Building and Assessing a Web-based, Accessible, Three-Dimensional Modeling Tool to allow High School Students to Explore Molecular Structure, Intermolecular Interactions, and Molecular Dynamics Simulations

by

Maya Mau

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Abstract

Chemical bonding is the basis of many fundamental ideas in chemistry but is a difficult concept to teach due to common simplifications in textbooks, inaccurate or confusing terminology, and inadequate traditional testing methods to assess student understanding. The EMMAs (Exploring Molecular Modeling Activities) are a series of educational activities designed by *Kotsalidis et al.* to teach high school chemistry students about noncovalent bonding through case studies and exploratory exercises using the 3D molecular visualization tool VMD (Visual Molecular Dynamics). A prior study on the EMMAs found that the activities improved student understanding of noncovalent interactions. However, VMD is not available on Chromebooks, the most commonly-used personal computers used by high school students, and it also requires installation. Consequently, my thesis builds and evaluates a web-based molecular visualization interface that implements the EMMAs, which will make these activities accessible to more students. We found that the web-based interface, despite some performance lags and potential to improve usability, was easier to use than VMD and other molecular visualization tools. Common feedback received involved requests to improve performance of rotation and loading, to add additional features to improve usability, and to improve the design to improve learnability. Future directions include incorporating focus group feedback before testing the web-based interface with the EMMAs at Wellesley High School in order to enable a more direct comparison between the original EMMAs study using VMD and the EMMAs with the web-based interface.

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1. Introduction

1.1. Teaching Chemical Bonding and Interactions

Chemical bonding is one of the most fundamental concepts in chemistry — it is the basis for understanding many important phenomena, explaining everything from protein structure to acid-base reactions.[1] However, it is often very difficult to teach chemical interactions effectively due to common simplifications in chemistry textbooks and even disagreements between scientists on key definitions within the topic.[2] Furthermore, there are many models that can be used to teach chemical interactions, each with their own accuracies and misrepresentations that are not always made clear in the classroom.[3]

Chemical bonds are best understood on a spectrum of bonding strength, from weak to very strong. The diagram below illustrates the approximate range of strengths of common types of interactions.

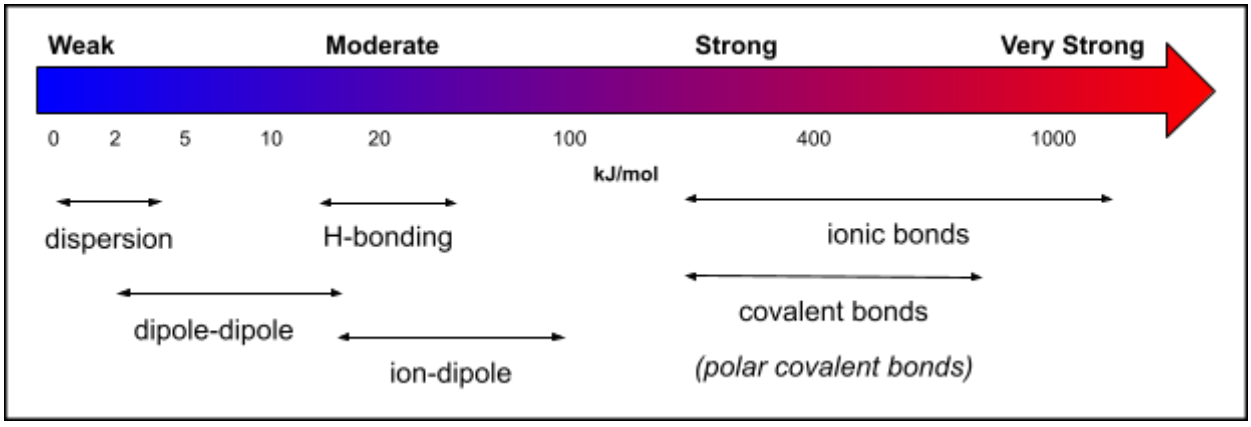

Figure 1. Relative Strengths (in kJ/mol) of commonly-taught chemical bonds, adapted from Sethio[4]

On the stronger end of the spectrum are ionic and covalent bonds, illustrated below. Covalent bonding occurs when electrons are shared between two atoms — molecules are often

defined as atoms held together by covalent bonds. For example, the molecule Cl_2 is held together by a covalent bond, where two electrons (one from each chlorine atom) are shared equally between the two atoms.

Meanwhile, ionic bonds occur when valence electrons are completely transferred between two atoms instead of shared, turning one atom into a positive cation and the other into a negative anion. Typically, the atom that donates electrons is a metal and the atom that accepts electrons is a nonmetal. Atoms are generally the most stable when they achieve a full octet, which is eight valence electrons in their outermost shell. The compound NaCl demonstrates this phenomenon — because the sodium atom Na has one electron in its outermost shell and the chlorine atom Cl has seven, the sodium atom donates an electron to the chlorine atom such that both have full octets. This forms the ionic compound NaCl, more commonly known as table salt.

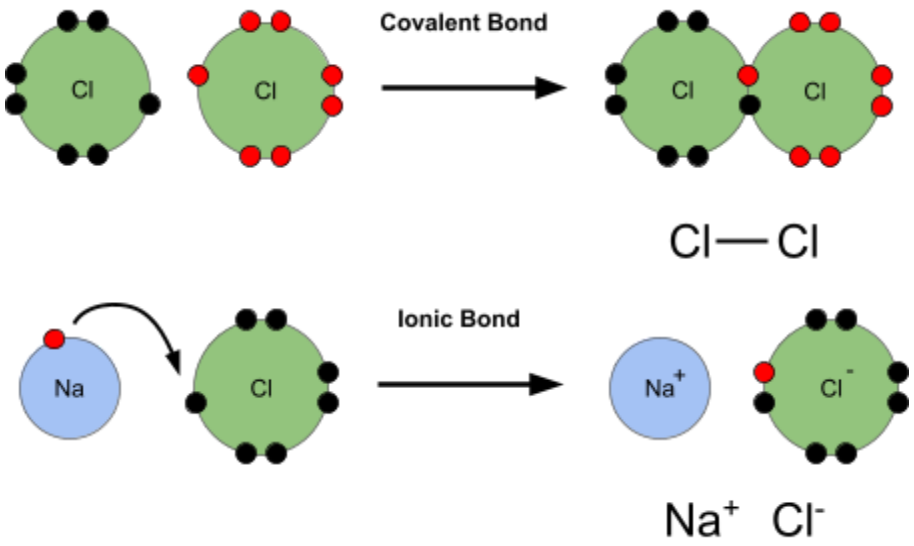

Figure 2. Ionic and covalent bonding (only valence electrons shown). The covalent molecule formed is Cl_2 and the ionic compound formed is NaCl. Cl_2 is also shown with a Lewis structure diagram below its cartoon representation.

Ionic and covalent bonds are two extremes of a spectrum of electron sharing/transfer, with ionic compounds involving the complete transfer of valence electrons between atoms and covalent molecules involving the perfect sharing of electrons. Somewhere between ionic and covalent bonds on the spectrum are polar covalent bonds, which are bonds that have both ionic and covalent character. For example, HCl is held together by a polar covalent bond. This bond is polar — electrons are shared unequally between the hydrogen and chlorine atom — because of the different electronegativities of hydrogen and chlorine. Electronegativity is defined as an atom's ability to attract electrons within a bond. Chlorine is much more electronegative than hydrogen, so the electrons shared by hydrogen and chlorine in a covalent bond are pulled closer to the chlorine. In this case, electrons are not shared equally between atoms but are not completely transferred, either.[5]

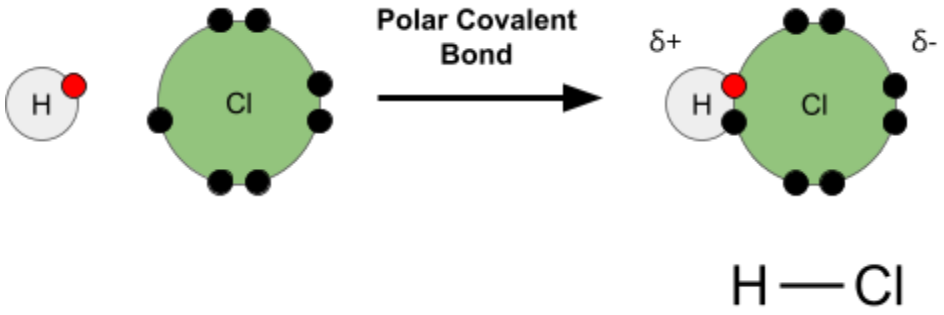

Figure 3. Polar covalent bonding between hydrogen and chloride, forming HCl. δ+ refers to a partial positive charge and δ- refers to a partial negative charge. HCl is also shown with a Lewis structure diagram below its cartoon representation.

Molecules are often defined as a group of atoms connected by covalent bonds. Ionic compounds are sometimes referred to as molecules, although this definition is considered incorrect by many— an ionic compound such as NaCl is connected together via ionic bonds, not covalent ones. Additionally, NaCl and other ionic compounds often dissolve in polar compounds

such as water, referred to as $NaCl_{(aq)}$ (aqueous), and exists as an ionic lattice outside of water, referred to as $NaCl_{(s)}$ (solid). The idea that ionic compounds are molecules can lead to the misconception that an ionic solid is composed of individual NaCl "molecules," when in fact they are built up by ionic lattices held together by strong ionic bonds.[6] This is one of many examples of how the nuances of using certain terms in chemical bonding can lead to confusion for students.

Ionic and covalent bonds are stronger than most other types of chemical interactions. Indeed, they are often taught as "bonded" interactions. On the weaker side of the spectrum of strength are forces such as London dispersion forces, dipole-dipole forces, and hydrogen bonding — these are often taught as "non-bonded" interactions. These forces happen mainly due to electrostatic interactions or fluctuations and often occur between molecules (intermolecular), but this is not always the case. The "bonded" vs. "non-bonded" distinction causes interactions to be categorized artificially instead of based on a spectrum, but this model is often used for simplicity. The rest of this section will discuss these forces from weakest to strongest, shown on the continuum in Figure 1.

London dispersion forces occur between both polar and nonpolar groups, but are especially important for interactions between nonpolar groups — groups with even charge distributions. Even though nonpolar groups do not have regions of positive and negative charge, there exist temporary electron fluctuations within these groups that result in instantaneous, weak dipole moments. These temporary dipole moments cause London dispersion forces between nonpolar groups.[7] In the example below, each I_2 molecule is composed of a covalent bond that involves complete equal sharing of electrons because both iodine atoms have the same

electronegativity. Thus, I_2 is considered nonpolar, but can experience temporary electron fluctuations that create the weak dipole moments necessary for London dispersion forces.

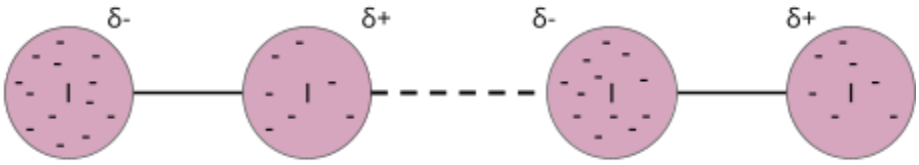

Figure 4. London dispersion forces between two I_2 molecules. Electron density is shown using "-".

Meanwhile, dipole-dipole forces occur between polar groups. Each polar group can be created by the existence of one or more polar covalent bonds, i.e., differences in electronegativity can cause an uneven distribution of charge due to the unequal sharing of electrons between atoms. This uneven distribution of charge causes partially positively and negatively-charged regions within a group — an example of this is the molecule HCl, shown below. As a result, dipole-dipole forces can occur between the positive and negative ends of two different polar groups.

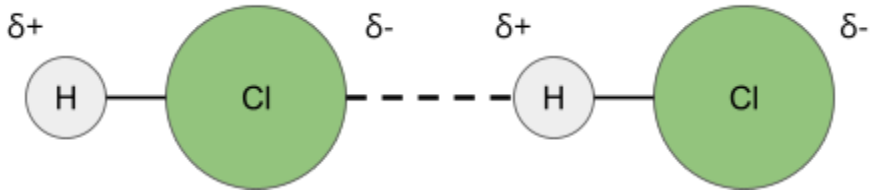

Figure 5. Two HCl molecules interacting through dipole-dipole forces. Each HCl is held together by a polar covalent bond.

Hydrogen bonds, which are very strong dipole-dipole interactions, occur when a group containing a hydrogen covalently bonded to a very electronegative atom (often oxygen, nitrogen, or fluorine) interacts with an electronegative, partially negatively-charged atom that has a lone

pair. When a hydrogen atom covalently bonds with a very electronegative atom, it results in a particularly uneven sharing of electrons — i.e., a particularly polar covalent bond. This causes a large partial positive charge on the hydrogen atom. The partially-positive hydrogen interacts with a lone pair on a partially-negatively charged electronegative atom on a different group. For example, water molecules interact with each other through hydrogen bonding, as illustrated in the figure below.[7] Extremely strong hydrogen bonds sometimes resemble covalent bonds, while weaker hydrogen bonds are more similar to London dispersion forces. Hydrogen bonds can be particularly strong because they have quantum mechanical effects beyond the simple electrostatic interactions that govern most other types of "noncovalent" bonding.[8]

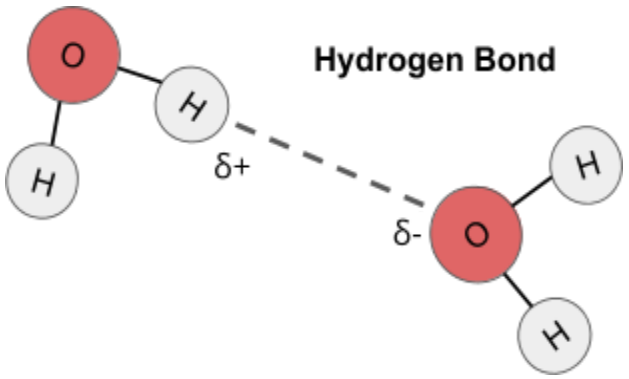

Figure 6. Hydrogen bonding between two water molecules.

Next on the spectrum are ion-dipole interactions, which occur between an ion and a polar species. In the figure below, a positive sodium cation interacts with the negative regions of two (polar) water molecules.

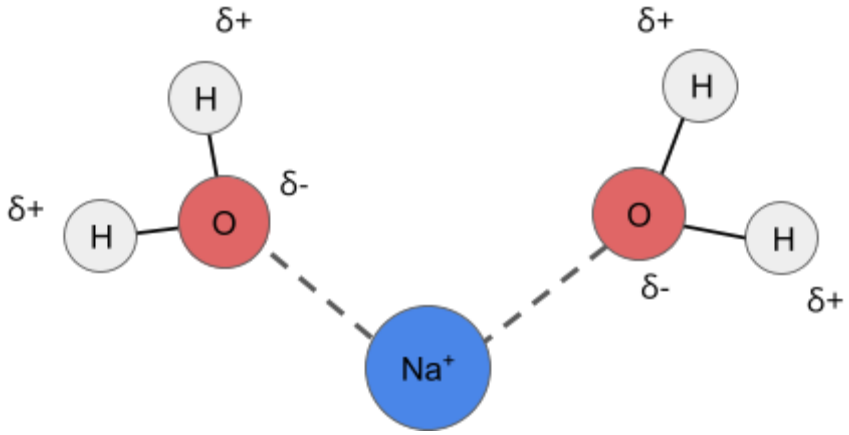

Figure 7. Ion-dipole interaction between water molecules and Na^+.

Ion-dipole interactions often occur when an ionic complex is dissolved in a polar solvent. As mentioned earlier, an ionic compound involves the electrostatic attraction between two oppositely-charged ions, often a metal cation (positively charged) and nonmetal anion (negatively charged). For example, NaCl is an ionic compound formed from a positively-charged sodium ion and a negatively-charged chloride ion. A polar solvent such as water can interact with the dissolved (or separated) ions from an ionic compound through electrostatic forces, where the partial positive or negative regions of the polar solvent are attracted to the negative or positive ions, respectively.[9]

In summary, chemical interactions are best understood along a spectrum of strength, with London Dispersion forces, dipole-dipole interactions, ion-dipole interactions, and hydrogen bonds on the weaker end and ionic and covalent interactions on the stronger end. However, chemical bonding is often taught not as a spectrum of strength but rather sorted into a few simplified and often misleading categories. Traditionally, bonding is taught in three main categories: covalent bonds, ionic bonds, and metallic bonds. Metallic bonds are often defined as a sea of electrons shared among a lattice of metal atoms.[1] Covalent and ionic bonds are

sometimes taught on a spectrum with bonds having both covalent and ionic character, but sometimes they are taught as distinct and unrelated categories. Even the textbooks that do teach covalent and ionic bonds on a spectrum often fail to place intermolecular forces on that spectrum, when in fact they can all be understood based on the same fundamental chemical principles.[10]

Students are also taught the concept of noncovalent bonds, which are often defined as bonds that do not share electrons. For example, dipole-dipole interactions, hydrogen bonds, ion-dipole interactions, and ionic bonds are considered noncovalent bonds. Additionally, many of these types of bonds are categorized as either intermolecular — occurring within molecules — or intramolecular — occurring between molecules. However, these labels are sometimes misused or imprecise. Typically, intramolecular bonds are considered much stronger than intermolecular bonds, but this is not always the case, and some types of bonds cannot even be labeled as purely one or the other. For example, even though ion-dipole interactions are often categorized as intermolecular forces, this is not entirely correct because the ions involved do not necessarily need to be molecular — ionic compounds are usually dissolved in aqueous solution and are sometimes not molecular, and it is debatable whether an ionic compound in its solid form is considered a molecule.[9]

Perhaps more importantly, while many of the bonds on the weaker end of the strength spectrum (London dispersion forces, dipole-dipole interactions, ion-dipole interactions, and hydrogen bonds) are often taught as intermolecular forces, all of these bonds can also occur *within* molecules, called intramolecular. For example, when a peptide (which is considered one molecule) folds into an alpha helix, its structure is held together by hydrogen bonds within the molecule.[11] Dipole-dipole or hydrogen bonding interactions can also occur within simpler

molecules. In the example below, o-nitrophenol has an -NO_2 group and an -OH group adjacent to each other on a benzene ring. The -NO_2 group has a partial negative charge on the oxygen connected to the nitrogen by a single bond due to resonance, and the -OH group has a partial positive charge on the hydrogen atom due to electronegativity differences between oxygen and hydrogen. Thus, the partially positive hydrogen atom can form a hydrogen bond with the partially negative oxygen atom.

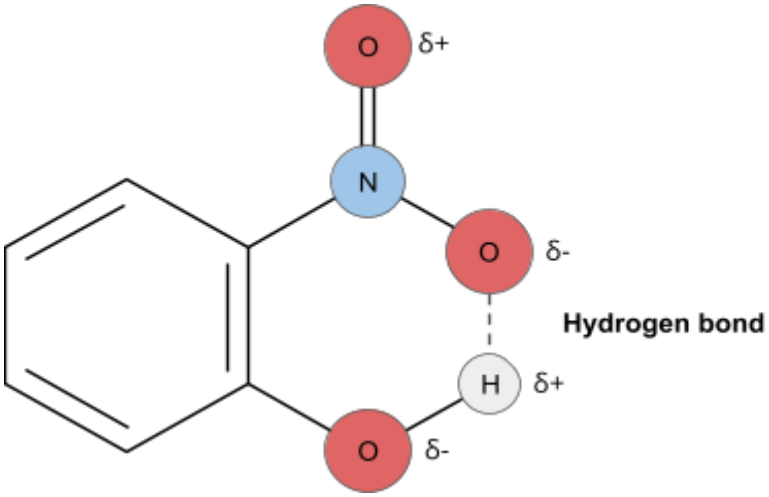

Figure 8. Hydrogen bonding within an o-nitrophenol molecule (intramolecular).

Ion-dipole interactions, also often taught as an "intermolecular" force, can also occur within a molecule. In the figure below, a peptide — which is a short chain of amino acids with an N-terminus on one side and a C-terminus on the other — is shown. The N-terminus is positively charged and the oxygen in the OH group of the serine side chain has a partial negative dipole. If the peptide is structured in such a way that the positively-charged N-terminus and OH group of the serine side chain are close together, they can interact via an ion-dipole interaction.

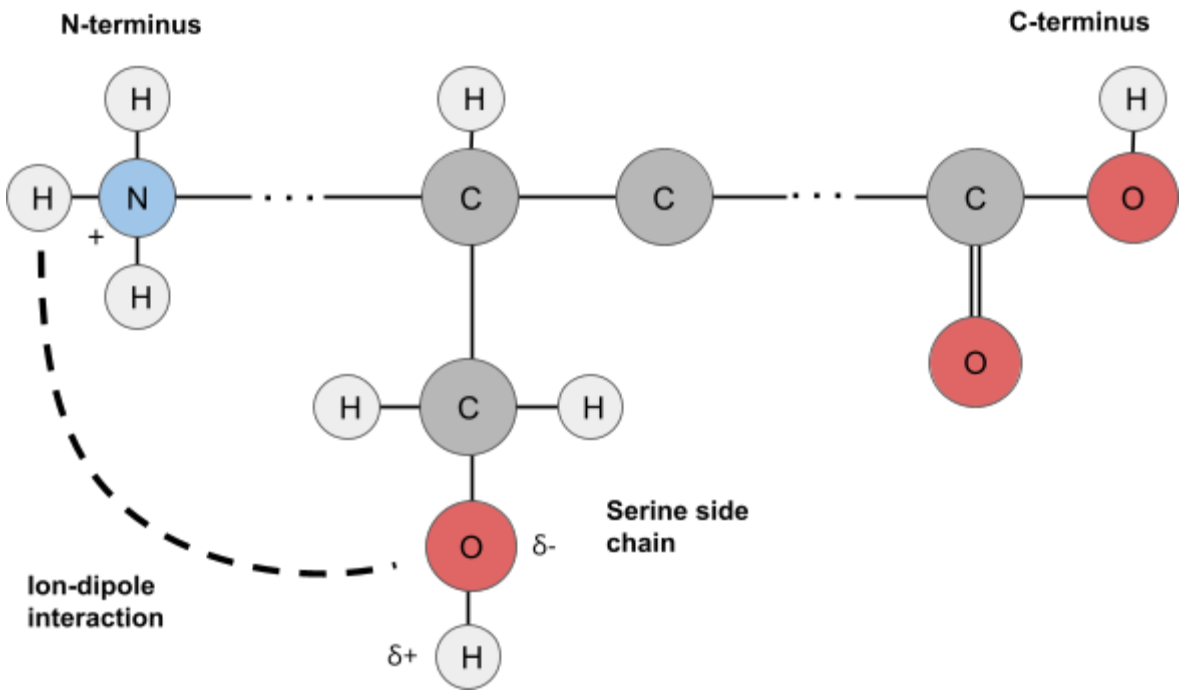

Figure 9. Ion-dipole interaction between the N-terminus of a peptide and a serine side chain.

As these examples of intramolecular interactions show, the term "intermolecular" can be misleading, with many so-called "intermolecular" forces happening both within *and* between molecules.[12]

Furthermore, each of the interaction types that are considered to be intermolecular — London dispersion, dipole-dipole, hydrogen bonding, and ion-dipole — are often taught separately and unrelated to each other (if mentioned at all),[10] when in fact chemical bonding exists on a spectrum, and though some can be understood through more specific models, all of them can ultimately be derived from related fundamental principles grounded in quantum mechanics. One common misconception that this method of teaching perpetuates is that covalent and ionic bonds are "real bonds", while noncovalent interactions such as hydrogen bonding are merely "forces."[10] However, the same, ultimate physical principles give rise to most types of

bonding, including noncovalent bonds. Thus, teaching noncovalent bonding requires nuance and ideally an emphasis on certain fundamental physical and chemical ideas.

As noted above, terminology surrounding chemical bonds can be confusing for students. As an additional example, the term "hydrogen bond" can suggest a covalent bond rather than a noncovalent one because it includes the word "bond," which typically implies a strong connection between atoms or groups, even though hydrogen bonds are generally far weaker than typical covalent bonds. Additionally, as noted above, noncovalent interactions are often referred to as intermolecular forces (IMFs) in general chemistry classes, which can be misleading[13] — while all intermolecular forces are noncovalent interactions, not all noncovalent interactions are IMFs. Again, many of these nuances are sometimes lost when teaching introductory chemistry,[2] making noncovalent interactions a difficult concept for many students to fully grasp.

Student confusion surrounding noncovalent interactions is further perpetuated by inadequate testing methods. Traditional testing techniques have difficulty picking up on misunderstandings regarding noncovalent interactions — students that perform well on traditional assessments often still have significant misconceptions surrounding noncovalent interactions. The nature of traditional testing methods, which often include multiple choice or written response questions,[13] may not properly assess student understanding because they do not require students to explicitly demonstrate their understanding of the nuances of bonding. As a result, these misunderstandings can be perpetuated across multiple years of chemistry instruction.

Furthermore, three-dimensional molecular structures are often represented using two-dimensional diagrams in traditional chemistry education. Although these two-dimensional diagrams (Lewis dot diagrams, Fisher projections, etc.)[14] are very informative representations for

three-dimensional molecules, it can be difficult for students to connect these two-dimensional representations to their three-dimensional realities.

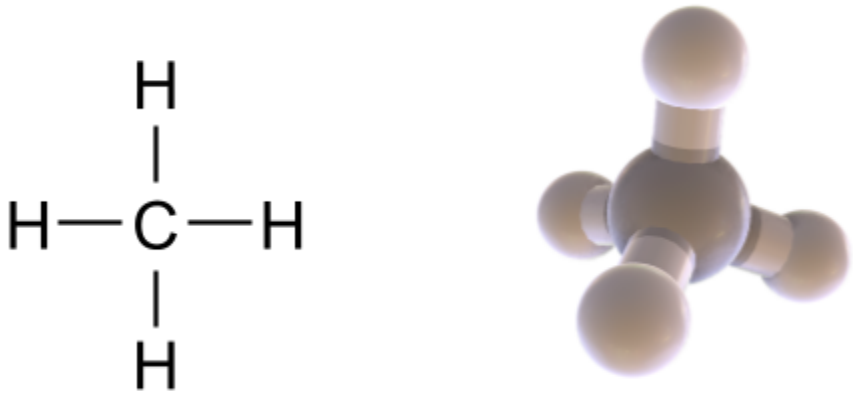

Figure 10. Lewis dot structure of CH_4 (left) and 3D model of CH_4[16] (right).

Another reason why noncovalent bonding is a difficult concept to understand is that sub-microscopic phenomena such as noncovalent bonding are inherently unobservable.[15] Students exist in a macroscopic world and thus cannot directly observe sub-microscopic phenomena, so it is easy to build incorrect mental models that result in misconceptions on the sub-microscopic level.[3] Additionally, shifting between macroscopic, sub-microscopic, and symbolic levels is difficult for students when learning new chemical concepts, especially when these shifts are not emphasized by educators.[17] The macroscopic level includes observable phenomena, such as color change in a beaker during a reaction. The sub-microscopic level includes non-observable phenomena, such as atoms, ions, or molecules — they must be represented by some sort of model. The symbolic level is the specific representation of sub-microscopic entities such as molecules, which includes chemical or mathematical equations representing relationships between entities.[3,14]

Each student inevitably develops a mental model when new information is taught, and these mental models are essential in drawing conclusions and supporting further learning. The goal in scientific education is to teach concepts in such a way that students have mental models that match scientific models — models widely accepted by the scientific community — as closely as possible. However, if models are not taught well, students can retain their inaccurate mental models and have difficulty transitioning between macroscopic, sub-microscopic, and symbolic levels.[14]

Models are also important not just for the information that they contain, but for the information they exclude. Despite their usefulness, models are only representations of natural phenomena that are assigned importance by scientists, and thus their limitations must be considered carefully. However, the idea that models are not entirely accurate, realistic depictions of phenomena is often a difficult concept for students to grasp — they often mistakenly believe that models are simply copies of reality.[18] It is thus useful to present multiple models of a single concept to students when teaching, but even this approach has its drawbacks — too many representations can be confusing[18] and can be detrimental to student understanding if each model's limitations are not properly discussed.[3,19] As a result, complex, unobservable chemical concepts such as noncovalent bonding can be difficult for students to understand, even after multiple years of chemistry education.

1.2. Existing modeling tools and their uses in chemical education

Computer-based visualizations and 3D models can be extremely useful pedagogical tools to help students understand concepts such as noncovalent interactions.[20] Molecular visualization can help students conceptualize three-dimensional models, picture molecular interactions, and enhance their own learning through exploratory activities and active learning.[12] Specifically,

interactive visualizations in which students can actively manipulate models to engage in hypothesis testing — that is, developing a hypothesis and engaging with the visualization to confirm or deny their hypothesis — can improve students' construction of mental models.[14] Indeed, interactivity with the learning process is typically viewed as an essential aspect of education that classrooms often lack.[17]

Before the advent of computers and computer graphics in the chemistry classroom, there was already evidence that the use of physical models — specifically, ones that could be manipulated by students — improved student understanding of molecular structure and helped them achieve higher performance on assessments.[21] Once computers and molecular visualization tools became more accessible, the use of three-dimensional representations in the curriculum increased rapidly.[22] Since then, it has been shown that using three-dimensional molecular visualization tools in chemistry education has positive effects on student learning outcomes.[23, 24, 19] However, many chemistry courses still use two-dimensional molecular representations to teach difficult concepts, even though some researchers claim that these flat, non-dynamic representations are not sufficient for building deeper levels of understanding — especially when it comes to abstract and unobservable concepts.[25]

In a study assessing the usefulness of incorporating Avogadro[26] — a free, open-source software with a user-friendly interface ideal for small molecules — researchers found that students who were taught with the visualization software incorporated into their lectures performed significantly better on chemistry exams compared to students taught without the software. Additionally, student feedback from the experimental group was very positive, saying that Avogadro was helpful for their learning and that they recommended its incorporation into the curriculum early on in chemistry education.[19]

Other research also supports this conclusion, showing that incorporating professional-level molecular visualization software into the curriculum enhances student learning, at both the high school and university level.[22,23,24] Ealy showed that including molecular modeling tools in an undergraduate general chemistry lab increased the knowledge gained by students at the microscopic level throughout the course.[24] Furthermore, educators frequently express positive sentiments towards the use of such tools in the classroom, emphasizing student engagement and interest.[19]

There are several existing molecular visualization tools that are often used for educational purposes, including software such as Jmol[27] or Proteopedia,[28] and more professional-level software packages such as PyMOL,[29] Chimera,[30] and VMD.[31] All of these software programs with the exception of Jmol require either MacOS, Linux, or Windows operating systems, and some are free while others cost money.

Jmol is an open source molecular visualization tool that can either be downloaded and used as a standalone software or embedded into existing websites. It can accept many different types of files (including PDB[32] files, which give information about atoms, including their coordinates within molecules in angstroms) and provides many features, including the ability to highlight different parts of a molecule, use different drawing/coloring methods, and others. However, Jmol uses its own scripting language that would require additional instruction to be able to use, meaning that it can be difficult to learn.[27] PyMOL, Chimera, and VMD all have similar features — each one has the capability to analyze molecular structure and visualize molecular dynamics simulation trajectories, and they also contain the features mentioned above for Jmol. Specifically, Visual Molecular Dynamics (VMD) is used by many researchers to visualize and analyze the movements and interactions of molecules. Despite being a

professional-level research tool, it can be used at the high school and undergraduate level to teach important chemistry concepts such as intermolecular interactions. However, software programs built for research are more advanced and thus may be harder for beginners to learn and use compared to software programs built specifically for chemistry education.[33]

1.3. Exploring Molecular Modeling Activities (EMMAs)

In 2022, Kotsalidis *et al.* developed a series of educational activities called EMMAs (Exploring Molecular Modeling Activities) with the goal of strengthening high school students' understanding of three-dimensional structure, intermolecular interactions, and molecular dynamics through 3D molecular representations and simulations. The EMMAs involve case studies, puzzles, and exploratory activities that aim to increase understanding in the above categories as well as to familiarize students with the professional-level research software VMD. They were designed to satisfy both Massachusetts state standards and the Next Generation Science Standards (NGSS). A more thorough table of specific learning goals with associated levels of Bloom's Taxonomy can be found in the original EMMAs paper.[12]

The activities use a case-based learning (CBL) approach, which involves teaching through case studies of realistic or real-life applications of chemistry concepts. Case-based learning has been shown to increase student engagement in the learning process due to its emphasis on the real-world applications of the technical content being taught — thus, case-based learning often results in better learning outcomes compared to traditional, non-case-based teaching.[34,35] In the EMMAs, students learn about noncovalent (and covalent) bonding through case studies involving Chronic Myeloid Leukemia (CML), a type of cancer characterized by a chromosomal abnormality that leads to overactive Abl kinase proteins that produce more white blood cells than the body needs. CML is commonly treated with drug molecules known as

tyrosine kinase inhibitors, including imatinib and ponatinib, which inhibit the protein's function and counteract its overactivity.[36] These drugs work by taking advantage of the fact that a small molecule called ATP is required to bind to the Abl kinase protein for it to function. The ATP molecule is required because it provides the Abl kinase protein with a phosphate group that is core to the kinase's role. The drugs (i.e., "inhibitors") work by binding to the ATP-binding pocket of the Abl kinase through noncovalent interactions — the same pocket that ATP would normally bind to. Thus, ATP can no longer bind to the protein and the protein becomes deactivated, or *inhibited* from performing its function.

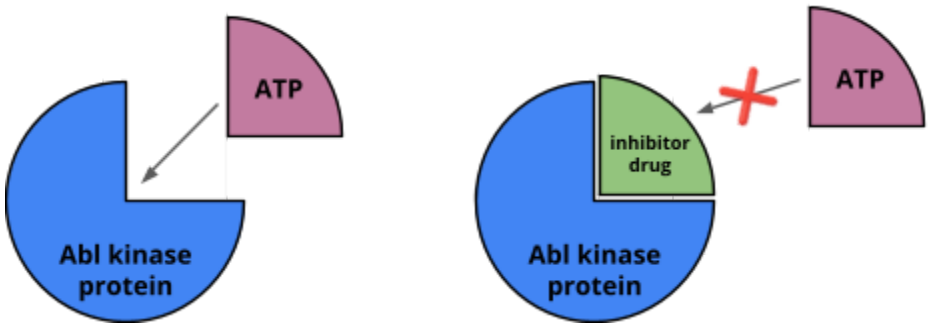

Figure 11. An Abl kinase protein binding with an ATP molecule, thus becoming activated (left), next to an Abl kinase protein with an inhibitor drug bound to the ATP-binding pocket instead, thus becoming deactivated (right).

Imatinib is used to introduce students to the idea of drug-target interactions when treating disease and when considering molecular dynamics in later activities, and ponatinib is used in several intermediate activities for students to visualize these interactions. Both imatinib and ponatinib interact with Abl kinase in part through hydrogen bonding (a form of noncovalent bonding). To teach students about hydrogen bonding as a type of noncovalent bond, as well as address some of the common misconceptions about noncovalent bonds mentioned in the introduction, students manipulate the ponatinib-protein complex in Activity 4 to identify all the

hydrogen bonds between the drug and protein using VMD's bond measurement tool as shown in Figure 12 below.

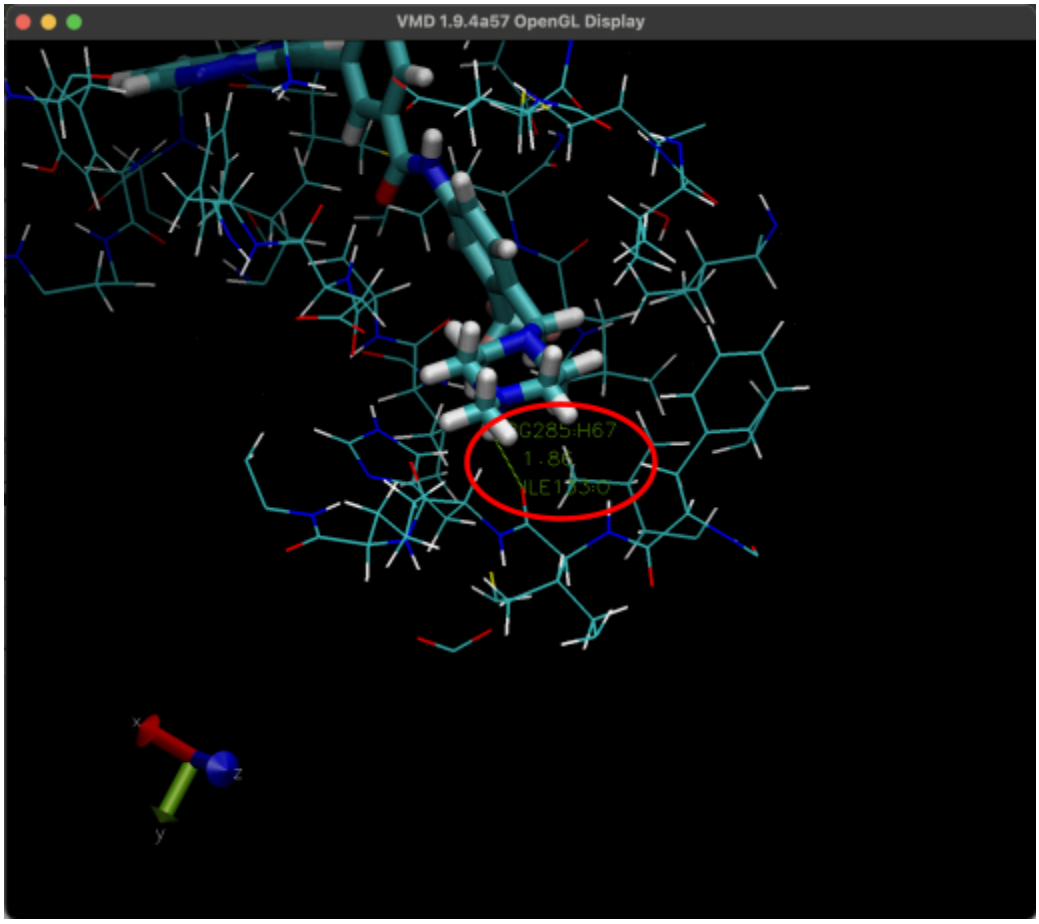

Figure 12. The Ponatinib drug and part of the Abl kinase protein that the drug binds to, visualized in VMD, from Activity 4 of EMMAs.[5] One hydrogen bond, shown as a dotted green line with a length of 1.86 angstroms, is circled in red.

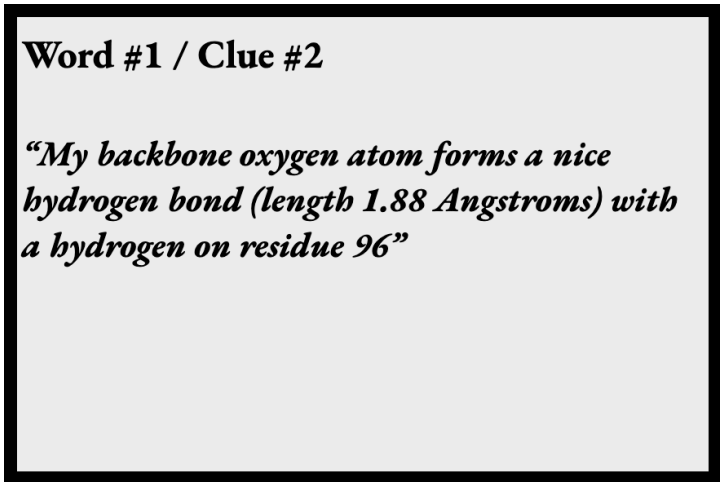

Figure 13. A clue from Activity 5 ("Secret Code Activity")

Similarly, in Activity 5, students use their knowledge of VMD, hydrogen bonding, and the drug-protein complex structure to piece together a series of letters that form a message. A more thorough overview of each activity is found in the next section, along with specific learning goals.

1.3.1. Description of Activities

Table 1. Summary of the EMMAs Activities and their Descriptions[5]

Activity	Description
1. CML Case Study	● Students complete a short reading about a fictional person with CML, followed by reading comprehension questions and two externally-made[32,33] videos about CML and how the imatinib drug binds to the Abl Kinase to inhibit its function. ● Teaches students about drug-target complexes and how biomolecular changes can cause disease to bridge the gap between macroscopic and microscopic levels.

2. Exploring ponatinib and Abl kinase	• Familiarizes students with the basic features of VMD by having them explore first a drug molecule and then its target protein separately. • These features include rotation, translation, and zoom operations, using various coloring and drawing methods, selecting parts of a molecule, determining distances between atoms, and using various graphical representations. • Teaches students about amino acids, molecular geometries, and atomic structure of molecules.
3. CML stories investigation	• Students complete a reading about different athletes diagnosed with CML and complete a summary of one of the cases. • Allows students to explore the real-life implications of disease and treatment, again bridging microscopic and macroscopic levels.
4. Exploring the ponatinib-Abl kinase complex	• Students learn how to create and navigate multiple representations within VMD to visualize multiple molecules simultaneously. • Students use the skills they learned in VMD to investigate the interactions within the drug-protein complex. • Students complete a short hydrogen bonding challenge where they use bond distances and atom types to determine the existence of hydrogen bonds within the complex.
5. Cracking the "secret code"	• Students use their knowledge of VMD, bonding, and interparticle forces to solve a secret code challenge. The clues provided are based on interactions between the drug and different amino acids of the protein, or molecular interactions within the protein itself. • Strengthens students' ability to identify amino acids. Reminds students of the following concepts: covalent bonds, hydrogen bonding, and hydrophobic interfaces. Reinforces student skills in using VMD
6. Molecular Simulation video modules	• Students watch a series of videos about the creation, theory, and applications of Molecular Dynamics (MD) simulations and answer comprehension questions. • Teaches students about basic physics concepts such as Newton's laws to help understand the creation of MD simulations.

7. Investigations of MD simulations	● Students use VMD to manipulate MD simulations and generate plots based on the simulations. ● Students learn various methods of analysis to understand drug-target interactions, including hydrogen bonding, distance, and fluctuation plots. ● Students again bridge macroscopic and microscopic levels by understanding connections between mutations and disease treatment.

1.3.2. Prior Study Methods and Findings

The following section is based on Kotsalidis *et al.*'s research on the learning outcomes of the EMMAs in high school classrooms, as described in the recent publication describing their implementation and assesment.[12] Initially, a version of these activities was implemented in a pilot study in Spring 2022, and feedback received was used to improve both the activities themselves and the survey questions used to evaluate them. In Spring 2023, Activities 1-6 were carried out with students enrolled in introductory college preparatory-level chemistry courses at Lincoln-Sudbury Regional High School in Massachusetts. VMD, which was necessary to complete the activities, was set up by an IT staff member at the school on desktop computers in the computer lab. The activities were completed over the course of a week near the end of the school year, after students had covered the standard curriculum instruction for noncovalent bonding. Students worked in small groups on Activities 2, 4, and 5, and completed Activities 1 and 3 for homework, while Activity 6 was done in-class independently followed by a whole class discussion (Activity 7 was not carried out).

The success of these activities was assessed using pre- and post-surveys that included Likert response, free response, and molecular drawing questions. Questions assessed student understanding of the concepts covered by these activities, general satisfaction with the

experience, and student attitudes towards science and self-identifying as a scientist. Overall, students expressed increased confidence regarding their ability to identify and analyze intermolecular interactions after engaging with the activities. For example, students were more likely to agree with statements like "How well two molecules interact with each other can be influenced by the location of their charges" and "I can picture molecules interacting in my mind" after completing the activities compared to before. Additionally, student drawings of drug-target interactions demonstrated a significant increase in understanding.

However, when asked what could be improved about the molecular modeling activities in the postsurvey questionnaire, the most common piece of feedback received from students (23%) was that they experienced challenges when learning and using VMD. Because VMD is a professional-level software used by students and researchers alike, it often requires a steep learning curve that can be difficult for high school students to overcome in the short period of time necessitated by the implementation of these activities. Indeed, some researchers believe that professional-level software intended for researchers have complex interfaces and were not constructed with pedagogical design in mind, thus making them inappropriate for use in early chemistry education.[33] While some argue that teaching students how to use professional-level software can be beneficial because it can illustrate the real-world utility of such software and introduce students to them early on,[12] there are drawbacks to this method as described.

Additionally, VMD is only available on MacOS and Linux operating systems, meaning that students who use Chromebooks — which are the most commonly used computer in 1:1 device programs in high schools across the United States[37] — would not be able to participate in these activities. In fact, all of the commonly-used molecular visualization software mentioned previously either require MacOS, Windows, or Linux operating systems, do not have enough

functionality to complete the EMMAs, or are not flexible enough to facilitate possible extensions and spontaneous student exploration.

VMD also requires installation, which means additional preparation time needs to be taken prior to implementing the activities. Installation also can differ based on the specific operating system or version, which can require additional time for troubleshooting by IT staff.[31]

1.4. Motivation

My thesis proposes the creation of a simplified, accessible web-based interface for molecular visualization and modeling that incorporates the EMMAs formerly available only using VMD. Specifically, the goal is to make the EMMAs accessible to students who use Chromebooks. Thus, the EMMAs — which have already been shown to be highly effective in teaching high school students about noncovalent forces and their real-world applications — will be available to more students, both in terms of ease of use (simplified interface) and ease of access (web-based, with no need to download and install software, making it more accessible to schools with fewer resources).

Providing more high schoolers access to the EMMAs will facilitate student exposure to the concepts of noncovalent forces, inter- and intramolecular interactions, and three-dimensional molecular structure before they develop common misconceptions surrounding noncovalent bonding. Even though these concepts are difficult to learn, using three-dimensional modeling and interactive activities in which students are allowed to explore and direct their own learning will guide them towards a deeper, more thorough understanding of the topic. Exposure to the EMMAs will also allow students to explore the interdisciplinary nature of science because these activities incorporate aspects of chemistry, biology, physics, computer science, and math.[12]

Exploration plays a key part in the learning process, and can help students gain a deeper understanding of any topic. When students are able to ask their own questions and answer them through open-ended exploration, they can construct hypotheses and gather information to confirm or deny them immediately.[14] In the EMMAs, exploration is facilitated throughout the activities. At the beginning, when students are still building their skills related to the visualization software, they are asked to experiment with different styles (e.g. ball-and-stick, lines, or space filling) and brainstorm ways in which they would be useful for different purposes. Later on, such as in Activity 4, students are asked to explore the ponatib-Abl kinase complex and find hydrogen bonds. In Activity 5 (the "Secret Code Activity"), students are able to use their newly-developed skills in VMD to explore the drug-protein complex and identify various amino acids based on clues, which requires a significant amount of self-directed decision making and exploration. When using VMD, students can choose their own stylings and colorings based on their current goal and navigate freely throughout the molecule. Ideally, the web-based interface would retain this vital ability to explore while being more accessible to more students by offering additional support through a simpler GUI (graphical user interface) and fewer options. Even though some aspects of the interface will be simpler than VMD (such as having fewer representation options and a simpler residue selection tool), students will still be able to carry out the necessary parts of each activity to reach similar learning goals.

2. Web-interface Design and Activity Modifications

This section will discuss the implementation details, features, and performance considerations of the web-based interface. We will compare the interface with VMD and explain

why certain features were kept or excluded. We will also outline technical decisions made to prioritize usability and performance considerations.

Broadly, the web-based interface will integrate the molecular visualization tool and the EMMAs activities together. The layout of the web-based interface, shown in Figure 14, will include three panels: a control panel (GUI) on the left, the visualization window in the middle, and a panel on the right where questions will be available for students to follow along.

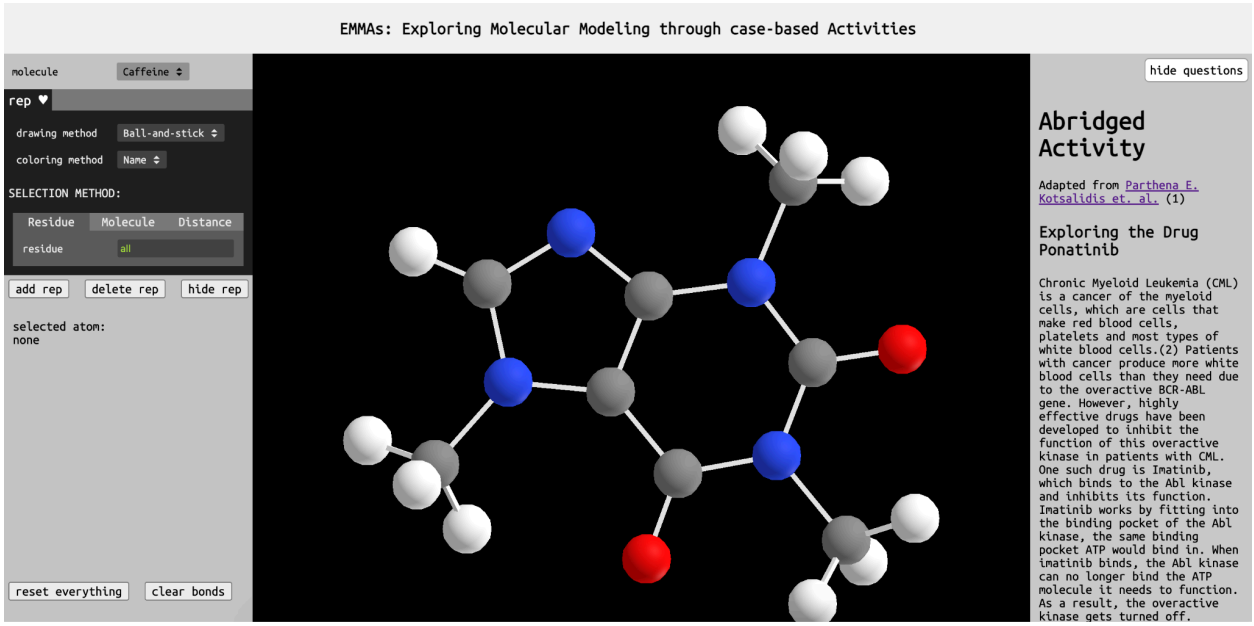

Figure 14. The basic layout of the web-based interface when first opened.

A combination of JavaScript, HTML, and CSS was used to code the web-interface. The open-source library *three.js*,[38] initially created by Ricardo Cabello (mrdoob on Github) with contributions from many others in Javascript, was used to generate the animated three-dimensional computer graphics used for molecular visualization. To create a simple and organized GUI, the *dat.GUI*[39] library, also created by Ricardo Cabello and others, was used. The code for the web-based interface is linked in the appendix for reference.

2.1. Common Use Cases of the Web-based Interface in EMMAs

This section will be used to describe a common use case of the web-based interface when completing the EMMAs. One useful feature of the web-based interface is to have the option for multiple representations, or copies, of a PDB file's contents superimposed on the screen. This feature enables students to isolate, identify, and distinguish between different parts of a PDB file. For example, both ponatinib (the drug) and Abl kinase (the protein) are present in the PDB file used in Activity 4 of the EMMAs. When the entire PDB file is loaded into the web interface, it is impossible to distinguish between ponatinib and Abl kinase, as shown below.

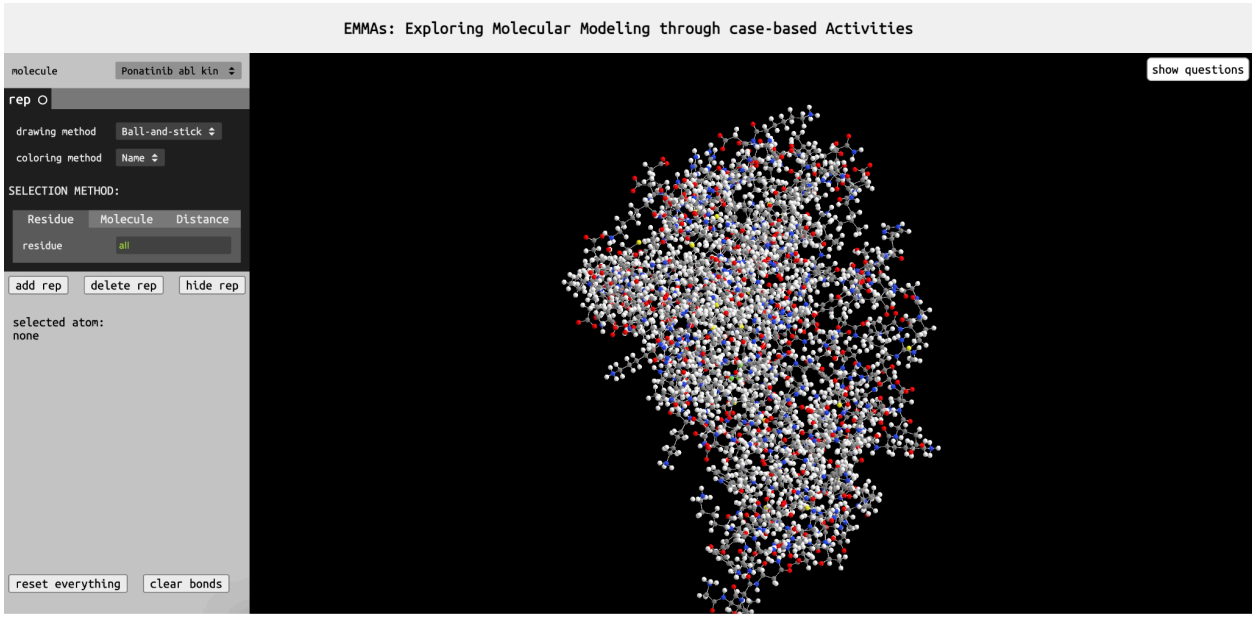

Figure 15. The Ponatinib Abl Kinase PDB file loaded into the web-based interface.

However, users can isolate the drug and protein and represent them using different colors and drawing methods. If a user switches to the selection method by "molecule" and enters "ponatinib" in the text box, they can make the drug visible while the rest of the PDB file disappears.

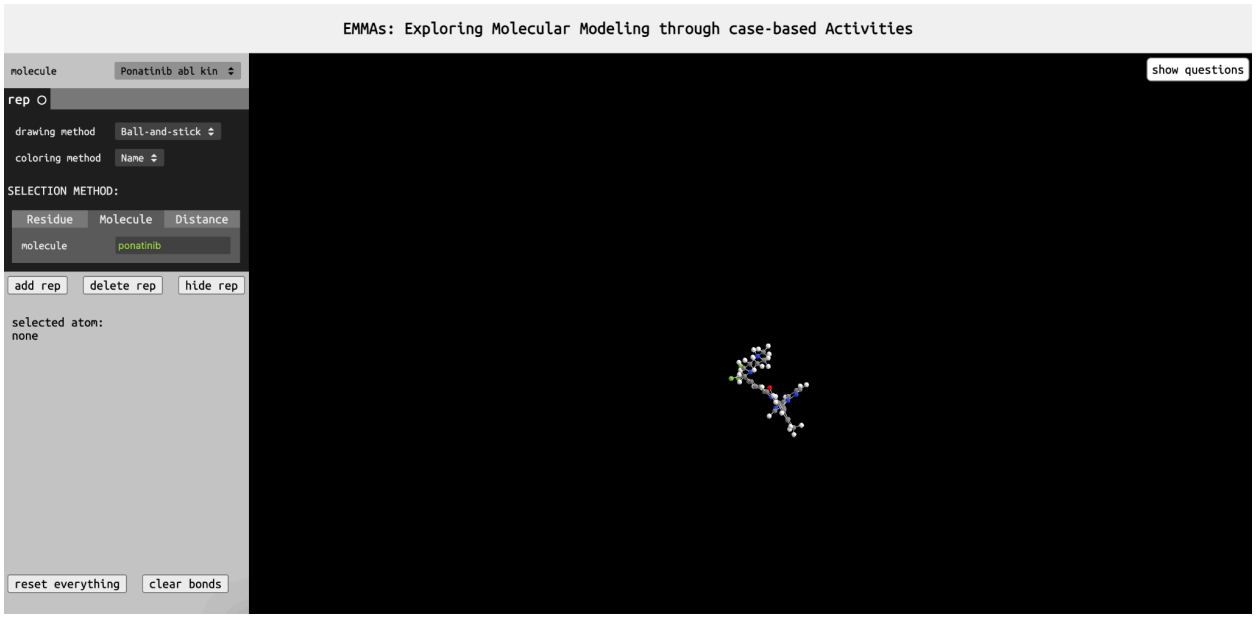

Figure 16. The Ponatinib Abl Kinase PDB file loaded into the web-based interface, with only "ponatinib" selected.

The drug can be set to the drawing method "space filling" to make it distinguishable from other atoms.

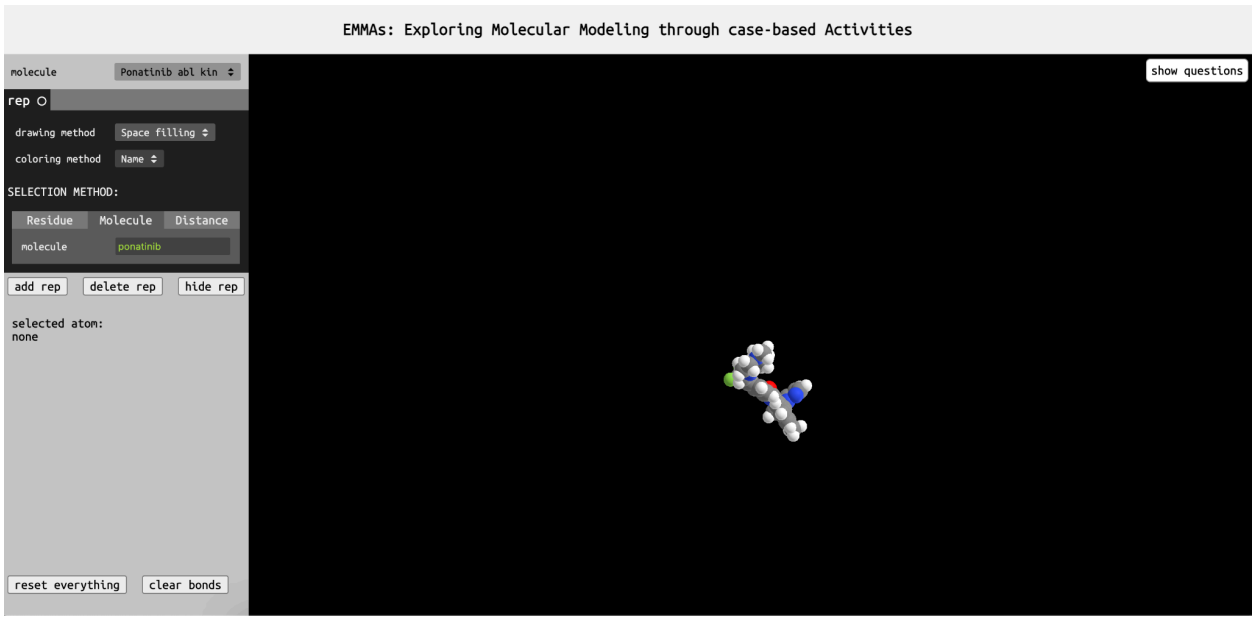

Figure 17. The Ponatinib Abl Kinase PDB file loaded into the web-based interface, with only "ponatinib" selected.

Next, a user can add an additional representation, or copy, of the PDB file to the screen.

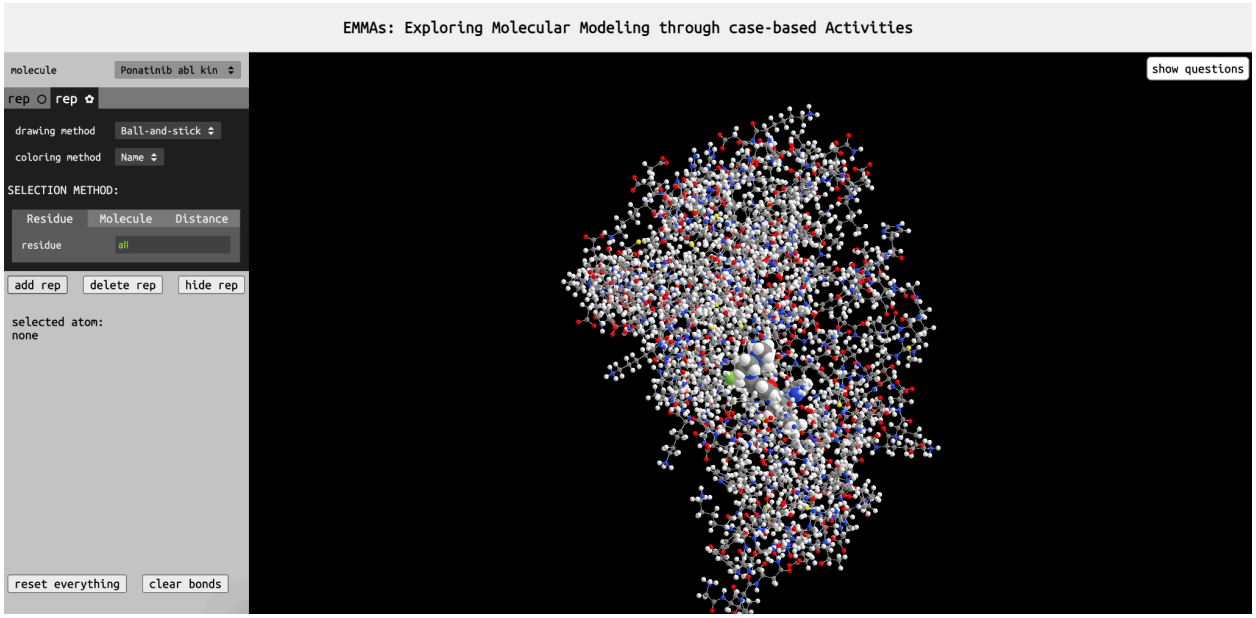

Figure 18. The Ponatinib Abl Kinase PDB file loaded into the web-based interface, with ponatinib selected in one representation and the entire PDB file selected in another.

The new representation on the screen can be changed to use the drawing method “lines” to make the difference between the drug and the protein more obvious.

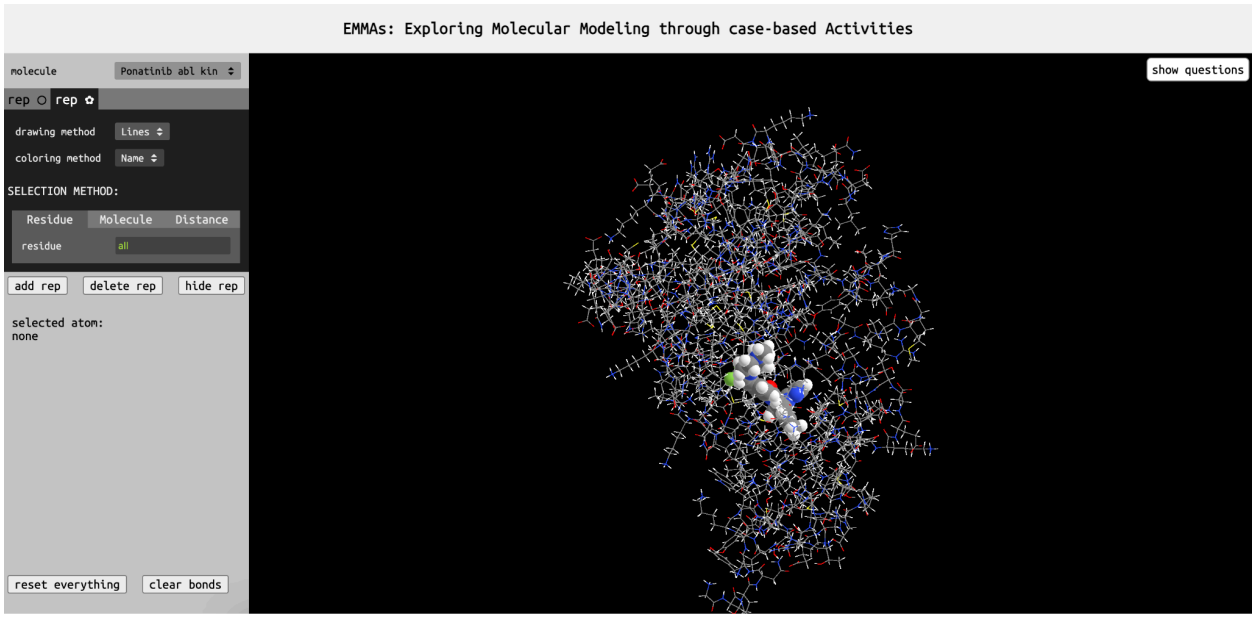

Figure 19. The Ponatinib Abl Kinase PDB file loaded into the web-based interface, with clear differences between the drug and protein.

Now, users can easily distinguish between the drug and protein. They could use the bond distance measurement tool to determine the distances between an atom on the drug and an atom on the protein, which may indicate the existence of a hydrogen bond between the drug and protein (as students are instructed to do at the end of EMMAs Activity 4).

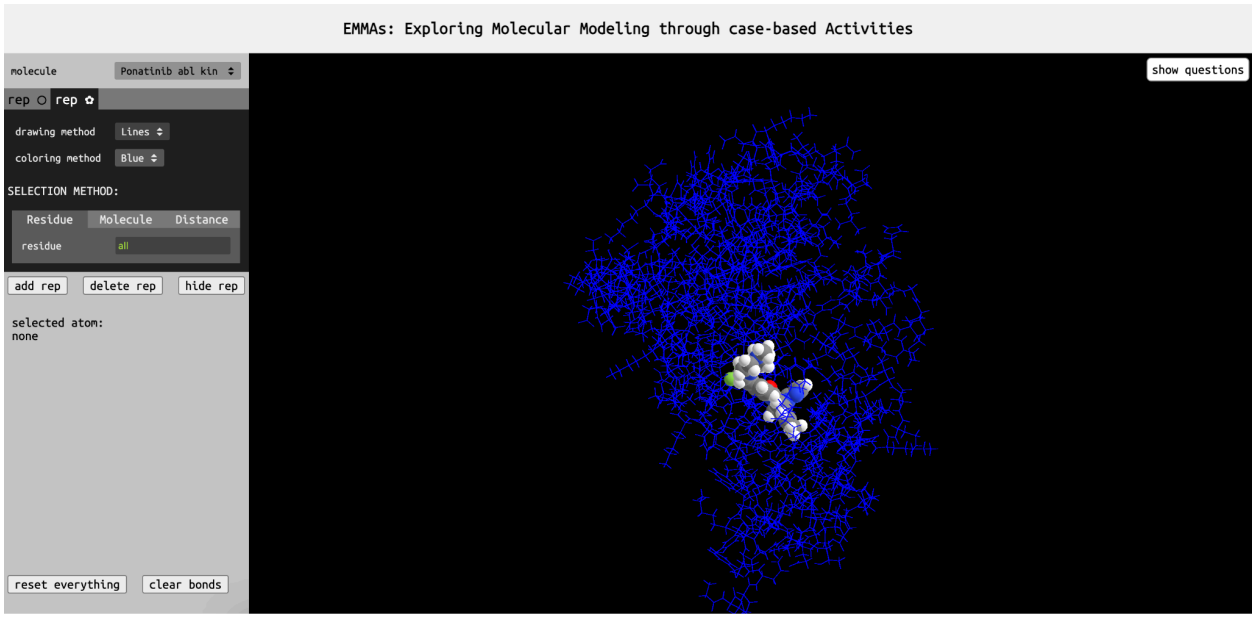

Figure 20. The Ponatinib Abl Kinase PDB file loaded into the web-based interface, with the protein molecule colored blue.

To make the drug and protein molecules even more distinct, users can change the coloring of each group — while this does remove the user's ability to distinguish between individual atom elements, it can increase contrast which is useful in certain visualization situations.

2.2. Differences between VMD and Web-based Interface

The web-based interface was designed to be simpler to use and offer fewer options than VMD as a molecular visualization tool. Nevertheless, we aim to reach similar levels of student understanding and satisfaction despite these differences. Student satisfaction could even potentially increase due to the hypothesized relative ease of using the web-based interface compared to VMD.

First, we decided to significantly decrease the number of options for drawing and coloring methods in the web-based interface due to more limited demands of the EMMAs activities and the typical range of exploration expected of high school students. The activities call for experimentation with a few drawing and color methods, but do not make use of most of the other options.[12] Thus, we decided to include only the most commonly-used drawing and coloring options that will still leave students the ability to make decisions and explore ideas beyond the activities.

We chose to simplify certain features of the interface that were pulled from VMD's functionality. In VMD, users navigate around the molecule using keypresses "S" to zoom in/out, "T" to translate, and "R" to rotate. After each key is pressed, the user drags the mouse to manipulate the molecule. Users can also press "C" and click on an atom to center rotation around that atom. Because these key presses and subsequent mouse drags may not be the most intuitive and easy to learn, we simplified navigation by using mouse clicks and drags for rotation, keyboard arrow keys for translation, and two finger pinching on the mouse pad to zoom in/out, which more closely align with common methods of mouse pad/keyboard navigation. The feature to center rotation around a single atom remains largely unchanged from VMD to the web-based interface — users are still able to press "C", click an atom, and center rotation around that atom.

VMD also allows users to select portions of the molecule based on a wide variety of criteria. This type of selection requires the user to enter specified syntax into a text box, which can sometimes be difficult to learn and requires greater attention to detail. In the EMMAs, the most commonly-used selection methods include selecting by residue number, chain ID, and distance from other residues. To make these selection methods more learnable for students, the web-based interface provides additional scaffolding by using drop-down menus and labeled text

boxes. We also referred to selection by chain as selection by molecule instead, as students may not be as familiar with the term "chain."

While VMD has the capability for users to create unlimited representations from a single molecule, the pilot web-based interface only allowed users to create up to four representations. The activities only ever require students to create up to two representations,[12] and having the ability to create up to four would allow students to extend their exploration beyond the scope of the activities while keeping the loading time of the larger molecules relatively short.

In the original EMMAs using VMD, students explored various useful drawing methods, including CPK (ball-and-stick), VDW (space filling, based on the radii of elements), lines, licorice (thicker, rounder lines), and ribbons (a simplified structure based on the secondary structure of protein[31]).[12] In the web-based interface, CPK, VDW, and lines were implemented for students to experiment with. Licorice was not implemented due to its similarity to lines, and ribbons was not implemented because its implementation would likely have required significant additional work.[40] However, in a future version of the web-based interface, it might be useful to have the option for the ribbon drawing method to visualize proteins and larger structures.

VMD has the ability to read in Molecular Dynamics (MD) trajectory files, which allow users to view a simulation, or "movie," of a system moving over time. This feature is used in Activity 7 of the EMMAs, where students are asked to manipulate MD simulations and learn various methods of analysis, including creating distance vs. time plots and identifying hydrogen bonds. However, due to time constraints and the fact that Activity 7 was not tested in the original EMMAs study, these features were not implemented in the pilot version of the web-based interface.

Below is a table of the VMD features used in the EMMAs activities, and whether or not they are carried over to the web-based interface.

Table 2. Molecular Visualization Software Features used in the EMMAs Activities with corresponding features in VMD and the Web-Based Interface (version 1, prior to focus group feedback)

Feature used in EMMAs	**VMD**	**Web-based interface**
Load in any PDB file	Load in PDB file from computer files	Choose from pre-loaded list of PDB files specific to the EMMAs
Movement	"T", "S", and "R" keypresses to translate, scale, and rotate the molecule "C" keypress to center around a specific atom	Mouse click and drag to rotate the molecule Arrow keypresses to translate the molecule Two-finger pinch to scale the molecule "C" keypress to center around a specific atom
Reset molecule view	"=" key press	"=" key press Reset button
Camera	Perspective & Orthographic	Orthographic
Axes	Ability to manipulate x-y-z axes	No ability to manipulate x-y-z axes
Drawing methods	29 different drawing methods	3 drawing methods
Coloring methods	22 different coloring methods	4 different coloring methods (3 solid colors and 1 coloring method by atomic element)
Distance between atoms	"2" key press, followed by clicking on two or more atoms	(Same as VMD)
Selecting Atoms	Text box for atom selection, can select by: ● Residue	Drop-down menus and tabs for atom selection, can select by:

	• Chain • Atom • Backbone • Distance • …	• Residue • Chain • Distance
Creating Multiple Representations	Can create unlimited representations	Can create up to 4 representations
Viewing MD trajectories	Yes	No

2.3. Three.js' PDB loader

JavaScript's *three.js* library offers a relatively comprehensive feature for loading in PDB files for visualization. However, in order to successfully load in the PDB files necessary for the EMMAs activities, several modifications to the original PDBloader.js file were needed, which are described in the Appendix.

2.4. Loading Time Considerations

When a molecule is initially loaded into the website, several processes have to complete before the molecule renders on the screen. First, the PDB loader parses the PDB file and creates objects with atom and bond data that are processed through the website's main Javascript code. This code then creates *three.js* geometry objects of every atom and bond in the loaded molecule, which are then added to the scene and rendered. The web-based interface also has the ability to render a molecule in different drawing styles, which require different geometries (e.g., spheres for atoms in the ball-and-stick drawing method versus rectangles for atoms in the lines drawing method). Thus, each drawing method must have a different set of atom and bond geometries created, and because the web-based interface offers three different drawing styles, there must be three sets of atoms and bonds total.

All the necessary atom and bond geometries for each representation are created when the user first loads in the molecule instead of creating the necessary geometries when a user requests a new representation or drawing method. This decision was made because we believed that it was more important to have a faster loading time when users are manipulating atoms and bonds versus when users are loading in the PDB file for the first time.

In order to track separate representations within a single PDB file, we implemented independent copies of atoms and bonds for each representation where each separate copy would be toggled on and off or changed depending on the user's selection choices. However, this method limited the number of representations a user could make, because each new representation would create another copy of atoms and bonds which would be computationally expensive. Thus, as mentioned above, we decided to allow users to create up to four representations, which means that loading in any given molecule needs twelve sets of atoms and bonds (four representations multiplied by three drawing methods). Even with the limit of four representations, loading time and rotation time was relatively slow, especially on the tester Chromebook. Loading times are available in Table 6 of section 5.1. For reference, the drug-protein PDB file (containing Abl kinase, ponatinib, and some water molecules) has around 4600 atoms while the ponatinib PDB file contains 67 atoms.

2.5. Rotation Performance Considerations

In an early iteration of the web-based interface, rotation of the molecules in the larger PDB files used in the EMMAs (Abl kinase and ponatinib & Abl kinase) was very slow compared to rotation of the smaller molecules. To quantify the performance and determine the frames per second (FPS) rate, the scene was rotated automatically when animating the scene. On a

MacBook, the FPS for Abl kinase and ponatinib was approximately one sixth compared to ponatinib alone. Rotation was even slower on a tester chromebook.

Several options for optimizing performance were explored, including using *three.js*'s instancedMesh. Instead of creating new geometries for each atom and bond individually, instancedMesh can be used to reduce the number of draw calls and improve overall performance.[41] A simplified version of the website was created to test instancedMesh versus naive geometries, and two copies of atoms and bonds in the ball-and-stick drawing method were rendered in this version to simulate the number of complex geometries (e.g. icosahedrons with many vertices) there will be in the final version of the interface. The open-source Javascript package, *stat.js*,[42] was used to provide FPS data in the simplified version of the website, which are below. However, we decided not to implement instancedMesh geometries due to time constraints. Before conducting formal testing in Wellesley High School, I plan to implement instancedMesh geometries to improve performance.

Table 3. Rotation Performance of Web-based Interface on Different Computers

	Rotation in Frames per Second (FPS)			
Computer	**Ponatinib** (naive)	**Ponatinib** (instanced)	**Abl kinase & Ponatinib** (naive)	**Abl kinase & Ponatinib** (instanced)
Macbook Pro M1 2020 Memory: 16 GB	60	60	11	60
Chromebook Lenovo 14e	60	60	2	20

2.6. Activity Modifications

The original EMMAs implemented via VMD used Google Documents to guide students through each activity and provide a place for students to submit answers to their teachers. While students will continue to submit answers to questions using Google Documents in the modified EMMAs, questions from the activities will also be shown on the screen for users who don't have access to the EMMAs themselves to follow along. We decided to keep the system of Google Document submission due to the fact that both students and teachers are usually familiar with Google Workspace tools (a majority of K-12 classrooms use Google Workspace)[31], and the method of Google Document submission worked well in previous implementations of the EMMAs activities.[5] We briefly considered completely integrating the submission method with the web-based interface, but ultimately decided that there would be significant overhead related to coding various aspects of a submission tool, including: creating, managing, and verifying accounts for each student, storing student responses, submitting work to teachers for grading, etc.

The web-based implementation of the activities also called for a few small modifications of the original activities, including changing some of the instructions based on the feature changes from VMD to web-based interface (e.g. using arrow key presses to translate the molecule rather than the "T" keypress followed by a mouse drag).

3. Evaluation of Web-based Interface with EMMAs

This section will detail the informal and formal studies conducted to receive user feedback on the web-based interface. We will discuss the timeline of studies followed by study methodology and design.

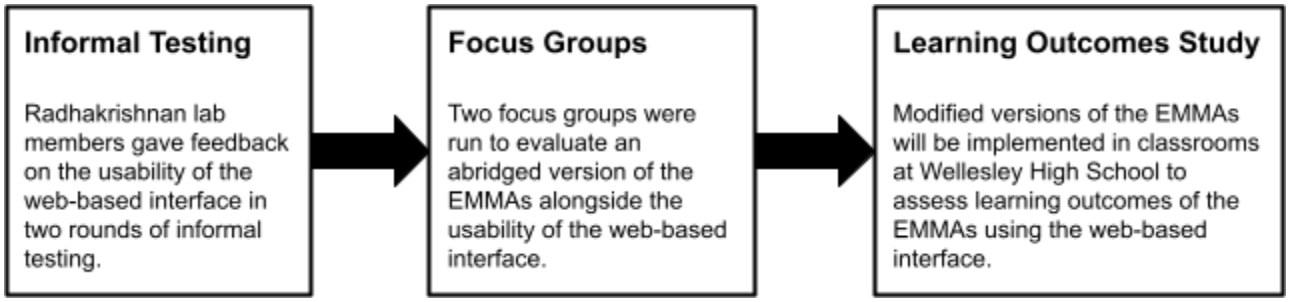

Figure 21. Flowchart of informal and formal testing of the web-based interface.

Informal testing of the web-based interface was first conducted with Radhakrishnan lab members at group meetings. Students were given a link to the web-based interface and asked to explore. After several rounds of pilot testing within the lab, we plan to conduct two more formal studies to evaluate the web-interface's usability and effectiveness as a chemistry education tool. A more detailed discussion of the two formal studies is below.

3.1. Usability Study Design

To gather more formal feedback concerning the usability of the web-based interface, we conducted a study within Wellesley College in the form of focus groups with necessary approvals from the IRB. The study was determined to be exempt, with minimal risks to student participants. The focus group participants were recruited from the Wellesley Computer Science Department, introductory CHEM 105 classes, and friends/acquaintances. Students completed informed consent forms that doubled as an RSVP for the focus group, and each chose a pseudonym to use throughout the study for anonymity. Although 12 students filled out the RSVP form stating their interest to attend, only 4 students participated in the focus groups due to time conflicts. Students had varying chemistry backgrounds — some students had completed high school chemistry and had not taken chemistry in college, while others had taken college-level

chemistry classes. As a result, most of the student participants had more exposure to chemistry compared to the target audience of the EMMAs.

First, students who signed up to participate in the focus group were sent an abridged, combined version of Activities 2 and 4 to complete before attending the focus group. Activities 2 and 4 were chosen because they collectively involved extensive use of VMD in their original form, so they were combined to efficiently get feedback on as much of the functionality of the web-based tool as possible. Some questions were shortened or taken out to focus more on the functionality of the interface rather than the chemistry content so that the feedback received would focus more on assessing the interface usability instead of evaluating chemistry learning outcomes. Additionally, a few questions were adjusted to fit the simpler functions of the web-based interface. The abridged version of the EMMAs is linked in the Appendix.

After completing the combined activity, students attended one of two focus groups. Focus group questions were split up into those concerning the activities/chemistry content and those concerning the usability of the interface, with more time spent on usability. Questions asked during the focus group are in Table 4. In many cases, follow-up questions that are not specified below were asked to delve deeper into participant responses.

Table 4. Focus group questions, organized by category.

Activities/Chemistry Content	Software Usability
● What was something you learned from the molecular modeling activities? ● Did anything about the activities surprise you? If so, how?	● What features of the software made navigation easy? ● What elements of the user interface were confusing to navigate?

• What did you enjoy about doing the molecular modeling activities? • What did you find difficult about doing the molecular modeling activities? • Which activity was your favorite, and why?	• Were there any surprises you experienced while using the software, or any features of the software that didn't work as expected? • Did the software run at an acceptable speed or was it laggy? • How easy was it to manipulate the molecule using the keyboard and mouse? Were there any specific controls/gestures that felt intuitive or difficult to use? • What changes could we make to the computer software to make it easier for students to use our molecular modeling activities?

The focus groups were audio-recorded to eliminate the need for note-taking during the discussion and later transcribed to extract feedback. Inductive coding — a common method of focus group analysis in the field of HCI — was used to analyze focus group results and identify common themes throughout student responses. Inductive coding involves a "bottom-up" approach in which researchers go through the coding process without pre-identified themes, and instead come up with themes as they read through the data.[43] First, the transcripts were read through several times to familiarize the researcher with the data. Each time, words or phrases in the text that were identified as belonging to potential themes were highlighted. A list of common themes was then compiled and consolidated with further analysis. After defining a list of themes, student quotes were then collected to illustrate each theme. Some quotes were modified by removing filler words and occasionally supplying contextual information in brackets to improve readability.

3.2. Learning Outcomes Study Design

After the thesis deadline, we plan to repeat the study done by Kotsalidis *et al.* that evaluated the original EMMAs and had been conducted with students at Lincoln Sudbury High School in Massachusetts. Our goal is to assess learning outcomes of the EMMAs when using the web-based interface instead of VMD as well as the usability of the interface. Our study will be conducted with students at Wellesley High School (a different high school was chosen due to logistical reasons).

Generally, this study will be conducted similarly to the original EMMAs study. A few questions from the original EMMAs activities will be adjusted to fit the simpler functions of the web-based interface. Similar pre- and post-survey questions used in the previous study will be used in this study to evaluate student learning outcomes from the activities, but one question assessing interface usability and accessibility will be added to the post-survey questionnaire. Results from Likert response-type questions will be analyzed using Wilcoxon signed rank tests while results from free response questions will be analyzed using a constant comparative method. We have already obtained the necessary Human Subjects Research approvals for this study from the Institutional Review Board (IRB).[5] However, because of the timing of the thesis deadline and the Wellesley High School academic year, we aim to conduct this study after the thesis deadline, so results from this study and more detailed methodology will not be included in this thesis.

Although we will not be able to compare the learning outcomes of this study directly with the learning outcomes of the previous study due to various uncontrollable variables, we hope to draw some tentative conclusions about the effectiveness of the web-based interface versus VMD.

Generally, we hope to observe similar rates of student satisfaction and improved learning outcomes from the pre- to post-survey questions.

4. Beta-Testing Results

Beta-testing the web-based interface through pilot testing and focus groups provided valuable feedback on the usability of the interface. This section will describe the feedback given by participants during these testing sessions, including specific features to implement, design improvements, and intuitive or unintuitive features of the interface.

4.1. Pilot Testing Results

Informal pilot testing of the web-based interface with Radhakrishnan lab members was conducted twice during the development of the interface. In both pilot testing rounds, lab members were given a link to the interface and asked to explore the interface's various features — without an abridged version of the EMMAs because most lab members have already had experience with some of the activities as well as various molecular modeling software programs. Thus, it was assumed that most lab members knew about common features and functionalities of similar interfaces.

The first round of pilot testing provided valuable feedback on bugs of the interface, design choices (such as font size), and suggestions for additional features. One major bug that was discovered occurred when multiple representations were added — some drawing methods (such as ball-and-stick and lines) would overlap and appear incorrectly. This bug would appear only after at least one iteration of deleting and adding another representation, and was quickly addressed after pilot testing. Users also noticed that clicking on atoms was not always reliable —

at certain angles, some atoms did not respond to mouse clicks. This issue caused problems when users tried to measure the distance between two atoms, for example.

Users also made suggestions for improving usability and accessibility of the interface, including limiting the extent to which a user can zoom in and out of the molecular visualization window and making font sizes of buttons and labels in the GUI larger with higher contrast. Suggestions were also made for additional features, many based on VMD's existing functionality. Additional features that were suggested included allowing users to click on atoms a second time to erase bond measurements, implementing the "C" keypress to allow rotation around a specific atom ("centering" the rotation), and implementing the "T" keypress to allow translation. These features were implemented soon after pilot testing concluded, with some adjustments.

In the second pilot testing round, lab members were given an updated version of the interface to explore. In this round, mouse clicking on atoms remained an issue, but all other bugs were eliminated and many of the new features added worked without bugs.

4.2. Focus Group Results

Transcripts from both focus groups were analyzed using inductive coding for common codes, or main ideas expressed by students. Codes were then sorted into three main categories, listed below. In the following few subsections, codes are expanded upon and illustrated with select quotes pulled from the transcripts.

Table 5. Summary of the EMMAs Activities and their Descriptions.

Categories of Codes			
Ease of use (positive)	**Ease of use (negative)**	**Suggestions for Improvement**	**Chemistry Content**
● Easier to use than existing molecular visualization software programs ● Intuitive to use ● No obvious bugs	● Unintuitive keyboard presses ● Slow performance ● Bugs	● Include dropdown menus for selection tools ● Include help menu ● Molecule could be simpler for an introductory chemistry activity	● Difficulty understanding activities

4.2.1. Ease of Use (Positive)

Students who had previous experience with various molecular visualization software programs said that the web-based interface was easier to learn and use compared to others, such as Pymol, Chimera, and VMD. Representative participant quotes included:

> "I think it's a lot…easier to use than Pymol."

> "I think it was pretty similar to the software that we used in Biochem [Chimera]. It was a very good accessible version of that."

Some students found the software to be intuitive, as exemplified by the following quote:

> "I think [the buttons] were pretty intuitive."

Even though most students agreed that the interface was easy to use, some students expressed confusion about the purpose of certain features. When prompted specifically about the feature to add/delete/hide tabs, one student said that the feature itself worked well, but also asked about the purpose of such a feature. Once the purpose of the feature was explained and demonstrated, the student said the feature made more sense.

After asking about the intuitiveness of the interface in general, more specific questions were asked about the usability of certain features. Because many students mentioned skimming parts of the abridged EMMAs activity, none of the students had attempted to use the centering feature where the key "C" is pressed to center rotation around a specific atom. Thus, students were prompted to try the centering feature during the focus group, after which students were able to use the feature with little difficulty.

4.2.2. Ease of Use (Negative)

Students had mixed feelings about the speed of the interface, both in relation to the manipulation and loading time of larger molecules. However, in most cases, students noticed the decrease in performance when rendering larger molecules regardless. In response to question 4 concerning performance of the web-interface, one student said:

> "[The lag] was noticeable, but it wasn't too bad"

However, another student said:

> "…as someone with a very short attention span, I think there were times I thought it was broken when it was just loading."

Thus, all students noticed the lag in performance when rendering larger molecules, but one didn't mind the lag while others thought the lag was disruptive.

4.2.3. Suggestions for Improvement

Students also made suggestions for improving the web-based interface itself. One student, prompted by the discussion about the performance of the molecular interface, made the suggestion that perhaps the speed of rotation could be improved if the activities used a simpler molecule:

> "I'm not sure if it's necessary for introductory courses to experience this complex of a molecule."

It was mentioned multiple times that a help menu with additional information about keyboard presses and atom colors would be very helpful, especially for future users who do not follow along with the activities on a separate Google document. Additionally, students suggested having a drop-down menu for molecule selection rather than needing to type in "ponatinib" or "abl kinase" to select each respective molecule. One student discovered a minor bug with the distance selection method. Someone else expressed difficulty splitting their laptop screen between the interface and the activities. They mentioned that they needed to zoom out in the interface window to see the molecule, which resulted in the menu shrinking to a near-illegible size.

Another student mentioned that pressing the key "2" to turn on the bond measurement tool seemed unintuitive. They suggested using some sort of button on the interface to toggle the bond measurement tool on and off instead. Additionally, someone suggested including additional

default information about bond angles, bond connectivity, and potentially other relevant information within the displayed molecule(s) or selections therein — comparing this interface to other common molecular visualization software they had used before:

> "I know other software kind of gives you one atom and maybe a bond, or bond angle, stuff like that."

One student also mentioned difficulties they encountered with the activities themselves. They expressed difficulty mapping the 3D representation of the molecule on the interface to the correct 2D representation in the activities, saying:

> "When I was on section 3 — amino acid residue selections — I couldn't identify the amino acid [on] the reference sheet, I couldn't match it to [the interface]."

Overall, students said that the interface was easy to use and fairly intuitive. However, common feedback included implementing helpful features and improving the lag of rotation.

4.2.4. Chemistry Content

Generally, when asked if they had learned anything from the abridged activity, students expressed that they did not gain new knowledge through completing the activity. Three students already had extensive chemistry knowledge of the topics being taught — they had taken at least one introductory chemistry or biochemistry class in college, and most had taken additional chemistry classes beyond that.

One student mentioned that they had trouble learning through activities and therefore did not gain new knowledge from the experience, saying:

> "I generally have a difficult time learning through activities, so I can't say I learned anything, but I also think this is a reflection of me in chemistry in which I was not the strongest student."

Additionally, some students did not fully complete the activity and instead skimmed through the chemistry content, focusing more on exploring the various features of the interactive interface.

5. Discussion and Future Work

The results of the focus groups provided valuable insight into the usability of the web-based interface. However, because the focus groups only had 4 participants in total, feedback was limited in scope and depth. First, most students had taken chemistry courses after high school, so focus group participants generally had more knowledge than the target audience for the EMMAs. Additionally, some students had prior experience with different molecular visualization software, and many only skimmed the chemistry content of the activities. Indeed, half of the students recruited for this study were recruited from the Chemistry department, mainly due to convenience and closeness to the study — it is likely that this project was more interesting to students taking chemistry courses, and their familiarity with the chemistry concepts taught may have made them more willing to engage with content and activities. Although recruitment materials were sent to the Computer Science department, only one student from that department signed up to participate in this study, and that student happened to have taken a biochemistry course at Wellesley to fulfill a distribution requirement. In future studies of this nature, it may be helpful to recruit students from a larger group and begin the recruitment process earlier. While some professors in the Chemistry Department publicized the study in relevant

classes, this form of recruitment may have been more effective had it occurred for a longer period of time.

Another option to increase the quality and quantity of student participation in a future study would be to integrate the activity into a chemistry course at the college through direct partnership with a professor. This method would make it more likely that students make the time to complete the activity (abridged or not) in its entirety, and would automatically result in more student participation.

Overall, students who had previous experience with molecular visualization software found the web-based interface to be easier to use than others, including VMD. This feedback suggests that using the web-based interface to host the EMMAs may lower the learning curve students experience while learning how to use the interface — one of the main goals of this thesis. However, previous experience with similar molecular visualization software programs may have skewed some students' perceptions of the relative difficulty of using the software. Students who had not previously used molecular visualization software programs may still find the web-based interface difficult to use, although hopefully less so compared to a program like VMD.

Based on student responses to the first set of questions concerning the chemistry content of the activities, students did not express significant gains in the activity's intended learning outcomes. However, this could have been due to several factors. First, most students had previously taken college-level chemistry or biochemistry classes, and thus did not encounter any new information while completing the activities — which were designed for introductory high school chemistry students. Second, some students reported skimming the activities instead of answering the questions thoroughly. Third, using the abridged version of the EMMAs may have

impacted student learning because the abridged version excluded some chemistry information and repetitive questions that may have reinforced certain concepts. Furthermore, students were instructed to spend around one hour outside the focus groups completing the abridged EMMAs. The instructed amount of time may not have been enough time for students to process and understand the chemistry content fully, and students may or may not have actually spent one hour to complete the activity. However, results concerning the learning outcomes of the EMMAs are not as important as results concerning the usability of the interface since the primary goal of running the focus groups was to receive feedback about usability. Moreover, as mentioned previously, learning gains were evident when the EMMAs were formally assessed in a more controlled environment with actual high school students.[12]

It is also important to note that the abridged version of the EMMAs was designed specifically for the focus groups, and students who actually complete these activities in the classroom will use the full, unabridged activities. Students who complete the full version of the activities will likely engage with the chemistry content more thoroughly, over a longer period of time, and with additional scaffolding, which may mitigate these issues observed during the focus groups. Specifically, students who complete these activities in a high school chemistry class will be doing so in a classroom with teacher assistance. They will also have had prior instruction on noncovalent interactions and other chemistry topics which are covered in the EMMAs. The student who expressed difficulty with some of the chemistry concepts in the EMMAs had not taken chemistry in many years, so the skills they struggled with may not have been as difficult had they taken introductory high school chemistry more recently.

While students generally found the interface to be fairly intuitive, several suggestions for improving the learnability and user experience of the interface were made. These suggestions

were taken into consideration, and some of them were implemented after the focus groups while others are included in the Future Work portion of this section.

Nielsen's ten heuristic evaluation principles for interface design[44] are a useful framework with which to analyze focus group feedback relating to interface usability. The first principle, visibility of system status, states that the interface ought to keep the user informed about the status of the system within a reasonable amount of time. This principle is relevant when discussing performance of the interface. Many students noticed lag when rotating and loading in larger molecules, and some students felt that the lag was manageable while others found that the lag inhibited their experience. One student even interpreted lag as a software malfunction — it was then mentioned that a loading pop-up window with a clarifying message might help clarify that the software is loading and not malfunctioning, thus keeping the user aware of the system status. Increasing the user's awareness of the system status may also improve the predictability of the interface. In addition to adding a pop-up message to indicate that the system is processing rather than malfunctioning, further steps should be made to improve performance. After the focus groups, several options for improving performance were explored, including using instancedMesh geometries, Sprite objects, and adjusting the algorithm for loading molecules from PDB files.

One student also reported difficulty identifying the 2D molecular drawing from the 3D representation of a residue. This result suggests that additional examples or more scaffolding may be helpful to bridge the gap between 3D models of molecules and traditional, 2D representations — a skill that is often difficult to develop for students learning chemistry.[15] Neilsen's second principle, matching between system and the real world, can also help inform ways to address this piece of feedback. Using more commonly-used atom colors in molecules

rendered by the interface, for example, may help users recognize molecules more easily, thus shrinking the gap between 2D and 3D models.

Study participants also recommended including a help menu or additional documentation to provide users easy access to commonly-used keypress commands and controls. This feedback aligns with the tenth heuristic principle — help and documentation — which recommends that an interface provide clear, concrete instructions for users to complete tasks if necessary. Some students suggested replacing text boxes where a user would have to input text such as "ponatinib" or "abl kinase" with drop-down menus. Nielsen's fifth principle concerning error prevention suggests that an interface eliminates as many potential user errors as possible. Replacing text boxes with drop-down menus would prevent users from making typos. This adjustment would also minimize the number of things a user needs to memorize — an issue addressed by the sixth principle, which encourages interface designs to minimize a user's memory load by making options and actions clearly visible. However, it is important to note that implementing a drop-down menu would also limit flexibility of exploration — if, for example, a student wanted to explore beyond the molecules included in the activity. An alternative option to drop-down menus could be to implement auto completion of allowed input text, so that users could see possible inputs while still being able to type other text when exploring.

Overall, results from the focus group provided potential areas of improvement, particularly surrounding software performance and interface design. Many of the suggestions to improve user interface design were incorporated into the second iteration of the interface and are detailed below.

5.1. Interface Changes based on Focus Group Feedback

Several features of the interface were changed based on student feedback from the focus groups. First, the keypress “2” to turn on the bond distance measurement tool was changed to a keypress of “D” for distance, which is more intuitive since recalling “D” for distance is likely easier for users than the keypress “2”. Additionally, a loading screen was implemented during longer processes to inform the user of the interface status.

Furthermore, the way in which different representations of a single PDB file are tracked in the interface was changed due to performance issues regarding the rotation and rendering times of larger molecules. The initial implementation involved creating separate copies of atoms and bonds for each representation, but was very computationally expensive and did not allow for more than a few representations. In response to feedback on slow rotation and loading times, we explored a second implementation strategy to increase performance efficiency. The second method we used creates one copy of every atom and bond for each drawing method, but uses only one set of atoms and bonds to represent multiple copies of the PDB file. Instead of naively changing only the atoms and bonds belonging to the user’s currently-selected representation (like in the first method), the second method parses all of the user’s current selections across every representation and marks the appropriate objects visible or invisible. Thus, this method allows for users to create infinite representations without compromising on loading or rotation performance. The following table compares the loading time of large PDB files using the first and second methods. Ten trials were conducted for each method and corresponding averages and standard deviations were calculated.

Table 6. Loading Performance of Web-based Interface using Different Representation Tracking Methods.

	Loading Time of Drug-Protein PDB file (seconds)	
Computer	**First Method**	**Second Method**
Macbook Pro M1 2020 Memory: 16 GB	3.1 ± 0.1	2.3 ± 0.1
Chromebook Lenovo 14e	23 ± 6	11 ± 1

Table 7 is an updated version of Table 2, which again describes differences in features between VMD and the web-based interface, but with text in bold to point out changes to the interface made after incorporating focus group feedback.

Table 7. Molecular Visualization Software Features used in the EMMAs Activities with corresponding features in VMD and the Web-Based Interface (version 2, after focus group feedback)

Feature used in EMMAs	**VMD**	**Web-based interface**
Load in any PDB file	Load in PDB file from computer files	Choose from pre-loaded list of PDB files specific to the EMMAs
Movement	"T", "S", and "R" keypresses to translate, scale, and rotate the molecule "C" keypress to center around a specific atom	Mouse click and drag to rotate the molecule Arrow keypresses to translate the molecule Two-finger pinch to scale the molecule "C" keypress to center around a specific atom
Reset molecule view	"=" key press	"=" key press Reset button
Camera	Perspective & orthographic	Orthographic
Axes	Ability to change/remove	No ability to manipulate x-y-z

	x-y-z axes	axes
Drawing methods	29 different drawing methods	3 drawing methods
Coloring methods	22 different coloring methods	4 different coloring methods (3 solid colors and 1 coloring method by atomic element)
Distance between atoms	"2" key press, followed by clicking on two or more atoms	**"D" key press, followed by clicking on two or more atoms**
Selecting Atoms	Text box for atom selection, can select by: ● Residue ● Chain ● Atom ● Backbone ● Distance ● …	Drop-down menus and tabs for atom selection, can select by: ● Residue ● Chain ● Distance
Creating Multiple Representations	Can create unlimited representations	**Can create unlimited representations**

5.2. Features to be Implemented

Before formally testing the EMMAs using the web-based interface with students at Wellesley High School, I plan to implement as many of the following features as possible, with the others considered thereafter. Some of these features were suggestions from focus group feedback, while others were brainstormed earlier but postponed due to time constraints.

- **Usability improvements**
    - Help menu — to provide users with a list of commonly-used commands for easy reference, especially for users who are not following along with the EMMAs.
    - Drop-down menu for selecting by molecule — to make the process of selecting by molecule easier and less error-prone. Users will be able to choose from a menu

of “ponatinib” and “abl kinase” instead of typing in the molecule names, for example.

    - InstancedMesh geometries — to speed up performance for loading and rotating larger molecules.
    - Atom color adjustments — changing the colors of atoms in the web-based interface to match those used in the EMMAs activities, to improve consistency.

- **New features**
    - PDB loader — to provide users with the option to load in any PDB file.
    - Perspective camera — to provide users with an alternative to using the orthographic camera option.
    - Manual vs. Automatic bond loading — to provide users with the option to manually calculate bonds or use the bonds provided in the PDB file.
    - Ribbons Drawing Method — to allow users to visualize the secondary structure of proteins.
    - Single, double, and triple bond representations — to distinguish between different types of bonding.
    - MD trajectory viewing — to allow users to load in MD trajectories to create movies of systems moving over time.
    - Analysis tools — e.g., distance vs. time plots and an automatic hydrogen bond-finder, to allow users to analyze MD trajectories.

One feature that VMD lacks is the ability to visually differentiate between single, double, and triple bonds. In every drawing method, all bonds — regardless of type — appear the same.[45] However, being able to distinguish between single, double, and triple bonds is important because

they differ in both length and strength, which impact molecular structure and chemical behavior.[46] In a future iteration of the web-based interface, single, double, and triple bonds could be represented differently. The "bond finder" would be used to identify the differences based on their length. Typically, triple bonds are the strongest, followed by double bonds, and then single bonds. As bond strength increases, bond length decreases, so a triple bond between two atoms would be shorter than a single bond between the same two atoms. These bond length differences can be used to differentiate between the different types of bonds, but the handling of special situations such as resonance (which can be interpreted as "fractional" bonds) will need to be determined.

By implementing these features, the interface will be easier to learn and users will have additional freedom to change viewing settings or load in a different PDB file of their choice.

5.3. Current Limitations and Known Bugs

There are currently some limitations to the web-based interface that I will describe in this section. First, rotation and rendering performance on a Chromebook remain noticeably slow despite optimization, so other options (such as instancedMesh geometries) should be explored to increase performance. Second, issues with implementing Raycaster (a class within *three.js* that helps determine what objects a mouse click intersects with in 3D space) causes the user to be unable to click on atoms at certain distances from the camera. Fixing this issue will allow users to use the bond distance measurement tool and atom selector more reliably.

Additionally, some of the buttons and GUI shrink strangely when the interface window is compressed or expanded. Further HTML/CSS coding is required to make the interface more responsive to changes in window size. There are also several bugs and improvements that could be made when a user enters a value into a text box. First, error messages that are displayed when

a user enters an invalid selection value are not the most descriptive and do not always appear and disappear appropriately. Clearer and more consistent error messages would help users troubleshoot issues more quickly, increasing the usability of the interface. Second, since some key presses (such as “D” and “C”) are used to turn on and off certain mouse modes, these modes could be activated or deactivated unintentionally if a user enters text into a text box.

5.4. Future Testing

As mentioned in an earlier section, a formal study will be conducted with students at Wellesley High School to test the full EMMAs with the web-based interface. The goals of this study are to evaluate the learning outcomes of the EMMAs using the web-based interface and potentially draw an approximate comparison to the learning outcomes in the original EMMAs paper.

After running the initial focus groups, it was proposed that conducting contextual inquiry could be useful for gathering additional student feedback on the web-based interface. Contextual inquiry is a common type of study in the field of Human-Computer Interaction (HCI) that involves the detailed observation of a small sample of participants interacting with a user interface. This detailed observation is often conducted in context — that is, in the context of where a user would normally interact with the user interface. Users are asked questions throughout the contextual inquiry to gain a better understanding of their motivations and thought processes.[47]

While the focus group questions were useful to get general impressions and feedback concerning the interface, many student responses to the initial questions elicited additional back-and-forth questions between the moderator and study participants. Often, either the moderator or student asked for a demonstration of the interface to highlight specific issues or

clarify functionality. Conducting a contextual inquiry could provide a more structured environment for such demonstrations and promote more detailed feedback. To study the web-interface through a contextual inquiry, participants would be asked to complete a small part of the EMMAs as the researcher observes their interactions with the interface. While the participants move through the activity and interact with the interface, they would narrate their thoughts and actions to provide the researcher with insight into their motivations, confusions, and frustrations. The researcher could then ask participants to expand on certain opinions while the user is interacting with the interface. Generally, researchers could look out for errors (e.g., a student loads in the incorrect molecule for an activity), sources of confusion (e.g., a student is unsure how use the distance selection method to select part of a molecule), and feedback (e.g., a student mentions that a button's color contrast makes it difficult to read the button's text). Contextual inquiries could be recorded both through audio and screen capture to allow for more detailed analysis afterwards.

In conclusion, initial versions of the web-based interface were successfully implemented and preliminary assessment of the interface when applied to the EMMAs was conducted through informal pilot testing and focus groups. The interface implemented most of the features necessary to carry out the EMMAs based on VMD, taking into account usability and design principles. Feedback from pilot testing and focus groups was incorporated to improve usability and learnability, and additional features can be implemented to increase the scope and flexibility of the web-based interface. In the future, formal testing will be conducted at Wellesley High School to evaluate the learning outcomes of the EMMAs using the web-based interface, and

loose comparisons will be drawn between this study and the study conducted by Kotsalidis *et al.* to compare student satisfaction and understanding.

6. Appendix

6.1. Code Details

6.1.1. *three.js* Geometries

The web-based interface used *three.js* to render the three-dimensional atoms and bonds. Atoms were rendered using Icosahedron geometries (which become spherical with certain attributes) and bonds were rendered using Box geometries (the three-dimensional equivalent of a rectangle, in which boxes were elongated and made thinner to resemble lines). For the ball-and-stick drawing method, all atoms were made with the same radius, and for the space filling drawing method, each atom was given a radius based on its element. The lines drawing method only used Box geometries that were colored based on the identities of the atoms on each end.

6.1.2. Modifications to *three.js*'s PDB loader

Some of the code for parsing lines from each PDB file had indices that were misaligned from the columns in the PDB file for Abl kinase, and the standard PDB file format. For example, according to standard PDB file requirements, the third column containing atom identity information should stretch from index 12 to 15, inclusive (with 0-indexing), and requires that "Atom nomenclature begins with atom type."[48] However, the PDB loader provided by *three.js* parses index 12 to 14, exclusive, and does not do any further processing, which does not successfully extract atom type in some cases. Successful extraction of atom type would include

correcting the parsed indices and extracting the zeroth element of the parsed string, which is the modification made for the version of PDBloader.js used for the web-based interface. However, further modifications may be needed to allow the interface to load in any PDB file.

Additionally, *three.js'* PDB loader relies fully on the CONECT field of PDB files to load in bonds. CONECT fields can be used to indicate the existence of a bond between any pair of numbered atoms. However, many PDB files do not have CONECT fields, relying on a molecular visualization software's ability to determine the existence of bonds based on the identities of atoms and the distance between them. In VMD, bonds are found manually through a distance search and CONECT fields are ignored.[26] The abl kinase PDB file — which is used in the EMMAs activities — does not have any CONECT fields, which means that the web-based interface must be able to manually load in bonds. Each atom is compared to every other atom, and based on standard diatomic bond lengths,[49] it is determined if a bond exists. A variance value of 0.07 angstroms was determined through trial and error. However, in case a user wanted to use the CONECT field to load in bonds rather than manually load in bonds, that option can be made available in an "advanced settings" menu in the future.

Additional attributes were added to the atom and bond objects that PDBloader.js outputs, including residue number and chain, so that users can select atoms based on various identifiers. Formerly, the only information passed from the PDB file into the web-interface through the loader had included atom element, coordinate information, and color.

6.1.3. Camera and Controls

Perspective projection makes closer objects larger and further objects smaller while orthographic projection maintains object size despite distance from the camera. Perspective cameras are useful for realistic scenes while orthographic cameras are useful for keeping an

accurate representation of objects. In VMD, a user has the option to choose either camera. The web-based interface currently uses *three.js*'s OrthographicCamera,[50] and a perspective camera using *three.js*'s PerspectiveCamera can be added later to provide additional options to the user.

In *three.js*, the Controls class is used to allow the user to manipulate objects rendered on the screen using keyboard and mouse interactions. Various Camera Controls can be imported as add-ons to allow for user interaction with the scene. Generally, TrackBallControls are paired with PerspectiveCamera while OrbitControls are paired with OrthographicCamera. Before the keypress "C" was implemented to allow users to center rotation around a certain atom, the interface used OrbitControls. However, OrbitControls does not allow a user to change the center of rotation without moving the camera to the new center of rotation. In order to implement this feature, OrbitControls was replaced by CameraControls,[51] an open-source camera control package similar to OrbitControls with additional functionality.

6.2. Web-based Interface Code & Website

Thesis Version Interface	Working Version Interface
Code: https://github.com/maya-mau/molvisweb_thesis_version Website: maya-mau.github.io/molvisweb_thesis_version/	Code: https://github.com/maya-mau/molvisweb Website: maya-mau.github.io/molvisweb

6.3. EMMAs & Abridged EMMAs Links

Original EMMAs:

https://drive.google.com/drive/folders/1byRbWrgp3LuvUcV33CiAdegufWTosKFv?usp=sharing

Abridged EMMAs:

https://docs.google.com/document/d/1wKKsTkDP_oqxcLv5J0mBs62vavNyxFhi/edit?usp=sharing&ouid=112372929973118523497&rtpof=true&sd=true

Thesis Version EMMAs (modified)	Working Version EMMAs (modified)
https://drive.google.com/drive/folders/1fSrARyB99eVj-R7rADMGdC2GjbSzIWR9?usp=sharing 	https://drive.google.com/drive/folders/1TyMhYdRIeawEn1XgHaA3DwX0qAkapj59?usp=drive_link 

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