PBBR Proposal: Analysis of Molecules and Cells in Virtual Reality

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Proposal for UCSF Program for Breakthrough Biomedical Research (PBBR): Technologies, Methodologies and Cores. Instructions. Submission deadline: April 24, 2018, 5 pm.

Project title: Analysis of Molecules and Cells in Virtual Reality

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Summary: Develop virtual reality capabilities in ChimeraX in 3 areas: 1) cryoEM atomic model refinement, 2) 3d light microscopy measurement, and 3) multi-person VR collaboration, with several labs using and driving software developments.

Project Description

[*Description of the technology, methodology, or core, its significance, innovative features, potential impact, and availability elsewhere. Two page maximum excluding references.*]

The goal of this project is to develop virtual reality (VR) analysis software that enhances insight into mechanisms of macromolecules and cells. We have demonstrated VR capabilities within our next generation ChimeraX program to about 100 researchers and several hundred students. With surprising frequency researchers state they observed in VR new features of their lab's molecular structures and microscopy data that were missed with conventional desktop visualization. Areas where VR excels include immersive visualization for instance where the optimal view point is at a deeply buried drug binding site, data where geometric relations are primary such as hydrogen bonding and steric constraints in a binding site, time varying 3-dimensional data such as lightsheet microscopy where stereoscopic perception and head movement improve perception over 2D displays, and analysis that benefits from simultaneous hand and head movements such as refining atomic models in cryoEM density or rotating a bond in an atomic model while examining steric clashes. While cases abound where VR has strong advantages for analysis a major challenge is that user interfaces based on keyboard and mouse are not servicable in VR, because the headset completely blocks the user's view and the user holds position and rotation tracked hand controllers in each hand. Our current ChimeraX VR capabilites are the most advanced in the world for analyzing molecular and cellular structure. Matt Jacobon's lab at UCSF has used ChimeraX VR weekly during 2018 to analyze docking of potential drugs, to our knowledge the most extensive research use of VR for molecular analysis to date. This proposal aims to bring VR into routine use in the labs of three additional UCSF co-investigators with well-suited analysis problems in cryoEM and light microscopy, and advance VR capabilities for understanding drug and receptor interactions.

We propose to develop three VR capabilities: 1) interactive refinement of atomic models in high-resolution (3A) cryoEM maps, 2) measurements of 3D light microscopy time series, and 3) multi-person VR sessions for collaborative discussions of structures. To date our collaborators have used VR equipment in our lab space. To advance from demonstration VR capabilities to production use we will setup a VR headset in each of the co-investigator's labs, Adam Frost (cryoEM), Dyche Mullins and Max Krummel (light microscopy), Matt Jacobson (drug binding), train lab members and develop VR capabilities to address their current analysis problems. The bulk of the developments will be new software capabilities in ChimeraX developed by Tom Ferrin's lab driven by the analysis needs of the co-investigators. ChimeraX [Goddard 2017] is freely distributed and all developed VR tools will be available to the worldwide research community. This effort

will advance nascent VR analysis enabling new insights into molecular and cellular function and initiate routine use of VR complementing traditional desktop computing environments.

Advances in electron cryo-microscopy have allowed determination of atomic resolution structures of molecular complexes that had not been accessible to x-ray crystallography often because of difficulty forming crystals. The new cryoEM structures are mostly at resolutions near 3 Angstroms which pose difficult challenges for automated atomic model building methods. Even at higher resolutions of 1 to 2 Angstroms, interactive refinement where a researcher validates, fixes and extends automatically built models is routine. A state-of-the-art tool ISOLDE [Croll 2018] that is part of ChimeraX allows interactively adjusting residue positions, fixing register shifts in strands and helices, and correcting geometry using molecular dynamics (OpenMM) combined with forces that drive atoms into higher density regions. A video demonstration (https://www.youtube.com/watch?v=limaUsNAVL8) of ISOLDE illustrates the difficulty perceiving and correcting poorly fit density on conventional desktop computer displays. Errors in PDB deposited atomic models at 3-4 Angstroms resolution are common. We propose to interactive refinement with ISOLDE using virtual reality. Experience with current ChimeraX VR suggests this is an ideal use of VR where optimal perception of atomic geometry and density map features and immersive view points are critical. ChimeraX is the next generation of the Chimera software and is the primary visualization program used by the cryoEM research community.

Recent advances in 3d light microscopy, especially lightsheet microscopes have opened new frontiers in imaging living cells such as crawling neutrophils [Fritz-Laylin 2017]. The new microscopes reduce phototoxicity by illuminating only parts of the sample being imaged keeping the cells alive longer, and allow imaging at dramatically higher speeds, approximately one 3D volume per second capturing faster dynamics than was previously possible. The new data poses immense analysis challenges partly because of its large size (tens of Gbytes to Tbytes for single samples), but more essentially because the 4-dimensional time varying data is hard to explore in 2D on a computer screen. Current ChimeraX VR capabilities applied to crawling neutrophils moving through dense collagen networks with Lil Fritz-Laylin and Dyche Mullins and T-cells engaging with antigen presenting cells [Cai 2017] with En Cai and Max Krummel suggest VR is well suited to reveal insights about cell motility and dynamics. We propose to develop measurement and modeling VR capabilities for analyzing cell dynamics. While it is always desirable to automate analysis, the complex morphology and dynamics observed and newness of 3D motility data make this an ideal application for interactive analysis which can lead to automated methods.

Many current ChimeraX VR capabilities focus on understanding ligand binding to receptors and the effects of mutations. Residues can swapped, bonds rotated and molecular dynamics around a residue run in the VR environment. This proposal will extend these VR capabilities to for instance use rotamer libraries, compute and monitor changes to the hydrogen bonding network, and allow modifications to ligands, adding and removing groups. Matt Jacobson's lab uses the existing VR capabilities during weekly meetings where a presenter uses the VR headset while other group members see the ligand and receptor structures on a projector. This proposal will develop the capability to have multiple participants join the same VR scene in the same room or from remote locations. Each participant's head and hands will be shown in schematic form to allow pointing and all participants will be able to move and manipulate the molecules. We have started an implementation of this capability in ChimeraX but significant additional programming will be needed to synchronize changes to the molecular structures.

The new VR developments we propose are related capabilities. For example, cryoEM and binding site analysis are combined in a recent cryoEM study by Adam Frost and Peter Walters of a drug ISRIB that enhances cognition after traumatic brain injury through activating a large decameric translation initiation factor complex [Tsai 2018].

Most of the current ChimeraX VR capabilities have been developed without an explicit funding source. In

March 2018 we received a small Mary Anne Koda-Kimble seed award (10% FTE, 1 year) for developing molecular binding site VR tools. The capabilities have been described in a manuscript [Goddard 2018, link] under review at Journal of Molecular Biology for a special Biovisualization issue. While VR appears to be ideally suited to several structure analysis problems, the immature state of the technology makes it a high risk unproven tool not attractive to traditional funding agencies (NIH, NSF).

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