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Uncooked spaghetti in a colander: Injection of semiflexible polymers in a nanopore[⋆]

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Abstract. We study the flow injection of semiflexible polymers in a nanopore with a diameter smaller than the persistence length of the macromolecules. The suction model from de Gennes and Brochard is modified to take into account the effect of the rigidity of the polymer in the Odijk regime. We show that in this case of extreme confinement the flow threshold vanishes slowly and that in the limit of infinitely small nanopore the free energy barrier eventually disappears.

The injection of macromolecules in a confined environment as nanopores or nanochannels is a critical step to understand natural phenomena as cytoplasm-nucleus transport through the nuclear pore complex [1] or the synthesis of protein [2]. It is also important for applications like DNA, RNA or proteins sequencing by nanopores [3] or smart filtration of recombinant proteins. In all these cases the persistence length of the biomolecule l_p is larger than the diameter of the pore D. The stiffness of the macromolecule appears to be thus an important parameter of the injection and impacts the energy landscape of translocation. The statistics of a wormlike chain of contour length L trapped in a cylindrical pore of diameter D can be understood if a length scale $\lambda = D^{2/3} l_p^{1/3}$ is introduced. Odijk [4] has shown that if $L < \lambda$, it is a good approximation to view the chain as being completely rigid. Whenever $L \gg \lambda$, it is convenient to regard the stiff coil as a sequence of rigid segments, each of length λ. The free energy involved in forcing a stiff chain into a pore can be calculated by scaling arguments.

Experimentally, the injection of macromolecules has been achieved mostly using electrical forces. Depending on the size of the pore and the length of the molecule it has been shown that the rate of translocation was drift limited or imposed by the energy barrier of confinement [5,6]. The difficulty to achieve a quantitative prediction on the actual forces exerted on the molecules due to the presence of additional forces as electro-osmotic forces is a limitation to propose a simple theoretical description of such transport. Recently the use of hydrodynamical flows as a driving force to inject macromolecules has led successfully to a direct comparison between theory and single molecules experiments [7–9].

The flow injection of flexible macromolecules in confined environments has been studied by Daoudi, Brochard and de Gennes. They have proposed two complementary models (affine deformation and suction) that demonstrate the independence of the energy barrier on the pore size or the polymer mass. In the *affine deformation model* [10,11] a flexible polymer coil is squeezed laterally by the flow converging at the entrance of a pore: the chain enters a pore when its transverse size becomes smaller than the pore diameter. This occurs when the flow rate J is larger than a threshold $J_c = k_{\mathrm{B}}T/\eta$, where $k_{\mathrm{B}}T$ is the thermal energy and η the viscosity of the solvent. J_c is surprisingly independent of the pore size and polymer mass. In the *suction model* [12], the chain is pulled in the pore by the friction force exerted by the flow on the monomers which have entered the pore. The chain enters the pore when the hydrodynamic drag forces overcome the entropic forces due to confinement. This occurs above the same threshold J_c. Below the threshold, an energy barrier separates the state where the chain stays outside from the state where it fully invades the pore. Close to the threshold, the height of the barrier is of order $k_{\mathrm{B}}T$ and the transition between the two states is smooth because of thermal fluctuations.

The flow injection of semiflexible polymers ($D < l_p$) is relevant in the case of biomolecules injection and has not been studied analytically. In this regime injection corresponds to a high-energy barrier dominated by the entropy of the biomolecule Odijk segments. Here, we present the-

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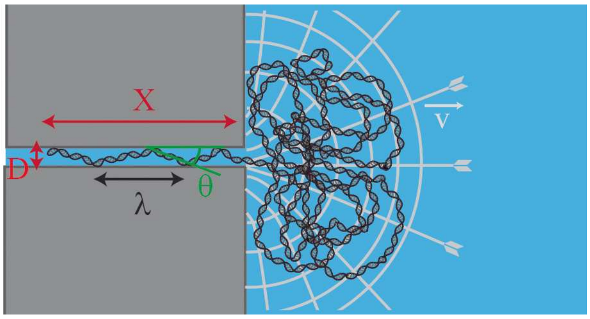

Fig. 1. A semiflexible macromolecule is injected into a nanopore of diameter D onto a length X. An individual Odijk segment of length λ forms an angle Θ with the injection flow.

oretical results on the flow-driven translocation of long semiflexible molecules. We determine the flow threshold for polymer injection in the regime where the rigidity of the macromolecule should be taken into account. We show that the flow threshold vanishes when the nanopore diameter goes to zero.

In the framework of the suction model, the free energy landscape of a tongue of polymer engaged in a nanopore of diameter D on a length X is expressed as

$$\Delta F = k_{\mathrm{B}}T \cdot X/D - \eta J (X/D)^2. \qquad (1)$$

The first term corresponds to the confinement energy of the polymer in the nanopore tube. It is considered to be $k_{\mathrm{B}}T$ per polymer blob entered in the tube. The second term originates from the work of the external hydrodynamical forces acting on the monomers of the macromolecules to confine it. The free energy barrier can be determined as the free energy maximum along the landscape

$$\frac{\Delta F^*}{k_{\mathrm{B}}T} = \frac{J_c}{J}\,. \qquad (2)$$

In order to consider nanopores narrower than the persistence length ($l_p > D$) we have to abandon the blob description of the suction model to a Odijk segment description. In this case the tongue of the polymer clogged in the nanopore is best described as a series of consecutive needles of length $\lambda = (l_p D^2)^{1/3}$ that form an angle θ such as $\sin\theta = D/\lambda$ with the wall of the nanopore (fig. 1). We can express the free energy landscape as follows:

$$\Delta F = k_{\mathrm{B}}T \cdot X/\lambda\cos\theta - \eta v \cdot C_{\theta\lambda R} X^2/\lambda\cos\theta. \qquad (3)$$

The first term corresponds to the confinement energy of the series of needles in the nanopore tube. It is considered to be $k_{\mathrm{B}}T$ per needle entered in the tube. The second term originates from the work of the external hydrodynamical forces acting on the needles. v is the speed of the driving fluid. $C_{\theta\lambda R}$ is the hydrodynamic coefficient of a cylinder of length λ and radius R positioned at an angle θ with the incident flow [13]:

$$C_{\theta\lambda R} = \frac{4\pi\lambda}{\ln(\lambda/R) - 1/2}\cos\theta + \frac{8\pi\lambda}{\ln(\lambda/R) + 1/2}\sin\theta. \qquad (4)$$

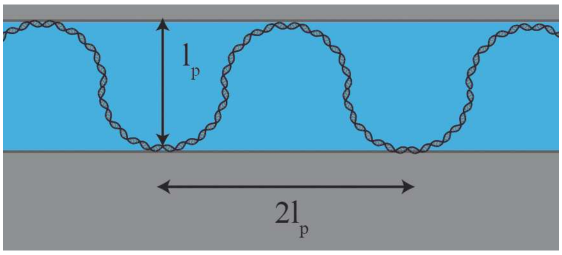

Fig. 2. A semiflexible macromolecule is injected into a nanopore of diameter $D \sim l_p$ and forms semicircular arches.

As in the suction model we can derive the free energy maximum of the landscape and then the new flow threshold J_c^o for semiflexible polymers in the Odijk regime. Here we consider $\log(\lambda/R) \gg 1$ which is correct for most biomacromolecules:

$$\frac{J_c^o}{J_c} = \frac{\ln(D^2 l_p/R)}{4\pi}\,\frac{(D/l_p)^{2/3}}{1 + 2(D/l_p)^{1/3}}\,. \qquad (5)$$

Then the flow threshold for a semiflexible polymer for $D \gg l_p$ is in this case dependent on the diameter D as $J_c^o \propto (D/l_p)^{2/3}$ and vanishes for very small nanopores but for $\lambda > R$. It is also possible to derive the attempt frequency for this translocation process. Following Auvray [14] the reorientation timescale for a rigid unit of the polymer under strong flow (*i.e.*, $r_c > l_p$, where r_c is the capture radius) scales as l_p^3/J. The attempt frequency at the threshold is then $k = J_c^o/l_p^3 \propto (D/l_p)^{2/3}$ which also goes to zero for very small nanopores.

In the case where $D \sim l_p$ (fig. 2) we consider that the polymer injected in the pore is a succession of archs of radius l_p. Following Odijk [4] it is then possible to derive W, the work of injection per arch, as

$$W/k_{\mathrm{B}}T = \frac{l_p}{2}\int_0^{\pi D/2} 4/D^2 \mathrm{d}s = \pi l_p/D. \qquad (6)$$

And then ΔF, the free energy of injection for the tongue of length X, is

$$\Delta F = k_{\mathrm{B}}TX/D - \frac{4\pi\eta J}{\ln(\lambda/R)}(X/D)^2. \qquad (7)$$

Finally, the free energy barrier ΔF^* is as in the suction model:

$$\Delta F^*/k_{\mathrm{B}}T = J_c/J \cdot \ln(\lambda/R). \qquad (8)$$

Then the flow threshold for a semiflexible polymer for the case $D \sim l_p$ is in this case weakly dependent on the diameter D.

In summary, when semiflexible polymers are injected into nanopores whose diameter is smaller than the persistence length of the polymer the flow threshold vanishes if $D \ll l_p$ as $(D/l_p)^{2/3}$. We can make here an analogy with a day-to-day experiment. If ones try to agitate uncooked spaghetti in a colander with a mesh size in the range of the pasta diameter, it will be observed that the spaghetti flow easily through the holes. On the contrary if the same experiment is reproduced with cooked spaghetti a very small proportion of the pasta will flow through the colander. Even if these experiments happen at very different scales, it appears that in both cases the increased flexibility of the object tends to limit its ability to translocate in confined environments.

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Author contribution statement

TA, LA, J-MDM and FM designed the model. J-MDM and FM wrote the article.

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