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# Coarse-grained molecular dynamics and continuum models for the transport of protein molecules

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## Abstract.

*We describe protein transport across nanopores in a coarse-grained modeling. Numerical results reproduce a rich phenomenology, from fast transport to long blockades. Main translocation features are maintained in a 1D description of the process in an appropriate potential of the mean force. A second-rank tensor is selected as descriptor of the molecular shape. Its dynamics is identified by a power-equivalence procedure and Cauchy-Born rule. The modeling is supplemented by heuristic approaches that appear adequate also in unconstrained dynamics.*

**Keywords:** translocation; stall; molecular dynamics; free-energy; langevin; continuum model; complex materials.

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## 1 INTRODUCTION

The transport of proteins across nanopores is a process called *translocation*. Membrane transport is a fundamental event in living organisms and has been recently studied *in vitro* through, for example, voltage-driven experiments in electro-chemical micro-fluidic cells (see [1] for the first pioneering work). The analysis presented is based on coarse-grained molecular dynamics (MD) simulations exploiting the so-called Gō-like model [2]. Equilibration, mechanical stretching and nanopore transport dynamics are developed and results compared. We interpret the results first through a standard 1D continuum approach, based on the Langevin equation taking into account the potential of the mean force relevant to a suitably-defined reaction coordinate, with the aim of summarizing appropriately the complex 3D phenomenology. Then, non-conventional continuum modeling is considered. We use a second rank tensor to summarize the 3D shape evolution of clusters of atoms in space, exploring several different dynamics. The analysis is performed in the framework of the mechanics of complex materials [3].

### 1.1 3D molecular dynamics simulations

This work is motivated by a recent experiment on Maltose Binding Protein (MBP) voltage-driven transport that explores the influence of denaturation on translocation pathways [4]. Short and long channel blockades, associated with the translocation of denaturated and partially folded MBP conformations respectively, are identified by large differences in the ion current drop durations. The above-mentioned Gō-like model is implemented as a natural approach to assess the impact of the molecule structural properties along translocation. The advantage of a coarse-grained description relies on the possibility to explore a large number of denaturation and pulling conditions so to accumulate robust statistics of transport events.

### 1.2 1D continuum approach

To interpret numerical results it is appropriate to built analytical models of the processes that occur in real translocations and to define statistical observable quantities to grasp and resume the essence of the phenomenon. In polymer translocation a set of reaction coordinates, to be considered appropriate, should smoothly trace without ambiguity the pathways between the two states with respect to the pore ends. In this framework, the translocation phenomenol-

ogy can be conveniently recast in the motion of an effective particle at place  $Q$ , undergoing a driven diffusion in the potential of mean force  $V(Q) = G(Q) + W(Q)$  [6]. Here  $G(Q)$  is the free-energy profile, while  $W(Q)$  is the work done by the importing force. In the present analysis, translocation is parametrized by a continuous approximation of the collective variable  $Q = N_{right} - N_{left}$ , with  $N_{right}$  and  $N_{left}$  the number of residues outside the pore on its *right* and *left* sides, respectively. The followed protocol involves a set of umbrella sampling simulations debiased by the multiple weighted histogram analysis method in order to achieve the free energy profile  $G(Q)$  [7]. 1D-Langevin runs provide the average residence time as a function of  $Q$ , to be compared with the 3D MD simulations.

### 1.3 3D continuum modeling

We propose a continuum model that captures, at least in a coarse way, the shape evolution of an isolated protein. A second-rank tensor  $\nu$  describes coarsely the molecule shape.  $\nu$  does not coincide with the moment of inertia tensor, as suggested in [8]. It is defined as the tensor such that the velocity of the  $i$ -th material point is given by the time rate of  $\nu$  applied to the  $i$ -th reference position vector (this approach is closer to what suggested in [9]). The evolution of  $\nu$  is governed by a balance of actions on the molecule. Such actions are identified at continuum level in terms of the ones occurring between every material point and its neighbors in the discrete scheme (this way we base our analysis on the suggestions given by Cauchy-Born rule). The identification is made in terms of power equivalence. The discrete values of the actions are obtained by numerical simulations. By assuming  $\det \nu > 0$ , the continuum evolution of  $\nu$  is depicted in terms of the eigenvalues of the symmetric component  $U$  of its polar decomposition ( $\nu = RU$ ). Results indicate limitations in case of free dynamics of the molecule while they show appropriateness for constrained dynamics, allowing us to accept the model for a number of constrained motions such as protein mechanical unfolding. The limitations concerning thermalization are overcome by selecting empirical formulations of the so-called *self-action*  $z_s$  (a quantity that, in the present setting, governs the evolution of  $\nu$  for  $\dot{\nu} = -z_s$ ).

## 2 RESULTS

### 2.1 3D molecular dynamics simulations outcomes

Here the translocation process in a model pore is analyzed. The resulting dynamics is affected by the protein denaturation state, similarly to the experimental evidence. Translocation of chemically unfolded MBP conformations requires relatively low forces and once the pulled terminus enters the pore, the transport proceeds uniformly. Native-like structures exhibit a richer phenomenology: stronger forces are required to trigger the transport that, once started, develops in a *stick-and-slip* fashion, through bottlenecks and jerky movements caused by the rearrangements of the folded part of the protein that has not yet engaged the pore, Figure 1 panels A and B. Here the issue is to identify the MBP structural motives responsible for the stalls. First, it is excluded that the stalling stages are related to the unfoldons (MBP segments that govern the mechanical unfolding in free space, see [10]), by comparing the unfolding pathways in translocation and mechanical stretching. Then, through an analysis of native contact maps, we show that the stalls are mainly due to the protein regions denser in long range native interactions, Figure 1C. For a similar stick and slip phenomenology, recently detected in translocation experiments, see [11, 12].

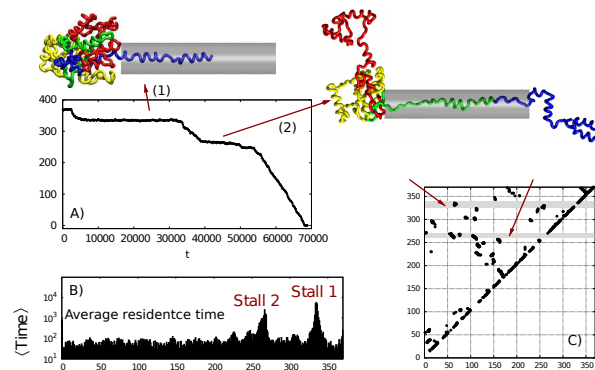


Figure 1: Panel A: Time evolution of  $N_{cis}$ , the residue number on the *cis*-side of the pore, for a folded MBP. Plateaus correspond to transport stalls. Panel B: Average time spent by the protein in different conformations. Panel C: MBP contact map. Horizontal rectangles highlight the critical areas responsible for the stalls (denser in native contacts).

## 2.2 1D continuum approach outcomes

Not only translocation bottlenecks but also free energy barriers are found to be related to the long-range structural properties of the protein, Figure 2A. The decomposition of the free energy in *internal energy* and *entropic* terms shows that the dominant energetic contribution can be estimated on the base of the protein native structure. The essential features of the dynamics are retained in the reduced 1D Langevin phenomenological model just describing the evolution of the already introduced collective variable  $Q$  in the relevant free energy landscape, Figure 2B.

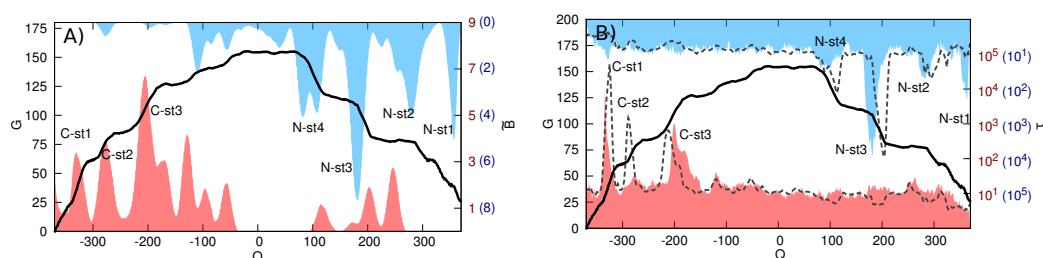


Figure 2: For N-pulling simulations (blue data) the  $y$ -axes are reversed. Panel A: Smoothed native contact density  $\tilde{B}_C(Q)$  (red) and  $\tilde{B}_N(Q)$  (blue) for C- and N-terminus pulling for MBP. The solid line denotes the MBP free energy  $G(Q)$ . Panel B: Solid histograms: average residence time  $\tau(Q)$  from non-equilibrium 3D MD simulations of MBP translocation. Solid line: free-energy profile  $G(Q)$  of MBP. Dashed lines:  $\tau(Q)$  from the 1D Langevin model.

## 2.3 3D continuum modeling outcomes

When dealing with small clusters of atoms or with the 76-residue-long protein Ubiquitin, the approach based on the homogeneous deformation hypothesis results robust only when the external forces exploited in the deformation process are included in the computation of the self-action (Figure 3A). In MBP translocation simulations the pres-

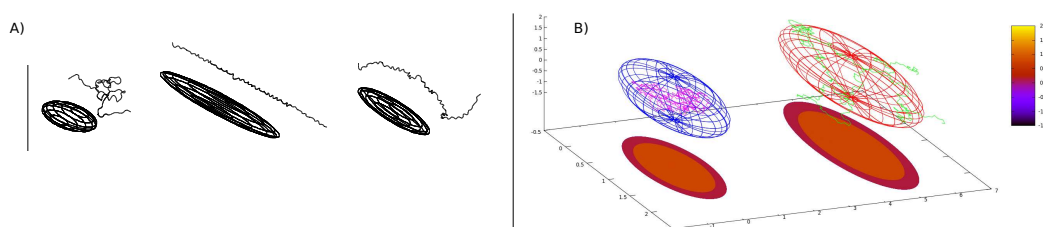


Figure 3: Panel A: Comparison between Ubiquitin dynamics and the evolution of the ellipsoid which semi-axes are the eigenvalues of  $\nu$ . Data refer to the model based on Cauchy-Born rule and power identification. From left: i) Beginning of mechanical pulling; ii) Maximum stretching state; iii) Beginning of refolding. Panel B: Comparison of the ellipsoids (and MBP conformations) for two different values of the structural stability of the MBP native state. Data are relevant to the heuristic approach computationally less demanding. It is apparent which molecule is unfolding just from the difference in the shape of the ellipsoids.

ence of the pore enhances the quality of the description. Indeed, the confinement acts similarly to a decrement of the temperature, limiting residue fluctuations inside the pore. Limitations arise in capturing thermal unfolding. In equilibration simulations the homogeneity is lost due to random single-bead oscillations that hide the overall unfolding process. The drawback can be overcome by selecting different descriptors of the protein evolution and related modified expressions of  $z_s$ , which arise from evaluations of the interaction mechanisms among material points in the molecule and by considering  $\nu$  a *work tensor density*. Several heuristic approaches have been investigated. All indicate appropriateness in the description of thermal unfolding. Figure 3B shows a qualitative example from the model that has resulted the most effective computationally: one of the protein undergoes thermal unfolding (bigger ellipsoid in red) while the other one remains compact.

### 3 CONCLUSIONS

Clarifying the physical and chemical principles involved in nanopore transport will remain a fertile field of research for the years to come, as it is only recently that scientists have developed suitable techniques to adequately tackle this issue. In this work it is shown that, according to coarse-grained native-centric models (whose main limitation is the absence of specific physico-chemical properties of protein residues), translocation of a protein-like structure is characterized by stall events, similarly to what detected in recent experiments. There is a tight correlation between the geometrical properties of the native structure and the stall pattern. The circumstance suggests that the stall sequence is specific for each protein and constitutes a sort of signature, potentially useful for protein misfolding detection. Stalls can be inferred just by analyzing the native contact map of a protein, possibly opening the way to systematic pre-screening of the proteome that could also take advantage of the 1D Langevin approach. In order to enhance the standard 1D continuum modeling, we introduce a morphological descriptor for clusters of atoms in space. The scheme falls within the setting of the mechanics of complex materials. It relies on our assumption of homogeneous deformation and on a power-based identification procedure. The approach captures the dynamics of a macromolecule in presence of external constraints. So, it can be used to represent the mechanical stretching of a protein in free space or the transport through a “long-enough” pore. It is not clear how much the inclusion of external forces is important in the formulation of the self-action  $z_s$  (they are essential for small clusters of atoms, but not for the larger MBP). The scheme should be further enriched in case a deforming environment was considered and/or the presence of a dense population of interacting macromolecules (a microstress would also arise). The approach is not able to catch thermal unfolding, for an evident lack of deformation homogeneity. It is possible to overcome that limitation by selecting a second-rank tensor  $\nu$  as descriptor of the single molecule with a different physical meaning. The relevant heuristic models are able to describe inhomogeneous deformations, but often are too computationally demanding. Finally, the approach could produce new ways to cluster molecular snapshots used to build up transition networks and to compute cut-based free energy profiles.

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