2024 SUPERCONVERGENCE BIOREVOLUTION SERIES: PREMONITIONS OF ALPHAFOLD 3

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At WisdomTree, we work with Dr. Jamie Metzl on a strategy that we term the *Biorevolution.* We believe that we are on the precipice of a remarkable period that could last a few decades where we challenge and ultimately evolve how we do such things as:

- Handle human health care.
- Consider growing food for an expanding global population.
- Generate novel materials, chemicals and energy from biological sources.
- Think about storing massive amounts of data with higher density and fidelity than we have in the past.

Dr. Metzl recently published the book *Superconvergence: How the Genetics, Biotech, and AI Revolutions Will Transform our Lives, Work, and World*. We aim to publish a series of blog posts that draw attention to some of the ideas presented in the book.

The bottom line: Thematic investing, in a sense, is about storytelling. *Superconvergence* does a great job to convey the narrative behind the WisdomTree BioRevolution Index, which is tracked, after fees and expenses, by the WisdomTree BioRevolution Fund (WDNA).

Thank You, ChatGPT…

In my opinion, the best thing about ChatGPT is how it made the concept of generative artificial intelligence (AI) accessible to almost anyone. In its early phases, the popularity of generative AI focused on generating text, but it has since evolved into generating images, sounds and videos. These systems can ingest massive amounts of data in training to better be able to predict the kinds of things that make sense in these different types of sequences. Similarly, if we have enough data on biological systems, it's possible that this data can be fed into generative models and predictions can be made that lead to being able to simulate biological systems under different types of conditions.

The power of these systems lies more in the fact that they can continually make predictions that might be thought provoking, and less about any of the predictions always being 100% accurate. When we shift our thinking into the world of biotechnology, it is not about predicting a cure but instead about predicting a novel path of research that may lead a researcher toward an interesting therapeutic result.

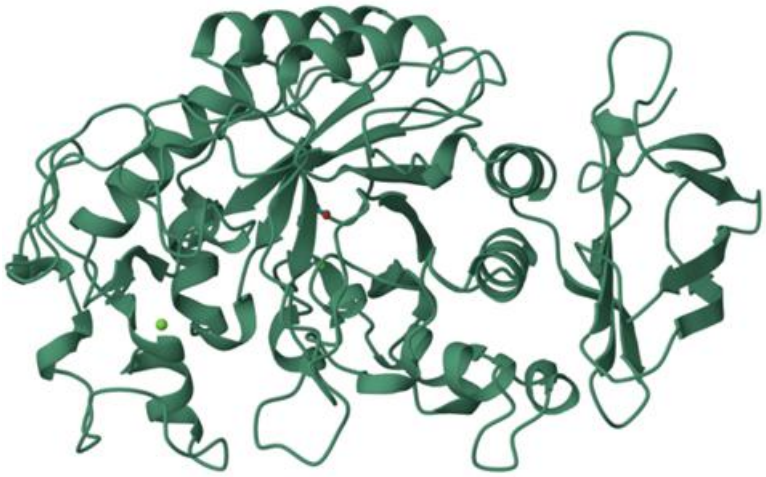
Can Generative AI Systems Predict Useful Protein Structures?

Predicting different series of words that make sense against a prompt or predicting the position of pixels within an image is one thing—predicting interrelationships between molecules in a biological system is something entirely different.

We show figure 1 simply to give anyone who does not have a background in molecular biology (I include myself in that group) an appreciation for the visual complexity of a single protein—in this case human salivary amylase (saliva) from the Protein Data Bank

in Europe. On looking at this, it's impossible to not be impressed with how scientists physically performing x-ray crystallography established the foundation of determining protein structure to begin with.

Figure 1: A Look at Human Saliva



Source: European Bioinformatics Institute, https://www.ebi.ac.uk/pdbe/entry/pdb/1smd.

Announcement of Alphafold in 2020

Professor John Moult, Co-Founder and Chair of Critical Assessment of Protein Structure Prediction (CASP), from the University of Maryland, said[1]:

> *We have been stuck on this one problem—how do proteins fold up—for nearly 50 years. To see DeepMind produce a solution for this, having worked personally on this problem for so long and after so many stops and starts, wondering if we'd ever get there, is a very special moment.*

CASP experiments aim at establishing the current "state of the art" in protein structure prediction, identifying what progress has been made and highlighting where future efforts may be productively focused. They occur every two years, with the first having taken place in 1994.[2]

Consider the challenge of predicting a protein's three-dimensional structure. In 1969, it was estimated that there could be something like 10^300 possible conformations for a typical protein. This tells us that a brute force type of approach where a system is looking at every possibility would not be feasible.[3]

Simulating a Cell

We can learn a lot from better, higher resolution simulations. On March 18, 2024, Nvidia announced an Earth Climate Digital Twin—the concept being that, if we can simulate climate and weather at an increasing resolution, we could use that to better understand and ultimately predict changes in weather and climate.[4] While the idea itself seems simple, collecting and processing enough data to have even a reasonable shot at being accurate enough to matter is not easy.

If we think of the difficulty and cost of organizing clinical trials to test different possible therapies, it's not much of a leap to think that, if we could only simulate the human body and all its underlying systems, we could both learn a lot and depend less on organizing human clinical trials.

It's interesting to step back and recognize that through the course of history we have analyzed DNA, rRNA, amino acids, proteins…it's clear that we are building our understanding piece by piece. The complexity involved at each of these steps is staggering.

From *Superconvergence*:

> *DeepMind founder Demis Hassabis told Eric Topol in 2022 that:*

> *One of my dreams in the next 10 years is to produce a virtual cell. What I mean by virtual cell is you model the whole function of the cell with an AI system. You could do virtual experiments on that cell, and the predictions that come out of that would hold when you check them in the wet lab. Can you imagine, if you had something like that, how much faster and more efficient that would make the whole drug discovery and clinical trials process? . . . You can think of what we've done with AlphaFold as the first step of the ladder. . . . Then you build up slowly, maybe to pathways and eventually to cells and then ultimately perhaps the whole organism. That's the dream.*[5]

Introducing AlphaFold 3!

Something funny about publishing writing on the internet or speaking on different podcasts is that, if you know how to search for it, you can find all sorts of predictions that people have made or aspirations that they have had, frozen in that moment in time. It's interesting to read that quote from Demis Hassabis in July 2024 when we know that AlphaFold 3 has been recently released.

On May 8, 2024, the following was published[6]:

> *Introducing AlphaFold 3, a new AI model developed by Google DeepMind and Isomorphic Labs. By accurately predicting the structure of proteins, DNA, RNA, ligands and more, and how they interact, we hope it will transform our understanding of the biological world and drug discovery.*

My admittedly amateur read is that if AlphaFold 3 was literally simulating a full cell, they'd have written that, so my interpretation is that this represents an important step on that path and that we should expect more and more versions that are able to incorporate a greater and greater resolution to cells and then ultimately living organisms. It's fascinating that even as the book *Superconvergence* was being published, the state of the art in seeking to predict protein structure moving toward cell simulation was continuing to advance. We sequenced the genome, we predicted how different proteins would fold, and now we are starting to predict how different molecules and proteins will interact. It appears that these advancements are coming faster and faster. Picturing a timeline in your mind's eye makes it very clear, in that the Human Genome Project was completed in 2003,[7] AlphaFold was announced in 2020[8] and AlphaFold 3 was announced in 2024.[9] As computational hardware and AI advances, the types of things that can be accomplished in biotechnology should also have that same advancement potential. The convergence of these different megatrends could make the coming years quite exciting.

[1] Source: The AlphaFold team, "AlphaFold: A Solution to a 50-Year-Old Grand Challenge in Biology," *Google DeepMind,* 11/30/20 https://deepmind.google/discover/blog/alphafold-a-solution-to-a-50-year-old-grand-challenge-in-biology/

[2] Source: Success Stories from Recent CASPs, *Protein Structure Prediction Center*, https://predictioncenter.org/index.cgi

[3] Source: Cyrus Levinthal (notes by A. Rawitch), 1969. "How to Fold Graciously," *Mössbauer Spectroscopy in Biological Systems:* Proceedings of a Meeting Held at Allerton House, March 17 and 18, 1969, Monticello, Ill., Organized by the University of Illinois at Urbana-Champaign, Departments of Chemistry and Physics.

[4] Source: NVIDIA Announces Earth Climate Digital Twin, *NVIDIA*, https://nvidianews.nvidia.com/news/nvidia-announces-earth-climate-digital-twin#:~:text=GTC%E2%80%94To%20accelerate%20efforts%20to,and%20climate%20at%20unprecedented%20scale.

[5] Source: Jamie Metzl, *Superconvergence: How the Genetics, Biotech, and AI Revolutions Will Transform our Lives, Work, and World*, 2024.

[6] Source: AlphaFold 3 Predicts the Structure and Interactions of All of Life's Molecules, *Google,* https://blog.google/technology/ai/google-deepmind-isomorphic-alphafold-3-ai-model/#life-molecules

[7] Source: Human Genome Project Timeline, *National Human Genome Research Institute,* https://www.genome.gov/human-genome-project/timeline#:~:text=More%20%2B-,2003,two%20years%20ahead%20of%20schedule.

[8] Source: The AlphaFold team, AlphaFold: A Solution to a 50-Year-Old Grand Challenge in Biology, *Google DeepMind,* 11/30/20, https://deepmind.google/discover/blog/alphafold-a-solution-to-a-50-year-old-grand-challenge-in-biology/

[9] Source: AlphaFold 3 Predicts the Structure and Interactions of All of Life's Molecules, *Google*, https://blog.google/technology/ai/google-deepmind-isomorphic-alphafold-3-ai-model/#life-molecules

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