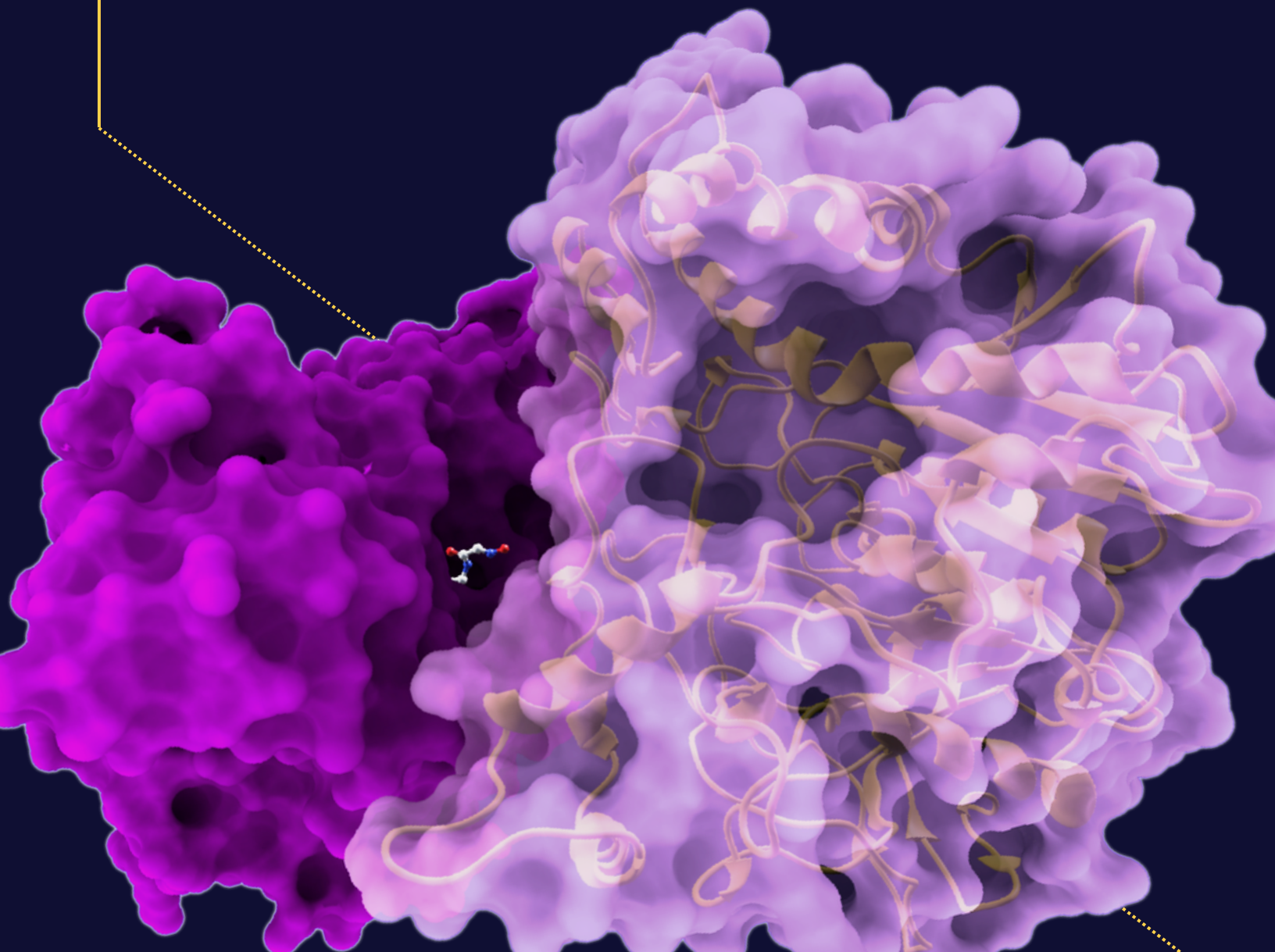
CASE STUDY

VR ENABLES STRUCTURAL BIOLOGISTS TO PERFORM INTUITIVE DRUG DESIGN

UCSD research group pairs VR with structural biology to pave the way for new treatments for nerve agent poisoning



Effective Structure-Based Drug Design aided by VR

Prof. Zoran Radić is a researcher at the SSPPS, at UC San Diego (UCSD). He studies one of the most powerful biological catalysts of the human nervous system, the enzyme acetylcholinesterase, or AChE, target of toxic nerve agents. At UCSD, Prof. Radić relies on structural and computational biology, biophysical studies, and enzyme kinetics to develop small molecules that are effective to treat nerve agent poisoning.

Structural-based drug design (SBDD) is becoming a fundamental part of industrial drug discovery projects and academic research, where three-dimensional data lay the foundation of the design process [1].

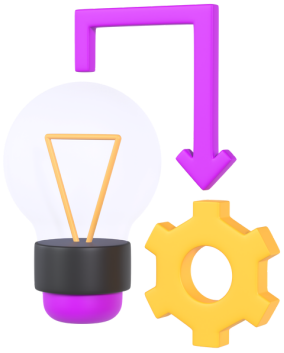
To rationally design antidotes, the team at UCSD needed a tool to boost their process in SBDD. The VR space offers the perfect environment to **gain intuition about molecular entities.** Scientists can investigate structures while **accessing experimental data** and computational tools. VR facilitates **real-time communication** across the organization, between institutions, and worldwide. This allows a rapid flow of ideas, preventing information loss and optimizing the discovery process.

Prof. Zoran Radić, UC San Diego

> "Virtual reality changed my perspective of macromolecules"

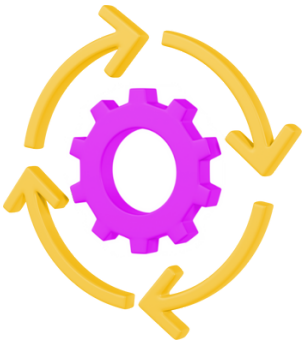
New tools to explore molecular structures

Scientists involved in structural enabled projects, like Prof. Radić's, rely heavily on accurate visualization of macromolecular structures and realize "**how important three-dimensional representations are, especially for [understanding] catalytically active proteins** [2]", where scientists have "to find a particular spot in the protein structure that accepts smaller molecules and acts on them [2]". They have to mentally picture how certain interactions take place between target proteins and small molecules. Representations using **2D screen views miss the immersive interactive component offered by 3D VR**. Radić always perceived the restrictions of 2D visualization when it comes to structural analysis, "it is like looking at molecules behind a window in 3D, you can't get in there [3]". To address the issue, he started looking into alternatives, experimenting with 3D stereo glasses and VR software solutions like Molecular Rift, which provided limited interaction with target macromolecules.
Then, in 2017 he discovered Nanome and started testing the early prototypes of the software. "What they had was already really impressive," Radić says. "**It looked much better than anything I had seen up to that point**, anywhere, in terms of molecular visualization [4]". From that point on, Prof. Radić became a Nanome power user, assisting the development of the software by providing feedback on how to meet researchers' needs.



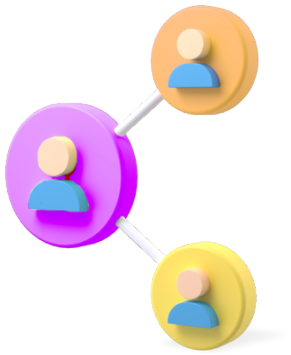
Immersive

Gain structural insights instantly



Integrated

Easy access to data and computational tools in VR



Collaborative

Boost local and remote collaborations

Virtual reality fits research workflows and delivers results

The virtual reality solution provided by Nanome is not only limited to visualizations. It offers design capabilities that push forward structure-enabled projects, as Radić says “I would call it **accelerated template-based drug design, it's accelerated because one can get into that molecule and instantaneously recognize what [ligand] fits and what does not fit** [3]”, all while being immersed in a three-dimensional environment “for me it works like an instantaneous focus on the topic. I am immediately focused on my atoms, molecules, and side chains. **Distractions are canceled out** [3]”

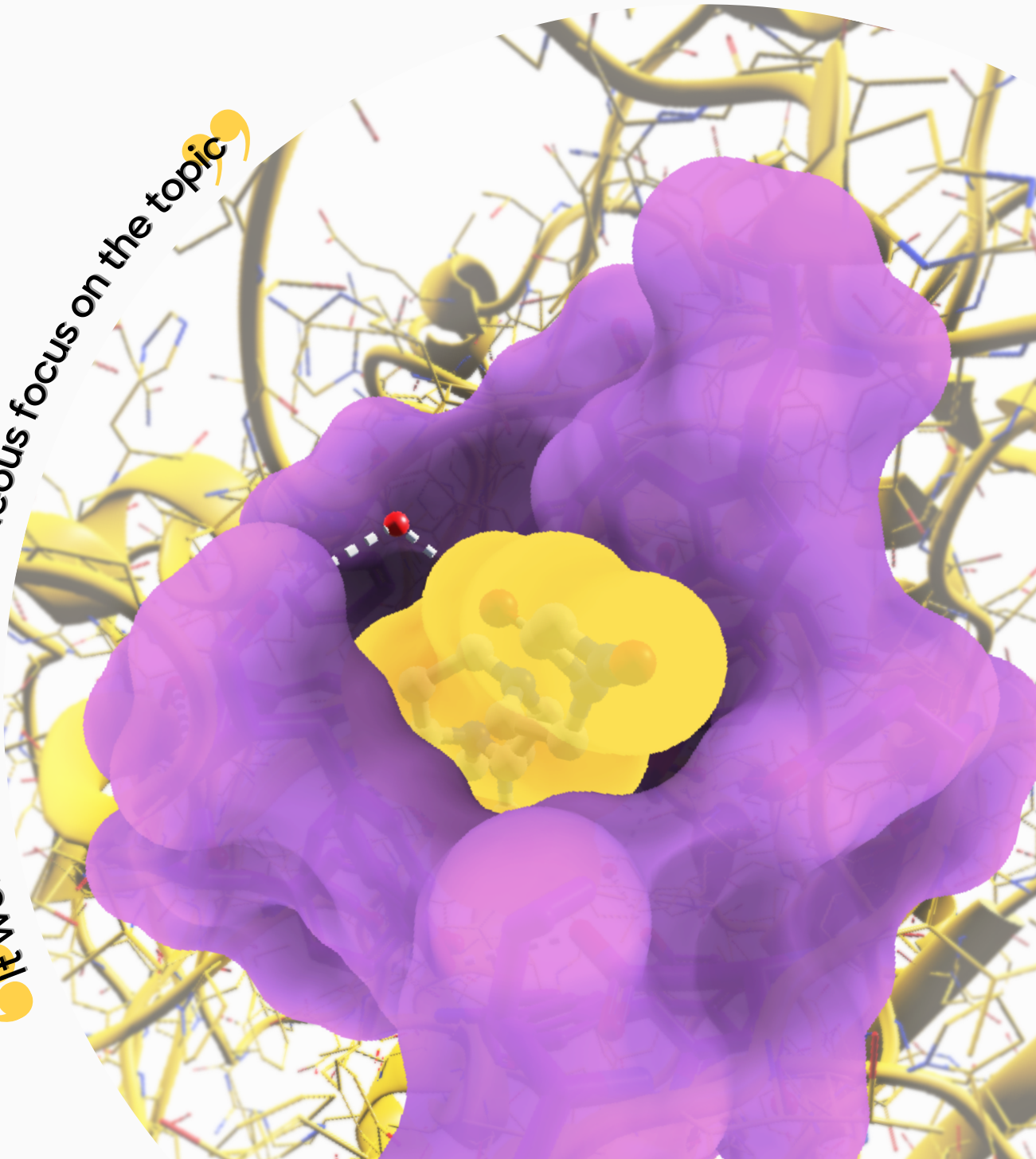
According to Prof. Radić, virtual reality “changed my perspective of macromolecules significantly [2]”, by enabling him to manipulate protein structures, study their interactions with other molecules, and — most importantly for drug discovery — design new compounds.

Nanome's **flexible plugin system** allows external software extensions to be added directly to the drug discovery workflow. In Radić’s case “**plugins are really useful to evaluate structures in VR**: we use minimization, which means we can build a small molecule in VR and then minimize it, we can dock it to a macromolecule using Smina Docking, a state-of-the-art docking software, we can form covalent conjugates, we can minimize, dock it and score it in real time [3]”.

In a study published in the *Journal of Biological Chemistry*, the Nanome software assisted the **structure-guided rational design of a library of compounds** to treat nerve agent poisoning. Thanks to the multiple plugins available within Nanome, scientists used VR in different stages of the design process, from the inspection of AChE X-ray structures to the validation and lead optimization of novel chemical entities [5].

In another publication, Radić's team compared different crystal structures of AChE and **analyzed the results of pairwise computational alignment** of ligand-free and ligand-bound macromolecular structures [6]. Nanome was the tool of choice for **visual examination.** The team observed that getting a correct perception of macromolecular architecture was greatly facilitated by the immersive visualization offered by the virtual space.

"It works like an instantaneous focus on the topic"



Improving presentations, collaboration and teaching at 360 degrees

Working with complex data naturally poses communication challenges. Prof. Radić found VR to be an "**outstanding presentation tool** [3]" and an excellent solution to tackle these long-standing challenges. He and his team noticed that "it always draws attention to people when you show up with a VR headset [3]" and now they routinely use **Nanome to present research findings** during conferences, meetings, and poster sessions, which in turn brings curiosity, interactions and creates occasions for new collaborations among scientists.

In addition to presentations, Nanome is extremely valuable to support real-time collaborations, giving scientists the chance to work interactively on projects despite geographical locations. For Radic, this was essential during the COVID-19 pandemic, explaining that "a group of students and I used to meet weekly in VR using Nanome. **It was really perfect because we were all at our homes, but at the same time joined in the same room, analyzing those structures together** [8]."

Furthermore, Radić experienced the advantages of Nanome for **teaching**, witnessing firsthand how **virtual reality boosts students' comprehension of the macromolecular 3D space**. Students find VR extremely valuable because "some [students] might have problems just imagining things in 3D when they only have it on paper, this [VR] would help understand the chemistry much better" and "I would be glad to have something like this in my school [2]"

References

[1] Batool M, et al. "A Structure-Based Drug Discovery Paradigm", Int. J. Mol. Sci. 2019, 20(11), 2783, doi: 10.3390/ijms20112783

[2] Science Metaverse Podcast, Episode 4, https://www.buzzsprout.com/1947666/10164309-episode-4-professor-zoran-radic

[3] Webinar "Virtual Reality to Aid Antidote Design: Structure-based design to treat organophosphate poisoning", guest: Zoran Radić, https://youtu.be/vlAkyku29jg

[4] Antonie Boessenkool, "Virtual View Of Molecular Interactions", California Business Journal, 2019, https://calbizjournal.com/virtual-view-of-molecular-interactions/

[5] Gorecki L, et al. "Rational design, synthesis, and evaluation of uncharged, "smart" bis-oxime antidotes of organophosphate-inhibited human acetylcholinesterase." J Biol Chem. 2020;295(13):4079-92, doi: 10.1074/jbc.RA119.012400.

[6] Radić Z. "Shifts in Backbone Conformation of Acetylcholinesterases upon Binding of Covalent Inhibitors, Reversible Ligands and Substrates". Crystals. 2021;11(12), doi: 10.3390/cryst11121557.