# Discussion by Thomas Hamelryck and Charles H Martin on Protein Folding

Thomas Hamelryck wrote:

Last year, Google DeepMind's team behind AlphaFold received the Nobel Prize for solving the protein folding problem, which had been an open problem for more than 50 years. AlphaFold2, like ChatGPT, relied on the Attention Mechanism to infer which amino acids are close together in space. Last year, AlphaFold3 incorporated a probabilistic diffusion model, and capacities to model additional biomolecules such as ligands and RNA.

Recently, however, my attention has been returning to AlphaFold's initial spectacular success in 2018 and its quite unrecognized probabilistic underpinnings.

AlphaFold1 creates a knowledge based potential based on two components, one concerning angles and one concerning distances, and ties them together with a third component -- a so-called reference potential.

This amounts to a little known version of Bayesian updating called Jeffrey Conditioning or Probability Kinematics. Though not acknowledged by the AlphaFold team in their publications, this approach clearly goes back to the seminal work of Manfred Sippl on heuristic knowledge based pairwise potentials in the 1990s, and later work on the probabilistic vindication of such potentials (see [1]).

How does it work? I've outlined the threefold structure below.

What is the big deal, you might ask?

Well, proteins are dynamic molecules and prediction can still be challenging, requiring bona fide probability distributions to describe epistemic and aleatoric uncertainity. AlphaFold1's clever yet obscured probabilistic approach based on seminal work by others in the period 1990-2015 might well be worth a second glance.

Apart from that, the hidden role of Bayesian Statistics in solving one of the greatest open scientific problems of the 20th century is rather cool.

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A screenshot of a math test

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Charles H Martin wrote:

To understand AlphaFold, start with John Jumper's PhD thesis. Here are on of the many papers he published then.

The basic idea is to mine the PDB and create an Effective Free Energy Potential to both remove the water from an MD simulation and also learn the effective potential for the dynamics of the side chains.

This was indeed a very old idea, first envisioned by our mutual PhD advisor Karl Freed in the 90s. Indeed, you can see the beginnings of this line of thinking in Freed's early work on the statistical field theory of polymer folding. Some of the very early work used the Mori formalism to model the motions of the backbone, and, later developed an effective potential for the water in an MD simulation.

The phenomenal work by Jumper combined ideas from statistical mechanics with ML w/ Contrastive Divergence to learn the Effective Free Energy for the side chain motions, leading to a model that could both predict the structure and the dynamics of small proteins.

Did other people try similar things ? You had to prove your model by entering it into the CASP competitions. And the Chicago team consistently performed excellently here.

Thomas Hamelryck replied:

There are indeed 1000s and 1000s of papers on so-called "knowledge based potentials" for protein structure prediction! It's a fascinating story. Although "potentials of mean force" indeed have a very precise physical meaning, the knowledge based potentials derived from the PDB are anything but. They are probabilistic constructs (see above post for the explanation of why they work, all the way up to AF1) and not potentials in the sense of the classic 1935 Kirkwood article. A classic reference on why these potentials are not Kirkwood mean force potentials is this article by Thomas & Dill, which appeared in JMB in 1996 (Quote: "Our results suggest that current statistical potentials may have limited value in protein folding algorithms and wherever they are used to provide energy-like quantities."): <https://www.sciencedirect.com/science/article/abs/pii/S0022283696901758>

A second classic paper on the dodgy physical interpretation of knowledge based potentials is by Ariel Ben-Naim, J. Chem. Phys, 1997. Quote: "It is also shown that the so-called “statistical potential” as derived from the data bank of protein structures is neither the potential nor the potential of mean force for pairs of amino-acid residues." <https://pubs.aip.org/aip/jcp/article-abstract/107/9/3698/477625/Statistical-potentials-extracted-from-protein?redirectedFrom=fulltext>

Charles H Martin replied:

the goal is not to interpret the potential. The goal is to use it

There are many cases in the theoretical chemistry where many body interactions are clearly present and even large and seemingly non-negligible, but can be neglected because they don’t materially affect the predictions.

the best example was predicting the ground state, structure of simple organic molecules.

In other cases, higher order, interactions are effectively averaged into the pair potentials .

Thomas Hamelryck replied:

I'm not sure what you mean. Understanding how AF1 / Probability Kinematics works opens up a wide range of possibilities for formulating probabilistic models of proteins. Given the many remaining open problems (disorder, folding pathways, RNA 3D prediction,...) this is quite a valuable insight.

Charles H Martin replied:

1) it is frequently the case in science that simple models work well beyond their apparent range of validity. While it is natural to study what an exact potential might be, these low level studies to do imply that the 'more naive 'effective potentials used are not useful.

2) you claimed that AlphaFold had " unrecognized probabilistic underpinnings. " As if somehow all of statistical mechanics and AI is nothing more than some trivial application of Bayesian statistics. As you noted, the idea of a potential of mean force is nearly 100 years old, and one does not need to use the specific numerical techniques of Bayesian statistics to learn a useful potential.

AI practitioners understand that Bayesian sampling are tough to use in practice because they struggle with high-dimensional spaces, convergence issues, computational costs, sensitive tuning, and multimodal distributions, often requiring approximations or advanced tools to work effectively

Jumper's genius is not just coming up with the ideas but also getting them to work in practice and at scale.

Thomas Hamelryck replied:

Absolutely, AlphaFold is a great accomplishment. I'll leave it at that.

# References

[1] [The original post of Thomas Hamelryck in Linkedin, March 19, 2025](https://www.linkedin.com/posts/activity-7308108590412718080-EtUv?utm_source=share&utm_medium=member_desktop&rcm=ACoAAAFZfUoBgPoGUucdnvtwuzPv79P8VHj6uvk)

[2] [Potentials of Mean Force for Protein Structure Prediction Vindicated, Formalized and Generalized, Thomas Hamelryck et al, 2010](https://github.com/dimitarpg13/deep_learning_and_neural_networks/blob/main/literature/articles/protein_folding/Potentials_of_Mean_Force_for_Protein_Structure_Prediction_Vindicated_Formalized_and_Generalized_Hamelryck_2010.pdf)

[3] [Knowledge-Based Potentials for Proteins, Manfred J. Sippl, U of Salzburg, 1997](https://github.com/dimitarpg13/deep_learning_and_neural_networks/blob/main/literature/articles/protein_folding/Knowledge-based_potentials_for_proteins_Sippl_1995.pdf)

[4] [New Methods Using Rigorous Machine Learning for Coarse-Grained Protein Folding and Dynamics, John Jumper, U of Chicago, 2017](https://github.com/dimitarpg13/deep_learning_and_neural_networks/blob/main/literature/articles/protein_folding/New_Methods_using_Rigorous_Machine_Learning_for_Coarse-Grained_Protein_Folding_and_Dynamics_Jumper_UChicago_2017.pdf)

[5] [Trajectory-based Training Enables Protein Simulations with Accurate Folding and Boltzmann ensembles in cpu-hours, John Jumper et al, 2017](https://github.com/dimitarpg13/deep_learning_and_neural_networks/blob/main/literature/articles/protein_folding/Trajectory-based_training_enables_protein_simulations_with_accurate_folding_and_Boltzmann_ensembles_in_cpu-hours_Jumper_2017.pdf)

[6] [Estimation of Effective Interresidue Contact Energies from Protein Crystal Structures: Quasi-Chemical Approximation, S. Miyazawa et al, 1985](https://github.com/dimitarpg13/deep_learning_and_neural_networks/blob/main/literature/articles/protein_folding/Estimation_of_Effective_Interresidue_Contact_Energies_from_Protein_Crystal_Structures-Quasi-Chemical_Approximation_Miyazawa_1987.pdf)