

The Universe of Neurotoxic Proteins

A Study of the Conformational Space of Polyglutamine

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Diseases of the old



Alois Alzheimer



George Huntington



James Parkinson



Hans G. Creutzfeldt
Alfons M. Jakob

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 - Intrinsically disordered proteins
 - Force in biology
- 2 Methods
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- 3 Results
 - Conformational polymorfism
- 4 Summary

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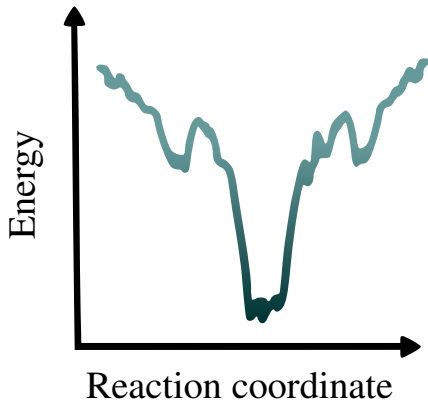
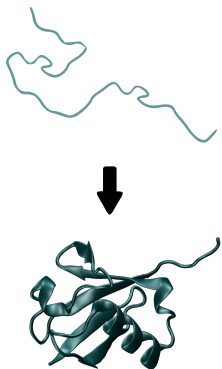
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The cell as a factory



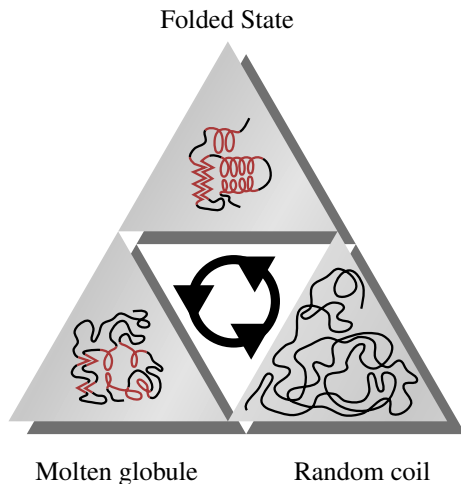
The cell as a factory

The folding paradigm



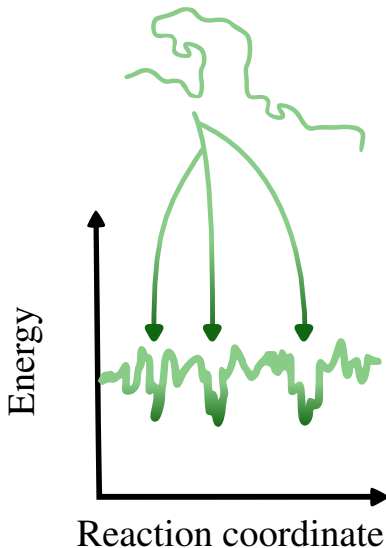
The cell as a factory

The protein trinity



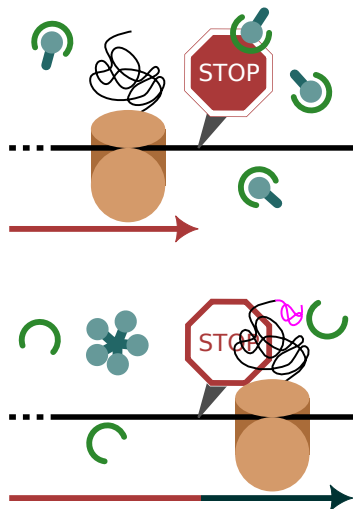
The cell as a factory

Intrinsically disordered proteins



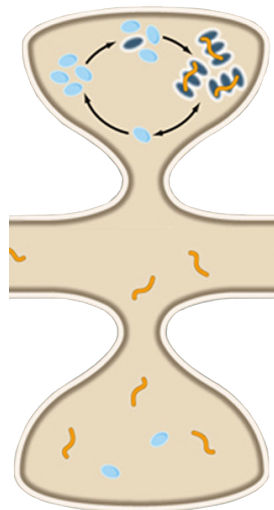
Intrinsically disordered proteins

Functional IDPs



Sup35

(Modified from Partridge & Barton 2000)

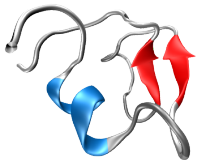


CPEB

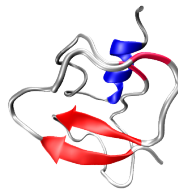
(Modified from Si *et al.* 2010)

Intrinsically disordered proteins

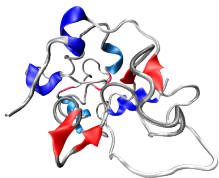
Toxic IDPs



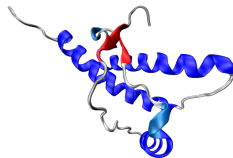
Alzheimer



Huntington



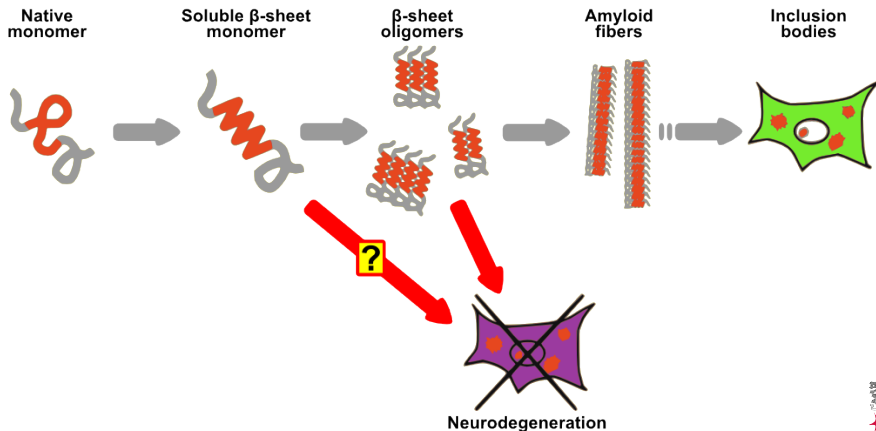
Parkinson



Creutzfeldt-Jakob

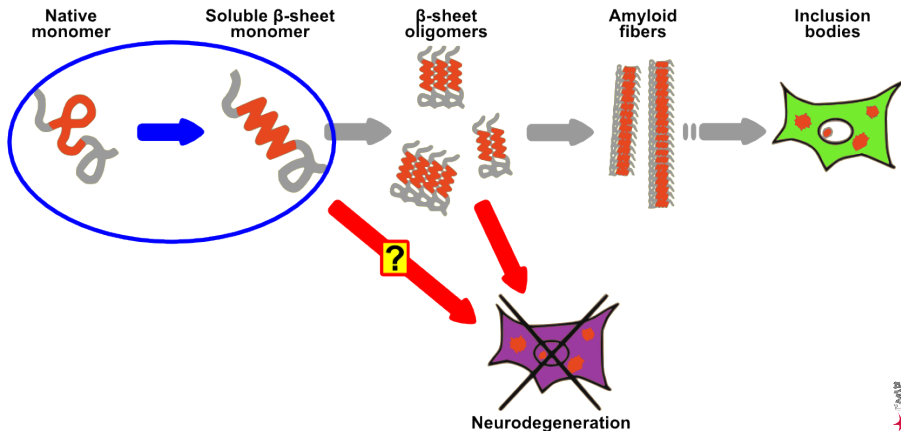
Intrinsically disordered proteins

Relation to disease: Neurodegeneration cascade



Intrinsically disordered proteins

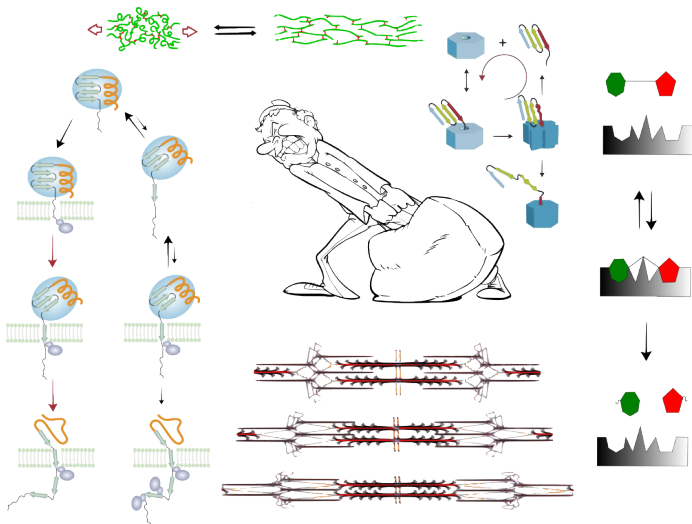
Relation to disease: Neurodegeneration cascade



Force in biology



Force in biology



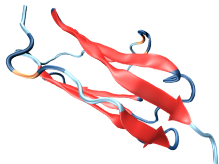
Alberts *et al.* 2002, Tskhovrebova & Trinik 2003, Neupert & Brunner 2002, Sauer *et al.* 2000

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Molecular Dynamics

Simulating movement

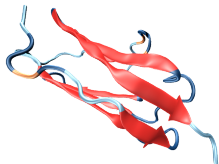


Experiment

$\approx 1 \mu\text{s}$ time resolution

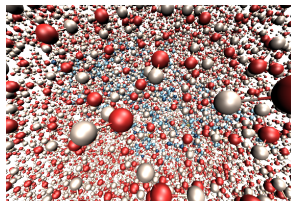
Molecular Dynamics

Simulating movement



Experiment

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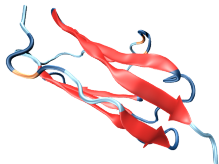


33872 atoms

$\approx 20 \text{ h/ps} \Rightarrow \approx 2200 \text{ yr}$

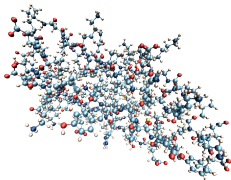
Molecular Dynamics

Simulating movement



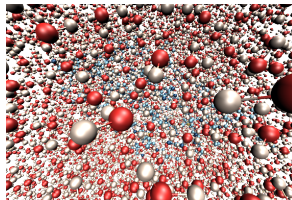
Experiment

$\approx 1 \mu\text{s}$ time resolution



1376 atoms

$\approx 20 \text{ min/ps} \Rightarrow \approx 37 \text{ yr}$

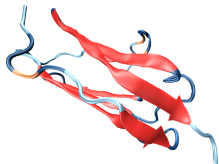


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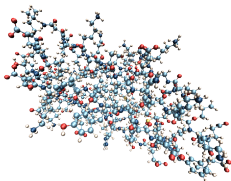
Molecular Dynamics

Simulating movement



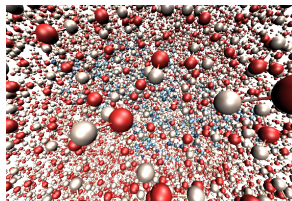
Experiment

$\approx 1 \mu\text{s}$ time resolution



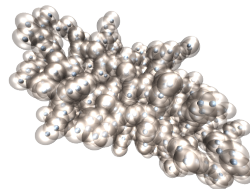
1376 atoms

$\approx 20 \text{ min/ps} \Rightarrow \approx 37 \text{ yr}$



33872 atoms

$\approx 20 \text{ h/ps} \Rightarrow \approx 2200 \text{ yr}$



89 atoms

$\approx .5 \text{ s/ps} \Rightarrow \approx 6 \text{ days}$

Molecular Dynamics

Bias Exchange Molecular Dynamics

UNBIASED



Molecular Dynamics

Bias Exchange Molecular Dynamics



Molecular Dynamics

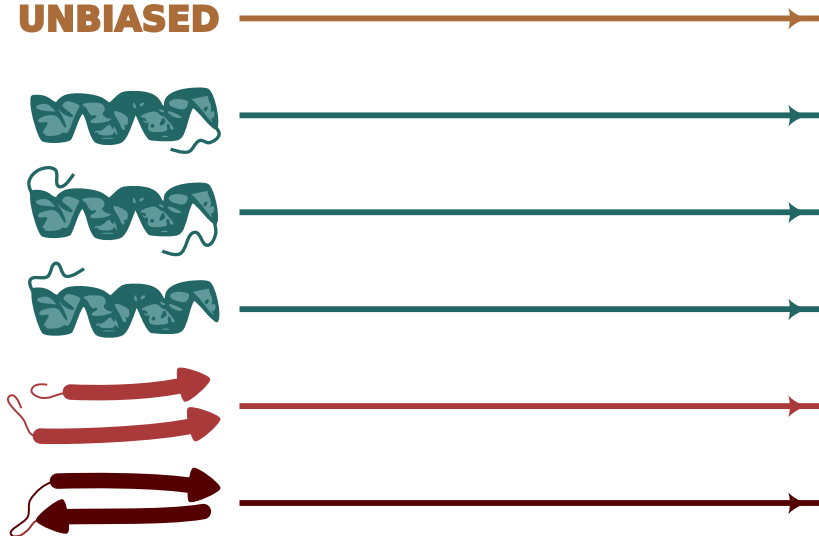
Bias Exchange Molecular Dynamics



Molecular Dynamics

Bias Exchange Molecular Dynamics

UNBIASED



Molecular Dynamics

Bias Exchange Molecular Dynamics

UNBIASED

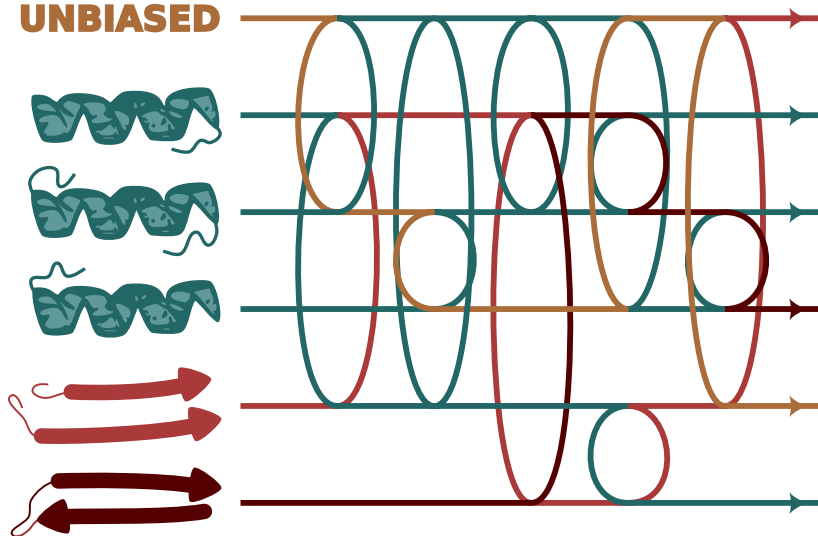


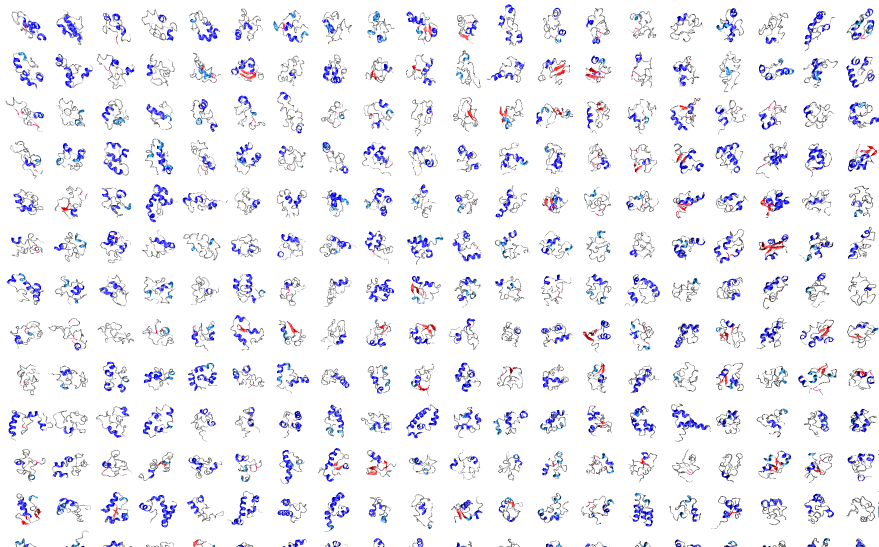
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Generated structures

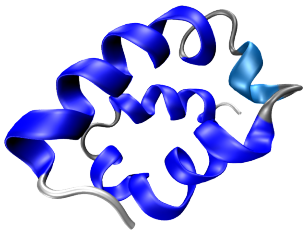
Independent conformers

246 conformations in 2 μ s



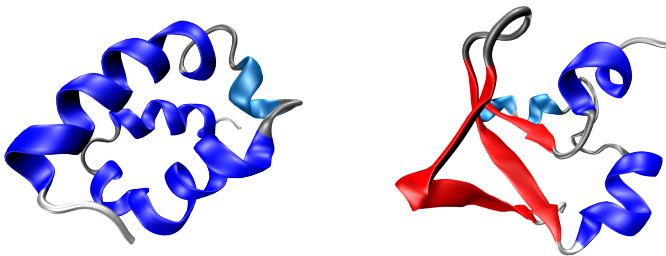
Generated structures

Structure and shape



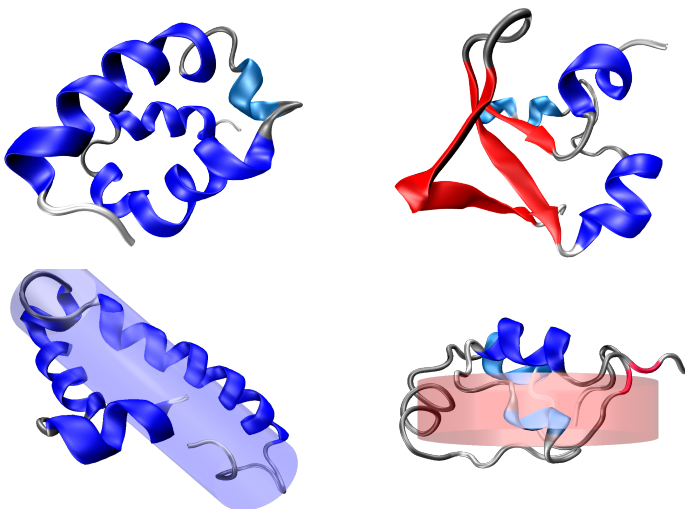
Generated structures

Structure and shape



Generated structures

Structure and shape



Descriptors of the structures

Structural descriptors

$$\langle z \rangle = \frac{2(\mathcal{K} + N - 1)}{N}$$

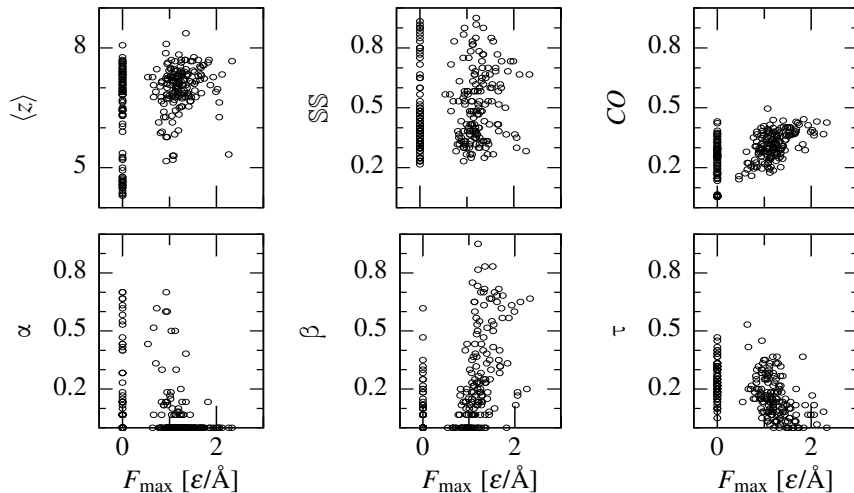
$$CO = \frac{1}{\mathcal{K} \cdot N} \sum_k \Delta_k$$

$$SS = \alpha + \beta + \tau$$

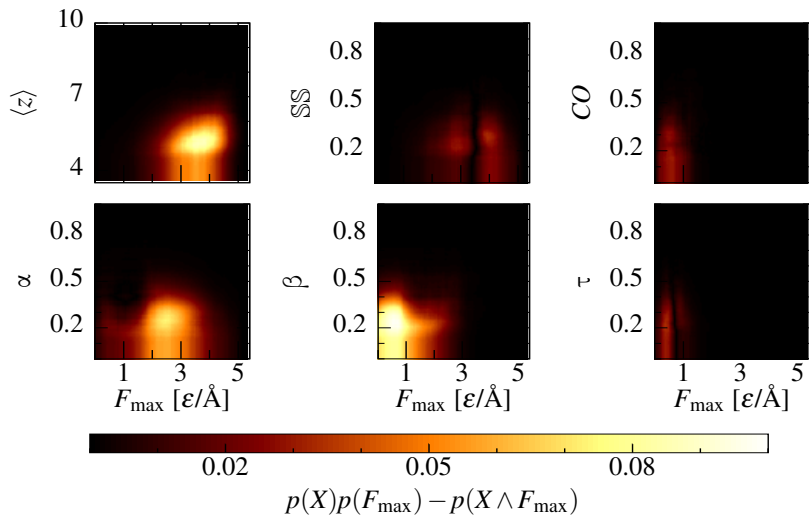
Dynamic descriptor

Mechanical stability, F_{\max}

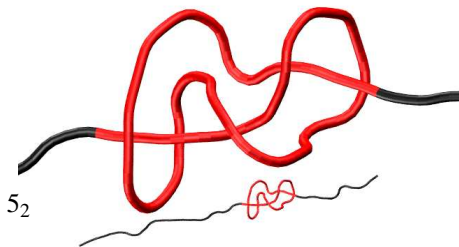
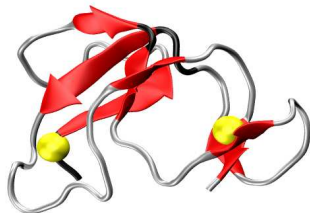
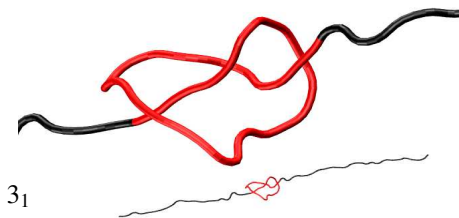
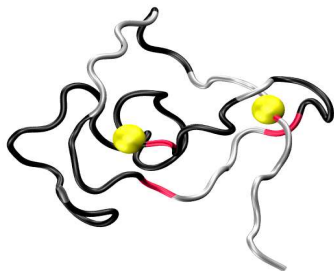
Descriptors of the structures



Descriptors of the structures

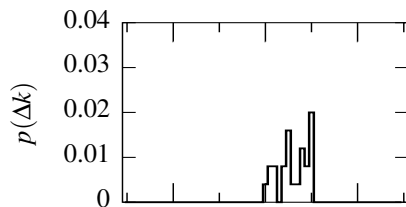
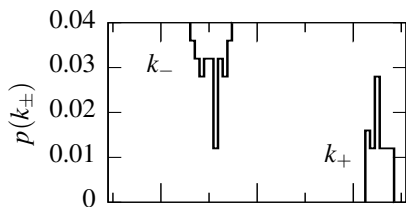


Knotted structures

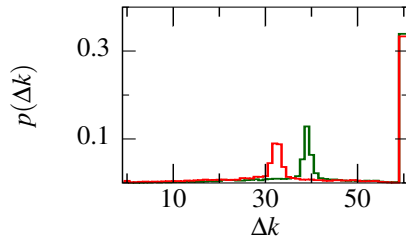
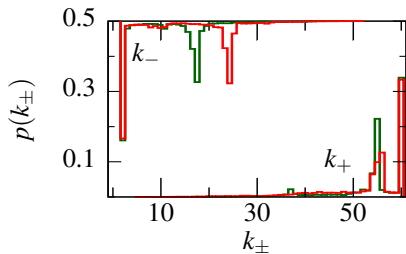


Knotted structures

Structure histogram



Time histogram



Summary

- We have successfully used bias exchange molecular dynamics to explore the conformational space of a 60-residue polyglutamine.
- We have identified a wide variety of structured conformations that present several different shapes, number of contacts, secondary structural elements and mechanical stabilities, among other descriptors, in agreement with experiments.
- We have discovered knotted conformations with an average width of 35 residues, close to the pathological threshold of many glutamine-related diseases, including Huntington.
- We propose knotting of the conformations as one of the possible toxicity mechanisms related to polyglutamine.

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Acknowledgements

Group Leader:

M. Carrión-Vázquez

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Unión Europea
Fondo Social Europeo
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