Why AlphaFold is Not Like AlphaGo

Terry B. Bollinger [1]
[1] *Apabistia Research, Ashburn, VA, USA 20147*

(Incepted 6 February 2021; Published 10 February 2021; Tweaked 2021-11-12.11:15)*

In sharp contrast to the fully virtualized, faster-than-human learning speeds of AlphaGo Zero, the learning speed of AlphaFold2 remains firmly attached to and limited by human experimental time.

DOI: https://doi.org/10.48034/20210206

This is about: Protein structure prediction,
Game theory models,
Language models

I. BACKGROUND

AlphaFold2 is the second major iteration of a protein structure predictor by Google-owned DeepMind Lab [1]. DeepMind is famous for creating AlphaGo Zero, the first game-playing system to transcend rules learned from human trainers [2]. When AlphaFold2 made a significant leap in protein prediction accuracy in the fourteenth annual CASP competition [3], even reserved publications like Nature became noticeably breathless in their praise of the results [4]. It was not just the impressive and well-proven leap in prediction accuracy that made AlphaFold2 notable, but also its association with the DeepMind brand and implicitly with the beyond-human learning successes of AlphaGo Zero.

But is this notoriety and acclaim fully justified? Beyond superficial name similarities, is the design of AlphaFold2 sufficient to enable a similar leap ahead of human knowledge and expertise in the same fashion as AlphaGo Zero did for game playing?

II. ANALYSIS

As of early 2021, the only technical description of the AlphaFold2 design is pages 22-24 of the CASP14 Abstract Book [5]. While brief, even this abstract is sufficient to detail critical differences between the AlphaGo Zero and AlphaFold2 and learning strategies.

AlphaFold2 begins with three vast databases (UniRef90, BFD, and MGnify clusters) of experimentally determined DNA-to-protein mapping data. This need for lab-collected data immediately and sharply distinguishes AlphaFold2 from AlphaGo Zero. AlphaGo Zero can self-train at computer speeds without human intervention because it has sufficient information to generate, play, and analyze all possible legal games within its universe. AlphaFold2's profound reliance on experimental data, in contrast, means that it is incapable of creating and learning from worlds entirely of its creation. The inability to simulate training universes accurately is a severe problem in all simulation-based AI training. One can easily *create* virtual worlds, but they are simplified expansions of rule sets that are smaller than those of the real world. Thus they inevitably lack critical clues and details whose acquisition is the deeper goal of all good training. Consequently, the training results are usually worthless.

In gaming (e.g., Go), this incompleteness of synthesizing accurate universes is not a problem because the virtual universe's underlying rules — the game rules — are all fully known in advance.

On this point alone, AlphaFold2 differs significantly from AlphaGo Zero. However, AlphaFold2 nonetheless excelled in solving a problem that has stymied biologists for decades. If not by accessing effective, computer-speed virtual world self-training, how did it achieve this?

AlphaFold2's success is based primarily on *attention* concepts. The abstract notes that "We found that existing deep-learning architectures overly favor sequence-local interactions and do not sufficiently account for global structural constraints. To remedy this, we have developed a novel, attention-based deep learning architecture to achieve self-consistent structure prediction."

Harshall Lamba [6] explains attention by showing how it helps translate languages. There is an even simpler explanation. Think of driving a motorcycle and seeing both a gnat and a truck heading towards you. To which one do you *pay attention*? For proteins, *paying attention* means recognizing constraints such as available space as amino acids accumulate and begin to fold up in a chain. Bottom-up methods tend to miss such miss broader-context issues.

**This document uses Kenobi versioning. The online name always points to the most recent document version, while ob1, ob2,… suffixes indicate obsolete releases of the document.*

III. CONCLUSIONS AND PATH FORWARD

The corpus-based AlphaFold2 architecture is incapable of accessing the beyond-human learning speeds seen in AlphaGo Zero. Thus, its use of the "Alpha" prefix is best understood not as a design spec but as good marketing.

The attention-based mechanisms behind AlphaFold2's impressive results amount to early steps in automating the human intelligence concept of *understanding* a problem. Human experts show "understanding" by immediately identifying how seemingly small systems changes may have dramatic consequences, both negative and positive, in other remote parts of those systems. How to automate understanding is a promising and evolving aspect of the general intelligence problem. As shown by the higher-level structural constraints that AlphaFold2 recognized, a less formal but more intuitive term for attention-based methods might be "big picture" analysis. Even as humans, we tend to acknowledge people capable of seeing the "big picture" — the full scope of future impacts of seemingly small changes — as more intelligent.

In the online discussion of Sabine Hossenfelder's analysis of AlphaFold2, which was the origin of this paper [7], more than one comment (Empischon, Jim Birch) pointed out the need for predictive architectures that focus not on corpora of earlier DNA-to-protein results but on a better quantum-physics level understanding of what happens at the ribosome "assembly point" for proteins. The need for assembly-point modeling increases if the long-term goal is self-training at computer speeds since any such approach must, as with AlphaGo Zero, abandon experimental data corpora derived only from comparisons of downstream results. A smaller set of quantum mechanical "game rules" for how proteins folds as they emerge from the ribosome would replace the corpora.

Modeling protein assembly at the ribosomal emergence point has not been done because it requires better and more efficient prediction of quantum mechanical dynamics than current approximation methods provide. Yuri Manin, one of the founders of quantum computing, recognized as far back as 1980 [8] the extreme energy and information efficiency with which a molecular machine can navigate a "labyrinthine system of passages" through complicated "attractors, separated by low energy barriers." It remains the case that a single biomolecule can, with blinding speed, perform computational tasks beyond the most advanced suites of classical hardware and software.

At least part of this energetics disparity may be of our own doing. Analyses and openly available software by J. M. Sellier [9], now with Ericsson, demonstrate that astonishingly fast and straightforward iterative loops in Wigner phase space can give quantum modeling results more typically thought to require supercomputers. From the theory side, recent work in both information self-healing [10] and on a renewed focus on diffuse Dirac fields rather than assuming point particles [11] suggest quantum mechanics may be simpler and smoother than most models assume. If so, it may yet turn out that organic molecules are "quantum balanced" in ways that allow them to implement insanely unlikely reactions without slipping into chaos. Thus, biological molecular machines may benefit from being adept at keeping classical chaos at bay, even (or especially) at room temperatures.

ACKNOWLEDGEMENTS

Thanks to Sabine Hossenfelder, Empishon, Jim Birch, and Roger Duncan for observations leading to this paper.

[1] C. Beattie, J. Z. Leibo, D. Teplyashin, T. Ward, M. Wainwright, H. Küttler, A. Lefrancq, S. Green, V. Valdés, A. Sadik and others, "DeepMind Lab," *arXiv preprint arXiv:1612.03801,* 2016.

[2] D. Silver, J. Schrittwieser, K. Simonyan, I. Antonoglou, A. Huang, A. Guez, T. Hubert, L. Baker, M. Lai, A. Bolton and others, "Mastering the game of Go without human knowledge," *Nature,* vol. 550, p. 354, 2017.

[3] J. Moult, "A decade of CASP: progress, bottlenecks and prognosis in protein structure prediction," *Current opinion in structural biology,* vol. 15, p. 285–289, 2005.

[4] E. Callaway, "Nature News: DeepMind's AI makes gigantic leap in solving protein structures," *Nature,* 30 11 2020.

[5] J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, K. Tunyasuvunakool, O. Ronneberger, R. Bates, A. Zidek, A. Bridgland and others, "High Accuracy Protein Structure Prediction Using Deep Learning (AlphaFold2) [Abstract]," in *Fourteenth Critical Assessment of Techniques for Protein Structure Prediction (Abstract Book),* 2020.

[6] H. Lamba, "Intuitive Understanding of Attention Mechanism in Deep Learning," *towards data science,* 20 3 2019.

[7] S. Hossenfelder, "Don't Fall for Quantum Hype," *Backreaction,* 06 2 2021.

[8] Y. I. Manin, "Biomolecules as Quantum Computers [from Computable and Uncomputable]," in *Computable and Uncomputable,* Soviet Radio, 1980, p. 14–15.

[9] J. M. Sellier, "A Signed Particle Formulation of Non-Relativistic Quantum Mechanics," *Journal of Computational Physics,* vol. 297, p. 254–265, 2015.

[10] B. Yan and N. A. Sinitsyn, "Recovery of Damaged Information and the Out-of-Time-Ordered Correlator," *Physical Review Letters,* vol. 125, p. 040605, 2020.

[11] C. T. Sebens, "Electromagnetism as Quantum Physics," *Foundations of Physics,* vol. 49, p. 365–389, 2019.