Alzheimer project (status)

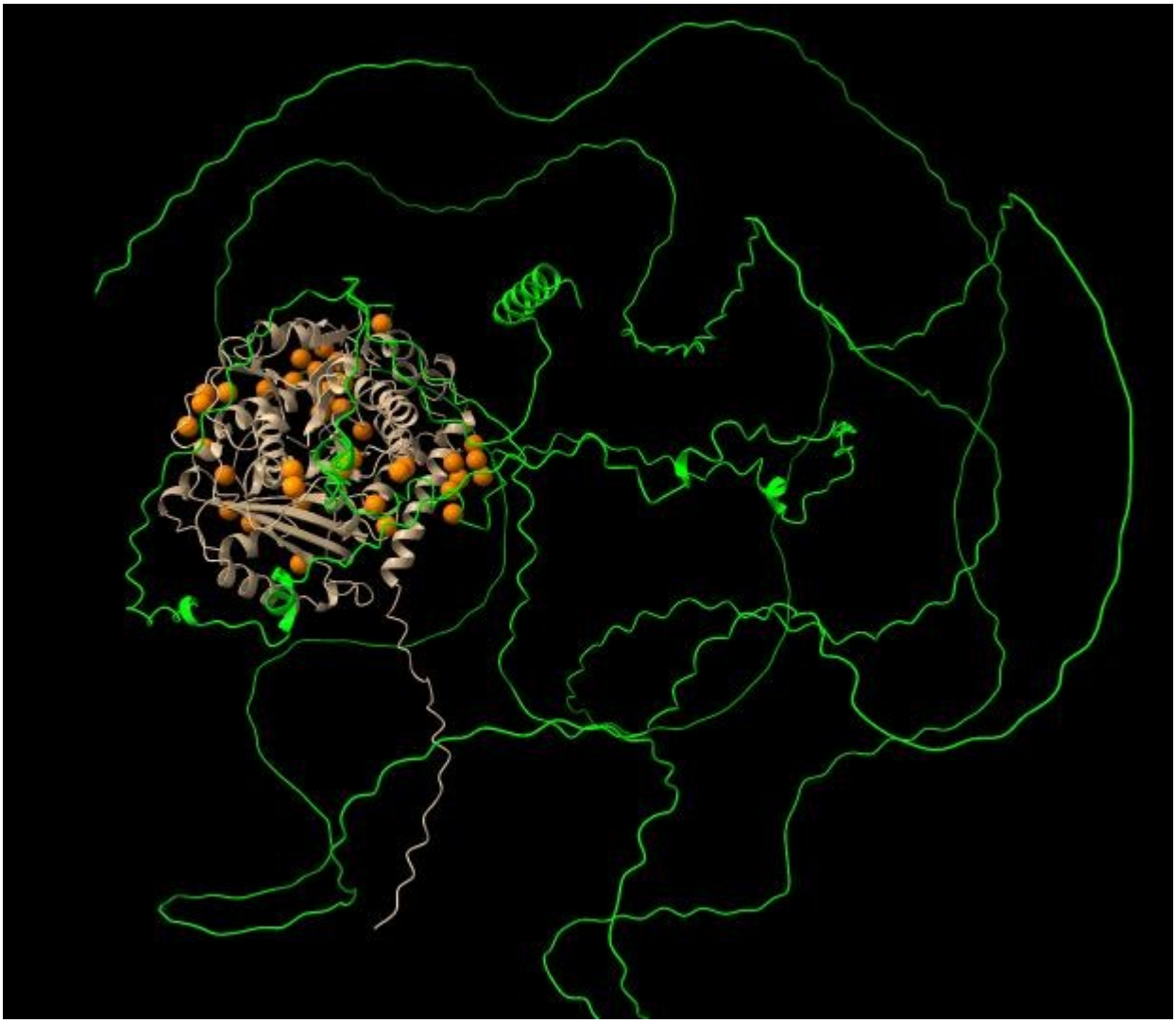
Date: Friday, May 8, 2026 at 09:38 p.m. EDT

I am making efforts to advance the Alzheimer project. The progress has been rather sluggish.

The primary issue is that the current software is either tailored for protein-protein docking or for small molecule-protein binding. So, for utilizing phosphorylated Tau protein in protein-protein docking, it is imperative that phosphorylation is disregarded; otherwise, the docking software will not function. Consequently, it appears that working with Tau fibrils is not feasible.

As a result, I have shifted the focus to Tau - Tubulin-Beta docking and inquired with AI regarding the sequence of events: What is the first?
- Is it Tau to Tubulin-Beta docking
- or is it Tau phosphorylation?
To my astonishment, AI insisted that docking occurs prior to phosphorylation. It may even be (??) reasonable to hypothesize that phosphorylation leads to the disconnection of Tau from Tubulin-Beta.

Therefore, I conducted a preliminary (very rough) assessment to determine if we can model this scenario. It seems we may (???).
- In step #1, I employed LightDock to facilitate the docking of Tau to Tubulin-Beta. The use of LightDock helps partially reduce the rigidity of both Tau and Tubulin-Beta.
- In step #2, I introduced the Tau(green)-Tubulin-Beta(gold) compound into Vina and executed phosphorylation (orange). To ensure a robust test, I incorporated 40 PO4 molecules, which is undoubtedly excessive. Please refer to the image below.



Currently, there remains a visible issue. If the AI is accurate, then TAU should primarily engage with a Tubulin-Beta tail (indicated by a gold line beneath the Tubulin-Beta directed towards the lower section of the image). I hope that we may accomplish this by initially attempting to dock 2-3 Tubulin-Beta proteins into compound, followed by docking Tau to that compound. If this approach does not yield results, then LightDock offers the capability to enforce a primary docking point. We will see.

Subsequently, we must assess the stability of a Tubulin-Beta-Tau-phosphorylated compound. Maybe, we will discover (???) that increased phosphorylation results in decreased stability of compounds. Now, we need a tool to evaluate the stability. The tool I have identified and managed to operate is Prodigy-Lig, but it is limited to working with ONLY a single PO4 molecule incorporated into the compound. That left us with the only viable option - to utilize GROMACS.

Upon reviewing GROMACS, I recognized that employing a large time step would be entirely INAPPROPRIATE, even for a preliminary assessment. However, the POSITIVE aspect is that there exists a consensus within the GROMACS community: If someone is solely interested in the stability of a compound, then compound that survived the initial 10 out of 200 nanoseconds (200 ns is a respectful simulation duration) is likely to be stable. With expected deployment of the Lenovo D2 and Power 9 (Richard has already started disassembling the P770 at SciNet), we could begin experimenting with GROMACS here.

We will see,