Mary Anne Koda-Kimble Seed Award for Innovation

APPLICATION FORM, 2017-2018

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Koda-Kimble Seed Award for Innovation

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All fields below must be completed:

Proposal title:

Exploring Drug Binding using Molecular Dynamics and Virtual Reality

Requested award amount:

$17,127 plus indirect costs (if applicable)

Principal applicant (Your last name, first name, title, dept.)

Goddard, Thomas
Computational and Data Science Research Specialist 4
Department of Pharmaceutical Chemistry, UCSF

List additional project collaborators (Last names, first names, titles, depts.)

Cortopassi Coelho, Wilian
Postdoctoral Scholar
Department of Pharmaceutical Chemistry, UCSF

Jacobson, Matt
Professor and Department Chair
Department of Pharmaceutical Chemistry, UCSF

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Grabe, Michael
Associate Professor
Cardiovascular Research Institute
Department of Pharmaceutical Chemistry, UCSF

Croll, Tristan
Research Fellow
Cambridge Institute for Medical Research

Ferrin, Thomas
Professor
Department of Pharmaceutical Chemistry, UCSF

Background: (250 words MAX)

Antibiotic and antiviral drug resistance can be conferred by mutations in the drug binding site, by either single residue changes or post-translational modifications such as methylation. The effects on drug binding of such mutations can be understood using molecular dynamics simulations. Consumer virtual reality headsets of ligand and neighboring receptor side-chains scaled to room-size allows a central vantage point that significantly improves perception of the stereochemistry of the binding site. The goal of this proposal is to enable molecular dynamics combined with virtual reality visualization to understand the effects of binding site modifications. The researcher will be able to interactively make and test the effects of many modifications in a short session. The consequences of receptor and ligand modifications can be probed to understand the biophysical constraints of the binding site. Interactive molecular dynamics and virtual reality can be used as an exploratory hypothesis testing tool to inform the design of computationally intensive searches for tighter binding ligands and analyses of specificity or drug resistance.

Hypothesis / Problem: (100 words MAX)

We will combine interactive molecular dynamics with virtual reality visualization to explore the effects of binding site modifications such as point mutations, methylation and ligand modifications. We will develop, validate on well-understood systems with structurally similar ligands, and distribute this easy to use capability within the UCSF ChimeraX software package, for researchers and in training students in UCSF's PhD programs and PharmD Pharmaceutical Sciences pathway. This will be a first working use of virtual reality for biomolecular research.

Methodology: (500 words MAX)

We aim to develop software for researchers and students to visualize the effects of binding site mutations of receptors and ligands using virtual reality headsets. Starting with an experimentally determined or computationally predicted structure of a ligand bound to receptor, it will allow modifying the receptor or ligand in simple ways (e.g. single residue mutations, methylations, removing or adding side groups to the ligand) using virtual reality hand controls and then observing interactive molecular dynamics in real-time as the ligand and receptor accommodate the change. It will be possible to undo and try new modifications. Quantifiable changes such as rearrangement of hydrogen bonding pattern will be shown. This will enable testing hypotheses within the scope of small perturbations that can be reached by short equilibration using molecular dynamics.

As a concrete example, Danica Fujimori's lab has described how methylation of adenosine 2503 of the 23S rRNA confers antibiotic resistance to strains of E. coli against several clinically used antibiotics [1]. While this adenosine is in proximity to the bound drugs seen in several available x-ray structures, the mechanism by which adding a second methylation (facing away from the drug), or removal of an endogenous methylation perturbs the binding site and confers resistance is not obvious from the few available conformations.

The key development we propose is to use consumer virtual reality headsets such as the HTC Vive and Oculus Rift to improve perception and understanding of binding sites through interactive modifications and molecular dynamics. All of the pieces for this visualization and analysis tool are available in the UCSF ChimeraX software developed by Tom Ferrin's lab where Tom Goddard is a core developer. Collaborator Wilian Coelho and others in Matt Jacobson's lab are routinely using the ChimeraX virtual reality capabilities to visualize bindings sites of static structures. Collaborator Michael Grabe proposed the core idea of this project to combine molecular dynamics with virtual reality visualization and uses the current static structure VR capabilities. Interactive molecular dynamics have been implemented in ChimeraX by collaborator Tristan Croll for structure refinement. Modifications such as swapping amino acids and identifying hydrogen bonds are a core capability of ChimeraX.

Three important technical problems will be addressed to combine the virtual reality and molecular dynamics capabilities. Virtual reality headsets require 90 frames per second rendering speeds, and any slowdown causes stuttering which can make the viewer nauseous. In order that the molecular dynamics not slow the rendering it will have to be run in a separate thread or process. We have prior experience doing this and confidence that it will work on typical VR-capable desktop computers. A second problem will be to determine the optimal molecular dynamics approximations for interactive use. We believe explicit solvent in the neighborhood of

the ligand will be important, and simulation limited to a zone around the ligand will be sufficient to handle small modifications. We will validate that the MD produces qualitatively correct results using well characterized systems from project collaborators. The third technical development will be user interface to allow modifying the structures, starting and stopping the molecular dynamics, and undoing to trying new modifications, using virtual reality hand controllers.

[1] Stojković V, Noda-Garcia L, Tawfik DS, Fujimori DG.
Antibiotic resistance evolved via inactivation of a ribosomal RNA methylating enzyme.
Nucleic Acids Research. 2016;44(18):8897-8907. doi:10.1093/nar/gkw699.

Budget details: (format as necessary)

10% FTE software development for 1 year (total of 200 hours): $17,127 plus indirect costs (if applicable)