



# User as a bitter tastant: Immersive experience within the binding region of a bitter taste receptor

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## Abstract

This paper describes the development of a Virtual Reality (VR) system to obtain mechanistic insights into receptor-ligand interactions from the perspective of a bitter taste. The system allows a human-user to "become" the tastant-ligand and interact with the bitter taste receptor in its binding region. Computational models of 15 bitter taste receptors were developed. Each model provides a comprehensive view of the varied structural and functional features of the bitter taste receptor. The user can obtain a view of the receptor protein model at a) the atomic level; b) the secondary structure; and, c) the surface. The system can be accessed by using a VR headset as well as through touch controllers. Users can navigate among and compare 3D models of the selected receptors, while also experiencing environmental feedback. The implications of such a study are critical to the field of drug-design in the clinical-pharmaceutical industry. Five domain-expert scientists and clinicians evaluated the usability of the VR system. Our work also represents an important educational tool.

**Keywords:** virtual reality; bitter tastant; biology; molecules; oculus rift

## 1. Introduction

Instructional technology is becoming popular in the STEM (science, technology, engineering, and mathematics) disciplines due to the availability and the advancement of information technology. Although this technology has been widely adopted, the primary drawback is its limited use and lack of availability, especially in the field involving a better understanding of the structure of bio-molecules (Safadel et al., 2016). The relative lack of availability of technology in this area makes it more challenging for students to learn about the structures of macromolecules and mechanisms of their dynamic behavior. This is no less true for students who have limited spatial-cognitive abilities. Also,

another limitation is that typical visualization is limited to only a few structural characteristics of these complex molecules, on a two-dimensional computer screen or a page. These visual limitations do not reveal critical structural, and hence, functional details of these bio-molecules (Safadel et al., 2016). Learning and research and critical conclusions with clinical consequences can be seriously hampered, for students, knowledge seekers, as well as high-level researchers and educators.

One of the approaches that can overcome the limitation of visualization of physical models is to create their 3D models (Dang et al., 2010). These virtual objects can help students to obtain better insights into these



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models, especially those with limited spatial cognition (Won et al., 2019). They create an opportunity for novel and unique perspectives that enhance our understanding of biological molecules. Some of these perspectives include viewing models from the 'inside-out.' This is known as being immersed in Virtual Reality (VR). VR has been used in the biomedical sciences to provide non-invasive perspectives of the human anatomy (e.g., views of heart, lung, kidney, skeleton, muscles, or brain, etc.). VR can also dig deeper through the tissues and organs to the atomic level of macromolecules, such as DNA and proteins. These virtual objects, in conjunction with VR, play an important role in many classrooms. To arrive at VR-driven immersion views, however, one has to create 3D models of these macromolecules. Creating 3D models is often expensive, especially for non-computer science researchers, because it requires a deep understanding of graphic design, expertise in the domain of science where models are being developed, and an experts level ability to use the model development software. (T. Nguyen et al., 2018; Nguyen et al., 2019a). One example of proteins where such development and insights are critical is in the chemical senses, specifically, in bitter taste receptors. Computational model development and immersion technology applied to these receptors is critical because experimental structures for these compounds are not available.

The ability to identify and respond to chemical and physical signals is crucial to animal survival (Andres-Barquin and Conte, 2004). Animals can perceive five senses: vision (sight), auditory (hearing), gustation (taste), olfaction (smell), and tactility (touch). The sense of taste allows an animal the ability to evaluate what it consumes. At its evolutionary basis, in addition to hedonistic responses, gustation helps in the ingestion of nutritious substances. It also prevents the consumption of potential toxins (Bachmanov and Beauchamp, 2007). Animals can perceive five basic tastes: sweet, bitter, salty, sour, and umami (Lindemann, 1996). The sense of taste is mediated by taste receptor cells, which are organized within the taste buds. Humans have roughly 10,000 taste buds within the oral cavity, each containing approximately 100 receptor cells (Bradbury, 2004). The primary function of taste buds is the perception of the taste sensation—the sensation of taste results when food particles react with the taste buds. As the food particles reduce in size within the oral cavity, during the process of mastication, they get dissolved in saliva. These molecules bind to the microvilli that are being projected from the taste receptor cells. It appears, however, that different taste sensations are mechanically different. Electrophysiological studies suggest that sour and salty tastants or molecules that elicit a gustatory response regulate the function of taste receptor cells through membrane channels (Andres-Barquin and Conte, 2004). Sweet, umami, and bitter tastes, on the other hand, are medi-

ated by receptors.

Motivated by the advancement of VR and immersion technology and its use in a similar biology setting, our main focus of this research work is to investigate how immersion technology and virtual reality can provide mechanistic insights into receptor-ligand interactions from the perspective of gustation related to the bitter taste. Thus, the contributions of this paper are as follows:

- We developed 15 computational models of bitter taste receptors.
- We transformed the developed computational models into 3D objects so they can be reused by domain scientists.
- We presented our approach to incorporate the developed 3D models into Virtual Reality.
- We evaluated the feasibility of our proposed VR application by consulting with domain experts

The rest of this paper is organized as follows. The next section describes background information and related literature to our approach. Section 3 presents our method and set up for the user experiment in a virtual environment. Experimental results are presented in Section 4. Lastly, Section 5 summarizes the paper and presents the outlook for future direction on this work.

## 2. Background and Related work

There are two mammalian taste families: T1R and T2R, both of which belong to the G protein-coupled receptor (GPCR) superfamily. GPCRs are characterized by the presence of seven TM helices/domains which transduce the plasma membrane (Bachmanov and Beauchamp, 2007). The T1R family is categorized as a class C GPCR, whereas T2R is a class A GPCR (Floriano et al., 2006). T1R has three domains: venus fly trap, cysteine-rich, and TM domains (Assadi-Porter et al., 2010). The T1R family is composed of three proteins: T1R1, T1R2, and T1R3, which are encoded by TAS1R1, TAS1R2 and TAS1R3 genes in humans, respectively (Treesukosol et al., 2011). The T1R2 and T1R3 heterodimers combine to form the sweet taste receptor (Assadi-Porter et al., 2010) while the T1R1 and T1R3 heterodimers combine to result in the umami taste receptor Dotson et al. (2010). In humans, twenty-five bitter taste receptors have been identified. These receptors belong to the T2R taste families. In this study, we focus on the T2R family of receptors.

Bitter taste receptors have the classical structure of a Class A G(TP-binding) Protein-Coupled Receptor. GPCR belong to classes ranging from Class A to Class E. GPCRs were first identified in 1970 by the American physician and molecular biologist, Robert J. Lefkowitz (Hill, 2006). G-protein coupled receptors (GPCR) are the largest membrane receptor family in eukaryotes. They play a crucial role in cardiovascular, neurological, reproductive, and endocrine func-

tions (Venkatakrishnan et al., 2013). This receptor family can identify a wide range of molecules such as lipids, amino acids, sugar, and peptide molecules. A single GPCR is composed of a single peptide that is corrugated into a globular shape and is nested within the plasma membrane. It has seven TM domains (the TM domains have the helical secondary structure), an extracellular domain, and an intracellular domain. Most common classifications of GPCRs are based on the sequence homology, from class A to E. Taste receptor families belong to the class A and class C GPCRs: it is important to understand the primary structural variance between the two GPCR classes. Class C GPCRs are composed of three domains: the TM domains are attached to the extracellular bi-lobed domain via cysteine-rich region, whereas the extracellular domains are not seen in class A GPCR. When a molecule interacts with the GPCR, it undergoes conformational changes, leading to interaction with G proteins (Li et al., 2002). G proteins are specialized proteins that can bind to GTP as well as GDP. These G proteins have three subunits: alpha, beta, and gamma.

GPCRs are crucial for many purposes. Olfactory receptors are responsible for the perception of olfaction, which is closely integrated with taste. Olfactory receptors constitute the biggest super-family of mammalian genomes (Oleander et al., 2013; Niimura et al., 2014). GPCRs also have a crucial role in drug-receptor interactions and are often a determinant for drug-design in the pharmaceutical industry. More than a hundred GPCRs are identified as targets for drugs, according to the US Food and Drug Administration (Hauser et al., 2018).

VR has been used in the biological setting to help scientists to design drug-like ligands with higher efficacy and lower toxicity (side-effects). For example, Tse et al. (2011) incorporated VR to facilitate drug discovery. In this process, biomedical experts and medicinal chemists can select a subset of ligands for further investigation (such as organic synthesis), augmented by distance, and bonding information. The usability of their work was measured by assessing the usability ligands that resulted from competing automated and interactive methods. Sharma et al. (2018) proposed an immersive VR application for teaching students to understand the complex concept of DNA structure. They generated DNA virtual models that are similar to the actual structures. These models were visualized in the VR setting with the help of Oculus Rift. Local community college students evaluated the VR application. The authors identified a 40 percent improvement in performance between pre- and post-test of the system. Tan and Waugh (2013) developed 3D models of molecules and embedded them into the VR environment; in this work, however, interactions were limited to viewing or displaying the artifacts, without providing the immersion experience. Hamdi and Ferreira (2006) presented

a molecular mechanics study using molecular dynamics. Although this study could be useful for research purposes, its applicability and ease of understanding at the student-level are limited.

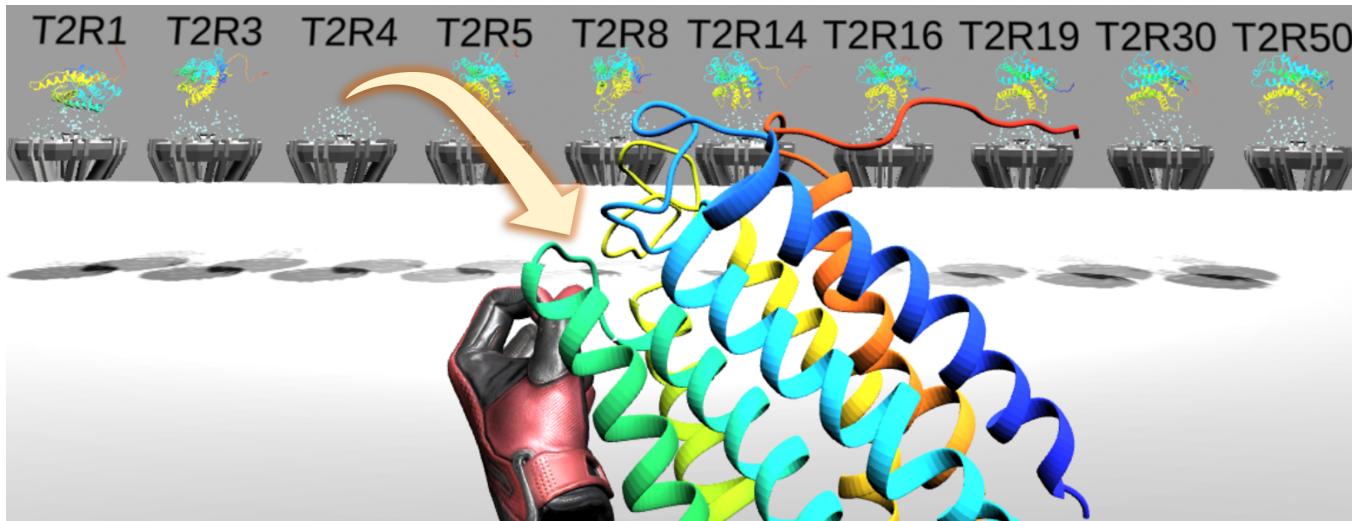
There is no doubt that the current literature reflects the increased use of VR technologies in the biomedical sciences. While these efforts enhance and foster a perceptual understanding of these molecules. The potential molecular elements that need to be studied, especially in the context of the domain of study, are however, vast and not covered by the current technology. Indeed, our work does not replace existing work but reinforces this application in the domain of education.

### 3. Materials and Methods

#### 3.1. Data Processing and 3D Model construction

One of the most challenging parts of our work was to produce 3D models for taste receptors. These proteins are bound within the cell membrane and are typically difficult to purify and crystallize. An experimentally derived structure (such as from x-ray crystallography) for these receptors is not available. *i*Ab initio or semi-empirical computational methodologies have to be adopted to create models for these receptor proteins. Our template-model, which was then used to develop the models for the taste receptor, was based on a rigorous protocol. This protocol took into account not only the structural features of a GPCR—those for which structures are identified but also the biochemical nature of a taste receptor protein. We aligned the taste receptor sequences with a published model of a human olfactory receptor, OR2A1, using homology modeling methods (Lai et al., 2014). As has been mentioned in the introduction section, bitter taste receptors resemble olfactory receptors and the classical Class A GPCR structures. In our protocol (Lai and Crasto, 2012) to develop these taste receptor computational models we:

- Used Hidden Markov Models to identify the transmembrane (TM) helical regions of the OR sequence (Krogh et al., 2001).
- Structurally aligned the helical regions identified above in the taste receptor sequence with the helical regions of high-resolution x-ray structures of rhodopsin Okada et al. (2004) and  $\beta$ -2-adrenergic receptors.
- Abstracted the N-termini, C-termini, and the extra- and intracellular loop regions from these alignments to optimize the structure of the helical regions of the taste receptor model.
- Used homology modeling to build the transmembrane helical scaffold of the receptor molecule from the template of rhodopsin (Okada et al., 2004) and  $\beta$ -2-adrenergic receptors (Rasmussen et al., 2007).
- Performed molecular dynamics simulations on each



**Figure 1.** Virtual reality of bitter taste receptors: Users grasped the T2R4 taste receptor from the model gallery and experience with its structure in their hands via the Oculus Touch controllers.

transmembrane helix individually; we used force fields from the CHARMM molecular structure software to parameterize the helical structures (Jo et al., 2008); we hydrated each helix; we then relaxed the geometries of the helices to canonical structures to remove any structural (and therefore, biochemical) features of the rhodopsin and  $\beta$ -2-adrenergic receptor helices. Though they have similar structures, the fundamental functions for these *template* receptors are different from those of taste or other chemosensory receptors.

- Determined the effective hydrophilicity for each helix and rotated the helix about its central vertical axis, such that the effective hydrophilicity was pointed into the binding region and away from the hydrophobic plasma membrane Crasto (2010).
- Reintroduced loops into the structure and build disulfide bridges between structurally neighboring cysteine amino acids
- Minimized the final structure of the taste receptor model using molecular dynamics calculations

These final bitter taste receptor computational models were transcribed into the standard protein structure PDB (Protein Data Bank), which is a textual file format to describe the three-dimensional structures of molecules. We developed computational models for 15 bitter taste receptors.

### 3.2. Model Generation and Experiment Setup

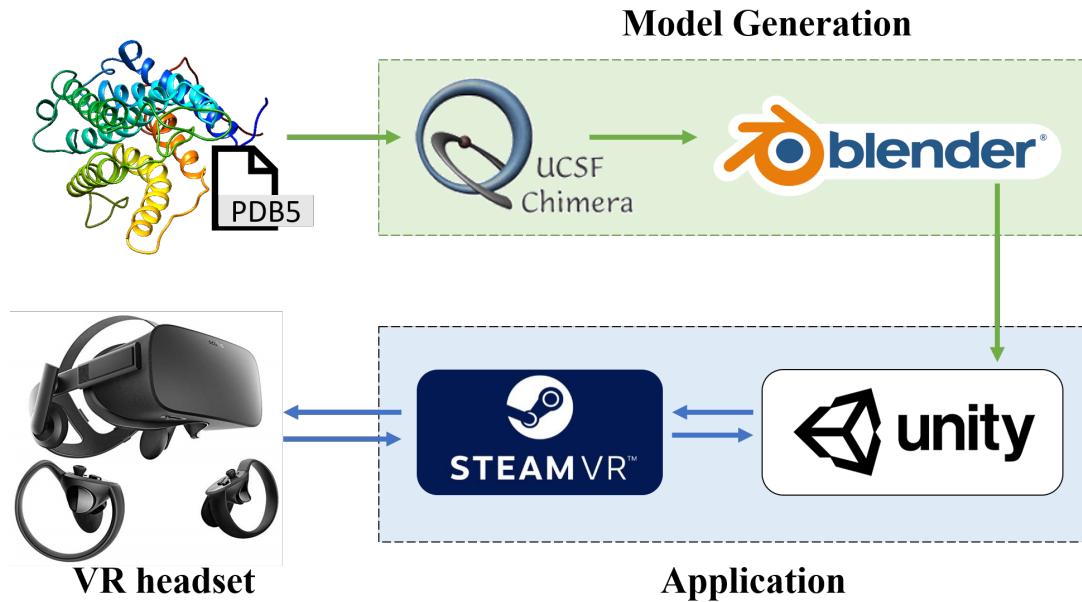
The PDB format describes the 3D structures of molecules; it is, however, not officially supported by notable VR rendering engines such as UnReal Engine or Unity. 3D molecules were converted to be compatible with a VR environment. The conversion pipeline process was shown in Figure 1, where the intermedi-

ate tool (i.e., UCSF Chimera software (Pettersen et al., 2004) was used to read the PDB files then converted them into the OBJ format. Although OBJ format can be displayed in the VR environment, its non-hierarchical design makes its size heavier compared to the hierarchical format (i.e., FBX) and thus may adversely affect rendering performance. Unfortunately, UCSF Chimera can only support export files in formats such as .obj, .pov, .rib, stl, .vrml or .x3d which are only ideal for 3D manipulation. To remedy this, we used another intermediate software, Blender, for the task of conversion recommended by (Nguyen and Dang, 2017).

All the original PDB files were converted into the FBX format. The process of putting 3D models into the VR environment was carried out in Unity (Dickson, 2015) leveraged because of an available VR headset. Unity not only enables users to create a wide range of interactions but also supports multiples VR headsets such as Oculus Rift, Valve Index, HTC Vive, Windows Mixed Reality. The SteamVR plugin serves as a bridge for the flow of VR content between the Unity and VR devices. In this paper, the experiment was set up with the Oculus Rift and touch controllers.

Figure 2 depicts the whole process from the receptor computational models (PDB5) to the rendering in the VR environment. To create the VR application and its functionalities, we followed the application design approach suggested by Shneiderman (2003) where tasks (or requirements) are identified first, and the application design is built to fulfill these tasks. After assessing the system and the tools, our domain experts recommended the following improvements:

- R1: Learners can see the molecule from different perspectives or differently stated; the bitter taste receptor can be observed from the inside-out view in an immersive setting.



**Figure 2.** Experiment setup flowchart for the immersive experience within the binding region of a bitter taste receptor from the receptor computational models (PDB5) to the resulted rendering.

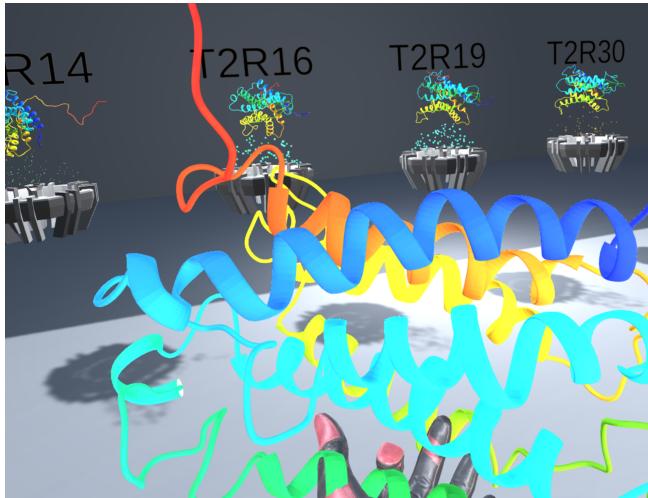
- R2: Users are capable of identifying and recognizing the characteristics of different complex molecules.
- R3: And finally, as being immersed in the VR environment, users should be able to sense the feedback from the virtual world.

The first requirement *R*<sub>1</sub> was fulfilled by using virtual hands (supported by the two touch controllers). They are programmed in such a way that when the 3D object is close enough to the virtual hands, users can use controllers to grasp the molecule and examine it from different angles. The inside-out experience can be enhanced through manipulating the receptor, such as rotating and scaling. Additionally, the availability of two controllers enables users to grasp two receptors at the same time for comparison and finding the similarity and differences among them (requirement *R*<sub>2</sub>). To improve the user-experience with the virtual world, haptic (sensory) feedback was introduced. Our current VR application supports three types of feedback (requirement *R*<sub>3</sub>): a) sound feedback – this feature is triggered every time users successfully performed an intended action such as grasp, scale or rotate, b) visual feedback – each receptor is placed in a location corresponding to its name, so when users misplaced a receptor, red color is highlighted indicating that there is a misalignment, c) vibration feedback – the touch controller triggers vibrations whenever the user grasps a 3D object. Sound and vibration feedback are mingled with each other to enhance user sensation in the virtual world. Figure 3 illustrates two examples of grasping and zooming the T2R1 receptor.

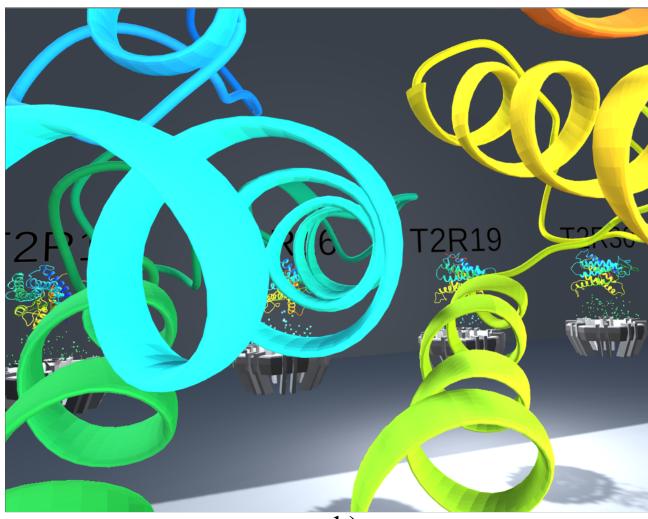
#### 4. User Study

Typically, two main techniques are used to evaluate the utility of the design of an application: empirical evaluation (testing with users) and heuristic evaluation (based on a set of rules) (Nielsen, 1995). Empirical evaluation is done when the application design is completed; heuristic evaluation is done during the development. In this work-in-progress research, we adapted the heuristic evaluation method to assess and justify our application. Nielsen (1995) recommended that in this technique, three to five evaluators are enough for the justification since much additional information cannot be gained by using larger numbers of evaluators. Therefore, we engaged five subjects who were experts in the visual design and medical domains. Our evaluator list consisted of a doctor of internal medicine, three medical students, and a computer science faculty member. The purpose of the study was to assess the usability of the VR interface before delivering it into an actual classroom. As mentioned earlier in the paper, VR can support learners with limited spatial cognitive style. To remove the ambiguity of the interpretation result, a mental rotation (Towle et al., 2005) test was administered to all subjects before they went through the VR application (the instrument is available at (Interactive Data Visualization Lab, 2020)). Based on the requirements of the VR application, the qualitative research questions of this study are as follows:

- Does the VR application allow users to perform tasks that they are intended to do?
- Does the VR application provide expected responses?



a)



b)

**Figure 3.** Interaction with the 3D model by using the Oculus touch: (a) Grasp and visually explore the T2R1 receptor and (b) Zoom in and investigate the T2R1 receptor from inside out using the Oculus touch controllers.

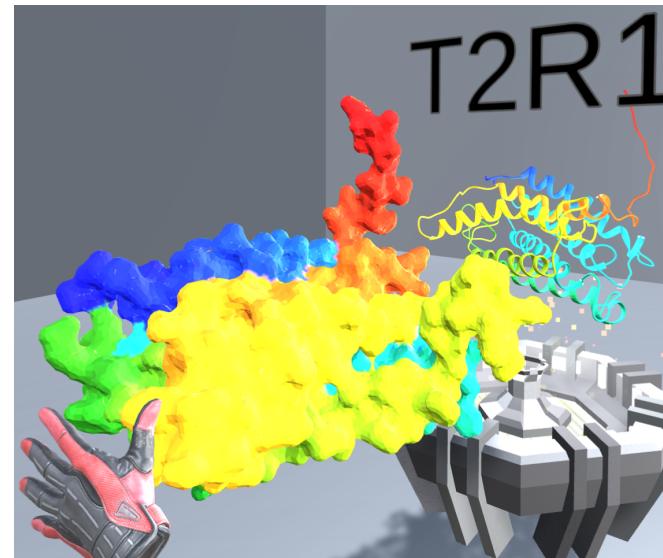
- Which component needs to be improved to enhance the user experience?

Before the testing was carried out, all the users were provided with training on how to use VR headset and controllers through a VR tutorial app provided by Oculus Rift. The evaluators trained for five minutes. After familiarizing themselves with the VR devices, participants took part in the experiments with the following guided activities: grasp 3D receptors with one or two controllers, put the object back to its original location; and, scale and rotate the object. The total duration for the experiment was 15 minutes.

**Results:** Overall, all five participants passed the mental test with the same score (the number of correct answers) as well as were able to perform the intended

actions in the VR environment. They, however, pointed out two limitations (which we have subsequently addressed): (a) text-labels for the receptors always faced in one direction, making it difficult to read when moving in the VR environment, (b) grasping the taste receptor from the inside view is sometimes challenging due to the size changes of the 3D objects. We received additional feedback to improve user experience, namely, to introduce a volumetric view of the bitter taste receptors.

We addressed the issues raised by the users: Issue (1) can be overcome by setting the text to point toward the VR headset; issue (2) is technically challenging, and it can be mitigated by incorporating more accurate hand controllers such as GloveOne (Technologies, 2019). We responded to feedback requesting a volumetric view of a receptor by upgrading this feature, as depicted in Figure 4. The different modes supported in our VR application can be triggered via a simple button click on the Oculus touch controllers.



**Figure 4.** The VR surface view of T2R1 taste receptor. This mode can be triggered on demand.

The stupendous success of VR adaptation in obtaining and enhancing the structural, mechanistic insights into taste receptors, but also the GPCR protein, which is also an important target protein for drugs, notwithstanding, there are many other domains of science that contribute towards the eventual development of a receptor model. These include; neuroscience, molecular biology, biochemistry, clinical trials, structural biology, bioinformatics, computational biology, and computer and information science.

## 5. Conclusion and Future work

This paper presents the work in progress of VR application for an immersive experience of receptor-ligand interactions from the perspective of the bitter taste. Several VR concepts were discussed in this research including user interactions with VR models (e.g., grasping the bitter taste receptor for an inside out view, navigating through the microscopic environment, and comparing two receptors using both hands), display modes (such as 3D structure or surface), and haptic feedback (such as visual, sound, and vibration of the touch controllers). We evaluated the usability of the VR application by conducting a test with five participants. Implications from the user study revealed that 3D visual representations of the genes and transcriptomes could be used in the medical application to understand their functionalities as well as support the drug design. The presence of newly created 3D models can be adapted to the classroom where young learners (as well as senior researchers in the domain of chemoreception) can play a role of the bitter tastant and try to find the binding region of a bitter taste receptor within an immersive microscopic environment that can trigger their motivation, learning, and additional scientific perspectives.

Our work confirmed the study of Nguyen et al. (2019b), where there is an opportunity to bring VR into the education of younger students. Future work will be focusing on supplementing the 3D molecules with the detail description in terms of both textual and sound. The Technology Acceptance Model will be adapted to assess the applicability of our tool in terms of perceived usefulness, perceived ease of use, perceived visual design, perceived task technology fit, and intention when applying our VR application in the classroom settings.

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