

AVERAGING AND LARGE DEVIATION PRINCIPLES FOR FULLY-COUPLED PIECEWISE DETERMINISTIC MARKOV PROCESSES AND APPLICATIONS TO MOLECULAR MOTORS

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ABSTRACT. We consider Piecewise Deterministic Markov Processes (PDMPs) with a finite set of discrete states. In the regime of fast jumps between discrete states, we prove a law of large number and a large deviation principle. In the regime of fast and slow jumps, we analyze a coarse-grained process associated to the original one and prove its convergence to a new PDMP with effective force fields and jump rates. In all the above cases, the continuous variables evolve slowly according to ODEs. Finally, we discuss some applications related to the mechanochemical cycle of macromolecules, including strained-dependent power-stroke molecular motors. Our analysis covers the case of fully-coupled slow and fast motions.

Key words: piecewise deterministic Markov process, averaging principle, large deviations, molecular motors.

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1. INTRODUCTION

Several systems in physics, chemistry, biology, control and optimization theory present a multiscale character due to interacting parts evolving on different relevant timescales. In the case of two relevant timescales, the dynamics is a combination of slow and fast motions and often the slow motion is supposed to be well approximated by averaging the effect of fast motion, considering the fast variables as locally equilibrated. This is the content of the *averaging principle*, which has been successfully applied in several contests. We just mention few examples. One of its first applications has been the study, due to Newton, of the precession of the equinoxes (see [A] for averaging methods in mechanics). An example in quantum mechanics is given by the Born-Oppenheimer approximation, based on the fact that electrons move much faster than nuclei. Recently, averaging methods have been applied also to model climate-weather interactions (see for example [CMP]).

The validity of the averaging principle has been rigorously proved for several models assuming that the fast motion is independent of the slow one, assumption which is not fulfilled by many real systems where fast and slow variables influence each other. A rigorous proof in a stochastic fully-coupled case, with additional results on large deviations, has been provided by [V1] and [V2] (the former contains errors, recently corrected in the latter). There the author considers a system described by variables $(x_t, \sigma_t) \in M \times N$, M and N being differential manifolds, such that the slow variable x_t evolves according to an ODE depending both on x_t and σ_t , while the fast variable σ_t undergoes a diffusion with local drift and variance depending again both on x_t and σ_t . In [K] the author has given among other an alternative proof of the averaging and large deviation principles for the fully-coupled model as above, with the extension that the fast variable σ_t varies in $N \times \Gamma$,

N being a differentiable manifold and Γ a finite set, by diffusion on N and random jumps in Γ .

We consider here a fully-coupled system whose state is described by a slow variable x_t varying in a differentiable manifold M (for simplicity of notation we take below $M = \mathbb{R}^d$) and by a fast variable σ_t varying in a finite set Γ . We will consider also the case that σ_t evolves fast only when varying inside some subclasses – metastates – of Γ . We call x_t the mechanical state of the system, and σ_t the chemical one. The mechanical state x_t evolves according to an ODE whose form depends on the chemical state σ_t , while σ_t is a continuous-time stochastic process with jump rates depending on the mechanical state x_t . In other words, the system we consider is a fully-coupled piecewise deterministic Markov process (PDMP). Our motivation and terminology come from molecular motors, but the same model is natural in other contexts as for example operations research, control theory and optimization (see [D2], [YZ]).

Molecular motors are proteins, hence biological macromolecules, working inside the cell at the nanometer scale as microscopic engines, powered by the chemical energy provided by ATP hydrolysis. Their tasks are various, as for example they can transport cargos along filaments or determine muscle contraction. Molecular motors can be in different structural states, that we simply call *chemical states*: attached to the filament, detached from the filament, bound to an ATP molecule, bound to the products of ATP hydrolysis and so on. Independently from the chemical state, there is a specific region of the molecular motor working as a lever-arm, able to swing and produce work, while the fuel (ATP) is collected from the environment and used to derive energy. The conformation of the lever-arm can be described by a continuous variable $x \in M$, that we call *mechanical state*. The above picture is known in the biophysical literature as power-stroke model, cross-bridge model and also lever-arm model, in contrast with the so called ratchet model (see [H] and references therein).

In order to investigate the functionality of molecular motors, it is enough to describe their state by means of the pair (x, σ) , whose dynamics can be modeled in a first approximation by a fully-coupled PDMP as discussed in Section 3. There is experimental evidence that the family Γ of chemical states is partitioned in subclasses $\Gamma_1, \Gamma_2, \dots, \Gamma_\ell$ inside which chemical jumps are much faster (see [D] and references therein). As implicitly assumed in biophysical papers as [VD], we also suppose that these jumps are faster than the mechanical relaxation time scale. Considering first the case $\ell = 1$, in the limit of high frequency of chemical jumps, we prove averaging and large deviation principles both for the slow motion of the mechanical state x and for the occupation measure associated to the chemical states visited in a fixed time interval. The analysis for the occupation measure is lacking in [K], moreover we provide a different and simpler derivation of the averaging and large deviation principles with respect to [V1], [V2] and [K]. In the case $\ell > 1$, the subclasses Γ_j can be treated as chemical metastates. We then show that in the limit of high jump-frequency the coarse-grained process describing the evolution of the mechanical state and the chemical metastate of the system weakly converges to a new PDMP with effective force fields (ODE's) and transitions rates. In Section 3 we discuss some biological consequences concerning molecular motors, while in a companion paper [FGR] we further investigate the model from a more physical viewpoint.

2. MODEL AND MAIN RESULTS

We consider systems whose states are described by a pair $(x, \sigma) \in \mathbb{R}^d \times \Gamma$, where $\Gamma = \{\sigma_1, \sigma_2, \dots, \sigma_{|\Gamma|}\}$ is a finite set. The variable x will define the *mechanical state* of the system and the variable σ its *chemical state*.

When the chemical state is σ , the system evolves mechanically according to the ODE

$$\dot{x}(t) = F_\sigma(x(t), t) \quad (2.1)$$

where the force field $F_\sigma : \mathbb{R}^d \times [0, \infty) \rightarrow \mathbb{R}^d$ is a continuous function, locally Lipschitz w.r.t. x . This means that, given $T > 0$ and a compact subset $\mathcal{K} \subset \mathbb{R}^d$, there exists a positive constant K such that

$$|F_\sigma(x, t) - F_\sigma(x', t)| \leq K|x - x'|, \quad \forall x, x' \in \mathcal{K}, t \in [0, T]. \quad (2.2)$$

Below we will specify some additional assumption on F_σ assuring that the solution $x(t)$ of (2.1) starting in a given point $x \in \mathbb{R}^d$ is uniquely determined in each time interval $[0, T]$.

In order to specify how the system jumps from one chemical state to the other, for each $\sigma \in \Gamma$ let $\gamma_\sigma(x, t)$ be a measurable positive function on $\mathbb{R}^d \times [0, \infty)$ and let $p(\sigma, \sigma'|x, t)$ be a function defined on $\Gamma \times \Gamma \times \mathbb{R}^d \times [0, \infty)$ with the following properties:

- (i) $\forall \sigma, \sigma', p(\sigma, \sigma'|\cdot, \cdot)$ is measurable,
- (ii) $\forall x, t, \sigma, p(\sigma, \cdot|x, t)$ is a probability measure on Γ such that $p(\sigma, \sigma|x, t) = 0$.

The mechanochemical evolution of the system is described as follows. Suppose the system starts at time zero in the state (x_0, σ_0) . Call $x_0(t)$ the solution of (2.1) with $\sigma = \sigma_0$, such that $x_0(0) = x_0$. Let τ_1 be a random variable with value in $(0, \infty]$ s.t.

$$P(\tau_1 > t) = \exp\left(-\int_0^t \gamma_{\sigma_0}(x_0(s), s) ds\right).$$

Note that the r.h.s. decreases in t and equals 1 if $t = 0$, thus implying that τ_1 is well defined. Then, in the random time interval $[0, \tau_1)$ the state of the system is given by $(x_0(t), \sigma_0)$. If $\tau_1 = \infty$, we have done. Otherwise, choose a chemical state $\sigma_1 \in \Gamma$ with probability $p(\sigma_0, \sigma_1|x_0(\tau_1), \tau_1)$, and call $x_1(t)$ the solution on $[\tau_1, \infty)$ of the Cauchy problem

$$\begin{cases} \dot{x}_1(t) = F_{\sigma_1}(x_1(t), t), & t \geq \tau_1, \\ x_1(\tau_1) = x_0(\tau_1). \end{cases}$$

Now let τ_2 be a random variable with values in $(\tau_1, \infty]$, such that

$$P(\tau_2 > t) = \exp\left(-\int_{\tau_1}^t \gamma_{\sigma_1}(x_1(s), s) ds\right), \quad t \geq \tau_1.$$

Then in the time interval $[\tau_1, \tau_2)$ the state of the system is given by $(x_1(t), \sigma_1)$.

In general, denoting by τ_k the time of the k -th chemical jump and by $(x_k(t), \sigma_k)$ the evolution of the system in the time interval $[\tau_k, \tau_{k+1})$, one has that τ_{k+1} is a random variable with value in $(\tau_k, \infty]$ such that

$$P(\tau_{k+1} > t) = \exp\left(-\int_{\tau_k}^t \gamma_{\sigma_k}(x_k(s), s) ds\right), \quad t \geq \tau_k. \quad (2.3)$$

Moreover, $\dot{x}_k(t) = F_{\sigma_k}(x_k(t), t)$ on $[\tau_k, \tau_{k+1})$ and at time τ_{k+1} the system jumps to a new chemical state $\sigma_{k+1} \in \Gamma$ with probability $p(\sigma_k, \sigma_{k+1}|x_k(\tau_{k+1}), \tau_{k+1})$, while the mechanical state remains the same, i.e. $x_k(\tau_{k+1}) = x_{k+1}(\tau_{k+1})$. Setting $\tau_0 = 0$, the evolution

$(x(t), \sigma(t))$ is then defined as

$$(x(t), \sigma(t)) = (x_k(t), \sigma_k), \quad \text{if } \tau_k \leq t < \tau_{k+1}. \quad (2.4)$$

Note that the path $x(t)$ is continuous and piecewise C^1 . In order to have a well defined dynamics over $[0, T]$, it is necessary that a.s. the system makes a finite number of jumps in the time interval $[0, T]$. We will discuss below under which conditions this automatically happens.

As proven in [D1], [D2], the above stochastic process is a strong Markov process, called *piecewise deterministic Markov process* (PDMP) with (x, t) -dependent characteristics (F, p, γ) , defined as

$$F = \{F_\sigma\}_{\sigma \in \Gamma}; \quad p = \{p(\sigma, \sigma' | \cdot, \cdot)\}_{\sigma, \sigma' \in \Gamma}; \quad \gamma = \{\gamma_\sigma\}_{\sigma \in \Gamma}.$$

The time dependent generator L_t reads

$$L_t g(x, \sigma) = F_\sigma(x, t) \cdot \nabla_x g(x, \sigma) + \gamma_\sigma(x, t) \sum_{\sigma' \in \Gamma} p(\sigma, \sigma' | x, t) (g(x, \sigma') - g(x, \sigma)) \quad (2.5)$$

for functions $g : \mathbb{R}^d \times \Gamma \rightarrow \mathbb{R}$ regular in $x \in \mathbb{R}^d$. A characterization of the domain of the so called *extended generator* of the process is given in [D1], [D2]. Defining the transition rate

$$r(\sigma, \sigma' | x, t) := \gamma_\sigma(x, t) p(\sigma, \sigma' | x, t).$$

for a chemical jump from σ to σ' at time t when being in the state (x, σ) , the above generator can be written as

$$L_t g(x, \sigma) = F_\sigma(x, t) \cdot \nabla_x g(x, \sigma) + \sum_{\sigma' \in \Gamma} r(\sigma, \sigma' | x, t) (g(x, \sigma') - g(x, \sigma)). \quad (2.6)$$

Since knowing (F, r) is equivalent to knowing (F, p, γ) , we call both these families of functions *characteristics* of the PDMP.

Given x, t we define $L_c(x, t)$ as the contribution to L_t coming only from the chemical transitions at the mechanical state x , i.e. $L_c(x, t)$ is the operator on $\Gamma^{\mathbb{R}}$ s.t.

$$L_c(x, t)g(\sigma) = \sum_{\sigma' \in \Gamma} r(\sigma, \sigma' | x, t) (g(\sigma') - g(\sigma)), \quad g : \Gamma \rightarrow \mathbb{R}.$$

For fixed x, t , $L_c(x, t)$ is the generator of the time-homogeneous Markov chain on the space Γ which jumps from σ to σ' with probability $p(\sigma, \sigma' | x, t)$ after having waited an exponential time with parameter $\gamma_\sigma(x, t)$ in the state σ (note that here t has to be thought of as a fixed parameter).

We collect here our technical assumptions recalling that $[0, T]$ is the time interval on which the evolution of the system will be observed.

- Assumption (A1): a.s. the number of chemical jumps in the interval $[0, T]$ is finite.
- Assumption (A2): for any pair $(x, t) \in \mathbb{R}^d \times [0, T]$, the time-homogeneous Markov chain on Γ with generator $L_c(x, t)$ is ergodic, i.e. it visits with positive probability any state in Γ , for any starting point. We call $\mu(\cdot | x, t)$ its unique invariant probability measure on Γ .
- Assumption (A3): the transition rates $r(\sigma, \sigma' | \cdot, \cdot)$ are nonnegative functions and belong to $C^1(\mathbb{R}^d \times [0, T])$.

- Assumption (A4): each force field $F_\sigma(x, t)$ is a continuous function in $(x, t) \in \mathbb{R}^d \times [0, T]$ and is locally Lipschitz in x , i.e. for each compact subset $\mathcal{K} \subset \mathbb{R}^d$ there exists a constant $K > 0$ such that

$$|F_\sigma(x, t) - F_\sigma(y, t)| \leq K|x - y|, \quad \forall x, y \in \mathcal{K}, t \in [0, T]. \quad (2.7)$$

Moreover, we assume that there exist constants $\kappa_1, \kappa_2 > 0$ such that

$$|F_\sigma(x, t)| \leq \kappa_1 + \kappa_2|x|, \quad \forall x \in \mathbb{R}^d, t \in [0, T]. \quad (2.8)$$

Only in Section 2.3, when considering fast and slow chemical jumps, we will slightly change assumption (A2).

Let us give some comments on the above assumptions. Assumption (A1) implies that the chemical evolution is well defined a.s. A simple criterion assuring (A1) is the following:

$$\sup_{\sigma \in \Gamma, x \in \mathbb{R}^d, t \in [0, T]} \gamma_\sigma(x, t) < \infty. \quad (2.9)$$

Indeed, calling c the l.h.s., the random number of chemical jumps in the interval $[0, T]$ is dominated by N_T , N being a Poisson point process with rate c . This follows at once observing that, due to (2.3), given τ_k the random time $\tau_{k+1} - \tau_k$ is larger than $a \geq 0$ with probability bounded from below by e^{-ca} . Weaker sufficient conditions are also possible.

Due to the Perron–Frobenius Theorem, assumption (A2) implies that the time homogeneous Markov chain with generator $L_c(x, t)$ admits a unique invariant measure $\mu(\cdot|x, t)$ to which the Markov chain converges as time goes to ∞ . If (A2) is not satisfied then it is simple to exhibit different invariant measures, hence (A2) is equivalent to the existence of a unique invariant measure. Always due to Perron–Frobenius Theorem, $\mu(\sigma|x, t) > 0$ for each $\sigma \in \Gamma$. We call $\mu(\cdot|x, t)$ the *quasistationary measure* of the chemical evolution (frozen in x, t).

We observe that our assumptions imply the following fact: for each compact $\mathcal{K} \subset \mathbb{R}^d$, there exists $\kappa > 0$ such that

$$|r(\sigma, \sigma'|x, t) - r(\sigma, \sigma'|y, t)| \leq \kappa|x - y|, \quad (2.10)$$

$$|\gamma_\sigma(x, t) - \gamma_\sigma(y, t)| \leq \kappa|x - y|, \quad (2.11)$$

$$|\mu(\sigma|x, t) - \mu(\sigma|y, t)| \leq \kappa|x - y|, \quad (2.12)$$

for all $x, y \in \mathcal{K}, t \in [0, T], \sigma, \sigma' \in \Gamma$. Indeed, (2.10) and (2.11) trivially follow from assumption (A3), while (2.12) can be derived from assumptions (A2) and (A3) (see Appendix C, where it is proven that $\mu(\sigma|x, t)$ is C^1 in x, t).

Finally, let us point out some consequences of assumption (A4), some of which will be useful later. To this aim we introduce the averaged vector field $\bar{F} : \mathbb{R}^d \times [0, T] \rightarrow \mathbb{R}^d$ defined as

$$\bar{F}(x, t) := \sum_{\sigma \in \Gamma} \mu(\sigma|x, t) F_\sigma(x, t). \quad (2.13)$$

It is simple to check that the force field \bar{F} satisfies assumption (A4). As consequence, one can easily prove the following result (see Appendix C):

Lemma 2.1. *Let $f : [0, T] \rightarrow \mathbb{R}$ be a continuous function. Then, given $s \in [0, T]$ and $x_0 \in \mathbb{R}^d$, the Cauchy problems*

$$\begin{cases} \dot{x}(t) = F_\sigma(x(t), t)f(t), \\ x(s) = x_0, \end{cases} \quad (2.14)$$

and

$$\begin{cases} \dot{x}(t) = \bar{F}(x(t), t), \\ x(s) = x_0, \end{cases} \quad (2.15)$$

have unique solutions in the time interval $[s, T]$.

Another consequence of assumption (A4) is described in Lemma C.1 in the Appendix. The reader can check that all our proofs work in general for continuous force fields $F_\sigma : \mathbb{R}^d \times [0, T] \rightarrow \mathbb{R}^d$ that are locally Lipschitz w.r.t. x , such that (2.14) and (2.15) have unique solutions, and such that the content of Lemma C.1 remains valid. Finally, we note that (A4) is satisfied whenever each F_σ is continuous in (x, t) and Lipschitz in x uniformly in t , namely (2.7) is satisfied with $\mathcal{K} = \mathbb{R}^d$.

When $|\Gamma| = 2$ the above PDMP can be used to model motor proteins with two main chemical states, for example *detached* and *attached state* respectively. In order to shorten the notation, we denote by 0 the detached state and by 1 the attached state, hence $\Gamma = \{0, 1\}$. Note that it must be $p(0, 1|x, t) = p(1, 0|x, t) = 1$, hence the generator L_t at time t becomes

$$\begin{aligned} L_t f(x, \sigma) := & (1 - \sigma)F_0(x, t) \cdot \nabla_x f(x, 0) + \sigma F_1(x, t) \cdot \nabla_x f(x, 1) + \\ & (1 - \sigma)\gamma_0(x, t) [f(x, 1) - f(x, 0)] + \sigma\gamma_1(x, t) [f(x, 0) - f(x, 1)]. \end{aligned}$$

In this case, the measure

$$\mu(0|x, t) := \frac{\gamma_1(x, t)}{\gamma_0(x, t) + \gamma_1(x, t)} \quad \mu(1|x, t) := \frac{\gamma_0(x, t)}{\gamma_0(x, t) + \gamma_1(x, t)} \quad (2.16)$$

is the only invariant measure $\mu(\cdot|x, t)$ of the Markov chain on Γ with time-independent generator $L_c(x, t)$. Moreover, it is also reversible.

We are first interested in analyzing the limiting behavior of PDMPs where the time scale of the chemical transitions is much smaller than the time scale of mechanical relaxation, i.e. σ is a fast variable and x is a slow variable. To this aim, we introduce the parameter $\lambda > 0$ and study the evolution on $[0, T]$ of the PDMP starting in (x_0, σ_0) with characteristics $(F, p, \lambda\gamma)$ as $\lambda \uparrow \infty$. We call $P_{x_0, \sigma_0}^\lambda$ its law and write $E_{x_0, \sigma_0}^\lambda$ for the associated expectation. For this model we can state a law of large numbers corresponding to the averaging principle and a large deviation principle.

2.1. Averaging principle.

Theorem 2.2. *Given $(x_0, \sigma_0) \in \mathbb{R}^d \times \Gamma$, call $x_*(t)$ the unique solution of the Cauchy problem*

$$\begin{cases} \dot{x}_*(t) = \bar{F}(x_*(t), t), \quad t \in [0, T], \\ x_*(0) = x_0, \end{cases} \quad (2.17)$$

where the averaged force field \bar{F} is defined as in (2.13).

Then, for any $\delta > 0$, $\sigma \in \Gamma$ and for any continuous function $f : [0, T] \rightarrow \mathbb{R}$ it holds

$$\lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda \left(\left| \int_0^T f(t) \chi(\sigma(t) = \sigma) dt - \int_0^T f(t) \mu(\sigma|x_*(t), t) dt \right| > \delta \right) = 0, \quad (2.18)$$

$$\lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda \left(\sup_{0 \leq t \leq T} |x(t) - x_*(t)| > \delta \right) = 0. \quad (2.19)$$

Note that the PDMP with law $P_{x_0, \sigma_0}^\lambda$ has paths in the Skorohod space $D([0, T], \mathbb{R}^d \times \Gamma)$ but, as clear from the above statement, in order to describe the asymptotic behavior as $\lambda \uparrow \infty$ it is necessary to think the mechanical evolution $x(t)$ up to time T as an element of the space $C[0, T]$ endowed with the uniform norm, and to identify the chemical evolution $\sigma(t)$ to the measure-valued vector $\rho(t)dt \in \mathcal{M}[0, T]^\Gamma$, where $\rho_\sigma(t) = \chi(\sigma(t) = \sigma)$ and $\mathcal{M}[0, T]$ denotes the space of finite nonnegative Borel measures on $[0, T]$ endowed with the weak topology. This means that $\mu_n \rightarrow \mu$ if and only if $\mu_n(f) \rightarrow \mu(f)$ for each $f \in C[0, T]$, where $\mu(f) := \int_0^T f(y)\mu(dy)$ for a generic measure μ . Having in mind the above topologies, the law of large numbers states that the mechanochemical evolution $(x(t), \rho(t)dt)$ converges in probability to $(x_*(t), \mu(\cdot | x_*(t), t)dt)$ as elements of the space $C[0, T] \times \mathcal{M}[0, T]^\Gamma$.

2.2. Large deviation principle. In order to state the large deviation principle for the above PDMP, it is convenient to isolate a special subset of $C[0, T] \times \mathcal{M}[0, T]^\Gamma$. To this aim we introduce the set $L[0, T]$ of Lebesgue measurable functions $f : [0, T] \rightarrow [0, 1]$, identified up to subsets of zero Lebesgue measure. Then we define Υ as

$$\Upsilon := \left\{ (x, \rho) \in C[0, T] \times L[0, T]^\Gamma : \sum_{\sigma \in \Gamma} \rho_\sigma(\cdot) = 1 \text{ a.e. } , \right. \\ \left. x(t) = x_0 + \sum_{\sigma \in \Gamma} \int_0^t F_\sigma(x(s), s) \rho_\sigma(s) ds, \quad \forall t \in [0, T] \right\}, \quad (2.20)$$

where x_0 is the starting mechanical state of the system (recall that the system starts in a deterministic state (x_0, σ_0) at time 0).

The set Υ has to be thought of as topological subspace of $C[0, T] \times \mathcal{M}[0, T]^\Gamma$ via the identification

$$(x(t), \rho_\sigma(t))_{t \in [0, T], \sigma \in \Gamma} \rightarrow (x(t), \rho_\sigma(t)dt)_{t \in [0, T], \sigma \in \Gamma}.$$

It can be proved (see Lemma A.2 in the Appendix) that Υ is a compact subspace of $C[0, T] \times \mathcal{M}[0, T]^\Gamma$, and its topology can be derived from the metric d defined as

$$d((x, \rho), (\bar{x}, \bar{\rho})) = \|x - \bar{x}\|_\infty + \sum_{\sigma \in \Gamma} \left(\sup_{0 \leq t \leq T} \left| \int_0^t [\rho_\sigma(s) - \bar{\rho}_\sigma(s)] ds \right| \right). \quad (2.21)$$

It is clear that for each stochastic evolution $(x(t), \sigma(t))_{t \in [0, T]}$ of the system, the path

$$(x(t), \chi(\sigma(t) = \sigma))_{t \in [0, T], \sigma \in \Gamma} \quad (2.22)$$

is an element of Υ . In what follows we call $Q_{x_0, \sigma_0}^\lambda$ the law on Υ of the random path (2.22), when $(x(t), \sigma(t))_{t \in [0, T]}$ is chosen with law $P_{x_0, \sigma_0}^\lambda$.

Before stating our second main result we introduce some notation: we set

$$W := \{(\sigma, \sigma') \in \Gamma \times \Gamma : \sigma \neq \sigma'\}, \quad (2.23)$$

and, given a nonnegative measure π on Γ and nonnegative numbers $r(\sigma, \sigma')$, with $(\sigma, \sigma') \in W$, we define the function $j(\pi, r)$ as

$$j(\pi, r) := \sup_{z \in (0, \infty)^\Gamma} \sum_{(\sigma, \sigma') \in W} \pi(\sigma) r(\sigma, \sigma') \left[1 - \frac{z_{\sigma'}}{z_\sigma} \right], \quad (2.24)$$

i.e.

$$j(\pi, r) := \sup_{z \in (0, \infty)^\Gamma} - \sum_{\sigma \in \Gamma} \pi(\sigma) \frac{(\mathcal{L}z)_\sigma}{z_\sigma} \quad (2.25)$$

where \mathcal{L} is the generator of the continuous-time Markov chain on Γ jumping from σ to $\sigma' \neq \sigma$ with rate $r(\sigma, \sigma')$. We can finally state our large deviation principle (LDP):

Theorem 2.3. *Given $(x_0, \sigma_0) \in \mathbb{R}^d \times \Gamma$, the family of probability measures $Q_{x_0, \sigma_0}^\lambda$ on Υ satisfies a LDP with parameter λ and with rate function $J : \Upsilon \rightarrow [0, \infty)$ defined as*

$$J(x, \rho) = \int_0^T j(\rho(t), r(\cdot, \cdot | x(t), t)) dt \quad (2.26)$$

where j has been defined in (2.24), (2.25).

Moreover, if the quasistationary measures $\mu(\cdot | x, t)$ are reversible for the chemical generators $L_c(x, t)$, then

$$J(x, \rho) = - \int_0^T \left\langle \sqrt{\frac{\rho(\cdot(t))}{\mu(\cdot | x(t), t)}}, L_c(x(t), t) \sqrt{\frac{\rho(\cdot(t))}{\mu(\cdot | x(t), t)}} \right\rangle_t dt \quad (2.27)$$

where $\langle \cdot, \cdot \rangle_t$ denotes the scalar product in $L^2(\Gamma, \mu(\cdot | x(t), t))$.

We recall that the above LDP means that

$$\limsup_{\lambda \uparrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(C) \leq -J(C), \quad \forall C \subset \Upsilon \text{ closed}, \quad (2.28)$$

$$\liminf_{\lambda \uparrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(O) \geq -J(O), \quad \forall O \subset \Upsilon \text{ open}, \quad (2.29)$$

where

$$J(S) = \inf_{(x, \rho) \in S} J(x, \rho), \quad S \subset \Upsilon.$$

Moreover, the function J must be a lower semi-continuous function such that $J \not\equiv \infty$.

We point out that $j(\rho(t), r(\cdot, \cdot | x(t), t))$ corresponds to the large deviation functional in $\rho(t)$ of the empirical measure associated to the time-homogeneous and continuous-time Markov chain on Γ jumping from σ to another chemical state σ' with transition rate $r(\sigma, \sigma' | x(t), t)$, t being thought of as a fixed parameter here [dH]. As the reader will observe, this LDP for time-homogeneous Markov chains will be one of the main ingredients in our proof of Theorem 2.2. Other details on the variational problem (2.24) will be given in Section 4.

In the case of two chemical states, since we know the form of the quasistationary measure (see (2.16)) and that it is reversible w.r.t. the chemical generator L_c , the above theorem implies:

Corollary 2.4. *In the case of two chemical states, $\Gamma = \{0, 1\}$, the family of probability measures $Q_{x_0, \sigma_0}^\lambda$ on Υ satisfies a large deviation principle with parameter λ and with rate function $J : \Upsilon \rightarrow [0, \infty]$ given by*

$$J(x, \rho) = \int_0^T \left[\sqrt{\rho_0(t) \gamma_0(x(t), t)} - \sqrt{\rho_1(t) \gamma_1(x(t), t)} \right]^2 dt. \quad (2.30)$$

2.3. Coarse-grained process. We finally consider the PDMP with fast and slow chemical jumps and study the asymptotic behavior of the coarse-grained process obtained from the original one by keeping knowledge of the mechanical state and only of the chemical metastate of the system. More precisely, we consider a partition of Γ , $\Gamma = \Gamma_1 \cup \Gamma_2 \cup \dots \cup \Gamma_\ell$ where $|\Gamma_i| \geq 1$. We rename the elements of Γ by calling $\sigma_{i,1}, \sigma_{i,2}, \dots, \sigma_{i,n_i}$ the elements of Γ_i . The probability $P_{x_0, \sigma_0}^\lambda$ is now the law of the PDMP starting in (x_0, σ_0) with generator

$$L_t g(x, \sigma) = F_\sigma(x, t) \cdot \nabla_x g(x, \sigma) + \sum_{\sigma' \in \Gamma: \sigma' \neq \sigma} \lambda(\sigma, \sigma') r(\sigma, \sigma' | x, t) (g(x, \sigma') - g(x, \sigma)), \quad (2.31)$$

where

$$\lambda(\sigma, \sigma') := \begin{cases} \lambda & \text{if } \sigma, \sigma' \in \Gamma_i \text{ for some } i, \\ 1 & \text{otherwise.} \end{cases}$$

Note that the chemical jumps between states in the same chemical class Γ_i take place in a short time of order $O(1/\lambda)$, while chemical jumps between states in different chemical classes take place in times of order $O(1)$. Hence, it is natural to call the classes Γ_i *chemical metastates*. Below, we denote by

$$\Gamma^{(\ell)} := \{1, 2, \dots, \ell\}$$

the family of metastates Γ_i , writing i for the metastate Γ_i . When the rates $r(\sigma, \sigma' | x, t)$ do not depend on the mechanical state x , the chemical evolution is determined by a time-inhomogeneous Markov chain on Γ with strong and weak interactions and this situation has been studied in detail [YZ]. We consider here the fully-coupled case where the transition rates of the chemical jumps depend on the mechanical state. As discussed in [YZ][Chapter 7], it is simple to give examples where $P_{x_0, \sigma_0}^\lambda$ does not converge weakly as $\lambda \uparrow \infty$ since the family $\{P_{x_0, \sigma_0}^\lambda : \lambda > 0\}$ is not tight. Nevertheless, one can obtain from $P_{x_0, \sigma_0}^\lambda$ a λ -dependent coarse-grained process weakly converging to a new PDMP. In order to describe precisely this result it is convenient to fix some notation. We can write the chemical generator $L_c(x, t)$ as

$$L_c(x, t) = \widehat{L}_c(x, t) + \lambda \widetilde{L}_c(x, t), \quad (2.32)$$

where $\widehat{L}_c(x, t)$ and $\widetilde{L}_c(x, t)$ are both λ -independent Markov generators on Γ parametrized by x and t . Trivially, $\widetilde{L}_c(x, t)$ has a diagonal-block form:

$$\widetilde{L}_c(x, t) = \begin{pmatrix} \widetilde{L}_c^1(x, t) & & & \\ & \widetilde{L}_c^2(x, t) & & \\ & & \ddots & \\ & & & \widetilde{L}_c^\ell(x, t) \end{pmatrix},$$

where $\widetilde{L}_c^i(x, t)$ is a Markov generator on Γ_i .

We can now state our assumptions. We keep our previous assumptions (A1), (A3) and (A4), while we replace assumption (A2) with the following (A2')

- Assumption (A2'): for each $i \in \Gamma^{(\ell)}$ and $(x, t) \in \mathbb{R}^d \times [0, T]$, the generator $\widetilde{L}_c^i(x, t)$ is irreducible on Γ_i .

Motivated by assumption (A2'), we write $\mu_i(\cdot | x, t)$ for the unique invariant probability measure on Γ_i , i.e. $\mu_i(\cdot | x, t)$ is the quasistationary measure for the generator $\widetilde{L}_c^i(x, t)$.

Given $i \in \Gamma^{(\ell)}$ and $(x, t) \in \mathbb{R}^d \times [0, T]$ we define the vector field

$$F_i(x, t) := \sum_{\sigma \in \Gamma_i} F_\sigma(x, t) \mu_i(\sigma | x, t). \quad (2.33)$$

Given a state $\sigma \in \Gamma$ we define $\alpha(\sigma)$ as $\alpha(\sigma) = i$ if $\sigma \in \Gamma_i$, moreover we denote by $R_{x_0, \sigma_0}^\lambda$ the law on $D([0, T], \mathbb{R}^d \times \Gamma^{(\ell)})$ obtained as image of $P_{x_0, \sigma_0}^\lambda$ under the map $(x(t), \sigma(t)) \rightarrow (x(t), \alpha(\sigma(t)))$ (we will often write $\alpha(t)$ in place of $\alpha(\sigma(t))$). $R_{x_0, \sigma_0}^\lambda$ is the law of the above mentioned coarse-grained process. Note that in general this process is not Markovian, however it converges to a PDMP:

Theorem 2.5. *Given $T > 0$, as λ goes to ∞ the law $R_{x_0, \sigma_0}^\lambda$ weakly converges to the law of the PDMP on $\mathbb{R}^d \times \Gamma^{(\ell)}$ with generator*

$$L_s g(x, i) = F_i(x, s) \cdot \nabla_x g(x, i) + \sum_{j \neq i} r(i, j | x, s) (g(x, j) - g(x, i)), \quad (2.34)$$

where, given $1 \leq i \neq j \leq \ell$,

$$r(i, j | x, s) := \sum_{\sigma \in \Gamma_i} \sum_{\sigma' \in \Gamma_j} \mu_i(\sigma | x, s) r(\sigma, \sigma' | x, s). \quad (2.35)$$

Note that, due to assumptions (A1) and (A4), both the chemical and mechanical evolutions for the original PDMP and the limiting one are well defined.

2.4. Outline of the paper. The remaining part of the paper is organized as follows: in Section 3 we discuss some biological applications, in Section 4 we consider the variational problem (2.24): we show that the r.h.s. of (2.26) equals the r.h.s. of (2.27) if $\mu(\cdot | x(s), s)$ is reversible w.r.t. $L_c(x(s), s)$ and we show other results useful for the proof of the LDP, in Section 5 we prove the LLN stated in Theorem 2.2, in Section 6 we prove the LDP stated in Theorem 2.3 and in Section 7 we prove the asymptotic behavior of the coarse-grained process described in Theorem 2.5. Finally, in the Appendix we prove some technical results used in the paper.

3. SOME BIOLOGICAL APPLICATIONS

In this section we discuss an application of the above averaging principles for PDMPs to molecular motors. Further results will be presented in a companion paper [FGR].

As already said, molecular motors (MMs) are proteins working as engines on the nanometer scale, they generate forces of piconewton order and are usually powered by the chemical energy derived from ATP hydrolysis. Most of them are linear motors, i.e. they proceed in a given direction along some filament, which has a function similar to a railways track. We refer the interested reader to [H].

In the power stroke picture, force is generated by the swinging motion of some part of the protein (the *lever-arm*). In order to study the working of the MM, its state can be described simply by the pair (x, σ) , where x is a continuum variable specifying the configuration of the lever-arm, while σ is a discrete variable describing the chemical state of the MM (i.e. bound to or detached from the track filament, bound to ATP or to the hydrolysis products). Given the chemical state σ , the evolution of the mechanical state is determined by Newtonian laws as

$$m\ddot{x} = -\gamma\dot{x} + F_\sigma(x, t) + \xi(t), \quad (3.1)$$

where $\gamma\dot{x}$ denotes the friction force, $F_\sigma(x, t)$ is the force field defined as $F_\sigma(x, t) = -\nabla_x U_\sigma(x, t)$, $U_\sigma(x, t)$ being the free energy, and $\xi(t)$ denotes the thermal force due to the environment. Since the inertia effects are negligible and the dynamics is overdamped [H], one can disregard the term $m\ddot{x}$. In what follows, we will neglect also the thermal force $\xi(t)$ as first approximation. Indeed, contrary to the modeling of MMs as Brownian ratchets, in the power stroke picture the thermal force $\xi(t)$ is not relevant for many qualitatively aspects. Taking $\gamma = 1$ without loss of generality, (3.1) reduced to equation (2.1). Despite our approximation, the thermal fluctuations remain essential in the chemical kinetics, since the chemical jumps are stochastic and must satisfied the detailed balance equation:

$$\frac{r(\sigma, \sigma'|x, t)}{r(\sigma', \sigma|x, t)} = \exp \left\{ -\beta [U_{\sigma'}(x, t) - U_\sigma(x, t)] \right\}, \quad \forall \sigma, \sigma' \in \Gamma, \quad (3.2)$$

where β is the inverse temperature and, as before, $r(\sigma, \sigma'|x, t)$ denotes the probability rate for a jump from σ to another state σ' . Due to the above considerations, the mechanochemical evolution of the MM can be described by a PDMP satisfying the detailed balance equation (3.2). Since there is experimental evidence that some jump rates must depend on x , the PDMP is fully-coupled (see [D] and references therein).

In this section we show how instabilities in the response to external solicitations of MMs follow from the multiscale character of the system by means of the averaging principle stated in Theorem 2.5. Let us first explain what one means by instabilities (see [J],[VD] for some examples). In ordinary conditions a MM moves typically in a given direction along the filament, at a given averaged speed v depending on environmental parameters as temperature and ATP concentration. If some external force opposes to the motion, the MM slows down and eventually stops at the stall force f_s . The observed instability is of the following kind: in some range of the values of the environmental parameters the MM does not stall, rather for force values close to f_s it can proceed in both directions along the filament.

Inspired by [VD] we study this phenomenon by means of a PDMP with three chemical states and one dimensional mechanical variable so that the full state is described by $(x, \sigma) \in \mathbb{R} \times \Gamma$ where $\Gamma = \{0, 1, 2\}$. For the interpretation of the different chemical states we refer to [VD], we only mention that when $\sigma = 1, 2$ the MM is attached to the filament (but in different ways), while in state $\sigma = 0$ the MM is detached. The force fields are defined as

$$\begin{cases} F_0(x) = -x \\ F_1(x) = -x - f \\ F_2(x) = -(x - 1) - f. \end{cases} \quad (3.3)$$

This is the most simple choice to give the mechanical variable an equilibrium position in each state. Here f is a control parameter, representing the external force exerted on the filament, and therefore on the MM when bound to the filament. These one dimensional force fields admit three convex potential functions:

$$\begin{cases} U_0(x) = \frac{1}{2}x^2 \\ U_1(x) = \frac{1}{2}x^2 + fx \\ U_2(x) = \frac{1}{2}(x - 1)^2 + fx + \epsilon \end{cases} \quad (3.4)$$

such that $-\partial_x U_\sigma(x) = F_\sigma(x)$. Here ϵ is a second control parameter, which can be related to the ATP concentration. Finally, the transition rates $r(\sigma, \sigma'|x)$ must satisfy the detailed

balance equation (3.2) and assumptions (A1) and (A3). There is experimental evidence that the jumps between states 1 and 2 are much faster than the other chemical jumps and it is reasonable to suppose that the jumps between states 1 and 2 are faster than the mechanical evolution (see [D], [VD] and references therein). Hence, Γ can be partitioned in two chemical metastates $\{0\}$ and $\{1, 2\}$, while the rates $r(1, 2|x)$ and $r(2, 1|x)$ can be rescaled by a factor λ . We assume these rates to be positive, thus implying assumption (A2') of Section 2.3. Note that the rescaling does not alter the validity of the detailed balance equation (3.2). By Theorem 2.5, as $\lambda \uparrow \infty$, the coarse-grained PDMP converges weakly to a new PDMP with state space $\mathbb{R} \times \{0, *\}$ (0 refers to the metastate $\{0\}$ and $*$ refers to the metastate $\{1, 2\}$). The force field in the metastate $\{0\}$ coincides with F_0 , while in the metastate $*$ is given by F_* defined as

$$F_*(x) = \frac{e^{\beta\Delta U(x)}}{1 + e^{\beta\Delta U(x)}} F_1(x) + \frac{1}{1 + e^{\beta\Delta U(x)}} F_2(x), \quad (3.5)$$

where $\Delta U(x) = U_2(x) - U_1(x)$. Note that assumptions (A2') and (A4') are fulfilled. It must be noted that while the force fields in (3.3) have a single equilibrium point, $F_\sigma(x) = 0$, the force field $F_*(x)$ may have more than one depending on the value of the control parameters ϵ, β and f . To this aim, we proceed as follows: First we observe that

$$F_*(x) = F_1(x) + \frac{1}{1 + e^{\beta\Delta U(x)}} (F_2(x) - F_1(x)) = -x - f + \frac{1}{1 + e^{\beta\Delta U(x)}}.$$

Let us take $f = 0$. Since $\Delta U(x) = U_2(x) - U_1(x) = -x + 1/2 + \epsilon$, we obtain

$$\partial_x F_*(x) = -1 + \frac{\beta y}{(1 + y)^2}, \quad y := e^{\beta(\frac{1}{2} - x + \epsilon)}.$$

Let us analyze the region of positive slope

$$I_+ = \{x \in \mathbb{R} : \partial_x F_*(x) > 0\} = \{x : \beta y(x) > (1 + y(x))^2\}.$$

Since $y > 0$, $I_+ = \emptyset$ if $\beta \leq 4$. If $\beta > 4$, then I_+ is the finite interval (a_-, a_+) such that

$$y(a_\pm) = \frac{\beta - 2 \mp \sqrt{\beta^2 - 4\beta}}{2}.$$

Note that the r.h.s. is always positive. Since $y(0) = e^{\beta(\frac{1}{2} + \epsilon)}$, $0 \in I_+$ if $\beta > 4$ and

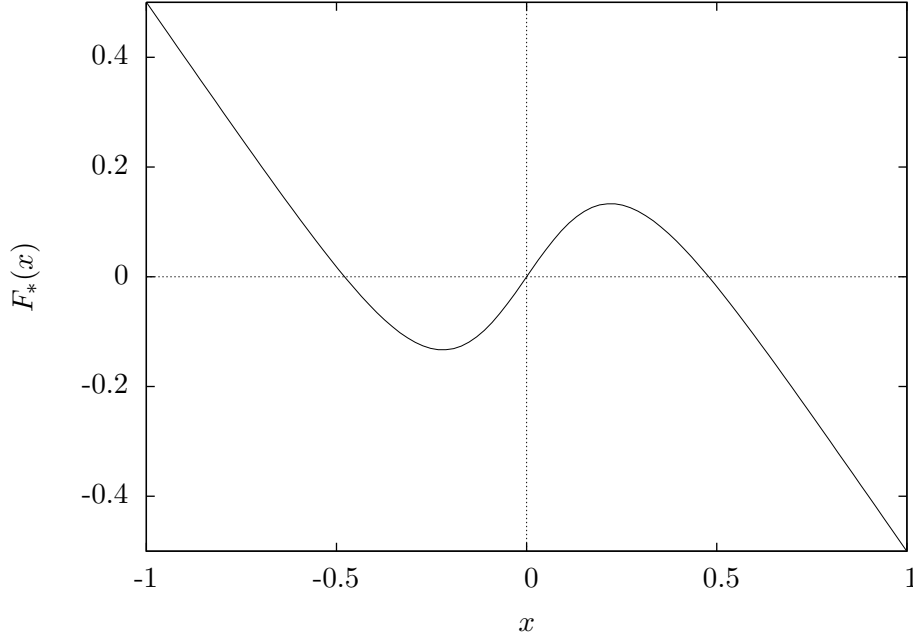
$$-\frac{1}{2} + \frac{1}{\beta} \log \left(\frac{\beta - 2 - \sqrt{\beta^2 - 4\beta}}{2} \right) < \epsilon < -\frac{1}{2} + \frac{1}{\beta} \log \left(\frac{\beta - 2 + \sqrt{\beta^2 - 4\beta}}{2} \right). \quad (3.6)$$

In conclusion, if $f = 0$, $\beta > 4$ and (3.6) is satisfied, then $\partial_x F_*(x) > 0$ only in a given interval I_+ containing the origin, while $\lim_{x \rightarrow \pm\infty} F_*(x) = \mp\infty$. Since adding f has the only effect to translate the graph of F_* along the ordinate axis, we conclude that for a suitable value of f the equation $F_*(x) = 0$ has three solutions $x_- < 0 < x_+$ and that

$$F_*(x) \begin{cases} > 0 & \text{if } x < x_-, \\ < 0 & \text{if } x_- < x < 0, \\ > 0 & \text{if } 0 < x < x_+, \\ < 0 & \text{if } x > x_+. \end{cases}$$

See Figure 3 below. Now it is simple to check that if the new PDMP starts in the mechanical state $x_0 < 0$ [$x_0 > 0$], then $x(t)$ eventually enters the absorbing interval $(x_-, 0)$ [$(0, x_+)$]. Due to the description of the power stroke mechanism (see [FGR]), this implies that typically the motor moves towards left in the first case and towards right in

the latter. Hence, for suitable parameters ε and β associated to ATP concentration and temperature and for suitable external forces f the MM can move in both directions of the filament, depending on the initial configuration of the lever–arm. This behavior is a form of instability in the response of the MM. We point out that for the original PDMP with three states, there is only one absorbing interval given by $(0, 1)$ which $x(t)$ eventually enters a.s. Hence, the instability is related to the ergodicity breaking of the system.



4. THE VARIATIONAL PROBLEM (2.24)

In this section, we briefly analyze the variational problem (2.24). Part of the content of Lemma 4.1 below is well known, nevertheless we recall its derivation since we need some additional developments in order to prove the LDP.

We call \mathcal{S} the subset of $[0, \infty)^W$ given by the elements $c \in [0, \infty)^W$ satisfying the following irreducibility condition: given $\sigma \neq \sigma'$ in Γ there exists a finite sequence $\sigma_1, \sigma_2, \dots, \sigma_n$ such that $\sigma_1 = \sigma$, $\sigma_n = \sigma'$ and $c(\sigma_i, \sigma_{i+1}) > 0$ for all $i = 1, \dots, n-1$. We define $\mathcal{J} : [0, \infty)^W \rightarrow \mathbb{R}$ as

$$\mathcal{J}(c) = \sup_{z \in (0, \infty)^\Gamma} \hat{\mathcal{J}}(c, z), \quad \hat{\mathcal{J}}(c, z) := \sum_{(\sigma, \sigma') \in W} c(\sigma, \sigma') \left(1 - \frac{z_{\sigma'}}{z_\sigma}\right). \quad (4.1)$$

Lemma 4.1. *The function \mathcal{J} is convex and continuous, and takes values in $[0, \infty)$. Moreover, for each $c \in \mathcal{S}$, the supremum on $(0, \infty)^\Gamma$ of the function $\hat{\mathcal{J}}(c, \cdot)$ is a maximum and the set of maximum points is given by the ray $\{t\tilde{z} : t > 0\}$, where $\tilde{z} \in (0, \infty)^\Gamma$ is the unique solution of the system*

$$\sum_{\sigma' \in \Gamma} c(\sigma, \sigma') \frac{z_{\sigma'}}{z_\sigma} = \sum_{\sigma' \in \Gamma} c(\sigma', \sigma) \frac{z_\sigma}{z_{\sigma'}}, \quad \sigma \in \Gamma, \quad (4.2)$$

such that $\sum_{\sigma \in \Gamma} z_\sigma^2 = 1$.

Proof. Since \mathcal{J} is the supremum of a family of linear functions in $c \in [0, \infty)^W$ parametrized by z , \mathcal{J} is convex and lower semicontinuous on the set $[0, \infty)^W$, which is a locally simplicial

set (see [R][Chapter 10]). Hence we can apply Theorem 10.2 in [R] implying that \mathcal{J} is upper semicontinuous. This concludes the proof of the continuity of \mathcal{J} . Since $0 = \widehat{\mathcal{J}}(c, \underline{1}) \leq \mathcal{J}(c) \leq \sum_{(\sigma, \sigma') \in W} c(\sigma, \sigma') < \infty$, we get that $\mathcal{J}(c) \in [0, \infty)$.

Let us now assume that $c \in \mathcal{S}$ and prove the conclusion of the Lemma. We can write $\mathcal{J}(c) = [\sum_{(\sigma, \sigma') \in W} c(\sigma, \sigma')] - \inf_{z \in (0, \infty)^\Gamma} \Phi(z)$, where

$$\Phi(z) := \sum_{(\sigma, \sigma') \in W} c(\sigma, \sigma') \frac{z_{\sigma'}}{z_\sigma}, \quad z \in (0, \infty)^\Gamma. \quad (4.3)$$

Hence it is enough to prove the analogous statements for the infimum of Φ . Since $\Phi(z) = \Phi(\gamma z)$, for all $\gamma > 0$, in order to study its infimum we can restrict Φ to the set $\mathcal{A} := \{z \in (0, \infty)^\Gamma : \sum_{\sigma \in \Gamma} z_\sigma^2 = 1\}$. Trivially Φ is a positive function. Let $z^{(n)} \in \mathcal{A}$ be a minimizing sequence for Φ , i.e. a sequence such that

$$\lim_{n \rightarrow \infty} \Phi(z^{(n)}) = \inf_{z \in (0, \infty)^\Gamma} \Phi(z).$$

Due to the fact that \mathcal{A} is relatively compact in \mathbb{R}^Γ , at cost to take a subsequence, we can assume that $z^{(n)}$ is convergent. Let us first suppose that $\tilde{z} = \lim_{n \rightarrow \infty} z^{(n)}$ is such that there exists some $\sigma \in \Gamma$ with $\tilde{z}_\sigma = 0$. Then necessarily also $\tilde{z}_{\sigma'} = 0$ for any σ' such that $c(\sigma, \sigma') > 0$. In fact, otherwise, we would have:

$$\Phi(z^{(n)}) \geq c(\sigma, \sigma') \frac{z_{\sigma'}^{(n)}}{z_\sigma^{(n)}} \xrightarrow{n \rightarrow \infty} +\infty.$$

Iterating this argument and using the fact that $c \in \mathcal{S}$, we deduce that necessarily $\tilde{z} = 0$ but this is incompatible with the fact that \tilde{z} belongs to the closure of \mathcal{A} . Therefore, it must be $\tilde{z} \in \mathcal{A}$. Since the function Φ is continuous on \mathcal{A} , we conclude that

$$\inf_{z \in (0, \infty)^\Gamma} \Phi(z) = \lim_{n \rightarrow \infty} \Phi(z^{(n)}) = \Phi(\tilde{z}),$$

and the infimum is a minimum. Since \tilde{z} is a minimum point for the C^∞ function Φ on $(0, \infty)^\Gamma$, it must be $\nabla \Phi(\tilde{z}) = 0$. As follows from the computations below, this identity coincides with the system of equations (4.2). Finally, we prove that such a system has a unique solution on \mathcal{A} . Indeed, straightforward computations give that

$$\begin{aligned} \frac{\partial \Phi}{\partial z_{\tilde{\sigma}}}(z) &= \sum_{\sigma: \sigma \neq \tilde{\sigma}} \left(c(\sigma, \tilde{\sigma}) \frac{1}{z_\sigma} - c(\tilde{\sigma}, \sigma) \frac{z_\sigma}{z_{\tilde{\sigma}}^2} \right), \\ \frac{\partial^2 \Phi}{\partial z_{\tilde{\sigma}}^2}(z) &= \sum_{\sigma: \sigma \neq \tilde{\sigma}} 2c(\tilde{\sigma}, \sigma) \frac{z_\sigma}{z_{\tilde{\sigma}}^3}, \\ \frac{\partial^2 \Phi}{\partial z_{\tilde{\sigma}} \partial z_{\hat{\sigma}}}(z) &= -c(\tilde{\sigma}, \hat{\sigma}) \frac{1}{z_{\tilde{\sigma}}^2} - c(\hat{\sigma}, \tilde{\sigma}) \frac{1}{z_{\hat{\sigma}}^2}, \quad \tilde{\sigma} \neq \hat{\sigma}. \end{aligned}$$

Setting

$$c(\sigma, \tilde{\sigma} | z) = \begin{cases} c(\sigma, \tilde{\sigma}) \frac{z_{\tilde{\sigma}}}{z_\sigma}, & \text{if } \sigma \neq \tilde{\sigma}, \\ -\sum_{\sigma': \sigma' \neq \sigma} c(\sigma, \sigma') \frac{z_{\sigma'}}{z_\sigma}, & \text{if } \sigma = \tilde{\sigma}, \end{cases}$$

the above computations imply for each $z \in (0, \infty)^\Gamma$ that

$$\sum_{\sigma \in \Gamma} \sum_{\tilde{\sigma} \in \Gamma} a_\sigma a_{\tilde{\sigma}} \frac{\partial^2 \Phi}{\partial z_\sigma \partial z_{\tilde{\sigma}}}(z) = -2 \sum_{\sigma \in \Gamma} \sum_{\tilde{\sigma} \in \Gamma} \frac{a_\sigma}{z_\sigma} c(\sigma, \tilde{\sigma} | z) \frac{a_{\tilde{\sigma}}}{z_{\tilde{\sigma}}}, \quad a \in \mathbb{R}^\Gamma. \quad (4.4)$$

On the other hand, from the system of identities (4.2), it is simple to derive that, whenever $\nabla\Phi(z) = 0$, it holds

$$\sum_{\sigma} \sum_{\tilde{\sigma}} c(\sigma, \tilde{\sigma}|z) (b_{\tilde{\sigma}} - b_{\sigma})^2 = -2 \sum_{\sigma} \sum_{\tilde{\sigma}} b_{\sigma} c(\sigma, \tilde{\sigma}|z) b_{\tilde{\sigma}}, \quad b \in \mathbb{R}^{\Gamma}. \quad (4.5)$$

Setting $b_{\sigma} = a_{\sigma}/z_{\sigma}$ in (4.5) and comparing the resulting identity with (4.4), we obtain that

$$\sum_{\sigma} \sum_{\tilde{\sigma}} a_{\sigma} a_{\tilde{\sigma}} \frac{\partial^2 \Phi}{\partial z_{\sigma} \partial z_{\tilde{\sigma}}}(z) = \sum_{\sigma} \sum_{\tilde{\sigma}} c(\sigma, \tilde{\sigma}|z) \left(\frac{a_{\tilde{\sigma}}}{z_{\tilde{\sigma}}} - \frac{a_{\sigma}}{z_{\sigma}} \right)^2 \quad (4.6)$$

if $\nabla\Phi(z) = 0$. Hence, this last condition implies that the r.h.s. of (4.6) is zero if and only if $a_{\sigma}/z_{\sigma} = a_{\tilde{\sigma}}/z_{\tilde{\sigma}}$ whenever $c(\sigma, \tilde{\sigma}) > 0$. Due to the fact that $c \in \mathcal{S}$, this implies that the vector a is proportional to z . We observe that the tangent space in z to \mathcal{A} , i.e. $T_z\mathcal{A}$, is given by the \mathbb{R}^{Γ} -vectors orthogonal to z . Hence, if $z \in \mathcal{A}$ satisfies $\nabla\Phi(z) = 0$ then the map $\Phi|_{\mathcal{A}}$ (Φ restricted to \mathcal{A}) has strictly positive defined Hessian in z , thus implying that z is a strict local minimum. On the other side, if $z \in \mathcal{A}$ is an extremal point of $\Phi|_{\mathcal{A}}$ then $\nabla\Phi(z)$ is orthogonal to the tangent space $T_z\mathcal{A}$, which is given by all vectors orthogonal to z . But, since $\Phi(tz) = \Phi(z)$ for all $t > 0$, by differentiating this equality in $t = 1$ we obtain that $\nabla\Phi(z) \cdot z = 0$. In conclusion: the set of extremal points of $\Phi|_{\mathcal{A}}$ coincides with the set $\{z \in \mathcal{A} : \nabla\Phi(z) = 0\}$ and we know that all these points are strict local minima of $\Phi|_{\mathcal{A}}$. Hence, there can be at most one local minimum point. \square

We note that, given $c \in \mathcal{S}$, there exists a small ball B in \mathbb{R}^W centered in c such that $B \cap [0, \infty)^W \subset \mathcal{S}$. Hence, we think of \mathcal{S} as a manifold of dimension $|W|$ with boundary, embedded in \mathbb{R}^W . Given $c \in \mathcal{S}$, we write $\tilde{z}(c)$ for the unique point of maximum of $\hat{\mathcal{J}}(c, \cdot)$ in \mathcal{A} described in the above lemma. Then, the map $\tilde{z}(c)$ is regular:

Lemma 4.2. *The function $\tilde{z} : \mathcal{S} \rightarrow \mathcal{A}$ is C^1 , i.e. there exists a C^1 function $g : \mathcal{U} \rightarrow \mathcal{A}$ from an open subset $\mathcal{U} \subset \mathbb{R}^W$ containing \mathcal{S} , whose restriction to \mathcal{S} coincides with \tilde{z} .*

Proof. Let us first consider the smooth function $G : \mathbb{R}^W \times \mathcal{A} \rightarrow \mathbb{R}^{\Gamma}$ defined as

$$G(c, z)_{\sigma} = \sum_{\sigma' \neq \sigma} (c(\sigma', \sigma)/z_{\sigma'} - c(\sigma, \sigma')z_{\sigma'}/z_{\sigma}^2).$$

Let us fix $c \in \mathcal{S}$ and write \tilde{z} for $\tilde{z}(c)$. Due to the computations in the proof of Lemma 4.1, $G(c, z) = \nabla_z \Phi(z)$ for each $z \in (0, \infty)^{\Gamma}$, the function $\Phi(z)$ being defined in (4.3). In particular, $G(c, \tilde{z}) = 0$. Moreover, we know that the tangent map $T_z G(c, \cdot)$ from $T_z \mathcal{A}$ to \mathbb{R}^{Γ} is a linear monomorphism for $z = \tilde{z}$, since the Hessian of $\Phi|_{\mathcal{A}}$ in \tilde{z} is strictly positive. We call $V_{\tilde{z}}$ the image of $T_{\tilde{z}} \mathcal{A}$ by the tangent map $T_{\tilde{z}} G(c, \cdot)$. Then $V_{\tilde{z}}$ has dimension $\kappa - 1 = |\Gamma| - 1$ as $T_{\tilde{z}} \mathcal{A}$. In particular, there exists $\tilde{\sigma} \in \Gamma$ such that $\pi_{\tilde{\sigma}}(W_{\tilde{z}})$ has dimension $\kappa - 1$, where $\pi_{\tilde{\sigma}}$ is the canonical orthogonal projection $\pi_{\tilde{\sigma}} : \mathbb{R}^{\Gamma} \rightarrow \mathbb{R}^{\Gamma \setminus \{\tilde{\sigma}\}}$. This implies that the smooth composed map $H : \mathbb{R}^W \times \mathcal{A} \rightarrow \mathbb{R}^{\Gamma \setminus \{\tilde{\sigma}\}}$ defined as $H = \pi_{\tilde{\sigma}} \circ G$ has isomorphic tangent map $T_{\tilde{z}} H(c, \cdot)$ from $T_{\tilde{z}} \mathcal{A}$ to $\mathbb{R}^{\Gamma \setminus \{\tilde{\sigma}\}}$. Hence we can apply the Implicit Function Theorem for differential manifolds and conclude the following: there exist a neighborhood U of c in \mathbb{R}^W , a neighborhood V of \tilde{z} in \mathcal{A} and a C^1 map $f : U \rightarrow V$ such that i) $H(c', f(c')) = 0$ for all $c' \in U$ and ii) if $H(c', z) = 0$ for some $c' \in U$ and $z \in V$ then $z = f(c')$. At this point, we only need to prove that $G(c', f(c')) = 0$ for all $c' \in U$ in order to conclude that $\tilde{z}(c') = f(c')$. If $H(c', z) = 0$ then $G(c', z)_{\sigma} = 0$ for all $\sigma \in \Gamma \setminus \{\tilde{\sigma}\}$. On the other hand, for all $(c', z) \in \mathbb{R}^W \times (0, \infty)^{\Gamma}$ it holds $\sum_{\sigma} z_{\sigma} G(c', z)_{\sigma} = 0$. Hence, if

$H(c', z) = 0$, it must be

$$G(c', z)_{\tilde{\sigma}} = z_{\tilde{\sigma}}^{-1} \sum_{\sigma: \sigma \neq \tilde{\sigma}} z_{\sigma} G(c', z)_{\sigma} = 0,$$

thus concluding the proof. \square

We give now another technical result which will be useful for the proof in Appendix B:

Lemma 4.3. *Fix $c \in [0, \infty)^W$. Then, $\mathcal{J}(c) = 0$ if and only if*

$$\sum_{\sigma' \in \Gamma} c(\sigma, \sigma') = \sum_{\sigma' \in \Gamma} c(\sigma', \sigma). \quad (4.7)$$

Proof. Let us first prove the claim for $c \in \mathcal{S}$. If (4.7) is verified, then it is trivial to check that $z \in (0, \infty)^{\Gamma}$ such that $z_{\sigma} \equiv 1/\sqrt{|\Gamma|}$ satisfies (4.2), and therefore it is its unique normalized solution. Then, by direct computation, $\mathcal{J}(c) = \widehat{\mathcal{J}}(c, z) = 0$. If (4.7) is not verified, then the above z is not a solution of (4.2). This implies that $\mathcal{J}(c) > \widehat{\mathcal{J}}(c, z)$. But trivially $\widehat{\mathcal{J}}(c, z) = 0$, thus implying that $\mathcal{J}(c) > 0$.

We now extend the result to general $c \in [0, \infty)^W$. To this aim define $c_* \in [0, \infty)^W$ setting $c_*(\sigma, \sigma') \equiv 1$. Trivially, c_* belongs to \mathcal{S} and satisfies (4.7). Suppose first that c satisfies (4.7). Then each vector $\lambda c + (1 - \lambda)c_*$ with $\lambda \in [0, 1]$ satisfies (4.7), and moreover belongs to \mathcal{S} having only positive entries. By the first part, we conclude that $\mathcal{J}(\lambda c + (1 - \lambda)c_*) = 0$ for all $\lambda \in [0, 1]$. Due to the continuity of \mathcal{J} (see Lemma 4.1) we conclude that $\mathcal{J}(c) = 0$. Let us now suppose that c does not fulfill (4.7) and prove that $\mathcal{J}(c) > 0$. By convexity of \mathcal{J} (see Lemma 4.1), for each $\lambda \in [0, 1]$ it holds

$$\mathcal{J}(\lambda c + (1 - \lambda)c_*) \leq \lambda \mathcal{J}(c) + (1 - \lambda)\mathcal{J}(c_*) = \lambda \mathcal{J}(c). \quad (4.8)$$

On the other hand, all vectors $\lambda c + (1 - \lambda)c_*$ with $\lambda \in [0, 1]$ belong to \mathcal{S} and do not satisfy (4.7). Due to the first part, taking $\lambda = 1/2$ we conclude that $\mathcal{J}(1/2(c + c_*)) > 0$. This together with (4.8) implies that $\mathcal{J}(c) > 0$. \square

Let us now come back to the variational problem (2.24) and derive some results about it from the previous observations.

Given a nonnegative measure π on Γ and nonnegative numbers $r(\sigma, \sigma')$, $(\sigma, \sigma') \in W$, we define $c[\pi, r] \in [0, \infty)^W$ as

$$c[\pi, r](\sigma, \sigma') := \pi(\sigma)r(\sigma, \sigma'), \quad \forall (\sigma, \sigma') \in W. \quad (4.9)$$

Then (recall (2.24) and (4.1))

$$j(\pi, r) = \mathcal{J}(c[\pi, r])$$

and the previous results on the variational problem associated to \mathcal{J} give information on the variational problem associated to j . In particular, we stress that due to (4.9) the system of identities (4.2) coincides with the stationarity of the measure π w.r.t. the Markov generator $R(\cdot, \cdot | z)$ on Γ defined as

$$R(\sigma, \sigma' | z) = \begin{cases} r(\sigma, \sigma') \frac{z_{\sigma'}}{z_{\sigma}}, & \text{if } \sigma \neq \sigma', \\ -\sum_{\tilde{\sigma}: \tilde{\sigma} \neq \sigma} r(\sigma, \tilde{\sigma}) \frac{z_{\tilde{\sigma}}}{z_{\sigma}}, & \text{if } \sigma = \sigma'. \end{cases}$$

Recall the definition of the function $\tilde{z}: \mathcal{S} \rightarrow \mathcal{A}$. Given a nonnegative measure π on Γ and $(x, s) \in \mathbb{R}^d \times [0, T]$, we define

$$\tilde{z}(\pi, x, s) := \tilde{z}(c[\pi, r(\cdot, \cdot | x, s)]) \quad (4.10)$$

if $c[\pi, r(\cdot, \cdot|x, s)]$ belongs to \mathcal{S} .

Let us now take a strictly positive measure π on Γ , i.e. $\pi(\sigma) > 0$ for all $\sigma \in \Gamma$. Then, by Assumption (A2) $c[\pi, r(\cdot, \cdot|x, s)]$ belongs to \mathcal{S} . If the quasistationary measure $\mu(\cdot|x, s)$ is reversible for the chemical generator $L_c(x, s)$ with jump rates $r(\sigma, \sigma'|x, s)$, then the solution $\tilde{z} \in \mathcal{A}$ of the system (4.2) with $c = c[\pi, r(\cdot, \cdot|x, s)]$ can be computed explicitly. Indeed, setting

$$\tilde{z}_\sigma = Z \sqrt{\frac{\pi(\sigma)}{\mu(\sigma|x, s)}}, \quad \sigma \in \Gamma \quad (4.11)$$

(where Z is the normalizing constant assuring that $\tilde{z} \in \mathcal{A}$), one has the detailed balance equation

$$\pi(\sigma)r(\sigma, \sigma'|x, s)\frac{\tilde{z}_{\sigma'}}{\tilde{z}_\sigma} = \pi(\sigma')r(\sigma', \sigma|x, s)\frac{\tilde{z}_\sigma}{\tilde{z}_{\sigma'}}, \quad (4.12)$$

and consequently the validity of (4.2). Due to Lemma 4.1 we conclude that

$$j(\pi, r(\cdot, \cdot|x, s)) = \widehat{\mathcal{J}}(c[\pi, r(\cdot, \cdot|x, s)], \tilde{z}) = \sum_{(\sigma, \sigma') \in W} \pi(\sigma)r(\sigma, \sigma'|x, s) \left(1 - \sqrt{\frac{\pi(\sigma')\mu(\sigma|x, s)}{\pi(\sigma)\mu(\sigma'|x, s)}} \right). \quad (4.13)$$

If π is not strictly positive, we can take a sequence π_n of strictly positive measure on Γ such that $\pi_n(\sigma) \rightarrow \pi(\sigma)$ for each $\sigma \in \Gamma$. This implies that

$$c[\pi_n, r(\cdot, \cdot|x, s)] \rightarrow c[\pi, r(\cdot, \cdot|x, s)].$$

Since, as proved in Lemma 4.1, \mathcal{J} is continuous on $[0, \infty)^W$, we obtain that

$$j(\pi_n, r(\cdot, \cdot|x, s)) = \mathcal{J}(c[\pi_n, r(\cdot, \cdot|x, s)]) \rightarrow \mathcal{J}(c[\pi, r(\cdot, \cdot|x, s)]) = j(\pi, r(\cdot, \cdot|x, s)).$$

The above limit allows to extend (4.13) also to the case of general $\pi \in [0, \infty)^\Gamma$ with the convention to set $\pi(\sigma)r(\sigma, \sigma'|x, s)\left(1 - \sqrt{\frac{\pi(\sigma')\mu(\sigma|x, s)}{\pi(\sigma)\mu(\sigma'|x, s)}}\right)$ equal to zero if $\pi(\sigma) = 0$.

This facts imply at once (2.27) assuming (2.26)

5. PROOF OF THEOREM 2.2

Our proof of the law of large numbers in the time interval $[0, T]$ is based on a two scales argument. We give some comments on our strategy for what concerns the mechanical evolution, similar arguments hold for the chemical one. We first divide the interval $[0, T]$ in M subintervals $I_k = [k\delta, (k+1)\delta]$, $\delta := T/M$, $k \in \{0, 1, \dots, M-1\}$. We denote by $P_{x, \sigma, t}^\lambda$ the law of the PDMP starting at (x, σ) at time t with λ -accelerated chemical jumps, and by $x_*(\cdot|x, t)$ the solution of the Cauchy system

$$\begin{cases} \dot{z}(s) = \bar{F}(z(s), s), & s \geq t, \\ z(t) = x. \end{cases} \quad (5.1)$$

We recall that $P_{x_0, \sigma_0, 0}^\lambda = P_{x_0, \sigma_0}^\lambda$. Then we prove that given $\beta \in (0, 1)$ there exists $M = M(\beta)$ such that for each $k \in \{0, 1, \dots, M-1\}$ the following holds: starting at time $k\delta$ in an arbitrary state (x', σ') the random mechanical trajectory $(x(t) : t \in I_k)$ deviates from $(x_*(t|x', k\delta) : t \in I_k)$ typically less than $\beta\delta$. This is the content of Lemma 5.1 below. Having this result we can derive (2.19) of Theorem 2.2 as follows: in order to compare the mechanical trajectory $(x(t) : t \in [0, T])$ with $(x_*(t|x_0, 0) : t \in [0, T])$ ($x(t)$ being now the

random mechanical trajectory when starting at state (x_0, σ_0) at time zero) we fix $\beta > 0$, take $M = M(\beta)$ as above and by means of Lemma 5.1 for each $k \in \{0, 1, \dots, M-1\}$ we compare $x(\cdot)$ restricted to the time interval I_k with the path $(x_*(t|x(k\delta), k\delta) : t \in I_k)$. As second step, we compare this last path with $(x_*(t|x_0, 0) : t \in I_k)$. Due to the Lipschitz property of the force fields, we will show below that

$$\begin{aligned} \sup_{t \in I_k} |x_*(t|x(k\delta), k\delta) - x_*(t|x_0, 0)| &\leq \\ C|x_*(k\delta|x(k\delta), k\delta) - x_*(k\delta|x_0, 0)| &= C|x(k\delta) - x_*(k\delta|x_0, 0)|. \end{aligned} \quad (5.2)$$

This bound allows to implement by a recursive procedure all the above estimates going from one δ -subinterval to the next one.

In addition to δ , another scale plays a crucial role. Indeed, in order to prove Lemma 5.1 we first divide each time interval $I_k = [k\delta, (k+1)\delta]$ in N subintervals $\{I_{k,n}\}_{0 \leq n < N}$, where $I_{k,n} = [k\delta + n\varepsilon, k\delta + (n+1)\varepsilon]$ and $\varepsilon := \delta/N$. Then we prove that the PDMP on $I_{k,n}$ obtained from the original one by freezing the chemical jump rates at time $k\delta + n\varepsilon$ has a not too large entropy w.r.t. to the original PDMP on $I_{k,n}$. This entropy estimate allows to bound the probability for a deviation of order at least $\beta\varepsilon$ of the mechanical trajectory on $I_{k,n}$ from the expected asymptotic one.

Let us now enter into the technical details of the proof:

Lemma 5.1. *Fix a constant $\beta \in (0, 1)$, a continuous function $f : [0, T] \rightarrow \mathbb{R}$ and a compact set $\mathcal{K} \subset \mathbb{R}^d$. Then there exists a positive integer M such that for all $\sigma_0, \sigma \in \Gamma$, for all $k \in \{0, 1, \dots, M-1\}$, setting $\delta = T/M$ it holds*

$$\lim_{\lambda \uparrow \infty} \sup_{x_0 \in \mathcal{K}} P_{x_0, \sigma_0, k\delta}^\lambda \left(\sup_{k\delta \leq t \leq k\delta + \delta} |x(t) - x_*(t|x_0, k\delta)| \geq \beta\delta \right) = 0, \quad (5.3)$$

$$\lim_{\lambda \uparrow \infty} \sup_{x_0 \in \mathcal{K}} P_{x_0, \sigma_0, k\delta}^\lambda \left(\left| \int_{k\delta}^{k\delta + \delta} f(t) [\chi(\sigma(t) = \sigma) - \mu(\sigma | x_*(t|x_0, k\delta), t)] dt \right| > \beta\delta \right) = 0. \quad (5.4)$$

Before proving the above lemma, let us explain how to derive from it Theorem 2.2:

Proof of Theorem 2.2.

Let us prove (2.19). We start with some general consideration. As proved in Lemma C.1, there exists a compact \mathcal{K}' such that $x(t) \in \mathcal{K}'$ for all $t \in [0, T]$, $P_{x_0, \sigma_0}^\lambda$ -a.s. and for all $\lambda > 0$. By the same lemma, there exists a compact \mathcal{K} containing \mathcal{K}' such that $x_*(t|x', s) \in \mathcal{K}$ for all $x' \in \mathcal{K}'$ and $s < t$ in $[0, T]$. We take the positive constant K as in (2.7) for \mathcal{K} as described above, and by taking K large enough we assume that (2.7) is satisfied also by the averaged field \bar{F} . Then, we take M as in Lemma 5.1 (since we are now only interested in proving (2.19), we can fix the function f in Lemma 5.1 arbitrarily). We divide the interval $[0, T]$ in M subintervals $I_k = [k\delta, (k+1)\delta]$, where $k = 0, 1, \dots, M-1$ and $\delta = T/M$. For each k , we define

$$\begin{aligned} \Delta_k &:= \sup_{t \in I_k} |x(t) - x_*(t|x_0, 0)|, \\ \mathcal{A}_k &:= \{|x(t) - x_*(t|x(k\delta), k\delta)| < \beta\delta \ \forall t \in I_k\}. \end{aligned}$$

Due to Lemma 5.1 and the Markov property of PDMPs, we have that

$$P_{x_0, \sigma_0}^\lambda(\mathcal{A}_k^c) = E_{x_0, \sigma_0}^\lambda [P_{x_0, \sigma_0}^\lambda(\mathcal{A}_k^c | x(k\delta), \sigma(k\delta))] \leq \sup_{x \in \mathcal{K}, \sigma \in \Gamma} P_{x, \sigma, k\delta}^\lambda(\mathcal{A}_k^c) \rightarrow 0. \quad (5.5)$$

This implies that

$$\lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda(\mathcal{A}^c) = 0, \quad \mathcal{A} := \bigcap_{k=0}^{M-1} \mathcal{A}_k. \quad (5.6)$$

Assuming the event $\bigcap_{j=0}^k \mathcal{A}_j$ to be verified, since $x_*(t|x_0, 0) = x_*(t|x_*(k\delta|x_0, 0), k\delta)$ and applying Gronwall inequality as in Lemma C.1, we obtain that

$$\begin{aligned} \Delta_k &\leq \sup_{t \in I_k} |x(t) - x_*(t|x(k\delta), k\delta)| + \sup_{t \in I_k} |x_*(t|x(k\delta), k\delta) - x_*(t|x_0, 0)| \\ &< \beta\delta + e^{K\delta} |x(k\delta) - x_*(k\delta|x_0, 0)| \leq \beta\delta + e^{K\delta} \Delta_{k-1}. \end{aligned} \quad (5.7)$$

Due to the event $\bigcap_{j=0}^k \mathcal{A}_j$, we can iterate the above procedure and conclude that $\Delta_{k-1} < \beta\delta + e^{K\delta} \Delta_{k-2}$ and so on. At the end we obtain that the event $\bigcap_{j=0}^k \mathcal{A}_j$ implies the event

$$\mathcal{B}_k := \{ \Delta_0 < \beta\delta \text{ and } \Delta_j < \beta\delta + e^{K\delta} \Delta_{j-1} \forall j = 1, 2, \dots, k \}.$$

Setting $z = e^{K\delta}$, it is simple to check by induction that the event \mathcal{B}_k implies that for each $j = 0, 1, \dots, k$ it holds

$$\Delta_j \leq \beta\delta(1 + z + z^2 + \dots + z^j) \leq \beta\delta \frac{z^{M+1} - 1}{z - 1} = \beta\delta \frac{e^{KM} - 1}{e^{K\delta} - 1} \leq \beta(e^{KM} - 1)/K \quad (5.8)$$

(in the last inequality we have used that $e^x - 1 \geq x$ for any $x \geq 0$). Hence, \mathcal{A} implies (5.8) for all $j = 0, 1, \dots, M-1$ and therefore it implies that

$$\sup_{0 \leq t \leq T} |x(t) - x_*(t|x_0, 0)| \leq \beta(e^{KM} - 1)/K. \quad (5.9)$$

Due to arbitrariness of β , this implies (2.19).

Let us now prove (2.18). We take M as in Lemma 5.1, where f is the same function appearing in Theorem 2.2 and \mathcal{K} is defined as above. Using the same arguments as above, it is simple to derive from Lemma 5.1 that $P_{x_0, \sigma_0}^\lambda(\mathcal{C}) = 1 - o(1)$, where \mathcal{C} denotes the event

$$\mathcal{C} = \left\{ \left| \int_{k\delta}^{k\delta+\delta} f(t) \left[\chi(\sigma(t) = \sigma) - \mu(\sigma | x_*(t|x(k\delta), k\delta), t) \right] dt \right| \leq \beta\delta, \right. \\ \left. \forall k \in \{0, 1, \dots, M-1\} \right\}.$$

By assumption (A3) we know that there exists a constant $\kappa > 0$ such that (2.12) holds for all $x, y \in \mathcal{K}$ and for all $t \in [0, T]$. Hence, we can estimate

$$\begin{aligned} \left| \int_{k\delta}^{k\delta+\delta} f(t) \left[\mu(\sigma | x_*(t|x(k\delta), k\delta), t) - \mu(\sigma | x_*(t|x_0, 0), t) \right] dt \right| &\leq \\ \kappa \|f\|_\infty \delta \sup_{t \in I_k} |x_*(t|x(k\delta), k\delta) - x_*(t|x_0, 0)|. \end{aligned} \quad (5.10)$$

Trivially,

$$|x_*(t|x(k\delta), k\delta) - x_*(t|x_0, 0)| \leq |x_*(t|x(k\delta), k\delta) - x(t)| + |x(t) - x_*(t|x_0, 0)|.$$

If \mathcal{A} is verified, the first addendum in the r.h.s. is bounded by $\beta\delta$ (recall that \mathcal{A} implies \mathcal{A}_k), while the second addendum is bounded by $\Delta_k \leq \beta(e^{KM} - 1)/K$. Therefore, we can

conclude that whenever the event \mathcal{A} is verified the r.h.s. of (5.10) is bounded from above by

$$\kappa \|f\|_\infty \delta (\beta \delta + \beta(e^{KT} - 1)/K).$$

Using the triangular inequality, we conclude that the event $\mathcal{A} \cap \mathcal{C}$ implies that

$$\begin{aligned} \left| \int_0^T f(t) \left[\chi(\sigma(t) = \sigma) - \mu(\sigma | x_*(t|x_0, 0), t) \right] dt \right| &\leq \\ M\beta\delta + M\kappa\|f\|_\infty\delta(\beta\delta + \beta(e^{KT} - 1)/K) &= \\ T\beta[1 + \kappa\|f\|_\infty(\delta + (e^{KT} - 1)/K)] &= C(T, K, \kappa, f)\beta. \end{aligned} \quad (5.11)$$

Due to the arbitrariness of β and since $P_{x_0, \sigma_0}^\lambda(\mathcal{A} \cap \mathcal{C}) = 1 - o(1)$, the above estimate implies (2.18). This concludes the proof of the averaging principle stated in Theorem 2.2. \square

We can now concentrate on the core of the law of large numbers, given by Lemma 5.1:

Proof of Lemma 5.1. We stress that β has to be considered as a fixed constant. We will play with two length scales: δ and ε , defined below. $C, c', \tilde{c}, c_i, \dots$ will denote non random positive constants independent from δ and ε , that can change from line to line and that can depend on β . For simplicity of notation we take $k = 0$ (the arguments remain valid in the general case). As the reader can check, in order to prove Lemma 5.1 we will consider the process only when the mechanical trajectory $x(t)$ lies inside a given compact set (uniformly in the starting point $x_0 \in \mathcal{K}$). Hence, at cost to take a larger Lipschitz constant K in (2.7), we can assume (2.7), (2.10), (2.12) and (2.11) to hold for all $x, y \in \mathbb{R}^d$ with $\kappa = K$. This allows to much simplify the notation.

We first prove (5.3) and explain how to choose M . To this aim we observe that due to Lemma C.1 there exists a compact subset $\widehat{\mathcal{K}} \subset \mathbb{R}^d$ such that $x_*(t|x_0, 0) \in \widehat{\mathcal{K}}$ for each $t \in [0, T]$ and $x_0 \in \mathcal{K}$. We define the compact set \mathcal{K}' as

$$\mathcal{K}' := \cup_{x \in \widehat{\mathcal{K}}} B(x, T), \quad (5.12)$$

where $B(x, T)$ denotes the closed ball centered at x with radius T . Given a pair $(x, t) \in \mathcal{K}' \times [0, T]$ we consider the continuous-time homogeneous Markov chain on Γ with transition rates $r(\sigma, \sigma') := r(\sigma, \sigma' | x, t)$, $\sigma \neq \sigma'$. Note that this Markov chain is ergodic and has $\mu(\cdot | x, t)$ as stationary probability. We call $Q_{\tilde{\sigma}, x, t}$ its law when starting in the state $\tilde{\sigma}$. We will use the following uniform large deviation estimate

$$\limsup_{u \rightarrow \infty} \sup_{(x, t) \in \mathcal{K}' \times [0, T], \sigma, \sigma' \in \Gamma} \frac{1}{u} \ln Q_{\sigma', x, t} \left[\left| \frac{1}{u} \int_0^u [\chi(\sigma(s) = \sigma) - \mu(\sigma | x, t)] ds \right| \geq \frac{\beta}{20(a_* + 1)|\Gamma|} \right] =: -W_1 < 0, \quad (5.13)$$

where

$$a_* := \max_{\sigma' \in \Gamma} \max_{s \in [0, T]} \max_{x' \in \mathcal{K}'} |F_{\sigma'}(x', s)|, \quad (5.14)$$

and W_1 is a strictly positive constant. The result (5.13) follows from lemma B.1 in Appendix B.

We now introduce a second positive constant W_2 defined as

$$W_2 = K + 2 + a_*. \quad (5.15)$$

Finally we define the constant $\delta := T/M$, where M is the smallest positive integer such that

$$\delta \leq \min\{W_1/(4c_3), 2\beta/(5W_2)\}, \quad (5.16)$$

where the positive constant c_3 depends only on the compact \mathcal{K} and will be defined in (5.32).

Let us now prove (5.3) for $k = 0$. In order to shorten the notation we write $x_*(t)$ instead $x_*(t|x_0, 0)$. We stress that $x_*(t)$ depends on x_0 , although x_0 has been omitted in the notation. We define the random time τ in terms of the exit time from the $\beta\delta$ -tube $\mathcal{A}_{\beta\delta}$ around $x_*(t)$:

$$\tau := \inf\{t \geq 0 : (x(t), t) \notin \mathcal{A}_{\beta\delta}\},$$

where

$$\mathcal{A}_{\beta\delta} := \{(x, t) \in \mathbb{R}^d \times [0, \delta] : |x - x_*(t)| \leq \beta\delta\}. \quad (5.17)$$

Note that, since $\beta\delta \leq T$, for each $x_0 \in \mathcal{K}$ the above tube $\mathcal{A}_{\beta\delta}$ is included in $\hat{\mathcal{K}}$. We want to prove that $\tau \geq \delta$ with probability $1 - o(1)$ as $\lambda \uparrow \infty$, which is equivalent to (5.3). Up to the Markov time τ the PDMP is determined only by its characteristics restricted to $\mathcal{A}_{\beta\delta}$. Since we will follow the process only up to time τ , due to (2.7) and (2.10), at cost of changing the characteristics outside $\mathcal{A}_{\beta\delta}$ without loss of generality we can assume that

$$|F_\sigma(x, t) - F_\sigma(x_*(t), t)| \leq K\delta, \quad (5.18)$$

$$|r(\sigma, \sigma'|x, t) - r(\sigma, \sigma'|x_*(t), t)| \leq K\delta, \quad (5.19)$$

$$|\gamma_\sigma(x, t) - \gamma_\sigma(x_*(t), t)| \leq K\delta, \quad (5.20)$$

for all $x \in \mathbb{R}^d$ and $t \in [0, \delta]$. Using (5.18) and the fact that $\tau \leq \delta$, one easily obtains that, given $m = 1, 2, \dots, d$, $P_{x_0, \sigma_0}^\lambda$ -a.s. it holds

$$\begin{aligned} x(t)_m &= x(0)_m + \int_0^t F_{\sigma(s)}(x(s), s)_m ds \\ &= x(0)_m + \int_0^t F_{\sigma(s)}(x_*(s), s)_m ds + \mathcal{E}_1, \quad \forall t \leq \tau, \end{aligned} \quad (5.21)$$

where the error term \mathcal{E}_1 can be bounded as $|\mathcal{E}_1| \leq K\delta^2$.

Given an integer N , we divide the interval $[0, \delta]$ in N subintervals of length $\varepsilon := \delta/N$. We now explain how to fix the constant ε . The first requirement is that $\varepsilon \leq \delta^2$. Moreover, consider the functions $F_\sigma(\cdot, \cdot)$ on $\mathcal{K}' \times [0, T]$. Since they are uniformly continuous, there exists $\varepsilon_1 > 0$ such that $|F_\sigma(x_1, s_1) - F_\sigma(x_2, s_2)| \leq \delta$ for any $x_1, x_2 \in \mathcal{K}'$, $s_1, s_2 \in [0, T]$ such that $|x_1 - x_2| \leq \varepsilon_1$ and $|s_1 - s_2| \leq \varepsilon_1$. We require that

$$\varepsilon \leq \min\{\varepsilon_1, \varepsilon_1/C_0\},$$

where

$$C_0 = \sup_{(x, s) \in \mathcal{K}' \times [0, T]} |\bar{F}(x, s)|, \quad \bar{F}(x, s) = \sum_{\sigma \in \Gamma} F_\sigma(x, s) \mu(\sigma|x, s).$$

We note that this condition implies that

$$|F_\sigma(x_*(s), s)_m - F_\sigma(x_*(t), t)_m| \leq \delta \quad (5.22)$$

for all $m = 1, \dots, d$, all $\sigma \in \Gamma$ and all $s, t \in [0, T]$ such that $|s - t| \leq \varepsilon$. Indeed, for such s, t it holds

$$|x_*(s) - x_*(t)| = \left| \int_s^t \bar{F}(x_*(u), u) du \right| \leq C_0 |s - t| \leq \varepsilon_1.$$

This allows to derive (5.22) from our choice of ε_1 . By similar arguments we derive that for a suitable positive constant ε_2 it holds

$$|r(\sigma, \sigma' | x_*(s), s) - r(\sigma, \sigma' | x_*(t), t)| \leq \delta \quad (5.23)$$

for any $s, t, \in [0, T]$ such that $|s - t| \leq \varepsilon_2$ and for any $\sigma \neq \sigma'$ in Γ . We fix ε s.t. $\varepsilon \leq \varepsilon_2$. Similarly, there exists a positive constant ε_3 such that

$$|\mu(\sigma | x_*(s), s) - \mu(\sigma | x_*(t), t)| \leq \frac{\beta}{20(a_* + 1)|\Gamma|} \quad (5.24)$$

for any $s, t, \in [0, T]$ such that $|s - t| \leq \varepsilon_3$ and for any σ in Γ . We fix ε s.t. $\varepsilon \leq \varepsilon_3$.

Writing

$$\int_0^t F_{\sigma(s)}(x_*(s), s)_m ds = \sum_{\sigma \in \Gamma} \int_0^t F_{\sigma}(x_*(s), s)_m \chi(\sigma(s) = \sigma) ds,$$

due to (5.21), (5.22) and the condition $\varepsilon \leq \delta^2$, it holds

$$x(t)_m = x(0)_m + \sum_{\sigma \in \Gamma} \sum_{j=0}^{\lfloor t/\varepsilon \rfloor - 1} F_{\sigma}(x_*(j\varepsilon), j\varepsilon)_m \int_{j\varepsilon}^{j\varepsilon + \varepsilon} \chi(\sigma(s) = \sigma) ds + \mathcal{E}_2, \quad \forall t \leq \tau, \quad (5.25)$$

where the error term \mathcal{E}_2 can be bounded as $|\mathcal{E}_2| \leq |\mathcal{E}_1| + \delta^2 + \delta^2 a_*$. Above, $\lfloor t/\varepsilon \rfloor$ denotes the integer part of t/ε and the sum over j is set equal to zero if $\lfloor t/\varepsilon \rfloor = 0$. The condition $\varepsilon \leq \delta^2$ is necessary in order to bound the error term $\int_{\lfloor t/\varepsilon \rfloor \varepsilon}^t F_{\sigma(s)}(x_*(s), s)_m ds$.

We claim that there exist positive constants c, c' independent of ε and δ such that the λ -accelerated PDMP with unrescaled characteristics satisfying (5.18), (5.19) and (5.20) fulfills the bound

$$P_{x', \sigma', j\varepsilon}^{\lambda} \left(\left| \int_{j\varepsilon}^{j\varepsilon + \varepsilon} [\chi(\sigma(s) = \sigma) - \mu(\sigma | x_*(s | x_0, 0), s)] ds \right| > \frac{\beta\varepsilon}{10(a_* + 1)|\Gamma|} \right) \leq e^{-c\lambda\varepsilon}, \quad (5.26)$$

for any $j = 1, 2, \dots, N - 1$, any $x_0 \in \mathcal{K}$, any $x' \in \mathbb{R}^d$ s.t. $|x' - x_*(j\varepsilon | x_0, 0)| \leq \beta\delta$, for any $\sigma, \sigma' \in \Gamma$ and for any $\lambda \geq c'/\varepsilon$. We recall that a_* has been defined in (5.14). Above we used again the notation $x_*(\cdot | x_0, 0)$ in order to stress the dependence on x_0 .

Before proving (5.26) let us explain how it allows to conclude the proof of Lemma 5.1. First we show that, due to (5.25), (5.26) and the Markov property, with probability at least $1 - (\delta/\varepsilon)e^{-c\lambda\varepsilon}|\Gamma|$ it holds

$$x(t)_m = x(0)_m + \sum_{\sigma \in \Gamma} \sum_{j=0}^{\lfloor t/\varepsilon \rfloor - 1} F_{\sigma}(x_*(j\varepsilon), j\varepsilon)_m \int_{j\varepsilon}^{j\varepsilon + \varepsilon} \mu(\sigma | x_*(s), s) ds + \mathcal{E}_3, \quad \forall t \leq \tau, \quad (5.27)$$

where the modulus of the error \mathcal{E}_3 can be bounded as $|\mathcal{E}_3| \leq |\mathcal{E}_2| + \beta\delta/10$. To this aim, we define the event $\mathcal{B}_j(\sigma)$ for $j = 0, 1, \dots, N - 1$ as $\mathcal{B}_j(\sigma) := \mathcal{C}_j(\sigma) \cap \{j\varepsilon + \varepsilon \leq \tau\}$ where

$$\mathcal{C}_j(\sigma) := \left\{ \left| \int_{j\varepsilon}^{j\varepsilon + \varepsilon} [\chi(\sigma(s) = \sigma) - \mu(\sigma | x_*(s), s)] ds \right| > \frac{\beta\varepsilon}{10(a_* + 1)|\Gamma|} \right\}. \quad (5.28)$$

Conditioning on time $j\varepsilon$ and using the Markov property we can estimate

$$P_{x_0, \sigma_0}^{\lambda}(\mathcal{B}_j(\sigma)) = P_{x_0, \sigma_0}^{\lambda}(\mathcal{C}_j(\sigma); j\varepsilon + \varepsilon \leq \tau) = E_{x_0, \sigma_0}^{\lambda} [P_{x(j\varepsilon), \sigma(j\varepsilon), j\varepsilon}(\mathcal{C}_j(\sigma)) \chi(j\varepsilon + \varepsilon \leq \tau)].$$

At this point, we observe that the condition $j\varepsilon \leq \tau$ implies that $|x(j\varepsilon) - x_*(j\varepsilon)| \leq \beta\delta$, thus allowing to estimate the probability $P_{x(j\varepsilon), \sigma(j\varepsilon), j\varepsilon}(\mathcal{C}_j(\sigma))$ from above by $e^{-c\lambda\varepsilon}$ due to (5.26). In particular, we obtain that

$$P_{x_0, \sigma_0}^\lambda(\mathcal{B}) \leq N|\Gamma|e^{-c\lambda\varepsilon}, \quad \mathcal{B} := \cup_{\sigma \in \Gamma} \cup_{j=0}^{N-1} \mathcal{B}_j(\sigma).$$

Finally, we note that the event \mathcal{B}^c implies for any σ that $\mathcal{C}_j(\sigma)$ is not fulfilled whenever the interval $[j\varepsilon, j\varepsilon + \varepsilon]$ is included in $[0, \tau]$. Hence, in this case in (5.25) one can substitute $\chi(\sigma(s) = \sigma)$ by $\mu(\sigma|x_*(s), s)$ with an error bounded by $\beta\varepsilon N/10 = \beta\delta/10$. This leads to (5.27).

By applying again (5.22), (5.27) implies that

$$x(t)_m = x(0)_m + \sum_{\sigma \in \Gamma} \int_0^t F_\sigma(x_*(s), s)_m \mu(\sigma|x_*(s), s) ds + \mathcal{E}_4 = x_*(t)_m + \mathcal{E}_4, \quad \forall t \leq \tau, \quad (5.29)$$

where the error \mathcal{E}_4 can be bounded as $|\mathcal{E}_4| \leq |\mathcal{E}_3| + \delta^2$. Collecting all the previous estimates, we conclude that for all $x_0 \in \mathcal{K}$ it holds $|\mathcal{E}_4| \leq \beta\delta/10 + W_2\delta^2$, the constant W_2 being defined in (5.15). Hence, due to our choice (5.16), we can conclude that $|\mathcal{E}_4| \leq \beta\delta/2$. Hence, taking $t = \tau$ in (5.29), we conclude that with probability $1 - (\delta/\varepsilon)e^{-c\lambda\varepsilon}|\Gamma|$ it must be $|x(\tau) - x_*(\tau)| \leq \beta\delta/2$. Due to the continuity of the mechanical trajectories and the definition of τ , this implies that $\tau = \delta$. Coming back to (5.29) with this additional information we get (5.3) with $k = 0$. As already remarked, the same arguments allow to prove (5.3) for a generic k .

We point out that by the above method we have approximated the random integral

$$\int_{k\delta}^{k\delta+\delta} F_\sigma(x(s), s)_m \chi(\sigma(s) = \sigma) ds$$

by the new integral

$$\int_{k\delta}^{k\delta+\delta} F_\sigma(x_*(s), s)_m \mu(\sigma|x_*(s), s) ds.$$

Hence, the proof of (5.4) is completely analogous, since it is enough to replace the force field with the test function $f(s)$.

It remains now to prove (5.26). In order to simplify the notation, we write P^λ for the law $P_{x', \sigma', j\varepsilon}^\lambda$ of the λ -accelerated PDMP having unrescaled characteristics that satisfy (5.18), (5.19) and (5.20), starting in the state (x', σ') at time $j\varepsilon$ and evolving up to time $j\varepsilon + \varepsilon$. In addition, we write Q^λ for the law of the λ -accelerated PDMP restricted to the time interval $[j\varepsilon, j\varepsilon + \varepsilon]$, starting in the state (x', σ') at time $j\varepsilon$ and with characteristics $(F, \lambda\tilde{r})$, where the new unrescaled transition rates \tilde{r} are constant and are defined as

$$\begin{aligned} \tilde{r}(\sigma_1, \sigma_2) &:= \tilde{p}(\sigma_1, \sigma_2) \tilde{\gamma}_{\sigma_1}, \\ \tilde{p}(\sigma_1, \sigma_2) &:= p(\sigma_1, \sigma_2 | x_*(j\varepsilon), j\varepsilon), \\ \tilde{\gamma}_\sigma &:= \gamma_\sigma(x_*(j\varepsilon), j\varepsilon). \end{aligned}$$

Namely, the above rates correspond to the original rates read along the asymptotic trajectory x_* and frozen at time $j\varepsilon$. Note that this new PDMP is not coupled: the chemical evolution is a continuous-time homogeneous Markov chain, while the mechanical evolution is a function of the chemical one. One can compute and bound the Radon–Nikodym derivative

dP^λ/dQ^λ . Indeed, if $(x(t), \sigma(t))$ is an element in the Skohorod space $D([j\varepsilon, j\varepsilon + \varepsilon], \mathbb{R}^d \times \Gamma)$ with n jumps at times $\tau_1 < \tau_2 < \dots < \tau_n$, setting $\tau_0 = j\varepsilon$, $\sigma_0 := \sigma'$, $x_0 := x'$ and

$$\sigma_i := \sigma(\tau_i), \quad x_i := x(\tau_i), \quad i = 1, 2, \dots, n,$$

one has

$$\frac{dP^\lambda}{dQ^\lambda}(x(\cdot), \sigma(\cdot)) = \left[\prod_{i=1}^n \frac{r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i)}{\tilde{r}(\sigma_{i-1}, \sigma_i)} \right] \exp \left\{ -\lambda \int_{j\varepsilon}^{j\varepsilon + \varepsilon} (\gamma_{\sigma(s)}(x(s), s) - \tilde{\gamma}_{\sigma(s)}) ds \right\}. \quad (5.30)$$

The term in the square bracket can be rewritten as

$$\prod_{i=1}^n \frac{r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i)}{\tilde{r}(\sigma_{i-1}, \sigma_i)} = \exp \left\{ \sum_{i=1}^n [\ln r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i) - \ln \tilde{r}(\sigma_{i-1}, \sigma_i)] \right\}. \quad (5.31)$$

Due to (2.10), (5.23) and the assumption $\varepsilon \leq \varepsilon_2$ we conclude that

$$\begin{aligned} & |r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i) - \tilde{r}(\sigma_{i-1}, \sigma_i)| = |r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i) - r(\sigma_{i-1}, \sigma_i | x_*(j\varepsilon), j\varepsilon)| \\ & \leq |r(\sigma_{i-1}, \sigma_i | x(\tau_i), \tau_i) - r(\sigma_{i-1}, \sigma_i | x_*(\tau_i), \tau_i)| \\ & + |r(\sigma_{i-1}, \sigma_i | x_*(\tau_i), \tau_i) - r(\sigma_{i-1}, \sigma_i | x_*(j\varepsilon), j\varepsilon)| \leq (K+1)\delta. \end{aligned}$$

By applying Taylor expansion to the log function and using (5.31), we get that the term in the square bracket in (5.30) is bounded from above by $e^{c_0 n \delta}$ where n denotes the number of chemical jumps in the interval $[j\varepsilon, j\varepsilon + \varepsilon]$. The constant c_0 does not depend on $\beta, \varepsilon, \delta, j$ and is the same for all $x_0 \in \mathcal{K}$ and all pairs (x', σ') as in (5.26). Similarly one gets that the exponential in (5.30) is bounded from above by $e^{c_1 \lambda \varepsilon \delta}$, where the constant c_1 does not depend on $\beta, \varepsilon, \delta, j$ and is the same for all $x_0 \in \mathcal{K}$ and all pairs (x', σ') as in (5.26). Moreover, setting

$$C := \max_{\sigma \in \Gamma} \max_{(x, s) \in \mathcal{K}' \times [0, T]} \gamma_\sigma(x, s),$$

the random variable n is stochastically dominated by a Poisson random variable Z with mean $C\lambda\varepsilon$. Recalling that $E(e^{aZ}) = e^{C\lambda\varepsilon(e^a - 1)}$ and taking $a = 2c_0\delta$, we conclude that

$$E_{Q^\lambda} \left(\left| \frac{dP^\lambda}{dQ^\lambda} \right|^2 \right) \leq e^{2c_1 \lambda \varepsilon \delta + C\lambda\varepsilon(e^{2c_0\delta} - 1)} \leq e^{c_3 \lambda \varepsilon \delta}, \quad c_3 := 2c_1 + 2c_0 C \frac{e^T - 1}{T}. \quad (5.32)$$

Above we have used the inequality $e^x - 1 \leq \frac{e^T - 1}{T} x$ valid for all $x \in [0, T]$, which follows from the convexity of $x \rightarrow e^x$.

Due to (5.24) and our assumption $\varepsilon \leq \varepsilon_3$ we can bound

$$\int_{j\varepsilon}^{j\varepsilon + \varepsilon} |\mu(\sigma | x_*(s), s) - \mu(\sigma | x_*(j\varepsilon), j\varepsilon)| ds \leq \frac{\beta\varepsilon}{20(a_* + 1)|\Gamma|}.$$

Hence, calling \mathcal{D} the event

$$\mathcal{D} := \left\{ \left| \int_{j\varepsilon}^{j\varepsilon + \varepsilon} [\chi(\sigma(s) = \sigma) - \mu(\sigma | x_*(j\varepsilon), j\varepsilon)] ds \right| > \frac{\beta\varepsilon}{20(a_* + 1)|\Gamma|} \right\}$$

in order to conclude the proof of (5.26) we need to bound $P^\lambda(\mathcal{D})$. To this aim, we write $Q_{\sigma'}$ for the law of the continuous-time Markov chain on Γ starting at σ' , jumping from

σ_1 to σ_2 with transition rate $\tilde{r}(\sigma_1, \sigma_2)$. Note that $\mu(\cdot | x_*(j\varepsilon), j\varepsilon)$ is the invariant measure for this Markov chain. Then

$$Q^\lambda[\mathcal{D}] = Q_{\sigma'} \left[\left| \frac{1}{\lambda\varepsilon} \int_0^{\lambda\varepsilon} [\chi(\sigma(s) = \sigma) - \mu(\sigma | x_*(j\varepsilon), j\varepsilon)] ds \right| > \frac{\beta}{20(a_* + 1)|\Gamma|} \right] \quad (5.33)$$

We note that x' as in (5.26) must belong to the compact set \mathcal{K}' . Hence, due to (5.13), if $\lambda\varepsilon \geq c_4$ (c_4 being independent on ε, δ and being the same for all $(x', \sigma') \in \mathcal{K}' \times \Gamma$), then

$$Q^\lambda[\mathcal{D}] \leq e^{-\varepsilon\lambda W_1/2}, \quad (5.34)$$

where W_1 has been defined in (5.13).

Finally, we can apply Schwarz inequality together with (5.32) and (5.34) in order to conclude that

$$P^\lambda[\mathcal{D}] = E_{Q^\lambda} \left[\frac{dP^\lambda}{dQ^\lambda} \cdot \chi_{\mathcal{D}} \right] \leq E_{Q^\lambda} \left[\left(\frac{dP^\lambda}{dQ^\lambda} \right)^2 \right]^{1/2} Q^\lambda(\mathcal{D})^{1/2} \leq \exp \left\{ -\lambda\varepsilon [W_1/4 - c_3\delta/2] \right\}. \quad (5.35)$$

Since by definition (5.16) $c_3\delta/2 \leq W_1/8$, we obtain that $P^\lambda[\mathcal{D}] \leq e^{-\lambda\varepsilon W_1/8}$. This implies (5.26) with $c = W_1/8$ and $c' = c_4$. \square

6. PROOF OF THEOREM 2.3

We have now all the tools in order to prove the LDP. We recall that in Section 4 we proved (2.27) assuming (2.26). Here we start by analyzing the Radon–Nikodym derivative of the PDMP w.r.t. a perturbed version. To this aim let $V = \{V_\sigma\}_{\sigma \in \Gamma}$ be a family of C^1 functions $V_\sigma : [0, T] \rightarrow \mathbb{R}$ parameterized by $\sigma \in \Gamma$ and call $V'_\sigma(s) := \frac{dV_\sigma(s)}{ds}$ the corresponding derivatives. We introduce some perturbed rates according to the following definitions

$$\begin{aligned} \tilde{r}(\sigma, \sigma' | x, s) &:= r(\sigma, \sigma' | x, s) e^{V_{\sigma'}(s) - V_\sigma(s)}, \\ \tilde{\gamma}_\sigma(x, s) &:= \sum_{\sigma' \in \Gamma} \tilde{r}(\sigma, \sigma' | x, s). \end{aligned} \quad (6.1)$$

Writing $P_{x_0, \sigma_0}^{\lambda, V}$ for the law of the PDMP with characteristics $(F, \lambda\tilde{r})$ and denoting by $\tau_1 < \tau_2 < \dots < \tau_n$ the jump times of the path $\sigma(\cdot)$ in the time interval $[0, T]$, it holds

$$\begin{aligned} \frac{dP_{x_0, \sigma_0}^{\lambda, V}}{dP_{x_0, \sigma_0}^{\lambda, V}}(x, \sigma) &= \exp \left\{ \sum_{i=1}^n [V_{\sigma(\tau_i-)}(\tau_i) - V_{\sigma(\tau_i)}(\tau_i)] \right\} \\ &\quad \exp \left\{ -\lambda \sum_{\sigma' \in \Gamma} \int_0^T r(\sigma(s), \sigma' | x(s), s) (1 - e^{V_{\sigma'}(s) - V_\sigma(s)}) ds \right\}. \end{aligned} \quad (6.2)$$

In order to estimate the first exponential in (6.2) we observe that

$$\sum_{i=0}^n \int_{\tau_i}^{\tau_{i+1}} V'_{\sigma(s)}(s) ds = \sum_{i=0}^n [V_{\sigma(\tau_{i+1}-)}(\tau_{i+1}) - V_{\sigma(\tau_i)}(\tau_i)],$$

where we set $\tau_0 := 0$ and $\tau_{n+1} := T$. This implies that

$$\exp \left\{ \sum_{i=1}^n [V_{\sigma(\tau_i-)}(\tau_i) - V_{\sigma(\tau_i)}(\tau_i)] \right\} = \exp \left\{ - \left[V_{\sigma(T-)}(T) - V_{\sigma(0)}(0) - \int_0^T V'_{\sigma(s)}(s) ds \right] \right\}.$$

Writing $Q_{x_0, \sigma_0}^{\lambda, V}$ for the law of the perturbed process on Υ the above computations give

$$\frac{dQ_{x_0, \sigma_0}^{\lambda, V}}{dQ_{x_0, \sigma_0}^{\lambda}}(x, \rho) = \exp \{ -\lambda [J_V(x, \rho) + O(1/\lambda)] \}, \quad (6.3)$$

where

$$J_V(x, \rho) = \sum_{\sigma \in \Gamma} \sum_{\sigma' \in \Gamma} \int_0^T \rho(s) r(\sigma, \sigma' | x(s), s) (1 - e^{V_{\sigma'}(s) - V_{\sigma}(s)}) ds \quad (6.4)$$

and $O(1/\lambda)$ denotes a quantity bounded in modulus by c/λ , c being a positive constant depending only on $\{V_{\sigma}\}_{\sigma \in \Gamma}$ and T .

We point out that the function $J_V : \Upsilon \rightarrow \mathbb{R}$ is continuous. Indeed, if $(x^{(n)}, \rho^{(n)})$ converges to (x, ρ) then

$$\begin{aligned} & \left| J_V(x^{(n)}, \rho^{(n)}) - J_V(x, \rho) \right| \leq \\ & \sum_{\sigma} \sum_{\sigma'} \left| \int_0^T (\rho_{\sigma}^{(n)}(s) - \rho_{\sigma}(s)) r(\sigma, \sigma' | x(s), s) (1 - e^{V_{\sigma'}(s) - V_{\sigma}(s)}) ds \right| + \\ & c(V) \sum_{\sigma} \sum_{\sigma'} \int_0^T \rho_{\sigma}^{(n)}(s) \left| r(\sigma, \sigma' | x(s), s) - r(\sigma, \sigma' | x^{(n)}(s), s) \right| ds. \end{aligned} \quad (6.5)$$

Since $\rho_{\sigma}^{(n)} \rightarrow \rho_{\sigma}$ in $L[0, T]$ and since the transition rates are continuous, the first expression in the r.h.s. goes to zero as $n \rightarrow \infty$. Since $\|x^{(n)} - x\|_{\infty} \rightarrow 0$, by the continuity of the transition rates and the Dominated Convergence Theorem the second expression in the r.h.s. goes to zero, thus concluding the proof of the continuity of J_V .

Consider the function $J(x, \rho)$ defined in (2.26). This can be rewritten as

$$J(x, \rho) = \sup_z \sum_{\sigma} \sum_{\sigma'} \int_0^T \rho_{\sigma}(s) r(\sigma, \sigma' | x(s), s) \left[1 - \frac{z_{\sigma'}(s)}{z_{\sigma}(s)} \right] ds, \quad (6.6)$$

where the supremum is taken over the family of measurable functions $\{z_{\sigma}\}_{\sigma \in \Gamma}$, $z_{\sigma} : [0, T] \rightarrow (0, \infty)$. Approximating measurable functions by bounded C^1 functions, we obtain that the functional $J(x, \rho)$ defined in (2.26) can be expressed as

$$J(x, \rho) = \sup_V J_V(x, \rho), \quad (x, \rho) \in \Upsilon. \quad (6.7)$$

- *Regularity of J .* Trivially $J(x, \rho) < \infty$ for each $(x, \rho) \in \Upsilon$. Moreover, J is lower semi-continuous since due to the previous observations it is the supremum of the family of continuous functions J_V .

- *Proof of the upper bound (2.28).* Let us start with a generic subset $U \subset \Upsilon$. Given a family V of C^1 functions $\{V_{\sigma}(s)\}_{\sigma \in \Gamma}$, we can bound

$$\begin{aligned} Q_{x_0, \sigma_0}^{\lambda}(U) = Q_{x_0, \sigma_0}^{\lambda, V} \left(\frac{dQ_{x_0, \sigma_0}^{\lambda}}{dQ_{x_0, \sigma_0}^{\lambda, V}} \chi_U \right) & \leq e^{-\lambda \inf_{(x, \rho) \in U} [J_V(x, \rho) + O(\lambda^{-1})]} Q_{x_0, \sigma_0}^{\lambda, V}(U) \leq \\ & e^{-\lambda \inf_{(x, \rho) \in U} [J_V(x, \rho) + O(\lambda^{-1})]}. \end{aligned}$$

This implies that

$$\limsup_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^{\lambda}(U) \leq - \inf_{(x, \rho) \in U} J_V(x, \rho).$$

This holds for any choice of the functions V_σ . Optimizing over the V_σ we get

$$\limsup_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(U) \leq - \sup_V \inf_{(x, \rho) \in U} J_V(x, \rho). \quad (6.8)$$

At this point, we would like to invert the supremum and the infimum in the r.h.s. if U is given by some closed subset $C \subset \Upsilon$. To this aim we observe that (i) C is compact since it is a closed subset of the compact space Υ (see Lemma A.2), (ii) estimate (6.8) holds for each $U \subset \Upsilon$ and in particular for each open subset $U \subset \Upsilon$, (iii) $J_V(x, \rho)$ is continuous on Υ for each $V \in C^1[0, T]^\Gamma$. Hence, we can apply Lemma 3.3 in [KL] (note that $J_\beta(\mu)$ there coincides with our $-J_V(x, \rho)$), which together with (6.7) implies the upper bound

$$\limsup_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(C) \leq - \inf_{(x, \rho) \in C} \sup_V J_V(x, \rho) = - \inf_{(x, \rho) \in C} J(x, \rho) = -J(C).$$

- *Proof of the lower bound (2.29).*

We first introduce a special subset \mathcal{B} of Υ as

$$\mathcal{B} = \{(x, \rho) \in \Upsilon : \rho_\sigma \in C^1[0, T] \text{ and } \rho_\sigma(t) > 0 \forall \sigma \in \Gamma, t \in [0, T]\}.$$

As shown in Lemma A.3 in the Appendix, \mathcal{B} is a dense subset of Υ .

Let O be an open subset of Υ and fix $(x^*, \rho^*) \in O \cap \mathcal{B}$ (note that (x^*, ρ^*) exists since \mathcal{B} is dense in Υ). Define

$$\tilde{V}_\sigma(s) = \ln \tilde{z}_\sigma(\rho_\sigma^*(s), x^*(s), s), \quad (6.9)$$

where \tilde{z}_σ has been defined in (4.10). Since rates are assumed to be C^1 (see assumption (A3)), since $\{\rho_\sigma^*(s)r(\sigma, \sigma' | x^*(s), s)\}_{\sigma, \sigma'}$ belongs to the set \mathcal{S} defined at the beginning of Section 4 (see assumption (A2)) and due to Lemma (4.2), we get that $\tilde{V}_\sigma \in C^1[0, T]$. We take as perturbation $\tilde{V} = \{\tilde{V}_\sigma\}_{\sigma \in \Gamma}$.

Due to the fact that O is open we have for any δ small enough

$$Q_{x_0, \sigma_0}^\lambda(O) \geq Q_{x_0, \sigma_0}^\lambda(B_\delta(x^*, \rho^*)), \quad \forall \lambda > 0,$$

where $B_\delta(x^*, \rho^*)$ is the ball in Υ of radius δ and center (x^*, ρ^*) . We now use the following estimate

$$Q_{x_0, \sigma_0}^\lambda(B_\delta(x^*, \rho^*)) = Q_{x_0, \sigma_0}^{\lambda, \tilde{V}} \left(\frac{dQ_{x_0, \sigma_0}^\lambda}{dQ_{x_0, \sigma_0}^{\lambda, \tilde{V}}} \chi_{B_\delta(x^*, \rho^*)} \right) \geq Q_{x_0, \sigma_0}^{\lambda, \tilde{V}}(B_\delta(x^*, \rho^*)) \inf_{(x, \rho) \in B_\delta(x^*, \rho^*)} \frac{dQ_{x_0, \sigma_0}^\lambda}{dQ_{x_0, \sigma_0}^{\lambda, \tilde{V}}}(x, \rho). \quad (6.10)$$

Due to the particular choice of \tilde{V} (see Section 4), the law of large numbers stated in Proposition 2.2 implies that

$$\lim_{\lambda \rightarrow \infty} Q_{x_0, \sigma_0}^{\lambda, \tilde{V}}(B_\delta(x^*, \rho^*)) = 1.$$

Hence, we can derive from (6.10) and (6.3) that

$$\liminf_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(O) \geq - \sup_{(x, \rho) \in B_\delta(x^*, \rho^*)} J_{\tilde{V}}(x, \rho).$$

Due to the fact that this bound holds for any δ small enough we also have that

$$\liminf_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(O) \geq - \lim_{\delta \rightarrow 0} \sup_{(x, \rho) \in B_\delta(x^*, \rho^*)} J_{\tilde{V}}(x, \rho).$$

From the continuity in (x, ρ) of $J_{\tilde{V}}(x, \rho)$ we deduce that

$$\lim_{\delta \rightarrow 0} \sup_{(x, \rho) \in B_\delta(x^*, \rho^*)} J_{\tilde{V}}(x, \rho) = J_{\tilde{V}}(x^*, \rho^*) = J(x^*, \rho^*)$$

(the last identity follows from the definition of \tilde{V} and the results of Section 4).

Optimizing over all possible $(x^*, \rho^*) \in O \cap \mathcal{B}$ we finally get

$$\liminf_{\lambda \rightarrow \infty} \frac{1}{\lambda} \log Q_{x_0, \sigma_0}^\lambda(O) \geq - \inf_{(x, \rho) \in O \cap \mathcal{B}} J(x, \rho).$$

In order to conclude the proof of the lower bound we only need to show that

$$\inf_{(x, \rho) \in O \cap \mathcal{B}} J(x, \rho) = \inf_{(x, \rho) \in O} J(x, \rho). \quad (6.11)$$

Trivially, the l.h.s. is not smaller than the r.h.s. In order to prove the opposite inequality, fix $(x, \rho) \in \Upsilon$ and fix a sequence $(x^{(n)}, \rho^{(n)}) \in \mathcal{B}$ converging to (x, ρ) in Υ . By the construction of this approximating sequence given in the proof of Lemma A.3, we can assume that there exists a set $U \subset [0, T]$ whose complement has zero Lebesgue measure such that $\rho_\sigma^{(n)}(s) \rightarrow \rho_\sigma(s)$ and $x^{(n)}(s) \rightarrow x(s)$ for all $s \in U$ and $\sigma \in \Gamma$. Due to the continuity of the transition rates, this implies that

$$c^{(n)}(s)[\sigma, \sigma'] := \rho_\sigma^{(n)}(s) r(\sigma, \sigma' | x^{(n)}(s), s) \rightarrow \rho_\sigma(s) r(\sigma, \sigma' | x(s), s) =: c(s)[\sigma, \sigma'], \quad (6.12)$$

for all $s \in U$ and all $\sigma, \sigma' \in \Gamma$. Recall the function \mathcal{J} defined in (4.1), Section 4. Then, due to (6.12) and the continuity of \mathcal{J} (see Lemma 4.1), we obtain that

$$j(\rho^{(n)}(s), r(\cdot, \cdot | x^{(n)}(s), s)) = \mathcal{J}(c^{(n)}(s)) \rightarrow \mathcal{J}(c(s)) = j(\rho(s), r(\cdot, \cdot | x(s), s)) \quad (6.13)$$

for each $s \in U$. Since $\|x^{(n)} - x\|_\infty$ goes to zero as $n \uparrow \infty$ and due to the continuity of the transition rates, given $\varepsilon > 0$ we can find n_0 such that

$$\sup_{n \geq n_0} \sup_{s \in [0, T]} \sup_{\sigma, \sigma'} r(\sigma, \sigma' | x^{(n)}(s), s) \leq \sup_{s \in [0, T]} \sup_{\sigma, \sigma'} r(\sigma, \sigma' | x(s), s) + \varepsilon =: C.$$

Due to the definition (2.24) of j , this implies that

$$\begin{cases} j(\rho^{(n)}(s), r(\cdot, \cdot | x^{(n)}(s), s)) \leq C|\Gamma|^2, \\ j(\rho(s), r(\cdot, \cdot | x(s), s)) \leq C|\Gamma|^2, \end{cases} \quad (6.14)$$

for all s in $[0, T]$ and $n \geq n_0$. Now, due to (6.13), (6.14) and the dominated convergence theorem we can conclude that

$$J(x^{(n)}, \rho^{(n)}) = \int_0^T j(\rho^{(n)}(s), r(\cdot, \cdot | x^{(n)}(s), s)) ds \rightarrow \int_0^T j(\rho(s), r(\cdot, \cdot | x(s), s)) ds = J(x, \rho),$$

thus implying (6.11).

7. PROOF OF THEOREM 2.5

We first prove that the family $R_{x_0, \sigma_0}^\lambda$ is relatively compact and then characterize its limit points.

• *Relative compactness.* We use Prohorov theorem and Aldous compactness criterion (see for example [KL][Section 4.1]). Since $\Gamma^{(\ell)}$ is compact (endowed with the discrete topology), we only have to check that

(1) For each $t \in [0, T]$ and $\varepsilon > 0$, there exists a compact $\mathcal{K} \subset \mathbb{R}^d$ such that

$$R_{x_0, \sigma_0}^\lambda(x(t) \in \mathcal{K}) = P_{x_0, \sigma_0}^\lambda(x(t) \in \mathcal{K}) \leq \varepsilon, \quad \forall \lambda > 0, \quad (7.1)$$

(2) and that

$$\lim_{\theta \downarrow 0} \limsup_{\lambda \uparrow \infty} \sup_{\tau} R_{x_0, \sigma_0}^\lambda \left(|x(\tau) - x((\tau + \theta) \wedge T)| > \varepsilon \right. \\ \left. \text{or } \alpha(\tau) \neq \alpha((\tau + \theta) \wedge T) \right) = 0, \quad (7.2)$$

where τ varies among all stopping times bounded by T .

As observed in Lemma C.1, there exists a compact $\mathcal{K} \subset \mathbb{R}^d$ such that $x(t) \in \mathcal{K}$ for all $t \in [0, T]$ $P_{x_0, \sigma_0}^\lambda$ -a.s. and for all $\lambda > 0$. Since $|x(t) - x(s)| = \left| \int_s^t F_{\sigma(u)}(x(u), u) du \right|$, we conclude that there exists a positive constant $c > 0$ such that $|x(t) - x(s)| \leq c(t - s)$ for all $s < t$ in $[0, T]$, $P_{x_0, \sigma_0}^\lambda$ -a.s. and for all $\lambda > 0$. Hence, we only need to prove that

$$\lim_{\theta \downarrow 0} \limsup_{\lambda \uparrow \infty} \sup_{\tau} R_{x_0, \sigma_0}^\lambda \left(\alpha(\tau) \neq \alpha((\tau + \theta) \wedge T) \right) = 0. \quad (7.3)$$

Below we restrict to $\theta \in [0, 1]$, moreover we use the shorter notation $\tau_\theta := (\tau + \theta) \wedge T$. We can write

$$R_{x_0, \sigma_0}^\lambda \left(\alpha(\tau) \neq \alpha((\tau + \theta) \wedge T) \right) = E_{x_0, \sigma_0}^\lambda \left[P_{x_0, \sigma_0}^\lambda \left(\alpha(\tau) \neq \alpha(\tau_\theta) \mid x(\tau), \sigma(\tau), \tau \right) \right]. \quad (7.4)$$

Due to the strong Markov property of PDMPs, we can bound

$$P_{x_0, \sigma_0}^\lambda \left(\alpha(\tau) \neq \alpha(\tau_\theta) \mid x(\tau) = x, \sigma(\tau) = \sigma, \tau = t \right) \leq \\ P_{x_0, \sigma_0}^\lambda \left(\exists s \in (\tau, \tau_\theta] \text{ s.t. } \alpha(s) \neq \alpha(\tau) \mid x(\tau) = x, \sigma(\tau) = \sigma, \tau = t \right) \leq \\ P_{x, \sigma, t}^\lambda \left(\exists s \in (t, (t + \theta) \wedge T] \text{ s.t. } \sigma(s) \notin \Gamma_{\alpha(\sigma)} \right), \quad (7.5)$$

where $P_{x, \sigma, t}^\lambda$ denotes the law of the λ -rescaled PDMP starting in (x, σ) at time t .

Due to the discussion at the beginning, we know that $x(\tau)$ belongs to \mathcal{K} , thus implying that in the above expression we can restrict to points x belonging to \mathcal{K} . Similarly, starting in $x \in \mathcal{K}$ the λ -rescaled process with law $P_{x, \sigma, t}^\lambda$ cannot leave a fixed compact \mathcal{K}' (independent of λ, x, σ, t) in time $\theta \leq 1$. Hence, defining

$$c := \sup_{x' \in \mathcal{K}'} \sup_{u \in [0, T]} \max_{\sigma_1 \in \Gamma} \sum_{\sigma_2 \in \Gamma: \sigma_2 \neq \sigma_1} r(\sigma_1, \sigma_2 \mid x', u),$$

the number N of chemical jumps for the process $P_{x, \sigma, t}^\lambda$ in the interval $(t, (t + \theta) \wedge T]$ is stochastically dominated by a Poisson variable \widehat{N} of mean $c\lambda\theta$, uniformly in $(x, \sigma, t) \in \mathcal{K} \times \Gamma \times [0, T]$ and $\lambda \geq 1$. By similar arguments, whenever the process with law $P_{x, \sigma, t}^\lambda$ makes a chemical jump in the time interval $(t, (t + \theta) \wedge T]$, the probability that the jump is between different chemical metastates is bounded from above by C/λ , C not depending on $(x, \sigma, t) \in \mathcal{K} \times \Gamma \times [0, T]$, $\lambda \geq 1$. Therefore, conditioned to make n chemical jumps in

the time interval $(t, (t + \theta) \wedge T]$, the probability that at least one jump is between different chemical metastates is bounded from above by Cn/λ . Hence, we can estimate

$$P_{x,\sigma,t}^\lambda (\exists s \in [t, (t + \theta) \wedge T] \text{ s.t. } \sigma(s) \notin \Gamma_{\alpha(\sigma)}) \leq \sum_{n=1}^{\infty} P_{x,\sigma,t}^\lambda (N = n) Cn/\lambda \leq \sum_{n=1}^{\infty} P(\hat{N} = n) Cn/\lambda = (C/\lambda) E(\hat{N}) = cC\theta. \quad (7.6)$$

This allows to bound the r.h.s. of (7.5) by $cC\theta$ uniformly in $\lambda \geq 1$, thus implying the same bound for the first expression in (7.4). This concludes the proof of (7.3) and therefore the proof of the relative compactness of $\{R_{x_0,\sigma_0}^\lambda\}_{\lambda>0}$.

• *Characterization of the limit points.* Given a path $\sigma(t)$, define the times T_1, T_2, \dots as the consecutive times in $[0, T]$ at which the system jumps between different metastates, i.e.

$$T_1 = \inf \{t \in [0, T] : \alpha(\sigma(t)) \neq \alpha(\sigma(0))\}, \\ T_k = \inf \{t \in (T_{k-1}, T] : \alpha(\sigma(t)) \neq \alpha(\sigma(T_{k-1}))\}, \quad k \geq 2,$$

with the convention that $T_k = \infty$ if k is larger than the number of jumps in the time interval $[0, T]$ between different metastates. Fix $(x_0, \sigma_0) \in \mathbb{R}^d \times \Gamma$, a sequence $0 < t_1 < t_2 < \dots < t_n < T$ and fix $\sigma_1, \sigma_2, \dots, \sigma_n$ such that $\alpha(\sigma_i) \neq \alpha(\sigma_{i+1})$ for each $i = 0, 1, \dots, n-1$. In addition, fix $\delta > 0$ and $\varepsilon > 0$ small enough that $\varepsilon < T - t_n$ and $\varepsilon < t_{i+1} - t_i$ for each $i = 0, 1, \dots, n-1$, where $t_0 := 0$. Then define the event

$$\mathcal{A} = \{T_k \in (t_k - \varepsilon, t_k + \varepsilon) \text{ and } \sigma(T_k) = \sigma_k, \forall k = 1, 2, \dots, n\} \cap \left\{ \sup_{t \leq T_n} |x(t) - x_*(t)| < \delta \right\}, \quad (7.7)$$

where the path $(x_*(t) : t \in [0, T_n])$ is the only continuous path in \mathbb{R}^d such that

$$\dot{x}_*(t) = F_{\alpha(\sigma_k)}(x_*(t), t) \quad \forall t \in [T_k, T_{k+1}], \quad k = 0, 1, \dots, n-1. \quad (7.8)$$

In the above formula $T_0 := 0$ and the vector field F_i for $i \in \Gamma^{(\ell)}$ is the one defined in (2.33). We claim that

$$\lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda(\mathcal{A}) = \int_U du_1 du_2 \dots du_n \prod_{k=0}^{n-1} \left(e^{-\int_{u_k}^{u_{k+1}} \gamma_{\alpha(\sigma_k)}(x_*(s), s) ds} \times \sum_{\hat{\sigma}_k \in \Gamma_{\alpha(\sigma_k)}} \mu_{\alpha(\sigma_k)}(\hat{\sigma}_k | x_*(u_{k+1}), u_{k+1}) r(\hat{\sigma}_k, \sigma_{k+1} | x_*(u_{k+1}), u_{k+1}) \right), \quad (7.9)$$

where $u_0 := 0$, $U := \prod_{i=1}^n (t_i - \varepsilon, t_i + \varepsilon)$ and

$$\gamma_i(x, s) := \sum_{j \in \Gamma^{(\ell)} : j \neq i} r(i, j | x, s), \quad i \in \Gamma^{(\ell)}. \quad (7.10)$$

We first prove the above claim for $n = 1$. For simplicity of notation we write t in place of t_1 and σ' in places of σ_1 , while we call $\sigma_0, \sigma_1, \sigma_2, \dots, \sigma_r$ the finite sequence of states in $\Gamma_{\alpha(\sigma_0)}$ visited by the process before jumping to σ' . Then, defining now

$$\mathcal{A} = \left\{ T_1 \in (t - \varepsilon, t + \varepsilon), \sigma(T_1) = \sigma', \sup_{s \leq T_1} |x(s) - x_*(s)| < \delta \right\}, \quad (7.11)$$

we can write

$$\begin{aligned}
P_{x_0, \sigma_0}^\lambda(\mathcal{A}) &= \sum_{r=0}^{\infty} \sum_{\sigma_1, \sigma_2, \dots, \sigma_r} \int_{t-\varepsilon}^{t+\varepsilon} du \int_0^u d\tau_1 \int_{\tau_1}^u d\tau_2 \cdots \int_{\tau_{r-1}}^u d\tau_r \\
&\quad \exp \left\{ - \sum_{k=0}^r \int_{\tau_k}^{\tau_{k+1}} [\lambda \hat{\gamma}_{\sigma_k}(\tilde{x}(s), s) + b_{\sigma_k}(\tilde{x}(s), s)] ds \right\} \\
&\quad \left[\prod_{k=0}^{r-1} \lambda r(\sigma_k, \sigma_{k+1} | \tilde{x}(\tau_{k+1}), \tau_{k+1}) \right] r(\sigma_r, \sigma' | \tilde{x}(u), u) \chi \left(\sup_{s \leq u} |\tilde{x}(s) - x_*(s)| < \delta \right), \quad (7.12)
\end{aligned}$$

where in the above expression $\tau_0 := 0$, $\tau_{r+1} := u$, $\{\tilde{x}(s) : s \in [0, u]\}$ is the only continuous path on $[0, u]$ starting in x_0 such that

$$\dot{\tilde{x}}(s) = F_{\sigma_k}(\tilde{x}(s), s), \quad \forall s \in (\tau_k, \tau_{k+1}), \quad \forall k = 0, 1, \dots, r$$

and, for $\sigma \in \Gamma_{\alpha(\sigma_0)}$,

$$\begin{aligned}
\hat{\gamma}_\sigma(x, s) &= \sum_{\hat{\sigma} \in \Gamma_{\alpha(\sigma_0)}} r(\sigma, \hat{\sigma} | x, s), \\
b_\sigma(x, s) &= \sum_{\hat{\sigma} \in \Gamma \setminus \Gamma_{\alpha(\sigma_0)}} r(\sigma, \hat{\sigma} | x, s).
\end{aligned}$$

Let us call $\hat{P}_{x_0, \sigma_0}^\lambda$ the λ -rescaled PDMP with chemical states in $\Gamma_{\alpha(\sigma_0)}$, transition rates $\lambda r(\sigma, \sigma' | x, s)$ and vector fields $F_\sigma(x, s)$, $\sigma, \sigma' \in \Gamma_{\alpha(\sigma_0)}$. We write $\hat{E}_{x_0, \sigma_0}^\lambda$ for the associated expectation. Then it is simple to check that the r.h.s. of (7.12) equals

$$\hat{E}_{x_0, \sigma_0}^\lambda \left[\int_{t-\varepsilon}^{t+\varepsilon} du \exp \left\{ - \int_0^u b_{\sigma(s)}(x(s), s) ds \right\} r(\sigma(u), \sigma' | x(u), u) \chi \left(\sup_{s \leq u} |x(s) - x_*(s)| < \delta \right) \right]. \quad (7.13)$$

(Above we have used that $\sigma(u) = \sigma(u-)$ $\hat{P}_{x_0, \sigma_0}^\lambda$ -a.s.) One can compute the limit of (7.13) as $\lambda \uparrow \infty$ by means of the LLN given in Theorem 2.2, applied to $\hat{P}_{x_0, \sigma_0}^\lambda$. Indeed, we know that for each $\beta > 0$ $\hat{P}_{x_0, \sigma_0}^\lambda(\sup_{s \leq t+\varepsilon} |x(s) - x_*(s)| < \beta) \rightarrow 1$. This allows to write

$$P_{x_0, \sigma_0}^\lambda(\mathcal{A}) = \hat{E}_{x_0, \sigma_0}^\lambda \left[\int_{t-\varepsilon}^{t+\varepsilon} du \exp \left\{ - \int_0^u b_{\sigma(s)}(x_*(s), s) ds \right\} r(\sigma(u), \sigma' | x_*(u), u) \right] + o(1),$$

where here and below we denote $o(1)$ any quantity such that

$$\lim_{\beta \downarrow 0} \limsup_{\lambda \uparrow \infty} o(1) = 0.$$

It is simple to derive from Theorem 2.2 that

$$\lim_{\lambda \uparrow \infty} \hat{P}_{x_0, \sigma_0}^\lambda \left(\sup_{t-\varepsilon \leq u \leq t+\varepsilon} \left| \int_0^u b_{\sigma(s)}(x_*(s), s) ds - \int_0^u \gamma_{\alpha(\sigma_0)}(x_*(s), s) ds \right| > \beta \right) = 0,$$

since (recall (7.10))

$$\begin{aligned}
\gamma_{\alpha(\sigma_0)}(x_*(s), s) &= \sum_{\hat{\sigma} \in \Gamma_{\alpha(\sigma_0)}} \sum_{\tilde{\sigma} \in \Gamma \setminus \Gamma_{\alpha(\sigma_0)}} \mu_{\alpha(\sigma_0)}(\hat{\sigma} | x_*(s), s) r(\hat{\sigma}, \tilde{\sigma} | x_*(s), s) \\
&= \sum_{\hat{\sigma} \in \Gamma_{\alpha(\sigma_0)}} \mu_{\alpha(\sigma_0)}(\hat{\sigma} | x_*(s), s) b_{\hat{\sigma}}(x_*(s), s).
\end{aligned}$$

Hence we can write

$$P_{x_0, \sigma_0}^\lambda(\mathcal{A}) = \widehat{E}_{x_0, \sigma_0}^\lambda \left[\int_{t-\varepsilon}^{t+\varepsilon} du \exp \left\{ - \int_0^u \gamma_{\alpha(\sigma_0)}(x_*(s), s) ds \right\} r(\sigma(u), \sigma' | x_*(u), u) \right] + o(1),$$

At this point, one can apply again Theorem 2.2 and conclude that

$$P_{x_0, \sigma_0}^\lambda(\mathcal{A}) = \sum_{\widehat{\sigma} \in \Gamma_{\alpha(\sigma_0)}} \int_{t-\varepsilon}^{t+\varepsilon} du \exp \left\{ - \int_0^u \gamma_{\alpha(\sigma_0)}(x_*(s), s) ds \right\} \mu_{\alpha(\sigma_0)}(\widehat{\sigma} | x_*(u), u) r(\widehat{\sigma}, \sigma' | x_*(u), u) + o(1).$$

By taking the limit $\lambda \uparrow \infty$ and afterwards using the arbitrariness of β , we then obtain

$$\begin{aligned} \lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda(\mathcal{A}) &= \\ &= \sum_{\widehat{\sigma} \in \Gamma_{\alpha(\sigma_0)}} \int_{t-\varepsilon}^{t+\varepsilon} du \exp \left\{ - \int_0^u \gamma_{\alpha(\sigma_0)}(x_*(s), s) \right\} \mu_{\alpha(\sigma_0)}(\widehat{\sigma} | x_*(u), u) r(\widehat{\sigma}, \sigma' | x_*(u), u). \end{aligned} \quad (7.14)$$

This concludes the proof of (7.9) when $n = 1$. Let us now show how to prove (7.9) when the event \mathcal{A} is defined as in (7.7) with $n = 2$. The general case is completely similar. By the strong Markov property, we can write

$$P_{x_0, \sigma_0}^\lambda(\mathcal{A}) = E_{x_0, \sigma_0}^\lambda \left[\chi \left\{ T_1 \in (t_1 - \varepsilon, t_1 + \varepsilon), \sigma(T_1) = \sigma_1, \sup_{t \leq T_1} |x(t) - x_*(t)| \leq \delta \right\} f^\lambda(x(T_1), \sigma_1, T_1) \right], \quad (7.15)$$

where, for $s \leq t_2 - \varepsilon$,

$$f^\lambda(x', \sigma', s) := P_{x', \sigma', s}^\lambda \left(T_1 \in (t_2 - \varepsilon, t_2 + \varepsilon), \sigma(T_1) = \sigma_2, \sup_{s \leq t \leq T_1} |x(t) - z_*(t)| \leq \delta \right),$$

$z_*(t)$ being the path starting in x' at time s , such that $\dot{z}_*(t) = F_{\alpha(\sigma')}(z_*(t), t)$. Due to (7.14) with modified starting state and starting time, we know that $f^\lambda(x', \sigma', s)$ converges to $g(x', \sigma', s)$ defined as

$$g(x', \sigma', s) := \sum_{\widehat{\sigma} \in \Gamma_{\alpha(\sigma')}} \int_{t_2-\varepsilon}^{t_2+\varepsilon} du \exp \left\{ - \int_s^u \gamma_{\alpha(\sigma')}(x_*(s), s) \right\} \mu_{\alpha(\sigma')}(\widehat{\sigma} | x_*(u), u) r(\widehat{\sigma}, \sigma_2 | x_*(u), u). \quad (7.16)$$

By simple arguments (as the ones used in the proof of Lemma 5.1) one can improve (7.14) and conclude that, given a compact \mathcal{K} ,

$$\lim_{\lambda \uparrow \infty} \sup_{x' \in \mathcal{K}, \sigma' \in \Gamma, s \in [0, t_2 - \varepsilon]} \left| f^\lambda(x', \sigma', s) - g(x', \sigma', s) \right| = 0.$$

This allows to replace in (7.15), $f^\lambda(x(T_1), \sigma_1, T_1)$ with $g(x(T_1), \sigma_1, T_1)$ plus a negligible error as $\lambda \uparrow \infty$. The conclusion of the proof of (7.9) for $n = 2$ follows now from the LLN of Theorem 2.2 by the same arguments used in the proof of (7.14).

Having proved (7.9), we derive from it the following fact. Fix $(x_0, \sigma_0) \in \mathbb{R}^d \times \Gamma$, a sequence $0 < t_1 < t_2 < \dots < t_n < T$ and fix $i_1, i_2, \dots, i_n \in \Gamma^{(\ell)}$ such that $i_k \neq i_{k+1}$ for each $k = 0, 1, \dots, n-1$ ($i_0 := \alpha(\sigma_0)$). In addition, fix $\delta > 0$ and $\varepsilon > 0$ small enough that

$\varepsilon < T - t_n$ and $\varepsilon < t_{i+1} - t_i$ for each $i = 0, 1, \dots, n-1$ where $t_0 := 0$. Then define the event $\mathcal{C} = \mathcal{C}(\varepsilon, \delta)$ as

$$\mathcal{C} = \{T_k \in (t_k - \varepsilon, t_k + \varepsilon) \text{ and } \alpha(\sigma(T_k)) = i_k, \forall k = 1, 2, \dots, n\} \cap \left\{ \sup_{t \leq T_n} |x(t) - x_*(t)| < \delta \right\}, \quad (7.17)$$

where the path $(x_*(t) : t \in [0, T_n])$ is the only continuous path in \mathbb{R}^d such that

$$\dot{x}_*(t) = F_{i_k}(x_*(t), t) \quad \forall t \in [T_k, T_{k+1}], \quad k = 0, 1, \dots, n-1. \quad (7.18)$$

Then, summing in (7.9) over $\sigma_1, \sigma_2, \dots, \sigma_n$, we obtain

$$\lim_{\lambda \uparrow \infty} P_{x_0, \sigma_0}^\lambda(\mathcal{C}) = \int_U du_1 du_2 \dots du_n \prod_{k=0}^{n-1} \left(e^{-\int_{u_k}^{u_{k+1}} \gamma_{i_k}(x_*(s), s) ds} r(i_k, i_{k+1} | x_*(u_{k+1}), u_{k+1}) \right). \quad (7.19)$$

Since \mathcal{C} is an open subset of the Skohorod space $D([0, T], \mathbb{R}^d \times \Gamma^{(\ell)})$, we derive that for any limit point \mathcal{R} of the family $\{\mathcal{R}_{x_0, \alpha(\sigma_0)}^\lambda : \lambda > 0\}$ the probability $\mathcal{R}(\mathcal{C})$ is not larger than the r.h.s. of (7.19). By similar arguments, one obtains that the limit $P_{x_0, \sigma_0}^\lambda(\mathcal{C}')$ coincides with the r.h.s. of (7.19), where the event $\mathcal{C}' = \mathcal{C}'(\varepsilon, \delta)$ is defined as

$$\mathcal{C}' = \{T_k \in [t_k - \varepsilon, t_k + \varepsilon] \text{ and } \alpha(\sigma(T_k)) = i_k, \forall k = 1, 2, \dots, n\} \cap \left\{ \sup_{t \leq T_n} |x(t) - x_*(t)| \leq \delta \right\}. \quad (7.20)$$

Since \mathcal{C}' is closed, we derive that $\mathcal{R}(\mathcal{C}')$ is not smaller than the r.h.s. of (7.19). On the other hand, $\mathcal{C}'(\varepsilon', \delta') \subset \mathcal{C}(\varepsilon, \delta)$ for $\varepsilon' < \varepsilon$ and $\delta' < \delta$, hence $\mathcal{R}(\mathcal{C}'(\varepsilon', \delta')) \leq \mathcal{R}(\mathcal{C}(\varepsilon, \delta))$. By taking the limits $\varepsilon' \rightarrow \varepsilon$ and $\delta' \rightarrow \delta$, the above observations implies that

$$\mathcal{R}(\mathcal{C}) = \int_U du_1 du_2 \dots du_n \prod_{k=0}^{n-1} \left(e^{-\int_{u_k}^{u_{k+1}} \gamma_{i_k}(x_*(s), s) ds} r(i_k, i_{k+1} | x_*(u_{k+1}), u_{k+1}) \right). \quad (7.21)$$

The above family of identities parameterized by t_1, \dots, t_n , ε and δ allows to conclude that there exists a unique limit point and it must coincide with the law of the PDMP described in Theorem 2.5.

APPENDIX A. SOME TOPOLOGICAL PROPERTIES OF THE SPACE Υ

For the reader's convenience, in this Appendix we collect some properties of the metric space Υ that are used in the text. We stress that the definition of Υ given in (2.20) depends on the fixed initial mechanical state x_0 . We call $\mathcal{M}_*[0, T] \subset \mathcal{M}[0, T]$ the image of the map $L[0, T] \ni f \rightarrow f(t)dt \in \mathcal{M}[0, T]$ and we define $\mathcal{M}_*[0, T]^{\Gamma, 1}$ as the set of positive measures $(\rho_\sigma(t)dt)_{\sigma \in \Gamma}$ such that $\sum_{\sigma \in \Gamma} \rho_\sigma(t) = 1$ a.e.

Lemma A.1. *Given $\rho \in \mathcal{M}_*[0, T]^{\Gamma, 1}$, there exists a unique $x(t) \in C[0, T]$ such that*

$$x(t) = x_0 + \sum_{\sigma \in \Gamma} \int_0^t F_\sigma(x(s), s) \rho_\sigma(s) ds \quad \forall t \in [0, T]. \quad (A.1)$$

Moreover, the map that associates to each $\rho \in \mathcal{M}_[0, T]^{\Gamma, 1}$ the unique element $x(t) \in C([0, T])$ satisfying (A.1) is continuous.*

Proof. Due to (2.8), if $x(t)$ solves (A.1) it must be $|x(t)| \leq |x_0| + c_1 t + c_2 \int_0^t |x(s)| ds$. Then, applying Gronwall inequality, the path $x(t)$ must lie inside a compact \mathcal{K} , depending only on x_0 . We fix the constant K as in (2.7).

Let us define \mathcal{Q} as the subset

$$\mathcal{Q} := \{\rho \in \mathcal{M}_*[0, T]^{\Gamma, 1} : \rho_\sigma \in C[0, T] \forall \sigma \in \Gamma\}.$$

It is simple to check that \mathcal{Q} is dense in $\mathcal{M}_*[0, T]^{\Gamma, 1}$. Indeed, by using mollifiers, one can show that for each $\sigma \in \Gamma$ there exists a sequence $\rho_\sigma^{(n)}(s) \in C[0, T]$ such that $\rho_\sigma^{(n)}(s)$ converges to $\rho_\sigma(s)$ in $L^1[0, T]$ as $n \uparrow \infty$. At cost to normalize, we can assume that $\sum_\sigma \rho_\sigma^{(n)}(s) = 1$ for each $s \in [0, T]$.

If $\rho \in \mathcal{Q}$, existence and uniqueness of (A.1) can be proven by the same arguments used in the proof of Lemma 2.1, given in Appendix C. In order to prove existence for (A.1) when $\rho \in \mathcal{M}_*[0, T]^{\Gamma, 1}$, we take a sequence $\rho^{(n)} \in \mathcal{Q}$ such that $\rho_\sigma^{(n)}$ converges to ρ_σ in $L^1[0, T]$ as $n \uparrow \infty$. Consider the solutions $x^{(n)}(t) \in C[0, T]$ associated to $\rho^{(n)}$. We can bound

$$\sum_{\sigma \in \Gamma} \left| \int_0^t [\rho_\sigma^{(n)}(s) - \rho_\sigma^{(m)}(s)] F_\sigma(x^{(n)}(s), s) ds \right| \leq K_1 \sum_{\sigma \in \Gamma} \int_0^T |\rho_\sigma^{(n)}(s) - \rho_\sigma^{(m)}(s)| ds =: C_{n,m},$$

where $K_1 := \max_\sigma \max_{x \in \mathcal{K}, t \in [0, T]} |F_\sigma(x, t)|$. Due to (2.7) we can estimate

$$|x^{(n)}(t) - x^{(m)}(t)| \leq C_{n,m} + K \int_0^t |x^{(n)}(s) - x^{(m)}(s)| ds. \quad (\text{A.2})$$

Due to Gronwall lemma, we conclude that $\|x^{(n)}(t) - x^{(m)}(t)\|_\infty \leq C_{n,m} e^{KT}$. Since $C_{n,m}$ is arbitrarily small for n, m large, we conclude that the sequence $x^{(n)}$ is a Cauchy sequence in $C[0, T]$, and therefore it converges to some path $x \in C[0, T]$. Taking the limit $n \rightarrow \infty$ for equation (A.1) with x, ρ replaced respectively by $x^{(n)}, \rho^{(n)}$, due to the Dominated Convergence Theorem one concludes that $x(t)$ solves (A.1). Uniqueness follows from Gronwall inequality, since given two solutions $x_1(t)$ and $x_2(t)$ of (A.1) it must be $|x_1(t) - x_2(t)| \leq K \int_0^t |x_1(s) - x_2(s)| ds$.

Finally let us prove the continuity of the map $\mathcal{M}_*[0, T]^{\Gamma, 1} \ni \rho(t) \rightarrow x(t) \in C[0, T]$. We introduce a metric D on $\mathcal{M}_*[0, T]$ defined as

$$D(f_1(t)dt, f_2(t)dt) = \sup_{t \in [0, T]} \left| \int_0^t [f_1(s) - f_2(s)] ds \right|, \quad f_1, f_2 \in L[0, T]. \quad (\text{A.3})$$

It is simple to check that D is a distance on $\mathcal{M}_*[0, T]$. We claim that the topology induced by D coincides with the weak topology of $\mathcal{M}_*[0, T]$. To this aim, we only need to show that $D(f_n(t)dt, f(t)dt) \rightarrow 0$ if and only if $\int_0^T f_n(t)g(t)dt \rightarrow \int_0^T f(t)g(t)dt$ for each $g \in C[0, T]$. Given $h \in L[0, T]$ let $\hat{h}(t) = \int_0^t h(s)ds$ for $0 \leq t \leq T$. Since \hat{h} is a function of bounded variation, it is simple to check that $D(f_n(t)dt, f(t)dt) \rightarrow 0$ if and only if $\hat{f}_n(t) \rightarrow \hat{f}(t)$ for each $t \in [0, T]$. The proof that the weak convergence $f_n(t)dt \rightarrow f(t)dt$ coincides with the pointwise convergence of \hat{f}_n to \hat{f} follows the same arguments leading to the equivalence between the weak convergence of probability measures and the pointwise convergence of the associated distribution functions.

Take a sequence $\rho^{(n)} \in \mathcal{M}_*[0, T]^{\Gamma, 1}$ converging to some $\rho \in \mathcal{M}_*[0, T]^{\Gamma, 1}$. Consider also the corresponding $x^{(n)}(t), x(t) \in C[0, T]$ obtained from (A.1). Setting

$$C_n(t) := \sum_{\sigma \in \Gamma} \left| \int_0^t [\rho_\sigma^{(n)}(s) - \rho_\sigma(s)] F_\sigma(x(s), s) ds \right|,$$

due to (2.7) in assumption (A4) we have

$$|x^{(n)}(t) - x(t)| \leq C_n(t) + \sum_{\sigma \in \Gamma} \int_0^t \rho_\sigma^{(n)}(s) |F_\sigma(x(s), s) - F_\sigma(x^{(n)}(s), s)| ds \leq C_n(t) + K \int_0^t |x^{(n)}(s) - x(s)| ds. \quad (\text{A.4})$$

Since $\rho_\sigma^{(n)}(s)ds$ weakly converges to $\rho_\sigma(s)ds$ on $[0, T]$ and therefore on $[0, t]$ and since $F_\sigma(x(s), s)$ is continuous in s , from the previous results on the metric D we conclude that $C_n(t) \rightarrow 0$ as $n \rightarrow \infty$ uniformly in $t \in [0, T]$. Due to the above observations we conclude that for each $\delta > 0$ there exists n_0 such that for each $t \in [0, T]$ and $n \geq n_0$ it holds

$$|x^{(n)}(t) - x(t)| \leq \delta + K \int_0^t |x^{(n)}(s) - x(s)| ds.$$

By Gronwall lemma it follows that $\|x^{(n)} - x\|_\infty \leq \delta e^{KT}$ for all $n \geq n_0$. This implies that $x^{(n)}(t)$ converges to $x(t)$ in the uniform norm of $C[0, T]$. \square

Lemma A.2. *The space Υ is a compact Polish metric space.*

Proof. First we prove that $\mathcal{M}_*[0, T]^\Gamma, 1$ is compact. It is a subset of the compact space $\{\rho \in \mathcal{M}[0, T]^\Gamma : \rho_\sigma[0, T] \leq T \forall \sigma \in \Gamma\}$, so that we just need to prove that it is closed. We first prove that $\mathcal{M}_*[0, T]$ is closed. To this aim, let μ_n be a sequence in $\mathcal{M}_*[0, T]$ converging to $\mu \in \mathcal{M}[0, T]$. Since given $g \in C[0, T]$ it holds $|\mu_n(g)| \leq \int_0^T |g(t)| dt$, by taking the limit we conclude that $|\mu(g)| \leq \|g\|_{L^1[0, T]}$. By density we obtain that the map $L^1[0, T] \ni g \rightarrow \mu(g) \in \mathbb{R}$ is a continuous linear functional with norm bounded by 1. Since the dual space of $L^1[0, T]$ is given by $L^\infty[0, T]$ endowed of the essential uniform norm, we can conclude that there exists $h \in L^\infty[0, T]$ with $\|h\|_\infty \leq 1$ such that $\mu(g) = \int_0^T g(t)h(t)dt$ for all $g \in C[0, T]$. Since $\mu(g) = \lim_{n \uparrow \infty} \mu_n(g) \geq 0$ for all $g \in C[0, T]$ with $g \geq 0$, the function h must be nonnegative a.e. This proves that $\mu \in \mathcal{M}_*[0, T]$ and $d\mu/dt = h$. Hence $\mathcal{M}_*[0, T]$ is a closed subspace of $\mathcal{M}[0, T]$. Consider now a sequence $\rho^{(n)} \in \mathcal{M}_*[0, T]^\Gamma, 1$ converging to ρ . Then necessarily for every $\sigma \in \Gamma$ it holds $\rho_\sigma \in \mathcal{M}_*[0, T]$. Moreover for each $g \in C[0, T]$ it holds

$$\int_0^T g(s)ds = \sum_{\sigma \in \Gamma} \int_0^T \rho_\sigma^{(n)}(s)g(s)ds \rightarrow \sum_{\sigma \in \Gamma} \int_0^T \rho_\sigma(s)g(s)ds = \int_0^T \left(\sum_{\sigma \in \Gamma} \rho_\sigma(s) \right) g(s)ds.$$

This implies that

$$\int_0^T g(s)ds = \int_0^T \left(\sum_{\sigma \in \Gamma} \rho_\sigma(s) \right) g(s)ds, \quad \forall g \in C[0, T].$$

Hence, $\sum_{\sigma \in \Gamma} \rho_\sigma(s) = 1$ a.s. and this means that $\rho \in \mathcal{M}_*[0, T]^\Gamma, 1$.

Compactness of $\Upsilon \subseteq \mathcal{M}[0, T] \times C[0, T]$ follows from the fact that it is the graph of a continuous function defined on a compact domain $\mathcal{M}_*[0, T]^\Gamma, 1 \subseteq \mathcal{M}[0, T]$. Completeness and separability of Υ follow from the fact that Υ can be thought as a closed subset of the space $C[0, T] \times \mathcal{M}[0, T]^\Gamma$, which is complete and separable. \square

Lemma A.3. *The set \mathcal{B} defined as*

$$\mathcal{B} = \{(x, \rho) \in \Upsilon : \rho_\sigma \in C^1[0, T] \text{ and } \rho_\sigma(t) > 0 \forall \sigma \in \Gamma, t \in [0, T]\}$$

is a dense subset of Υ .

Proof. Fix $(x, \rho) \in \Upsilon$. Then, by using mollifiers, one can show that for each $\sigma \in \Gamma$ there exists a sequence $\rho_\sigma^{(n)}(s) \in C^1[0, T]$ such that $\rho_\sigma^{(n)}(s)$ converges to $\rho_\sigma(s)$ in $L^1[0, T]$ as $n \uparrow \infty$. At cost to take $\max\{1/n, \rho_\sigma^{(n)}(s)\}$ we can assume that $\rho_\sigma^{(n)}$ is positive; at cost to normalize, we can assume that $\sum_\sigma \rho_\sigma^{(n)}(s) = 1$ for each $s \in [0, T]$. Since L^1 -convergence is stronger than $L[0, T]$ -convergence (where $L[0, T]$ is endowed with the metric defined by the r.h.s. of (A.3)), we obtain that $\rho_\sigma^{(n)}$ converges to ρ_σ in $L[0, T]$ as $n \uparrow \infty$. Let us call $x^{(n)}$ the solution of the Cauchy problem

$$\begin{cases} \dot{x}^{(n)}(t) = \sum_{\sigma \in \Gamma} \rho_\sigma^{(n)}(t) F_\sigma(x^{(n)}(t), t) & t \in [0, T], \\ x^{(n)}(0) = x_0. \end{cases}$$

Note that $x^{(n)}$ is well defined due to Lemma A.1. Then $(x^{(n)}, \rho^{(n)})$ belongs to \mathcal{B} and from Lemma A.1 we have that $\|x^{(n)} - x\|_\infty \rightarrow 0$. \square

APPENDIX B. A UNIFORM LARGE DEVIATION ESTIMATE

In this appendix we prove formula (5.13), keeping the same notation introduced in the proof of Lemma 5.1. Formula (5.13) follows immediately from the next lemma, valid under the assumptions stated in Section 2.

Lemma B.1. *For any $\delta > 0$ it holds*

$$\limsup_{u \rightarrow \infty} \sup_{(x,t) \in \mathcal{K}' \times [0, T], \sigma, \sigma' \in \Gamma} \frac{1}{u} \ln Q_{\sigma', x, t} \left[\left| \frac{1}{u} \int_0^u [\chi(\sigma(s) = \sigma) - \mu(\sigma|x, t)] ds \right| \geq \delta \right] < 0. \quad (\text{B.1})$$

Proof. We fix some notation. We call $\rho^{(u)}$ the empirical measure in the time interval $[0, u]$ defined as

$$\rho_\sigma^{(u)} := \frac{1}{u} \int_0^u \chi(\sigma(s) = \sigma) ds \quad \forall \sigma \in \Gamma.$$

This is an element of $\mathcal{M}^1(\Gamma)$, the set of probability measures on Γ . Moreover, we write $\mathcal{E} := \mathcal{K}' \times [0, T] \times \mathcal{M}^1(\Gamma)$. Note that \mathcal{E} is a Polish space. For any fixed $\sigma' \in \Gamma$ and for any time u we call $\widehat{Q}_{\sigma'}^u$ the map that associates to any measurable subset $S \subseteq \mathcal{E}$ the nonnegative number

$$\widehat{Q}_{\sigma'}^u(S) := \sup_{(x,t) \in \mathcal{K}' \times [0, T]} Q_{\sigma', x, t} \left(\left\{ (x, t, \rho^{(u)}) \in S \right\} \right) = \sup_{(x,t) \in \mathcal{K}' \times [0, T]} Q_{\sigma', x, t} \left(\rho^{(u)} \in S_{(x,t)} \right),$$

where $S_{(x,t)} := \{\rho \in \mathcal{M}^1(\Gamma) : (x, t, \rho) \in S\}$.

In order to obtain upper bounds on $\widehat{Q}_{\sigma'}^u(S)$, we proceed as follows. Given an arbitrary function $V : \Gamma \rightarrow \mathbb{R}$ we introduce, likewise in (6.1), the perturbed rate for a jump from σ to another chemical state σ' as

$$r^V(\sigma, \sigma'|x, t) := r(\sigma, \sigma'|x, t) e^{V_{\sigma'} - V_\sigma}. \quad (\text{B.2})$$

The law of the Markov chain on Γ with the above perturbed rates and with initial condition σ' is called $Q_{\sigma', x, t}^V$. Using a result analogous to (6.3) in this simpler framework and using

the notation introduced in Section 4, we obtain that

$$\begin{aligned}
\limsup_{u \rightarrow \infty} \frac{1}{u} \ln \left[\widehat{Q}_{\sigma'}^u(S) \right] &= \limsup_{u \rightarrow \infty} \frac{1}{u} \sup_{(x,t) \in \mathcal{K}' \times [0,T]} \ln \left[Q_{\sigma',x,t} \left(\rho^{(u)} \in S_{(x,t)} \right) \right] \\
&= \limsup_{u \rightarrow \infty} \frac{1}{u} \sup_{(x,t) \in \mathcal{K}' \times [0,T]} \ln \left[\mathbb{E}_{Q_{\sigma',x,t}^V} \left(\frac{dQ_{\sigma',x,t}}{dQ_{\sigma',x,t}^V} \chi \left(\rho^{(u)} \in S_{(x,t)} \right) \right) \right] \\
&\leq \limsup_{u \rightarrow \infty} \frac{1}{u} \sup_{(x,t) \in \mathcal{K}' \times [0,T]} \ln \left[\sup_{\rho^{(u)} \in S_{(x,t)}} \frac{dQ_{\sigma',x,t}}{dQ_{\sigma',x,t}^V} \right] \\
&= - \inf_{(x,t) \in \mathcal{K}' \times [0,T]} \inf_{\rho \in S_{(x,t)}} \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right) \\
&= - \inf_{(x,t,\rho) \in S} \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right)
\end{aligned}$$

We can now optimize over the arbitrary functions V obtaining

$$\limsup_{u \rightarrow \infty} \frac{1}{u} \ln \widehat{Q}_{\sigma'}^u(S) \leq - \sup_V \inf_{(x,t,\rho) \in S} \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right) \quad (\text{B.3})$$

We note that given a compact subset $C \subseteq \mathcal{E}$ a finite open cover O_1, \dots, O_n of C , it trivially holds that $\widehat{Q}_{\sigma'}^u(C) \leq \sum_{i=1}^n \widehat{Q}_{\sigma'}^u(O_i)$. Hence we can estimate

$$\limsup_{u \rightarrow \infty} \frac{1}{u} \ln \widehat{Q}_{\sigma'}^u(C) \leq \inf_{O_1, \dots, O_n} \max_{1 \leq j \leq n} \inf_V \sup_{(x,t,\rho) \in O_j} - \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right), \quad (\text{B.4})$$

where the first infimum is carried over all finite open covers $\{O_1, O_2, \dots, O_n\}$ of C . In order to bound the above r.h.s. we can apply Lemma 3.2 in [KL][Appendix 2]. Indeed, the assumption of this lemma are fulfilled since, as composition of continuous functions (see Lemma 4.1), the map

$$\mathcal{E} \ni (x, t, \rho) \in \mathcal{E} \rightarrow \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right) \in \mathbb{R}$$

is continuous for any V . As result we obtain that

$$\begin{aligned}
\limsup_{u \rightarrow \infty} \frac{1}{u} \ln \widehat{Q}_{\sigma'}^u(C) &\leq - \inf_{(x,t,\rho) \in C} \sup_V \widehat{\mathcal{J}} \left(c[\rho, r(\cdot, \cdot | x, t)], e^V \right) = \\
&\quad - \inf_{(x,t,\rho) \in C} j \left(\rho, r(\cdot, \cdot | x, t) \right) = j \left(\rho^*, r(\cdot, \cdot | x^*, t^*) \right), \quad (\text{B.5})
\end{aligned}$$

where (x^*, t^*, ρ^*) is a minimum point of the continuous function $(x, t, \rho) \rightarrow j(\rho, r(\cdot, \cdot | x, t))$ on the compact set C .

The statement of the lemma now follows from two simple facts. First: since the map $(x, t) \in \mathcal{K}' \times [0, T] \rightarrow \mu(\cdot | x, t) \in M^1(\Gamma)$ is continuous we have that for any fixed $\sigma \in \Gamma$ the set

$$C := \{ (x, t, \rho) \in \mathcal{K}' \times [0, T] \times \mathcal{M}^1(\Gamma) : |\rho_\sigma - \mu(\sigma | x, t)| \geq \delta \}$$

is compact. Second: from Remark 4.3 we have that the continuous function $j(\rho, r(\cdot, \cdot | x, t))$ is strictly positive on C and therefore also its minimum. \square

APPENDIX C. MISCELLANEA

In this last appendix, we prove Lemma 2.1 and we collect some technical results frequently used in the paper.

Proof of Lemma 2.1. We consider here only (2.15), since the Cauchy problem (2.14) can be treated similarly. First, we observe that due to (2.12) the field $\bar{F}(x, t)$ is continuous on $\mathbb{R}^d \times [0, T]$, is locally Lipschitz w.r.t. x and satisfies (2.8) with \bar{F} instead of F_σ . Then, due to Picard Theorem, the Cauchy problem (2.15) has locally a unique solution. We only need to show that there exists a global solution on $[s, T]$. Given $b > 0$ we define $M(b) = \max\{|\bar{F}(x, t)| : |x - x_0| \leq b, t \in [0, T]\}$. Then by Peano Theorem, there exists a C^1 solution $x(t)$ of (2.15) defined for $t \in [s, s + \alpha]$, where $\alpha := \min\{T - s, b/M(b)\}$. Due to (2.8), we know that

$$b/M(b) \geq b/(\kappa_1 + \kappa_2|x_0| + \kappa_2b).$$

We take $b = b(x_0)$ large enough that $b/M(b) \geq 1/(2\kappa_2)$. This implies that the solution of (2.15) exists always on the interval $[s, (s + 1/(2\kappa_2)) \wedge T]$, which does not depend on x_0 . By patching a finite number of paths, one obtains the global solution of (2.15). \square

Let us now show another consequence of Assumption (A4):

Lemma C.1. *Given σ an element of $D([0, T], \Gamma)$ and given $s \in [0, T]$, let $x(t|x_0, s)$ be the unique continuous and piecewise C^1 solution on $[s, T]$ of the ODE $\dot{x}(t) = F_{\sigma(t)}(x(t), t)$ starting at x_0 at time s . Then, for each compact subset $\mathcal{K} \subset \mathbb{R}^d$ there exists another compact subset $\mathcal{K}' \subset \mathbb{R}^d$, independent from the path $\sigma(t)$, such that*

$$\{x(t|x_0, s) : s \leq t \leq T, x_0 \in \mathcal{K}\} \subset \mathcal{K}'.$$

The same thesis holds if one replace $x(t|x_0, s)$ with the C^1 solution $x_(t|x_0, s)$ of the ODE $\dot{x}_*(t) = \bar{F}(x_*(t), t)$, starting at x_0 at time s .*

Proof. We give the proof only for $x(t|x_0, s)$ since the other case can be treated similarly. Due to (2.8), we can bound

$$|x(t|x_0, s)| \leq |x_0| + \int_s^t |F_{\sigma(u)}(x(u), u)| du \leq |x_0| + \kappa_1(t - s) + \kappa_2 \int_s^t |x(u|x_0, s)| du.$$

Due to the Gronwall inequality, the l.h.s. is therefore bounded by $(|x_0| + \kappa_1 T)e^{\kappa_2 T}$, thus implying the thesis. \square

Lemma C.2. *Assumptions (A2) and (A3) imply that $\mu(\sigma|x, t)$ is a C^1 function in x and t , for each $\sigma \in \Gamma$.*

Proof. We fix $(x_0, t_0) \in \mathbb{R}^d \times [0, T]$. By assumption (A2) and Perron–Frobenius Theorem, the right kernel of the matrix $L_c(x_0, t_0)$ has dimension one and is generated by the row $\mu(\cdot|x_0, t_0)$ (below, we will play with row and column vectors, the interpretation will be clear from the context and will be understood). Hence $L_c(x_0, t_0)$ has rank $n - 1$, where $n := |\Gamma|$. In particular, there exists $\sigma_0 \in \Gamma$ such that all the σ -columns v_1, v_2, \dots, v_{n-1} , with $\sigma \neq \sigma_0$, of the matrix $L_c(x_0, t_0)$ are independent. We define π as the canonical projection $\pi : \mathbb{R}^\Gamma \rightarrow \mathbb{R}^{\Gamma \setminus \{\sigma_0\}}$. Then we consider the map

$$F : \mathbb{R}^d \times [0, \infty) \times \mathbb{R}^\Gamma \ni (x, t, z) \rightarrow (\pi(z \cdot L_c(x, t)), \sum_{\sigma} z_\sigma \mu(\sigma|x_0, t_0) - a) \in \mathbb{R}^\Gamma,$$

where $a = \sum_{\sigma} \mu(\sigma|x_0, t_0)^2$. Note that F is C^1 and that $F(x_0, t_0, z_0) = 0$ where $z_0 := \mu(\cdot|x_0, t_0)$. We claim that the map $F(x_0, t_0, \cdot)$ has invertible tangent map $T_z F(x_0, t_0, z_0)$

in z_0 . Indeed, $T_z(x_0, t_0, z_0)$ maps $z \in \mathbb{R}^\Gamma$ in $z \cdot A \in \mathbb{R}^\Gamma$, where A is a $\Gamma \times \Gamma$ -matrix whose columns are given - a part the order - by v_1, v_2, \dots, v_{n-1} and z_0 . We already know that v_1, \dots, v_{n-1} are independent. Moreover, since $z_0 \cdot L_c(x_0, t_0) = 0$, v_1, \dots, v_{n-1} are all orthogonal to z_0 . This implies that all the columns of the matrix A are independent, and therefore A is invertible, thus proving our claim.

We can now apply the Implicit Function Theorem and derive that there exists an open neighborhood U of (x_0, t_0) and a C^1 map $h : U \rightarrow \mathbb{R}^\Gamma$ such that $F(x, t, h(x, t)) = 0$ for all $(x, t) \in U$. This implies that $(h(x, t) \cdot L_c(x, t))_\sigma = 0$ for all $\sigma \neq \sigma_0$. Since $L_c(x, t) \cdot \underline{1} = 0$, we know that

$$\sum_{\sigma \in \Gamma} (h(x, t) \cdot L_c(x, t))_\sigma = h \cdot L_c(x, t) \cdot \underline{1} = 0$$

thus implying that $(h(x, t) \cdot L_c(x, t))_{\sigma_0} = 0$. Moreover, since $h(x, t) \cdot z_0 = a \neq 0$, we conclude that $h(x, t)$ is a nonzero right eigenvector of $L_c(x, t)$ with eigenvalue 0. By Perron–Frobenius Theorem we have that

$$\mu(\sigma|x, t) = \frac{h_\sigma(x, t)}{\sum_{\sigma'} h_{\sigma'}(x, t)}, \quad \forall (x, t) \in U.$$

The above identity and the fact that h is C^1 imply that $\mu(\sigma|\cdot, \cdot)$ is C^1 . □

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