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## **Nanomechanics of macromolecules : Force-extension response of biological macromolecules**

*Manon Benedito<sup>1</sup>, Stefano Giordano<sup>2</sup>*

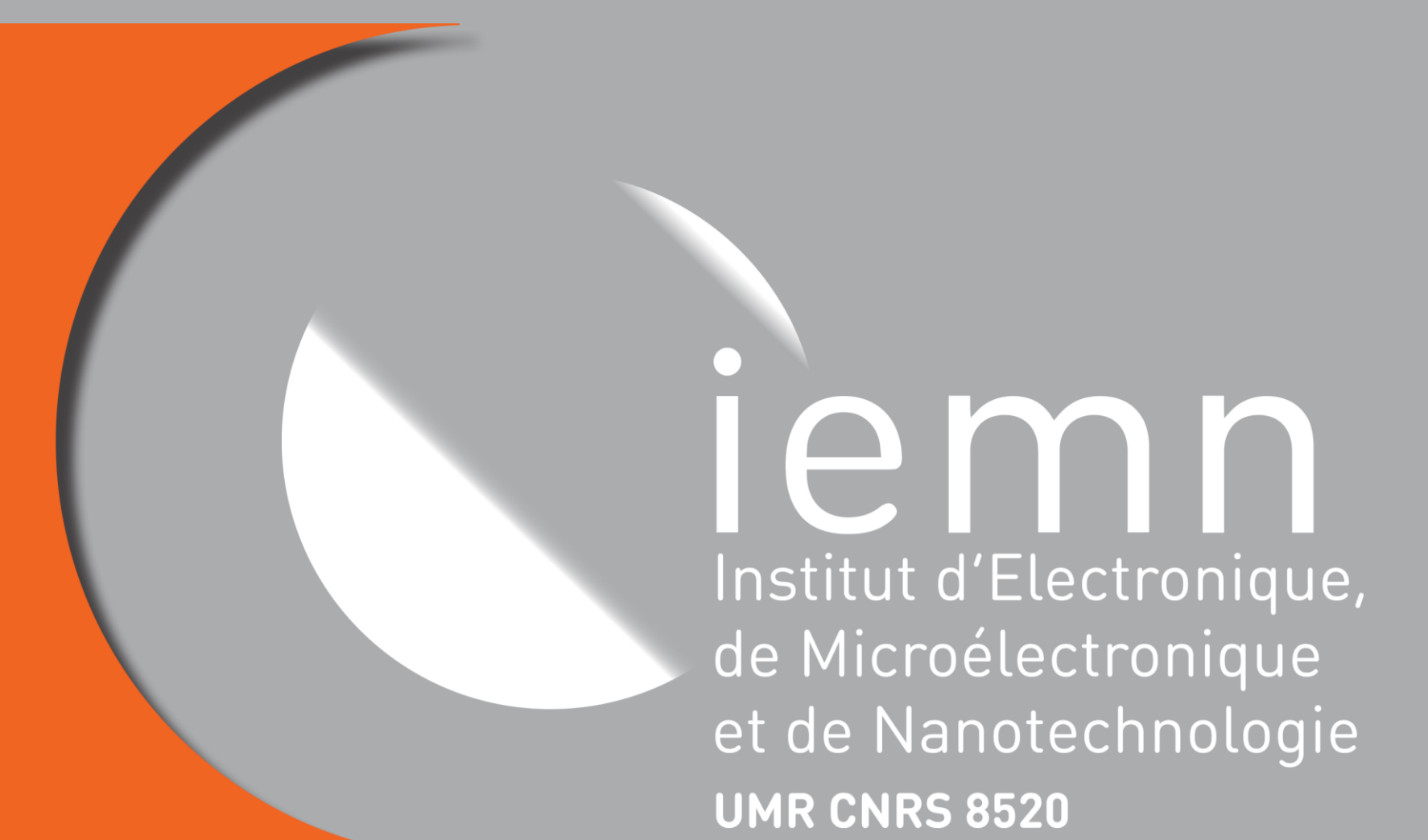
<sup>1,2</sup> Univ.Lille, CNRS, CentraleLille, ISEN, Univ.Valenciennes, LIA LICs/LEMAC, UMR8520- IEMN- Institute of Electronics, Microelectronics and Nanotechnology, F-59000Lille, France

The development in recent years of single-molecule force spectroscopy experiments allowed a better knowledge of macromolecules of biological interest, such as DNA and proteins. The work presented here describes the modelling of the macromolecules' response to deformation and to thermal fluctuations with the help of the statistical mechanics, through comparison with the experimental results obtained by single-molecule force spectroscopy, providing valuable information on the static and dynamic responses induced by applied forces. These analyses are even more important for bistable macromolecules with conformational transitions, thus corresponding to folding/unfolding processes and to two stable positions (folded and unfolded). In order to analytically obtain the force-deformation response of a chain composed of bistable units, it is necessary to calculate the partition functions, which are essential in the statistical mechanics and allow to obtain average values of parameters of interest. Thus, the bistable potential energy is decomposed into two parabolas, both corresponding to the folded and unfolded states and identified using the spin variable technique. Several extensions are added to this technique, in order to bring the model closer to reality, such as the extensibility of the bonds between the bistable units, the interactions existing among the bistable units, thanks to the Ising model, or again the heterogeneity, an important parameter to determine the unfolding sequence in proteins folding. Finally, the influence of the pulling speed on the force peaks is considered in the dynamic study, provided with the help of the Langevin method.

# AIMAN-FILMS

## Nanomechanics of macromolecules

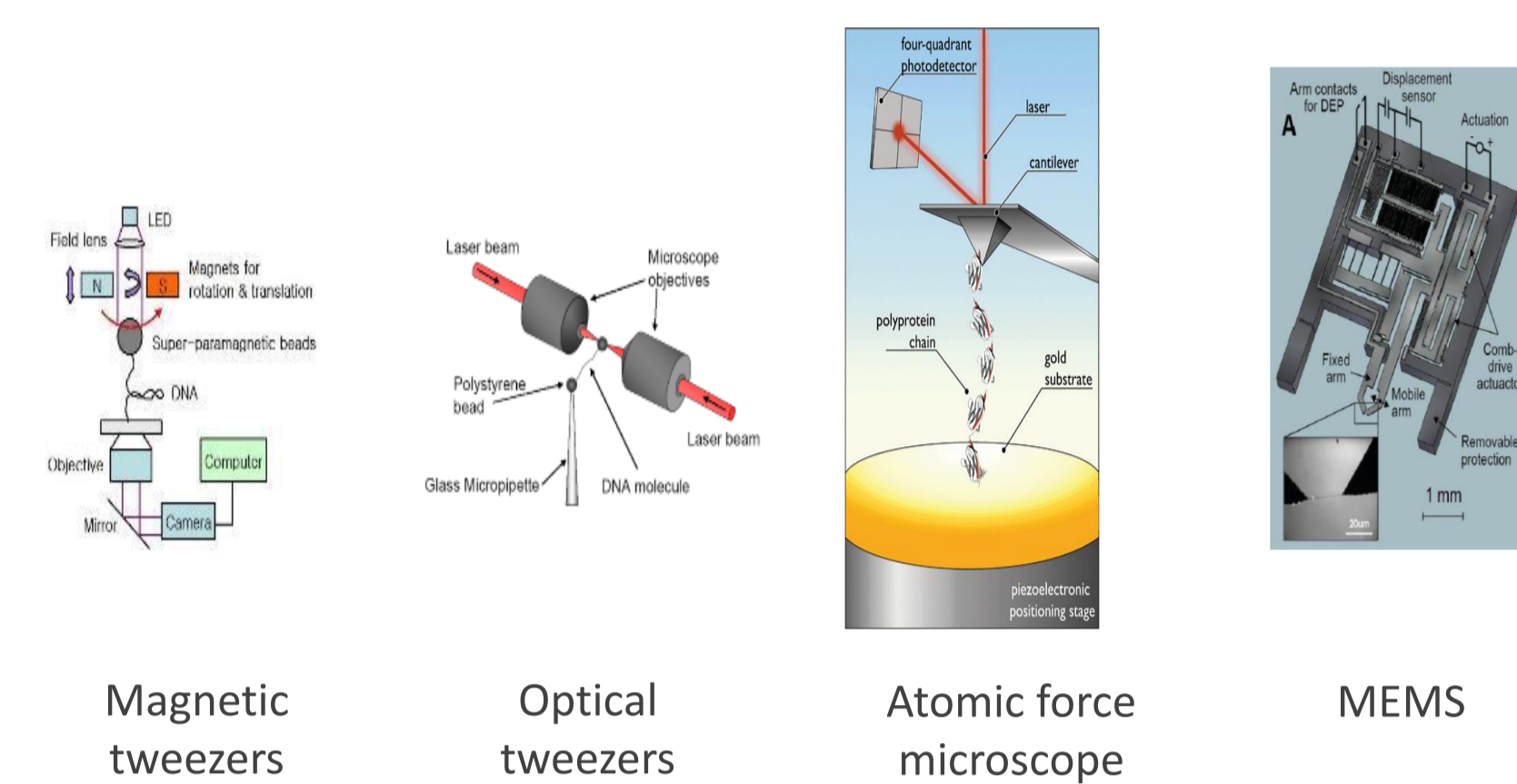
### Force-extension response of biological macromolecules



Manon Benedito, Stefano Giordano

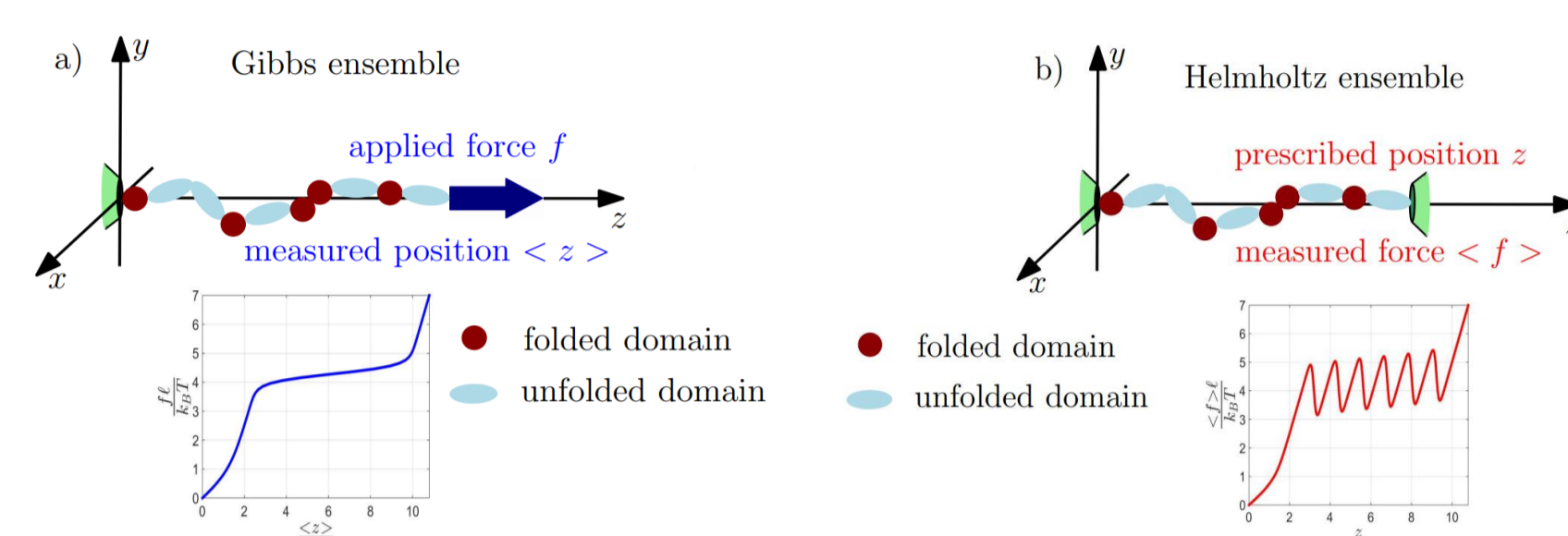
### General context

#### Single-molecule force spectroscopy



Devices with variable stiffness  $k$ :  $10^2$  pN.nm<sup>-1</sup> –  $10^4$  pN.nm<sup>-1</sup>

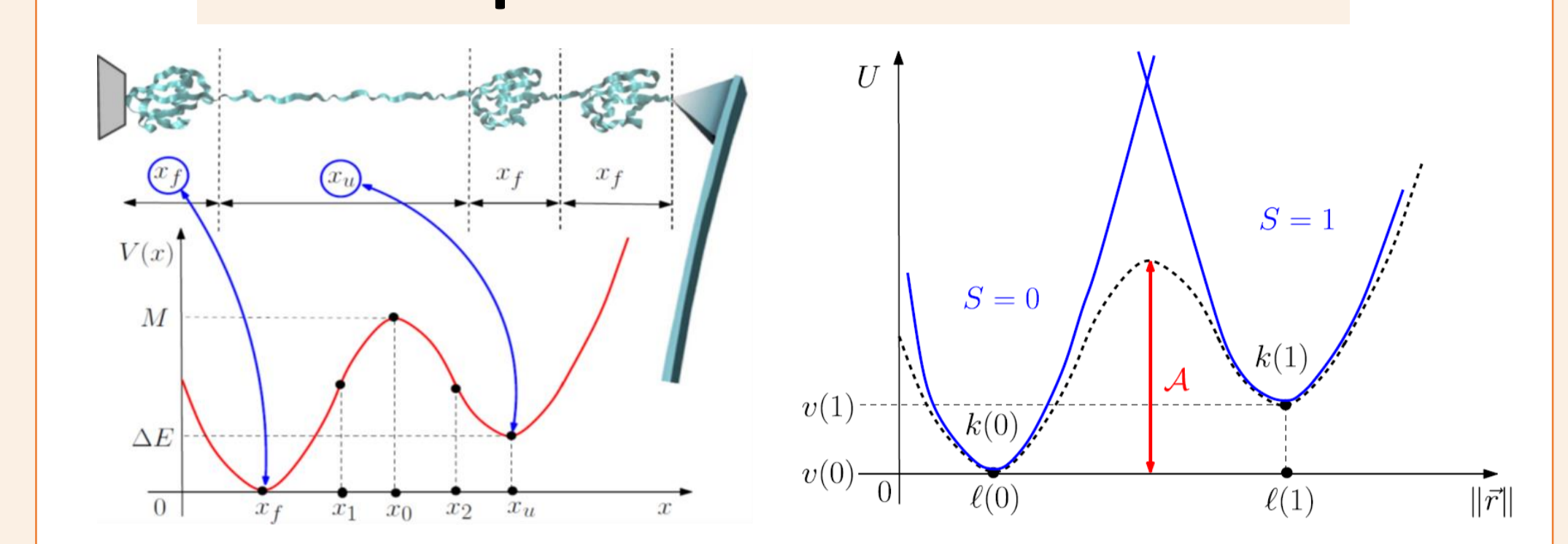
#### Gibbs and Helmholtz ensembles



- Applied force at the ends of the chain.
  - Isotensional condition.
  - Measured extension.
  - Plateau curve response.
- Imposed position at the ends of the chain.
  - Isometric condition.
  - Measured force.
  - Sawtooth-like curve response.

### Spin variable

#### Spin variable model



- Folded state:  $s = 0$ .
  - Unfolded state:  $s = 1$ .
  - Bistable freely jointed chain polymer model.
  - Inextensible bonds, no interactions among units, homogeneous units.
- $l(0)$  and  $l(1)$  are the folded and unfolded lengths of each domain;
  - $k(0)$  and  $k(1)$  are the stiffnesses characterizing each spring;
  - $v(1)-v(0)=\Delta E$  is the energy jump between the stable states.

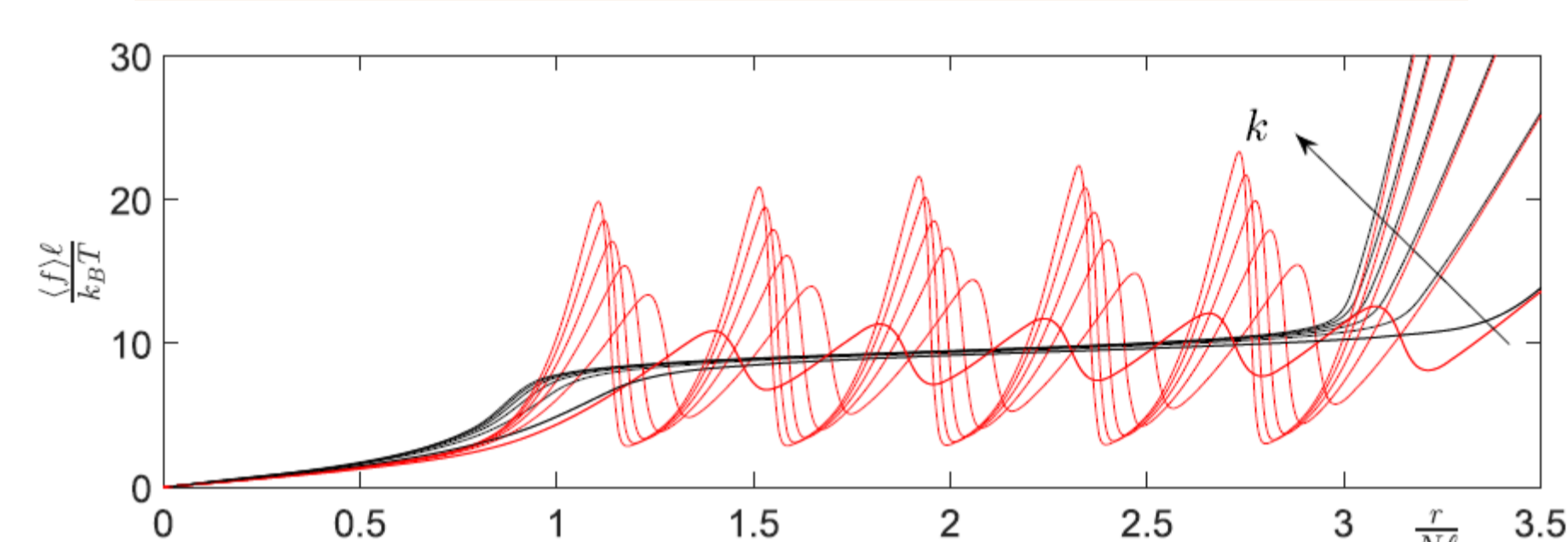
The **thermo-mechanical response** of macromolecules can be experimentally observed with **single-molecule force spectroscopy (SMFS)**. Recent sophisticated experiments offer a wider comprehension of intra and intermolecular forces. The **typical measure** realized with the help of SMFS is the **force-extension response**. A broad class of biological polymers such as RNA, DNA and diverse proteins showed a non-linear elastic response. One of the most important experiment concerns **the stretching of a double-stranded DNA**. The aim of our work is to model this force-extension relation by using **statistical mechanics**. As we consider small systems, different conditions must be studied, namely **the isotensional and the isometric conditions**, respectively associated to the **Gibbs and the Helmholtz ensembles**.

We introduced a new technique called the **spin variables method** to **theoretically analyze the behavior of bistable chains**, exhibiting the so-called **conformational transitions**. This method is based on the introduction of a sequence of « spin » variables, **able to describe the state of all elements of the chain**. Indeed, the exact calculation of the Gibbs and Helmholtz partition functions is complicated as the potential energy is represented by a double-well energy potential. Therefore, to define the system in a simpler way, we add **internal variables, belonging to the phase space and considered as standard variables of the statistical mechanics**. These variables are **discrete** and behave as spin variables. The spin variable allows to **identify the potential well explored by the domain** under consideration and to know if the chain is folded or unfolded. Hence, each potential well is now described by a quadratic potential, which simplifies calculations.

### Extensibility and interactions

#### Extensibility

- Freely jointed chain model.
- Bistable units undergoing conformational transitions.
- Here, the bonds between the units are **extensible** ( $k > 0$ , finite value).
- We observe a cooperative (synchronized) process in the Gibbs ensemble and a non cooperative (unsynchronized) process in the Helmholtz ensemble, confirming the experimental results.
- We note the **strong reduction of the force peaks with increasing the elastic constant**.
- We used for the first time **Hermite polynomials  $H_m$  with negative index** to solve the partition function integral.



Force-extension responses in Gibbs (black curves) and Helmholtz (red curves) ensembles for a system with variable extensibility  $k = 0, 4j$  N/m  $\forall j = 1, \dots, 6$ .

Benedito & Giordano, Journal of Chemical Physics 149, 054901 (2018)

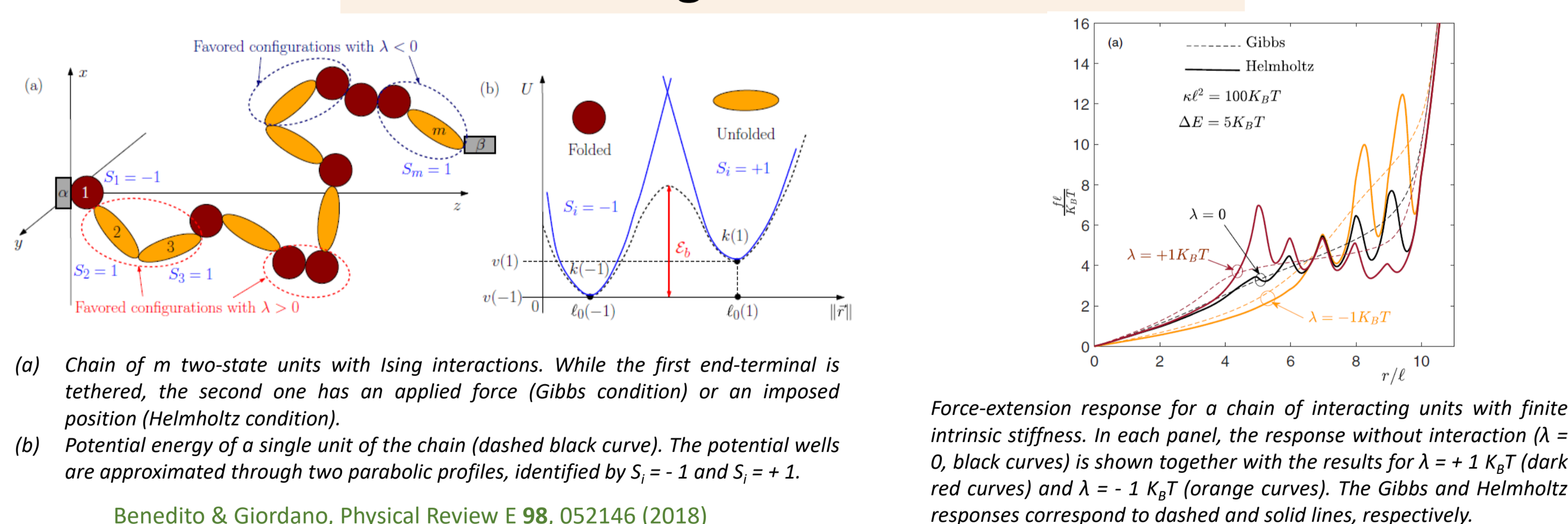
#### Gibbs partition function

$$Z_G(f) = \left( \frac{\sinh y}{y} + \phi \chi \frac{\sinh \chi y}{y} \right)^N \exp\left(\frac{N\alpha y^2}{2}\right)$$

#### Helmholtz partition function

$$Z_H(z) = -\frac{1}{2\pi} \sum_{p=0}^{N-1} \sum_{q=0}^{N-1} \binom{N-k}{p} \binom{N-k}{q} (-1)^{p+q} \times (\chi \phi)^p \left[ \sqrt{\frac{N\alpha}{2}} \right]^{2p} e^{-\frac{N\alpha}{2} H_{N-1} \left( \frac{\lambda}{\sqrt{2N\alpha}} \right)} + H(\lambda) \sum_{h=0}^{\lfloor \frac{N-1}{2} \rfloor} \frac{(-1)^{h-1} \pi \left( \frac{N-1}{2} \right)^{N-2} \left( \frac{N\alpha}{2\lambda^2} \right)^h}{h!(N-2-2h)! \left( \frac{N\alpha}{2\lambda^2} \right)^h}$$

#### Ising interactions



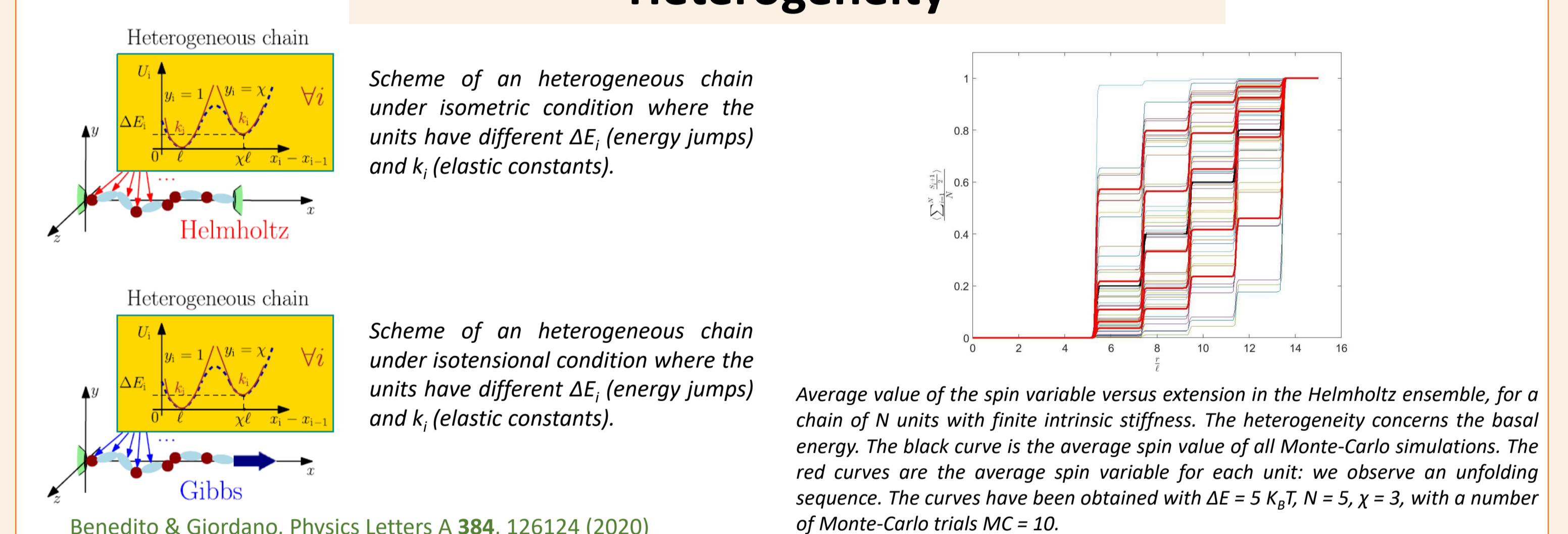
(a) Chain of  $m$  two-state units with Ising interactions. While the first end-terminal is tethered, the second one has an applied force (Gibbs condition) or an imposed position (Helmholtz condition).  
(b) Potential energy of a single unit of the chain (dashed black curve). The potential wells are approximated through two parabolic profiles, identified by  $S_1 = -1$  and  $S_2 = +1$ .

Force-extension response for a chain of interacting units with finite intrinsic stiffness. In each panel, the response without interaction ( $\lambda = 0$ , black curves) is shown together with the results for  $\lambda = +1 K_B T$  (dark red curves) and  $\lambda = -1 K_B T$  (orange curves). The Gibbs and Helmholtz responses correspond to dashed and solid lines, respectively.

- To represent **interactions existing among units**, we chose the **Ising model**. The **Ising coefficient,  $\lambda$** , allows to take account of interactions between units, bringing our model closer to the reality. This term is directly included in the Hamiltonian and can be associated to **affinity** in chemistry.
- If  $\lambda > 0$ , we consider that the interaction is **positive**, namely units in the same state (folded or unfolded) want to be close to each other. This case can be associated to an **ferromagnetic-like interaction**.
- If  $\lambda < 0$ , we consider that the interaction is **negative**, namely units in opposite state (folded and unfolded) want to be close to each other. This case can be associated to an **anti-ferromagnetic-like interaction**.
- It is possible to introduce in the spin variable model both the extensibility and the Ising interactions (see right panel). **Limiting cases** have been studied to find completely analytical solutions and compare them with our semi-analytical/semi-numerical model, for instance, strong ferromagnetic-like interactions.
- The Ising interactions induce a specific cooperativity, which can be detected in the modification of the hierarchy of forces in the sawtooth-like response, as recently observed in force spectroscopy experiments of proteins (e.g., in Filamin A).

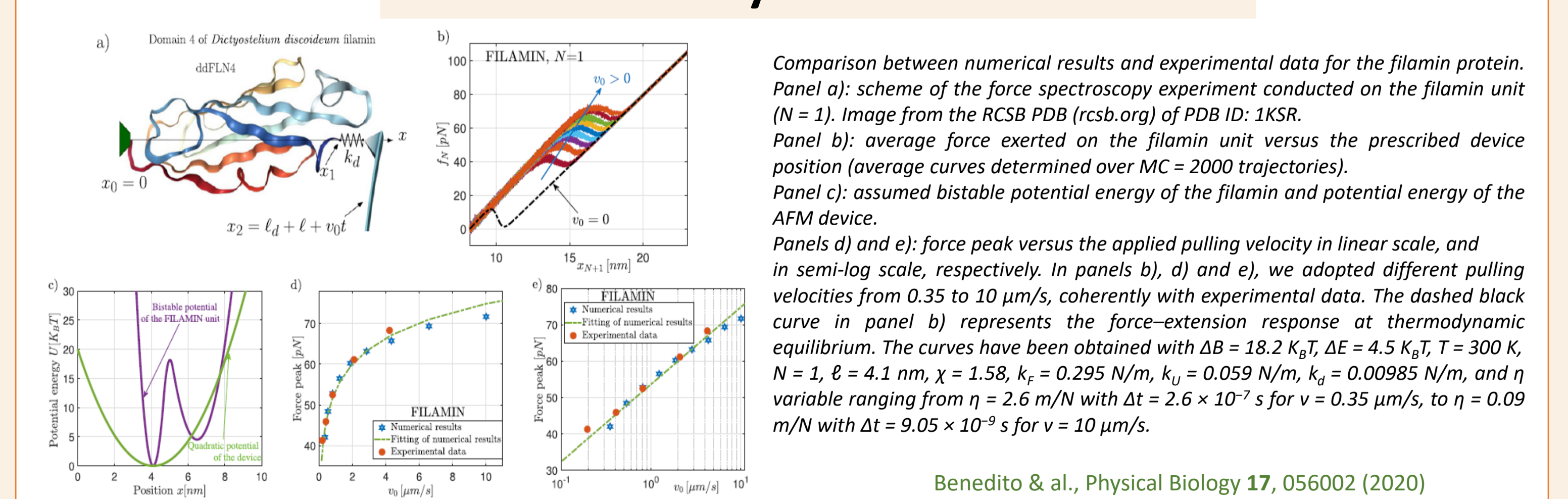
### Heterogeneity and dynamics

#### Heterogeneity



- Another aspect to consider to be even closer to the reality concerns the **heterogeneity** in chains of bistable units. The latter may concern elastic response, basal energy or other parameters characterizing the units. We suppose the system at **thermodynamic equilibrium**. In practice, this equilibrium corresponds to a very low pulling speed of extension of the chain.
- In the homogeneous case, all units are identical, so that all folded units have the same probability to fold or unfold at each event. This means that we can not obtain a folding/unfolding sequence because of the homogeneity of the chain. This is not the case in real experiments, where the **folding/unfolding sequence can be exactly identified** and depends on heterogeneous aspects of the chain (the quenched disorder breaks the symmetry). We propose this model to determine the actual folding/unfolding pathway and relative unfolding probabilities of units. We introduce the heterogeneity at the energetic level, using the **Monte-Carlo method** to generate basal energies.

#### Dynamics



- We propose to study the **unfolding processes under dynamic regime** in order to **better represent real SMFS experiments**. Indeed, about experiences in the Helmholtz ensemble, chain extension is progressively increased with a speed of around 1  $\mu\text{m/s}$ , which can generate **dynamic effects** corresponding to an **out-of-equilibrium statistical mechanics regime**.
- However, there are currently two methods to deal with this problem: the first one is the analytical calculation, which provides correct results only for very low extension speeds (equilibrium), and the second one is the numerical calculation (molecular dynamics), which can only be applied for high extension speeds, due to cost of calculation, which limits total time of simulation. This implies that we can not work with intermediary extension speeds, which are necessary to interpret the SMFS experiments.
- Therefore, we used the **Langevin equation** to study the out-of-equilibrium processes. As a result of the dynamics, force peaks depend on pulling velocity, and this dependence can be used to measure the energy barrier between folded and unfolded states, which plays a crucial role in determining characteristic times of the process.

