C DFT, Car-Parrinello and Classical Molecular Dynamics

C.1 Density Functional Theory and TDDFT

The DFT is based on two theorems formulated by Hohenberg-Kohn in the sixties: (1) in a given external nuclear configuration, the ground state multi electron wavefunction $\Psi(\mathbf{r},\mathbf{R})$ is in one to one correspondence with the ground state density $\rho(\mathbf{r})$, so that a unique density functional describing the energy can be defined

$$E[\rho] = T[\rho] + V_{\text{ext}}[\rho] + V_{\text{ee}}[\rho]$$

$$= T[\rho] + \int \rho(r)v(r)\,dr + V_{\text{ee}}[\rho]$$

(2) The Energy density functional is minimized by the density corresponding to the ground state and in that case it coincides with the ground state energy

$$\langle \tilde{\Psi}|\hat{H}|\tilde{\Psi}\rangle = T[\tilde{\rho}] + \int \tilde{\rho}(r)v(r)\,dr + V_{\text{ee}}[\tilde{\rho}] = E[\tilde{\rho}] \geq E_0[\rho]$$

The advantage of this formulation is that the Schrödinger equation, involving a multi-variable function, is transformed in a variational principle involving a single variable function, the density. Subsequently, Kohn and Sham had the idea of decomposing the multi-electron wave-function in the product of single electrons orbitals, so that the density becomes

$$\rho(r) = \sum_i^N |\phi_i(r)|^2$$

The variational equation can then be written as

$$\left\{ -\frac{1}{2}\nabla^2 + v(r) + V_{\text{H}}(r) + \frac{\delta E_{\text{xc}}[\rho]}{\delta n(r)} \right\} \phi_i(r) = \sum_j \Lambda_{ij}\phi_j(r)$$

i.e. the single electron Schrödinger equation in an effective potential called the Kohn-Sham potential that is the derivative of the Kohn-Sham energy with respect to the density. Λij are Lagrange multipliers that accounts for the orbitals orthonormality. The Kohn-Sham energy is

$$E^{\text{KS}}[\rho] = T_s[\rho] + \int dr\,v(r)\rho(r) + \frac{1}{2}\int dr\,V_{\text{H}}(r)\rho(r) + E_{\text{xc}}[\rho]$$

where $V(r)$ is the external potential (implicitly dependent on the nuclear coordinates), $V_H(r)$ is the Hartree potential (the coulomb part) and T_s the Kinetic part

$$T_s[\rho] = \sum_i^N \left\langle \phi_i \left| -\frac{1}{2}\nabla^2 \right| \phi_i \right\rangle$$

$E_{xc}[\rho]$, the exchange and correlation energy functional, is the only unknown part of the system, for which several different approximation are usually done[1]. Thus, a multi-electronic problem is decomposed in N single electron problems in an external effective potential that is the sum of the coulomb part plus the exchange and correlation part. This theory can be seen as an extension of the Hartree-Fock theory, and allows an extreme gain in the computational cost, making possible modeling systems up to 100 atoms, considerably larger than those addressable with multi-configuration quantum-chemical methods, with approximately the same accuracy for what concerns the ground state properties.

As already pointed out, the exchange and correlation functional is the only part of the energy functional that is not explicitly known. In principle, it contains all the exchange and correlation effects. In other words, all the problems and difficulties that one encounters in multi-electron

wave-function based methods, in DFT are hidden in $E_{xc}[\rho]$. Of course, in the general case $E_{xc}[\rho]$ is not know, however several accurate approximation are available for it[1]. The most popular are based on the Local Density Approximation (LDA): it is assumed that a system with a general non uniform electron density $\rho(\mathbf{r})$ is locally coincident with a uniform electron gas at the same density

$$E_{xc}[\rho] = \int \rho(\mathbf{r}) e_{xc}(\rho(\mathbf{r})) \mathrm{d}\mathbf{r}$$

where $e_{xc}(\rho)$ is the exchange and correlation energy density (single variable) function of a uniform electron gas. This, in turn can be evaluated quite accurately: their asymptotic behavior at small and large densities is exactly know through sum rules and the intermediate behavior was determined with Monte Carlo simulations of the uniform electron gas at different densities[1a]. More sophisticated functionals include gradient corrections (GGA, Generalized Gradient Corrected functionals) or corrections that improve the dispersive part of the VdW interaction, that is one of the main drawback of the LDA[1].

The DFT is a ground state theory. However its Time Dependent extension can account for excited states. In this case the variational principle involves the action functional and its general formulation is quite complex. Within the linear response theory, the excitation energies are located at the poles of the linear response function to an infinitesimal perturbation of an external potential. Using the TDDFT, equation defining the poles becomes an eigenvalues equation[1b]

$$\sum_{a'i'\sigma'} \left[\delta_{\sigma\sigma'}\delta_{aa'}\delta_{ii'}(\epsilon_{j\sigma} - \epsilon_{k\sigma})^2 + 2\sqrt{\epsilon_{a\sigma} - \epsilon_{i\sigma}} K_{ai\sigma,a'i'\sigma'}(\Omega)\sqrt{\epsilon_{a'\sigma'} - \epsilon_{i'\sigma'}} \right] \beta_{a'i'\sigma'}$$

$$= \Omega^2 \beta_{ai\sigma}$$

whose eigenvalues are the square of the excitation energies, and the eigenvectors are related to the oscillator strength (i.e. the intensity of the transition). In this equation, the kernel is

$$K_{jk\sigma,j'k'\sigma'}(\omega)$$

$$= \int \mathrm{d}^3 r \int \mathrm{d}^3 r' \varphi_{j\sigma}^*(\mathbf{r}) \varphi_{k\sigma}(\mathbf{r}) \left[\frac{1}{|\mathbf{r} - \mathbf{r}'|} + f_{xc\sigma\sigma'}(\mathbf{r}, \mathbf{r}', \omega) \right] \varphi_{j'\sigma'}(\mathbf{r}') \varphi_{k'\sigma'}^*(\mathbf{r}')$$

(φ are the Kohn-Sham orbitals and the index σ is the spin index), where f_{xc} is the second derivative of the exchange and correlation energy functional with respect to density. Again, as in the static DFT, one must use some approximation for f_{xc} , that is usually the Adiabatic LDA (i.e. simply taking the static exchange and correlation potential of LDA)[1b]. If the kernel were null, the poles would coincide with the differences between Kohn-Sham energy levels $\varepsilon_{i\sigma}$, that can be considered the zero order approximation for the excitation energies. The first order is obtained solving the above equations and involves a summation over all the KS orbitals. This brings a correction that in many cases can be very relevant, up to 50% of the zeroth order approximation. There is clearly a great amount of approximation in this formulation. The accuracy of the excitation energies obtained with this formulation ranges from 5% to 20%, and it is very dependent on the extension of the electron system, on its degree of delocalization[2]. However, excited state geometries and vibrational properties are quite accurately represented. Additionally, this method is the only one that can be applied to systems as large as the active sites of proteins.

C.2 Classical molecular dynamics
Within the all-atom classical molecular dynamics approach the potential energy surface on which the atoms move is approximated with a sum of analytical terms determined empirically. In principle, one can include many very different terms related to all relevant internal variables of the system

$$V(R) = \sum_b D_b[1 - \exp(-a(b - b_0))]^2 + \sum_\theta H_\theta(\theta - \theta_0)^2 + \sum_\phi H_\phi[1 + s\cos(n\phi)]$$

$$+ \sum_\chi H_\chi \chi^2 + \sum_b \sum_{b'} F_{bb'}(b - b_0)(b' - b'_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'}(\theta - \theta_0)(\theta' - \theta'_0)$$

$$+ \sum_b \sum_\theta F_{b\theta}(b - b_0)(\theta - \theta_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'\phi}(\theta - \theta_0)(\theta' - \theta'_0)\cos\phi$$

$$+ \sum_\chi \sum_{\chi'} F_{\chi\chi'}\chi\chi' + \sum_i \sum_{j>i}\left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} + \frac{q_i q_j}{r_{ij}}\right]$$

but the most common functional form chosen for biological system is

$$E = \sum_{\text{bonds}} k_b (d - d_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi \left[1 + \cos(n\phi + \delta)\right]$$

$$+ \sum_{\substack{\text{non-bonded} \\ \text{pairs AB}}} \left\{ \varepsilon_{AB}\left[\left(\frac{\sigma_{AB}}{r_{AB}}\right)^{12} - \left(\frac{\sigma_{AB}}{r_{AB}}\right)^6\right] + \frac{1}{4\pi\varepsilon_0}\frac{q_A q_B}{r_{AB}} \right\}$$

The first three terms of this FF describe the strength and geometry of the covalent bonds, while the second line describes the Van der Waals (i.e. core exclusion and dipole forces) and Coulomb terms (electrostatic terms)[3] (see Fig B.1). Implicit in this description is the idea that the system does not change the PES during the dynamics.
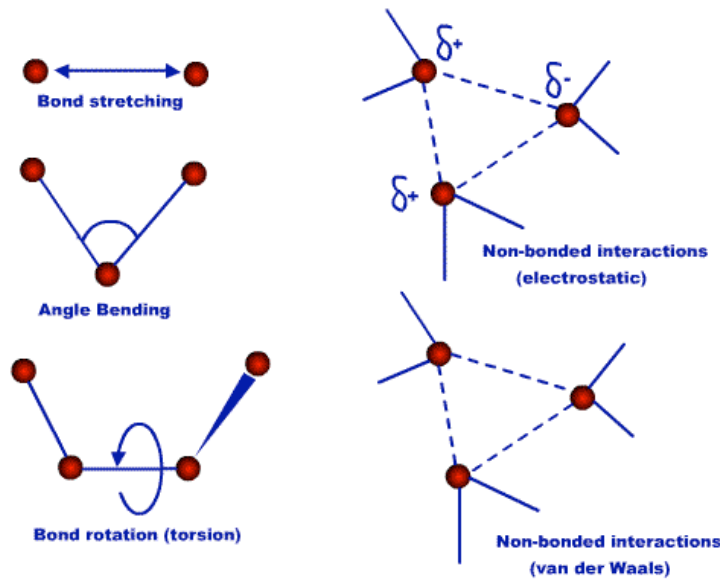

Fig B.1 Schematic description of the terms of the FF for biological molecules. On the left the "bonded interactions" corresponding to the first three terms of the FF equation. On the right, the non bonded (VdW and electrostatic).

There are several different FFs for proteins and nucleic acids, differing either for the kind or analytical form used, or for the parameterization procedure. The FF typically used for proteins or nucleic acids (Amber, Charmm), are based on the fitting of ab initio PES for small molecules and on the reproduction of thermodynamic structural data. Of course, a drawback of this kind of

approach is the transferability: these FFs are typically parameterized to work well for simulations at room temperature and do not give accurate results at different temperatures.In spite of these problems, the FF based approaches are the most used to simulate system of the size of proteins with very different methods of exploration of the configurational phase space.

One of these methods is the Classical Molecular Dynamics, consisting in the numerical solution of the classical equations of motion with the forces generated by a FF:

$$M_I \ddot{R}_I(t) = -\frac{\partial E}{\partial R_I}$$

Within the microcanonical ensemble, i.e. for simulations at constant total energy, the equations are solved with algorithms based on the Taylor expansion of the forces and velocities: at each time t, positions, velocities and forces are evaluated, and those at time t+Δt are generated as a function of them. For instance, in the velocity Verlet algorithm, one has

$$\mathbf{r}(t + \Delta t) = \mathbf{r}(t) + \Delta t \mathbf{v}(t) + \frac{\Delta t^2 \mathbf{a}(t)}{2}$$

$$\mathbf{a}(t + \Delta t) = \frac{\mathbf{f}(t + \Delta t)}{m}$$

$$\mathbf{v}(t + \Delta t) = \mathbf{v}(t) + \frac{1}{2}\Delta t[\mathbf{a}(t) + \mathbf{a}(t + \Delta t)]$$

However, in general a simulation at constant energy is not the most efficient way to explore the phase space of the system. The choice of the timestep Δt is crucial: it has to be the smallest possible for the integration to be accurate, but the largest possible for the integration to be fast. A good compromise is one tenth of the inverse of the largest typical frequency of the system.

The conditions most similar to the "real" ones are at constant temperature (and pressure). One way to keep constant the temperature is the scaling of velocities at each timestep

$$\underline{v}(t + \frac{1}{2}\Delta t) \leftarrow (2\eta - 1)\underline{v}(t - \frac{1}{2}\Delta t) + \eta\Delta t\frac{f(t)}{m}$$

$$\underline{r}(t + \Delta t) \leftarrow \underline{r}(t) + \Delta t\underline{v}(t - \frac{1}{2}\Delta t)$$

$$\eta = \sqrt{\frac{T_{ext}}{T}}$$

where η is an inverse coupling time with the thermal bath. Alternatively, one can introduce additional fictitious degrees of freedom to describe the coupling with the thermal bath (and/or with the pressure bath) to simulate accurately the canonical ensemble

$$H^* = \sum_i \frac{\mathbf{p}_i^2}{2m_i} + \phi(\mathbf{q}) + \frac{Q}{2}\zeta^2 + gkT\ln S$$

here ζ is the velocity (time derivative) associated to the fictitious degree of freedom S, ϕ the total potential energy and p,q the canonical variables. The fictitious mass Q and coupling constant g must be chosen to realistically regulate the velocity of energy flow between the thermal bath and the system. This formulation (Nose and Nose-Hoover coupling) ensures that the equilibrium distribution is that of the Canonical ensemble[4].

C.3 Stochastic molecular dynamics

Stochastic molecular dynamics can be used to simulate the effect of the random bumps of the solvent (e.g. water molecules) on the dynamics of the solute. The Langevin equation can be used to this aim

$$m_i \frac{\mathrm{d}^2 r_i}{\mathrm{d}t^2} = F_i(t) - \gamma m_i \frac{\mathrm{d}r}{\mathrm{d}t} + R_i(t)$$

where γ is a damping constant and R_i is the stochastic external force acting on a single atom. For the temperature to remain approximately constant, the energy loss due to damping must be equal on average to the energy gain due to the stochastic force, that can be expressed by the equation

$$< R_i(0)R_j(t) > = 2m_i \gamma k_\mathrm{B} T \delta_{ij}(t)$$

In some sense, the Langevin dynamics can be viewed as a special case of a thermostat.
In the over-damped limit, the second order term of the Langevin equation can be neglected. The equation is then recast in the form

$$\mathrm{d}r_i = \frac{D_i}{k_\mathrm{B}T} F_i(t)\mathrm{d}t + \bar{r}_i(t)$$

that is called the Brownian dynamics equation. The advantage with respect to the Langevin eqn is that this is a first order equation, more easy to solve or numerically integrate. In the practice, this means that larger time steps for integration can be chosen. The diffusion coefficient D_i is

$$D_i = \frac{k_\mathrm{B}T}{6\pi\eta(r_i + 1.4 \text{ Å})}$$

where r_i is the hydrodynamic radius of the considered atom, η is the viscosity of the solvent. D_i is related to γ of the Langevin equation via $\gamma = k_\mathrm{B}T/mD$.

C.4 Monte Carlo simulations

Molecular dynamics gives an idea of the realistic time scales involved in the dynamical evolution of a system, but is not the more efficient way to sample the phase space. Monte Carlo simulations are more efficient to this purpose. They essentially consist in a stochastic sampling where the new configuration at each time-step is considered valid on probabilistic bases. For instance, the algorithm of one the Metropolis Monte Carlo method is the following

1. given the starting configuration, evaluate the energy of the system, ε_0
2. make a random step and and evaluate the energy of the system in the new state ε_1
3. if $\varepsilon_1 < \varepsilon_0$ accept the new configuration with probability 1; otherwhise, accept the new configuration with probability exp(-$\Delta\varepsilon$/KT)
4. repeat from 1.

With this algorithm the system is sampled according to the Boltzman statistics. Monte Carlo Methods are often used when dynamics is not important (the time step has no more the meaning of a real time), but an efficient space sampling is important.

C.5 Car-Parrinello molecular dynamics

Car-Parrinello molecular dynamics is an efficient way to combine a quantum chemical description of electrons dynamics and a classical description of the nuclei dynamics in a unique frame. As we have seen in section 1, thanks to the very different masses and time scales of their dynamics, the electron dynamics can be separated by the nuclear dynamics by means of the so called adiabatic approximation, so that one is left with two sets of Schrödinger equations: that for electrons in the external potential due to the instantaneous current nuclear configuration, and that for nuclei, that experience an effective potential due to the electron distribution, called PES, that depends on which electronic state the system is in (ground or excited states). In most cases the motion of nuclei can be considered classical with a good approximation, so that the Schrödinger equation for nuclei can be substituted with the classical Newton equation. Additionally, the quantum problem for electron can be solved within the DFT frame, so that the Schrödinger equation for electron can be substituted by the set of Kohn-Sham equations (see above). In these conditions, the algorithm to for the dynamical evolution of the system can be the following

1. given the starting configuration, solve the KS equations for electrons
2. evaluate the energy of the system, and its derivatives with respect to the nuclear coordinates, i.e. the forces
3. using these forces, evolve the system of 1 timestep, using any of the aboved described algorithms for classical molecular dynamics
4. repeat from 1.

This is called Born-Oppeheimer molecular dynamics, and is often performed. At each timestep, the KS electronic equation must be solved, meaning a full cycle of electronic energy minimization, that can be done iteratively involving many electronic minimization steps.

The idea underlying Car-Parrinello molecular dynamics is to solve contemporaneously the equations for nuclei and electrons, i.e., one single electronic evolution step for each nuclear step. In the practice, this is realized in the following system of equations

$$M_I \ddot{\boldsymbol{R}}_I(t) = -\frac{\partial E^{\mathrm{KS}}}{\partial \boldsymbol{R}_I} + \sum_{ij} \Lambda_{ij} \frac{\partial}{\partial \boldsymbol{R}_I} \langle \phi_i \mid \phi_j \rangle$$

$$\mu \ddot{\phi}_i(t) = -\frac{\delta E^{\mathrm{KS}}}{\delta \langle \phi_i \mid} + \sum_j \Lambda_{ij} \mid \phi_j \rangle$$

where μ is a fictitious mass for a fictitious classical dynamics for the KS orbitals. If $\mu=0$ one obtains a variational equation that is equivalent to the KS equations for electrons. This remains approximately true for small values of μ. The algorithm to perform Car-Parrinello dynamics is the following

1. given the starting configuration, solve the KS equation for electrons
2. evaluate the forces through the derivative of E^{KS} with respect to nuclear positions and perform a nuclear step
3. at the same time evaluate the fictitious forces acting on orbitals (i.e. the functional derivative of E^{KS} with respect to orbitals) and perform an electronic evolution step; 2.+3. bring the system in a new nuclear AND electronic configuration
4. repeat from 2.

It is to be noted that only one electronic step is performed for only nuclear step, and the computationally demanding full electronic minimization is performed only in the starting configuration. In fact, if μ is small enough, the new electronic configuration corresponding to the new nuclear configuration will be already near enough to the minimal one (corresponding to the exact ground state). On the other side, μ must be large enough to ensure the use of reasonably large timesteps, in order to have a fast integration of the equations.

In summary, Car-Parrinello dynamics is a "trick" to adiabatically evolve the electrons always near the exact ground state as the nuclei move on the PES, although the real ground state is never exactly realized. But the distance of the electronic state from the real ground state is measured by μ, thus it can be made small in a controllable fashion.

C.6 Meta-Dynamics

As already pointed out, as the system become larger, the problem of an efficient phase space sampling becomes more and more relevant. We have already seen different ways to overcome this problem. One way is trying to speed-up the calculations, in order to have longer runs (Car-Parrinello dynamics, Classical Dynamics). Other routes involve using stochastic dynamics or Monte-Carlo methods.

Recently another route was proposed, that exploits the idea that for each process there is a small set of relevant collective variables essential to describe the process, while all the other variables

contribute to the free energy but are not relevant to the description of the processes. For instance, this is the case of the so called reaction coordinates. Calling these variables s_i, $i = 1,n$ one can consider the exploration of the free energy surface (FES) related to them, $F(s)$ (also called the "potential of mean force", that is, the free energy of the system as a function of a constrained variable) that is driven by the mean forces, i.e. the negative derivative of F with respect to s. The system tend to move forward the minimum of the free energy, and in principle can be evolved on the FES using any of the above described evolution algorithms. However we observe that at each (time)step one needs a free energy calculation to evaluate the forces, implying usually a set of (possibly short) simulations with constrained s_i, to average the total energy and obtain free energy. Thus the gain in computational cost might not be so large.
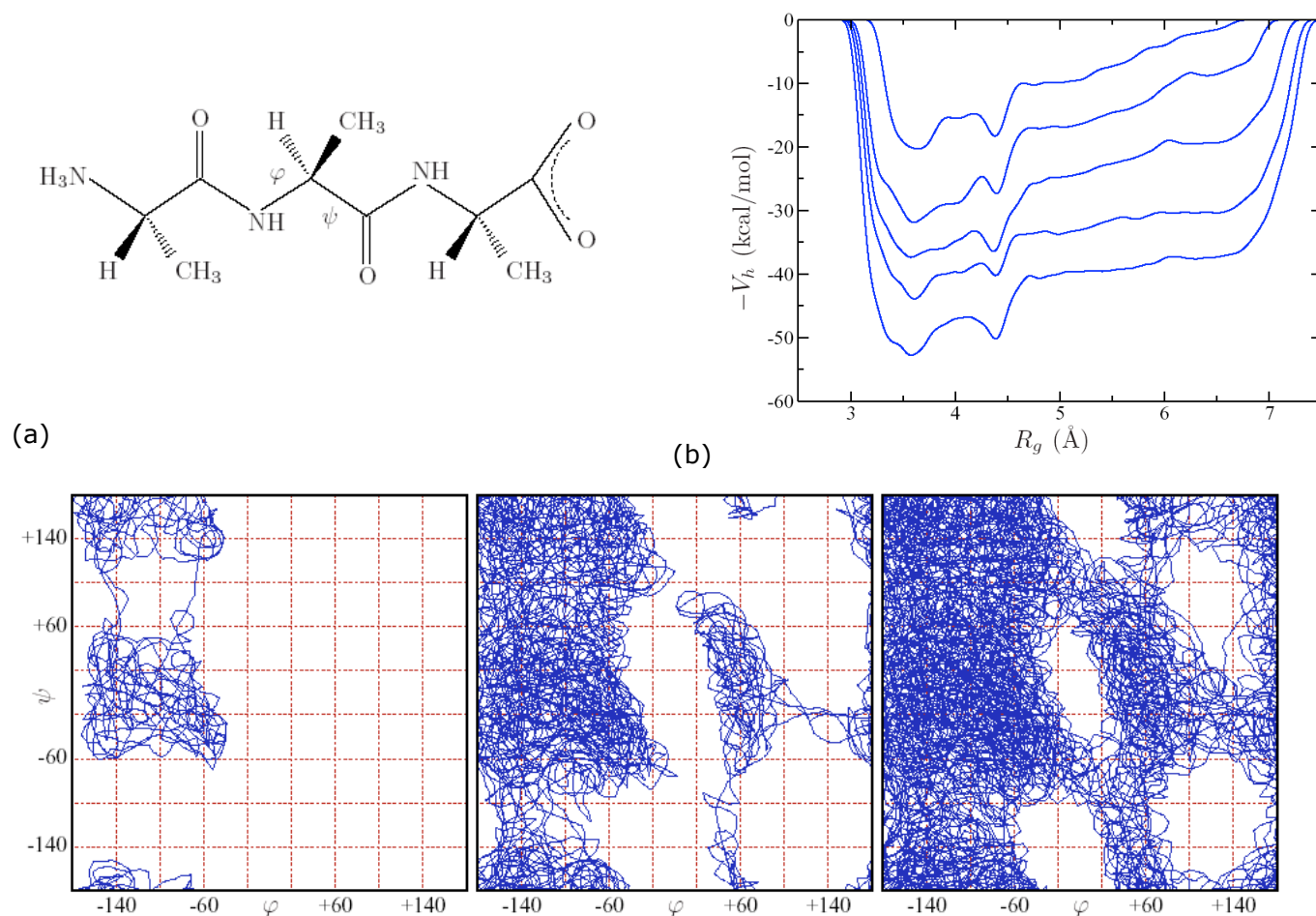

(a)

(b)

(c)

Fig C.1 (a) Representation of an alanine tripeptide (b) The chage of the (negative) metadynamic time dependent potential as a function of the gyration radius (the collective variable) (c) The population of the Ramachandran map of the tripeptide as a function of time

An idea to effectively "accelerate" dynamics and explore the $F(s)$ is to add to the real multi variable potential $V(x)$, from time to time, a Gaussian external potential with properly chosen width and height[5,6]

$$V_G(s(x), t) = w \sum_{\substack{t' = \tau_G, 2\tau_G, 3\tau_G, \ldots \\ t' < t}} \exp\left(-\frac{(s(x) - s(x_G(t')))^2}{2\delta s^2}\right)$$

so that the atoms move in a time-dependent external potential $V(x) + V_G(s(x),t)$ that has the effect of "repelling" the system from the configuration it is at the time when the Gaussian is added. If

the system is found in a potential well, the effect of this external potential is to move it out of the wells and explore more efficiently the phase space. Additionally, after some time has passed, the potential wells will be fillede and the negative of $V_G(s(x),t)$ will approximately equal the free energy

$$F_G(s, t) = -w \sum_{\substack{t' = \tau_G, 2\tau_G, 3\tau_G, \ldots \\ t' < t}} \exp\left(-\frac{(s - s(x_G(t')))^2}{2\delta s^2}\right)$$

We observe that this kind of approach can be applied to any system that is usually described by a classical molecular dynamics (even an effective classical molecular dynamics, for instance Car-Parrinello). The final result in any case is that, if the parameters are properly chosen, the system undergoes to an accelerated dynamics that rapidly escapes the energy minima to explore the adjacent minima. As in other sampling dynamics, the time is not a realistic time variable, although it is somewhat related to the evolutionary time on the FES. Additionally, after a reasonable time, the inverse of the effective time dependent potential is a good approximation of the potential of mean force with respect to the collective variable(s).

Fig C.1 illustrates these concepts on the simulation of an alanine tripeptide. The collective variable chosen is the gyration radius (an effective radius measuring the size of the system). As the time passes the free energy profiles is more and more well defined. The efficiency of the phase space sampling is demonstrated by the fact that the Ramachandran map is very accurately described during the simulation, indicating that the high energy barriers due to the rotation around the dihedrals can easily be overcome.

References
[1] J Thar, W Reckien, B Kirchener, Car Parrinello Molecular Dynamics Simulations and Biological systems, Top Curr Chem 268, 133-171 (2006)
[1a] DM Ceperley, BJ Alder, Phys Rev Lett 47, 566 (1980); D Ceperley Phys Rev B 1, 3126 (1978); B Tanatar DM Ceperley Phys Rev B 39, 5005 (1989).
[1b] MAL Marquez, EKU Gross, Annu Rev Phys Chem 55, 427-55 (2004)
[2] R Nifosí, P Amat, V Tozzini, J Comput Chem, in press.
[3] H M Senn, W Thiel QM/MM Methods for Biological Systems Top Curr Chem 268, 173-290 (2006)
[4]*Understanding Molecular Simulations* Frenkel, Smit, Academic Press Ed (1996)
[5] A Laio, A Rodrigues-Fortea, FL Gervasio, M Ceccarelli, M Parrinello, J Phys Chem B, 109 6714-6721 (2005)
[6] Babin V, Roland C, Darden TA, Sagui C, J Chem Phys. 125 204909 (2006)