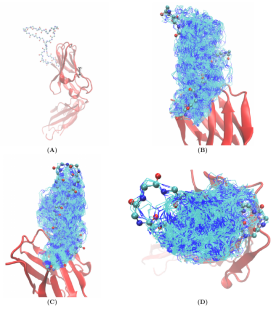
- *PostDoc position proposal:* Exploration and Prediction of the Energy Landscape for Peptides and Proteins
- Supervision: F. Cazals / Centre Inria at Université Côte d'Azur, France; D.J. Wales / Cambridge University



Keywords: theoretical biophysics, machine learning, kinematics, (structural) biology.

Context. Machine learning techniques have made significant progress in prediction of favourable structures from amino acid sequence in proteins. However, understanding and making predictions for the global energy landscape is a much harder problem. In particular, a key research goal is to predict the pathways by which functional forms of a protein are reached from an unfolded ensemble. Knowledge of these pathways has tremendous potential for important applications, especially drug design. For example, the transient conformations exposed during folding might provide good targets for binding of small molecules, with more specificity than the targets presented by the final functional state.

Goals. The key to navigating the relevant conformational space is to understand the interplay of the torsional angles that largely define the three-dimensional structure of a protein or peptide [1]. Extensive databases of local minima in this space, and the transition states that connect them, have been harvested in previous work [A,B,C,D], but remain largely unexploited for machine learning predictions.

The first step in this analysis is to try and predict whether two minima have a direct connection, and the next step would be to predict the corresponding transition state geometry. These capabilities are necessary to make predictions for the longer, multistep pathways associated with protein folding [1].

We have recently contributed several insights on these topics. First, using existing databases for tripeptides and the knowledge of the angular degrees of freedom the direct connectivity, we have shown that missing connections can be predicted reliably [Z]. Second, we have developed novel sampling strategies in torsion angle space, yielding diverse backbone conformations at an unprecedented pace [2,3].

We anticipate that combining these insights, as well as novel mixture models in torsion angle space, will yield important insights for folding pathways and kinetics. There is an exciting opportunity to advance the state-of-the-art in this field, which would have important and wide-ranging impacts.

Training. PhD thesis in machine learning or theoretical biophysics or computer science

Conditions. Postdoc position funded by Centre Inria at Université Côte d'Azur, France. The position is located in Sophia-Antipolis, French Riviera.

Supervision: F. Cazals (Inria; endowed chair, 3IA Cote d'Azur); D. Wales (Cambridge Uni.; endowed chair, 3IA Cote d'Azur) Contacts: frederic.cazals@inria.fr, davidjwales@gmail.com

[A] J.A. Joseph, K. Röder, D. Chakraborty, R.G. Mantell and D.J. Wales, Chem. Commun, 53, 6974-6988 (2017) Exploring biomolecular energy landscapes.

[B] D.J. Wales, Curr. Op. Struct. Biol., 20, 3-10 (2010) Energy Landscapes: Some New Horizons.

[C] K. Klenin, B. Strodel, D.J. Wales and W. Wenzel, Biochimica et Biophysica Acta, 1814, 977-1000 (2011). Modelling Proteins: Conformational Sampling and Reconstruction of Folding Kinetics.

[D] A.D. Keith, E.B. Sawyer, D.C.Y. Choy, Y. Xie, G.S. Biggs, O.J. Klein, P.D. Brear, D.J. Wales, P.D. Barker, Perspective: Phys Chem Chem Phys (2024) 26, 695. Combining experiment and energy landscapes to explore anaerobic heme breakdown in multifunctional hemoproteins.

[Z] K. Grewal and D. J. Wales, part III report, Cambridge University.

[1] K Lindorff-Larsen and S Piana and R.O. Dror and D.W. Shaw, How fast-folding proteins fold, Science (334), 2011.

[2] T. O'Donnell, V. Agashe and F. Cazals, Geometric constraints within tripeptides and the existence of tripeptide reconstructions, J. Comp. Chem. (44), 2023.

[3] T. O'Donnell and F. Cazals, Enhanced conformational exploration of protein loops using a global parameterization of the backbone geometry, J. Comp. Chem. (44), 2023.

- http://www-sop.inria.fr/teams/abs/positions/thesis24attention.pdf
- Exploration and Prediction of the Energy Landscape for Peptides and Proteins
- Exploration and Prediction of the Energy Landscape for Peptides and Proteins

Summary: