Fluid limit theorems for stochastic hybrid systems with application to neuron models

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Abstract

This paper establishes limit theorems for a class of stochastic hybrid systems (continuous deterministic dynamic coupled with jump Markov processes) in the fluid limit (small jumps at high frequency), thus extending known results for jump Markov processes. We prove a functional law of large numbers with exponential convergence speed, derive a diffusion approximation and establish a functional central limit theorem. We apply these results to neuron models with stochastic ion channels, as the number of channels goes to infinity, estimating the convergence to the deterministic model. In terms of neural coding, we apply our central limit theorems to estimate numerically impact of channel noise both on frequency and spike timing coding.

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1   Introduction

In this paper we consider stochastic hybrid systems where a continuous deterministic dynamic is coupled with a jump Markov process. Such systems were introduced in [6] as piecewise deterministic Markov processes. They have been subsequently generalized to cover a wide range of applications: communication networks, biochemistry and more recently DNA replication modeling [2, 15, 20, 23]. We are interested in the fluid limit for these systems considering the case of small jumps of size $1/N$ at high frequency N, with a view towards application to neural modeling.

The general class of model we consider is described in section 2.1, and for the sake of clarity, we describe here a simple example which retains the main features. Consider a population of N independent individuals, each of them being described by a jump Markov process $u_k(t)$ for $k = 1, ..., N$ with states 0 and 1, and with identical transition rates $\alpha > 0, \beta > 0$ as follows: As an

$$
0 \quad \overset{\alpha}{\underset{\beta}{\rightleftarrows}} \quad 1
$$
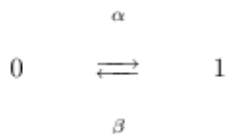
empirical measure, we define the proportion of individuals in state 1 at time t by:

$$
e_N(t) = \frac{1}{N}\sum_{k=1}^{N} u_k(t)
$$

The model becomes hybrid when we assume a global coupling through a variable $V_N \in \mathbf{R}$, in the sense that the rates $\alpha(V_N)$ and $\beta(V_N)$ are functions of V_N. This variable V_N is itself solution of a differential equation, between the jumps of $e_N(t)$:

$$
\frac{dV_N}{dt} = f(V_N, u_N)
$$

where $f : \mathbf{R}^2 \to \mathbf{R}$. In the general case, this model is extended with more general non-autonomous jump Markov processes, the global variable can be vector valued and the transition rates can be functions of the empirical measure (section 2.1).

We prove convergence in probability on finite time intervals,with techniques inspired by [1], of the solution X_N of the stochastic hybrid system to a deter-

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ministic limit $x = (v, g)$. For the example above, x is solution of:

$$\frac{dv}{dt} = f(v, g)$$
$$\frac{dg}{dt} = (1 - g)\alpha(v) - g\beta(v)$$

We derive a diffusion approximation and prove a functional central limit theorem that helps characterizing the fluctuations of both the discrete and continuous variables around the deterministic solution. We obtain that these fluctuations are a gaussian process which corresponds to the asymptotic law of the linearized diffusion approximation. We further obtain an exponential speed of convergence which relates the tail distribution of the error $E_N(T) = \sup_{[0,T]} |X_N - x|^2$ to the size parameter N and the time window T : for $\Delta > 0$ and N large,

$$P(E_N(T) > \Delta) \leq e^{-\Delta N H(T)} \tag{1}$$

Thus the convergence result can be extended to large time intervals $[0, T(N)]$, provided that $T = T(N)$ is such that $NH(T(N)) \to \infty$. Inequality (1.1) is a new result which provides an estimate to the required number N of individuals to reach a given level of precision. This number increases with the time scale on which one wants this precision to be achieved. For system subject to finite-size stochasticity, sometimes called demographic stochasticity it provides a relation between the reliability time-scale to the population size N. There are other ways of obtaining a law of large numbers, for example using the convergence of the master equation or of the generators [10]. We want to highlight here that our proof is based on exponential inequalities for martingales. Other ways of obtaining a law of large numbers would not be likely to provide an estimate such as (1.1).

Our mathematical reference on the fluid limit is the seminal paper [22] which contains a law of large numbers and a central limit theorem for sequences of jump Markov processes. Recently, a spatially extended version of these models has been considered in [1], for a standard neuron model. The author shows convergence in probability up to finite time windows to a deterministic fluid limit expressed in terms of a PDE coupled with ODEs. In the present paper, we consider a class of non-spatial models which however includes multi compartmental models, by increasing the dimension. We extend the results of [22] to stochastic hybrid models at the fluid limit.

Neurons are subject to various sources of fluctuations, intrinsic (membrane noise) and extrinsic (synaptic noise). Clarifying the impact of noise and variability in the nervous system is an active field of research [29], [11]. The intrinsic fluctuations in single neurons are mainly caused by ion channels, also called channel noise, whose impacts and putative functions are intensively investigated [37, 30, 28], mainly by numerical simulations. Our motivation is to study the intrinsic fluctuations in neuron models and we think that stochastic hybrid systems are a natural tool for this purpose. The channels open and close,

through voltage induced electromagnetic conformational change, thus enabling ion transfer and action potential generation. Because of thermal noise, one of the main features of those channels is their stochastic behavior.

In terms of modeling, our starting point is the stochastic interpretation of the Hodgkin-Huxley formalism [16]. In this setting, ion channels are usually modeled with independent Markov jump processes, whose transition rates can be estimated experimentally [35]. These stochastic discrete models are coupled with a continuous dynamic for the membrane potential, leading to a piecewise-deterministic Markov process. Thus, the individuals are the ion channels and the global variable V_N the voltage potential (cf. section 3.). Deterministic hybrid kinetic equations appear to be a common formalism suitable for each stage of nervous system modeling as shown in [8]. This latter study provides us with a framework to introduce stochastic hybrid processes to model action potential generation and synaptic transmission, as stochastic version of deterministic kinetic models coupled with differential equations through the transition rates. On the side of neuron modeling applications, the limit behavior of a similar but less general model is considered in [12], using an asymptotic development of the master equation as $N \to \infty$, which formally leads to a deterministic limit and a Fokker-Planck equation (Langevin approximation), providing the computation of the diffusion coefficients. The Langevin approximation is also studied in [34], but in a simplified case where the transition rates are constants (independent of V_N), which is actually the case studied in [22]. Our mathematical results extend these previous studies to a wider class of models (if we put aside the spatial aspects in [1]), providing a rigorous approach for the Langevin approximation, and establishing a central limit theorem which describe the effect of channel noise on the membrane potential [32]. The convergence speed provides a quantitative insight into the following question : if a neuron needs to be reliable during a given time-scale, what would be a sufficient number of ion channels? We thus provide a mathematical foundation for the study of stochastic neuron models, and we apply our results to standard models, quantifying the effect of noise on neural coding. In particular, both frequency coding (sec. 3.5.1) and spike timing coding (sec. 3.5.2) are numerically studied with Morris-Lecar neuron model with a large number of stochastic ion channels.

Generically, stochastic hybrid models in the fluid limit would arise in multiscale systems with a large population of stochastic agents coupled, both top-down and bottom-up, through a global variable, leading to an emergent cooperative behavior. Starting from a microscopic description (ion channels), the central limit theorem as stated in this paper leads to a description of the fluctuations of the global variable (membrane potential). So, in the perspective of applications, it would be interesting to investigate how our framework and results could be developed in other fields than neural modeling: for instance in chemical kinetics, in population dynamics, in tumor modeling, in economics or in opinion dynamics theory. In a more mathematical perspective, it would be interesting to consider a wider class of models, for instance by including spatial aspects as in [1] or by weakening the independence assumption. Other questions could be investigated, for instance concerning escape problems, first passage times and large deviations,

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whenever N is large or not.

Our paper is organized as follows. In section 2. we define our model and formulate the main results. In section 3., we apply our results to neuron models. In section 4. we give the proof of the law of large numbers and its convergence speed (**Theorem 2.1**) and in section 5. we give the proof of the Langevin approximation (**Theorem 2.2**) and central limit theorems (**Theorem 2.3-2.4-2.5**).

2 Model and main results

This section contains the definition of our general model and states the main theorems.

2.1 Model

Stochastic hybrid model ($\mathbf{S_N}$) Let $p, q, N \in \mathbf{N}^*$, and $r_j \in \mathbf{N}^*$ for all $1 \leq j \leq q$. Let $d = \sum_{j=1}^{q} r_j$. We define the stochastic hybrid model (S_N), whose solution

$$X_N(t) = (V_N(t), \mathbf{e}_N(t)) \in \mathbf{R}^p \times \mathbf{R}^d, \ t \geq 0$$

satisfies:

$$\frac{dV_N}{dt} = f(X_N)$$

and $\mathbf{e}_N = (e_N^{(1)}, ..., e_N^{(q)})$ with $e_N^{(j)} \in \mathbf{R}^{r_j}$, where the processes $e_N^{(j)}(t)$ are q independent jump Markov processes. Note that the differential equation for V_N is holding only between the jump times of the process $\mathbf{e}_N$, with updated initial conditions. For $1 \leq j \leq q$, processes $e_N^{(j)}(t)$ are characterized by,

- their state space : $E_N^{(j)} = \left\{ (x_1, ..., x_{r_j}) \in \{0, \frac{1}{N}, ..., 1\}^{r_j} \mid \sum_{k=1}^{r_j} x_k = 1 \right\}$

- their intensity $\lambda_N^{(j)}$: for $X = (V, \mathbf{e}) \in \mathbf{R}^p \times \mathbf{R}^d$, $\lambda_N^{(j)}(X) = N\tilde{\lambda}^{(j)}(X)$ with

$$\tilde{\lambda}^{(j)}(X) = \sum_{k=1}^{r_j} \mathbf{e}_k^{(j)} \sum_{l=1, \ l \neq k}^{r_j} \alpha_{k,l}^{(j)}(X)$$

- their jump law $\mu_N^{(j)}$: we define $u_a^{(j)} = (0, ..., 0, 1, 0, ..., 0) \in \mathbf{R}^{r_j}$ and $u_{a,b}^{(j)} = u_a^{(j)} - u_b^{(j)}$ for $1 \leq a, b \leq r_j$. The transition of an individual agent in the population j from one state a to another state b corresponds to a jump of $z = \frac{1}{N} u_{b,a}^{(j)}$ for the process $e_N^{(j)}$. Thus we define:

$$X + \frac{1}{N} \Delta X_{a,b}^j = (V, e^{(1)}, ..., \tilde{e}^{(j)}, ..., e^{(q)})$$

$$\tilde{e}^{(j)} = e^{(j)} + u_{a,b}^{(j)}$$

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So that the jump law for a jump of z is given by:

$$\mu_N^{(j)}(X, z) = \frac{\mathbf{e}_a^{(j)} \alpha_{a,b}(X)}{\tilde{\lambda}^{(j)}(X)} \text{ if } z = \frac{1}{N} u_{b,a}^{(j)},$$

for all $1 \leq a, b \leq r_j$ such that $\mathbf{e}_a^{(j)} \neq 0$ and $\mathbf{e}_b^{(j)} \neq 1$, and

$$\mu_N^{(j)}(X, z) = 0 \text{ otherwise.}$$

For a more formal definition we refer to [6].

For $1 \leq k \leq r_j$, the k-th component $\{e_N^{(j)}\}_k$ of vector $e_N^{(j)}$ can be interpreted as the proportion of agents of type j which are in the state k in a population of size N.

We show below in **Theorem 2.1** that this stochastic hybrid model has a limit as $N \to \infty$ which is the following deterministic model.

Deterministic model (D) We define the deterministic model (D), whose solution $X = (v, \mathbf{g}) \in \mathbf{R}^p \times \mathbf{R^d}$ with $\mathbf{g} = (\mathbf{g}^{(1)}, .., \mathbf{g}^{(q)})$ satisfies:

$$\begin{cases} \dot{v} = f(v, \mathbf{g}) \\ \dot{\mathbf{g}}_k^{(j)} = \sum_{1 \leq i \leq r_j, i \neq k} \alpha_{i,k}^{(j)}(X) \mathbf{g}_i^{(j)} - \alpha_{k,i}^{(j)}(X) \mathbf{g}_k^{(j)} \end{cases} \quad (D)$$

for all $1 \leq j \leq q$, $\forall 1 \leq k \leq r_j$. The first equation is the same as in the stochastic model (deterministic part) and the second equation corresponds to the usual rate equation, with a gain term and a loss term.

The following example illustrates the general model in a simpler relevant setting motivated by applications. This setting will be used in the proofs in section 4 and 5 in order to make the arguments clearer.

Example We consider the case where $p = q = 1$ and $r_1 = 2$. We can construct a stochastic hybrid process as follows: first let us introduce a collection of N independent jump Markov processes $u^{(k)}$ for $1 \leq k \leq N$ with $u_t^{(k)} : 0 \to 1$ with rate $\alpha(V_N)$ and $1 \to 0$ with rate $\beta(V_N)$:

$$\begin{array}{ccc} & \alpha(V_N) & \\ 0 & \rightleftarrows & 1 \\ & \beta(V_N) & \end{array}$$
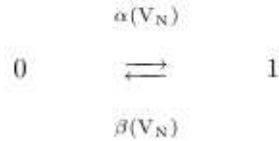
where V_N is defined below. We then consider $e_N(t) = (\{e_N\}_0(t), \{e_N\}_1(t))$ the proportions of processes in the states 0 and 1. In this case, the stochastic hybrid model (S_N) can be written as:

$$
\begin{cases}
\dot{V}_N(t) = f(V_N(t), e_N(t)) \\
e_N(t) = \left(\frac{1}{N} \sum_{k=1}^{N} \delta_0(u_t^{(k)}), \frac{1}{N} \sum_{k=1}^{N} \delta_1(u_t^{(k)}) \right) \\
V_N(0) = v_0; \ e_N(0) = (u_0, 1 - u_0)
\end{cases}
$$

Note that, if we define $u_N(t) = \frac{1}{N} \sum_{k=1}^{N} \delta_1(u_t^{(k)})$, then we have $e_N(t) = (1 - u_N(t), u_N(t))$, so that the solution is determined by the pair $X_N(t) = (V_N(t), u_N(t))$.

Thus, each member of the sequence of jump Markov processes $\{u_N\}_{N \geq 1}$ is characterized by

- its state space $E_N = \{0, \frac{1}{N}, \frac{2}{N}, ..., 1\}$,

- its intensity $\lambda_N(V_N(t), u) = N[u\beta(V_N(t)) + (1 - u)\alpha(V_N(t))]$. This intensity is time-dependent through $V_N(t)$.

- its jump law

$$
\mu_N(V_N(t), u, y) = \mu^+(V_N(t), u)\delta_{y, u + \frac{1}{N}} + \mu^-(V_N(t), u)\delta_{y, u - \frac{1}{N}}
$$

where $\mu^+(V, u) = \frac{(1-u)\alpha(V)}{u\beta(V) + (1-u)\alpha(V)}$ and $\mu^-(V, u) = \frac{u\beta(V)}{u\beta(V) + (1-u)\alpha(V)}$. This jump law is also time-dependent through $V_N(t)$.

The deterministic system (D) takes the form:

$$
\begin{cases}
\dot{v}(t) = f(v(t), g(t)) \\
\dot{g}(t) = (1 - g(t))\alpha(v(t)) - g(t)\beta(v(t)) \\
v(0) = v_0 \ ; \ g(0) = u_0
\end{cases}
$$

In the sequel, we will be interested in the asymptotic behavior of the stochastic hybrid models (S_N) under the limit fluid assumption. Let us now recall what this assumption means. Let (x_N) be a sequence of homogeneous Markov jump processes with state spaces $E_N \subset R^k$, intensities $\lambda_N(x)$ and jump law $\mu_N(x, dy)$. Define the flow as $F_N(x) = \lambda_N(x) \int_{E_N} (z - x)\mu_N(x, dz)$. The fluid limit occurs if the flow admits a limit and if the second order moment of the jump size converges to zero when $N \to \infty$. Our stochastic hybrid model is in the fluid limit since the jumps are of size $1/N$ and the intensity is proportional to N. This stems from the fact that we are modeling proportions in a population of independent agents. However, this independence assumption is not necessary to satisfy the fluid limit.

2.2 Law of large numbers for stochastic hybrid systems

We give here the first result concerning the convergence of the stochastic hybrid model (S_N), which is a functional law of large numbers on finite time windows.

Theorem 2.1 () *Let $\epsilon > 0$, $\delta > 0$, $T > 0$. Let us assume that the functions $\alpha_{i,j}$ and f are C^1, and satisfy the following condition:*

(H1): the solution v of (D) is bounded on $[0, T]$ and for all $N \geq 1$ the solution $V_N(t)$ of (S_N) is uniformly bounded in N on $[0, T]$.

Let X^{init} a given initial condition for (D) and $X = (v, \mathbf{g})$ its solution. Then there exists an initial condition X_N^{init} for (S_N) and $N_0 \geq 0$ such that $\forall N \geq N_0$, the solution $X_N = (V_N, \mathbf{e}_N^{(1)}, .., \mathbf{e}_N^{(q)})$ satisfies, for all $1 \leq j \leq q$ and $1 \leq k \leq r_j$:

$$\mathbf{P} \left[\sup_{0 \leq t \leq T} ||V_N(t) - v(t)|| \geq \delta \right] \leq \epsilon$$

$$\mathbf{P} \left[\sup_{0 \leq t \leq T} |\{\mathbf{e}_N^{(j)}\}_k(t) - \mathbf{g}_k^{(j)}(t)| \geq \delta \right] \leq \epsilon$$

Moreover, if we define

$$P_N(T, \Delta) = \mathbf{P} \left[\sup_{0 \leq t \leq T} ||V_N(t) - v(t)||^2 + \sum_{j=1}^{q} ||\mathbf{e}_N^{(j)}(t) - \mathbf{g}^{(j)}(t)||^2 > \Delta \right]$$

there exist two constants $B(T) > 0$ and $C > 0$ such that for Δ sufficiently small:

$$\limsup_{N \to \infty} \frac{1}{N} \log P_N(T, \Delta) \leq -\frac{\Delta e^{-B(T)T}}{CT} \tag{2}$$

Moreover if

(H2): assumption (H1) holds true on $[0, +\infty[$

then the constant $B(T) = BT$ is proportional to T.

Interpretation of the convergence speed We have obtained in (2.1) an upper bound for the convergence speed which can help to answer the following issue. Given a number of channels N, given an error Δ and a confidence probability $1 - p$ (e.g $p = 0.01$), the time window $[0, T]$ for which we can be sure (up to probability $1 - p$) that the distance between the stochastic and the deterministic solutions (starting at the same point) is less than Δ is given by (2.1). In section 3.3, we show numerical simulation results illustrating the obtained bound for the convergence speed for the stochastic Hodgkin-Huxley model.

Remark Assumption $(H2)$ and thus $(H1)$, are satisfied for most neuron models, for instance for the Hodgkin-Huxley (HH) model [4].

2.3 Langevin approximation

Our second result is a central limit theorem that provides a way to build a diffusion or Langevin approximation of the solution of the stochastic hybrid system (S_N). For $X = (v, \mathbf{e}) \in \mathbf{R}^p \times \mathbf{R}^\mathbf{d}$, for $1 \leq j \leq q$, $1 \leq i, k \leq r_j$, let

$$b_{j,k}(X) = \sum_{1 \leq i \leq r_j, i \neq k} \alpha_{i,k}^{(j)}(X)\mathbf{e}_i^{(j)} - \alpha_{k,i}^{(j)}(X)\mathbf{e}_k^{(j)}$$

$$H_{i,k}^{(j)} = \alpha_{i,k}^{(j)}(X)\mathbf{e}_i^{(j)} + \alpha_{k,i}^{(j)}(X)\mathbf{e}_k^{(j)}$$

$$\lambda_{j,k}(X) = \sum_{1 \leq i \leq r_j, i \neq k} H_{i,k}^{(j)}.$$

As before, $X_N(t) = (V_N(t), \mathbf{e}_N(t)) \in \mathbf{R}^p \times \mathbf{R}^{\mathbf{d}}$ is the solution of the stochastic hybrid model (S_N).

Let $R_N(t) = \{(R_N^{(j)})_k(t)\}_{1 \leq j \leq q,\ 1 \leq k \leq r_j}$ with $R_N^{(j)} \in \mathbf{R}^{r_j}$ be defined as

$$(R_N^{(j)})_k(t) = \sqrt{N} \left(\{\mathbf{e}_N^{(j)}\}_k(t) - \{\mathbf{e}_N^{(j)}\}_k(0) - \int_0^t b_{j,k}(X_N(s))ds \right)$$

Theorem 2.2 *Under the same hypotheses as in **Theorem 2.1**, the process R_N converges in law, as $N \to \infty$, to the process $R = \{(R^{(j)})_k(t)\}_{1 \leq j \leq q,\ 1 \leq k \leq r_j}$ with:*

$$R^{(j)}(t) = \int_0^t \sigma^{(j)}(X(s))dW_s^j$$

where

- $X = (v, \mathbf{g})$ *is the solution of the deterministic model (D) with initial condition $X^{init} = X_N^{init} = X_0$,*

- W^j *are independent standard r_j-dimensional Brownian motions,*

- $\sigma^{(j)}(X)$ *is the square root of matrix $G^{(j)}(X)$ s.t., for $1 \leq k, l \leq r_j$:*

$$\begin{cases} G_{k,k}^{(j)}(X) = \lambda_{j,k}(X) \\ G_{k,l}^{(j)}(X) = H_{k,l}^{(j)}(X) = G_{l,k}^{(j)}(X),\ l \neq k \end{cases}$$

This theorem leads to the following degenerate diffusion approximation $\tilde{X}_N = (\tilde{V}_N, \tilde{\mathbf{g}}_N) \in \mathbf{R}^p \times \mathbf{R}^d$, for N sufficiently large:

$$(2.2) \quad \begin{cases} d\tilde{V}_N = f(\tilde{X}_N(t))dt \\ d\tilde{\mathbf{g}}_N^{(j)} = b_j(\tilde{X}_N(t))dt + \frac{1}{\sqrt{N}}\sigma^{(j)}(\tilde{X}_N(t))dW_t^j \end{cases}$$

where $b_j(X)$ is the vector $(b_{j,k}(X))_{1 \leq k \leq r_j} \in \mathbf{R}^{r_j}$, $1 \leq j \leq q$.
Note that this approximation may not have the same properties as the original process, even in the limit $N \to \infty$ (when considering for instance large deviations [26]).

2.4   Functional central limit theorem and exit problem

Let $X_N = (V_N, \mathbf{e}_N^{(1)}, .., \mathbf{e}_N^{(q)})$ be the solution of the stochastic model (S_N) and $X = (v, \mathbf{g}^{(1)}, .., \mathbf{g}^{(q)})$ the solution of the deterministic system (D) with identical initial condition $X^{init} = X_N^{init} = X_0 \in \mathbf{R}^{p+d}$.
Consider the $(p+d)$-dimensional processes:

$$
Z_N = \begin{pmatrix} Y_N \\ \mathbf{P}_N^{(1)} \\ ... \\ \mathbf{P}_N^{(q)} \end{pmatrix} := \sqrt{N} \begin{pmatrix} V_N - v \\ \mathbf{e}_N^{(1)} - \mathbf{g}^{(1)} \\ ... \\ \mathbf{e}_N^{(q)} - \mathbf{g}^{(q)} \end{pmatrix}
$$

With this setting, we have the following result:

Theorem 2.3 *Under the same hypotheses as in* **Theorem 2.1** *the process Z_N converges in law, as $N \to \infty$ to the process*

$$
Z = \begin{pmatrix} Y \\ \mathbf{P}^{(1)} \\ ... \\ \mathbf{P}^{(q)} \end{pmatrix}
$$

whose characteristic function $\Psi(t, \theta) = \mathbf{E}\left[e^{i<\theta, Z(t)>} \right]$ satisfies the following equation:

$$
\frac{\partial \Psi}{\partial t} = \sum_{j=1}^{q} \left\{ \sum_{l \in L} \sum_{k=1}^{r_j} \theta_k^{(j)} \frac{\partial b_{j,k}}{\partial x_l} \frac{\partial \Psi}{\partial \theta_l} - \frac{1}{2} \sum_{k,l=1}^{r_j} \theta_k^{(j)} \theta_l^{(j)} G_{k,l}^{(j)} \Psi \right\} + \sum_{m=1}^{p} \sum_{l \in L} \theta_m \frac{\partial f^m}{\partial x_l} \frac{\partial \Psi}{\partial \theta_l}
$$

where $G_{k,l}^{(j)}$, $\frac{\partial f^m}{\partial x_l}$ and $\frac{\partial b_{j,k}}{\partial x_l}$ are evaluated at $X(t)$, for $1 \leq m \leq p$, $1 \leq j \leq q$, $1 \leq k \leq r_j$ and $l \in L$, with $\theta = ((\theta_m)_{1 \leq m \leq p}, (\theta_k^{(j)})_{1 \leq j \leq q, \ 1 \leq k \leq r_j}) = (\theta_l)_{l \in L}$, and $L = \{(m)_{1 \leq m \leq p}, \ (j,k)_{1 \leq j \leq q, \ 1 \leq k \leq r_j}\}$.

Let us define $\tilde{Z}_N := \left(\tilde{Y}_N, \tilde{P}_N\right) := \sqrt{N}\left(\tilde{X}_N - X\right) \in \mathbf{R}^p \times \mathbf{R}^d$, where we recall that $\tilde{X}_N$ is the Langevin approximation defined in (2.2). Thus, for $1 \leq j \leq q$, and $1 \leq k \leq r_j$:

$$
\begin{aligned}
d\tilde{Y}_N &= \sqrt{N}(f(\tilde{X}_N) - f(X))dt \\
d\tilde{P}_N^{j,k} &= \sqrt{N}(b_{j,k}(\tilde{X}_N) - b_{j,k}(X))dt + \sigma^{(j)}(\tilde{X}_N)dW_t^j
\end{aligned}
$$

As an asymptotic linearization of $\tilde{Z}_N$, we define the diffusion process $\Theta = (\gamma, \pi) \in \mathbf{R}^p \times \mathbf{R}^d$ by:

$$
\begin{aligned}
d\gamma_m &= \sum_{l \in L} \frac{\partial f^m}{\partial x_l} \Theta_l dt \\
\\
d\pi_{j,k} &= \sum_{l \in L} \frac{\partial b_{j,k}}{\partial x_l} \Theta_l dt + \sum_{k'=1}^{r_j} \sigma_{k,k'}^{(j)}(X) dW_t^{j,k'}
\end{aligned}
$$

Theorem 2.4 *The processes Z and Θ have the same law.*

A computation of the moments equations for the limit process Z for the example of section 2.1 is provided in Appendix B.
Using the central limit theorem 2.3, we provide in the next theorem a characterization of the fluctuations of first-exit time and location for the stochastic hybrid process X_N. Let $\phi : \mathbf{R}^{p+d} \to \mathbf{R}^{p+d}$ be continuously differentiable. Define

$$\tau_N := \inf\{t \geq 0; \phi(X_N(t)) \leq 0\}$$

$$\tau := \inf\{t \geq 0; \phi(X(t)) \leq 0\}$$

the first passage times through $\phi = 0$ respectively for the stochastic hybrid process and for its deterministic limit.

Theorem 2.5 *Assume the initial condition $X(0)$ satisfies $\phi(X(0)) > 0$. Suppose $\tau < \infty$ and $\nabla\phi(X(\tau)).F(X(\tau)) < 0$. Denote the random variable*

$$\pi(\tau) := -\frac{\nabla\phi(X(\tau)).Z(\tau)}{\nabla\phi(X(\tau)).F(X(\tau))}$$

Then the following convergences in law hold when $N \to \infty$:

$$\sqrt{N}(\tau_N - \tau) \to \pi(\tau)$$

$$\sqrt{N}(X_N(\tau_N) - X(\tau)) \to Z(\tau) + \pi(\tau)F(X(\tau))$$

3 Application to neuron models

In this section, we show how our previous theorems can be applied to standard neuron models taking into account ion channel stochasticity.

3.1 Kinetic formalism in neuron modelling

Kinetic models can be used in many parts of nervous system modelling, such as in ion channel kinetics, synapse and neurotransmitters release modelling. Deterministic kinetic equations are obtained as a limit of discrete stochastic models (hybrid or not) as the population size, often the number of channels, is large.

As already mentioned in the introduction, compared to our general formalism, the stochastic individuals are the ion channels and the global variable V_N the voltage potential. Constituted of several subunits called gates, voltage-gated ion channels are metastable molecular devices that can open and close. There exist different types of channels according to the kind of ions, and they are distributed within the neuron membrane (soma, axon hillock, nodes of Ranvier, dendritic spines) with heterogeneous densities.

In what follows, we consider the model of Hodgkin and Huxley, which has been extended in different ways to include stochastic ion channels. In numerical

studies, different versions have been used, from a *two-state gating* interpretation *e.g.* [31] to a *multistate Markov* scheme [7, 28]. In [32], two of these models are compared, one with a complete multistate Markov scheme, and the other inspired from [24] with a multistate scheme for the sodium ion and a two-state gating for the potassium ion. We are here considering only single-compartment neuron, but in order to deal with spatial heterogeneities of axonal or ion channels properties for instance, multi-compartmental models can be introduced as a discretized description of the spatial neuron, with Ohm's Law coupling between compartments.

3.2 Application of the law of large numbers to Hodgkin and Huxley model

Classically, the Hodgkin-Huxley model (HH) is the set of non-linear differential equations (3.1-3.4) which was introduced in [16] to explain the ionic mechanisms behind action potentials in the squid giant axon.

$$C_m \frac{dV}{dt} = I - g_L(V - V_L) - g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) \quad (3)$$

$$\frac{dm}{dt} = (1-m)\alpha_m(V) - m\beta_m(V) \quad (4)$$

$$\frac{dh}{dt} = (1-h)\alpha_h(V) - h\beta_h(V) \quad (5)$$

$$\frac{dn}{dt} = (1-n)\alpha_n(V) - n\beta_n(V) \quad (6)$$

where I is the input current, $C_m = 1\mu F/cm^2$ is the a capacitance corresponding to the lipid bilayer of the membrane, $g_L = 0.3mS/cm^2$,$g_{Na} = 120mS/cm^2$, $g_K = 36ms/cm^2$ are maximum conductances and $V_L = 10.6mV$, $V_{Na} = 115mV$, $V_K = -12mV$ are resting potentials, respectively for the leak, sodium and potassium currents. The functions α_x, β_x for $x = m, n, h$ are opening and closing rates for the voltage-gated ion channels (see [16] for their expression). The dynamics of this dynamical system can be very complex as shown in [14], but for our purpose let us describe only schematically the behavior of this system as the parameter I is varied (see [27] for more details). First for all I there exists a unique equilibrium point. For $0 < I < I_1 \approx 9.8\mu A/cm^2$, this equilibrium point is stable, and for $I_0 < I < I_1$ where $I_0 \approx 6.3\mu A/cm^2$ this equilibrium coexists with a stable limit cycle and possibly many unstable limit cycles. At $I = I_1$ and $I = I_2$ occur two Hopf bifurcations. For $I_1 < I < I_2 \approx 153\mu A/cm^2$, the equilibrium point is unstable and coexists with a stable limit cycle. For $I > I_2$, there are no more limit cycles, and the equilibrium point is stable. This bifurcation structure can be roughly interpreted as follows : for I small the system converges to an equilibrium point, and for I sufficiently large, the system admits a large amplitude periodic solution, corresponding to an infinite sequence of action potentials or spikes and the spiking frequency is modulated by the input current I.

There are two stochastic interpretations of the Hodgkin-Huxley model involving either a multistate Markov model or a two state gating model. We now present them briefly and we apply our theorems to each of them. A comparison of these deterministic limits obtained for these models is given in Appendix A and establishes an equivalence between the deterministic versions as soon as initial conditions satisfy a combinatorial coincidence relationship. This question is further studied in [19], where the reduction of the law of jump Markov processes to invariant manifolds is investigated.

Multistate Markov model This model has two types of ion channels : one for sodium and the other for potassium. The kinetic scheme describing the Markov jump process for one single potassium channel is the following:
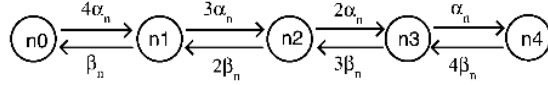
And for sodium channel:
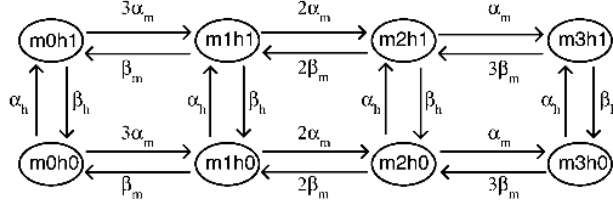
All the coefficients in these two schemes are actually functions of the membrane potential, and can be found in [16]. The state spaces are:

$$E_1 = \{n_0, n_1, n_2, n_3, n_4\}$$

$$E_2 = \{m_0h_1, m_1h_1, m_2h_1, m_3h_1, m_0h_0, m_1h_0, m_2h_0, m_3h_0\}$$

The open states are respectively n_4 ($r_1 = 5$) and m_3h_1 ($r_2 = 8$). The proportion of open potassium channels is denoted by $u_N^{(1)} := \{e_N^{(1)}\}_{n_4}$ and the proportion of open sodium channels by $u_N^{(2)} := \{e_N^{(2)}\}_{m_3h_1}$. In this model, The membrane potential dynamic is given by the equation:

$$\dot{V}_N(t) = -g_{Na}u_N^{(2)}(t)(V_N(t) - V_{Na}) - g_K u_N^{(1)}(t)(V_N(t) - V_K) - g_L(V(t) - V_L) + I$$

where $I \in \mathbf{R}$ is a constant applied current. With the notations of the previous sections, $f(v, u^{(1)}, u^{(2)}) = -g_{Na}u^{(2)}(v - V_{Na}) - g_K u^{(1)}(V_N(t) - V_K) - g_L(v - V_L) + I$ and for example, $\alpha_{k,j}^{(1)}(v) = 3\alpha_n(v)$ if $k = n_1$, $j = n_2$ and $\alpha_{k,j}^{(2)}(v) = 2\beta_m(v)$ if $k = m_2h_0$, $j = m_1h_0$.

Applying **Theorem 2.1**, we obtain a deterministic version of the stochastic Hodgkin-Huxley model when $N \to \infty$, provided we choose the initial conditions

appropriately:

$$\begin{cases} \dot{v} = -g_{Na}e^{(2)}(t)(v(t) - V_{Na}) - g_K e^{(1)}(t)(v(t) - V_K) - g_L(V(t) - V_L) + I \\ \dot{\mathbf{g}}_k^{(j)} = \displaystyle\sum_{1 \le i \le r_j, i \ne k} \alpha_{i,k}^{(j)}(v)\mathbf{g}_i^{(j)} - \alpha_{k,i}^{(j)}(v)\mathbf{g}_k^{(j)}, \ \forall 1 \le j \le 2, \ \forall 1 \le k \le r_j \\ V(0) = v_{init} \\ \mathbf{g}^{(j)}(0) = \mathbf{g}_{init}^{(j)} \end{cases}$$

with $e^{(j)} = \mathbf{g}_{r_j}^{(j)}$, and where the rate functions $\alpha_{m,p}^{(j)}$ are given in the above schemes, for $j \in \{1, 2\}$.

Two-state gating model Another way of building a stochastic Hodgkin-Huxley model is to consider that the channels can be decomposed into independent gates. Each gate can be either open (state 1) or closed (state 0):

with $z \in \{m, n, h\}$. The channel is open when all gates are open.
So, here, $q = 3$ and $E_1 = E_2 = E_3 = \{0, 1\}$. If we denote $u_N^{(z)}(t) := \{e_N^{(z)}\}_1$ the proportion of open gates z, for $z \in \{m, n, h\}$, the membrane potential dynamic is then given by:

$$\begin{aligned} \dot{V}_N(t) &= -g_{Na}(u_N^{(m)}(t))^3 u_N^{(h)}(t)(V_N(t) - V_{Na}) \\ &\quad - g_K(u_N^{(n)}(t))^4(V_N(t) - V_{Na}) - g_L(V_N(t) - V_L) + I \end{aligned}$$

which corresponds to $f(v, u^{(m)}, u^{(h)}, u^{(n)}) = -g_{Na}(u^{(m)})^3 u^{(h)}(v - V_{Na}) - g_K(u^{(n)})^4(v - V_{Na}) - g_L(v - V_L) + I$. In Figure 1, we give a sample trajectory of this two-state gating stochastic Hodgkin-Huxley system.
Applying **Theorem 2.1** gives the classical formulation of the 4-dimensional Hodgkin-Huxley model:

$$\begin{cases} \dot{v} = -g_{Na}(u^{(m)}(t))^3 u^{(h)}(t)(v(t) - V_{Na}) - g_K(u^{(n)}(t))^4(v(t) - V_{Na}) \\ \quad - g_L(V(t) - V_L) + I \\ \dot{u}^{(z)}(t) = (1 - u^{(z)}(t))\alpha_z(v(t)) - u^{(z)}(t)\beta_z(v(t)), \ z \in \{m, n, h\} \end{cases}$$

3.3 Exponential convergence speed

We illustrate by numerical simulations the upper bound obtained in (2.1) for the stochastic Hodgkin-Huxley model with a two-state gating scheme. The number of sodium channels N_{Na} and potassium channels N_K are proportional
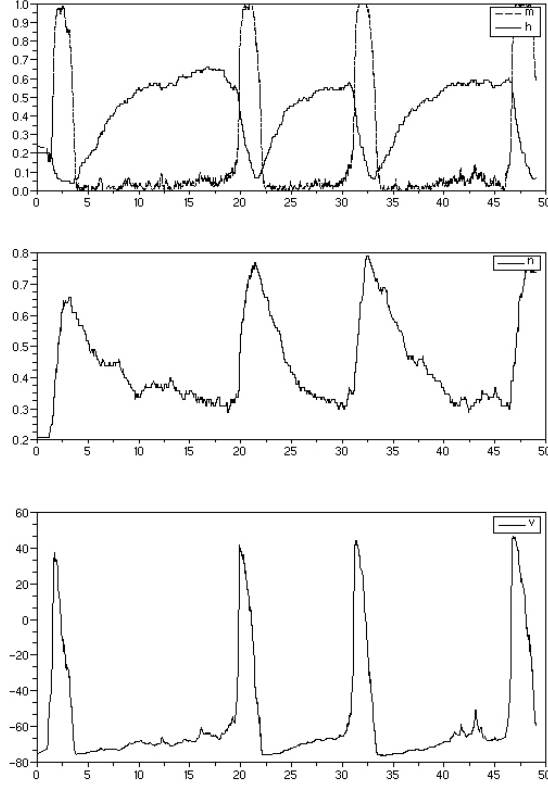
Figure 1: Illustrative sample trajectory of a two-state gating stochastic Hodgkin-Huxley model with $N = 20$ (cf. section 3.). Top: variables m, h for the sodium channel (without unit). Middle: variable n for potassium channel (without unit). Down: variable V for membrane potential (unit: mV). Abscissa: time (arbitrary units). Since m, n and h correspond to proportions of open gates, if one of them is equal to 1, it means that all the corresponding gates are open. An increase in the membrane potential V causes an increase in the proportion of open m (sodium) gates, which in turn implies an increase of V. This positive feedback results in a spike initiation. Meanwhile, a further increase of V is followed by a decrease of the deactivation variable h, which closes the sodium channels. This inhibition effect acts at a slower time-scale, enabling a decrease of V. This decrease is strengthened by the dynamic of variable n (proportion of open potassium gates).

to the area S of the membrane patch. Thus, instead of N, S will denote the size parameter. For the squid giant axon, the estimated densities for the ion channels used in the simulations are $\rho_{Na} = 60 \mu m^{-2}$ and $\rho_{N_K} = 18 \mu m^{-2}$.

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We now display the results of numerical simulations of

$$P_S(T, \Delta) = \mathbf{P} \left[\sup_{0 \leq t \leq T} ||V_S(t) - v(t)||^2 + \sum_{j=1}^{q} ||\mathbf{e}_S^{(j)}(t) - \mathbf{g}^{(j)}(t)||^2 > \Delta \right]$$

using Monte-Carlo simulations. We recall that from (2.1):

$$\limsup_{S \to \infty} \frac{1}{S} \log P_S(T, \Delta) \leq -\frac{\Delta e^{-BT^2}}{CT} = C(T)$$

In Fig. 2, the simulation estimations of $C_S(T) = \frac{1}{S} \log P_S(T, \Delta)$ are shown for different values of T and S and can be compared to the theoretical bound $C(T)$. Simulations are made without input current, meaning that the stochastic solution is supposed to fluctuate around the equilibrium point of the deterministic system in a neighborhood of size proportional to $S^{-1/2}$. When S increases, the simulation curve $C_S(T)$ is expected to pass below the theoretical bound $C(T)$. For higher input currents, still subthreshold ($I < I_c$), but close to the bifurcation, channel noise will induce spontaneous action potentials. For appropriate Δ, the probability $P_S(T, \Delta)$ can be interpreted as the probability that the first spontaneous action potential (SAP) occurs before time T. Thus the convergence speed bound gives an upper bound of the repartition function of this first SAP time.

For higher input currents $I > I_c$, the deterministic solution will be attracted by a stable limit cycle, which corresponds to repetitive action potentials. In this case, channel noise can introduce a jitter in the spiking times. Thus, if one considers the supremum of the errors between the stochastic and the deterministic solutions, this supremum will be quite large (approximately the size of an action potential) as soon as the difference between the stochastic spiking times and the deterministic ones is of order the time course of an action potential (2 ms). Thus, the supremum of the difference is not appropriate here and we will see in the following section how to quantify the impact of channel noise on the spiking frequency.

3.4   Application of the central limit theorems

In this section, we show how to investigate the fluctuations around a stable fixed point (sub-threshold fluctuations) and the fluctuations around a stable limit cycle (firing rate fluctuations) using Theorem 2.3. Let us consider a class of two-dimensional models, corresponding to the **Example** of section 2.1. This class contains reductions of the previous two-state gating Hodgkin-Huxley model, or other models such as the Morris-Lecar model [25]. Consider the process, with the notations of the **Example**:

$$\begin{pmatrix} Y_N \\ P_N \end{pmatrix} = \begin{pmatrix} \sqrt{N}(V_N - V) \\ \sqrt{N}(e_N - g) \end{pmatrix}$$
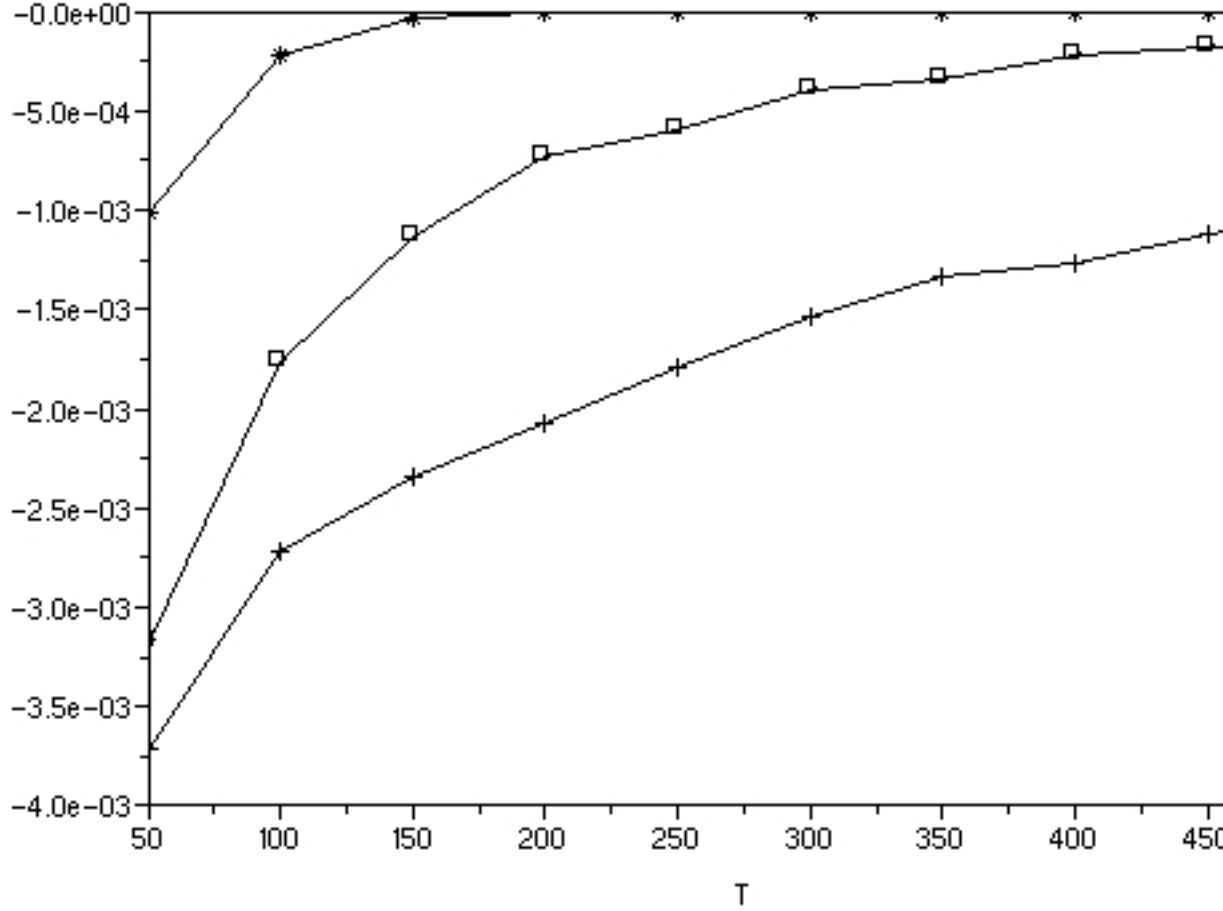
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Figure 2: Simulation results of the Hodgkin-Huxley model with a "two-state gating" scheme with input current $I = 0$: this figure shows the quantity $\frac{1}{S} \ln P_S(T, \Delta)$ as a function of T, where S is the area of the patch, and is thus proportional to N. Stars : $S = 250\mu m^2$ (corresponding to $N_{Na} = 15000$ and $N_K = 5000$) ; Empty boxes : $S = 500\mu m^2$; Crosses: $S = 750\mu m^2$. Lines are guide for the eye.

with initial conditions $(P_N(0), Y_N(0)) = (0,0)$. Then the 2-dimensional process $Z_N = (P_N, Y_N)$ converges in law, as $N \to \infty$, towards the process $Z = (P, Y)$,

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whose characteristic function is given by:

$$\mathbf{E}\left[e^{i(\theta_1 P(t)+\theta_2 Y(t))}\right] = e^{\theta_1^2 A_t + \theta_2^2 B_t + \theta_1 \theta_2 C_t}$$

Thus, defining Σ_s the square root matrix of $\Gamma_s := \begin{pmatrix} A'_s & C'_s/2 \\ C'_s/2 & B'_s \end{pmatrix}$, for $0 \leq s \leq t$, Z can be written as a gaussian diffusion process:

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

where W is a standard two-dimensional brownian motion [4].
From the equation for the characteristic function obtained in **Theorem 2.3**, one derives that the triple $y = (A, B, C)$ is solution of the system $\dot{y}_t = M_t y_t + E_t$ defined as:

$$\begin{pmatrix} \dot{A}_t \\ \dot{B}_t \\ \dot{C}_t \end{pmatrix} = \begin{pmatrix} 2b'_u & 0 & b'_v \\ 0 & 2f'_v & f'_u \\ 2f'_u & 2b'_v & b'_u + f'_v \end{pmatrix} \begin{pmatrix} A_t \\ B_t \\ C_t \end{pmatrix} + \begin{pmatrix} -\frac{1}{2}\lambda(V, u) \\ 0 \\ 0 \end{pmatrix} \quad (\mathbf{M})$$

with initial conditions $(0, 0, 0)$, and $\lambda(v, u) = \sqrt{(1-u)\alpha(v) + u\beta(v)}$. The partial derivatives f'_v, f'_u, b'_v, b'_u and λ are evaluated at the deterministic solution (V_t, g_t) .
We remark that, if J is the Jacobian matrix at the point (V_t, g_t), and if its spectrum is $\mathrm{sp}(J) = \{\lambda_1, \lambda_2\}$ then the spectrum of M is $\mathrm{sp}(M) = \{2\lambda_1, 2\lambda_2, \lambda_1 + \lambda_2\}$. Two different situations can be considered:

- Starting from a fixed point (V_0, u_0) of the deterministic system, the matrix $M_t = M(V_t, u_t)$ and the vector $E_t = E(V_t, u_t)$ are constant. One can derive an explicit analytical solution diagonalizing the matrix M. The time evolution for the variance and covariance of the difference between the deterministic solution and the stochastic one then depends on the stability (λ_1, λ_2) of the considered fixed point.

- Around a stable limit cycle (periodic firing): M_t and E_t are T-periodic functions. Using suitable coordinates and following Floquet's theory (see [3]), stability would be given by the spectrum of the solver $R(T) : (A_0, B_0, C_0) \rightarrow (A_T, B_T, C_T)$. As explained in [17], even if the real parts of the eigenvalues of the jacobian matrix are strictly negative for all time, unstable solutions may exist. In section 3.5 we investigate numerically the fluctuations around a stable limit cycle for the Morris-Lecar system.

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[4]The condition that the matrix Γ_s admits a real square root matrix can be reduced to $A'_s + B'_s \leq 0$ because one can show that $\det(\Gamma_s) = A'_s B'_s - C'^2_s/4 = 0$ for all $s \geq 0$. This condition is thus always satisfied because : $A'_0 + B'_0 \leq 0$, A'_s and B'_s have the same sign, and (A'_s, B'_s, C'_s) cannot cross $(0, 0, 0)$ by uniqueness of the solution of $z' = Mz$ (satisfied by y'). The computation of the matrix Σ_s gives:

$$\Sigma_s = \frac{\sqrt{-2(A'_s + B'_s)}}{A'_s + B'_s}\Gamma_s$$

If we consider

$$\left(\begin{array}{c} \tilde{Y}_N \\ \tilde{P}_N \end{array} \right) = \left(\begin{array}{c} \sqrt{N}\left(\tilde{V}_N - V\right) \\ \sqrt{N}\left(\tilde{u}_N - u\right) \end{array} \right)$$

where $(\tilde{V}_N, \tilde{u}_N)$ is the Langevin approximation, then the moments equations, written for the linearized version around the deterministic solution, give the same matrix Γ_s at the limit $N \to \infty$. But for finite N the linearized process is not gaussian (see Appendix B). Thus, our mathematical result can be directly related to the simulations results obtained in [32]: in this paper simulations of two neuron models with a large number of stochastic ion channels are made, and the fluctuations of the membrane potential below threshold exhibit approximately gaussian distributions, but only for a certain range of resting potentials. For smaller resting potentials, the shape of the distribution remained unclear as it was more difficult to compute. Our approach shows that, at finite N, for any range of the resting potentials the distribution is non-gaussian, but when $N \to \infty$, the distribution tends to a gaussian, which corresponds to the approximate gaussian distribution observed in the simulations of [32].

3.5 Quantifying the effect of channel noise on neural coding

Neurons encode incoming signals into trains of stereotyped pulses referred to as action potentials (APs). It is the mean firing frequency, that is the number of APs within a given time window, and the timing of the APs that are the main conveyors of information in nervous systems. Channel noise due to the seemingly random fluctuations in the opening and closing times of transmembranar ion channels induces jitter in the AP timing and consequently in the mean firing frequency as well. We show in the next subsections how our results can be applied to quantify these phenomena. The impact of channel noise on frequency coding is investigated in sec 3.5.1 and on spike timing coding in section 3.5.2. We close this section by some remarks concerning non-markovian processes arising when considering synaptic transmission in sec.3.5.3.

3.5.1 Numerical study of the variance of spiking rate for Morris-Lecar model

In this subsection, applying Theorem 2.3 to the Morris-Lecar system, we investigate the impact of channel noise on the variance of the firing frequency. The Morris-Lecar system was introduced in [25] to account for various oscillating states in the barnacle giant muscle fiber. We denote by $X = (V, m, n)$ the

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solution of:

$$C_m \frac{dV}{dt} = I - g_L(V - V_L) - g_{Ca}m(V - V_{Ca}) - g_K n(V - V_K) := F_v(X) \quad (7)$$

$$\frac{dm}{dt} = \lambda_m(V)(M_\infty(V) - m) := F_m(X) \quad (8)$$

$$\frac{dn}{dt} = \lambda_n(V)(N_\infty(V) - n) := F_n(X) \quad (9)$$

whrer $\lambda_m(V) = \cosh((V-V_1)/2V_2)$, $\lambda_n(V) = \phi_n*\cosh((V-V_3)/2V_4)$, $M_\infty(V) = (1 + \tanh[(V - V_1)/V_2)])/2$ and $N_\infty(V) = (1 + \tanh[(V - V_3)/V_4)])/2$. We introduce as in the previous sections a stochastic version X_N of this model with stochastic ion channels, replacing the differential equation for m and n by birth-and-death processes with voltage-dependent opening rates $\alpha_m = \lambda_m M_\infty$, $\alpha_n = \lambda_n N_\infty$ and closing rates $\beta_n = \lambda_n(1-N_\infty)$. According to the parameters of the model, the deterministic system $(3.5-3.7)$ may have a stable limit cycle x^{LC} for some values of $I \in [I_{min}, I_{max}]$ (see [25]). This corresponds to a phenomenon of regular spiking, characterized by its rate. Assuming that the time length of a spike is almost constant, we suggest a proxy for this spiking rate:

$$r(T) := \frac{1}{T} \int_0^T \phi_{th}(x(s))ds$$

where ϕ_{th} is a sigmoid threshold function. In a similar way, we define the stochastic spiking rate by:

$$r_N(T) := \frac{1}{T} \int_0^T \phi_{th}(X_N(s))ds$$

As a candidate for ϕ_{th}, we choose $\phi_{th}(V) := \frac{e^{c(V-V_{th})}}{1+e^{c(V-V_{th})}}$ where c and V_{th} are two parameters.
A consequence of the central limit theorem for X_N is the following weak convergence:

$$\sqrt{N}\left[r_N(T) - r(T)\right] \Rightarrow R(T) = \frac{1}{T} \int_0^T Z(s).\nabla\phi_{th}(x(s))ds$$

where Z is the weak limit of $\sqrt{N}\left[X_N - x\right]$:

$$Z(s) = \int_0^s \Sigma(u)dW_u$$

$R(T)$ is a gaussian random variable with zero mean. For simplicity we consider the case where ϕ_{th} is only a function of the membrane potential V. Then the variance of $R(T)$ is:

$$\sigma_R^2(T) = \mathbf{E}\left[R(T)^2\right] = \frac{2}{T^2} \int_0^T \int_0^s S_v(s')\phi'_{th}(V(s'))ds'\phi'_{th}(V(s))ds \quad (10)$$

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where $S_v(s) = \Sigma_{1,1}(s)$ is the variance of $\sqrt{N}(V_N(s) - V(s))$.

To estimate numerically the variance $\sigma_R^2(T)$, the first step is to determine numerically the limit cycle, then solve the moment equations (Appendix C) and immediately deduce $\Sigma(s)$. Thus the variance σ_R^2 can be computed using formula (3.8) without any stochastic simulation. In Fig. 3 we show our numerical results, where we plot in C-F., as a function of the input current I, the normalized variance $\xi(T)$ defined as:

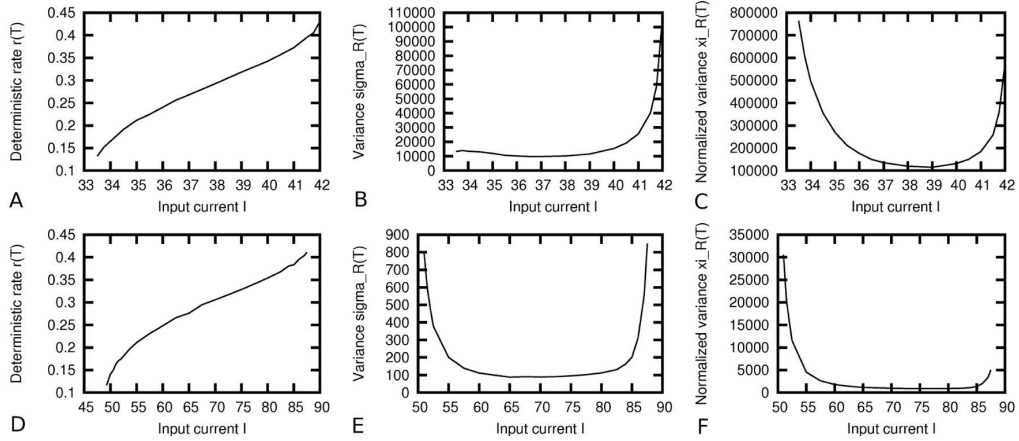$$\xi(T) := \frac{\sigma_R^2(T)}{r(T)^2}$$

Figure 3: Impact of channel noise on the spiking rate. First row (ABC) : Class I regime. Second row (DEF) Class II regime. [A-D]. Deterministic rate $r(T)$ versus input current I ($\mu A/cm^2$). [B-E]. Variance $\sigma_R^2(T)$ versus input current I ($\mu A/cm^2$). [C-F]. Normalized variance $\xi(T)$ versus input current I ($\mu A/cm^2$). Parameters : for all figures $T = 2000ms$, $c = 10$, $V_{th} = 0mV$, $C_m = 20\mu F/cm^2$, $V_1 = 0mV$, $V_2 = 15mV$, $V_3 = 10mV$, $g_{Ca} = 4mS/cm^2$, $g_K = 8mS/cm^2$, $g_L = 2mS/cm^2$, $V_K = -70mV$, $V_L = -50mV$, $V_{Ca} = 100mV$, $\phi_n = 0.1$ and $V_4 = 20mV$ for Class II (DEF) and $V_4 = 10mV$ for Class I (ABC).

Comments The value of $\xi(T)$ depends on a combination of the linear stability along the cycle and on the variance of the noise (which is multiplicative) along the cycle. If one wants to have the quantity $\frac{\mathbf{E}[(r_N(T) - r(T))^2]}{r(T)^2}$ of order 1, then the number N of channels should be of order $\xi(T)$. Interestingly, this gives much smaller values for Class II than for Class I regime. In both cases, it corresponds to a reasonably small number of channels when I is not too close from bifurcation points.

3.5.2 Impact of channel noise on latency coding in the Morris-Lecar model

Whereas frequency coding requires an integration of the input signal over a relatively long time, individual spike time coding does not require such an integration. The time to first spike, called latency, depends on the value of the suprathreshold input. Thus it may have an interpretation in term of neural coding, and it has been shown in several sensory systems [36] that the first spike latency carries information. For example, a recent study [13] concerning the visual system suggests that it allows the retina to transfer rapidly new spatial information. Impact of external noise on latency coding have been investigated in numerical studies [9] with stochastic simulations. We apply Theorem 2.5 to the Morris-Lecar model to investigate the impact of internal channel noise on first spike time. We chose the parameters (see 3) to obtain a Class I neuron model in the excitable regime. In this setting, there exists a unique steady state $X^* = (V^*, m^*, n^*)$. Starting from this equilibrium point, the impact of an input at $t = t_0$ is equivalent to an instantaneous shift of the membrane potential $V^* \to V^* + A$, where $A > 0$ is the amplitude of this shift. Eventually the system goes back to its steady state, but if A is higher than a threshold A_{th} then a spike is emitted before going back to the steady state, whereas if A is lower than A_{th} no spike is emitted. For $A > A_{th}$, we define the latency time $T(A)$ as the elapsed time between t_0 and the spike. More precisely, let $(V_A(t), m_A(t), n_A(t))$ for $t \geq t_0$ be the solution of Morris-Lecar equations with initial conditions $X(t_0) = (V(t_0) = V^* + A, m(t_0) = m^*, n(t_0) = n^*)$. We define a spike as a passage of the membrane potential $V_A(t)$ through a threshold V_{th}. Then, with $t_0 = 0$ for simplicity, the latency time $T(A)$ can be written as $T(A) := \inf\{t \geq 0; V_A(t) > V_{th}\}$. As shown in Fig.4.A, the more $A > A_{th}$ is close to A_{th}, the longer is the latency time $T(A)$. The same setting can be extended in the stochastic case, defining a random variable $T_N(A)$. Applying Theorem 2.5, with $\phi(V, m, n) = V_{th} - V$, we express the variance $P(A)$ of the limit of $\sqrt{N}(T_N(A) - T(A))$ as $N \to \infty$:

$$P(A) = \frac{S_v(T(A))}{F_v(X(T(A)))^2} \tag{11}$$

In (3.9), $S_v(T(A))$ is the variance of the V-component Z_v of Z, where we recall that Z is the limit of $\sqrt{N}(X_N - X)$ (see Theorem 2.3). The value of $S_v(T(A))$ is obtained from the numerical integration of the moments equations (..). The results are displayed in Fig.4, where the variance $P(A)$ and a normalized variance $P(A)/T(A)^2$ are plotted against the amplitude A (4.B). In 4.D the variance $P(A)$ is plotted against the latency time $T(A)$ (4.D). From (3.9), it appears that $P(A)$ is determined by two distinct contributions : the variance $S_v(T(A))$ (4.E) and the crossing speed $F(X(T(A)))$ (4.F) which actually does not influence much the variance $P(A)$. One way to interpret the results is the following: if N is large, of order $P(A)$, then $\mathbf{E}[(T_N(A) - T(A))^2]$ is of order 1. Thus, as an illustration, in order to keep $\mathbf{E}[(T_N(A) - T(A))^2]$ of order 1, the required number of channels would be of order 10^2 for a latency time of 10ms and of
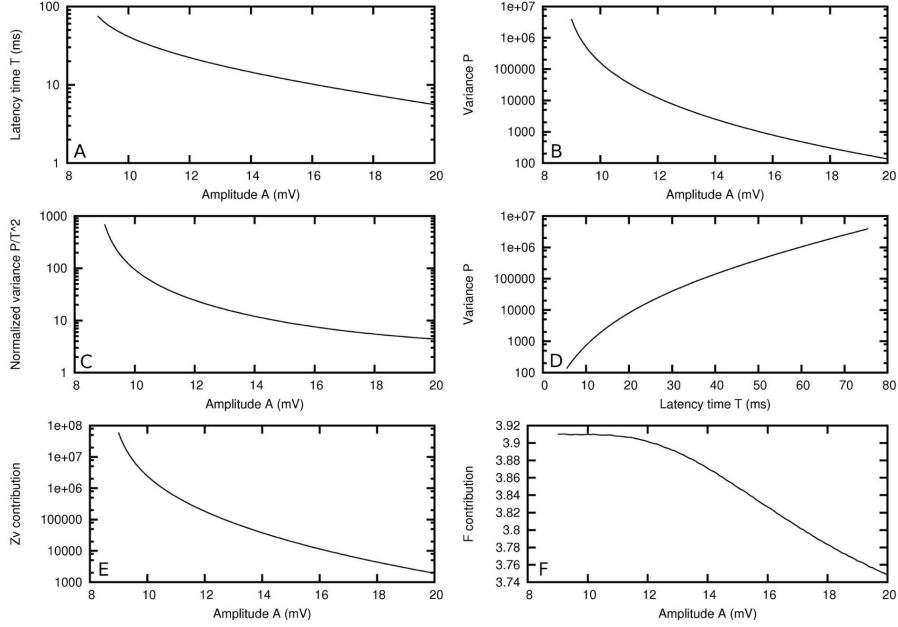
Figure 4: Impact of channel noise on latency coding. [A]. Latency time $T(A)$ versus amplitude A. [B]. Variance $P(A)$ versus amplitude A. [C]. Normalized variance $P(A)/T(A)^2$ versus amplitude A. [D]. Variance $P(A)$ versus latency time $T(A)$. [E]. Variance $S_v(A)$ versus amplitude A. [F]. Crossing speed $F_v(X(T(A)))$ versus amplitude A. Same parameters as in 3 Class I, with input current $I = 32\mu A/cm^2$.

order 10^5 for latency time of 60ms.

3.5.3 Synaptic transmission and non-markovian processes

In section 3.5.1, the quantity of interest was the firing frequency. However, the synaptic transmission between a neuron A and a neuron B has its own time scales. Therefore, neuron B's input, called post-synaptic potential $\Psi^{A \to B}$, may be modeled as a functional of neuron A's membrane potential $\{V_A(t)\}_{t \geq 0}$. Although synaptic transmission is presumably a non-linear process, one can consider as a first approximation (cf. [21]) that the process of interest is obtained directly by the convolution of the process V_A with some kernel $K^{A \to B}$:

$$\Psi^{A \to B}(t) = \int_0^t K^{A \to B}(t - s)V(s)ds$$

The mathematical analysis of the impact of channel noise on this variable can be done in the light of theorems 2.1 and 2.3. Using the general notations for the stochastic process and its deterministic limit, we define $\Psi_N(t) =$

$\int_0^t K(t,s)X_N(s)ds$ and $\Psi(t) = \int_0^t K(t,s)x(s)ds$.

Law of large numbers Define

$$S_N(T) = \sup_{s \in [0,T]} |\Psi_N(t) - \Psi(t)|^2$$

Clearly, using Cauchy-Schwartz inequality:

$$\mathbf{P}(S_N(T) > \Delta) \leq P_N(T, \eta(T)^{-1}\Delta)$$

with

$$\eta(T) = T \sup_{t \in [0,T]} \int_0^t |K(t,s)|^2 ds$$

The convergence of Ψ_N to Ψ with the same kind of exponential convergence speed is thus a direct consequence of Theorem 2.1.

Gaussian fluctuations We know (Theorem 2.3) that $\sqrt{N}(X_N - x)$ converges weakly to the diffusion $H(t) = \int_0^t R(u)dW_u$. As a consequence, $\Omega_N = \sqrt{N}(\Psi_N - \Psi)$ converges also weakly, to the following process:

$$\Omega(t) = \int_0^t K(t,s) \left(\int_0^s R(u)dW_u \right) ds$$

With an integration by part, one can rewrite:

$$\Omega(t) = \int_0^t Z(t,s)dW_s$$

with

$$Z(t,s) = \int_s^t K(t,u)du R(s)$$

The process Ω is gaussian and one can easily compute its variance as $\int_0^t Z(t,s)^2 ds$. However, it is non markovian, and some issues concerning the first hitting times of such processes are solved in [33].

4   Proof of the law of large numbers

In this section we give the proof for **Theorem 2.1**. This proof is inspired from [1], except for the exponential martingale bound. In order to simplify the notation and to make the arguments clearer and more intuitive, we write the proof for the case of a single channel type with state space $\{0,1\}$ and transition rates given by the scheme:

In this case, the stochastic model (S_N^0) is:

$$\dot{V}_N(t) = f(V_N(t), u_N(t)); V_N(0) = V_0$$

$$u_N(t) = \frac{1}{N} \sum_{k=1}^N \delta_1(u_t^{(k)}); u_N(0) = u_0^{(N)}$$

$$
\begin{array}{ccc}
& \alpha(V_N) & \\
0 & \rightleftarrows & 1 \\
& \beta(V_N) &
\end{array}
$$
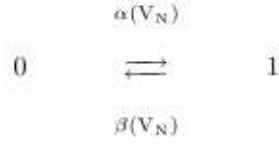
where $u_t^{(k)} : 0 \rightarrow 1$ with rate $\alpha(V_N(t))$ and $1 \rightarrow 0$ with rate $\beta(V_N(t))$, for all $1 \leq k \leq N$

The deterministic solution (v, u) satisfies:

$$
\begin{cases}
\dot{v}(t) = f(v(t), u(t)) \\
\dot{u}(t) = (1 - u(t))\alpha(v(t)) - u(t)\beta(v(t)) \\
v(0) = v_0 \ ; \ u(0) = u_0
\end{cases}
$$

In order to complete the proof, few slight changes in the notation can be done:

- in order to work with more general jump Markov processes with finite state space, essentially all the expressions of the form $\delta_0(u)\alpha(v) - \delta_1(u)\alpha(v)$ should be replaced by

$$
\sum_{i \neq j} \alpha_{i,j}(v, u)\delta_{e_i}(u) - \alpha_{j,i}(v, u)\delta_{e_j}(u)
$$

- in order to include q different channel types (different ions), one should just write the same arguments for all the q processes $\{\mathbf{e}_N^{(j)}(t)\}$ for $1 \leq j \leq q$ and include all the $||\mathbf{e}_N^{(j)}(t) - \mathbf{e}^{(j)}(t)||$ for $1 \leq j \leq q$ in the function $f(t)$ of Gronwall lemma application in section 3.4.

4.1 Decomposition in a martingale part and a finite variation part

Decomposition We decompose the difference between the stochastic and the deterministic processes as a sum of a martingale part M_N and a finite variation part Q_N as follows:

$$
[u_N(t) - u_N(0)] - [u(t) - u(0)] = M_N(t) + \int_0^t Q_N(s)ds
$$

where we define:

$$
Q_N(t) = \frac{1}{N} \sum_{i=1}^N \left[\delta_0(u_t^{(i)})\alpha(V_N(t)) - \delta_1(u_t^{(i)})\beta(V_N(t)) \right] - \dot{u}(t)
$$

$$
M_N(t) = [u_N(t) - u(t)] - [u_N(0) - u(0)] - \int_0^t Q_N(s)ds
$$

Lemma As defined above, $(M_N(t))$ is a $\{F_t\}$-martingale.

Proof For $h > 0$, define $\Delta M_N(t,h) = \frac{1}{h}\mathrm{E}\left[M_N(t+h) - M_N(t)|F_t\right]$, then:

$$
\begin{aligned}
\Delta M_N(t,h) &= \frac{1}{h}\frac{1}{N}\sum_{i=1}^{N}\mathrm{E}\left[\delta_1(u_{t+h}^{(i)})|F_t\right] - \mathrm{E}\left[\delta_1(u_t^{(i)})|F_t\right] \\
&\quad - \frac{1}{h}\mathrm{E}\left[\int_t^{t+h}\left[\frac{1}{N}\sum_{i=1}^{N}\delta_0(u_s^{(i)})\alpha(V_s) - \delta_1(u_s^{(i)})\beta(V_s)\right]ds|F_t\right] \\
&\quad - \frac{1}{h}\left[u(t+h) - u(t)\right] + \frac{1}{h}\int_t^{t+h}\dot{u}(s)ds
\end{aligned}
$$

The last line converges clearly to 0 as $h \to 0$, and the two first terms compensate as $h \to 0$. So we have:

$$
\lim_{h\to 0}\frac{1}{h}\mathrm{E}\left[M_N(t+h) - M_N(t)|F_t\right] = 0
$$

Therefore

$$
\frac{d}{ds}\mathrm{E}[M_N(t+s)|F_t]|_{s=0} = 0
$$

By dominated convergence we have:

$$
\frac{d}{ds}\mathrm{E}[M_N(t+s)|F_t]|_{s=s_0} = \mathrm{E}\left[\frac{d}{du}\mathrm{E}[M_{t+s_0+u}|F_{t+s_0}]|_{u=0}|F_t\right] = 0
$$

Finally:

$$
\mathrm{E}[M_N(t+h)|F_t] = \mathrm{Cst} = M_N(t) \quad \otimes
$$

4.2 Martingale bound

In this part we want to obtain a bound in probability for the martingale part. We introduce the jump measure and the associated compensator:
We define two random measures on $]0,T] \times \{0,1\}$:

- jump measure : $\kappa_i = \displaystyle\sum_{t\in]0,T],u_t^{(i)}\neq u_{t-}^{(i)}} \delta_{(t,u_t^{(i)})}$

- compensator :

$$
\nu_i(dt,dy) = \left[\beta(V_N(t))\delta_1(u_{t-}^{(i)})\delta_0(y) + \alpha(V_N(t))\delta_0(u_{t-}^{(i)})\delta_1(y)\right]dt
$$

We can rewrite $Q_N(s)$ and $M_N(t)$:

$$
\int_0^t Q_N(s)ds = \frac{1}{N}\sum_{i=1}^{N}\int_{]0,T]\times\{0,1\}}(\delta_1(y) - \delta_1(u_{t-}^{(i)}))\nu_i(ds,dy) - \int_0^t \dot{u}(s)ds
$$

$$
M_N(t) = \frac{1}{N}\sum_{i=1}^{N}\int_{]0,T]\times\{0,1\}}(\delta_1(y) - \delta_1(u_{t-}^{(i)}))(\kappa_i - \nu_i)(ds,dy)
$$

Then we have the following proposition:

Proposition Let $T > 0$, $\epsilon > 0$, $\delta > 0$. Then there exists N_0 such that $\forall N \geq N_0$,

$$\mathrm{P}\left[\sup_{0 \leq t \leq T} M_N(t)^2 \geq \delta\right] \leq \epsilon$$

Proof Let us first recall that from standard results about residual processes ([18]) we have:

$$
\begin{aligned}
\mathrm{E}\left[M_N(t)^2\right] &= \frac{1}{N^2}\sum_{i=1}^N \mathrm{E}\left[\int_{]0,T]x\{0,1\}}(\delta_1(y) - \delta_1(u_{t-}^{(i)}))^2(\kappa_i - \nu_i)(ds, dy)\right] \\
&= \frac{1}{N^2}\sum_{i=1}^N \mathrm{E}\left[\int_{]0,T]}\beta(V_N(s))\delta_1(u_{s-}^{(i)}) + \alpha(V_N(s))\delta_0(u_{s-}^{(i)})ds\right]
\end{aligned}
$$

Therefore, we can get a bound for $\mathrm{E}\left[M_N(t)^2\right]$:

$$\mathrm{E}\left[M_N(t)^2\right] \leq C_1\frac{t}{N}\max\left(||\alpha||_\infty, ||\beta||_\infty\right)$$

where $||\alpha||_\infty$ and $||\beta||_\infty$ are finite because α and β are continuous and assumption (H1). We then use Chebychev inequality and Doob inequality for L^2 martingales:

$$\mathrm{P}\left[\sup_{0 \leq t \leq T} M_N(t)^2 \geq \delta\right] \leq \frac{1}{\delta}\mathrm{E}\left[\sup_{0 \leq t \leq T} M_N(t)^2\right] \leq \frac{4}{\delta}\mathrm{E}\left[M_N(t)^2\right]$$

and $\mathrm{E}\left[M_N(t)^2\right] \leq \frac{\epsilon\delta}{4}$ for all $N \geq N_0.\otimes$

In order to obtain a better estimate for the convergence rate, we derive here an exponential bound for the martingale part. Our proof is inspired from techniques developed in [5].

Proposition Let $T > 0, \eta > 0$. There exists a constant C_η such that for all $\delta \in]0, \eta C_\eta T[$:

$$\mathrm{P}\left[\sup_{0 \leq t \leq T} |M_N(t)| \geq \delta\right] \leq 2\exp\left(-\frac{\delta^2 N}{2C_\eta T}\right)$$

Proof We define, for $x = (u, v)$, $\theta \in R$:

$$m_N(x, \theta) = \int_R e^{\theta y}\lambda_N(x)\mu_N(x, dy) = N\lambda(x)[e^{\theta/N}\mu^+(x) + e^{-\theta/N}\mu^-(x)]$$

$$
\begin{aligned}
\phi_N(x, \theta) &= \int_R [e^{\theta y} - 1 - \theta y]\lambda_N(x)\mu_N(x, dy) \\
&= \int_0^1 \frac{\partial^2 m_N}{\partial \theta^2}(x, r\theta)\theta^2(1 - r)dr
\end{aligned}
$$

The second equality stems from integration by part. And, if $|\theta| < N\eta$,

$$|\frac{\partial^2 m_N}{\partial \theta^2}(x, r\theta)| = \left| N\lambda(x)\frac{1}{N^2}[e^{r\theta/N}\mu^+(x) + e^{-r\theta/N}\mu^-(x)] \right| \le \frac{C_\eta}{N}$$

So, $|\phi_N(x, \theta)| \le \frac{1}{2}\frac{C_\eta}{N}\theta^2$. Let us define

$$Z_N^\epsilon(t) = \exp[\epsilon M_N(t) - \int_0^t \phi_N((u_N(s), V_N(s)), \epsilon)ds]$$

$(Z_N^\epsilon(t))$ is a martingale thanks to Doléans Formula:

$$Z_N^\epsilon(t) = 1 + \int_0^t \int_R Z_N^\epsilon(s^-)[e^{\epsilon y} - 1](\mu - \nu)(ds, dy)$$

Then we note $\tau = \inf\{t; M_N(t) > \delta\}$. On $\{\tau \le t\}, Z_N^\epsilon(\tau) \ge \exp\{\delta\epsilon - \frac{t\epsilon^2 C_\eta}{2N}\}$. And by optional stopping theorem:

$$\mathrm{E}[Z_N^\epsilon(\min(t, \tau))] = \mathrm{E}[Z_N^\epsilon(0)] \ge \mathrm{E}[Z_N^\epsilon(\tau)1_{\tau \le t}] \ge \mathrm{P}(\tau \le t)\exp\{\delta\epsilon - \frac{t\epsilon^2 C_\eta}{2N}\}$$

So, $\mathrm{P}\left[\sup_{0 \le t \le T}|M_N(t)| > \delta\right] = \mathrm{P}(\tau \le T) \le \exp\{-\delta\epsilon + \frac{T\epsilon^2 C_\eta}{2N}\}$.

Finally when $\delta \in]0, \eta C_\eta T[$, with $\epsilon = \frac{\delta N}{C_\eta t}$, and applying the same argument to $-M_N(t)$ we get the result.$\otimes$

4.3 Finite Variation Part

In this section we use the Lispchitz property of α and β to provide a bound for the finite variation part, in order to apply later Gronwall Lemma.

Lemma There exists $C_1 > 0$ independent of N such that:

$$|Q_N(t))| \le C\left(|u_N(t) - u(t)| + |V_N(t) - v(t)|\right)$$

Proof

$$\begin{aligned}
Q_N(t) &= \frac{1}{N}\sum_{i=1}^N \delta_0(u_t^{(i)})\alpha(V_N(t)) - (1 - u(t))\alpha(v(t)) \\
&\quad - \frac{1}{N}\sum_{i=1}^N \delta_1(u_t^{(i)})\beta(V_N(t)) - u(t)\beta(v(t))
\end{aligned}$$

Let us start with the second term of the difference, called $Q^{1\to 0}$:

$$
\begin{aligned}
Q^{1\to 0} &= \frac{1}{N}\sum_{i=1}^{N}\delta_1(u_t^{(i)})\beta(V_N(t)) - u(t)\beta(v_t)\\
&= \frac{1}{N}\sum_{i=1}^{N}\delta_1(u_t^{(i)})\beta(V_N(t)) - u(t)\beta(V_N(t)) + u(t)\left(\beta(V_N(t)) - \beta(v(t))\right)\\
&= \beta(V_N(t))\left(u_N(t) - u(t)\right) + \underbrace{u(t)}_{\in [0,1]}\left(\beta(V_N(t)) - \beta(v(t))\right)
\end{aligned}
$$

Then,

$$
|Q^{1\to 0}| \leq ||\beta||_\infty |u_N(t) - u(t)| + K_\beta |V - v(t)|
$$

where K_β is the Lipschitz coefficient of β. We do the same for the other term of the difference:

$$
|Q^{0\to 1}| \leq ||\alpha||_\infty |u_N(t) - u(t)| + K_\alpha |V_N(t) - v(t)|
$$

So the proof is complete, with $C_1 = \max(||\alpha||_\infty, ||\beta||_\infty, K_\alpha, K_\beta)$ $\otimes$

If more general transition rates $\alpha(v,u)$ and $\beta(v,u)$ depend on v *and* u, one would need to replace $||\alpha||_\infty$ and $||\beta||_\infty$, respectively by $||\alpha||_\infty + K_\alpha^{(u)}$ and $||\beta||_\infty + K_\beta^{(u)}$, where $K_\alpha^{(u)}, K_\beta^{(u)}$ are the Lipschitz coefficients associated with the second variable u.

4.4 Proof of theorem 2.1

Law of large numbers We want to apply Gronwall Lemma to the function:

$$
f(t) = |V_N(t) - v(t)|^2 + |u_N(t) - u(t)|^2
$$

From the previous section we have a good control on the martingale term and the following estimate:

Corollary There exists $C_2 > 0$ independent of N such that:

$$
\begin{aligned}
|u_N(t) - u(t)|^2 &\leq 4[|u_N(0) - u(0)|^2 + C_2 T \int_0^t |u_N(s) - u(s)|^2 ds\\
&+ C_2 T \int_0^t |V_N(s) - v(s)|^2 + M_N(t)^2]
\end{aligned}
$$

Proof As $u_N(t) - u(t) = u_N(0) - u(0) + M_N(t) + \int_0^t Q_N(s)ds$ and $(x + y + z)^2 \leq 4(x^2 + y^2 + z^2)$, the result is a direct application of the previous lemma and of Cauchy-Schwarz inequality.$\otimes$ We need now to work on $|V_N(t) - v(t)|^2$,

using hypothesis (H1) , with $K_1 = \sup_{N} \sup_{s \in [0,T]} \left| \frac{\partial f}{\partial v}(V_N(s), u_N(s)) \right|$ and $K_2 = \sup_{N} \sup_{s \in [0,T]} \left| \frac{\partial f}{\partial u}(V_N(s), u_N(s)) \right|$.

Between the jumps, we have:

$$\frac{d}{dt}\left(|V_N(t) - v(t)|^2\right) = 2\left(f(V_N(t), u_N(t)) - f(v(t), u(t))\right)(V_N(t) - v(t))$$

Thus,

$$\begin{aligned}
|V_N(t) - v(t)|^2 &= 2\int_0^t [f(V_N(s), u_N(s)) - f(v(s), u(s))](V_N(s) - v(s))\, ds \\
&\quad + |V_N(0) - v_0|^2 \\
&\leq |V_N(0) - v_0|^2 + 2K_1 \int_0^t |V_N(s) - v(s)|^2 ds \\
&\quad + 2K_2 \int_0^t |u_N(s) - u(s)||V_N(s) - v(s)| ds \\
&\leq |V_N(0) - v_0|^2 + 2K_1 \int_0^t |V_N(s) - v(s)|^2 ds \\
&\quad + K_2 \int_0^t |u_N(s) - u(s)|^2 ds + K_2 \int_0^t |V_N(s) - v(s)|^2 ds
\end{aligned}$$

where we used successively Cauchy-Schwartz inequality and $ab \leq \frac{1}{2}(a^2 + b^2)$. Putting together this inequality with the Corollary we obtain:

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

where $B = B(T) = \max(2K_1(T) + K2(T), C_2 T)$ does not depend on N and is linear w.r.t T if (H2) holds, and

$$A = |u_N(0) - u_0|^2 + |V_N(0) - v_0|^2 + K_A \sup_{0 \leq s \leq T} M_s^2$$

If we control the initial conditions, then, with the control we have on the martingale part, A can be chosen arbitrarily small (with high probability) and we can conclude with Gronwall Lemma.

Exponential convergence speed If the initial conditions are the same for the stochastic and deterministic model, we actually have a exponentially fast convergence, thanks to the exponential bound for the martingale part: there exists a constant $C_m > 0$ such that:

$$\limsup_{N \to \infty} \frac{1}{N} \log P \left[\sup_{0 \leq t \leq T} |V_N(t) - v(t)|^2 + |u_N(t) - u(t)|^2 > \Delta \right] \leq -\frac{\Delta e^{-B(T)T}}{2 K_A C_m T}$$

30

5 Proof of the central limit theorems

As before, we write the proofs for the case of a single channel type with state space $\{0,1\}$ and transition rates given by the scheme:

$$0 \quad \underset{\beta(V_N)}{\overset{\alpha(V_N)}{\rightleftharpoons}} \quad 1$$

5.1 Langevin approximation

In this case, Theorem 2.2 can be written as follows:

Let $b(u,v) = (1-u)\alpha(v) - u\beta(v)$, and (V_N, u_N) solution of the stochastic model (S_N). Then, the process $R_N(t) = \sqrt{N}\left(u_N(t) - u_N(0) - \int_0^t b(u_N(s), V_N(s))ds\right)$ converges in law, as $N \to \infty$, towards the process $R(t)$ defined as a stochastic integral:

$$R(t) = \int_0^t \sqrt{(1-u(s))\alpha(V(s)) + u(s)\beta(V(s))}dB_s$$

where B is a standard brownian motion and $u(t), V(t)$ is the unique solution of:

$$\dot{V} = f(V, u)$$

$$\dot{u} = (1-u)\alpha(V) - u\beta(V)$$

$$\forall N, \ u(0) = u_0 = u_N(0)$$

$$\forall N, \ V(0) = V_0 = V_N(0)$$

This result provides the following degenerate diffusion approximation $(\tilde{V}_N, \tilde{u}_N)$, for N sufficiently large:

$$d\tilde{V}_N(t) = f(\tilde{V}_N(t), \tilde{u}_N(t))dt$$

$$d\tilde{u}_N(t) = \left[(1 - \tilde{u}_N(t))\alpha(\tilde{V}_N(t)) - \tilde{u}_N(t)\beta(\tilde{V}_N(t))\right]dt + \sigma_N(\tilde{u}_N(t), \tilde{V}_N(t))dB_t$$

$$\sigma_N(u)^2 = \frac{1}{N}\left[(1-u)\alpha(v) + u\beta(v)\right] = \frac{1}{N}\lambda(v, u)$$

Let $g(u,v) = \lambda_N(u,v)[\frac{1}{N^2}\mu^+(u,v) + \frac{1}{N^2}\mu^-(u,v)] = (1-u)\alpha(v) + u\beta(v)$.
Note that in the multidimensional case, the real valuedfunction g above becomes a $d \times d$-matrix. Since the different channel types j are supposed to independent, this matrix would be bloc diagonal, with blocs of size r_j, thus assuring the independence of the q (r_j-dimensional Brownian motions) $W^{(j)}$ in Theorem 2.

The blocs of size r_j are given by the matrix $G^{(j)}$ of theorem 2, and arise from the calculation of the covariances:

$$G_{i,j}^{(j)}(x) = N\lambda_N(x) \int_E z_i z_j \mu_N(x, z)$$

Proof of Theorem 2.2   We adapt the proof given by Kurtz [22]: we prove the convergence of characteristic functions plus tightness. The tightness property follows from the inequality:

$$P[\sup_{s \leq T} |R_N(s)| > \delta] \leq \frac{tN}{\delta^2} ||g||_\infty$$

Let $\phi_N(t, \theta) = \mathbf{E}[e^{i\theta R_N(t)}]$ the characteristic function of R_N. Let $h(M_N(t)) = e^{i\theta R_N(t)}$, $\sqrt{N} M_N(t) = R_N(t)$, $\psi(u) = \frac{e^{iu}-1-iu+u^2/2}{u^2}$, $\xi(u) = e^{iu} - 1 - iu = u^2\psi(u) - u^2/2$. We then have:

$$
\begin{aligned}
\phi_N(t, \theta) - 1 &= \mathbf{E}[h(M_N(t))] - h(0) \\
&= \int_0^t \mathbf{E}[\lambda_N(s) \int_{E_N} h(w - u_N(s) + M_N(s)) - h(M_N(s)) \\
&\quad - (w - u_N(s))h'(M_N(s))\mu_N(s, dw)]ds \\
&= \int_0^t \mathbf{E}[e^{i\theta R_N(s)}\lambda_N(s) \int_{E_N} \xi(\theta\sqrt{N}(w - u_N(s))\mu_N(s, dw)]ds \\
&= -\int_0^t \mathbf{E}\left[\frac{1}{2}e^{i\theta R_N(s)}\lambda_N(s) \int_{E_N} N\theta^2(w - u_N(s))^2\mu_N(s, dw)\right] ds \\
&\quad + \int_0^t \mathbf{E}[e^{i\theta R_N(s)}\lambda_N(s) \int_{E_N} N\theta^2(w - u_N(s))^2 \\
&\quad \times \psi\left(\sqrt{N}\theta(w - u_N(s))\right)\mu_N(s, dw)]ds
\end{aligned}
$$

where $\lambda_N(s)$ stands for $\lambda_N(u_N(s), V_N(s))$ and $\mu_N(s, dw)$ for $\mu_N(u_N(s), V_N(s), dw)$. The second term in the last equality, call it $K_N(\theta)$, converges to 0 as $N \to \infty$ by dominated convergence, and because $\psi\left(\sqrt{N}\theta(w - u_N(s))\right) = \psi\left(\pm\theta/\sqrt{N}\right) \to 0$ as $\lim_{u \to 0} \psi(u) = 0$. So we have:

$$
\begin{aligned}
\phi_N(t, \theta) - 1 &= -\int_0^t \mathbf{E}\left[\frac{1}{2}e^{i\theta R_N(s)}\theta^2 g(u_N(s), V_N(s))\right] ds + K_N(\theta) \\
&= -\frac{1}{2}\int_0^t \theta^2 g(u(s), V(s))\phi_N(s, \theta)ds \\
&\quad + \frac{1}{2}\int_0^t \theta^2\mathbf{E}\left[(g(u(s), V(s)) - g(u_N(s), V_N(s)))e^{i\theta R_N(s)}\right] ds \\
&\quad + K_N(\theta)
\end{aligned}
$$

Again, the second term in the last equality, call it $J_N(\theta)$, converge to 0 as $N \to \infty$, because of the convergence of u_N and V_N to u and V.(cf. Theorem

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2.1)

By Gronwall lemma, we conclude that $\phi_N(t, \theta) \to \phi(t, \theta)$ with:

$$\phi(t, \theta) = \exp\{-\frac{1}{2}\theta^2 \int_0^t g(u(s), V(s)) ds\} \quad \otimes$$

5.2   Functional central limit theorem

Let (V_N, u_N) be the solution of the simplified stochastic model (S_N) and (V, u) of the deterministic model (D) introduced in the Example of section 2. Consider the process:

$$\begin{pmatrix} P_N \\ Y_N \end{pmatrix} = \begin{pmatrix} \sqrt{N}(u_N - u) \\ \sqrt{N}(V_N - V) \end{pmatrix}$$

If the initial conditions satisfy $(P_N(0), Y_N(0)) = (0, 0)$, the 2-dimensional process (P_N, Y_N) converges in law, as $N \to \infty$, towards the process (P, Y), with characteristic function:

$$\mathbf{E}\left[e^{i(\theta_1 P(t) + \theta_2 Y(t))}\right] = e^{\theta_1^2 A(t) + \theta_2^2 B(t) + \theta_1 \theta_2 C(t)}$$

The functions A, B and C are solutions of the system:

$$\begin{pmatrix} A' \\ B' \\ C' \end{pmatrix} = \begin{pmatrix} 2b'_u & 0 & b'_v \\ 0 & 2f'_v & f'_u \\ 2f'_u & 2b'_v & b'_u + f'_v \end{pmatrix} \begin{pmatrix} A \\ B \\ C \end{pmatrix} + \begin{pmatrix} -\frac{1}{2}\lambda(V, u) \\ 0 \\ 0 \end{pmatrix} \quad (\mathbf{M})$$

with initial conditions $(0, 0, 0)$, and with $\lambda(v, u) = \sqrt{(1-u)\alpha(v) + u\beta(v)}$.

Proof of Theorem 2.3   Just as in the proof of Theorem 2.2, let us define:

$$\phi_N(t, \theta) = \mathbf{E}\left[e^{i(\theta_1 P_N(t) + \theta_2 Y_N(t))}\right]$$

Let us also define $Z_N = (u_N - u, V_N - V)$, $X_N = (u_N, V_N)$, $X = (u, V)$, and $h(x, y) = e^{i\sqrt{N}(\theta_1 x + \theta_2 y)}$. Then:

$$\begin{aligned}
\phi(t, \theta) - 1 &= \mathbf{E}\left[h(Z_N(t)) - h(Z_N(0))\right] \\
&= \int_0^t \mathbf{E}[N\lambda(X_N(s)) \int_{E_N} \{h(w - u(s), V_N(s) - V(s)) \\
&\quad - h(Z_N(s))\} \mu(X_N(s), dw) \\
&\quad - b(X(s))h'_x(Z_N(s)) + (f(X_N(s)) - f(X(s))) h'_y(Z_N(s))] ds
\end{aligned}$$

So $\phi_N(t, \theta) - 1 = G_N(\theta, t) + H_N(\theta, t)$ with

$$\begin{aligned}
G_N(\theta, t) &= \int_0^t \mathbf{E}\left[\Omega_N(s)\left\{(e^{i\theta_1\sqrt{N}/N} - 1)\mu_+ + (e^{-i\theta_1\sqrt{N}/N} - 1)\mu_-\right\}\right] ds \\
\Omega_N(s) &= N\lambda(X_N(s))h(Z_N(s)), \ \mu_{+/-} = \mu_{+/-}(X_N(s)) \\
H_N(\theta, t) &= \int_0^t i\mathbf{E}\left[-\theta_1\sqrt{N}b(X(s))h(Z_N(s)) + \theta_2\sqrt{N}\{f(X_N(s)) - f(X(s))\}\right] ds
\end{aligned}$$

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Then in order to use the asymptotic development of e^x when $x \to 0$ we introduce the function $K(u) = e^{iu} - 1 - iu + u^2/2$. Then, knowing that $\mu_+ + \mu_- = 1$:

$$G_N(\theta, t) = \int_0^t \mathbf{E}\left[\Omega_N(s)\left\{i\frac{\theta_1}{\sqrt{N}}(\mu_+ - \mu_-)(X_N(s)) - \frac{\theta_1^2}{2N} + K(\theta_1/\sqrt{N})\right\}\right] ds$$

Since $b(x) = \lambda(x)(\mu_+(x) - \mu_-(x))$, we have :

$$
\begin{aligned}
G_N(\theta, t) &= \int_0^t \mathbf{E}\left[i\theta_1\sqrt{N}b(X_N(s))h(Z_N(s))\right] ds \\
&+ \int_0^t \mathbf{E}\left[-\frac{\theta_1^2}{2}\lambda(X_N(s))h(Z_N(s))\right] ds \\
&+ \int_0^t \mathbf{E}\left[NK(\theta_1/\sqrt{N})h(Z_N(s)\right] ds
\end{aligned}
$$

Therefore:

$$
\begin{aligned}
\phi_N(t, \theta) - 1 &= \int_0^t \mathbf{E}\left[-\frac{1}{2}\theta_2^2\lambda(X_N(s))h(Z_N(s))\right] ds \ (A) \\
&+ \int_0^t \mathbf{E}\left[h(Z_N(s))i\theta_1\sqrt{N}\left\{b(X_N(s)) - b(X(s))\right\}\right] ds \ (B) \\
&+ \int_0^t \mathbf{E}\left[h(Z_N(s))i\theta_2\sqrt{N}\left\{f(X_N(s)) - f(X(s))\right\}\right] ds \ (C) \\
&+ \int_0^t \mathbf{E}\left[h(Z_N(s))NK(\theta_1/\sqrt{N})\lambda(X_N(s))\right] ds \ (D)
\end{aligned}
$$

Using the derivatives of b and f, and the convergence of X_N to X we can make a development of the sum $B + C$:

$$
\begin{aligned}
B + C &= \int_0^t \mathbf{E}[h(Z_N)i\sqrt{N}\{(u_N - u)(\theta_1 b'_u + \theta_2 f'_u) \\
&+ (V_N - V)(\theta_1 b'_v + \theta_2 f'_v)\}]ds\} + \epsilon_N(t, \theta)
\end{aligned}
$$

where we dropped the s and where b'_u, b'_v, f'_u, f'_v are taken at $X_N(s)$.
Noting that $h(Z_N)i\sqrt{N}(u_N - u) = h'_x(Z_N)$ and $h(Z_N)i\sqrt{N}(V_N - V) = h'_y(Z_N)$, we have:

$$B + C = \int_0^t \mathbf{E}\left[h'_x(Z_N)(\theta_1 b'_u + \theta_2 f'_u) + h'_y(Z_N)(\theta_1 b'_v + \theta_2 f'_v)\right]$$

And the term D converges to zero as $N \to \infty$ by dominated convergence since $K(u)/u^2$ is bounded and converges to 0.
As we have the convergence in Theorem 2.1 of X_N to X,we get the convergence of $\phi_N(t, \theta)$ to $\Psi(t, \theta)$, satisfying:

$$
\begin{aligned}
\frac{\partial\Psi}{\partial t}(t, \theta) &= -\frac{1}{2}\theta_1^2\lambda(X(t))\Psi(t, \theta) + (\theta_1 b'_u(X(t)) + \theta_2 f'_u(X(t)))\frac{\partial\Psi}{\partial\theta_1} \\
&+ (\theta_1 b'_v(X(t)) + \theta_2 f'_v(X(t)))\frac{\partial\Psi}{\partial\theta_2}
\end{aligned}
$$

Tightness stems from the Markov property and the following estimate obtained in the proof Theorem 2.1:

$$\mathbf{P}\left[\sup_{0\le t\le T}||\sqrt{N}\left[V_N(t)-v(t)\right]||^2+\sum_{j=1}^{q}||\sqrt{N}\left[\mathbf{e}_N^{(j)}(t)-\mathbf{g}^{(j)}(t)\right]||^2>\Delta\right]$$

$$\le\exp\left\{-\frac{(\Delta/N)Ne^{-B(T)T}}{CT}\right\}$$

The announced convergence in law follows.

To solve the PDE, we set $\Psi(t,\theta)=e^{\theta_1^2 A(t)+\theta_1\theta_2 C(t)+\theta_2^2 B(t)}$. Then, substituting in the initial equation, and identifying the coefficients, we get the system $(\mathbf{M})$. $\otimes$

Proof of Theorem 2.4 We want to prove that the process Z has the same law as the limit as $N\to\infty$ of the difference between the Langevin approximation linearized around the deterministic solutions and the deterministic solution itself, scaled by $\sqrt{N}$. We write it in the general case, not only in dimension two as above. First we identify the equations satisfy by the moments of Z starting from the equation satisfied by the characteristic function. We make the ersatz:

$$\psi(t,\theta)=e^{-\frac{1}{2}\theta\Gamma(t)\theta^T}$$

The matrix Γ_t corresponds to the variance/covariance matrix. We plug this expression into the equation satisfied by ψ as given in theorem 2.3:

$$\frac{\partial\Psi}{\partial t}=\sum_{j=1}^{q}\left\{\sum_{l\in L}\sum_{k=1}^{r_j}\theta_k^{(j)}\frac{\partial b_{j,k}}{\partial x_l}\frac{\partial\Psi}{\partial\theta_l}-\frac{1}{2}\sum_{k,l=1}^{r_j}\theta_k^{(j)}\theta_l^{(j)}G_{k,l}^{(j)}\Psi\right\}$$

$$+\sum_{m=1}^{p}\sum_{l\in L}\theta_m\frac{\partial f^m}{\partial x_l}\frac{\partial\Psi}{\partial\theta_l}$$

The ensemble of indices L can be writen $L=L_v\cup L_u$ where $L_v=\{1\le m\le p\}$ and $L_u=\{(j,k),\ 1\le j\le q,\ 1\le k\le r_j\}$. To identify the equations satisfied by Γ_{ab} we distinguish the following cases:

- $a\in L_v$ and $b\in L_v$: $\frac{1}{2}\Gamma'_{ab}=\sum_{l\in L}\left[\frac{\partial f^a}{\partial x_l}\Gamma_{bl}+\frac{\partial f^b}{\partial x_l}\Gamma_{al}\right]$

- $a\in L_v$ and $b\in L_u$, $b=(j,k)$: $\frac{1}{2}\Gamma'_{ab}=\sum_{l\in L}\left[\frac{\partial b_{j,k}}{\partial x_l}\Gamma_{al}+\frac{\partial f^a}{\partial x_l}\Gamma_{bl}\right]$

- $a\in L_u$, $a=(j,k)$ and $b\in L_v$: $\frac{1}{2}\Gamma'_{ab}=\sum_{l\in L}\left[\frac{\partial b_{j,k}}{\partial x_l}\Gamma_{bl}+\frac{\partial f^b}{\partial x_l}\Gamma_{al}\right]$

- $a \in L_u$, $a = (j, k)$ and $b \in L_v$, $b = (j', k')$:

$$\frac{1}{2}\Gamma'_{ab} = \sum_{l \in L} \left[\frac{\partial b_{j,k}}{\partial x_l}\Gamma_{bl} + \frac{\partial b_{j',k'}}{\partial x_l}\Gamma_{al} \right] + \frac{1}{2}G^{(j)}_{k,k'}\mathbf{1}_{j=j'}$$

We then write the equations satisfied by $K^{(N)}(t) = \sqrt{N}(\tilde{X}_N(t) - X(t)) = (Y^m_N, P^{j,k}_N)$, where $\tilde{X}_N$ is the Langevin approximation defined in section 2.4, and where X is the deterministic limit:

$$dY^m_N = \sqrt{N}(f^m(\tilde{X}_N) - f^m(X))dt$$
$$dP^{j,k}_N = \sqrt{N}(b_{j,k}(\tilde{X}_N) - b_{j,k}(X))dt + \sigma^{(j)}(\tilde{X}_N)dW^j_t$$

When we linearize around the deterministic solution, we obtain the following equations:

$$d\tilde{Y}^m_N = \sum_{l \in L} \frac{\partial f^m}{\partial x_l}K^{(N)}_l dt$$
$$d\tilde{P}^{j,k}_N = \sum_{l \in L} \frac{\partial b_{j,k}}{\partial x_l}K^{(N)}_l dt + \left(\sum_{k'=1}^{r_j} \sigma^{(j)}_{k,k'}(X) + \frac{1}{\sqrt{N}}\Omega^{(j)}_{k,k'} \right) dW^{j,k'}_t$$

where the terms $\frac{1}{\sqrt{N}}\Omega^{(j)}_{k,k'}$ comes from the linearization of $\sigma^{(j)}_{k,k'}(\tilde{X}_N)$, we do not need to specify them here because they go to zero as $N \to \infty$.

It is now clear that the moments equations for this linear diffusion system tends the system satisfied by Γ_{ab} as $N \to \infty$.

Proof of Theorem 2.5 The convergence of X_N to X a.s. uniformly on finite time intervals, obtained in Theorem 2.1, implies that $\tau_N \to \tau$ a.s. In order apply Theorem 2.3, let us introduce Z_N through the following decomposition:

$$\sqrt{N}(\phi(X(\tau)) - \phi(X(\tau_N))) = \sqrt{N}\left[\phi\left(X(\tau_N) + \frac{1}{\sqrt{N}}Z_N(\tau_N) \right) - \phi(X(\tau_N)) \right]$$
$$- \sqrt{N}\phi(X_N(\tau_N))$$

As $N \to \infty$, we claim that the right hand side converges in law to $\nabla\phi(X(\tau)).Z(\tau)$ since $\sqrt{N}\phi(X_N(\tau_N))$ converges in law to zero. Indeed, as $\phi(X_N(\tau_N)) \le 0$ and $\phi(X_N(\tau^-_N)) \ge 0$,

$$|\sqrt{N}\phi(X_N(\tau_N))| \le |\sqrt{N}(\phi(X_N(\tau_N)) - \phi(X_N(\tau^-_N)))|$$

There exists θ_N on the line between $X_N(\tau_N)$ and $X_N(\tau^-_N)$ such that

$$|\sqrt{N}(\phi(X_N(\tau_N)) - \phi(X_N(\tau^-_N)))| = |\nabla\phi(\theta_N).(Z_N(\tau_N) - Z_N(\tau^-_N))|$$

which converges in law to zero since $Z_N \to Z$ and Z is continuous. The claim follows. By continuity, $\phi(X(\tau)) = 0$, so that $\sqrt{N}(\phi(X(\tau)) - \phi(X(\tau_N)))$ is asymptotic to

$$-\nabla\phi(X(\tau)).F(X(\tau))\sqrt{N}(\tau_N - \tau)$$

Thus $\sqrt{N}(\tau_N - \tau)$ converges in law to $\pi(\tau)$. To finish the proof we remark that $\sqrt{N}(X_N(\tau_N) - X(\tau)) = Z_N(\tau_N) + \sqrt{N}(X(\tau_N) - X(\tau))$ which converges in law to $Z(\tau) + \pi(\tau)F(X(\tau))$.

A   Comparison between two deterministic limits of different stochastic Hodgkin-Huxley models

We want to compare the two following systems deterministic (A.1) and (A.2), with f, α, β continuously differentiable functions, α and β non-negative, k an integer ≥ 1:

$$\begin{cases} \frac{dV}{dt} = f(V, u^k) \\ \frac{du}{dt} = (1-u)\alpha(V) - u\beta(V) \end{cases} \tag{12}$$

$$\begin{cases} \frac{d\hat{V}}{dt} = f(\hat{V}, x_k) \\ \frac{dx_j}{dt} = (k-j+1)x_{j-1}\alpha(\hat{V}) + (j+1)x_{j+1}\beta(\hat{V}) \\ -x_j\left(j\beta(\hat{V}) + (k-j)\alpha(\hat{V})\right) \\ \forall 0 \leq j \leq k \end{cases} \tag{13}$$

System (A.1) corresponds to the classical "Hodgkin-Huxley" model, with only two variables for simplicity, and the system (A.2) is a $(k+2)$-dimensional system, where x_j, $0 \leq j \leq k$ is the proportion of channels in the state j, and $j = k$ is the *open* state.

Proposition   Let $V_0 \in R$ and $u_0 \in [0, 1]$. If the following conditions on the initial values are satisfied:
$V(0) = \hat{V}(0) = V_0$ and $\forall 0 \leq j \leq k$, $C_k^j u(0)^{k-j}(1 - u(0))^j = x_{k-j}(0) = C_k^j u_0^{k-j}(1 - u_0)^j$ Then, for all $t \geq 0$, $V(t) = \hat{V}(t)$ (same potential) and $u(t)^k = x_k(t)$ (the proportion of open channels is $u(t)^k$).
Moreover, for all $1 \leq j \leq k$, for all $t \geq 0$, $x_{k-j}(t) = C_k^j u(t)^{k-j}(1 - u(t))^j$

Proof   Consider (V, u) the unique solution of (1) for $V(0) = V_0$ and $u(0) = u_0$. Let $y_j(t) = C_k^j u(t)^{k-j}(1 - u(t))^j$, $0 \leq j \leq k$. Then $(V, y_k, ...y_0)$ is a solution of (2) (just need to compute y_j' and write it in function of y_{j-1} and y_{j+1}). As the initial values are equal (by hypothesis) : $x_{k-j}(0) = C_k^j u_0^{k-j}(1 - u_0)^j = y_{k-j}(0)$, by uniqueness $(V, y_k, ..., y_0) = (\hat{V}, x_k, ...x_0)$ for all $t \geq 0$.

Remark   The result is essentially the same for more complicated Markov schemes, as the sodium multistate Markov model.

B Moments equations for linearized Langevin approximation

From **Theorem 2.2**, one can build a diffusion approximation $(\tilde{V}_N, \tilde{e}_N)$ of the stochastic hybrid process (V_N, e_N) given in the Example of section 2.1:

$$\begin{cases} d\tilde{V}_N(t) = f(\tilde{V}_N(t), \tilde{e}_N(t))dt \\ d\tilde{e}_N(t) = b(\tilde{e}_N(t), \tilde{V}_N(t))dt + \sqrt{\frac{\lambda(\tilde{e}_N(t), \tilde{V}_N(t))}{N}} dB_t \\ b(v, e) = [(1-e)\alpha(v) - e\beta(v)] \\ \lambda(v, e) = [(1-e)\alpha(v) + e\beta(v)] \end{cases}$$

We want to write the moments equations for the linearized version of

$$\begin{pmatrix} \tilde{P}_N \\ \tilde{Y}_N \end{pmatrix} = \begin{pmatrix} \sqrt{N}\,(\tilde{e}_N - e) \\ \sqrt{N}\left(\tilde{V}_N - V\right) \end{pmatrix}$$

with (V, e) the deterministic solution. The linearized equations are given by:

$$\begin{cases} dY_N^L = (f_V' Y_N^L + f_e' P_N^L)dt \\ dP_N^L = (b_V' Y_N^L + b_e' P_N^L)dt + \left[\sqrt{\lambda_t} + \frac{1}{2\sqrt{N\lambda_t}}(\lambda_V' Y_N^L + \lambda_e' P_N^L)\right] dB_t \end{cases}$$

with $\lambda_t = \lambda(V(t), e(t))$. We define $m_1^N = \mathbf{E}[Y_N^L]$, $m_2^N = \mathbf{E}[P_N^L]$, $S_1^N = \mathbf{E}[(Y_N^L - m_1)^2]$, $S_2^N = \mathbf{E}[(P_N^L - m_2)^2]$ and $C_{12}^N = \mathbf{E}[(Y_N^L - m_1)(P_N^L - m_2)]$. Then we have the following system of 5 equations:

$$\begin{cases} \frac{dm_1^N}{dt} = f_V' m_1 + f_e' m_2 \\ \frac{dm_2^N}{dt} = b_V' m_1 + b_e' m_2 \end{cases}$$

$$\begin{cases} \frac{dS_1^N}{dt} = 2f_V' S_1 + 2f_e' C_{12} \\ \frac{dS_2^N}{dt} = 2b_e' S_2 + 2b_V' C_{12} + \left[\sqrt{\lambda_t} + \frac{1}{2\sqrt{N\lambda}}(\lambda_N' m_1 + \lambda_e' m_2)\right]^2 \\ \qquad + \left(\frac{\lambda_V'}{2\sqrt{N\lambda_t}}\right)^2 S_1 + \left(\frac{\lambda_e'}{2\sqrt{N\lambda_t}}\right)^2 S_2 + 2\frac{\lambda_V' \lambda_e'}{4N\lambda_t} C_{12} \\ \frac{dC_{12}^N}{dt} = b_V' S_1 + f_e' S_2 + (f_V' + b_e') C_{12} \end{cases}$$

At the limit $N \to \infty$ and with $A = -2S_2$, $B = -2S_1$ and $C = -C_{12}$ this system is the same as the one found in application of **Theorem 2.3** in section 3.

C Moments equations for the Morris-Lecar system

The moments equations used in section 3.5.1 and 3.5.2 are the following linear non-homogeneous system of differential equations:

$$
\begin{bmatrix} S_m \\ S_n \\ S_v \\ C_{mv} \\ C_{nv} \\ C_{mn} \end{bmatrix} = M(t) \begin{bmatrix} S_m \\ S_n \\ S_n \\ C_{mv} \\ C_{nv} \\ C_{mn} \end{bmatrix} + \begin{bmatrix} B_1 \\ B_2 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}
$$

with

$$
M(t) = \begin{bmatrix}
2\frac{\partial F_m}{\partial m} & 0 & 0 & 2\frac{\partial F_m}{\partial V} & 0 & 0 \\
0 & 2\frac{\partial F_n}{\partial n} & 0 & 0 & 2\frac{\partial F_n}{\partial V} & 0 \\
0 & 0 & 2\frac{\partial F_v}{\partial V} & 2\frac{\partial F_v}{\partial m} & 02\frac{\partial F_v}{\partial n} & 0 \\
\frac{\partial F_v}{\partial m} & 0 & \frac{\partial F_m}{\partial V} & \frac{\partial F_v}{\partial V} + \frac{\partial F_m}{\partial m} & 0 & \frac{\partial F_v}{\partial n} \\
0 & \frac{\partial F_v}{\partial n} & \frac{\partial F_n}{\partial V} & 0 & \frac{\partial F_v}{\partial V} + \frac{\partial F_n}{\partial n} & \frac{\partial F_v}{\partial m} \\
0 & 0 & 0 & \frac{\partial F_n}{\partial V} & \frac{\partial F_m}{\partial V} & \frac{\partial F_m}{\partial m} + \frac{\partial F_n}{\partial n}
\end{bmatrix}
$$

all the functions being evaluated at $X(t) = (V(t), m(t), n(t))$ solution of (3.5-3.7) and with $B_1(t) = (1 - m(t))\alpha_m(V(t)) + m(t)\beta_m(V(t))$, $B_2(t) = (1 - n(t))\alpha_n(V(t)) + n(t)\beta_n(V(t))$.

Aknowledgements

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