWYN J. H. and IMENNOV N. S. and FAMULARE M. 413
and SHEA-BROWN E., *Phys. Rev. E*, **83** (2011) 041908 414
 - [12] HONG QIAN H. XUE-JUAN ZHANG X. J. and QIAN M., 415
EPL, **106** (2014) 1002. 416
 - [13] LUCHINSKY D. G. and ET AL. , *J. Stat. Mech.*, (2009) 417
P01010. 418
 - [14] GOLDMAN D.E., *J. Physiol (Lond.)*, **27** (1943) 37. 419
 - [15] HILLE B., *J. Gen. Physiol.*, **66** (1975) 535. 420