Accelerated dynamics: Mathematical foundations and algorithmic improvements

Tony Lelièvre*

January 7, 2015

Abstract

We present a review of recent works on the mathematical analysis of algorithms which have been proposed by A.F. Voter and co-workers in the late nineties in order to efficiently generate long trajectories of metastable processes. These techniques have been successfully applied in many contexts, in particular in the field of materials science. The mathematical analysis we propose relies on the notion of quasi stationary distribution.

1 Introduction

This article is a review of recent works whose aim is to lay the mathematical foundations of algorithms used in computational statistical physics, namely accelerated dynamics techniques introduced by A.F. Voter and co-workers in the late nineties. These methods have been proposed in order to efficiently sample trajectories in the context of molecular dynamics.

Molecular dynamics is used in various application fields (biology, chemistry, materials science) in order to simulate the evolution of a molecular system, namely interacting particles representing atoms or group of atoms. The typical dynamics one should have in mind is the Langevin dynamics:

\[
\begin{align*}
\frac{dq_t}{dt} &= M^{-1}p_t dt \\
\frac{dp_t}{dt} &= -\nabla V(q_t) dt - \gamma M^{-1}p_t dt + \sqrt{2\gamma \beta^{-1}} dW_t
\end{align*}
\] (1)

where \((q_t, p_t)\) denotes the positions and momenta of the particles at time \(t \geq 0\), \(M\) is the mass tensor, \(V\) is the potential function which, to a given set of positions \(q\), associates its energy \(V(q)\), \(\gamma > 0\) is a friction parameter, \(\beta = (k_B T)^{-1}\) is proportional to the inverse temperature and \(W_t\) is a standard Brownian motion.

In the following, we assume that \(q_t \in \mathbb{R}^d\) where \(d\) is typically very large (say 3 times the number of particles) but generalizations to dynamics on manifolds

*Université Paris-Est, CERMICS (ENPC), INRIA, 6-8 Avenue Blaise Pascal, F-77455
Marne-la-Vallée. The work of T. Lelièvre is supported by the European Research Council under the European Union’s Seventh Framework Programme (FP/2007-2013) / ERC Grant Agreement number 614492. T. Lelièvre would like to thank very instructive discussions with D. Perez and A.F. Voter on accelerated dynamics, as well as his co-authors D. Aristoff, A. Binder, C. Le Bris, M. Luskin, F. Nier, D. Perez and G. Simpson.
systems with constraints) are straightforward. When \( \gamma = 0 \), the Langevin dynamics is nothing but the Hamiltonian dynamics. The terms involving \( \gamma \) model the fact that the system is at a given temperature. Indeed, under loose assumptions on \( V \), this dynamics is ergodic with respect to the canonical measure (NVT ensemble): for any test function \( \varphi : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R} \),

\[
\lim_{T \to \infty} \frac{1}{T} \int_0^T \varphi(q_t, p_t) \, dt = Z^{-1} \int \varphi(q, p) \exp(-\beta(p^T M^{-1} p/2 + V(q))) \, dp dq
\]

where \( Z = \int \exp(-\beta(p^T M^{-1} p/2 + V(q))) \, dp dq < \infty \). In the following, we will also consider the overdamped Langevin dynamics which is obtained from (1) in the limit \( \gamma \to \infty \) or \( M \to 0 \) (see for example [9, Section 2.2.4]):

\[
dX_t = -\nabla V(X_t) \, dt + \sqrt{2\beta^{-1}} \, dW_t
\]

where \( X_t \in \mathbb{R}^d \) denotes the position of the particles. Again, under loose assumptions on \( V \), this dynamics is ergodic with respect to the canonical measure \( \tilde{Z}^{-1} \exp(-\beta V(x)) \, dx \) where \( \tilde{Z} = \int \exp(-\beta V(x)) \, dx \). The aim of molecular simulations is to compute macroscopic properties from the models (1) or (2) at the atomistic level (\( V \) being the main modelling ingredient). In this article, we are particularly interested in so-called dynamical quantities, namely macroscopic observables which depend on the path \((q_t, p_t)_{t \geq 0}\) or \((X_t)_{t \geq 0}\). For example, one would like to sample the paths which go from one region of the phase space to another one, in order to compute the typical time to observe such transitions or the intermediate states along the transition path.

The numerical difficulty associated with such computations is that the timescale at the microscopic level is much smaller than the timescale at the macroscopic level. More precisely, the timestep required to obtain a stable discretization of the above dynamics is much smaller than the timescale associated with the macroscopic observables of interest. In other words, one has to simulate very long trajectories of a high dimensional stochastic dynamics. In practice, for many applications, a naive discretization of the dynamics is not sufficient to reach the timescales of interest, since it would require up to typically \( 10^{15} \) iterations (the timescale at the atomistic level - bond vibration - is indeed of the order of \( 10^{-15} \) s, while transitions between metastable regions occur may over timescales ranging from microseconds to seconds).

The idea of accelerated dynamics is to take benefit from this timescale discrepancy in order to simulate more efficiently paths over very long times. Indeed, the typical trajectories of (1) or (2) are metastable: this means that the trajectory remains trapped for very long times in some region of the phase space, before hopping to another region where it again remains trapped. These regions are called metastable states. Metastability originates from energetic barriers (the path to leave the state requires to climb above a saddle point of the potential energy \( V \)) or from entropic barriers (the path to leave the state goes through a narrow corridor, due to some steric constraints in the system for example), or more generally from a combination of energetic and entropic effects. The bottom line is thus that behind the continuous state space dynamics (1) or (2), there is a discrete state space jump process (encoding the
jumps from metastable states to metastable states). Actually, discrete state space Markov dynamics are also very much used in molecular dynamics: there are called kinetic Monte Carlo or Markov state models, see for example [15]. And continuous state space models are typically used in order to parametrize these Markovian models (namely to compute the jump rates between metastable states) using for example Arrhenius (or Eyring-Kramers) formulas. The accelerated dynamics of A.F. Voter follow a different path: the principle is to use the underlying jump process in order to accelerate the sampling of the original dynamics, in the spirit of a predictor-corrector schemes. These are thus numerical methods to efficiently generate the underlying jump process among metastable states.

In the following, we will assume that we are given a mapping

\[ S : \mathbb{R}^d \rightarrow \mathbb{N} \]

which to a given set of positions \( x \in \mathbb{R}^d \) associates \( S(x) \), the label of the state in which \( x \) lies. One should think of the states

\[ S^{-1}(\{n\}) = \{x \in \mathbb{R}^d, S(x) = n\} \]

for \( n \in \mathbb{N} \)

as the metastable states mentioned above. This mapping thus defines a partition of the state space. Let us make two comments on this mapping. First, an important message from the mathematical analysis we present below is that whatever the mapping \( S \), the accelerated dynamics algorithms are consistent: they give the correct result in some limiting regime. For example for the parallel replica method, in the limit when the correlation time - a numerical parameter introduced below - goes to infinity, the generated dynamics are statistically correct. In particular if some of the states happen not to be metastable, or if for one specific realization, the stochastic process does not remain trapped in one of this state (because, for example, it enters the state with a too large velocity), the algorithms are still consistent. Second, as will become clear below, the numbering of the states do not need to be known a priori: the states are numbered as the simulation goes, when they are successively discovered by the stochastic process.

Three algorithms have been proposed by A.F. Voter and co-workers. The idea is that if the stochastic process remains trapped for a very long time in a given state \( S = S^{-1}(\{n\}) \) (for some given \( n \)), then there are ways to generate the exit event from this state much more efficiently than by running the original dynamics until the exit time. The exit event is fully characterized by two random variables: the exit time and the exit point from \( S \), which are defined by considering the first hitting time and point on the boundary \( \partial S \). Let us roughly describe the ideas behind the three algorithms.

In the Parallel Replica method [14], the principle is to simulate in parallel many trajectories following the original dynamics [1] or [2], to consider the first exit event among the replicas, and to generate from this first exit event a consistent exit time and exit point. The gain is thus obtained in terms of wall clock time. This algorithm can be seen as a way to parallelize a computation
in time, which is not an easy problem in general due to the sequential nature of time evolutions.

In the hyperdynamics [13], the idea is to modify the potential $V$ within the state $S$ in order to accelerate the exit from the state for the original dynamics (1) or (2). Again, using an appropriate time rescaling, it is possible to generate from the observed exit event on the biased potential an exit event which is consistent with what would have been observed on the original unbiased potential $V$.

The Temperature Accelerated Dynamics (TAD) [12] consists in considering the original dynamics (1) or (2) at a higher temperature than the original one. The idea is then that under appropriate assumptions, there is a way to infer from the exit events observed at high temperature the exit event which would have been observed at the original lower temperature.

The ultimate aim of these three techniques is thus to generate efficiently the so-called state-to-state dynamics ($S(q_t)$) $t \geq 0$ (for (1)) or ($S(X_t)$) $t \geq 0$ (for (2)), with the correct statistical properties. Let us emphasize that the objective is to get the correct law on the paths (in order to compute dynamical quantities), not only on the time marginals for example.

A crucial mathematical tool to understand these techniques is the Quasi-Stationary Distribution (QSD) introduced in Section 2. We will then describe the mathematical results which have been obtained so far on the three algorithms: Parallel Replica in Section 3, hyperdynamics in Section 4 and Temperature Accelerated Dynamics in Section 5. A few concluding remarks are provided in Section 6.

2 The Quasi-Stationary Distribution and the decorrelation step

Let us consider a fixed state $S = S^{-1}({\{n\}})$ and let us focus for simplicity on the overdamped Langevin dynamics (2). We assume that $S$ is a bounded regular subset of $\mathbb{R}^d$. Let us consider the first exit time from $S$:

$$T_S = \inf\{t \geq 0, X_t \notin S\}.$$

2.1 The QSD

Let us start with the definition of the QSD.

**Definition 1.** A probability measure $\nu$ with support in $S$ is called a QSD for the Markov process $(X_t)_{t \geq 0}$ if and only if

$$\forall t > 0, \forall A \subset S, \nu(A) = \frac{\int_S \mathbb{P}(X_t^x \in A, t < T_S^x) \nu(dx)}{\int_S \mathbb{P}(t < T_S^x) \nu(dx)}.$$

In other words, $\nu$ is a QSD if, when $X_0$ is distributed according to $\nu$, the law of $X_t$ conditionally to the fact that $(X_s)_{0 \leq s \leq t}$ remains in the state $S$ is still $\nu$, for all positive $t$.

The QSD satisfies three properties which will be crucial in the following. We refer for example to [6] for a proof of these results and to [4] for more general results on QSDs.
Proposition 2. Let \((X_t)_{t \geq 0}\) follow the dynamics with an initial condition \(X_0 \in S\). Then, there exists a probability distribution \(\nu\) with support in \(S\) such that
\[
\lim_{t \to \infty} \mathcal{L}(X_t | T_S > t) = \nu.
\]
The distribution \(\nu\) is the QSD associated with \(S\).

A consequence of this proposition is the existence and uniqueness of the QSD. The QSD can thus be seen as the longtime limit of the process conditioned to stay in the well. This proposition can be useful to understand what is a metastable state. A metastable state is a state such that the typical exit time is much larger than the local equilibration time, namely the time to observe the convergence to the QSD in (4).

Let us now give a second property of the QSD.

Proposition 3. Let \(L = -\nabla V \cdot \nabla + \beta^{-1} \Delta\) be the infinitesimal generator of \((X_t)_{t \geq 0}\) (satisfying (2)). Let us consider the first eigenvalue and eigenfunction associated with the adjoint operator \(L^* = \text{div} (\nabla V + \beta^{-1} \nabla)\) with homogeneous Dirichlet boundary condition:

\[
\begin{aligned}
L^* u_1 &= -\lambda_1 u_1 \text{ on } S, \\
\quad u_1 &= 0 \text{ on } \partial S.
\end{aligned}
\]

The QSD \(\nu\) associated with \(S\) satisfies:
\[
d\nu = \frac{u_1(x) dx}{\int_S u_1(x) dx}
\]
where \(dx\) denotes the Lebesgue measure on \(S\).

The QSD thus has a density with respect to the Lebesgue measure, which is nothing but the ground state of the Fokker-Planck operator \(L^*\) associated with the dynamics with absorbing boundary conditions.

Finally, the last property of the QSD concerns the exit event, when \(X_0\) is distributed according to \(\nu\).

Proposition 4. Let us assume that \(X_0\) is distributed according to the QSD \(\nu\) in \(S\). Then the law of the couple \((T_S, X_{T_S})\) (namely the first exit time and the first exit point) is fully characterized by the following properties:

- \(T_S\) is exponentially distributed with parameter \(\lambda_1\) (defined in Equation (5) above)
- \(T_S\) is independent of \(X_{T_S}\)
- The law of \(X_{T_S}\) is given by: for any bounded measurable function \(\varphi : \partial S \to \mathbb{R}\),
  \[
  \mathbb{E}^\nu(\varphi(X_{T_S})) = -\frac{\int_{\partial S} \varphi \partial_n u_1 d\sigma}{\beta \lambda_1 \int_S u_1(x) dx}
  \]
  where \(\sigma\) denotes the Lebesgue measure on \(\partial S\) induced by the Lebesgue measure in \(\mathbb{R}^d\) and the Euclidean scalar product, and \(\partial_n u_1 = \nabla u_1 \cdot n\) denotes the outward normal derivative of \(u_1\) on \(\partial S\).
This Proposition explains the interest of the QSD. Indeed, if the process is distributed according to the QSD in $S$ (namely, from Proposition 2, if it remained for a sufficiently long time in $S$), then the exit event from the state $S$ is Markovian, in terms of state-to-state dynamics. This is reminiscent of what is assumed to build kinetic Monte Carlo models (see [15]).

Remark 5. The existence of the QSD and the convergence of the constrained process towards the QSD for the Langevin process (1) requires extra work compared to the overdamped Langevin process (2). For results in that direction, we refer to the recent manuscript [11].

2.2 The decorrelation step

The accelerated dynamics algorithms will be based on the assumption that the process remained sufficiently long in the state $S$ so that one can consider it is distributed according to the QSD $\nu$. Then, using this assumption, various techniques are used in order to efficiently generate the exit event from $S$, starting from the QSD (see the next sections).

A natural preliminary question is therefore: how to assess in practice that the limit has been reached in (4) ? This is done in the so-called decorrelation step which consists in waiting for a given time $\tau_{corr}$ (a so-called decorrelation time) before assuming that the local equilibrium $\nu$ has been reached. This correlation time can be state dependent, and is typically supposed to be known a priori.

From a mathematical viewpoint, $\tau_{corr}$ should be chosen sufficiently large so that the distance between the law of $X_{\tau_{corr}}$ conditioned to $T_S \geq \tau_{corr}$ and the QSD $\nu$ is small. In [6], we prove the following:

**Proposition 6.** Let $(X_t)_{t\geq 0}$ satisfies (2) with $X_0 \in S$. Let us consider $-\lambda_2 < -\lambda_1 < 0$ the first two eigenvalues of the operator $L^*$ on $S$ with homogeneous Dirichlet boundary conditions on $\partial S$ (see Proposition 3 for the definition of $L^*$). Then, there exists a constant $C > 0$ which depends on the law of $X_0$, such that, for all $t \geq \frac{C}{\lambda_2-\lambda_1}$,

$$\sup_{\|f\|_{L^\infty} \leq 1} |E(f(T_S - t, X_{T_S})|T_S \geq t) - E(f(T_S, X_{T_S}))| \leq C \exp(-((\lambda_2 - \lambda_1)t)).$$

In other words, the total variation norm between the law of $(T_S - t, X_{T_S})$ conditioned to $T_S \geq t$ (for any initial condition $X_0 \in S$), and the law of $(T_S, X_{T_S})$ when $X_0$ is distributed according to $\nu$, decreases exponentially fast with rate $\lambda_2 - \lambda_1$. This means that $\tau_{corr}$ should be chosen of the order $1/(\lambda_2 - \lambda_1)$. Of course, this is not a very practical result since computing these eigenvalues is in general impossible. From a theoretical viewpoint, this result tells us that the local equilibration time is of the order $1/(\lambda_2 - \lambda_1)$, so that, the state $S$ will be metastable if this time is much smaller than the exit time (which is typically of the order of $1/\lambda_1$, see Proposition 3).

Let us mention the recent work [3] where we propose a numerical method to approximate the time to reach the QSD using a Fleming-Viot particle process together with stationarity statistical tests. The interest of the approach is
demonstrated on toy examples (including the 7 Lennard-Jones cluster), but it remains to test this technique on higher dimensional problems.

From now on, we assume that the decorrelation step has been successful, and we look for efficient techniques to generate the exit event (namely a sample of the random variables \((T_S, X_{T_S})\)). Let us describe successively the three algorithms which has been proposed by A.F. Voter and co-workers.

3 The Parallel Replica method

Figure 1: The Parallel Replica method: many exit events are simulated in parallel, all starting from the QSD in \(S\). The blue trajectory represents the reference walker which stays sufficiently long within \(S\) so that we can assume the blue point is distributed according to the QSD. The red points represent i.i.d. initial conditions distributed according to the QSD. The black trajectories are simulated in parallel.

Let us assume that we are given an initial condition \(X_0 \in S\) such that \(X_0\) is distributed according to the QSD in \(S\). Let us assume that we are given a computer with many CPUs in parallel. The idea of the parallel replica method is to distribute \(N\) independent initial conditions \((X^i_0)_{1 \leq i \leq N}\) in \(S\) according to the QSD \(\nu\), to let them evolve according to (2) driven by independent motions (so that the replicas remain independent) and then to consider the first exit event among the replicas:

\[
I_0 = \arg \min_{i \in \{1, \ldots, N\}} T^i_S \quad \text{where} \quad T^i_S = \inf \{ t \geq 0, X^i_t \notin S \}. \tag{7}
\]

The integer \(I_0 \in \{1, \ldots, N\}\) is the index of the first replica which exits \(S\), and \(\min(T^1_S, \ldots, T^N_S) = T^{I_0}_S\). The effective exit time is set as \(N\) times the first exit time, and the effective exit point is nothing but the exit point for the first exit event. See Figure 3 for a schematic illustration of the method.

The consistency of the method is a corollary of Proposition 4. Indeed using the fact that, starting from the QSD, the exit time is exponentially distributed and independent of the exit point, we easily obtain that

\[
NT^{I_0}_S = N \min(T^1_S, \ldots, T^N_S) \overset{\mathcal{L}}{=} T^1_S \tag{8}
\]
which means that the effective exit time has the correct law and
\[ X_{I_0}^{f_0} \overset{\text{L}}{=} X_{T_{S_0}}^{1} \]
which means that the first exit point of the replica \( I_0 \) (the first one to exit among \( N \)) has the same law as the first exit point of any of them. Moreover \( N T_{S_0}^f = N \min(T_{S}^1, \ldots, T_{S}^N) \) and \( X_{I_0}^{f_0} \) are independent, so that we have proven the following Lemma.

**Lemma 7.** Let \( I_0 \) be the index of the first replica exiting \( S \), defined by (7). Then we have the equality in law:
\[
\left( N T_{S_0}^{f_0}, X_{T_{S_0}^{f_0}}^{f_0} \right) \overset{\text{L}}{=} \left( T_{S}^1, X_{T_{S}^1}^1 \right).
\]

This Lemma shows that the parallel replica is exact: the law of the effective exit time and exit point is exactly the law of the exit time and exit point which would have been observed for only one replica.

Let us make a few remarks on this algorithm. First, the full algorithm actually iterates three steps:

- The **decorrelation step** (see Section 2.2), where a reference walker is run following the dynamics (2) until it remains trapped for a sufficiently long time in one of the sets \( S^{-1}\{n\} \), so that it can be assumed to be distributed according to the QSD \( \nu \) associated with this set. During this step, the algorithm thus consists simply in integrating the original dynamics. No error is introduced and there is no computational gain.

- The **dephasing step** which is a preparation step during which \( N \) independent initial conditions distributed according to \( \nu \) are sampled, each one on a different CPU. This is done in parallel. During this step, the simulation clock is stopped. This step is thus pure overhead. This step requires appropriate algorithms to sample the QSD such as rejection algorithm or Fleming-Viot particle systems (see [6]). For example, the rejection algorithm consists in running independently walkers following the dynamics (2) (starting from a point within \( S \)) and to consider the final point of the trajectory conditionally to the fact that the walker remains in the state, for a sufficiently long trajectory (typically for the time \( \tau_{\text{corr}} \) introduced in Section 2.2).

- The **parallel step**, just described above, which consists in running the \( N \) replicas independently in parallel, and in waiting for the first exit event among the \( N \) replicas. The simulation clock is then updated by adding the effective exit time \( N T_{S_0}^f \). The exit point \( X_{I_0}^{f_0} \) is used as the initial condition of the reference walker for the next decorrelation step. The computational gain of the whole algorithm comes from this step which divides the wall clock time to sample the exit event by the number of replicas \( N \).
In practice, if the rejection algorithm is used in the dephasing step, one actually does not need to wait for the $N$ replicas to be dephased to proceed to the parallel step, see [14, 6, 3].

In view of the above discussions, the errors introduced in the algorithm have two origins. First, in the decorrelation step, $\tau_{\text{corr}}$ should be chosen sufficiently large so that at the end of the decorrelation step, the reference walker is indeed distributed according to a probability law sufficiently close to the QSD. The convergence result of Proposition [6] shows that the error is of the order $O(\exp(-\tau_{\text{corr}}/(\lambda_2 - \lambda_1)))$. Second, in the dephasing step, the sampling algorithm of the QSD should be sufficiently precise in order to obtain i.i.d. samples distributed according to $\nu$. For the rejection algorithm, independence is ensured, and the accuracy is again related to the convergence result of Proposition [6]. For Fleming-Viot particle process, some correlations are introduced among the replicas, and it is an open problem to evaluate the error introduced by these correlations. As already mentioned above, in [3], we recently proposed an algorithm to compute on-the-fly a good correlation time, while sampling the QSD, using a Fleming-Viot particle process.

The parallel replica is thus a very versatile algorithm. In particular it applies to both energetic and entropic barriers. The only errors introduced in the algorithm are related to the rate of convergence of the conditioned process to the QSD. The algorithm will be all the more efficient than the convergence time to the QSD is small compared to the exit time (namely the states are metastable): in this case, the speed-up in terms of wall clock time is linear as a function of $N$. We refer to [3, Section 5.1] for a discussion of the parallel efficiency of the algorithm.

Let us finally mention the recent work [2] where we propose an extension of the Parallel Replica algorithm to Markov chains (namely discrete-in-time stochastic processes). This is indeed a relevant question since in practice, the continuous-in-time dynamics (such as (1) or (2)) are approximated by discrete-in-time Markov Chains using appropriate time discretization schemes. The algorithm has to be slightly adapted since, starting from the QSD (which is still perfectly well defined in this context), the exit time is not exponentially distributed but has a geometric law. Therefore, the formula [5] does not hold and is replaced by the following: for $T^1, \ldots, T^N$ i.i.d. random variables geometrically distributed,

$$N(\min(T^1, \ldots, T^N) - 1) + \min(i \in \{1, \ldots, N\}, T^i = \min(T^1, \ldots, T^N)) \leq T^1.$$ 

This yields a natural adaptation of the original Parallel Replica algorithm to Markov chains.

### 4 The hyperdynamics

Let us again assume that we are given an initial condition $X_0 \in S$ such that $X_0$ is distributed according to the QSD in $S$. In other words, let us assume that we are at the end of the decorrelation step: the reference walker stayed sufficiently long in $S$. 

9
The principle of the hyperdynamics algorithm is then to raise the potential inside the state in order to accelerate the exit from $S$. The algorithm thus requires a biasing potential $\delta V : S \to \mathbb{R}$, which satisfies appropriate assumptions detailed below. The algorithm then proceeds as follows:

- Equilibrate the dynamics on the biased potential $V + \delta V$, namely run the dynamics (2) on the process $(X_{\delta V}^t)_{t \geq 0}$ over the biased potential conditionally to staying in the well, up to the time the random variable $X_{\delta V}^t$ has distribution close to the QSD $\nu_{\delta V}$ associated with the biased potential. This first step is a preparation step, which is pure overhead. The end point $X_{\delta V}^t$ will be used as the initial condition for the next step.

- Run the dynamics (2) over the biased potential $V + \delta V$ up to the exit time $T_S^{\delta V}$ from the state $S$. The simulation clock is updated by adding the effective exit time $BT_S^{\delta V}$ where $B$ is the so-called boost factor defined by

$$B = \frac{1}{T_S^{\delta V}} \int_0^{T_S^{\delta V}} \exp(\beta \delta V(X_t^{\delta V})) \, dt. \quad (9)$$

The exit point is then used as the starting point for a new decorrelation step.

See Figure 2 for a schematic illustration of the method.

Roughly speaking, the assumptions required on $\delta V$ in the original paper [13] are twofold:

- $\delta V$ is sufficiently small so that the exit event from the state $S$ still satisfies the standard assumptions used for kinetic Monte Carlo models and transition state theory.

- $\delta V$ is zero on (a neighborhood) of the boundary $\partial S$.

The derivation of the method relies on explicit formulas for the laws of the exit time and exit point, using the transition state theory. The aim of the
The mathematical analysis presented below is to give a rigorous set of assumptions to make this algorithm consistent.

The algorithm we present here is actually slightly different from the way it is introduced in the original paper [13]. Indeed, in the original version, the local equilibration steps (decorrelation step and equilibration step on the biased potential) are omitted: it is assumed that the states are sufficiently metastable (for both the original potential and the biased potential) so that these local equilibrations are immediate. It would be interesting to check if the modifications we propose here improve the accuracy of the method.

Let us now discuss the mathematical foundations of this technique, and in particular, a way to understand the formula (9) for the boost factor. We actually need to compare two exit events. The first one is the exit event for the original process \(X_t\) following the dynamics (2), starting from the QSD \(\nu\) associated with the state \(S\) and the dynamics with potential \(V\). The second one is the exit event for the process \(X_{t}^{\delta V}\) following the dynamics (2) on the biased potential \(V + \delta V\), starting from the QSD \(\nu_{\delta V}\) associated with the state \(S\) and the dynamics with potential \(V + \delta V\). Referring to Proposition 4, comparing the two exit events amounts to understanding how the first eigenvalue \(\lambda_1\) and the normal derivative of the first eigenvector \(\partial_n u_1\) are modified when changing the potential from \(V\) to \(V + \delta V\). Let us denote \(\lambda_1(V)\) (resp. \(\lambda_1(V + \delta V)\)) and \(\partial_n u_1(V)\) (resp. \(\partial_n u_1(V + \delta V)\)) the first eigenvalue and the normal derivative when considering the original potential \(V\) (resp. the biased potential \(V + \delta V\)).

In [8], we prove the following.

**Theorem 8.** Let us make the following assumptions on \(V\). We assume there exists an open set \(S^-\) such that \(S^- \subset S\) and:

- **Regularity:** \(V\) and \(V|_{\partial S}\) are Morse functions.
- **Localization in \(S^-\)** of the eigenvectors associated with small eigenvalues:
  1. \(|\nabla V| \neq 0\) in \(\overline{S} \setminus S^-\);
  2. \(\partial_n V > 0\) on \(\partial S^-\);
  3. \(\min_{\partial S^-} V \geq \min_{\partial S^-} V\);
  4. \(\min_{\partial S^-} V - \text{cvmax} > \text{cvmax} - \min_{S^-} V\) where \(\text{cvmax} = \max\{V(x), x \text{ s.t. } |\nabla V(x)| = 0\}\).
- **Non degeneracy of exponentially small eigenvalues:** The critical values of \(V\) in \(S^-\) are all distinct and the differences \(V(y) - V(x)\) are all distinct, where \(x \in \mathcal{U}^{(0)}\) ranges over the local minima of \(V|_{S^-}\) and \(y \in \mathcal{U}^{(1)}\) ranges over the critical points of \(V|_{S^-}\) with index 1.

Let us also assume that the biasing potential \(\delta V\) is such that

- \(V + \delta V\) satisfies the same assumptions as the ones on \(V\) above;
- \(\delta V = 0\) on \(\overline{S} \setminus S^-\).
Then, there exists $c > 0$ such that, in the limit $\beta \to \infty$,

$$\lambda_1(V + \delta V) = \frac{\int_S e^{-\beta(V + \delta V)} (1 + \mathcal{O}(e^{-\beta c}))}{\int_S e^{-\beta V}(1 + \mathcal{O}(e^{-\beta c}))}, \quad (10)$$

$$\frac{\partial_n [u_1(V + \delta V)]}{\partial S} = \frac{\partial_n [u_1(V)]}{\partial S} + \mathcal{O}(e^{-\beta c}) \quad \text{in} \quad L^1(\partial S). \quad (11)$$

The proof is based on results from semi-classical analysis for boundary Witten Laplacians.

Notice that the formula (10) provides a justification of the formula (9) for the boost factor. Indeed, by assuming that $T^{3V}_S$ is sufficiently large, we have by an ergodic property:

$$B = \frac{1}{T^{3V}_S} \int_0^{T^{3V}_S} \exp(\beta \delta V(X^V_t)) \, dt.$$

$$\simeq \frac{\int_S \exp(\beta \delta V) \exp(-\beta(V + \delta V))}{\int_S \exp(-\beta(V + \delta V))}$$

$$= \frac{\int_S \exp(-\beta V)}{\int_S \exp(-\beta(V + \delta V))}$$

$$\simeq \frac{\lambda_1(V + \delta V)}{\lambda_1(V)}. \quad (12)$$

By multiplying the exit time on the biased potential $V + \delta V$ by $\frac{\lambda_1(V + \delta V)}{\lambda_1(V)}$, we indeed obtain (in law) the exit time on the original potential $V$. Moreover, the estimate (11) shows that (up to exponentially small errors in the limit of small temperature), the first exit point from $S$ for the biased potential has the same distribution as the first exit point from $S$ for the original potential (see Equation (6) in Proposition 4).

A practical aspect we do not discuss here at all is the effective construction of the biasing potential $\delta V$. In the original article [13], A.F. Voter proposes a technique based on the Hessian $\nabla^2 V$. A well-known method in the context of materials science is the bond-boost method introduced in [10].

Notice that, contrary to the Parallel Replica method, the hyperdynamics is, at least for our mathematical analysis, limited to energetic barriers (see assumptions (iii) and (iv) in Theorem 8). On the other hand, for very high energetic barriers, hyperdynamics is in principle much more efficient: the Parallel Replica method only divides the exit time by $N$ (the number of replicas), while for deep wells, the boost factor $B$ is very large.

5 The Temperature Accelerated Dynamics

Let us finally introduce the Temperature Accelerated Dynamics (TAD), see [12]. Let us assume again that we are at the end of the decorrelation step: the reference walker stayed sufficiently long in $S$. The principle of TAD is to increase the temperature (namely increase $\beta^{-1}$ in (2)) in order to accelerate the exit from $S$. The algorithm consists in
• Simulating many exit events from $S$ at high temperature, starting from the QSD at high temperature,

• Extrapolating the high temperature exit events to low temperature exit events using the Arrhenius law.

As for the hyperdynamics algorithm, in the original paper [12], no equilibration step is used: it is assumed that the states are sufficiently metastable at both high and low temperatures so that the convergence to the QSD is immediate. Let us now describe more precisely how the extrapolation procedure is made.

Let us consider the exit event from $S$, at a given temperature. The set $S$ is surrounded by $I$ neighboring states and let us denote by $\partial S_i$ the common boundary with the $i$-th neighboring state, $i \in \{1, \ldots, I\}$. The sets $\partial S_i$ thus form a partition of the boundary $\partial S$. Let us introduce, for $i \in \{1, \ldots, I\}$, the saddle point $x_i \in \partial S_i$ which is the lowest in energy on $\partial S_i$: in the small temperature regime, the paths leaving the state $S$ through $\partial S_i$ will leave through a neighborhood of $x_i$ (this can be inferred from results from the large deviation theory for example). Let us also denote by $x_0$ the global minimum of $V$ on $S$. We refer to Figure 3 for a schematic representation of the geometry. The interesting quantities to define the exit events are:

• The probability to exit through $\partial S_i$ which writes (see Proposition 4):

$$p(i) = \mathbb{P}(X_{T_S} \in \partial S_i) = -\frac{\int_{\partial S_i} \partial_n u_1 \, d\sigma}{\beta \lambda_1 \int_S u_1(x) \, dx}.$$  

• And the parameter of the exponential random variable $T_S$:

$$\lambda_1 = 1/\mathbb{E}(T_S).$$

Notice that one way to rewrite the exit event is to attach to each exit region $\partial S_i$ (or to each saddle point $x_i$) a rate

$$k(i) = \lambda_1 p(i)$$

Figure 3: The Temperature Accelerated Dynamics: exit events are simulated at higher temperature and then extrapolated to the original smaller temperature.
and to consider $I$ independent exponential random variables $\tau_i$ with parameter $k(i)$. The exit event is then given by

- the exit time $\min(\tau_1, \ldots, \tau_I) \equiv T_S$
- and the exit region $\arg\min(\tau_1, \ldots, \tau_I)$, since, for $i \in \{1, \ldots, I\}$, $\mathbb{P}(\arg\min(\tau_1, \ldots, \tau_I) = i) = p(i)$.

This description of the exit event in terms of rates attached to neighboring saddle points is exactly what is used for kinetic Monte Carlo models [15]. The TAD algorithm requires an approximation of the rate $k(i)$, namely the Arrhenius law:

$$k(i) = \lambda_i p(i) \simeq \eta_i \exp\left( -\beta(V(x_i) - V(x_0)) \right)$$  \hspace{1cm} (12)

where $\eta_i$ is independent of $\beta$. In the original paper [12], the Arrhenius law is justified using the (harmonic) transition state theory.

Let us now go back to the TAD algorithm. Using the underlying kinetic Monte Carlo model presented above, and using the Arrhenius law [12], one observes that:

$$\frac{k^{hi}(i)}{k^{lo}(i)} = \frac{\lambda^{hi}_i p^{hi}(i)}{\lambda^{lo}_i p^{lo}(i)} \simeq \exp\left( -(\beta^{hi} - \beta^{lo})(V(x_i) - V(x_0)) \right)$$ \hspace{1cm} (13)

where, with obvious notation, $\beta^{lo}$ denotes the inverse low temperature, $\beta^{hi}$ the inverse high temperature, and the superscripts $lo$ and $hi$ refer to the associated quantities respectively at low and high temperature. The extrapolation formula (13) is used in TAD in order to infer the exit event at low temperature from the exit events observed at high temperature, by using the formula:

$$(\tau_1^{lo}, \ldots, \tau_I^{lo}) \overset{L}{\equiv} (\Theta^1 \tau_1^{hi}, \ldots, \Theta^I \tau_I^{hi})$$ \hspace{1cm} (14)

where

$$\Theta^i = \frac{k^{hi}(i)}{k^{lo}(i)} \simeq \exp\left( -(\beta^{hi} - \beta^{lo})(V(x_i) - V(x_0)) \right)$$

is a multiplicative factor constructed from the ratio of the rates (13). In the equality in law in (14) the random variables $\tau_i^{hi/lo}$ are, as described above, exponential random variables with parameter $k^{hi/lo}(i)$. To have analytical formula for the correction factors $\Theta_i$ and make the algorithm practical, the Arrhenius is assumed to be exact and one uses in practice $\Theta^i = \exp( - (\beta^{hi} - \beta^{lo})(V(x_i) - V(x_0)))$.

The TAD algorithm thus consists in running the dynamics at high temperature, observing the exit events through the saddle points on the boundary of the state, and updating the exit time and exit region that would have been observed at low temperature. More precisely, if exits through the saddle points $\{s_1, \ldots, s_k\} \subset \{1, \ldots, I\}$ have been observed, one computes $\min(\Theta^{s_1} \tau^{hi}_{s_1}, \ldots, \Theta^{s_k} \tau^{hi}_{s_k})$ and $\arg\min(\Theta^{s_1} \tau^{hi}_{s_1}, \ldots, \Theta^{s_k} \tau^{hi}_{s_k})$ to get the exit time and the exit region at low temperature.

The interest of TAD compared to a brute force saddle point search is that it is not required to observe exits through all the saddle points in order to obtain
a statistically correct exit event. Indeed, a stopping criterium is introduced to stop the calculations at high temperature when the extrapolation procedure will not modify anymore the low temperature exit event (namely will not modify \( \min(\Theta_{s_1}, \ldots, \Theta_{s_k}) \), \( \{s_1, \ldots, s_k\} \subset \{1, \ldots, I\} \) being the saddle points discovered up to the stopping time). This stopping criterium requires to provide some a priori knowledge, typically a lower bound on the barriers \( V(x_i) - V(x_0) \) (there is also a variant using a lower bound on the prefactors \( \eta_i \) in (12)). In some sense, TAD can be seen as a clever saddle point search, with a rigorous way to stop the searching procedure.

If the Arrhenius law (12) is exactly satisfied, one can check that the TAD algorithm simulates an exit event which is statistically exact. The mathematical question raised by this algorithm is thus to estimate the difference between the ratio of the rates \( \frac{\lambda_{hi} p_{hi}(i)}{\lambda_{lo} p_{lo}(i)} \) and the estimate deduced from the Arrhenius law \( \exp(- (\beta_{hi} - \beta_{lo}) (V(x_i) - V(x_0))) \) (see the extrapolation formula (13) above). In [1], we consider as a first step the case of a one dimensional potential, where \( S \) is a single well, and we prove that in the limit \( \beta_{hi}, \beta_{lo} \to \infty \) with \( \beta_{lo}/\beta_{hi} \) fixed,

\[
\frac{\lambda_{hi} p_{hi}(i)}{\lambda_{lo} p_{lo}(i)} = e^{- (\beta_{hi} - \beta_{lo}) (V(x_i) - V(x_0))} \left( 1 + O \left( \frac{1}{\beta_{hi}} \right) \right) .
\] (15)

The extension of this result to a high dimensional setting is a work under progress.

Notice that, compared to the hyperdynamics, TAD is based on an additional assumption, namely the Arrhenius law. We expect that this implies larger error for TAD than for the hyperdynamics: for the hyperdynamics the error in (10)–(11) is exponentially small in the limit \( \beta \to \infty \), while for TAD, the error scales like \( 1/\beta \) in (15). The interest of TAD compared to the hyperdynamics is that it does not require a biasing potential, which may be complicated to build in some situation.

### 6 Conclusion and discussion

We presented three algorithms which have been proposed by A.F. Voter and co-workers in order to efficiently generate the state-to-state dynamics associated with a metastable stochastic process.

We proposed an analysis of these algorithms based on the notion of quasi-stationary-distribution (QSD). As explained above, starting from the QSD within a well, the exit event is Markovian since the exit time is exponentially distributed and independent of the next visiting state. From a theoretical viewpoint, the QSD thus seems to be an interesting intermediate to relate Markovian dynamics in continuous state space (such as the Langevin [1] or the overdamped Langevin [2] dynamics) with Markovian dynamics in discrete state space (kinetic Monte Carlo models or Markov state models). It also gives a natural definition of a metastable region (see [7]) as a region where the stochastic process reaches local equilibrium (namely the QSD) before exiting.

Going from Parallel Replica to Hyperdynamics to TAD, the assumptions required for the algorithm to be correct are more and more stringent. Indeed,
for Parallel Replica, no assumptions is required beyond the fact that a good estimate of $\tau_{\text{corr}}$ is available (to assess the convergence of the QSD). Hyperdynamics requires additional assumptions on the potential: the metastability of the state should come from energetic barriers (at least for our mathematical analysis to apply). Finally, the TAD algorithm requires in addition the Arrhenius law to be satisfied. Likewise, going from Parallel Replica to Hyperdynamics to TAD, the errors introduced by the algorithm are expected to be larger and larger. On the other hand, the expected computational gain with Parallel replica is typically smaller than for the two other methods. In addition, comparing hyperdynamics with TAD, the interest of TAD is that it does not require the construction of a biasing potential, which is a difficult task in general.

One practical aspect we did not discuss above is the choice of the partition of the configurational space into states (in other words, the choice of the function $S$). Let us focus on the Parallel Replica algorithm for simplicity. We already mentioned that thanks to the decorrelation step, the algorithm is consistent whatever the choice of the partition. However, the efficiency of the algorithm highly depends on the choice of the partition: the states should be metastable regions, so that the stochastic process reaches the local equilibrium (the QSD) before leaving the state. How to design a good partition is a difficult question. For a system with high energy barriers (this is often the case for application in materials science for example), the original idea of A.F. Voter and co-workers is to define the states as the basins of attraction of the local minima of $\nabla V$ for the simple gradient dynamics $\dot{x} = -\nabla V(x)$. For a system with more diffusive or entropic barriers (this is typically the case for biological applications), one could think of defining the states using relevant reaction coordinates (see for example [5] where the states are defined in terms of the molecular topology of the molecule of interest). Notice that choosing a good partition also implies being able to estimate the correlation time within each state either from some a priori knowledge, or some on-the-fly estimates [3].

Let us finally mention the mathematical questions raised by these algorithms and that we would like to investigate in the future.

Concerning the TAD algorithm, the analysis of the validity of the Arrhenius law starting from the QSD has only been done for the moment in a one-dimensional situation. The extension to a more general setting is a work under progress.

We would like to stress that all these algorithms are used in practice with the Langevin dynamics [1]. The mathematical results we presented above assumed that the dynamics was the overdamped Langevin [2]. Therefore, some works have to be done to extend these results to the Langevin dynamics. There are mainly two difficulties. First, the infinitesimal generator associated with the overdamped Langevin is symmetric (in an appropriate weighted $L^2$ space) while this is not the case for Langevin, which implies that the study of the spectrum of the infinitesimal generator for Langevin is more complicated. In addition, the fact that the domain of interest is typically bounded in position but not in velocity implies additional difficulties. We refer to the recent work [11] by F. Nier, which gives in particular some conditions for the existence of an isolated
smallest eigenvalue (and therefore of the QSD) for the Fokker-Planck operator associated with the Langevin dynamics. Second, while there is an extensive literature on the spectrum of the infinitesimal generator of the overdamped Langevin dynamics in the small temperature regime (semi classical analysis for Schrödinger operators and Witten laplacians), this is not the case for the Langevin dynamics. This means that the analysis of the hyperdynamics or TAD will certainly be more involved for Langevin than for overdamped Langevin.

References

[1] D. Aristoff and T. Lelièvre. Mathematical analysis of temperature accelerated dynamics. *SIAM Multiscale Modeling and Simulation*, 12(1):290–317, 2014.

[2] D. Aristoff, T. Lelièvre, and G. Simpson. The parallel replica method for simulating long trajectories of markov chains. *AMRX*, 2:332–352, 2014.

[3] A. Binder, G. Simpson, and T. Lelièvre. A generalized parallel replica dynamics. [http://arxiv.org/abs/1404.6191](http://arxiv.org/abs/1404.6191), 2014.

[4] P. Collet, S. Martínez, and J. San Martín. *Quasi-Stationary Distributions*. Springer, 2013.

[5] O. Kum, B.M. Dickson, S.J. Stuart, B.P. Uberuaga, and A.F. Voter. Parallel replica dynamics with a heterogeneous distribution of barriers: Application to n-hexadecane pyrolysis. *J. Chem. Phys.*, 121:9808–9819, 2004.

[6] C. Le Bris, T. Lelièvre, M. Luskin, and D. Perez. A mathematical formalization of the parallel replica dynamics. *Monte Carlo Methods Appl.*, 18(2):119–146, 2012.

[7] T. Lelièvre. Two mathematical tools to analyze metastable stochastic processes. In Andrea Cangiani, Ruslan L. Davidson, Emmanuel Gourgoulis, Alexander N. Gorban, Jeremy Levesley, and Michael V. Troyakov, editors, *Numerical Mathematics and Advanced Applications 2011*, pages 791–810. Springer Berlin Heidelberg, 2013.

[8] T. Lelièvre and F. Nier. Low temperature asymptotics for quasi-stationary distributions in a bounded domain, 2013. [http://arxiv.org/abs/1309.3898](http://arxiv.org/abs/1309.3898).

[9] T. Lelièvre, M. Rousset, and G. Stoltz. *Free energy computations: A mathematical perspective*. Imperial College Press, 2010.

[10] R.A. Miron and K.A. Fichthorn. Accelerated molecular dynamics with the bond-boost method. *J. Chem. Phys.*, 119(12):6210–6216, 2003.

[11] F. Nier. Boundary conditions and subelliptic estimates for geometric Kramers-Fokker-Planck operators on manifolds with boundaries. [http://arxiv.org/abs/1309.5070](http://arxiv.org/abs/1309.5070), 2014.
[12] M.R. Sorensen and A.F. Voter. Temperature-accelerated dynamics for simulation of infrequent events. *J. Chem. Phys.*, 112(21):9599–9606, 2000.

[13] A.F. Voter. A method for accelerating the molecular dynamics simulation of infrequent events. *J. Chem. Phys.*, 106(11):4665–4677, 1997.

[14] A.F. Voter. Parallel replica method for dynamics of infrequent events. *Phys. Rev. B*, 57(22):R13 985, 1998.

[15] A.F. Voter. *Radiation Effects in Solids*, chapter Introduction to the Kinetic Monte Carlo Method. Springer, NATO Publishing Unit, 2005.