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Master equation of proteins in interaction with implicit or explicit solvent.

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Theoretical studies of protein folding on lattice models rely on the assumption that water close to amino-acids is always in thermal equilibrium all along the folding pathway. Within this framework, it has always been considered that out-of-equilibrium properties, such as folding time, could be evaluated equivalently from an averaging over a collection of trajectories of the protein with water described either explicitly or through a mean-field approach. To critically assess this hypothesis, we built a two-dimensional lattice model of a protein in interaction with water molecules that can adopt a wide range of conformations. This microscopic description of the solvent has been used further to derive an effective model by averaging over all the degrees of freedom of the solvent. At thermal equilibrium, the two descriptions are rigorously equivalent, predicting the same folded conformation of the protein. The model allows exact calculations of some relaxation properties using the master equations associated to both solvent descriptions. The kinetic patterns associated to the folding pathways are remarkably different. In this work we demonstrate, that an effective description of the solvent can not describe properly the folding pathway of a protein. The microscopic solvent model, that describes correctly the microscopic routes, appears to be the only candidate to study folding kinetics.

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Proteins folding is a hot topic of the biophysics field and the question of the mechanisms which governs its kinetics is still in debate. The two ingredients guiding a protein towards its native structure are the distribution of the intrachain interactions and the solvent effect[1]. Thus, the solvation of hydrophobic compounds at thermal equilibrium has been widely studying to extract the key role of the water in protein folding[2–7].

However, in most of the works using lattice models for protein, the effect of the solvent is usually taken into account by a temperature independent, structure-less, parameter which simply increases the strength of the some intrachain contact[8, 9]. The lattice model using such couplings also provided numerous kinetics works using Monte Carlo simulations [10–13] or evolutions of the master equation[14–20]. In these works, as the potential associated to each protein structure results from an average over the degrees of freedom, the kinetics is guided by transition rates between chain conformations in interaction with an effective solvent whose mean energy does not depend on the temperature. However, numerous experimental results showing the importance of the relaxation of the first shell solvent on the folding kinetics illuminate the importance of the degrees of freedom of the first shell solvent for the fast kinetics of folding[21–24]

In a few recent works, the contribution of the solvent effect on the configurational Hamiltonian becomes temperature dependent because they result from an average over the water configurations. In these models, the solvent around the proteins is modeled by its energy spectra which takes into account of the formation or breakage of the water hydrogen bonds. Such an approach gave an explanation of cold denaturation[25, 26].

Recently, we calculated the kinetics of the folding of a protein model in interaction with implicit water

model[27] where the role of the hydrogen bonds of the first shell solvent was taken into account.

Here, we compare the results obtained for the kinetics of folding of protein where each chain structure is in interaction with a highly degenerated microscopic solvent in one hand and with the equivalent effective solvent in an other hand. A micro-state of the system "protein-solvent" is given by the conformation of the protein and the position of the atoms of water (the solvent configuration). We calculated the evolution in time of the probability of occurrence of each protein-solvent micro-state toward the native structure of the protein, using a master equation approach and starting far from equilibrium.

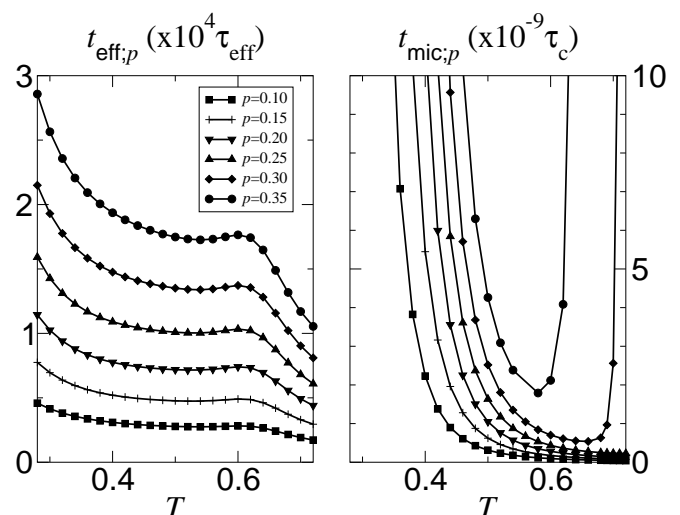


FIG. 1: Time after which the probability of occurrence of the native state equals some values p as function of the temperature starting from an equiprobability of each protein-solvent configurations. Calculations are performed with the explicit (left) and the implicit (right) solvent models.

The waiting times to observe the native structure with a probability p , noted $t_{\text{mic};p}$ are calculated as functions of the temperature for p varying from 0.10 to 0.30 by steps of 0.05.

On an other hand, the effective solvent model is introduced by integrating out the water degrees of freedom of the same solvent model and by computing the free energy of hydration of each protein conformation. Simulations start from the equivalent initial condition to that stated for the microscopic model calculation. The evolution in time of the probabilities of the protein conformations is also computed using a master equation and the waiting times, $t_{\text{eff};p}$, to observe the native structure with a probability p are also calculated under the same conditions.

The curve of $t_{\text{mic};p}(T)$ and $t_{\text{eff};p}(T)$, shown in fig.1, present clearly different shapes and orders of magnitude.

Model. The protein is modeled by a self avoiding walk chain whose the twelve beads are positioned on the nodes of a two-dimensional lattice. The number of intrachain contacts of the chain conformation m is $C_m = \sum_{i \geq j+3} \Delta_{ij}^{(m)}$ where $\Delta_{ij}^{(m)} = 1$, if the monomers i and j are first neighbors on the lattice, and 0 otherwise. The accessible surface area to the solvent is $A_m = 2N + 2 - 2C_m$ [26].

The bulk contribution is taken as a mean effect which increases with respect of the number of intrachain contacts and the first shell contribution increases with the accessible surface area to the solvent. One configuration ($\beta = 0$) of the first shell is well ordered and the other are disorganized.

The Hamiltonian of the micro-state where the protein is in conformation m , the first shell in configuration β and the bulk in structure α is:

$$\mathcal{H}_{m\alpha\beta}^{\text{mic}} = \sum_{i>j} B_{ij} \Delta_{ij}^{(m)} + 2C_m \varepsilon_{\text{bk}} + \sigma(\beta) A_m \varepsilon_{\text{sh}}$$

$$\text{for } 1 \leq \alpha \leq g_{\text{bk}}^{2C_m} \quad \text{and} \quad \begin{cases} \sigma(0) = 0 \\ \sigma(\beta) = 1 \text{ if } 1 \leq \beta \leq g_{\text{sh}}^{A_m} \end{cases}$$

The intrachain couplings B_{ij} between monomers i and j are drawn at random from a Gaussian distribution centered on $B_0 = -2$ with standard deviation equals 1 [8]. The values of the solvent parameters are ranked as follow $\varepsilon_{\text{bk}} = 0.4$, $\varepsilon_{\text{sh}} = 0.8$, $g_{\text{bk}} = 3.3$ and $g_{\text{sh}} = 3.5$ [27].

The Hamiltonian of each protein structure m takes two values following that of β . The ground state, noted $(-)$, is associated to a value of $\sigma = 0$ (for $\beta = 0$) and the excited state, $(+)$, to $\sigma = 1$ (for $\beta > 0$). The Hamiltonian and the degeneracy of the macro-states ($m\sigma$) are :

$$\mathcal{H}_{m\sigma}^{\text{mac}} = \sum_{i>j} B_{ij} \Delta_{ij}^{(m)} + 2C_m \varepsilon_{\text{bk}} + \sigma A_m \varepsilon_{\text{sh}}$$

$$g_{m\sigma} = \sum_{\alpha=1}^{g_{\text{bk}}^{2C_m}} \sum_{\beta=0}^{g_{\text{sh}}^{A_m}} \delta(\sigma - \sigma(\beta)) = g_{\text{sh}}^{\sigma A_m} g_{\text{bk}}^{2C_m}$$

where $\delta(x) = 1$ if $x = 0$ and 0 otherwise.

Then, the partition function may be written as :

$$\begin{aligned} Z(T) &= \sum_m \sum_{\alpha=1}^{g_{\text{bk}}^{2C_m}} \sum_{\beta=0}^{g_{\text{sh}}^{A_m}} \exp\left(-\frac{\mathcal{H}_{m\alpha\beta}^{\text{mic}}}{T}\right) && \text{(micro - states)} \\ &= \sum_m \sum_{\sigma=0}^1 g_{m\sigma} \exp\left(-\frac{\mathcal{H}_{m\sigma}^{\text{mac}}}{T}\right) && \text{(macro - states)} \\ &= \sum_m \exp\left(-\frac{\mathcal{H}_m^{\text{eff}}(T)}{T}\right) && \text{(effective)} \end{aligned}$$

The temperature dependent effective Hamiltonian of conformation m , where the solvent degrees of freedom have been integrating out, is given by :

$$\mathcal{H}_m^{\text{eff}} = -T \ln \sum_{\alpha=1}^{g_{\text{bk}}^{2C_m}} \sum_{\beta=0}^{g_{\text{sh}}^{A_m}} \exp\left(-\frac{\mathcal{H}_{m\alpha\beta}^{\text{mic}}}{T}\right)$$

that is to say,

$$\begin{aligned} \mathcal{H}_m^{\text{eff}} &= \sum_{i>j} B_{ij} \Delta_{ij}^{(m)} + 2C_m \varepsilon_{\text{bk}} \\ &\quad - T \ln \left[g_{\text{bk}}^{2C_m} \left(1 + g_{\text{sh}}^{A_m} \exp\left(-\frac{A_m \varepsilon_{\text{sh}}}{T}\right) \right) \right] \end{aligned}$$

The effective Hamiltonian has been written to satisfy to the partition function which determines the properties of the system at equilibrium but out-of-equilibrium, this function have no more a clear physical meaning.

The probability of occurrence of the conformation m at equilibrium is : $P_m^{\text{eq}} = \exp(-\mathcal{H}_m^{\text{eff}}/T) / Z(T)$. The native conformation is the structure of the largest probability determined by a full enumeration of the conformational space.

Dynamics of the microscopic solvent model.

The out-of-equilibrium probability of occurrence of the micro-state ($m\alpha\beta$) at time t is denoted $P_{m\alpha\beta}^{\text{mic}}(t)$. It evolves following the master equation[27]:

$$\frac{dP_{m\alpha\beta}^{\text{mic}}(t)}{dt} = \sum_{m'\alpha'\beta'} X_{m\alpha\beta, m'\alpha'\beta'} P_{m'\alpha'\beta'}^{\text{mic}}(t)$$

where

$$X_{m\alpha\beta, m'\alpha'\beta'} = \frac{V_{mm'}^{(0)}}{\tau_{m,m'}^{\text{mic}}} a_T(\mathcal{H}_{m\alpha\beta}^{\text{mic}}, \mathcal{H}_{m'\alpha'\beta'}^{\text{mic}})$$

is the microscopic transition rate between the configurations ($m'\alpha'\beta'$) to ($m\alpha\beta$) and the diagonal terms are:

$$X_{m\alpha\beta, m\alpha\beta} = - \sum_{m'\alpha'\beta'} X_{m'\alpha'\beta', m\alpha\beta}$$

with $V_{mm'}^{(0)} = 1$ and $\tau_{m,m'}^{\text{mic}} = \tau_c$ if the chain structures m and m' are connected by a one-monomer move and

$V_{mm}^{(0)} = 1$ and $\tau_{mm}^{\text{mic}} = \tau_s$ for the solvent modifications which keep the chain structure unchanged. The acceptance function, $a_T(x, x') = [1 + \exp((x - x')/T)]^{-1}$, satisfies to the microscopic detailed balance condition. These probabilities evolves using an Euler algorithm [16] :

$$P_{m\alpha\beta}^{\text{mic}}(t + \delta t) = P_{m\alpha\beta}^{\text{mic}}(t) + \delta t \sum_{m'\alpha'\beta'} X_{m\alpha\beta, m'\alpha'\beta'} P_{m'\alpha'\beta'}^{\text{mic}}(t)$$

The out-of-equilibrium probability of occurrence of the macro-state ($m\sigma$), at time t is :

$$\mathcal{P}_{m\sigma}^{\text{mac}}(t) = \sum_{\alpha\beta} P_{m\alpha\beta}^{\text{mic}}(t) \delta(\sigma - \sigma(\beta))$$

Then, at time $t + \delta t$, it becomes:

$$\begin{aligned} \mathcal{P}_{m\sigma}^{\text{mac}}(t + \delta t) &= \sum_{\alpha\beta} P_{m\alpha\beta}^{\text{mic}}(t + \delta t) \delta(\sigma - \sigma(\beta)) \\ &= \sum_{\alpha\beta} P_{m\alpha\beta}^{\text{mic}}(t) \delta(\sigma - \sigma(\beta)) \\ &+ \sum_{\alpha, \beta} \delta t \sum_{m'\alpha'\beta'} X_{m\alpha\beta, m'\alpha'\beta'} P_{m'\alpha'\beta'}^{\text{mic}}(t) \delta(\sigma - \sigma(\beta)) \end{aligned}$$

Using the following equality $\sum_{\sigma'} \sum_{\alpha'\beta'} \delta(\sigma' - \sigma(\beta')) f_{\beta'} = \sum_{\alpha'\beta'} f_{\beta'}$, it comes:

$$\begin{aligned} \mathcal{P}_{m\sigma}^{\text{mac}}(t + \delta t) &= \sum_{\alpha\beta} P_{m\alpha\beta}^{\text{mic}}(t) \delta(\sigma - \sigma(\beta)) \\ &+ \delta t \sum_{m'} \sum_{\sigma'} \sum_{\alpha'\beta'} \sum_{\alpha, \beta} \delta(\sigma' - \sigma(\beta')) \delta(\sigma - \sigma(\beta)) \\ &\frac{V_{mm'}^{(0)}}{\tau_{m, m'}^{\text{mic}}} a_T(\mathcal{H}_{m\alpha\beta}^{\text{mic}}, \mathcal{H}_{m'\alpha'\beta'}^{\text{mic}}) P_{m'\alpha'\beta'}^{\text{mic}}(t) \\ &= \mathcal{P}_{m\sigma}^{\text{mac}}(t) + \delta t \sum_{m'} \sum_{\sigma'} Y_{m\sigma, m'\sigma'} \mathcal{P}_{m'\sigma'}^{\text{mac}} \end{aligned}$$

with

$$Y_{m\sigma, m'\sigma'} = g_{m\sigma} \frac{V_{mm'}^{(0)}}{\tau_{m, m'}^{\text{mic}}} a_T(\mathcal{H}_{m\sigma}^{\text{mac}}, \mathcal{H}_{m'\sigma'}^{\text{mac}}) \quad (1)$$

The increment of time is chosen as $\delta t = 1/\max_{m\sigma} \{Y_{m\sigma, m\sigma}\} \ll 1$ in order to maintain the sum of the probabilities equals to 1. The form of the transition rates $Y_{m\sigma, m'\sigma'}$ implies that the probability distribution converges to $\mathcal{P}_{m\sigma}^{\text{mac}}(t) \rightarrow g_{m\sigma} \exp(-\mathcal{H}_{m\sigma}^{\text{mac}}/T)/Z(T)$.

The simulations starts with the initial condition : $\mathcal{P}_{m\sigma}^{\text{mac}}(0) = g_{m\sigma}/\sum_{m\sigma} g_{m\sigma}$ which set the same initial weight to any micro-state.

The time needed to observe the native structure, with a probability p is noted $t_{\text{mic};p}$ or in other words : $\sum_{\sigma=0}^1 \mathcal{P}_{\text{Nat}, \sigma}^{\text{mac}}(t_{\text{mic};p}) = p$.

Dynamics of the effective solvent model. Consider now the evolution of the probability of occurrence, $P_m^{\text{eff}}(t)$ of the chain structure m in interaction with an effective solvent starting with the initial effective probability $P_m^{\text{eff}}(0) = \sum_{\sigma} \mathcal{P}_{m\sigma}^{\text{mac}}(0)$.

at time $t = 0$. The effective probabilities evolve following the master equation :

$$\frac{dP_m^{\text{eff}}(t)}{dt} = \sum_{m'} V_{mm'} P_{m'}^{\text{eff}}(t)$$

where $V_{mm'} = V(m' \rightarrow m)$ is the transition rate from conformations m' to m . In order to satisfy to the condition of the convergence towards the equilibrium probability distribution, a solution for the rate is :

$$V_{mm'} = \frac{V_{mm'}^{(0)}}{\tau_{\text{eff}}} a_T(\mathcal{H}_m^{\text{eff}}, \mathcal{H}_{m'}^{\text{eff}}) \quad (2)$$

where τ_{eff} is the effective time associated to a chain move. Defining $V_{mm} = -\sum_{m' \neq m} V_{m'm}$ and using the Euler algorithm the evolution equation reads:

$$P_m^{\text{eff}}(t + \delta t_{\text{eff}}) = P_m^{\text{eff}}(t) + \delta t_{\text{eff}} \sum_{m'} V_{mm'} P_{m'}^{\text{eff}}(t)$$

with $\delta t_{\text{eff}} = 1/\max_m \{V_{mm}\}$. Obviously, the probability distribution tends towards $P_m^{\text{eff}}(t) \rightarrow P_m^{\text{eq}}$. The probability of the native structure reaches p at a time, denoted by $t_{\text{eff};p}$.

In contrast with the previous approach, the solvent degrees of freedom are integrated first, here, and afterwards the transition rates are calculated using the effective potential. This is the procedure usually applied in lattice model of protein where the attractive term between monomers results indeed of an average of the solvent degrees of freedom.

Discussion. We address now, the question of a possible equivalence between both descriptions after rewriting the effective characteristic time of the transition between two chain structures would be a, time independent function of the parameters associated to the two connected chain conformations. At this purpose, we require to satisfy the following equality for every protein conformation:

$$P_m^{\text{eff}}(t) = \mathcal{P}_{m-}^{\text{mac}}(t) + \mathcal{P}_{m+}^{\text{mac}}(t)$$

$$\Rightarrow \frac{dP_m^{\text{eff}}(t)}{dt} = \frac{d\mathcal{P}_{m-}^{\text{mac}}(t)}{dt} + \frac{d\mathcal{P}_{m+}^{\text{mac}}(t)}{dt}$$

$$\begin{aligned} \Rightarrow \sum_{m'} \frac{V_{mm'}^{(0)}}{\tau_{\text{eff}}} a_T(\mathcal{H}_m^{\text{eff}}, \mathcal{H}_{m'}^{\text{eff}}) P_{m'}^{\text{eff}}(t) &= \\ \sum_{m'} \sum_{\sigma'} \sum_{\sigma} g_{m\sigma} \frac{V_{mm'}^{(0)}}{\tau_{m, m'}^{\text{mic}}} a_T(\mathcal{H}_{m\sigma}^{\text{mac}}, \mathcal{H}_{m'\sigma'}^{\text{mac}}) \mathcal{P}_{m'\sigma'}^{\text{mac}}(t) & \end{aligned}$$

As only chain moves may be considered, the above equation leads to :

$$\tau_{\text{eff}} = \tau_c \frac{a_T(\mathcal{H}_m^{\text{eff}}, \mathcal{H}_{m'}^{\text{eff}}) P_{m'}^{\text{eff}}(t)}{\sum_{\sigma'} \sum_{\sigma} g_{m\sigma} a_T(\mathcal{H}_{m\sigma}^{\text{mac}}, \mathcal{H}_{m'\sigma'}^{\text{mac}}) \mathcal{P}_{m'\sigma'}^{\text{mac}}(t)}$$

where it appears clearly that τ_{eff} depends on the time in this equation.

This definitively proves that the kinetics of folding of the proteins can not be understood using protein-solvent models where the degrees of freedom of water have been integrating out in a conformational free energy of solvation.

However, we mention that some relations may be found for extreme temperatures. At very low temperature, as $\mathcal{H}_m^{\text{eff}} \rightarrow \mathcal{H}_{m-}^{\text{mac}} - T \ln g_{m-}$, and as we may assume that the excited states always have a nil non-equilibrium probability, the above equation leads to an effective characteristic time, only depending on the ground states of the two connected chain conformations:

$$\tau_{\text{eff}}^{mm'} = \frac{1 + \exp(\Delta\mathcal{H}_{mm'}^-/T)}{g_{m-} + g_{m'-} \exp(\Delta\mathcal{H}_{mm'}^-/T)} \tau_c$$

with $\Delta\mathcal{H}_{mm'}^- = \mathcal{H}_{m-}^{\text{mac}} - \mathcal{H}_{m'-}^{\text{mac}}$. Putting this results into eq.2, it comes $V_{mm'} = Y_{m-,m'-}$ and assuming that only the ground states of the protein structures are visited, the two kinetics becomes equivalent. In a similar way, at very high temperature (under which the protein is unfolded), as $\mathcal{H}_m^{\text{eff}} \rightarrow \mathcal{H}_{m+}^{\text{mac}} - T \ln g_{m+}$ and as we may assume that only the excited states have a non nil probability to occur, an equivalent relation between both characteristic time (where the - are replaced by some +) may be found which leads to $V_{mm'} = Y_{m+,m'+}$. In both extreme temperature cases, it is possible to rewrite effective kinetics equations equivalent to the microscopic ones but that is not feasible at medium temperature.

Conclusion. Waiting times to observe some proportions of folded proteins have been calculated using a microscopic description of the solvent and the equivalent mean effect on the chain conformation weights. In both cases, the evolution of the system depends on the ratio of the difference of (free) energies, induced by the attempted moves, over the temperature.

In the first simulations, the (huge) configurational space is composed of all the protein and solvent microstates. The result of the acceptance function of move depends on the energy associated to the microscopic configurations. In other words, the protein and the solvent evolves by performing structural changes between microscopic realizations of the system but the calculations converge slowly towards the equilibrium distribution of the protein conformation, as the value of δt is very small.

In the latter, the conformational space is smaller but the folding takes places in an "free energy" landscape. However, for not too small temperature, the solvation entropy contribution to the values of the effective Hamiltonian leads to free energy values smaller than the ground state energy for each protein structures. As a consequence, the folding takes place in a conformational space in which the values of the effective Hamiltonian are not associated to a physical realization. Here, the simulations converge very fast towards equilibrium (as $\delta t_{\text{eff}} \ll \delta t$) but... by following non-physical routes.

As a consequence, an microscopic solvent model is the only good candidate to study the out-of-equilibrium folding of proteins and the effective solvent may only be restricted to the study of equilibrium properties.

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