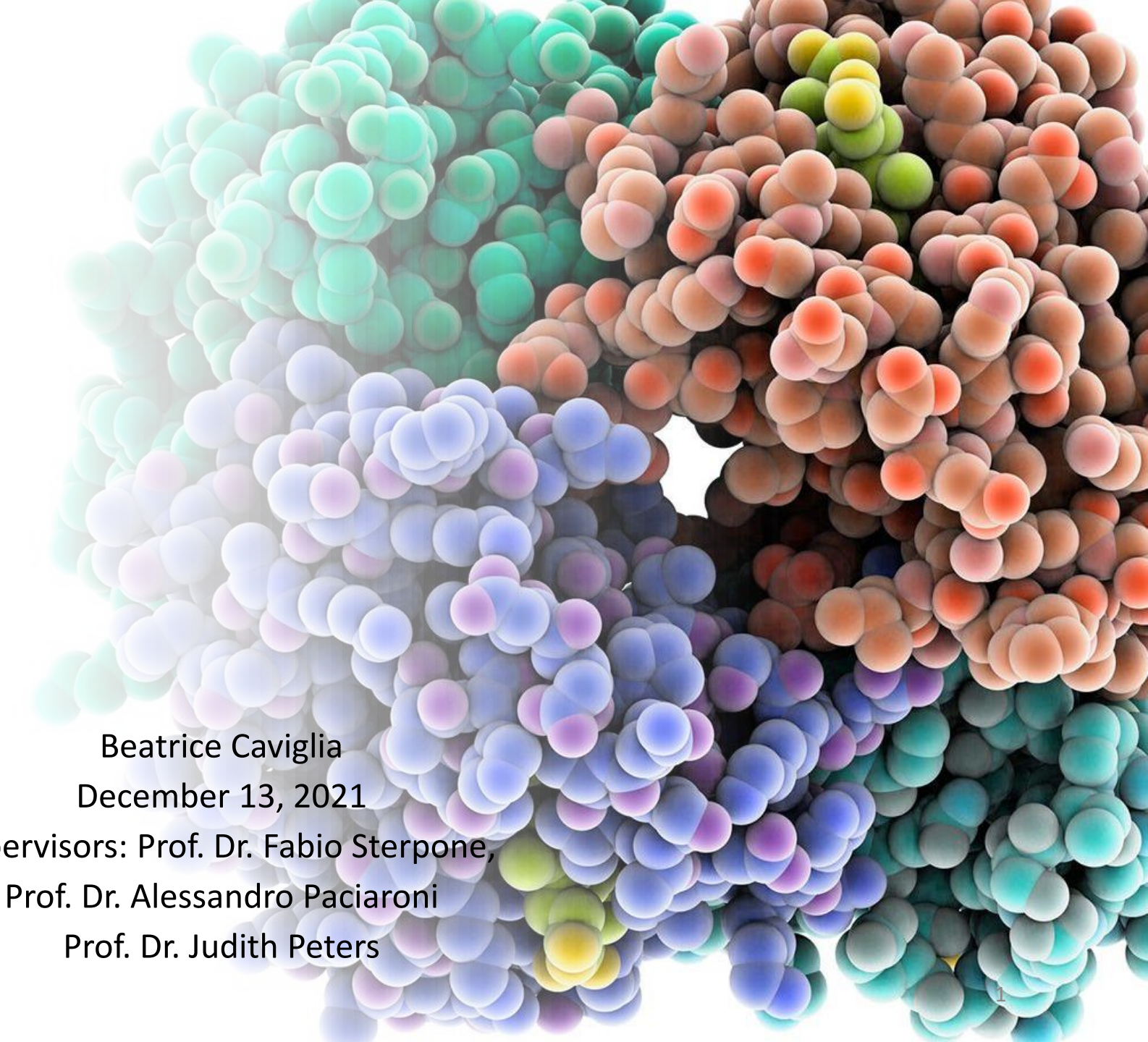
PhD in Physics at the University of Perugia Topic: Arrest of Proteome dynamics at cell death temperature

Research Project

Beatrice Caviglia

December 13, 2021

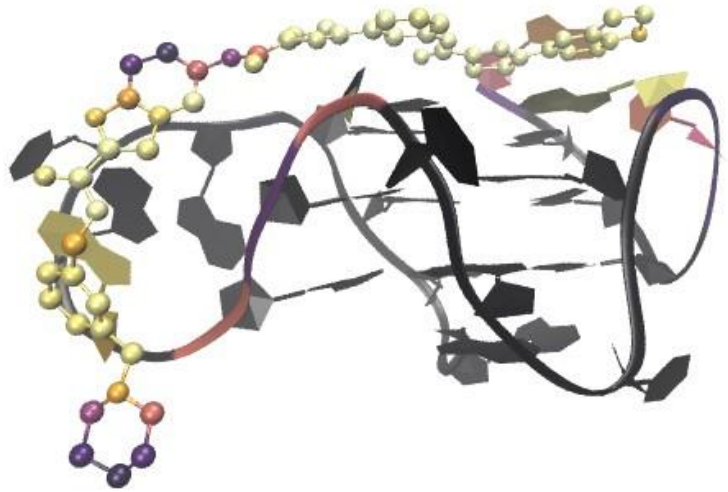
Supervisors: Prof. Dr. Fabio Sterpone,
Prof. Dr. Alessandro Paciaroni
Prof. Dr. Judith Peters

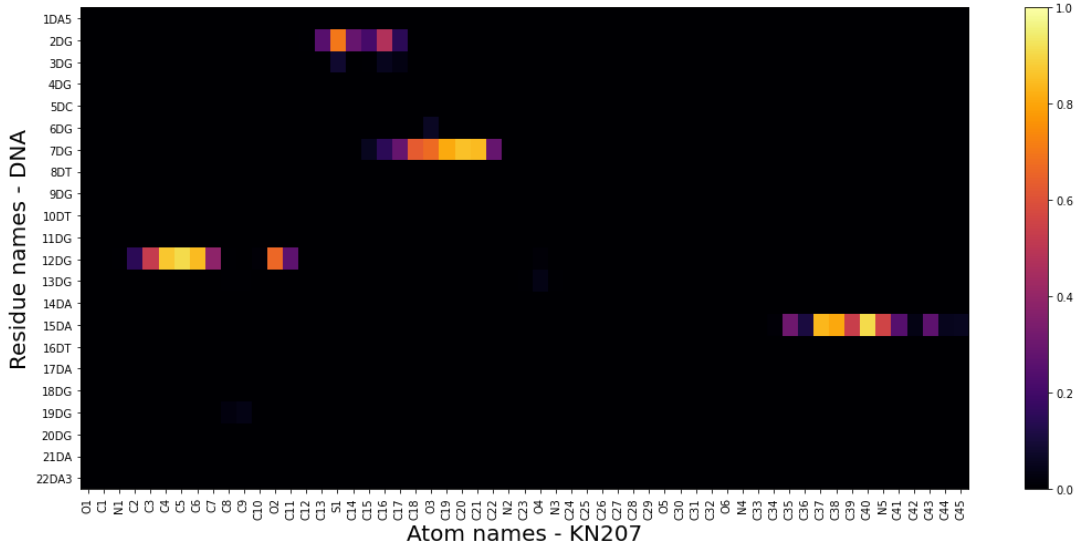


Background

- Mathematics BSc. at Ruprecht Karls University of Heidelberg
- Complex Systems Modeling MSc. at King‘s College London

→Research project for master thesis: In silico investigation of three novel molecules binding to G-quadruplex DNA using Molecular Dynamics

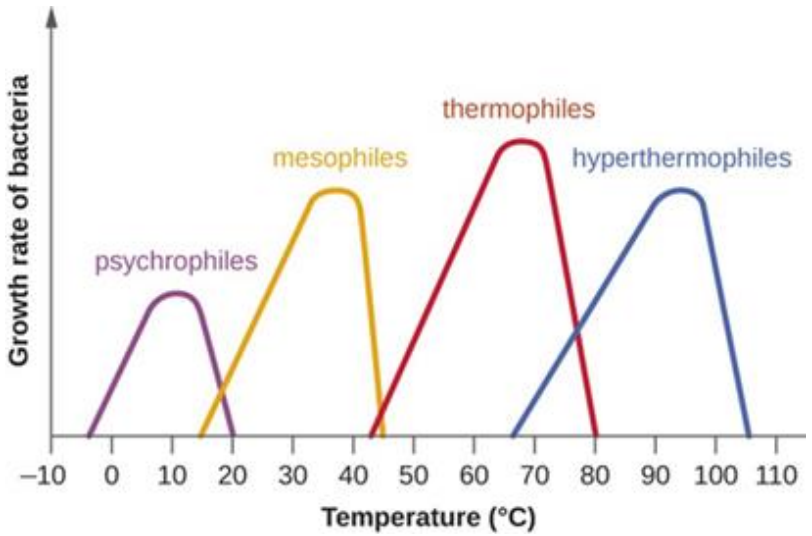


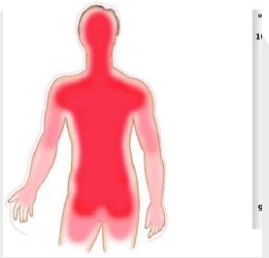


Contact Map: Showing probability of contact of atoms in DNA and small molecule

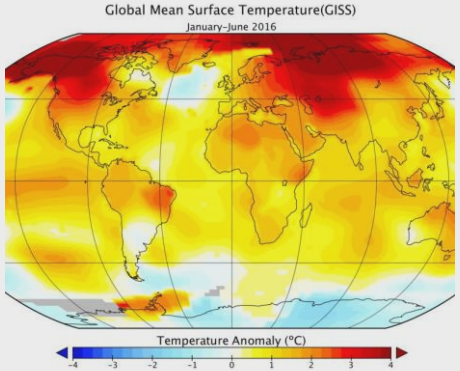
Introducing Research Project

- Temperature is an important determinant in the study of living organisms and cells

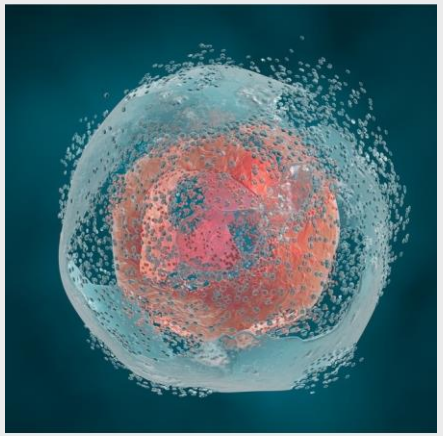




Metabolism



Global warming

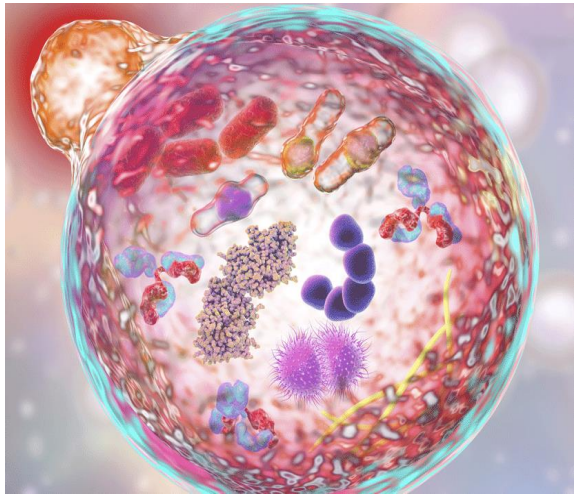


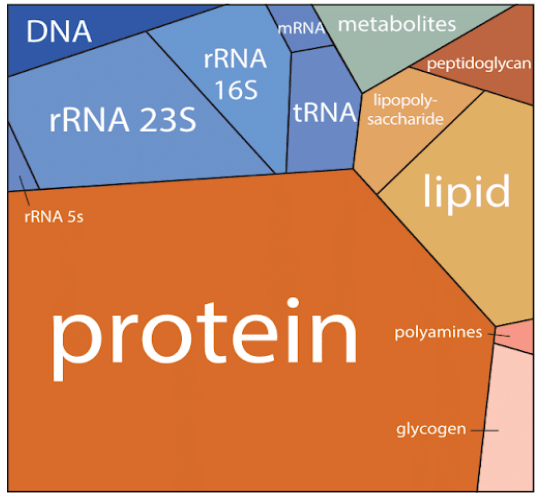
Cancer therapy:
Temperature
induced cell death

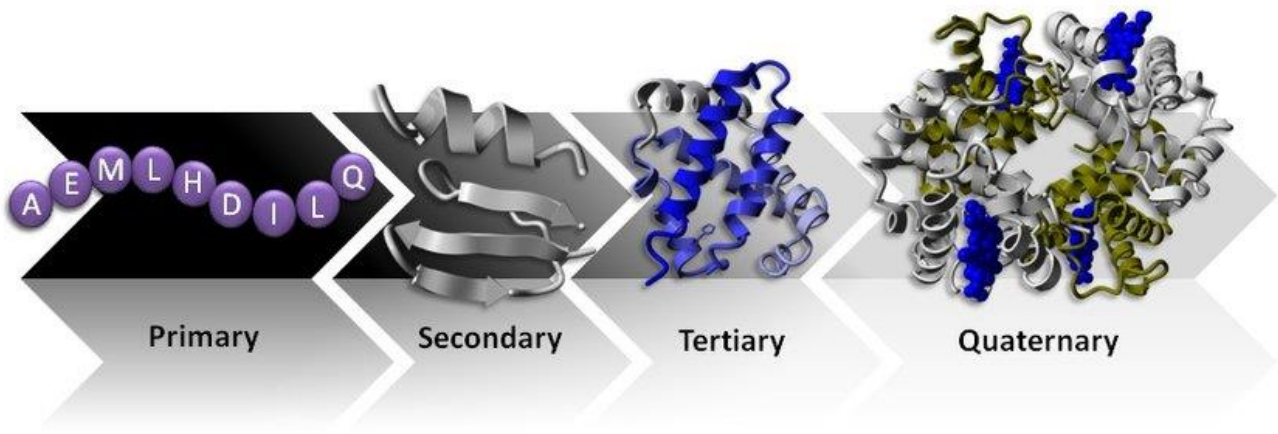
→ The effects of temperature increase are of great interest in a variety of fields

Arrest of proteome dynamics at the cell death temperature

- Proteins are the most abundant component in cells
- Proteins that reside cells have four different levels of structure

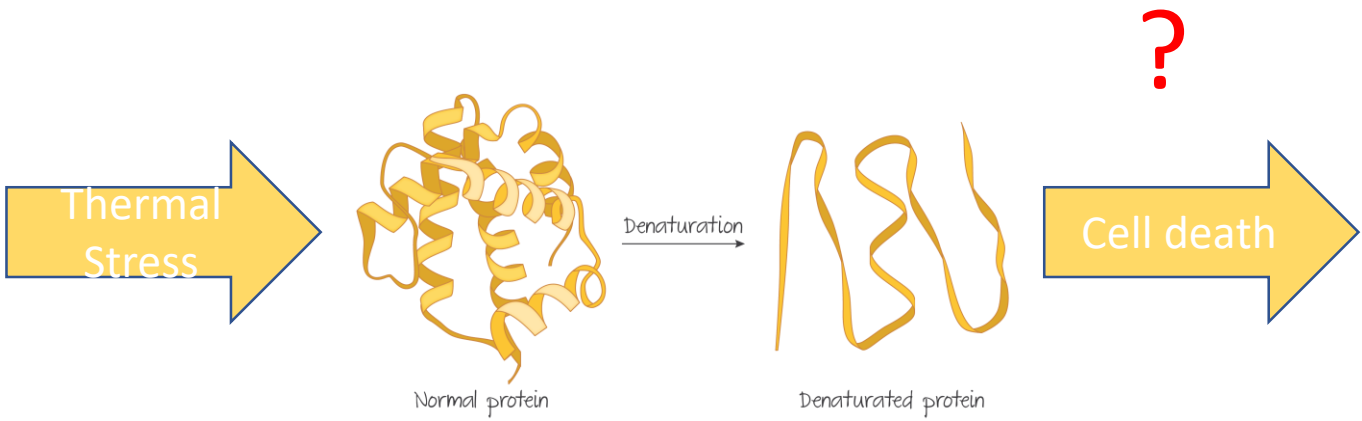






Arrest of proteome dynamics at the cell death temperature

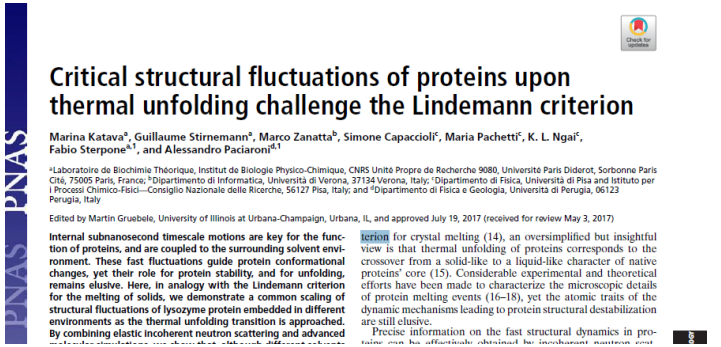
- Increase in temperature leads to protein denaturation
- Protein denaturation is thought to be the cause of cell death
- Thermal sensitivity of proteins is largely uncharacterized
- Is it the whole set of proteins that triggers cell death or only a set of essential proteins?



Dynamics as Proxy to Monitor Cell Death

- Important and uncharacterized aspect of temperature induced cell death is the dynamics inside a cell
- Proteins live in crowded environment where unfolding of set of proteins might impact on physical properties of cytoplasm and dynamics
- Proteins perform local structural fluctuations

→ Lindemann-like criterion: Critical value of fluctuations upon which proteins unfold



PNAS

Critical structural fluctuations of proteins upon thermal unfolding challenge the Lindemann criterion

Marina Katava[a], Guillaume Stirnemann[a], Marco Zanatta[b], Simone Capaccioli[c], Maria Pachetti[c], K. L. Ngai[c], Fabio Sterpone[a,1], and Alessandro Paciaroni[d,1]

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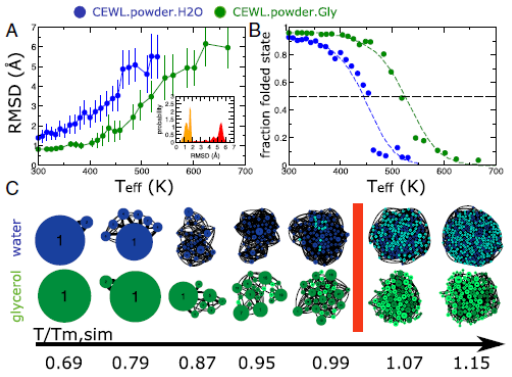
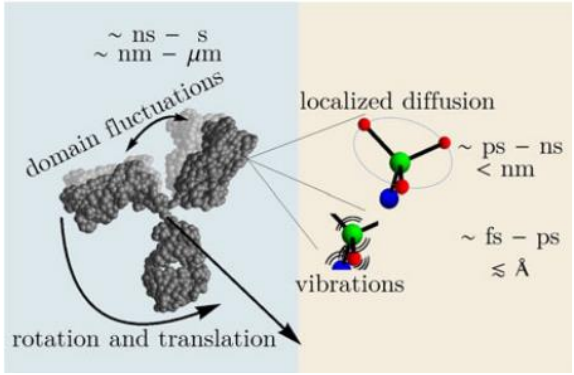
Edited by Martin Gruebele, University of Illinois at Urbana-Champaign, Urbana, IL, and approved July 19, 2017 (received for review May 3, 2017)

Internal subnanosecond timescale motions are key for the function of proteins, and are coupled to the surrounding solvent environment. These fast fluctuations guide protein conformational changes, yet their role for protein stability, and for unfolding, remains elusive. Here, in analogy with the Lindemann criterion for the melting of solids, we demonstrate a common scaling of structural fluctuations of lysozyme protein embedded in different environments as the thermal unfolding transition is approached. By combining elastic incoherent neutron scattering and advanced



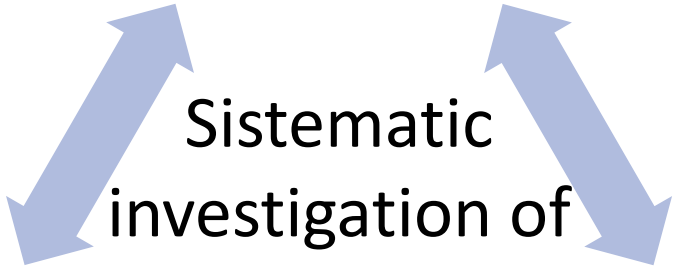


Ongoing collaboration

Prof. Dr. Alessandro Paciaroni, University of Perugia

Marie-Therese Giudici and Marianne Guiral,

BIP, Marseille



Sistematic investigation of dynamical aspects of cell death

Stepan Timr, PostDoc

Daniele Di Bari, PhD

Prof. Dr. Fabio Sterpone

CNRS, Paris

Prof. Dr. Judith Peters

ILL, University of Grenoble

Objectives of the Project

- Extend ongoing investigation on link between proteome structure, proteome dynamics, and cell death upon thermal stress combining experimental and theoretical studies

→ Psychrophile, Thermophile, Hyperthermophile

→ Reveal whether a set of protein unfolding triggers cell death

→Explore connection between dynamics of cytoplasm and local fluctuations of individual proteins and global melting of proteome

→Increase the understanding on how unfolding of a limited number of proteins affects cell functionality

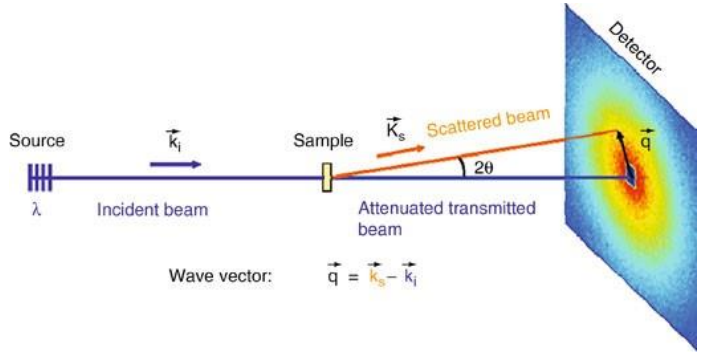
Methods of the Project

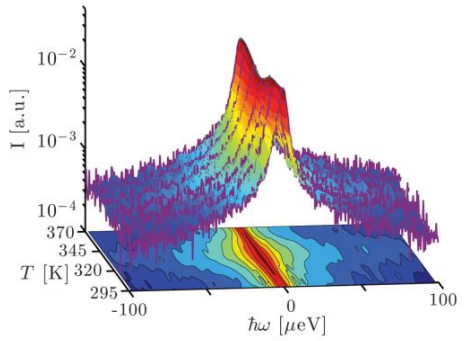
1) Neutron Scattering: main experimental technique

→Thermal neutron wavelengths and energies correspond to inter-atomic distances and energies

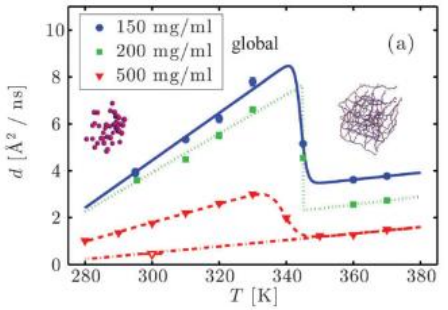
→Low absorption for protein atoms

→ Penetrate deeply into sample and important isotope effects





$$S(q,\omega) = \mathscr{R} \otimes \{\beta(q)[A_0(q)\mathscr{L}_\gamma(\omega) + (1 - A_0(q))\mathscr{L}_{\gamma+\Gamma}(\omega)] + \beta_{D_2O}\mathscr{L}_{\gamma_{D_2O}}(\omega)\}$$

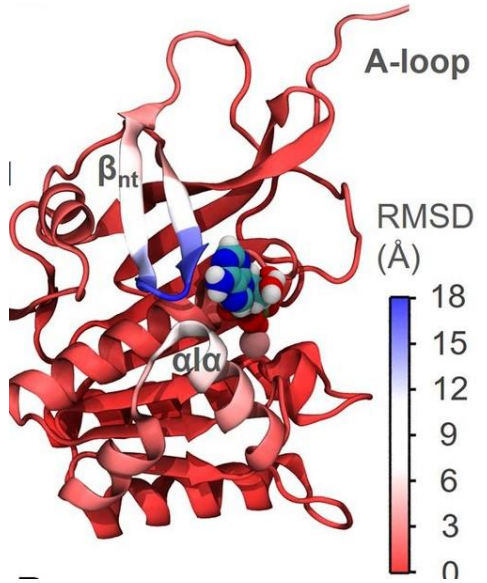


Methods of the Project

2) Molecular dynamics: Computer simulation tool based on Newton‘s equation of motion

→Complement experimental studies, but also extremly useful under extreme conditions

→Protein coarse-grained model developed by group of Prof. Dr. F. Sterpone



$$F(t) = ma(t) \quad a(t) = \frac{d}{dt}v(t) \quad v(t) = \frac{d}{dt}r(t)$$

$$r(t+\Delta t) = 2r(t) - r(t-\Delta t) + \frac{F(t)}{m}\Delta t^2$$

$$v(t) = \frac{1}{2\Delta t}[r(t+\Delta t) - r(t-\Delta t)]$$

$$F_i = -\frac{\partial U(r)}{r_i} \quad U(r) = U_{vdW}(r) + U_C(r) + U_{intram}(r)$$

Thank you for listening