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Open Systems and Propagation of Chaos in Neuroscience

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Abstract

The voltage-gated ion channels system is an example of a classical open system. This work establishes conditions on open ion channel dynamics for which a modified Hodgkin-Huxley equation for the membrane voltage arises as propagation of chaos. This is the approach we propose in order to study the mesoscopic voltage-gated ion channel dynamics together with the macroscopic voltage equation.

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Introduction

A neuron is a type of cell found throughout the body, although most of the concentration of these are found in the brain. The cell body or soma is covered by a membrane which has, on both sides, ions, mainly: potassium (K^+), sodium (Na^+), calcium (Ca^{2+}), chloride (Cl^-) and negatively charged particles, denoted by A^- (anions). The concentration of ions on both sides of the membrane is different, which causes differences between internal and external electric charges. This situation leads to a diffusion of ions (but not A^-), which crosses the membrane through certain specific channels for each species called ion channels. The voltage or the membrane potential is defined as the difference between the internal and external charge of the membrane divided by the capacitance. Regarding the behavior of the voltage, we can identify 3 phases: depolarization, repolarization and after-potential hyperpolarization. In the depolarization, the voltage rises in the positive sense, first gradually to reach a threshold and then, abruptly, it is reversed. Inverted peak potential is called action potential (or spike), which is the only signal that propagates from the soma to the end of the axon. In the repolarization, the potential falls rapidly in a negative direction to a resting potential. In the after-potential hyperpolarization, the voltage is temporarily located at negative values in comparison to the resting potential. In this phase, the refractory period arises: a period in which the excitable cell cannot

respond to a stimulus.

Alan Hodgkin and Andrew Huxley, Nobel Prize winners in 1963, proposed in 1952 a deterministic macroscopic model to explain the underlying mechanism that generates these 3 phases. The model was generated from the circuit theory and experimental observations in a squid giant axon. They observed that the action potential, as well as the initiation, is mainly due to conductances of sodium and potassium channels (see [19]).

Through the years, there have been some stochastic versions of the Hodgkin-Huxley model (H-H model, for short) in order to explain the internal fluctuations in a neuron or its channel noise (see, e.g., [1], [14], [15] and [27]). In [1] and [27] the ion channels mechanism in the H-H model is presented as a limit jump Markov processes whose transition rates are coupled.

The current research goes further. Instead of these jump processes, it attempts to describe the mesoscopic dynamics of the voltage-gated sodium and potassium channels together with the macroscopic voltage variation, where such dynamics are represented by nonlinear stochastic differential equations.

Due to the underlying noise at that level, the paradigm of open system arises: the dynamics involved must consider an added noise, which represents the interaction with the rest (reservoir) or the environment. That is, the natural object that we are interested in analyzing cannot be considered inseparable from its own movement and then, the influence of the environment makes our phenomenon inherently stochastic.

The ideal model we propose, under suitable assumptions, can be recovered as a limit of interacting particle systems, property known as Propagation of Chaos (see,

e.g., [30], [6], [31], for uses/applications).

Regarding the statistical tools used in this framework, in [19] they employed Boltzmann's principle in order to represent the relationship between the molecules on the inside and the proportion on the outside of the cell membrane. That analysis uses microscopic information to get a global distribution of molecules. That is, it goes from the microscopic information to get a macroscopic measure. In [7], e.g., the microscopic Eyring multibarrier rate theory has been applied to explain macroscopic characteristics as neuronal oscillations. Again, this goes from the microscopic level to macroscopic level. Nevertheless, we can find some works relating to statistical applications on the macroscopic level. For example, in [20], based on empirical observations of opening/closing times of a sodium channel, they discuss the validity of the assumptions involved in some models, as the H-H model. Also, in [9] they establish a statistical test to contrast the hypothesis that ion channels work independently and identically. In [8], the authors describe the density of the times between spikes by introducing sources of noise and modifying the Hodgkin and Huxley equations.

In this work, the statistics provided are based on the possibility of observing and measuring two kinds of data: macroscopic data (the membrane potential and a simple ion dynamic), and mesoscopic data (the voltage-gated process and ions crossing the membrane). Hypothetical situations are simulated. However, advances in the technology have allowed to observe more closely the nature of the ion channel mechanism, and hence, a better understanding of these phenomena (see [5]). Thus, we hope to be soon able to get measures on specific mesoscopic/microscopic data that allow us to contrast the goodness fit of some models.

In Chapter 1, the original H-H model and its stochastic version through jump

Markov processes are given. Chapter 2 is devoted to introduce the mesoscopic voltage-gated system together with the macroscopic voltage variation and the particle system which approximates this under the propagation of chaos property. Also, a statistical and simulated study of a microscopic ion system seen as a counting process is introduced, as well as macroscopic statistics. Finally, in Chapter 3, a metastability study under a slow/fast system is provided.

Chapter 1

Preliminaries

This chapter is devoted to the review of important results concerning the stochastic approximations of the H-H model, within the same macroscopic level which this model was originally posed. It will allow us to distinguish between the approach proposed in the following chapters: the mesoscopic dynamic of the voltage sensors movement seen as an open system, where random features are inherently part of the system when the interaction between the main system with the reservoir is considering.

1.1 The Hodgkin-Huxley model

The H-H model describes the membrane potential V of a typical neuron, basically, on the mean behavior of K^+ and Na^+ ion channels through its voltage-gated processes. Each channel contains four gates, depending on the voltage variation, which can be in one of the two states: open or closed. A channel is in an open state (conductance) if all gates are in an open state. Otherwise, the channel is in a closed state (non-conductance). The voltage equation is given by:

$$C\frac{dV}{dt} = I - \overline{g}_K n^4(V - E_K) - \overline{g}_{Na} m^3 h(V - E_{Na}) - \overline{g}_L(V - E_L) \tag{1.1.1}$$

$$= I - I_K - I_{Na} - I_L,$$

where C is the membrane capacitance, I represents external stimulus ($= 0\mu\text{A/cm}^2$ in this work), and I_K, I_{Na} and I_L are potassium, sodium and Ohmic leak currents, respectively; $\overline{g}_J$, $(J = K, Na, L)$, represents the maximum conductance and E_K, E_{Na} and E_L are the Nernst equilibrium potentials (for details, see [19] or [21]). The quantities n, m and h represent the probability that a gate is in an open state. In the case of potassium channels, 4 gates are of the same type (n) and, in the case of sodium channels, there are 3 gates of the same type (m) and 1 of another type (h). These quantities satisfy the master equations:

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n,$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

and

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h,$$

where

$$\alpha_n(V) = 0.01\frac{10 - V}{\exp(\frac{10-V}{10}) - 1},$$

$$\beta_n(V) = 0.125\exp(-\frac{V}{80}),$$

$$\alpha_m(V) = 0.1\frac{25-V}{\exp(\frac{25-V}{10})-1},$$

$$\beta_m(V) = 4\exp(-\frac{V}{18}),$$

$$\alpha_h(V) = 0.07\exp(-\frac{V}{20}),$$

and

$$\beta_h(V) = 0.1\frac{1}{\exp(\frac{30-V}{10})+1}$$

Originally Hodgkin and Huxley assumed, although supported by experimental observations made on the squid giant axon, that ions can only cross the membrane when four particles occupy a certain region of the membrane: four similar in the potassium case and three of activation and one of inactivation in the sodium case. That is, at that time, they only conjectured the existence of such gates. Thus, the functional structure of transition rates in the above master equations, as well as the values that appear in them, were obtained using Boltzmann's principle for the distribution of molecules on the inside-outside the cell and by plotting, and then fitting, different voltage values with stationary solutions of such equations (that is, equaling those derivatives to zero), once taken on this kinetic.

1.2 H-H model as a limit of jump Markov processes

Often, the probability that a gate is in an open state is replaced by the proportion of open gates. For this reason, we will show that the H-H model for the membrane potential (Equation (1.1.1)) arises as a limit of the proportion of open gates. In order to explain the underlying noise in the channel mechanism (see, e.g., [13] for channel noise), in [1], [14], [15] and [27], the authors have built these state transitions through two-state Markov processes: 1 if the gate is open and 0 if the gate is closed. But, given the nature of the phenomenon described in the H-H model, the transition rates are coupled by the membrane potential.

Consider a neuron with N_K potassium ion channels and N_{Na} sodium ion channels. Define by $\{e_i^n\}_{i=1,\dots,4N_K}$, $\{e_i^m\}_{i=1,\dots,3N_{Na}}$ and $\{e_i^h\}_{i=1,\dots,N_{Na}}$, sequences of stochastic jump processes where each sequence is independent of the others (actually, asymptotically independent, as we will see) and its elements are determined by:

$$e_i^j : \xi_2 \overset{\psi^j_{\xi_1,\xi_2}(V_N)}{\longrightarrow} \xi_1, \tag{1.2.1}$$

where $\xi_1, \xi_2 = 0, 1$, $\xi_1 \neq \xi_2$; $\psi^{\cdot}_{1,0}(V_N(t)) = \alpha^{\cdot}(V_N(t))$, $\psi^{\cdot}_{0,1}(V_N(t)) = \beta^{\cdot}(V_N(t))$ and $N = N_K + N_{Na}$, $j = n, m, h$. Here, each sequence represents the corresponding voltage-gated process.

In particular, Equation (1.1.1) can be rewritten as:

$$\begin{cases} \frac{dV_N}{dt} = f(V_N, u_n, u_m, u_h) \\ u_N = \frac{1}{N}\sum_{i=1}^N e_i^j \end{cases}, \tag{1.2.2}$$

where $f \in \mathbb{R} \times [0,1] \times [0,1] \times [0,1]$ and the e_i^j's are defined as in (1.2.1). Note

that Equation (1.2.2) is defined only between the u_j-jumps (i.e., between jumps the process is deterministic). Processes defined between jumps, whose jumps follow a jump Markov process, were introduced by Davis in [10] as piecewise deterministic Markov processes.

Under suitable initial conditions, the solution $Y_N = (V_N, u_n, u_m, u_h)$ of (1.2.2) converges in probability as N_K and N_{Na} grow to infinity, uniformly on bounded intervals $[0, T]$, to the solution $y = (v, g_n, g_m, g_h)$ of the deterministic differential equation:

$$\frac{dv}{dt} = f(v, g_n, g_m, g_h), \tag{1.2.3}$$

where g_j satisfies:

$$\frac{dg_j}{dt} = (1 - g_j)\alpha_j(v) - g_j\beta_j(v), \tag{1.2.4}$$

for $j = n, m, h$, when the following conditions are satisfied ([1], [27]):

H.1 α_j and $\beta_j \in C^1$.

H.2 $f \in C^1$.

H.3 The process v from (1.2.3)-(1.2.4) is bounded on $[0, T]$, $T > 0$, and for all $N \geq 1$ the process V_N from (1.2.2) is uniformly bounded in N on $[0, T]$.

Since the process of opening /closing by assumptions are asymptotically independent among species, we can consider the study of only one gate type. Thus, hereinafter we will consider the equation:

$$\begin{cases} \frac{dV_N}{dt} = f(V_N, u_N) \\ u_N = \frac{1}{N}\sum_{i=1}^{N} e_i \end{cases}, \tag{1.2.5}$$

where the e_i's are analogously defined as in (1.2.1). Now, the deterministic system is given by:

$$\frac{dv}{dt} = f(v, g), \tag{1.2.6}$$

where g satisfies:

$$\frac{dg}{dt} = (1 - g)\alpha(v) - g\beta(v) \tag{1.2.7}$$

Assume that conditions H.1-H.3 are satisfied for this reduced case. Thus, we have the following theorems whose proofs can be found in [27].

From now on, $D^{\intercal}$ will denote the transpose of the matrix/vector D.

1.2.1 Law of Large Numbers

Theorem 1.2.1. *Let $y^{init} = (v_0, g_0) \in \mathbb{R} \times [0, 1]$ be an initial condition of (1.2.6)-(1.2.7). For all $\delta, \varepsilon > 0$, there exists an initial condition $Y_N^{init} = (V_N(0), u_N(0))$ from (1.2.5) and $N_0 = N_0(\delta, \varepsilon) \geq 0$ such that for all $N \geq N_0$ the solution $Y_N = (V_N, u_N)$ of (1.2.5) satisfies:*

$$P[\sup_{0 \leq t \leq T} \mid V_N(t) - v(t) \mid > \delta] < \varepsilon$$

and

$$P[\sup_{0 \leq t \leq T} \mid u_N(t) - g(t) \mid > \delta] < \varepsilon,$$

for all fixed $T > 0$.

1.2.2 Central Limit Theorem

Theorem 1.2.2. *Let (v, g) be the solution of (1.2.6)-(1.2.7) and (V_N, u_N) solution of (1.2.5). Define:*

$$\begin{pmatrix} u_N^* \\ V_N^* \end{pmatrix} = \begin{pmatrix} \sqrt{N}(u_N - g) \\ \sqrt{N}(V_N - v) \end{pmatrix},$$

with initial conditions $\begin{pmatrix} u_N^*(0) & V_N^*(0) \end{pmatrix}^\intercal = \begin{pmatrix} 0 & 0 \end{pmatrix}^\intercal$. *Also, define* $b(v, g) = (1 - g)\alpha(v) - g\beta(v)$, $\lambda^*(v, g) = \sqrt{(1-g)\alpha(v) + g\beta(v)}$ *and* $\Gamma_t = \begin{pmatrix} \dot{A}_t & \dot{C}_t/2 \\ \dot{C}_t/2 & \dot{B}_t \end{pmatrix}$, *such that* $Y = \begin{pmatrix} A & B & C \end{pmatrix}^\intercal$ *satisfies* $\dot{Y}_t = M_t Y_t + E_t$, *where:*

$$M_t = \begin{pmatrix} 2b'_g & 0 & b'_v \\ 0 & 2f'_v & f'_g \\ 2f'_g & 2b'_v & b'_g + f'_v \end{pmatrix}$$

and

$$E_t = \begin{pmatrix} -\frac{1}{2}\lambda^*(v, g) \\ 0 \\ 0 \end{pmatrix},$$

with initial conditions $\begin{pmatrix} 0 & 0 & 0 \end{pmatrix}^\intercal$.

Then:

$$\begin{pmatrix} u_N^* \\ V_N^* \end{pmatrix} \xrightarrow{\mathcal{L}} Z,$$

where Z is a Gaussian process such that:

$$Z_t = \int_0^t \Sigma_s dW_s,$$

and Σ is the square root matrix of Γ.

Remark Some authors (e.g., [14] and [27]) approach the master equation (1.2.7) by a diffusion (Langevin approximation). This is because the quantity:

$$R_N(t) = \sqrt{N}\left(u_N(t) - u_N(0) - \int_0^t \left[\alpha(V_N(s))(1-u_N(s)) - \beta(V_N(s))u_N(s)\right] ds\right)$$

is a martingale (see [27]), and by Theorem 1.2.2:

$$R_N \xrightarrow{\mathcal{L}} R,$$

where for all $t \in [0,T]$ $R(t) = \int_0^t \sqrt{\alpha(v_s)(1-g(s)) + \beta(v_s)g(s)}dB_s$, and $B.$ is a standard Brownian motion. Then, another way to incorporate a source of noise in the voltage model is to consider the stochastic differential equation:

$$du_N(t) = \alpha(V_N(t))(1-u_N(t))dt - \beta(V_N(t))u_N(t)dt$$

$$+\sqrt{\frac{\alpha(V_N(t))(1-u_N(t))dt + \beta(V_N(t))u_N(t)}{N}}dB_t,$$

instead of only the proportion of open gates.

Chapter 2

Modified Hodgkin-Huxley equations

Now, we are going to present our stochastic approach under the prescription of the open systems. It will take into account stochastic equations for the voltage sensors movement, which are located at a mesoscopic scale. That is, at this level the dynamic is presented within a random environment, with a continuous space-state, while the ideal macroscopic voltage equation remains deterministic. The consistency of our model will be analyzed using a particle system approximation from the mesoscopic level and verifying, as in Theorem 1.2.1, that we can recover the ideal macroscopic equation by taking a limit on empirical functions. In this case, such property holds when propagation of chaos occurs. Also, we will deal with some statistics concerning flow currents and open times distribution, but using the whole coupled system. The aim of this is to propose statistical criteria for contrasting classical paradigms about the gating process.

2.1 Mesoscopic voltage-gated dynamics

The H-H model describes the macroscopic and deterministic membrane potential dynamics. Nevertheless, the voltage-gated process can be treated at a mesoscopic level, and then, as an open system. In [4] can be found an extensive work about the role of the voltage-gated processes on the gating processes and how they operate. Also, an overview about how through the years and the advancement of technology such kind of structures have been observed inside the channel, can be found in [5].

Besides the spatial level, jump processes described in the previous chapter are still at a macroscopic level because they describe the behavior of each gate in a discrete state space and where the noise is hidden in the randomness of the jump times. Here, we will focus on the mesoscopic level, where the noise arises naturally in the prescription of open systems.

We will describe the dynamics of these gates through stochastic differential equations, which represent the position of the voltage sensors in an ion channel. We are going to impose sufficient conditions on the structure of such equations in order to connect appropriately with (1.1.1), regarding its structure. A simple scheme for the gates behavior is in Fig. 2.1.

We will describe the voltage sensor movement by introducing a real-valued continuous stochastic process X on some complete probability space $(\Omega, \mathcal{F}, P)$. In other words, X will represent the position of a typical sensor, where there is a subset χ of its space-state $\mathbb{R}$ such that when $X \in \chi$, it will allow the opening of its corresponding gate.

Our ideal model will be:

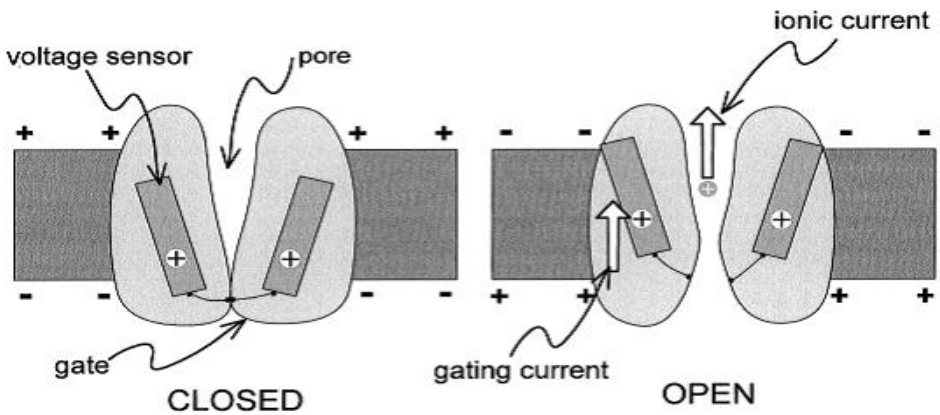

Figure 2.1: A simple schematic view of the parts forming a voltage-dependent ion channel.

$$\begin{cases} \frac{dV_t}{dt} = \int_{\mathbb{R}} f(V_t, x)\mu_t(dx) \\ dX_t = -U'(X_t)dt + h(V_t)dt + \sigma dW_t \\ \mu_t = Law(X_t) \end{cases}, \tag{2.1.1}$$

where $V_0 \in E \subset \mathbb{R}$ and $X_0 \in \mathbb{R}$ is an independent bounded random variable, independent of the Brownian motion W, which is taken as usual with $\sigma > 0$. Here, V describes the voltage o membrane potential variation depending on a typical voltage sensor X through its law μ. This is a kind of non-linearity, known as non-linearity in a McKean sense (see, [25]). The function $U(x) = -x^2/2 + x^4/4$ is a symmetric double-well potential with bottoms at ± 1, which represents the two main states of a sensor: *up* (or open) or *down* (or closed); the function h is the voltage dependent force responsible for the depth variation of the potential U. That is, for one basin of U representing the open state , say $(0, \infty)$, and according to the voltage variation, there are periods where the sensors tend to open which will imply that h tends to take positive values and then, the depth of the right-side basin will become deeper than the left-side one. All the opposite when the sensors tend to close. The Brownian

motion W represents the environment influence or the interaction with the *reservoir*. It also allows the movement of the process X from one basin of U to the other.

Comment:

In (2.1.1) we can distinguish those two different scales mentioned at the beginning of this chapter: the macroscopic and the mesoscopic one. The voltage variation V is still deterministic and represents the evolution of a general characteristic; while X is an open system where the interaction with the environment brings randomness. Thus, the interaction between both processes is achieved through a spatial leveling, which is the role that performs the law of X as a macroscopic characteristic of the its dynamic.

The structural model assumptions are:

A.1 $f : E \times \mathbb{R} \longrightarrow E$ is a C^1 Lipschitz function on $E \times \mathbb{R}$, with constant $R > 0$.

A.2 V is bounded on any bounded time horizon $[0, T]$.

A.3 $h : E \longrightarrow \mathbb{R}$, is a C^1 Lipschitz function on E, with constant K, and where there is a positive constant κ such that:

$$\sup_{v \in E} \mid h(v) \mid = \kappa$$

This last assumption means that the depths of U will vary in a limited form.

In order to be consistent with the original structure of the H-H model, we are going to consider that the function $f(v, x)$ can be written as $\tilde{f}(v, F(x))$, where $F : \mathbb{R} \longrightarrow [0, 1]$ is a non decreasing Lipschitz function, where it will perform a similar a role as g did in (1.2.6). An example of such a function is the Laplace cumulative distribution function:

$$\begin{cases} \frac{1}{2}\exp\{\frac{x-u}{b}\}, & x < u \\ 1 - \frac{1}{2}\exp\{-\frac{x-u}{b}\}, & x \geq u \end{cases},$$

where $u \in \mathbb{R}$ and $b > 0$.

As we defined F as a non decreasing function, we can consider that the open state of X (*up* state) is $(0, \infty)$.

Besides, we have chosen a Brownian noise with the purpose of representing a balanced reservoir (zero-mean martingale property) and recurrence (Definition 2.1.1). We need the recurrence property in order to be consistent with the biological phenomenon, where we are assuming that the voltage-gated process is always on. But first, let us examine the existence and uniqueness of a solution of (2.1.1) on every finite time horizon $[0, T]$. We can rewrite this by considering $Z = (V, X)^\intercal \in E \times \mathbb{R} = H$ and the applications:

$$\phi : \underset{(z,y)}{H \times \mathbb{R}} \underset{\longrightarrow}{\longrightarrow} \underset{(f(v,y),0)^\intercal}{E \times \{0\}}$$

and

$$b : \underset{z}{H} \underset{\longrightarrow}{\longrightarrow} \underset{(0,-U'(x)+h(v))^\intercal}{\{0\} \times \mathbb{R}}$$

By denoting $B = b + \phi$ and $\tilde{W} = (0, W)^\intercal$, we have that (2.1.1) is equivalent to the system:

$$\begin{cases} dZ_t = \int_{E\times\mathbb{R}} B(Z_t, y)\pi_t(du, dy)dt + \sigma d\tilde{W}_t \\ \pi = Law(V, X) = \delta_E \otimes \mu \end{cases},$$

with $Z_0 = (V_0, X_0)^\intercal$, and where we have $\int_{E\times\mathbb{R}} B(Z, y)\pi_t(du, dy) = \int_{\mathbb{R}} B(Z, y)\mu_t(dy)$. This case is similar to that seen in [30], Chapter I, with the difference that the drift

function B therein, is globally Lipschitz and not locally Lipschitz as in our case (this is because U' is locally Lipschitz). In that reference, the existence and uniqueness of a strong solution (trajectorial and in law) is guaranteed under a globally Lipschitz condition on its drift (Theorem 1.1). Nevertheless, the "stochastic part" of (2.1.1), X, does not explode because it is almost surely in between two continuous recurrent Markov processes (as will see in the Proofs of Proposition 2.1.1 and Lemma 2.1.2), and together with A.2, we have that (2.1.1) does not explode. Hence, we can use a stopping procedure in order to show the existence and uniqueness of a strong solution for (2.1.1), or equivalently, for the above system Z. We are going to adapt the argument given in [24], Chapter 2, p Theorem 3.4.

On the existence and uniqueness of a solution of (2.1.1)

For all $n \geq 1$, define the truncated function:

$$B_n(z,\cdot) = \begin{cases} B(z,\cdot), & \| z \| \leq n \\ B(nz/\| z \|,\cdot) & \| z \| > n \end{cases}$$

Then, according Theorem 1.1 from [30], there exists a unique strong solution to the equation (label as (T-2.1.1)):

$$Z_{t,n} = Z_0 + \int_0^t \int_{E\times\mathbb{R}} B_n(Z_{s,n}, y)\pi_s(du, dy)ds + \sigma\tilde{W}_t,$$

for all finite time horizon, since the truncated drift function satisfies a globally Lipschitz condition. For any $0 < T < \infty$, define the stopping time:

$$\tau^n = \inf\{t \geq 0 : \| Z_{t,n} \| \geq n\} \wedge T$$

We have that $\{\tau^n\}_{n\geq 1}$ is nondecreasing (since $Z_{t,n} = Z_{t,n+1}$, for $0 \leq t \leq \tau^n$), and for almost all $\omega \in \Omega$, there exists an integer $n_0(\omega) = n_0$ such that $\tau^n = T$, whenever $n \geq n_0$ (since by the nonexplosive condition $\inf\{t \geq 0 :\| Z_{t,n} \|\geq n\} \uparrow \infty$ when $n \uparrow \infty$). Now, define:

$$Z_t = Z_{t,n_0},$$

for all $t \in [0, T]$. Thus, we have $Z_{t\wedge\tau^n} = Z_{t\wedge\tau^n,n,}$ and by (T-2.1.1):

$$Z_{t\wedge\tau^n} = Z_0 + \int_0^{t\wedge\tau^n} \int_{\mathbb{R}} B_n(Z_s, y)\mu_s(dy)ds + \sigma\tilde{W}_{t\wedge\tau^n}$$

$$= Z_0 + \int_0^{t\wedge\tau^n} \int_{\mathbb{R}} B(Z_s, y)\mu_s(dy)ds + \sigma\tilde{W}_{t\wedge\tau^n}$$

Finally, letting $n \uparrow \infty$, we have that Z_t is a strong solution of (2.1.1) for all $t \in [0, T]$. Uniqueness follows from uniqueness of $Z_{t,n}$ of (T-2.1.1), for all $t \in [0, T]$.

Remark The above stopping argument was outlined in [24], Chapter 2, Theorem 3.4-Theorem 3.5, to prove the existence and uniqueness of strong solutions when drift and/or diffusion coefficients are locally Lipschitz and satisfy certain growth conditions. In particular, Theorem 3.5 will be established later in order to show the existence and uniqueness of a solution of a "particle system" which will be used as an approximation of (2.1.1). Although, above we used that the process (2.1.1) does not explode, such a property is part of a wider property which will be defined below.

Definition 2.1.1. Let Y be a continuous-time real valued stochastic process. Denote $P^{s,y}(\cdot) = P(\cdot \mid Y_s = y)$. Consider for any integer $n \geq 1$ the sets $\Lambda_n = \{y \in \mathbb{R} :\mid y \mid< n\}$, and define the following increasing sequence of stopping times:

$$\tau_n = \inf\{t \geq 0 : Y_t \notin \Lambda_n\}$$

and its limit $\tau = \lim_{n\uparrow\infty} \tau_n$.

- A process Y is said to be regular if for all $(s, y) \in \mathbb{R}_+ \times \mathbb{R}$,

$$P^{s,y}(\tau = \infty) = 1$$

- Let $\mathcal{O} \in \mathcal{B}(\mathbb{R})$. A process Y is said to be recurrent relative to $\mathcal{O}$ ($\mathcal{O}$-recurrence) if it is regular and for every $(s, y) \in \mathbb{R}_+ \times \mathcal{O}^c$ we have:

$$P^{s,y}(\tau_{\mathcal{O}^c} < \infty) = 1,$$

where $\tau_{\mathcal{O}^c}$ is the first exit time from $\mathcal{O}^c$ starting at $(s, y) \in \mathbb{R}_+ \times \mathcal{O}^c$.

A process Y is said to be recurrent if it is recurrent relative to any nonempty open set in $\mathcal{B}(\mathbb{R}) - \{\mathbb{R}\}$.

Proposition 2.1.1. *Under A.3, X is recurrent.*

Before starting the proof of Proposition 2.1.1, we need the following lemma.

Lemma 2.1.2. *Consider the next three continuous stochastic processes defined on a certain complete probability space $(\Omega, \mathcal{F}, P)$: M, N and O, which take their values in $\mathbb{R}$, such that for all $t \in \mathbb{R}_+$ they satisfy:*

$$M_t \leq N_t \leq O_t,$$

almost surely. If M and O are recurrent, then N is recurrent

Proof. Let $\mathcal{O}$ be a nonempty open set in $\mathcal{B}(\mathbb{R}) - \{\mathbb{R}\}$ such that $(a, b) \in \mathcal{O}$, with $a < b$. Note that, regularity of N immediately holds since it is in between two regular processes. Let $s \in \mathbb{R}_+$.

First case: $O_s(\omega) = o_s \leq a \Rightarrow M_s(\omega) = m_s \leq N_s(\omega) = n_s \leq a$. By recurrence property and continuity of M, there exists a stopping time $T' \in [s, \infty)$, almost surely,

such that $M_{T'} = a$. Thus, by continuity of N, there exists a stopping time $T'' \in [s, T']$, almost surely, such that $N_{T''} \in (a, b)$, and then recurrence property holds.

Second case: $M_s(\omega) = m_s \geq b \Rightarrow O_s(\omega) = o_s \geq N_s(\omega) = n_s \geq b$. Then, recurrence property of N is obtained analogously as in the previous case.

Third case: $N_s(\omega) = n_s \in (a, b)$. By recurrence property and continuity of such processes, there exists a stopping time $T''' \in (s, \infty)$, almost surely, such that $O_{T'''} = a$ or $M_{T'''} = b$. Restarting at $s = T'''(\omega)$, we go back to one of the two previous cases.

□

Proof. (Proposition 2.1.1) Consider the equations:

$$dX_t^{st_-} = -U'(X_t^{st_-})dt - \kappa dt + \sigma dW_t,$$

$$dX_t^{st_+} = -U'(X_t^{st_+})dt + \kappa dt + \sigma dW_t,$$

and X as in (2.1.1), where $X_0^{st_-} = X_0^{st_+} = X_0$; the same parameter $\sigma > 0$ and function U for all of these three processes, and the Brownian motions involved are all indistinguishable. By A.3, we know that for all $v \in E$, $h(v) \in [-\kappa, \kappa]$. For all $t \in \mathbb{R}_+$, we claim that:

$$X_t^{st_-} \leq X_t \leq X_t^{st_+},$$

almost surely. Indeed, for any $t \in \mathbb{R}_+$, consider the processes $a_\pm(t) = \int_0^t h(V_s)ds \pm \kappa t$, where a_+ and $-a_-$ are always nonnegative. We have that:

$$X_t = X_0 - \int_0^t U'(X_s)ds + \int_0^t h(V_s)ds + \sigma W_t =$$

$$X_0 - \int_0^t U'(X_s)ds - \kappa t + \sigma W_t + a_+(t) = X_0 - \int_0^t U'(X_s)ds + \kappa t + \sigma W_t + a_-(t)$$

$$= X_t^{st_-} + a_+(t) = X_t^{st_+} + a_-(t),$$

and hence $X_t \in [X_t^{st_-}, X_t^{st_+}]$.

Now, by the previous lemma, it is enough to prove the recurrence of $X^{st_\pm}$.

Note that the corresponding generators are given by:

$$L_\pm = b_\pm(x)\frac{\partial}{\partial x} + \frac{1}{2}\sigma^2\frac{\partial^2}{\partial x^2},$$

where $b_\pm(x) = x - x^3 \pm \kappa$. Consider the functions:

$$Q_\pm(x) = \exp\{-2\int_0^x \frac{b_\pm(y)}{\sigma^2}dy\}$$

and

$$\mathcal{W}_\pm(x) = \int_0^x Q_\pm(y)dy$$

It is easily seen that $L_\pm\mathcal{W}_\pm = 0$ and $\mathcal{W}_\pm(x) \to \pm\infty$ when $x \to \pm\infty$.

To conclude, we recall Lemma 3.9 from [23]:

Lemma *Suppose that a process Y almost surely exits from each bounded domain in a finite time. Then a sufficient condition for $\mathcal{O}$-recurrence is that there exists a nonnegative function $V(t,y)$ in the domain $\{t > 0\} \times \mathcal{O}^c$ such that:*

$$V_R = \inf_{t>0, |y|\geq R} V(t,y) \underset{R\uparrow\infty}{\longrightarrow} \infty$$

and

$$LV \leq 0$$

Thus, the functions $\mathcal{W}_{\pm}(x)\text{sign}(x)$ satisfy the assumptions of the previous lemma for every $x \in \mathbb{R}$, and therefore, the processes $X^{st_{\pm}}$ are recurrent relative to every nonempty open set $\mathcal{B}(\mathbb{R}) - \{\mathbb{R}\}$. Hence, the proposition holds.

□

Now, consider a strictly increasing sequence of compact sets in $\mathbb{R}$, $\{\Lambda_l\}_{l\in\mathbb{N}}$, such that:

$$\bigcup_{l\in\mathbb{N}} \Lambda_l = \mathbb{R}$$

Let Y be a continuous-time real-valued stochastic process. Define for any $l \in \mathbb{N}$:

$$\tau_l = \inf\{t \geq 0 : Y_t \notin \Lambda_l\}$$

We will say that a stochastic process Y is moving "locally in time" when it will be stopped at time $t = \tau_l$, for any $l \in \mathbb{N}$. For convenience, those sets can be taken as $\Lambda_l = \{| y |\leq L\}$, for $L \in \mathbb{N}$.

One of our aims is to recover the model (2.1.1) by using a particle system which will play the role as the jump Markov processes did concerning the original H-H model in Section 1.2.

Consider an iid sequence of usual Brownian motions $\{W^1, ..., W^N\}$ and define:

$$\begin{cases} dV_t^N = \frac{1}{N}\sum_{i=1}^N f(V_t^N, X_t^{i,N})dt \\ dX_t^{i,N} = -U'(X_t^{i,N})dt + h(V_t^N)dt + \sigma dW_t^i \end{cases}, \tag{2.1.2}$$

where $V_0^N = V_0$ and $\{X_0^{i,N}\}_{i=1,...,N} = \{X_0^i\}_{i=1,...,N} \overset{iid}{\sim} X_0$. So, the idea is to prove that (2.1.2) can be used as an approximation of the *ideal* model (2.1.1). We will show first the existence and uniqueness of a solution of (2.1.2).

Theorem 2.1.3. *Under assumptions A.1-A.3, (2.1.2) has a unique strong solution.*

Our proof is based on a general result from [24] (Chapter 2, Theorem 3.5), which we will establish below.

Theorem 2.1.4. *Let $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, P)$ be a complete filtered probability space. Let $B(t) = (B_1(t), ..., B_m(t))^\intercal$, $t \geq 0$, be a m-dimensional Brownian motion defined on the space. Let y_0 be an $\mathcal{F}_0$-measurable $\mathbb{R}^d$-valued random variable such that $E \parallel y_0 \parallel^2 < \infty$. Let $0 < T < \infty$. Let $\theta : \mathbb{R}^d \times [0, T] \longrightarrow \mathbb{R}^d$ and $\phi : \mathbb{R}^d \times [0, T] \longrightarrow \mathbb{R}^{d\times m}$ be both Borel measurable. Consider the d-dimensional stochastic differential equation of Ito type:*

$$dy(t) = \theta(y(t), t)dt + \phi(y(t), t)dB(t),$$

with initial condition $y(0) = y_0$. Assume that:

(a) (Locally Lipschitz condition) For every integer $n \geq 1$ there exists a positive constant K_n such that, for all $t \in [0, T]$ and all $y, z \in \mathbb{R}^d$ with $\parallel y \parallel \vee \parallel z \parallel \leq n$,

$$\parallel \theta(y, t) - \theta(z, t) \parallel^2 \vee \parallel \phi(y, t) - \phi(z, t) \parallel^2 \leq K_n \parallel y - z \parallel^2$$

(b) (Growth condition) There exists a positive constant C, such that for all $(y, t) \in \mathbb{R}^d \times [0, T]$,

$$y^\intercal \theta(y, t) + \frac{1}{2} \parallel \phi(y, t) \parallel^2 \leq C(1 + \parallel y \parallel^2)$$

Then, there exists a unique strong solution $y(\cdot)$ to the above stochastic differential equation with $E(\sup_{t\in[0,T]} \| y(t) \|^2) < \infty$.

Note that equation (2.1.2) can be rewritten as:

$$d\begin{pmatrix} V_t^N \\ X_t^{1,N} \\ \vdots \\ X_t^{N,N} \end{pmatrix} = \begin{pmatrix} \frac{1}{N}\sum_{i=1}^N f(V_t^V, X_t^{i,N}) \\ -U'(X_t^{1,N}) + h(V_t^N) \\ \vdots \\ -U'(X_t^{N,N}) + h(V_t^N) \end{pmatrix} dt + \Sigma d\tilde{W}(t)$$

$$\begin{pmatrix} V_0^N \\ X_0^{1,N} \\ \vdots \\ X_0^{N,N} \end{pmatrix} = \begin{pmatrix} V_0 \\ X_0^1 \\ \vdots \\ X_0^N \end{pmatrix},$$

where $\tilde{W}(t) = (W_t^1, ..., W_t^N)^\intercal$ and Σ is a $(N+1)\times N$-matrix such that:

$$\Sigma^\intercal \Sigma = I_d \sigma^2,$$

where I_d is the $N \times N$-matrix identity. Thus, the drift is given by:

$$\begin{pmatrix} \frac{1}{N}\sum_{i=1}^N f(V^V, X^{i,N}) \\ -U'(X^{1,N}) + h(V^N) \\ \vdots \\ -U'(X^{N,N}) + h(V^N) \end{pmatrix} \tag{2.1.3}$$

Proof. (Theorem 2.1.3)

First, note that by definition $E \mid V_0 \mid^2 < \infty$ and $E \mid X_0^i \mid^2 < \infty$, because they are bounded random variables. By A.1 and A.3 we know that f and h are Lipschitz with constant R and K, respectively; h is bounded by κ, but U' is locally Lipschitz.

Specifically, for every integer $n \geq 1$ and for all $x, y \in \mathbb{R}$ such that $\mid x \mid \vee \mid y \mid \leq n$, a Lipschitz coefficient can be obtained as:

$$\mid U'(x) - U'(y) \mid \leq \mid x - y \mid + \mid x^3 - y^3 \mid$$

$$\leq \mid x - y \mid + \mid x - y \mid\mid x^2 + xy + y^2 \mid \leq \mid x - y \mid (1 + 3n^2),$$

and it implies that the drift part described in (2.1.3) is also locally Lipschitz and then, condition (a) in Theorem 2.1.4 is satisfied.

Now, consider the following application for all $(v, \tilde{z}) \in E \times \mathbb{R}^N$, $\tilde{z} = (z_1, .., z_N)$, as:

$$G : (v, z) \longrightarrow (\frac{1}{N}\sum_{i=1}^{N} f(v, z_i), -U'(z_1) + h(v), ..., -U'(z_N) + h(v))'$$

Thus, in order to prove the theorem, it is enough to show that condition (b) in Theorem 2.1.4 holds for our case, that is, there exists some positive constant C such that:

$$(v, \tilde{z})G(v, \tilde{z}) + \frac{1}{2}N\sigma^2 \leq C(1 + (v, \tilde{z})(v, \tilde{z})^{\intercal}) \tag{2.1.4}$$

We have that:

$$(v, \tilde{z})G(v, \tilde{z}) = \frac{1}{N}\sum_{i=1}^{N} vf(v, z_i) + \sum_{i=1}^{N} z_i(-U'(z_i) + h(v))$$

$$= \frac{1}{N}\sum_{i=1}^{N} vf(v, z_i) + \sum_{i=1}^{N}(z_i^2 - z_i^4 + z_i h(v)) \leq \frac{1}{N}\sum_{i=1}^{N} vf(v, z_i) + \sum_{i=1}^{N}(z_i^2 + z_i h(v))$$

Now, we can take $(u, x) \in E \times \mathbb{R}$ such that $f(u, x) = e \in E$ (by A.1 and A.2), and then introduce this in the last inequality as:

$$\frac{1}{N}\sum_{i=1}^{N} vf(v,z_i)+\sum_{i=1}^{N}(z_i^2+z_ih(v)) = \frac{1}{N}\sum_{i=1}^{N} v(f(v,z_i)-f(u,x)+f(u,x))+\sum_{i=1}^{N}(z_i^2+z_ih(v))$$

By taking absolute values in the last line, we obtain:

$$(v,\tilde{z})G(v,\tilde{z}) \leq \frac{1}{N}\sum_{i=1}^{N} \mid v \mid\mid f(v,z_i)-f(u,x)+f(u,x) \mid + \sum_{i=1}^{N} \mid z_i^2+z_ih(v) \mid$$

$$\leq \mid v \mid\mid f(u,x) \mid + \frac{1}{N}\sum_{i=1}^{N} \mid v \mid\mid f(v,z_i)-f(u,x) \mid + \sum_{i=1}^{N} z_i^2 + \sum_{i=1}^{N} \mid z_i \mid\mid h(v) \mid$$

$$\leq \mid v \mid\mid e \mid + R \mid v \mid\mid v-u \mid + \frac{R \mid v \mid}{N}\sum_{i=1}^{N} \mid z_i - x \mid + \sum_{i=1}^{N} z_i^2 + \kappa \sum_{i=1}^{N} \mid z_i \mid$$

$$\leq \mid v \mid\mid e \mid + Rv^2 + \mid v \mid\mid u \mid + \frac{R \mid v \mid}{N}\sum_{i=1}^{N} \mid z_i \mid + \frac{R \mid v \mid\mid x \mid}{N}$$

$$+ \sum_{i=1}^{N} z_i^2 + \kappa \sum_{i=1}^{N} \mid z_i \mid$$

Let $\overline{C} = \max\{\mid e \mid, R, \mid u \mid, R \mid x \mid, 1, \kappa\}$. Then,

$$(v,\tilde{z})G(v,\tilde{z}) \leq \overline{C}\left(2 \mid v \mid + v^2 + \sum_{i=1}^{N} \mid z_i \mid (\frac{\mid v \mid}{N}+1) + \frac{\mid v \mid}{N} + \sum_{i=1}^{N} z_i^2\right)$$

Note that, by one hand we have:

$$2 \mid v \mid + v^2 \leq (\mid v \mid + 1)^2 \leq 2(v^2+1)$$

and by the other one:

$$\sum_{i=1}^{N} \mid z_i \mid (\frac{\mid v \mid}{N} + 1) + \frac{\mid v \mid}{N} + \sum_{i=1}^{N} z_i^2 \leq \sum_{i=1}^{N} \left(\mid z_i \mid (\frac{\mid v \mid}{N} + 1) + \frac{\mid v \mid}{N} + z_i^2 \right)$$

$$\leq \sum_{i=1}^{N} \left(\mid z_i \mid (\frac{\mid v \mid}{N} + 1) + (\frac{\mid v \mid}{N} + 1)^2 + z_i^2 \right) \leq \sum_{i=1}^{N} \left(z_i + (\frac{\mid v \mid}{N} + 1) \right)^2$$

$$\leq \sum_{i=1}^{N} \left(2z_i^2 + 4\frac{v^2}{N^2} + 4 \right) \leq 2\sum_{i=1}^{N} z_i^2 + 4v^2 + 4N$$

Putting all together we obtain:

$$(v, \tilde{z})G(v, \tilde{z}) \leq \overline{C} \left(2 \mid v \mid + v^2 + \sum_{i=1}^{N} \mid z_i \mid (\frac{\mid v \mid}{N} + 1) + \frac{\mid v \mid}{N} + \sum_{i=1}^{N} z_i^2 \right)$$

$$\leq \overline{C} \left(2(v^2 + 1) + 2\sum_{i=1}^{N} z_i^2 + 4v^2 + 4N \right) = \overline{C} \left(6v^2 + 2\sum_{i=1}^{N} z_i^2 + (4N + 2) \right)$$

$$\leq \overline{C}(4N + 2)(v^2 + \sum_{i=1}^{N} z_i^2 + 1)$$

Finally, by choosing $C = 2\max\{\overline{C}(4N + 2), N\sigma^2/2\}$, (2.1.4) holds and therefore the theorem applies.

□

Now, for the following theorem, let $\{Z^i = (V, X^i)^\intercal\}_{i=1,\ldots,N}$ be an iid sequence from (2.1.1). We will show a propagation of chaos' result, that is, a solution Z^i of (2.1.1) can be approximated by one $Z^{i,N} = (V^N, X^{i,N})^\intercal$, solution of (2.1.2), when N goes to

infinity, with $X_0^{i,N} = X_0^i$, $V_0^N = V_0$ and indistinguishable Brownian motions. Before setting this, we are going to recall Gronwall's lemma.

Lemma 2.1.5. *(Gronwall's lemma) Suppose that $T > 0$ and $g : [0,T] \longrightarrow \mathbb{R}$ is continuous. Suppose further that there are constants $A, B > 0$ such that:*

$$g(t) \leq A + B \int_0^t g(s)ds$$

for all $t \in [0,T]$. Then $g(t) \leq A \exp\{Bt\}$.

Remark Gronwall's lemma can be applied when the continuity assumption is replaced by integrability assumption.

Theorem 2.1.6. *Under A.1-A.3, for any fixed i:*

$$Z^{i,N} \xrightarrow{P} Z^i,$$

locally in time, when N goes to infinity.

Proof. Since initial conditions are bounded random variables, we can choose $\overline{M} \in \mathbb{N}$ such that:

$$P(X_0^i \in [-\overline{M}, \overline{M}]) = 1,$$

for any i. For any $M \geq \overline{M}$, define $\tau_M = \tau_M^+ \wedge \tau_M^-$, where $\tau_M^+ = \inf\{t \geq 0 : X_t^{st_+,i} > M\}$, $\tau_M^- = \inf\{t \geq 0 : X_t^{st_-,i} < -M\}$ and the processes $X^{st_\pm,i}$ satisfy:

$$dX_t^{st_\pm,i} = -U'(X_t^{st_\pm,i})dt \pm \kappa dt + \sigma dW_t^i,$$

where $X_0^{st_\pm,i} = X_0^i$ and the processes $X^{st_\pm,i}$ have the same Brownian motion as X^i (note that, as shown in Proposition 2.1.1, $X^i, X^{i,N} \in [X^{st_-,i}, X^{st_+,i}]$ and then, for any $T \geq 0$, $X_t^i, X_t^{i,N} \in [-M, M]$, for all $t \in [0, T \wedge \tau_M]$).

Let $0 < T < \infty$. For all $t \in [0, T \wedge \tau_M]$, we have:

$$\| Z_t^i - Z_t^{i,N} \|^2 \leq 2T(1+M^2)^2 \int_0^t \| X_s^{i,N} - X_s^i \|^2 \, ds +$$

$$2TK^2 \int_0^t \| V_s^N - V_s \|^2 \, ds + \| \frac{1}{N} \int_0^t \sum_{k=1}^N (f(V_s^N, X_s^{k,N}) - \int_{\mathbb{R}} f(V_s, x)\mu_s(dx)) ds \|^2,$$

where we used $(a+b)^2 \leq 2a + 2b$, Cauchy-Schwarz inequality, A.3 and the fact that, for all $t \in [0, T \wedge \tau_M]$, $| U'(X_t^i) - U'(X_t^{i,N}) | \leq (1+M^2) | X_t^{i,N} - X_t^i |$. Now, let $D = \max\{K, R\}$. By introducing $\{f(V, X^k)\}_{k=1,..,N}$ in the last line and using Lipschitz property of f, we obtain for all $t \in [0, T \wedge \tau_M]$:

$$\| Z_t^i - Z_t^{i,N} \|^2 \leq$$

$$2T(1+M^2)^2 \int_0^t | X_s^{i,N} - X_s^i |^2 \, ds + 4TD^2 \int_0^t | V_s - V_s^N |^2 \, ds + \frac{4TD^2}{N} \sum_{k=1}^N \int_0^t | X_s^{k,N} - X_s^k |^2 \, ds$$

$$+ \frac{1}{N^2} \| \sum_{k=1}^N \int_0^t (f(V_s, X_s^k) - \int_{\mathbb{R}} f(V_s, x)\mu_s(dx)) ds \|^2$$

Taking expectations and under the fact that the $f(V, X^k)$'s are iid and $(X^{k,N} - X^k)$'s have the same distribution, for all $t \leq T \wedge \tau_M$ we get:

$$E(\sup_{s \leq t} \| Z_s^i - Z_s^{i,N} \|^2) \leq$$

$$2T(1+M^2)^2\int_0^t E(\sup_{u\le s}\mid X_u^{i,N}-X_u^i\mid^2)ds+4TD^2\int_0^t E(\sup_{u\le s}\mid V_u-V_u^N\mid^2)ds$$

$$+4TD^2\int_0^t E(\sup_{u\le s}\mid X_u^{i,N}-X_u^i\mid^2)ds$$

$$+\frac{T}{N^2}\sum_{k=1}^N\int_0^t E(\sup_{u\le s}\parallel f(V_uX_u^k)-\int_{\mathbb{R}} f(V_u,x)\mu_u(dx)\parallel^2)ds,$$

where the last line is a $O(1/N)$ quantity. Let $G_M=\max\{2T(1+M^2)^2,4TD^2\}$. Finally, define $\xi^N(t)=E(\sup_{s\le t}\parallel Z_s^i-Z_s^{i,N}\parallel^2)$. Then:

$$\xi^N(t)\le O(1/N)+G'_M\int_0^t\xi^N(s)ds,$$

where $G'_M\ge G_M$ is a suitable constant, and by Gronwall's lemma we get:

$$\xi^N(t)\le O(1/N)\exp\{TG'_M\}$$

Therefore, the result follows.

□

Remark This result is similar to Theorem 1.4 in [30], except that the drift part therein satisfies a globally Lipschitz property. However, as noted before, the processes $X^{st_\pm,i}$ defined in the above proof are recurrent (Proof of Proposition 2.1.1) and the corresponding stopping time τ_M satisfies: $\tau_M\wedge T\uparrow T$ when $M\uparrow\infty$, for any $0<T<\infty$. Thus, we have that a Lipschitz coefficient for $U'(x)$ is almost sure finite. Having this in mind, it is enough for us to get the local convergence as stated.

In general, propagation of chaos in interacting particle systems is useful for approximating nonlinear differential equations or nonlinear PDE's describing, e.g., ideal state evolution of physical systems (see, e.g, [30], [6] and references therein).

2.1.1 Some consequences

Estimation of h: h is an unknown function, but we can estimate it if the gate dynamics are continuously observable. From (2.1.2), taking the N equations and averaging them, we will obtain:

$$\theta(N,t) = \frac{1}{N}\sum_{i=1}^{N}\left(X_t^{i,N} - X_0^{i,N} + \int_0^t U'(X_s^{i,N})ds\right) = \int_0^t h(V_s^N)ds + \frac{\sigma}{N}\sum_{i=1}^{N} W_t^i$$

So, as $\sigma\sum_{i=1}^{N} W_t^i/N$ is a martingale which goes to zero uniformly on $[0,T]$ for all $T>0$ finite when N goes to infinity (by Doob's inequality) and h is a bounded and continuous function, we have that, by Theorem 2.1.6, $\theta(N,\cdot) \xrightarrow{P} \theta_\cdot = \int_0^\cdot h(V_s)ds$ on any finite time horizon $[0,T]$, when N goes to infinity.

That is to say, $\theta(N,\cdot)$ is a consistent estimator of $\theta_\cdot$ on any finite time horizon $[0,T]$. The point here is that we may recover $\int_0^\cdot h(V_s)ds$ without observing V, but the mesoscopic sensor dynamics which, obviously, is somewhat more complicated than the observation of mesoscopic information as the dynamic of the voltage variation.

It is a well-known fact that the parameter σ can be obtained as:

$$\sigma^2 = \lim_{n\to\infty}\frac{1}{t}\sum_{k=1}^{2^n}\left(X^{j,N}_{t\frac{k}{2^n}} - X^{j,N}_{t\frac{(k-1)}{2^n}}\right)^2,$$

$\forall t \in (0,T]$, $\forall j = 1,...,N$.

Remark As mentioned in the Introduction, the previous estimator of the integral of h is given under the hypothetical situation that we are able to observe and measure/codify the sensors movement. In the following section we have to assume that we can observe the open channel times, as usual (see, e.g., [20]), and ions crossing the channels which has been studied under experimental and simulated situations (see, e.g., [3], [29] and [7]).

2.2 On testing the H-H model

We are going to propose two ways in which the original hypothesis on the H-H model can be tested. The first one consists in analyzing the movement of ionic charges through the channels from a sample of ion channels, under a very simple model, which will allow us to generate the ion currents and to check whether the structure of the ion currents suggested by the H-H model are valid (i.e., $H_0 : I_{[ion]} = \overline{g}_{[ion]} P_o (V - E_{[ion]})$, where P_o is the probability that an $[ion]$ channel is open). The second one consists in observing the open/closed times of an ion channel together with the voltage variation and to check the original assumptions for the Markovianity of the gating process (a goodness fit test). For the first testing case, we need mesoscopic information, but in the second one, we only ask for macroscopic information.

With respect to the second method, unlike works as [20] and the hidden Markov model method in [11], we are going to deal with the fully coupled model, that is, by taking the voltage variation together with the gating process. Although, experimental observations and simulations therein are made under different fixed values for the membrane potential (e.g., observing the gating activity of a particular ion channel under fixed values for the voltage). Nevertheless, the methods that we will present

are general, in the sense that they can be applied for such approximations.

Due to the computational cost, our simulations are shown under fixed values for the voltage or the decoupled case (see [26] for simulations of the gating activity under the H-H model and its diffusion o Langevin approximation), but in our first method (general structure of currents), they can be justified by considering that the underlying gating process works in a different time-scale. This is something that we are going to see, in more details, in the next chapter.

2.2.1 Recovering f through an ion system: a simple case

Actually, the H-H model for the membrane potential comes from a particular choice of a function f satisfying the assumption H.2. Here, we suggest a way to estimate f by relating the electric current (which is the current intensity generated from an ion system) with the stochastic intensity of a process representing ions crossing ion channels. Also, we see how we can contrast the H-H model hypothesis from that estimation. The methodology we suggest will be described under a very simple case.

Consider a simple neuron which contains only K^+ channels (see Fig. 2.2). This neuron has impermeable anions (A^-) on the inside and permeable potassium ions on both sides. So, the equation for the membrane potential in this case is given by:

$$C\frac{dV}{dt} = -I_K = -\overline{g}_K \mu^4 (V - E_K) \tag{2.2.1}$$

If we consider $C = 1\mu\text{F/cm}^2$, then $f(V, \mu) = -I_K$.

Define the simple channel dynamic as $Y_t = 1$, if the channel is open at time t and $Y_t = 0$, otherwise.

The number of ion charges entering and leaving the neuron can be defined as

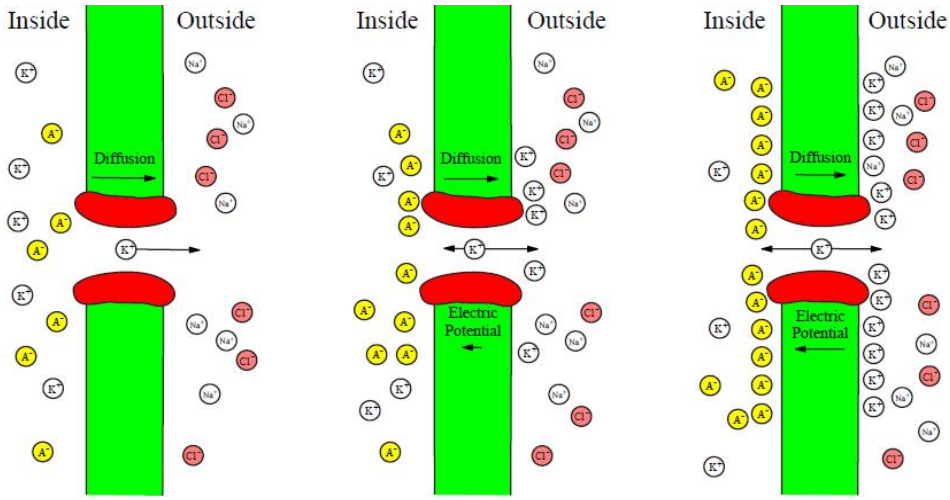

Figure 2.2: Diffusion of K^+ ions through the membrane.

$\int Y_{s-} d\overleftarrow{N}_s(V_s)$ and $\int Y_{s-} d\overrightarrow{N}_s(V_s)$, respectively, where the system $(\overleftarrow{N}(V), \overrightarrow{N}(V))$ represents the number of charges (unit charges, in our case) arriving at the channel in their respective orientations (from outside-to-inside the cell and from inside-to-outside the cell, respectively).

By biophysical considerations, we will assume the existence of a compensator of $(\overleftarrow{N}(V), \overrightarrow{N}(V))$, given by $(\int \overleftarrow{\varphi}_s(V_s)ds, \int \overrightarrow{\varphi}_s(V_s)ds)$ (for technical considerations see, e.g., [22]). That is, the elements of $(\overleftarrow{N}(V) - \int \overleftarrow{\varphi}_s(V_s)ds, \overrightarrow{N}(V) - \int \overrightarrow{\varphi}_s(V_s)ds)$ are martingales with respect to its natural filtration. The functions $\overleftarrow{\varphi}(V)$ and $\overrightarrow{\varphi}(V)$ are called the stochastic intensity of $\overleftarrow{N}(V)$ and $\overrightarrow{N}(V)$, respectively. Thus, we have that the elements of

$$\left(\overleftarrow{M}, \overrightarrow{M}\right)$$

$$= \left(\int Y_{s-} d\overleftarrow{N}_s(V_s) - \int Y_{s-} \overleftarrow{\varphi}_s(V_s)ds, \int Y_{s-} d\overrightarrow{N}_s(V_s) - \int Y_{s-} \overrightarrow{\varphi}_s(V_s)ds\right),$$

are also martingales, with respect to its natural filtration.

Those elements generate the electric current I_K. As the Hodgkin-Huxley paradigm uses a mean field approach to approximate the ion electric currents involved, the electric current at time t, $I_K(t) = -f(V_t, \mu_t)$ (deterministic current intensity) should be equal to:

$$\frac{dE(\int_0^t Y_{s-}\overrightarrow{\varphi}_s(V_s)ds - \int_0^t Y_{s-}\overleftarrow{\varphi}_s(V_s)ds)}{dt}$$

(We are saying that the physical current intensity is equivalent to the expectation of the stochastic intensity).

We want to contrast this fact by means of a confidence interval for

$$(V_0 - V) = -\int f(V_s, \mu_s)ds = \int I_K(s)ds$$

Consider a sample in n channels:

$$\begin{pmatrix} \int Y^1_{s-}d\overleftarrow{N}^1_s(V_s) & \int Y^1_{s-}d\overrightarrow{N}^1_s(V_s) \\ \vdots & \vdots \\ \int Y^n_{s-}d\overleftarrow{N}^n_s(V_s) & \int Y^n_{s-}d\overrightarrow{N}^n_s(V_s) \end{pmatrix}$$

Here, we assume that we can choose an arbitrary number of channels which satisfy some properties of randomness. To construct a statistical test for checking the classical structure of the H-H model, we need to be in the ideal system where all the channels are iid. Thus, we need an infinity number of channels (in practice obviously this does not hold, but we can ask, in some cases, for a large number of them). This implies that the rows of the previous matrix can be seen as a random sample. Also assume that those components cannot jump at the same time. This fact implies that

the elements of $\left(\overset{\leftarrow}{M}^{i}, \vec{M}^{i}\right)_{i=1,\dots,n}$, given by:

$$\left(\int Y^i_{s-} d\overset{\leftarrow}{N}^{i}_s(V_s) - \int Y^i_{s-} \overset{\leftarrow}{\varphi}^{i}_s(V_s)ds, \int Y^i_{s-} d\vec{N}^{i}_s(V_s) - \int Y^i_{s-} \overset{\rightarrow}{\varphi}^{i}_s(V_s)ds\right),$$

satisfy:

$$< \overset{\leftarrow}{M}^{i}, \overset{\leftarrow}{M}^{j} >= 0,$$

for $i, j = 1, ..., n$ and $i \neq j$.

Define:

$$\overset{\leftarrow}{\mathcal{M}}^{n} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \overset{\leftarrow}{M}^{i}$$

and

$$\overset{\rightarrow}{\mathcal{M}}^{n} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \vec{M}^{i}$$

We have the following proposition.

Proposition 2.2.1.

$$\overset{\rightarrow}{\mathcal{M}}^{n} - \overset{\leftarrow}{\mathcal{M}}^{n} \xrightarrow{\mathcal{L}} \Lambda,$$

where it satisfies for all $t \in \mathbb{R}_+$:

$$\Lambda_t = \int_0^t \sqrt{(E[Y_{s-}\overset{\rightarrow}{\varphi}_s(V_s)] + E[Y_{s-}\overset{\leftarrow}{\varphi}_s(V_s)])} dB_s,$$

and where B is an usual Brownian motion.

To prove the proposition, we are going to use the Central Limit Theorem for Local Martingales from [28], where in our particular case of a square integrable martingale $\mathcal{M}^n$, it is enough to show that:

- (Lindeberg condition) For all $\epsilon > 0$ and $t > 0$,

$$\sum_{s \leq t} E(\mid \triangle \mathcal{M}_s^n \mid^2 1_{\{|\triangle \mathcal{M}_s^n| > \epsilon\}}) \underset{n \uparrow \infty}{\longrightarrow} 0,$$

where $\triangle \mathcal{M}_s^n = \mathcal{M}_s^n - \mathcal{M}_{s-}^n$.

- For all $t \in \mathbb{R}_+$,

$$< \mathcal{M}^n, \mathcal{M}^n >_t \xrightarrow{P} \mathcal{A}(t),$$

when $n \uparrow \infty$, and where $\mathcal{A}(\cdot)$ is a continuous increasing real function such that $\mathcal{A}(0) = 0$.

Under those conditions we will get for all $t \in \mathbb{R}_+$:

$$\mathcal{M}_t^n \xrightarrow{\mathcal{L}} \mathcal{M}_t = \int_0^t \sqrt{\mathcal{A}(s)} dB_s,$$

where B is a usual Brownian motion.

Proof. As the elements of $\left(\overset{\leftarrow}{M}{}^i, \vec{M}{}^i\right)_{i=1,\ldots,n}$ cannot jump together, we have that:

$$\max\{\mid \triangle \overset{\rightarrow}{\mathcal{M}}{}_t^n \mid, \mid \triangle \overset{\leftarrow}{\mathcal{M}}{}_t^n \mid\} \leq \frac{1}{\sqrt{n}},$$

for all $t \in \mathbb{R}_+$ which implies that Lindeberg condition is satisfied. Also, we have that the associated increasing processes satisfy:

$$< \overset{\rightarrow}{\mathcal{M}}{}^n, \overset{\rightarrow}{\mathcal{M}}{}^n >_t = \frac{1}{n} \sum_{i=1}^n \int_0^t Y_{s-}^i \overset{\rightarrow}{\varphi}{}_s^i(V_s) ds \xrightarrow{P} \int_0^t E[Y_{s-} \overset{\rightarrow}{\varphi}_s(V_s)] ds$$

and

$$< \overleftarrow{\mathcal{M}}^n, \overleftarrow{\mathcal{M}}^n >_t = \frac{1}{n}\sum_{i=1}^{n}\int_0^t Y^i_{s-}\overleftarrow{\varphi}^i_s(V_s)ds \xrightarrow{P} \int_0^t E[Y_{s-}\overleftarrow{\varphi}_s(V_s)]ds,$$

for all $t \in \mathbb{R}_+$, by the Weak Law of Large Numbers. By a simple tightness argument, we get:

$$< \overrightarrow{\mathcal{M}}^n, \overrightarrow{\mathcal{M}}^n > \xrightarrow{P} \int E[Y_{s-}\overrightarrow{\varphi}_s(V_s)]ds$$

and

$$< \overleftarrow{\mathcal{M}}^n, \overleftarrow{\mathcal{M}}^n > \xrightarrow{P} \int E[Y_{s-}\overleftarrow{\varphi}_s(V_s)]ds,$$

uniformly on any finite time horizon $[0, T]$.

Therefore, by Central Limit Theorem for Local Martingales, the proposition holds.

□

Consider now the following hypothesis:

$$H_0 : E[\int Y_{s-}\overrightarrow{\varphi}_s(V_s)ds - \int Y_{s-}\overleftarrow{\varphi}_s(V_s)ds] = \int I_K(s)ds$$

Under H_0 and with n large enough, an asymptotic confidence interval for $\int I_K(s)ds$ of $(1-\alpha)\%$, is given by:

$$\left(\frac{1}{n}\sum_{i=1}^{n}\int Y^i_{s-}d[\overrightarrow{N}^i_s(V_s) - \overleftarrow{N}^i_s(V_s)] \pm Z_{(1-\alpha/2)}\sqrt{\frac{\int(E[Y_{s-}\overrightarrow{\varphi}_s(V_s)] + E[Y_{s-}\overleftarrow{\varphi}_s(V_s)])ds}{n}}\right),$$

where $Z_{(1-\alpha/2)}$ is the $(1-\alpha/2)$-percentile from the standard normal distribution.

Comment

In a typical neuron, we have many ionic species involved. Thus, to apply this methodology we have to consider all of those ionic species, which makes this somewhat impractical. Nevertheless, according to the Hodgkin-Huxley paradigm, we can extend these results by including only a few ionic species which are the most influential in the voltage variation: potassium, sodium and, maybe, chloride, where the latter is the most responsible for the Ohmic leak current I_L (see [21]).

A simulated result

By considering (2.1.1) where the process X is at a mesoscopic level, we have that, besides the spatial level, the dynamic of X may work faster than the macroscopic dynamic of V. So, during an interval of time $[0, T]$, we may approximate the law of X by freezing h (see next chapter).

Here, we assume that difference. Suppose that there exists $v' \in E$ such that $h(v') = 0$. Freeze h at v'.

With a diffusion coefficient $\sigma_\star = 1$, the sensors dynamic are depicted in Fig. 2.3.

With $\overset{\leftarrow i}{N}_1(V_1) \overset{iid}{\sim} Poisson(20)$ and $\overset{\rightarrow i}{N}_1(V_1) \overset{iid}{\sim} Poisson(100)$, for $i = 1, ..., 30$, the estimated physical compensator and its estimated error are shown in Fig. 2.4.

2.2.2 On testing H-H model by observing one channel macroscopically

Here, we will not need to simplify the model as (2.2.1), but only to observe the open/closed times of an ion channel (K^+ or Na^+) and the voltage variation. We want to check the original assumptions of the gating process and not only the structure of ion currents. In order to illustrate our method, we will take the K^+ case as reference.

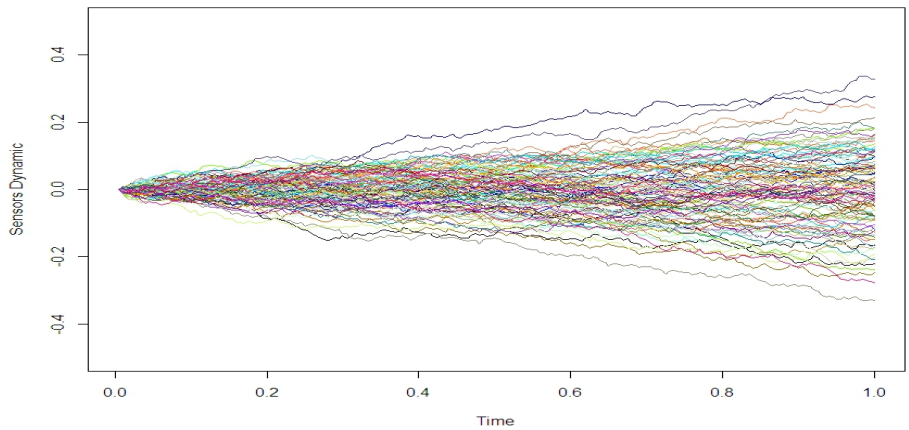

Figure 2.3: A random sample of 120 voltage sensors, with initial conditions equal to 0.

Let $Y \in \{0, 1\}$ be the dynamic of a typical K^+ channel whose states are 1 if the channel is open and 0 otherwise. Here, we are going to assume that we can only observe those states of a particular K^+ channel and the voltage variation V. We want to contrast that our observations come from the process $Y = \prod_{j=1}^{4} e_j$, where the e_j's are iid and its common probability dynamic follows the coupled master equation:

$$\frac{dp}{dt} = (1 - p)\alpha(V) - p\beta(V)$$

As we know, each e_j represents the discrete voltage-gated state, which we assume to be recurrent (by biological considerations).

Without loss of generality, we will start at $Y_0 = 1$. Also, as usual, the e_j's and Y are right continuous with left-hand limits. Note that, since we only observe (Y, V) (and not the subunits), we cannot know which is the state of the e_j's configuration when $Y = 0$.

To begin, we will slightly modify some notations. Consider for all $t', t \in \mathbb{R}_+$ the

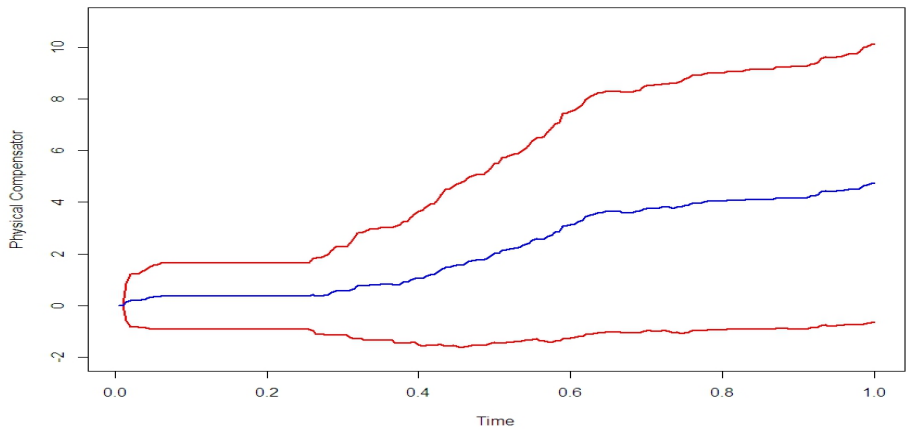

Figure 2.4: The estimated physical compensator (blue) and its functional confidence interval (red), with $\alpha = 0.05$.

flow $\Phi(t, v_{t'})$, which denotes the solution of the voltage equation at time $t+t'$ starting at $V_{t'} = v_{t'}$.

Define $\tau_{1,o} = 0$, $\tau_{1,c} = \inf\{t > 0 : \triangle Y_t = -1\}$, $\tau_{2,o} = \inf\{t > \tau_{1,c} : \triangle Y_t = 1\}$, $\tau_{2,c} = \inf\{t > \tau_{2,o} : \triangle Y_t = -1\}$, and so on, where $\triangle Y_t = Y_t - Y_{t-}$. Consider $\tau_i^o = \tau_{i,c} - \tau_{i,o}$ and $\tau_i^c = \tau_{i+1,o} - \tau_{i,c}$. Now, note that under the H-H model assumptions, for each $i \in \mathbb{N}$ and $t \in \mathbb{R}_+$ our null hypothesis is given by:

$$H_0 : P^{t_{i,o}, v_{t_{i,o}}}(\tau_i^o > t) =$$

$$P[\tau_i^o > t \mid (\tau_{i,o}, V_{\tau_{i,o}}) = (t_{i,o}, v_{t_{i,o}})] = \exp\{-\int_0^t \lambda(\Phi(s, v_{t_{i,o}}))ds\}, \tag{2.2.2}$$

where $\int_0^t \lambda(\Phi(s, v_u))ds = 4\int_u^{u+t} \beta(V_s)ds$. To evaluate the conditional law of τ_i^c, we have to do calculations involving to condition on different e_j's states that we cannot really observe. Thus, under our setting H_0 has to be reduced to the classical behavior

of the open times $\{\tau_i^o\}$. However, if V were fixed, rate transitions involved are no longer dependent on voltage and then, we can be able to analyze τ_i^c as well.

From (2.2.2), for all $i \in \mathbb{N}$ and $t \in \mathbb{R}_+$ we have that:

$$\lambda(\Phi(t, v_{t_{i,o}})) = f_{t_{i,o}, v_{t_{i,o}}}(t)/P^{t_{i,o}, v_{t_{i,o}}}(\tau_i^o > t),$$

where $f_{v_{t_{i,o}}}(t)$ is the density of τ_i^o given $(\tau_{i,o}, V_{\tau_{i,o}}) = (t_{i,o}, v_{t_{i,o}})$. That is, if $E^{t_{i,o}, v_{t_{i,o}}}(\cdot) = E[\cdot \mid (\tau_{i,o}, V_{\tau_{i,o}}) = (t_{i,o}, v_{t_{i,o}})]$, we have:

$$E^{t_{i,o}, v_{t_{i,o}}}(\mathcal{N}_t^i) = E^{t_{i,o}, v_{t_{i,o}}}\left(\int_0^t J_{s-}^i \lambda(\Phi(s, V_{\tau_{i,o}}))ds\right),$$

where $\mathcal{N}_t^i = 1_{\{\tau_i^o \leq t\}}$ and $J_t^i = 1_{\{\tau_i^o > t\}}$. As the e_j's states are recurrent, we have $\mathcal{N}_0^i = 0$ a.s. for all $i \in \mathbb{N}$ and then, the process $\mathcal{N}^i$ can be written as follows:

$$\mathcal{N}_t^i = \int_{(0,t]} J_{s-}^i \kappa_i(ds),$$

for all $t \in \mathbb{R}_+$, where $\kappa_i = \sum_{s \in (0,t], \mathcal{N}_s^i > \mathcal{N}_{s-}^i} \delta_s$. Let $m_i = \kappa_i - \nu_i$, with $\nu_i(ds) = \lambda(\Phi(s, V_{\tau_{i,o}}))ds$. Hence, under $P^{t_{i,o}, v_{t_{i,o}}}$ and H_0, ν_i is the predictable projection of κ_i (see [22]). In other words, under the complete filtered space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, P^{t_{i,o}, v_{t_{i,o}}})$, where $\mathcal{F}_t = \sigma(Y_s, s \leq t)$, we have that:

$$\mathcal{M}_t^i = \int_{(0,t]} J_{s-}^i m_i(ds)$$

is a $\mathcal{F}_t$-martingale with

$$< \mathcal{M}^i, \mathcal{M}^i >_t = \lim_{n \uparrow \infty} \sum_{k=1}^{2^n - 1} (\mathcal{M}_{\frac{t(k+1)}{2^n}}^i - \mathcal{M}_{\frac{tk}{2^n}}^i)^2$$

$$= \int_{(0,t]} J_{s-}^i \nu_i(ds),$$

for all $t \in \mathbb{R}_+$.

In order to extend this for all $i \in \mathbb{N}$, we are going to consider the extended measure $\overline{P} = \bigotimes_{i=1}^{\infty} P^{t_{i,o}, v_{t_{i,o}}}$ and its corresponding filtered space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, \overline{P})$. We will call it "the observable space". Note also that the $\mathcal{M}^i$'s are $\overline{P}$-independent under H_0 (here the Markov property of the e_j's intervenes), and if we denote by $\overline{E}$ and $\overline{V}$ the expectation and the variance on the observable space, respectively, we get:

$$\overline{V}(\mathcal{M}^{\cdot}_{\cdot}) = \overline{E}(\mathcal{M}^{\cdot 2}_{\cdot}) = \int_{(0,\cdot]} \overline{P}(\tau^o_{\cdot} > s)\lambda(\Phi(s, v_{t_{\cdot,o}}))ds = \overline{E} < \mathcal{M}^{\cdot}, \mathcal{M}^{\cdot} >.$$

$$= \int_{(0,\cdot]} f_{t_{\cdot,o}, v_{t_{\cdot,o}}}(s)ds = F_{t_{\cdot,o}, v_{t_{\cdot,o}}}(\cdot) = \overline{E}(\mathcal{N}^{\cdot}_{\cdot})$$

For the following theorem, denote by $\mathcal{L}$ the law induced by $\overline{P}$. From this, a statistical test can be set.

Theorem 2.2.2. *Under H_0, we have:*

$$\frac{1}{\sqrt{N}} \sum_{i=1}^{N} \mathcal{M}^i \xrightarrow{\mathcal{L}} \mathcal{Z},$$

when $N \longrightarrow \infty$, and where $\mathcal{Z}$ is a Gaussian process such that for all $t \in \mathbb{R}_+$:

$$\mathcal{Z}_t = \int_0^t \sqrt{A(s)} dB_s,$$

where B is a standard Brownian motion and $A \in [0,1]$ is a strictly increasing deterministic function.

Proof. As the states of Y are recurrent, there exist $\lambda_\star$ and $\lambda^\star$ such that $0 < \lambda_\star \leq \lambda(\Phi(\cdot,\cdot)) \leq \lambda^\star < \infty$. Let $\mathcal{S}^N = (1/\sqrt{N}) \sum_{i=1}^{N} \mathcal{M}^i$. Then, we have that $\mathcal{S}^N_t$ is a $\mathcal{F}_t$-martingale such that it satisfies $\mid \triangle \mathcal{S}^N_t \mid \leq (1 + \lambda^\star)/\sqrt{N} = O(1/\sqrt{N})$.

Now, note that for all $t \in \mathbb{R}_+$:

$$< \mathcal{S}^N, \mathcal{S}^N >_t = \frac{1}{N} \sum_{i=1}^{N} \int_{(0,t]} J^i_{s-} \nu_i(ds) = \mathcal{A}^N(t) \leq \lambda^\star t$$

Thus, by the Weak Law of Large Numbers, we get:

$$\mathcal{A}^N(t) - \overline{E}(\mathcal{A}^N(t)) = \mathcal{A}^N(t) - \frac{1}{N} \sum_{i=1}^{N} F_{t_{i,o}, v_{t_{i,o}}}(t) \xrightarrow{\overline{P}} 0,$$

for all $t \in \mathbb{R}_+$. This implies that, if for any $t \in \mathbb{R}_+$ $A^N(t) = (1/N) \sum_{i=1}^{N} F_{t_{i,o}, v_{t_{i,o}}}(t)$ has a limit, then it will be the same as the limit of $\mathcal{A}^N(t)$. Note also that $A^N(\cdot) \in [0,1]$, where $A^N(t) \uparrow 1$ when $t \uparrow \infty$ and $A^N(t) \downarrow 0$ when $t \downarrow 0$. The function A^N satisfies the subadditive property $A^{N+M} \leq A^N + A^M$, for all $N, M \in \mathbb{N}$, and therefore by Fekete's Subadditive Lemma we have $\lim_N (A^N/N) = \liminf_N (A^N/N) = A$. Note that by dominated convergence A also satisfies $A(t) \uparrow 1$ when $t \uparrow \infty$ and $A(t) \downarrow 0$ when $t \downarrow 0$.

Finally, we conclude the proof using again the Central Limit Theorem for Local Martingales from [28].

□

Thus, for N large enough we reject H_0 at α (probability of "type I error") if $\mid S^N_\cdot \mid > Z_{(1-\alpha/2)} \sqrt{A^N(\cdot)}/\sqrt{N}$, where $S^N_\cdot = (1/N) \sum_{i=1}^{N} \mathcal{M}^i_\cdot$ and A^N is as in the preceding proof.

Remarks a) In the works cited at the beginning of this section, the open times in particular are treated as an homogeneous process, that is, all of those times are iid. That happens when we consider fixed values for the voltage. Also, in [11] the hidden model follows a simple two-states homogeneous Markov chain, which excessively

simplifies what happen with closing times when we observe the phenomenon during a long time.

b) Although the presented method may be easier to implement in practice than the previous, it has the disadvantage that we deal only with the open times. So, it is a partial testing. One thing we can say about the closed times $\{\tau_i^c\}$ is that, for all $i \in \mathbb{N}$, the expected value for τ_i^c given $(\tau_{i,c}, V_{\tau_{i,c},}) = (t_{i,c}, v_{t_{i,c}})$, say ξ_i^c, is less than

$$\xi_i^c(\star) = \int_0^\infty t\psi(\Phi(t, v_{t_{i,c}})) \exp\{-\int_0^t \psi(\Phi(s, v_{t_{i,c}}))ds\}dt,$$

which is bounded by some positive interval and where $\int_0^t \psi(\Phi(s, v_{t_{i,c}}))ds = \int_{t_{i,c}}^{t+t_{i,c}} \alpha(V_u)du$. As in the previous theorem, we have that:

$$\liminf_N \frac{1}{N}\sum_{i=1}^N \xi_i^c(\star) = \lim_{N\to\infty}\frac{1}{N}\sum_{i=1}^N \xi_i^c(\star) \leq \lim_{N\to\infty}\frac{1}{N}\sum_{i=1}^N \xi_i^c$$

and thus, we immediately reject the Hodgkin-Huxley hypothesis if this is not satisfied (for large N, in practice).

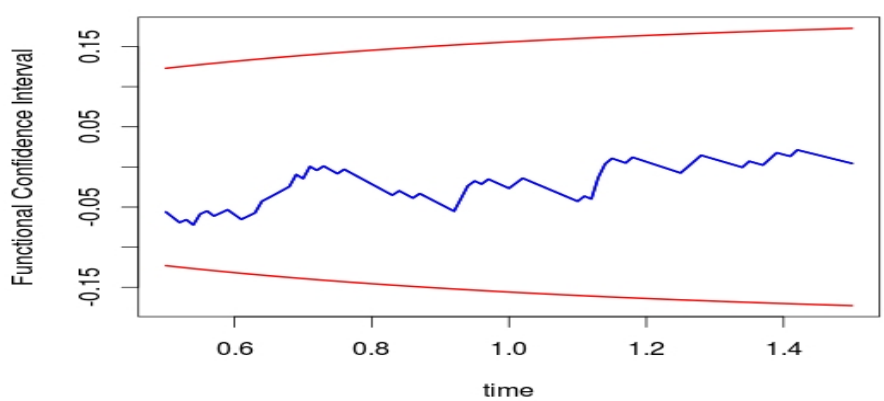

Figure 2.5: Statistical test under H_0 with $\alpha = 0.05$ and $N = 100$, in the uncoupled case, with $\lambda \equiv 1$. In blue is the process S^N, and in red curves $\pm Z_{(1-\alpha/2)}\sqrt{A^N(\cdot)}/\sqrt{N}$

Chapter 3

Estimating the first exit times from the basin of attractions under a slow/fast system

Regarding the possible different time scales involved in (2.1.1) as we suggested in 2.2.1, in this chapter we are going to consider a slow/fast version of (2.1.1) by taking into account a new parameter $0 < \delta << 1$, such that:

$$\begin{cases} \frac{dV_t}{dt} = \int_{\mathbb{R}} f(V_t, x)\mu_t(dx) \\ \delta dX_t = -U'(X_t)dt + h(V_t)dt + \sigma dW_t \end{cases}, \tag{3.0.1}$$

retaining the same conditions of (2.1.1) and A.1-A.3 satisfied, but now $\sigma = \sigma(\delta)$ introduces a third time scale. This because of in the Brownian motion time intervenes at its variance. Thus, the parameter δ accounts for differences in time scales.

Thus, this chapter is basically aimed at the study of metastability of the system (3.0.1). We are going to start by analyzing the equation:

$$dX_t^\gamma = -U'(X_t^\gamma)dt + \gamma dt + \sigma dW_t, \tag{3.0.2}$$

with $X_0^\gamma = x$ fixed, and where we have frozen at some value $v' \in E$ with $h(v') = \gamma$.

Consider the main system of the previous equation, given by:

$$dx_t^\gamma = (g(x_t^\gamma)dt + \gamma)dt, \tag{3.0.3}$$

with $x_0^\gamma = x$ and $g(x) = -U'(x)$. Note that g' vanishes at $\pm\sqrt{1/3}$, where $-\sqrt{1/3}$ and $\sqrt{1/3}$ are the minimum and maximum of g, respectively; and by symmetry $g(\sqrt{1/3}) = -g(-\sqrt{1/3})$.

Let $\gamma \in \mathcal{V}(0, g(\sqrt{1/3}))$, where $\mathcal{V}(0, g(\sqrt{1/3}))$ denotes a centered ball of radius $g(\sqrt{1/3})$. We have that the set $\{x \in \mathbb{R}_+ : g(x) = -\gamma\}$ is composed by three equilibrium points of (3.0.3): $x_-(\gamma) < x_0(\gamma) < x_+(\gamma)$, where $x_\pm(\gamma)$ are stable points and $x_0(\gamma)$ is unstable. Let $\mathcal{E}$ be the range of h. We are going to consider from now on that $\gamma \in \mathcal{E} \cap \mathcal{V}(0, g(\sqrt{1/3}))$. If the main system of X from (2.1.1) (i.e., without the Brownian motion) always keeps three stable points, then the range of h is in $\mathcal{V}(0, g(\sqrt{1/3}))$.

We have the following.

Proposition 3.0.3. *Let $X_0^\gamma = x_0^\gamma = x \in \mathbb{R}$. Then:*

$$X^\gamma \xrightarrow{P} x^\gamma,$$

locally in time, when $\sigma \downarrow 0$.

Proof. Consider any $0 < M' < \infty$ such that $x \in \mathcal{V}(0, M')$. Define:

$$\tau_\gamma^{M'} = \inf\{t \geq 0 :| X_t^\gamma | \vee | x_t^\gamma |> M'\},$$

Now, note that for all $0 < T < \infty$ and $t \in [0, T \wedge \tau_\gamma^{M'}]$,

$$\int_0^t \mid g(X_s^\gamma) - g(x_s^\gamma) \mid ds \leq (1 + 3M'^2) \int_0^t \mid X_s^\gamma - x_s^\gamma \mid ds$$

Let $A(T) = \sup_{t \in [0,T]} \mid W_t \mid$. Then, for all $t \in [0, T \wedge \tau_\gamma^{M'}]$ and using Gronwall's lemma we obtain:

$$\mid X_t^\gamma - x_t^\gamma \mid \leq \sigma A(T) \exp\{T(1 + 3M'^2)\}$$

Thus, the proposition holds.

□

Let $G(x, \gamma) = g(x) + \gamma$ and consider:

$$\delta dX_t^{\gamma,\delta} = G(X_t^{\gamma,\delta}, \gamma)dt + \sigma dW_t, \tag{3.0.4}$$

with $X_0^{\gamma,\delta} = x$. Making a time change $\tilde{X}_t^\gamma = X_{\delta t}^\gamma$ (homogenization of time scale) we get:

$$d\tilde{X}_t^\gamma = G(\tilde{X}_t^\gamma, \gamma)dt + \sigma_\delta dW_t, \tag{3.0.5}$$

where $\sigma_\delta = \sigma/\sqrt{\delta}$.

Now, define:

$$V_\pm(\gamma) = -2 \int_{x_\pm(\gamma)}^{x_0} G(x, \gamma)dx$$

and the basins of attraction $D_1(\gamma) = (-\infty, x_0(\gamma))$ and $D_2(\gamma) = (x_0(\gamma), \infty)$. Note that $V_\pm(\gamma)/2$ are the barrier heights of the double-well potential $\mathcal{U}(x, \gamma) = -x^2/2 + x^4/4 - x\gamma$, with the respective bottoms at $x_\pm(\gamma)$.

Let $\tilde{\tau}_i^\gamma = \inf\{t \geq 0 : \tilde{X}_t^\gamma \notin D_i(\gamma)\}$ and $\tau_i^\gamma = \inf\{t \geq 0 : X_t^{\gamma,\delta} \notin D_i(\gamma)\}$, for $i = 1, 2$.

The following proposition says about the estimated first exit times that the processes (3.0.4) and (3.0.5) leave the basin of attractions, under a small noise assumption.

Proposition 3.0.4. *Assume* $\sigma = \sigma(\delta) = \sqrt{c\delta(\ln(\delta^{-1}))^{-1}}$, *for some* $0 < c < \infty$. *Then, for any* $\epsilon > 0$*:*

$$\lim_{\delta \downarrow 0} P^x(\exp\{[V_+(\gamma) - \epsilon](\sigma_\delta^2)^{-1} < \tilde{\tau}_2^\gamma < \exp\{[V_+(\gamma) + \epsilon](\sigma_\delta^2)^{-1}\} \tag{3.0.6}$$

$$= \lim_{\delta \downarrow 0} P^x(\delta^{-(V_+(\gamma)-\epsilon)c^{-1}} < \tilde{\tau}_2^\gamma < \delta^{-(V_+(\gamma)+\epsilon)c^{-1}}) = 1$$

if $x \in D_2(\gamma)$, *and*

$$\lim_{\delta \downarrow 0} P^x(\exp\{[V_-(\gamma) - \epsilon](\sigma_\delta^2)^{-1} < \tilde{\tau}_1^\gamma < \exp\{[V_-(\gamma) + \epsilon](\sigma_\delta^2)^{-1}\} \tag{3.0.7}$$

$$= \lim_{\delta \downarrow 0} P^x(\delta^{-(V_-(\gamma)-\epsilon)c^{-1}} < \tilde{\tau}_1^\gamma < \delta^{-(V_-(\gamma)+\epsilon)c^{-1}}) = 1$$

if $x \in D_1(\gamma)$.

The previous results have been established in [16]; (3.0.6) and (3.0.7) were originally proved by Freidlin and Wentzell in [17], in Chapter 4, Theorem 4.2.

Since τ_i^γ is distributed as $\delta\tilde{\tau}_i^\gamma$, for $i = 1, 2$, under the same assumptions of the previous proposition we have:

$$\lim_{\delta \downarrow 0} P^x(\delta^{(c-V_+(\gamma)+\epsilon)c^{-1}} < \tau_2^\gamma < \delta^{(c-V_+(\gamma)-\epsilon)c^{-1}}) = 1$$

if $x \in D_2(\gamma)$, and

$$\lim_{\delta\downarrow 0} P^x(\delta^{(c-V_-(\gamma)+\epsilon)c^{-1}} < \tau_1^\gamma < \delta^{(c-V_-(\gamma)-\epsilon)c^{-1}}) = 1$$

if $x \in D_1(\gamma)$.

Comments:

(1) Note that if $x \in D_1(\gamma)$ and $c > V_-(\gamma)$, the process in (3.0.4) leaves $D_1(\gamma)$ immediately when $\delta \downarrow 0$. But, if $c < V_-(\gamma)$, the process in (3.0.4) will always remain in $D_1(\gamma)$, with probability 1. An analogous statement holds for the first exit time from $D_2(\gamma)$.

(2) The parameter σ is physically relating to the heath transference with the reservoir. For example, Proposition 3.0.2 says that when that heat transference is disappearing, our open system is becoming an isolated system. Such limits in thermodynamics are known as adiabatic limits.

(3) We can rewrite (3.0.1) under the time change $\tilde{X}_t = X_{\delta t}$:

$$\begin{cases} \frac{d\tilde{V}_t}{dt} = \delta \int_{\mathbb{R}} f(\tilde{V}_t, x)\mu_t(dx) \\ d\tilde{X}_t = G(\tilde{X}_t, h(\tilde{V}_t))dt + \sigma_\delta dW_t \end{cases}, \tag{3.0.8}$$

where $\delta \sup_{v,u} \mid f(v,u) \mid$ can be small enough. Thus, this is the reason why we could use (3.0.2) in order to approximate X in (2.1.1), although in 2.2.1 we have taken $\sigma_\star = \sigma_\delta = 1$, hence, in that case, the assumption of Proposition 3.0.3 does not hold. Also, note that the Fokker-Planck equation of (3.0.5) is given by:

$$\frac{\partial P^{x,\gamma}}{\partial t} = \frac{\partial (U'(y)P^{x,\gamma})}{\partial y} - \gamma \frac{\partial P^{x,\gamma}}{\partial y} + \frac{\sigma_\delta^2}{2}\frac{\partial^2 P^{x,\gamma}}{\partial y^2} \tag{3.0.9}$$

Thus, we say that it is possible that the voltage dynamic, seen at a mesoscale, varies slowly and therefore, the voltage sensor dynamic looks like a Markovian process.

Now, we are going to use (3.0.9) in order to obtain a stationary estimation of the $\tilde{\tau}_i^{\gamma}$'s. Assume first $\mathcal{U}(x_-(\gamma),\gamma) > \mathcal{U}(x_+(\gamma),\gamma)$. Consider $\mid y - x_+(\gamma) \mid$ small. We have that:

$$\mathcal{U}(y,\gamma) \approx \mathcal{U}(x_+(\gamma),\gamma) + \frac{1}{2}\mathcal{U}''(x_+(\gamma),\gamma)(y - x_+(\gamma))^2$$

(the derivative is taken on the first component), and then, for any finite time t and σ_δ^2 very small ($\mid y - x_+(\gamma) \mid \sim \sigma_\delta$), the solution of (3.0.9) may be approximated by:

$$P_t^{\gamma}(y) = \mathcal{N} \exp\left\{-\frac{2}{\sigma_\delta^2}[\mathcal{U}(x_+(\gamma),\gamma) + \frac{1}{2}\mathcal{U}''(x_+(\gamma),\gamma)(y - x_+(\gamma))^2]\right\},$$

where

$$\mathcal{N}^{-1} \approx \exp\left\{-\frac{2}{\sigma_\delta^2}\mathcal{U}(x_+(\gamma),\gamma)\right\}\sqrt{\frac{2\pi\sigma_\delta^2}{\mathcal{U}''(x_+(\gamma),\gamma)}}$$

That is:

$$P_t^{\gamma}(y) = \sqrt{\frac{\mathcal{U}''(x_+(\gamma),\gamma)}{2\pi\sigma_\delta^2}} \exp\left\{-\frac{1}{\sigma_\delta^2}\mathcal{U}''(x_+(\gamma),\gamma)(y - x_+(\gamma))^2]\right\} \tag{3.0.10}$$

This means that, when σ_δ^2 is small enough, the deterministic stationary state at $x_+(\gamma)$ is the more stable state in the stochastic stationary state. But, (3.0.10) is no longer valid in the long term due to the bistable component (the process will jump to the other basin, with probability 1).

Also, under the previous stationary considerations, in [18], Chapter 9, we can find that first exit time $\tilde{\tau}_2^{\gamma}$, when the "particle" initially near $x_+(\gamma)$, is given approximately by:

$$\frac{2\pi}{\sqrt{\mid \mathcal{U}''(x_0(\gamma)) \mid \mathcal{U}''(x_+(\gamma))}} \exp\left\{\frac{V_+(\gamma)}{\sigma_\delta^2}\right\}$$

A similar result for $\tilde{\tau}_1^\gamma$ we can get, under analogous assumptions. We have to be careful with the previous expression: when the adiabatic limit is taking place, the above first exit time grows exponentially. Thus, it has to be taken only as an expected time approximation that our process will take to escape from its basins, when we have a relatively small perturbation.

Further, we can take advantage of the approaches we have done and the typical behavior of the voltage according to their phases, to estimate h. In the previous chapter, as a direct consequence of Theorem 2.1.6, we found a consistent estimator of $\int h(V_t)dt$. Now, we will show how to estimate h under the slow/fast system we are dealing, in an adiabatic limit, and after having carried out some approximations according to the voltage phases. The assumption that the range of h is in $\mathcal{V}(0, g(\sqrt{1/3}))$ is not necessary. Nevertheless, we are going to also be interested in contrasting this assumption by testing the hypothesis H_0: "The range of h is in $\mathcal{V}(0, g(\sqrt{1/3}))$". To describe the method, we will take as reference the K^+ channels.

Typically, the K^+ channels start to open at the beginning of the repolarization phase until the end of the after-potential hyperpolarization phase. This means that, during theses phases and under H_0, we hope that $\mathcal{U}(x_-(h), h) \geq \mathcal{U}(x_+(h), h)$. Fig. 3.1 shows the behavior of potassium and sodium conductances.

By observing the voltage behavior, let $[T_0, T]$ be the time interval between the repolarization and the after-potential hyperpolarization phases. For δ small enough, we will approximate (3.0.8) in the following way: Consider a partition of $[T_0, T]$ of the form $[T_i, T_{i+1}]$, with $i = 0, 1..., n-1$, $T_n = T$ and $\Delta = T_{i+1} - T_i > 0$. Let

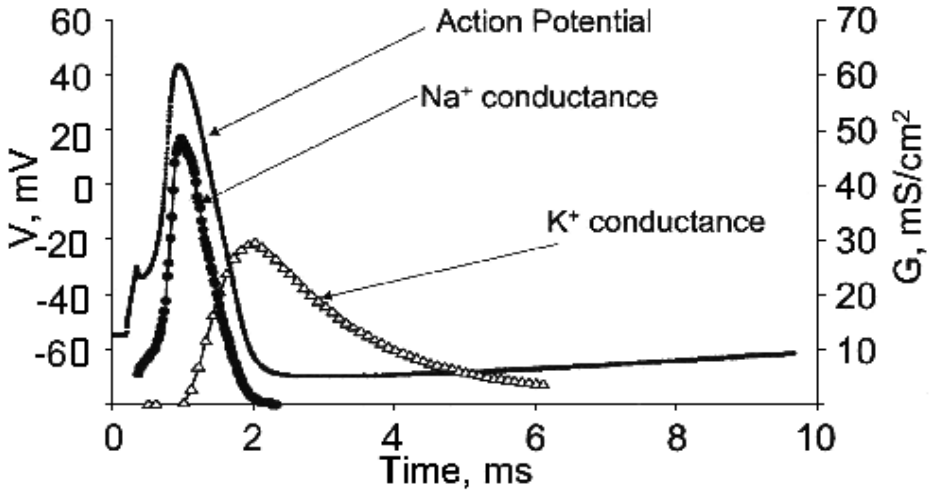

Figure 3.1: K^+ and Na^+ conductances according to the voltage variation, shifted in ≈ -60mV from the original H-H model.

$\gamma_i = h(V_{(T_i+T_{i+1})/2})$ and

$$d\tilde{X}_t^{\gamma_i} = -U'(\tilde{X}_t^{\gamma_i})dt + \gamma_i dt + \sigma_\delta dW_t,$$

if $t \in [T_i, T_{i+1}]$, with $\tilde{X}_0^{\gamma_i} = x$. For any $i = 0, ..., n-1$ we have:

$$\frac{1}{\Delta}\left(\tilde{X}_{\tilde{T}_{i+1}}^{\gamma_i} - \tilde{X}_{\tilde{T}_i}^{\gamma_i} + \int_{T_i}^{T_{i+1}} U'(\tilde{X}_t^{\gamma_i})dt\right) = \gamma_i + \varsigma_i^\delta = \hat{\gamma_i}^\delta, \tag{3.0.11}$$

where $\varsigma_i^\delta \sim N(0, \sigma_\delta^2/\Delta)$ and the sequence $\{\varsigma_i^\delta\}_{i=0,...,n-1}$ is an iid sequence. By Proposition 3.0.2, it is clear that if $\sigma_\delta \downarrow 0$ when $\delta \downarrow 0$ we have that $\hat{\gamma_i}^\delta \xrightarrow{P} \gamma_i$. Also, note that under H_0 and within these time intervals, we expect γ_i belongs to $[0, g(\sqrt{1/3}))$, for any $i = 0, ..., n-1$.

A confidence interval can be obtained as:

$$I_i^\delta = \hat{\gamma}_i \pm Z_{1-\alpha/2}\sqrt{\frac{\sigma_\delta^2}{\Delta}}$$

That is to say, we do not reject H_0 at α-level, whenever $I_i^\delta \cap [0, g(\sqrt{1/3})) \neq \emptyset$, for all $i = 0, ..., n-1$.

Nevertheless, this contrast is ideally suited under an adiabatic limit. That is to say, we have to ensure first:

$$\sigma_\delta = \sqrt{\lim_{n\to\infty} \frac{1}{t} \sum_{k=1}^{2^n} \left(\tilde{X}^N_{t\frac{k}{2^n}} - \tilde{X}^N_{t\frac{(k-1)}{2^n}} \right)^2},$$

is small enough, for any $0 < t < \infty$. Specifically, we have to check whether $0 < \sigma_\delta, \delta << 1$.

If that is not met, we have to take a sample of particles $\{\tilde{X}_t^{\gamma_i,k}\}_{t\in[T_i,T_{i+1}],i=0,...,n-1}^{k=1,...,N}$. That is, for any $i = 0, ..., n-1$:

$$\frac{1}{N\Delta} \sum_{k=1}^{N} \left(\tilde{X}^{\gamma_i,k}_{T_{i+1}} - \tilde{X}^{\gamma_i,k}_{T_i} + \int_{T_i}^{T_{i+1}} U'(\tilde{X}_t^{\gamma_i,k}) dt \right) = \gamma_i + \varsigma_i^N = \hat{\gamma}_i^N, \tag{3.0.12}$$

where $\varsigma_i^N \sim N(0, \sigma_\delta^2/[N\Delta])$ and $\{\varsigma_i^N\}_{i=0,...,n-1}$ is an iid sequence. In such a case, the law of $\{\varsigma_i^N\}_{i=0,...,n}$ does not depend on δ. Therefore, by the Law of Large Numbers $\hat{\gamma}_i^N \xrightarrow{P} \gamma_i$, for any $i = 0, ..., n-1$, whenever $N \uparrow \infty$. The confidence intervals are given by:

$$I_i^N = \hat{\gamma}_i^N \pm Z_{1-\alpha/2} \sqrt{\frac{\sigma_\delta^2}{N\Delta}}$$

The criterion for testing the null hypothesis above is similar, ideally suited for N large enough.

Within the depolarization phase, we expect $\mathcal{U}(x_-(h), h) \leq \mathcal{U}(x_+(h), h)$ and an analogous methodology can be applied for checking whether the γ_i's belong to $(-g(\sqrt{1/3}), 0]$.

Comment:

If δ were quite small, then h varies slowly, which also could imply that h changes the sign (if it does) nearly quickly. Thus, this can be thought as the range of h is not far from 0, and then, it probably belongs to $\mathcal{V}(0, g(\sqrt{1/3}))$.

A note on a Large Deviations result

We are going to finish this chapter by giving a Large Deviation result for a stochastic process whose law is described by Equation (3.0.9). For details, about this theory see [12]. Nevertheless, the result we are going to apply comes from [2].

Here, we fix γ and assume that $\gamma \in \mathcal{V}(0, g\sqrt{1/3})$. The dynamic we will study is giving by:

$$dX_t^\delta = -U'(X_t^\delta)dt + \gamma dt + \sigma_\delta dW_t, \tag{3.0.13}$$

with $X_0^\delta = x_0 \in \mathbb{R}$. The special case we will deal is when $\sigma_\delta \propto \delta$. Thus, without loss of generality, assume that $\sigma_\delta = \delta$.

The main result from [2] will be established below, but adapted to our case of one dimension. Consider the general stochastic evolution:

$$dY_t^\delta = b_\delta(Y_t^\delta)dt + \delta\vartheta_\delta(Y_t^\delta)dB_t, \tag{3.0.14}$$

where $Y_0^\delta = y_0 \in \mathbb{R}$ and B is a standard Brownian motion.

Let $0 < T < \infty$ and consider a fix time horizon $[0, T]$. Let $\mathcal{C} = \mathcal{C}([0, T], \mathbb{R})$ be the space of continuous paths $[0, T] \longrightarrow \mathbb{R}$ endowed with the topology of uniform convergence. Set $\mathcal{C}_x = \mathcal{C}_x([0, T], \mathbb{R})$ as the closed hyperplane of the paths starting at $x \in \mathbb{R}$. Let $\mathcal{H} = \mathcal{H}([0, T], \mathbb{R})$ be the subspace of $\mathcal{C}_0$ of paths that are absolutely continuous and whose derivative is square integrable on $[0, T]$ and endowed with the

Hilbert norm $|\cdot|_1$, that is,

$$| h |_1^2 = \int_0^T | \dot{h}_s |^2 \, ds$$

For $h \in \mathcal{C}_0$ we set:

$$I(h) = \begin{cases} \frac{1}{2} | h |_1^2, & if \quad h \in \mathcal{H} \\ \infty, & if \quad h \notin \mathcal{H} \end{cases}$$

Consider the following assumptions: There exist measurable functions $b : \mathbb{R} \longrightarrow \mathbb{R}$ and $\vartheta : \mathbb{R} \longrightarrow \mathbb{R}$, such that

(A) for every $h \in \mathcal{H}$ and $y_0 \in \mathbb{R}$ the ordinary differential equation

$$\dot{y}_t = b(y_t) + \vartheta(y_t)\dot{h}_t,$$

with $y_{t=0} = y_0$, has a unique solution on $[0, T]$.

(B) Let $S_{y_0}(h)$ denote the solution of the above equation. Therefore $S_{y_0} : \mathcal{H} \longrightarrow \mathcal{C}_{y_0}$.For any $a > 0$, the restriction of S_{y_0} to the compact set $K_a = \{| h |_1 \leq a\}$ is continuous with respect to the uniform norm: for any $\{h_n\}_n \subset K_a$ such that $| h - h_n | \underset{n\to\infty}{\longrightarrow} 0$ with $h \in K_a$ then $| S_{y_0}(h_n) - S_{y_0}(h) | \underset{n\to\infty}{\longrightarrow} 0$.

(C) For every $R > 0$, $\rho > 0$, $a > 0$, $c > 0$ there exist $\delta_0 > 0$, $\alpha > 0$ such that, if $\delta < \delta_0$,

$$P(| Y^\delta - y | > \rho, | \delta B - h | \leq \alpha) \leq \exp\{-R/\delta^2\},$$

uniformly for $| h |_1 \leq a$ and $| y_0 | \leq c$, where $y = S_{y_0}(h)$.

The main theorem from [2] (Theorem 2.4) states the following.

Theorem 3.0.5. *Suppose that b_δ, ϑ_δ are locally Lipschitz continuous and Equation (3.0.14) has a strong solution for every $\delta > 0$. Then, if (A), (B) and (C) hold, the family $\{Y^\delta\}_\delta$ from 3.0.14 satisfies a Large Deviation Principle (LDP) on $\mathcal{C}_{y_0}$ with inverse speed δ^2 and good rate function*

$$\lambda(y) = \inf\{I(h) : S_{y_0}(h) = y\},$$

with the understanding $\lambda(y) = \infty$ if $\{I(h) : S_{y_0}(h) = y\} = .$ This means that

$$\limsup_{\delta\to 0} \delta^2 \log P(Y^\delta \in F) \leq -\inf_{\psi\in F} \lambda(\psi)$$

$$\liminf_{\delta\to 0} \delta^2 \log P(Y^\delta \in G) \geq -\inf_{\psi\in G} \lambda(\psi),$$

for every closed set $F \subset \mathcal{C}_{y_0}([0,T],\mathbb{R})$ and open set $G \subset \mathcal{C}_{y_0}([0,T],\mathbb{R})$ and that the level sets of λ are compact.

In our case we have $b_\delta(x) = b(x) = -U'(x) + \gamma$ and $\vartheta_\delta \equiv 1$. Then, the corresponding ordinary differential equation for every $h \in \mathcal{H}$ and $x_0 \in \mathbb{R}$, is given by:

$$\dot{x_t} = -U'(x_t) + \gamma + \dot{h_t}, \tag{3.0.15}$$

with $x_{t=0} = x_0$. Uniqueness of a solution of the above equation can be seen as a consequence of uniqueness of solutions of the systems that we have been studying in this work. Thus, (A) holds in our case.

As $\gamma \in \mathcal{V}(0, g\sqrt{1/3})$, $-U' + \gamma$ is a double-well potential, with minimums at $x_\pm$ and a maximum at $x_\star$ ($x_- < x_\star < x_+$). If $h \in K_a$, by defining $x_0^\pm = x_0 \pm a$, we have that, $x \in [x^-, x^+]$ on $[0,T]$, where

$$\dot{x}_t^{\pm} = -U'(x_t^{\pm}) + \gamma,$$

with $x_{t=0}^{\pm} = x_0^{\pm}$. It is a well-known fact that the solutions of the above equations will be attracted exponentially fast to the well at which its initial conditions belong to (at least that one of the both initial conditions starts at $x_\star$, which will imply that the corresponding solution will be stuck at $x_\star$).

Let us denote by $S_{x_0}(h)$ the solution of (3.0.15). Let $\{h_n\}_n \subset K_a$ such that $\mid h(t) - h_n(t) \mid \underset{n\to\infty}{\longrightarrow} 0$ with $h \in K_a$, for any $t \in [0,T]$. Denote $x^n = S_{x_0}(h_n)$. As noted above, if $h \in K_a$ then $S_{x_0}(h)$ belongs to a compact set on $[0,T]$, and as the drift part of (3.0.15) is locally Lipschitz, there exists a positive constant L such that for all $t \in [0,T]$ we get:

$$\mid S_{x_0}(h)(t) - S_{x_0}(h_n)(t) \mid = \mid x_t - x_t^n \mid$$

$$\leq \int_0^t \mid U'(x_s) - U'(x_s^n) \mid ds + \mid h(t) - h_n(t) \mid$$

$$\leq L \int_0^t \mid x_s - x_s^n \mid ds + \mid h(t) - h_n(t) \mid \leq L \int_0^t \mid x_s - x_s^n \mid ds$$

$$+ \sup_{t\in[0,T]} \mid h(t) - h_n(t) \mid$$

By Dini's theorem we have $\sup_{t\in[0,T]} \mid h(t) - h_n(t) \mid = \mid h - h_n \mid = o(1)$, and using Gronwall's lemma we get that $\mid S_{x_0}(h) - S_{x_0}(h_n) \mid \underset{n\to\infty}{\longrightarrow} 0$. Thus, (B) holds in our case.

Finally, Theorem 2.9 in [2] states that (C) holds if $b(x) = -U'(x) + \gamma$ in (3.0.15) is locally Lipschitz and has a sublinear growth condition (we set this condition regarding

our case, where in (3.0.13) the coefficients do not depend on δ as in the case in [2]). For any finite time horizon $[0, T]$ and $a > 0$, we know that if $h \in K_a$, the solution of (3.0.15) on $[0, T]$, with $x_0 \in \mathbb{R}$, is bounded. Specifically, if $x_0^+ > x_+$ or $x_0^- < x_-$, then $\mid x \mid \leq \mid x_0^+ \mid \vee \mid x_0^- \mid$, because x goes exponentially fast to its corresponding attraction point (or it remains at $x_\star$, if it starts at this value). Otherwise, $\mid x \mid \leq \mid x_+ \mid \vee \mid x_- \mid$. Therefore, under this situation which is that we have to deal and is stressed at the final of Section 2 in [2], the sublinear growth can be controlled:

$$\mid b(x) \mid = \mid -U'(x) + \gamma \mid \leq \mid \gamma \mid + \mid x \mid\mid 1 - x^2 \mid \leq \mathcal{K}(1 + \mid x \mid),$$

where $\mathcal{K} = \max\{\mid \gamma \mid, 1 + [Bound(\mid x \mid)]^2\}$. Then, the LDP applies in our case.

Conclusions

We saw that we can approximate the solution of the Hodgkin-Huxley equations using jump Markov processes whose jumps vanish when the number of ion channels goes to infinity. Nevertheless, such jump processes still are at a macroscopic level and then they don't capture the specific open system which describes the underlying randomness acting on the closed mechanical system.

In this work, we proposed a mesoscopic voltage-gate ion channel dynamics as an open system where a version of the macroscopic H-H model for the voltage variation is consistently recovered when propagation of chaos occurs. To use our proposed system instead of jump Markov processes, has the advantage of looking at the mesoscopic voltage-gated dynamics. Also, it gives a feasible explanation according to the consistency theorem (Theorem 2.1.6), for the ion channel dynamic and the nature of its underlying noise.

Also, we saw two criteria for testing the original Hodgkin-Huxley assumptions. In the first one, and under a simple case, we saw that we may recover the function f (the structure) through an ion system by relating statistically the current intensity and the intensity of the ion system seen as a counting process; a simulated result was obtained by approximating (2.1.1) by slow/fast equations. The second one was

devoted to check the gating original assumptions instead of only the structure, but under macroscopic information, which can be more realistic to implement.

Finally, and following the previous point, we suggested that we can consider different time scales in the system (2.1.1) by introducing a small parameter and a time change (Equation (3.0.8)). This because the voltage sensor dynamic is at a mesoscopic level. Under that scheme, we obtained some results about the first exit times from the basin of attractions as well as new theoretical approaches to estimate h.

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