PHAISTOS – software for inference of protein structure

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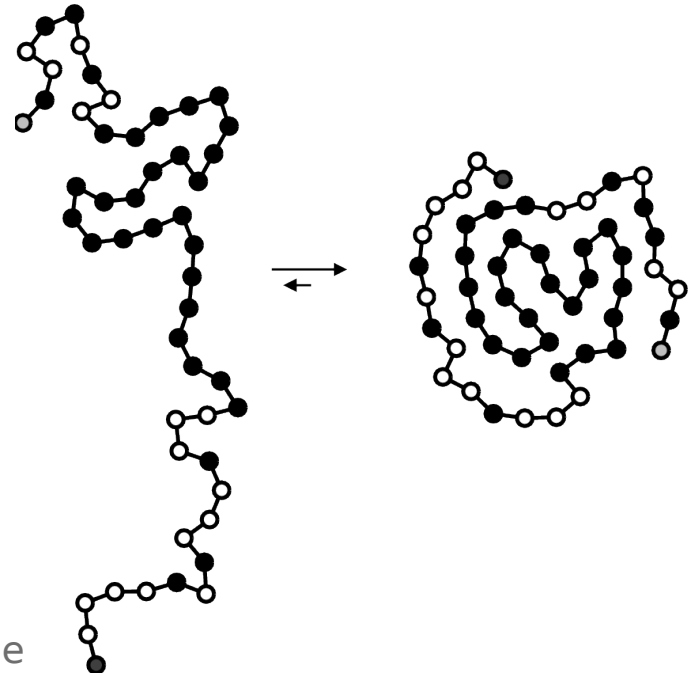
The structural bioinformatics group

- Bioinformatics Center, KU
  - Two PhD students, one postdoc
- The protein folding problem
  - Biotechnology
    - Enzyme design
  - Medicine
    - Drugs, vaccines
  - New materials
    - Spider silk
- Proteins are linear polymers of amino acids
  - 20 different amino acids
  - Hydrophobic amino acids on the inside
  - Hydrophylic amino acids on the outside
- Sequence encodes a compact 3D shape
  - Protein fold, hydrophobic effect
- Predicting structure from sequence
  - A main open problem in biology and physics

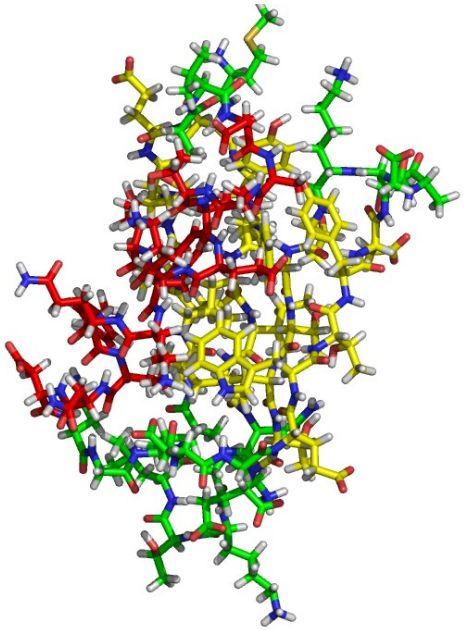


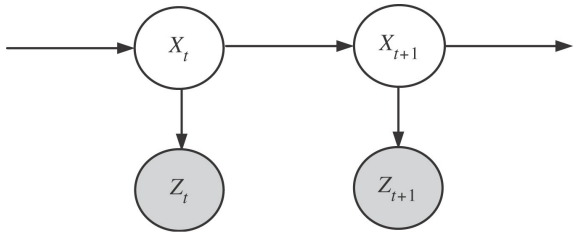
Physics, probabilities, machine learning

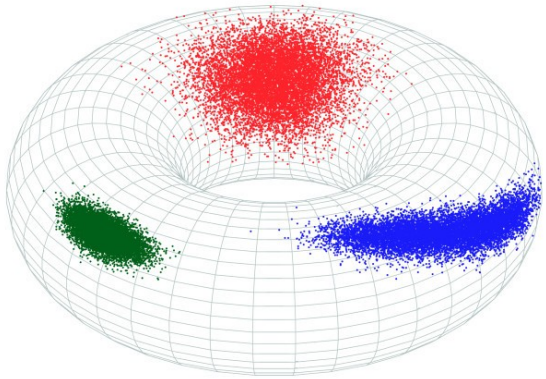
Protein folding problem is a problem in physics
- Fold a protein using physical energy functions

However, it is also a problem in applied statistics
- We extract information from known protein structures using probabilistic models and machine learning
  - Bayesian networks
  - Directional statistics
  - Deep learning
- Combined with physics where needed

Our aims
- Prediction of protein structure from sequence
- Inference of protein structure from sparse data
  - NMR, SAXS, hydrogen exchange,...
- Simulation of protein dynamics
- Protein engineering and design







PHAISTOS

Protein structure prediction, simulation and inference

- Boomsma, W., Frellsen, J., Harder, T., Bottaro, S., Johansson, KE., Tian, P., Stovgaard, K., Andreetta, C., Olsson, S., Valentin, J., Antonov, L., Christensen, A., Borg, M., Jensen, J., Lindorff-Larsen, K., Ferkinghoff-Borg, J., Hamelryck, T. (2013) PHAISTOS: A framework for Markov chain Monte Carlo simulation and inference of protein structure. **J. Comput. Chem.** 34, 1697-705.
- Markov chain Monte Carlo based
  - As opposed to molecular dynamics
- Probabilistic models guide the conformational sampling
  - TORUSDBN, **PNAS** 2008, 2014
- Energy functions
  - OPLS, PROFASI, CHARMM
- Main developer Wouter Boomsma
- Several groups are involved at KU
  - Jan Jensen
  - Kresten Lindorff-Larsen

Freely available from Sourceforge

- Implemented in C++
- http://sourceforge.net/projects/phaistos/

www.phaistos.org

Use case: Prediction of stability

MUMU is a probabilistic model of the local environment of amino acids in protein structures

- Johansson, KE., Hamelryck, T. (2013) A simple probabilistic model of multibody Interactions in proteins. **Proteins** 81, 1340-50.

-Main developer Kristoffer E. Johansson

Can be used to evaluate how well an amino acid "fits" into a given structure

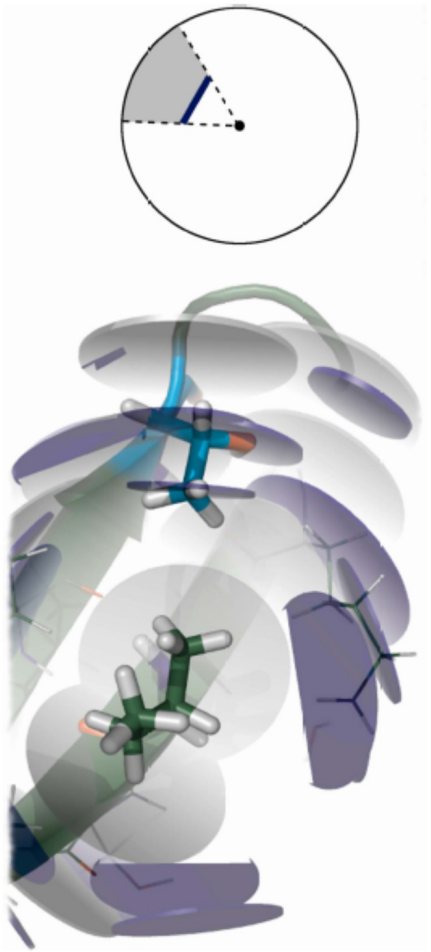
- Amino acid neighbors, volume, backbone angles

$$P(A_i|\mathbf{A}_{\sim i}, \mathbf{X}) = P(A_i|C_i, N_i, V_i, \Phi_i, \Psi_i) = P(A_i|E_i)$$

- Very fast, 30.000 amino acids/minute

Web service

- Fast screening of protein mutants



MUMU example

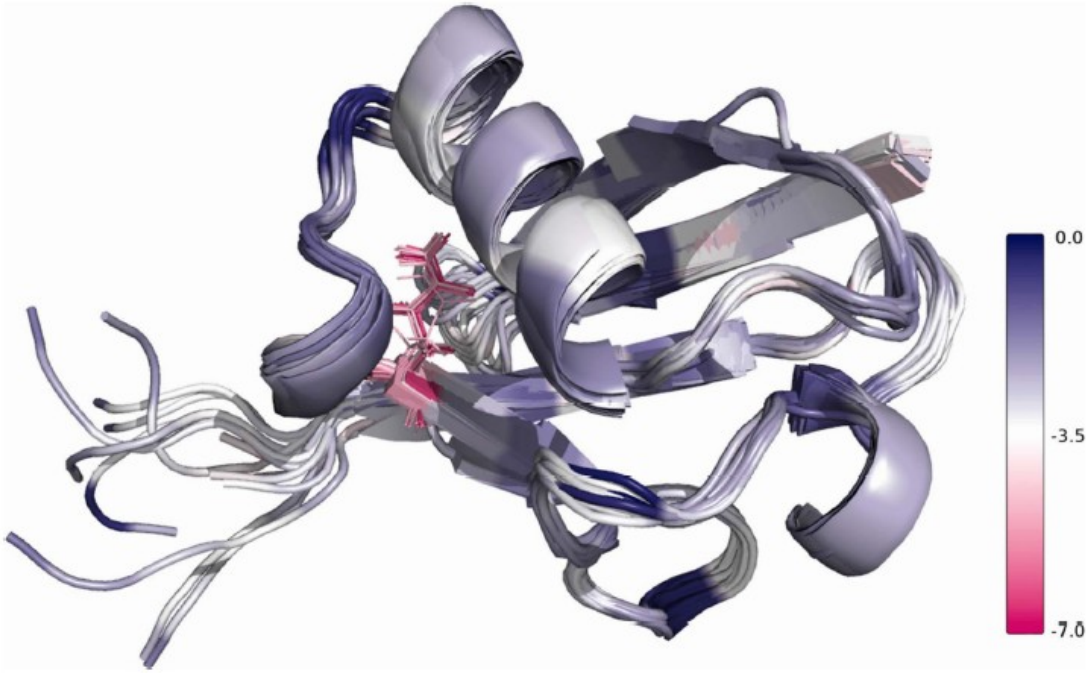


Figure 6

Structural representative ensemble of ubiquitin with residues colored according to the MuMu probability, $\log P(A_i|E_i)$. Log probabilities are indicated in the color bar. Magenta residues have low probability and are thus an unlikely combination of side chain and environment. The side chain of Gln-41 is shown to emphasize that this amino acid has low probability in all structures.

Conclusions & acknowledgements

Phaistos

- Inference of protein structure
- Probabilistic models, physical energy functions
- Use case: protein stability

Acknowledgments

- Wouter Boomsma (TORUSDBN, PHAISTOS, CRISP)
- Jan Valentin (reference ratio *de novo* prediction)
- Sandro Bottaro (CRISP local move)
- Jes Frellsen (MUNINN, reference ratio)
- Kristoffer E. Johansson (MUMU)
- Simon Olsson (TYPHON, ensembles)
- Tim Harder (BASILISK, TYPHON)
- Pengfei Tian (PROFASI implementation)

Collaborators

- Jan Jensen, Kresten Lindorff-Larsen, KU
- Kanti Mardia, John T. Kent, Leeds, UK
- Jesper Ferkinghoff-Borg, DTU, Denmark

http://www.binf.ku.dk
http://www.phaistos.org

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