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# THE TARDIS FRAMEWORK: A VIRTUAL JOURNEY THROUGH SPACE AND TIME

Thesis for the Degree of Doctor of Philosophy in  
Methods and Models for Molecular Sciences

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Academic Year 2020/2021

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# INTRODUCTION

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Human's life on Earth is profoundly anchored to the metric scale, or what we could define the macroscopic world. Indeed, our reality – or at least the only one that we are able to perceive – is composed of physical objects that are at the foundation of our daily interactions. As human beings, we are used to exploit our senses to understand the world around us, and this inner curiosity to discover something new is what has taken us to the present days. A deep thirst for knowledge is what has brought us from looking at the sky with fear and devotion, to be sending landers on Mars searching for signs of life.

In the last centuries, it has become increasingly clear that everything around us could be broken down and inspected at a deeper level, down to the nanoscale and beyond. Nowadays, the microscopic level remains a largely unexplored territory that is ruled by the laws of quantum mechanics: its physical behavior is probabilistic, with pairs of conjugate observables being intrinsically not measurable with arbitrary precision.

In the same way, the manipulation of the time scale is becoming a concrete possibility. Human beings are not – and probably will never be – able to travel to the past nor to the future. However, memories and ancient knowledges belonging to a distant past can be preserved and even experienced nowadays: the evolution in time of events lends itself to being stretched or shrunk to our likings and needs. Our abilities let us explore what *has been* and what *will be*: the reproduction of the creation of a supernova can be shown in a few seconds, while a simulation of the interaction between an anti-tumor drug and a DNA chain can be slowed down from the picosecond to the second.

In this context, virtual reality (VR) technologies play an important role in many research fields, as three-dimensional virtual environments extend users'

perception and increase their ability to tackle massive amounts of data coming from multiple and different sources, such as static and dynamic molecular simulations, or even the possibility of inspecting archeological excavations through hand-free natural interaction. Moreover, the more we explore time and space ranges, the more we need to find a way to create representations understandable on a human scale: we are used to manipulate three-dimensional objects, which is why virtual reality solutions are well suited for this kind of researches.

Restoration processes and preservation of timeless treasures in cultural heritage; creation of new materials in engineering; faster diagnosis, drug formulation and surgical planning in medicine; finding answers about the universe evolution and the origin of life in astronomy and astrobiology: these are only a few possible “macroscopic” scenarios than can be placed at different levels of the time scale and spatial scale, but they all find their answers at the “microscopic” level, studying the same matter we are made of. In these virtual realities, we can become the masters of time and space, bending them to our desire of curiosity.

This contribution represents an attempt at finding a connection between macroscopic and microscopic levels by taking advantage of virtual reality tools for navigating between them. This is the reason behind the chosen name of the framework we propose: *“Time And Relative Dimension In Space”* (TARDIS) is the name of the time machine and spacecraft belonging to Doctor Who – a fictional Time Lord from the Gallifrey planet – and used for travelling in time and space.

Our case studies get inspiration from heterogeneous fields – restoration of cultural goods, biochemistry, and astrochemistry – in order to achieve deeper insights into issues and questions that researchers face every day, by descending to the very essence of the matter itself.

The thesis is organized as follows. Chapter 1 introduces VR and its evolution during the years in the chemistry, biology, cultural heritage and

astrochemistry fields, followed by a survey of the most widespread molecular viewers. Chapter 2 discusses the main components of the TARDIS framework and their implementation. Chapter 3 analyzes some case studies and the interaction details. Chapter 4 discusses some planned developments of the aforementioned framework.

# 1 VIRTUAL REALITY FOR MULTIDISCIPLINARY DATA VISUALIZATION

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*“We are speaking about a technology that uses computerized clothing to synthesize shared reality. It recreates our relationship with the physical world in a new plane, no more, no less. It doesn't affect the subjective world; it doesn't have anything to do directly with what's going on inside your brain. It only has to do with what your sense organs perceive.”*

— Jaron Lanier, pioneer of Virtual Reality [1]

## 1.1 A BRIEF INTRODUCTION TO VIRTUAL REALITY

After more than 30 years from the introduction of the term “virtual reality” (VR) by the visionary Jaron Lanier, it is still possible to find many different definitions. For example, a minimal one proposed by Gigante [2] states that:

*VR is characterized by the illusion of participation in a synthetic environment rather than external observation of such an environment. VR relies on three-dimensional (3D), stereoscopic, head-tracked displays, hand/body tracking and binaural sound.*

*VR is an immersive, multi-sensory experience.*

The first sentence highlights right away the *illusion of participation*, meaning the level of sensation of being inside the virtual environment as if it is the real one.

The most popular definitions of VR, some of which are collected in Ref. [3], tend to focus more on the technological aspects, such as the simulation of the environment, the need for head mounted displays for stereoscopy, sensors for

tracking the user's movements, spatial audio for immersion, wired clothing for haptic feedbacks. It is reasonable to infer that a good VR experience is made of the right combination of these different elements, depending on the result to be achieved.

The synonym "virtual environment" is taking off on "virtual reality" over time, as recreating a faithful virtual representation of the whole reality is not practically doable because of the extreme complexity of the reproduction of all the stimuli that a person can experience in real life. Furthermore, the main aim of the experience is not the reproduction of a perfect copy of reality, but rather, the reproduction of a very specific environment.

Different key elements have been recognized for the creation of a proper VR experience [4]:

- a) *immersion* is the perception of being physically present in a non-physical world, and can be enhanced by good stimuli, such as realistic 3D graphic, spatial audio, haptic feedbacks;
- b) *sense of presence*, also known as "sense of *being there*", is a measure of the involvement of the user, which means to feel as if the mediated experience is actually real;
- c) *interaction* is the ability to exchange data with the system, by sending input (through controllers or the body) and receiving output (as screen images, sounds, haptic feedbacks and so on);
- d) *participants and creators*, as VR is a medium for communication between people<sup>1</sup>;
- e) *virtual world* is an imaginary or realistic space in which the experience takes place.

All these elements are strictly connected in the creation of a good VR experience. The virtual world must reflect the expectations of the participant

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<sup>1</sup> It is worth noticing that VR experiences have been created also for zebra fishes [5] and praying mantises [6].

in order to enhance the immersion. A good sense of presence is achievable with – but not strictly correlated to – the quality of the devices and the possibility to interact in an easy and effective way with the system. A more natural interaction can help improving the sense of presence only if it fits the environment, for example if the user would perform the same action in the real world; otherwise, it is advisable to rely on a physical controller, which will improve the involvement. As Carrozzino and Bergamasco [7] suggested, immersion and interaction are two of the most important aspects of VR. However, visual information tends to override all the other senses, which implies that the sense of sight is the ultimate sensory effect of a VR application, hence immersion being its most important aspect. Ideally, a perfect VR experience acts on all of our senses (acoustic, haptic, smell, taste, and motion) and allows us to interact with the virtual environment in a natural way.

In order to guarantee a proper sense of presence inside the virtual reconstruction of a realistic environment, 3D data acquisition techniques such as photogrammetry and laser scanning can be exploited in order to build applications that are used for a variety of purposes, such as virtual museums, virtual reconstructions, and virtual explorations.

Among many VR devices, HTC Vive [8] and Oculus Rift [9] headsets guarantee an immersive experience. Thanks to technological evolution during the last 20 years, these immersive VR systems are improving in quality and lowering in price, making them available not only to specialized research centers but also to gamers and enthusiasts of the subject.

The fields of application for VR are the most varied: education, gaming, academic research in science and humanities, architectural design, simulations and training for military, astronauts, aviators and doctors, and many more. However, despite their potential, VR devices are still a niche tool mainly for academic visualization and educational purposes [10].

It is also true that VR technologies are increasingly being recognized for their educational potential and as an effective way to convey new knowledge to

people. In particular, affordable VR devices are offering new opportunities for the creation of new virtual experiences for stimulating interdisciplinary communication [11].

Between real life and VR lies the spectrum of Mixed Reality (MR), where real life and virtual scenes are mixed up. In this context, Augmented Reality (AR) is a variation of the virtual environment, as it allows the user to see the virtual objects superimposed upon the real world, with the aim of enriching reality [12]. Indeed, AR applications run on portable devices, such as smartphone and tablet, and for this reason, it is the most widely diffused virtual technology among consumers. In general, MR software run also on specific head mounted displays [13–15], through which the possibility to interact with the virtual objects can eventually be explored.

## 1.2 VR IN CHEMISTRY AND BIOLOGY

*We are sometimes told that chemistry is a modern science: that is not true. The moment that men's minds began to experiment on the constitution of matter, there was a science of chemistry.*

*Lyon Playfair [16]*

Chemistry is a conceptual subject, which needs the support of models and representations that can help describing the microscopic world that we are unable to see. Until a few years ago, plastic ball-and-sticks models were the best representation that scholars and researchers could give of a molecule. In the same way, biological researchers aim to investigate 3D structures of molecules such as proteins and viruses. These investigations can be done through computational simulations of their structure and properties, and the results can help in the design of new drugs and materials. Moreover, as the teaching of biology relies on visualizations of the relationship between molecular structure and biological functions, the visualizations of the results obtained from simulations can improve the understanding of abstract concepts, complex processes and to create mental models [17].

However, things have changed in the last decade, thanks to the introduction on the market of some virtual reality devices. VR can recreate an interactive, rich, thrilling and educational context, which can support educational activity. Furthermore, the evolution of computer technologies in VR allows achieving advanced evolution in data representation and visualization. Immersive VR systems can recreate abstract phenomena that cannot be experienced in practice or perceived by human senses. Suffice it to say that researchers are taking care of broadcasting how simple can be for teachers to develop virtual reality exercises for structural biology topics [18].

Different studies relate the benefits and the effectiveness of immersive and interactive VR to the fact that human beings manipulate tridimensional objects in their daily life. 3D virtual environments extend users' perception and increase their ability to tackle massive amounts of data coming from multiple and different sources, such as static and dynamic molecular simulations. In fact, direct experiences with the concepts make the students active participants to the learning process, thanks to the interactivity and feedbacks they receive from the virtual environment [19–21].

Merchant et al. performed a study on 387 students in order to investigate the potential of a 3D virtual world to enhance undergraduate students' learning of some chemistry concept. They found that students classified as having poor spatial ability showed significantly greater improvement in understanding the 3D nature of molecules if they did relevant activities in a 3D virtual world than those students who only worked with 2D images [20].

Romano et al. pointed out that desktop virtual environments could lead to the same – if not better – results in training and education though. In fact, even if immersive VR is the medium that should promote direct experience with the object as in the real world, it does not yet provide an experience as natural as the one in the real world because of the limitations of the current technology [22].

In a study that involved 37 teachers, Mikeopoulos et al. [17] demonstrated that VR solutions offer a motivating and safe educational environment where the user may experience new possibilities of interacting with unreachable objects, which in this case were plant cells and – more in general – the explanation of the photosynthesis process. However, the construction of knowledge also needs a solid and structured platform, which would actually lead to the necessary concentration for the learning process, instead of letting the tool prevail over the meaning of the experience.

The results obtained from a similar study, performed by Shim et al. [23], showed that a group of students who took part in the VR learning experience had significant better results at post-test than the group of students who did not. A more recent article confirmed this trend [24] by showing how students who actively participated to the experimental 3D projection of a lesson about the functioning of the human cell performed statistically better than the other control group. The students themselves motivated their results by highlighting that the disjuncture between what static images present and the verbal explanation in class usually contribute to misunderstanding.

In conclusion, it is evident that virtual reality is increasingly recognized for its educational potential and as an effective way to convey new knowledge to people. Lately, affordable VR devices are offering new opportunities for the creation of virtual experiences for stimulating interdisciplinary communication. VR supports interactive and collaborative activities, and it can transform the ways in which we learn and engage with one another. It allows for action, movement, and sometimes speech on the part of users. A prototype of such platform has been presented by Lee et al. [25] in the shape of a collaborative virtual reality environment, in which researchers in biology can work together in a synchronous or asynchronous way, in order to overcome limitations due to time zones and distance. If users cannot be present at the same time, they will be able to review the state of the saved work through dedicated VR

visualization software, and decide to integrate, discard or accept the obtained results.

### 1.3 VR IN CULTURAL HERITAGE PRESERVATION

*The cultural heritage may be defined as the entire corpus of material signs – either artistic or symbolic - handed on by the past to each culture and, therefore, to the whole of humankind. As a constituent part of the affirmation and enrichment of cultural identities, as a legacy belonging to all humankind, the cultural heritage gives each particular place its recognizable features and is the storehouse of human experience. The preservation and the presentation of the cultural heritage are therefore a corner-stone of any cultural policy.*

— UNESCO [26]

The advent of new technologies starting from the late '90 has revolutionized the way information is stored, retrieved, inspected and presented, and this is true for – tangible and intangible – cultural heritage data. The rapid evolution of technologies for the creation of digital models has transformed the work of cultural heritage (CH) researchers, archeologists and curators. Starting from the process of digitization, which allows to storage and organize big amounts of heterogeneous data in databases, VR technologies offer sensory experiences through various combinations of real and digital content. Numerous CH applications make use of 3D digital representations in museum kiosks, videos, and multimedia presentations.

Cultural heritage and digital technologies have been closely interconnected for years, which led to the development of databases and other data management systems to store and make use of archaeological dataset. The main reason behind this evolution is the necessity to preserve the huge heterogeneous set of information digitally, and offer a new and easier way to connect them. However, after a while this was not enough anymore: VR devices triggered new

ways of fruition of CH contents, giving the possibility to recreate destroyed ancient scenarios, but also to catch people's attention and attract them inside the museums. Besides, virtual experiences can solve one of the biggest problem that CH experts must face, which is the *inaccessibility* of cultural goods. Some artifacts may be unique pieces, or inseparable from larger assemblies, or difficult to manage because of their dimensions: a workflow that guarantee virtual free access to inaccessible archeological artifacts can overcome these difficulties. An example of this solution is shown in Fig. 1.



*Fig. 1: a screenshot from italyguides.it webpage, showing a preview of the interactive 3D reconstruction of the house of the Citharist in Pompeii [27].*

One of the first experiments of VR devices used in a cultural heritage context was run in the beginning of 2000s at the Foundation of Hellenic World's Cultural Center, where two different immersive, interactive and educational VR experiences have been offered to the visitors for discovery and exploring [28]. Despite the early stage of maturity of VR systems and the high costs, it was already evident that the exploring and learning experiences offered would have been difficult to obtain otherwise. Nowadays, VR technologies have evolved so much that users have the possibility to experience 3D-reconstructed heritage sites as a visitor, a traveler or even as a resident, depending on the scenario they are experiencing. In particular, the reconstructed environment

can be enriched with the possibility for the user to meet virtual humans [29] able to provide real-time feedback to the user's actions. On the other hand, in guided-tour type immersions (where the user is simply a passive observer), they usually show a predefined (“scripted”) behavior consisting of performing certain actions or talking, as part of the tour [30]. After collecting the results conducted on several studies about the usefulness of VR for learning in CH environments, Tost et al. [31] concluded that “VR is attractive and motivational, especially for younger visitors, and perceived as a useful tool for learning descriptive content about objects and processes. Nevertheless, learning or understanding will only be achieved if the physical and virtual interfaces are multisensorial and intuitive enough”.

A recent and extensive survey presented by Bekele et al. [32] showed how VR, AR and MR systems have proven to be a viable solution in both tangible and intangible CH applications, allowing navigation, interaction, and discovery in different scenarios and with a variety of purposes. In particular, the researchers proposed the following classification in decreasing order of the objectives of immersive VR experiences applied to CH: virtual museums, education, reconstruction, and exploration. For each one of these topics, immersive VR systems have provided several solutions in order to reach a wider public, and to enrich the experience by widening user’s perspective.

As already mentioned, cultural heritage is a crosscutting field, from the preservation of the physical objects and all their physical attributes to the fruition in the form of virtual reality experiences. Recent studies [33– 37] have shown why it is important to focus not only on visual data (such as the 3D model of an artwork), but also on all the issues related to the creation, storage, and access to metadata. In this context, VR plays an important role, as it offers the possibility to visualize and to interact with the virtual representation of the artwork in its original scale. At the same time, the collaboration among experts with heterogeneous backgrounds is gaining increasing importance in order to improve the understanding of the cultural good [38–40].

Actually, the analysis process on physical cultural goods – and therefore on their digital counterpart – produces a set of heterogeneous data, of which visual data are only a small part. The restoration of a cultural good represents a perfect example of a process that requires sophisticated data management need. In this context, the issue to be addressed regards the creation, archival and access to the available data – called *metadata* – related to the artifact, which have high variability (physicochemical data, textual information, 2D images, further 3D models, etc.). As Scopigno and Dellepiane [41] have discussed, the discoverability of an artwork cannot be bound to only a single visual representation. Indeed, the study of an artwork through sampling operations using multiple techniques produces numerous data streams that need to be handled and organized in a proper way, and browsed preferably with a single visual analysis tool, in order to correlate them correctly. Therefore, they proposed two alternative solution. SICAR (Italian acronym that stands for “Sistema Informativo per i Cantieri di Restauro”) [41] included an interesting collection of tools for integration and analysis of sampled data. The SICAR software is based on both web and Geographic Information Systems (GISs), and it can be used to characterize the surface of an artwork, linking available knowledge to specific regions defined over it. It is a good solution for mapping information directly on the 3D surface of the artwork; however, it appears to require a good expertise of the operator because of the complexity of use. Whether the GIS functionalities should not be needful, Scopigno and Dellepiane proposed an alternative solution called the 3D Heritage Online Presentor (3DHOP) web software, which offers high-resolution single object visualizations and intuitive manipulation features not requiring GIS. However, 3DHOP is not suited to manage complex scenes made of low-poly objects. Despite this drawback, it represents one of the most promising applications, thanks to its availability on the web and the possibility to manage heterogeneous sets of data.

In the recent years, cultural heritage and chemistry have become increasingly connected, due to the fundamental role of several chemical techniques in the

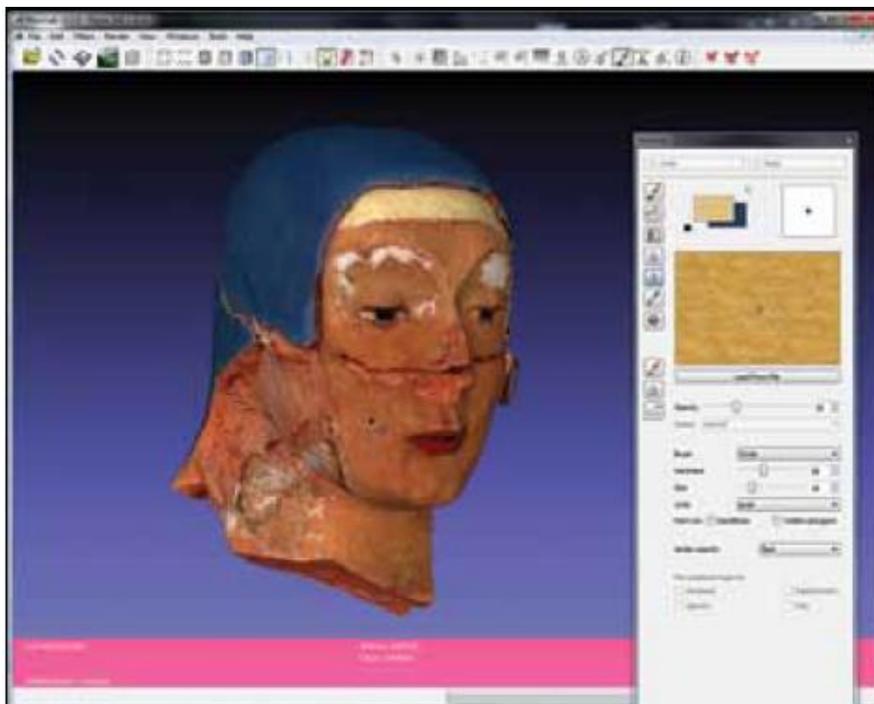
process of analysis and restoration of cultural heritage goods [42–45]. In this context, apart from mere visualization, the great challenge is to create new useful tools in the process of assessing conservation status, or to plan and document restoration of an artifact.

In 2004, when museums took advantage of digital catalogues for self-promotion, Tsirliganis et al. [34] discussed the potentiality of the digitization in the CH field for scientific and educational purposes, proposing a database for archaeological ceramic and glass artifacts. According to this study, the combination of mechanical properties, physicochemical characteristics, 3D imaging and mapping techniques could give rise to novel ways to register and present information. For each artifact, the proposed database can store digitized 2D images and 3D reconstructions, description, typological characteristics, historical information and point-wise surface data, forming a GIS-like environment for the object. A further interesting point about this study is the foresight about the implications on VR integration in the proposed system: in fact, in a few years, Oculus VR would have released the first Oculus Rift DK1, starting a new rise for VR experiences.

Meyer et al. [33] proposed an open-source web based solution dedicated to the exploitation of intra-site CH data, which makes it possible to explore and analyze data both at spatial and temporal levels. In this case, the proposed VR interaction takes advantage of a web solution, called X3D.

Scopigno et al. [46] presented different scenarios showing how digital 3D models can affect daily work in the CH field. First of all, digital 3D models help scholars studying artwork that are physically located far away, also giving them the possibility to exploit interactive visual analysis and tools for shape comparisons. Regarding archeologists' work, onsite documentation of excavations is an ideal application domain for 3D sampling solutions based on dense stereo matching or structure from motion, as these techniques have minimal hardware requirements and ease of use in all environments, and they allow building an online documentation that can be enriched and queried

anytime. In particular, these technologies can be exploited not only to produce visual representations, but also to test different reconstruction hypotheses for the restoration of damaged artworks, as shown in the case of the Madonna of Pietranico (see Fig. 2). Besides, painted decorations can benefit from these techniques, as curators can work on a digital representation of the original aspect of a damaged artwork before proceeding with the physical restoration process. It is possible indeed to hypothesize about an artwork's original color by analyzing traces of the original pigments found on the surface via macrophotography, multispectral images, constituent material analysis, and so on.



*Fig. 2: MeshLab repainting session of the Pietranico Madonna [46].*

A few years ago, Barone et al. [38] proposed RICH, an architecture conceived and developed at the Scuola Normale Superiore. This represented the first step toward the creation of a unified framework for collecting, promoting and sharing CH data. Within this architecture, the Virtual Reality Module (VRM) supports a broad variety of virtual reality and stereoscopic display devices. However, the possibility to investigate the microscopic data directly from the macroscopic level was not explored.

Despite the above discussion has emphasized the needs for a proper visualization of the heterogeneous data relevant in the CH context, to the best of our knowledge, none of the previous solutions consider the use of virtual reality devices for the visualization and interaction with the artworks.

## 1.4 VR IN ASTROCHEMISTRY

*Space ... is big. Really big. You just won't believe how vastly  
hugely mind-bogglingly big it is. I mean, you may think it's a long  
way down the road to the chemist, but that's just peanuts to space.*

— *Douglas Noel Adams [47]*

Astrochemistry deals with the study of the chemistry that occurs throughout the universe with the aim of understanding its evolution toward molecular complexity [48]. It is an interdisciplinary field that besides chemistry involves physics and astronomy, with the further support of geology and biology. All these sciences are applied together in order to understand the chemical evolution of the universe, with the starting point being the knowledge whether a molecule is present in the astronomical environment under consideration and, if so, its abundance.

This field is relatively recent. The interstellar medium (ISM) was considered a highly inhospitable place to host organic molecules. But almost 80 years ago, opinions started to change thanks to the identification of optical absorption lines of CN, CH and CH<sup>+</sup> [49–51]. Then, the discovery of the hydroxyl radical in the radio absorption spectrum of Cassiopea A took place [52] after another 30 years, together with the detection of ammonia by Townes and co-workers toward the center of our galaxy via its inversion transitions [53]. This discovery sanctioned the birth of astrochemistry.

We own most of our understanding about the composition of the interstellar medium and planetary atmospheres thanks to spectroscopic observations. In particular, thanks to the unprecedented resolution and sensitivity of modern

interferometric observatories, rotational spectroscopy has proven to be the method of choice for exploring the chemical composition of a variety of astronomical environments [54, 55]. Furthermore, infrared (IR) spectroscopy has revealed particularly useful in the understanding the composition of interstellar dust grains and in the exploration of the atmospheres of the so-called exo-planets [56–58]. In addition, increasing opportunities for IR spectroscopy will be offered by the Mid-Infrared Instrument (MIRI) installed in the James Webb Space Telescope whose launch is expected in 2021.

The study of astrochemistry is particularly relevant as it gives hints about how life as we know it has emerged. Indeed, the so-called interstellar complex organic molecules (iCOMS), in particular those with a strong prebiotic character, are the ones that have attracted more interest among the species discovered in the ISM, as they can represent the bridge between the matter in the Universe and living entities. Their discovery and analysis led to two possible alternative theories concerning the way life has emerged: endogenous and exogenous synthesis [59]. The former one, supported by the Miller-Urey experiment, sustains that prebiotic molecules were synthesized directly on our planet starting from simple precursors (e.g.  $\text{NH}_3$ ,  $\text{HCN}$ ,  $\text{H}_2\text{CO}$ ), water and some energy source. On the contrary, the exogenous theory suggests that prebiotic matter comes from asteroids, comets and meteorites, and it is supported by the numerous iCOMs observed in the ISM and the detection of carbonyl compounds, amino acids and nucleobases in carbonaceous chondrites [60]. It is therefore necessary to determine first of all which molecules populates the ISM, then to define how they could have synthesized in such an inhospitable environment, and finally to understand how simple molecules could have evolved to living entities. However, performing suitable laboratory experiments can be difficult, as a large number of physical-chemical parameters are needed for modeling the complex network of elementary reactions taking place in extraterrestrial objects. For this reason, modern quantum chemical methods are being used for studying unstable species and analyzing feasible reaction mechanisms [48, 61, 62].

Astronomical and astrochemical processes span a variety of scales (from the atomic scale up to several light-years) and time (from the femtosecond to  $10^7$ - $10^8$  years). Besides modeling, laboratory experiments and quantum chemical simulations, virtual reality techniques can overcome the limits imposed by excessively huge or excessively small spatial length and time intervals, stimulating insights and finding patterns on virtual representations of out-of-scale case study. As Puzzarini and Barone [63] state, the latest technologic evolutions led to an enrichment of the “pillars of science”, which are now theory, experiment, computational simulations and VR/AR representations. In this context, it is worth mentioning “Big Bang AR”, the informative mobile application developed by CERN and Google Arts & Culture that aims to answer some of the most important questions regarding all the big discoveries made during the last century in the astrochemistry field [64].

## 1.5 MOLECULAR VIEWERS: STATE OF THE ART

*I had a lurking question. Would it not be better if one could really 'see' whether molecules as complicated as the sterols, or strychnine were just as experiment suggested?*

— *Dorothy Hodgkin [65]*

In the previous sections, we explored different possibilities about how 3D virtual environments can extend user’s perception and increase the ability to tackle massive and heterogeneous amounts of data. Indeed, despite of the field of study, these large quantities of information need to be filtered and summarized. However, the need for the human intervention due to the distinctive insight ability remains fundamental: the human visual system offers an inimitable means to identify structures, regular patterns, relations, and anomalies in the images, thus providing a deeper understanding of the information. Building on this, scientific visualization aims at exploiting the power of human eyes and mind by meaningfully representing complex data sets through interactive computer graphics [66].

In this section, a brief description of the most widespread among the numerous desktop and VR software aimed at molecular visualization for academic research is provided. Some of these software tools were initially developed for desktop systems and have been adapted later for VR fruition, in order to make them usable with different devices, such as powerwall, CAVE, and head mounted display.

Despite the availability of several 2D molecular viewers supporting the visualization of periodic crystal structure, to the best of our knowledge there are no VR viewers dedicated to this purpose. The periodic structures, however, represent a perfect scenario to exploit VR technologies in order to gain chemical insights, e.g. by naturally interacting with the crystal.

### **1.5.1 RasMol**

RasMol [67] (which stands for “raster molecules”) is one of the oldest and most popular graphics programs for displaying macromolecules and small molecules stored as .PDB [68] files. It was developed at the Bioinformatics Research Unit at the University of Edimburgh, UK, in the early 1990s. Its source code is available on a public repository and is dual licensed under a GNU General Public License (GPL). It is possible to interact with the molecule through a console usable with commands or scripts.

### **1.5.2 Vesta**

VESTA [69] is a freely distributed 3D visualization program for structural models, investigation of crystal structures and volumetric data such as electron/nuclear densities, and crystal morphologies. Thus, VESTA helps in the understanding of crystal structures and a variety of physical quantities in three dimensions.

In addition to structural models and volumetric data, it enables the display of crystal morphologies by inputting Miller indices. Crystal faces can be overlapped with both structural models and isosurfaces of volumetric data.

Thus, the relationship between crystal morphologies and chemical bonds can be understood in three dimensions.

### 1.5.3 MolDraw

MOLDRAW [70, 71] is a program for the graphical manipulation of molecules and crystal structures, in order to analyze the conformation of molecules resulting both from diffraction techniques and from quantum mechanical calculations, and to study the detailed structure of crystalline materials. MOLDRAW is a freeware program for academic research, while it is not free for private companies of any kind and its usage is forbidden for projects linked to any extent to military activities.

### 1.5.4 GaussView

GaussView is a graphical interface used with the Gaussian [72] software. It aids in the creation of Gaussian input files, enables the user to run Gaussian calculations from a graphical interface without the need for using a command line instruction, and helps in the interpretation of Gaussian output (i.e. to plot properties, animate vibrations, and visualize computed spectra). An extensive list of features can be found in Ref. [73].

### 1.5.5 Gabedit

Gabedit [74] is a graphical user interface (GUI<sup>2</sup>) developed to facilitate the production of results from quantum chemical methods through various computational chemistry software (CCS), and to provide a thorough analysis of these results. Gabedit can build the molecule atom by atom, or fragment by fragment. Once geometry has been established, the user can create an input data file for any supported CCS, whose job can run either on the local computer or on a remote host server.

Gabedit is tuned to provide real-time visualization with modest hardware requirements. Visualization options include simple structures, series of structures, normal modes of vibration, molecular orbitals, total electron

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<sup>2</sup> To the purpose of this thesis, the GUI and UI acronyms are synonyms.

densities, density differences, molecular electrostatic potentials (MEPs), and any other volumetric data properties.

### **1.5.6 XCrySDen**

XCrySDen [75] (which stands for “Crystalline Structures and Densities”, while the X indicates that it runs under the X-Window environment) is a crystalline and molecular structure visualization program that facilitates the display of isosurfaces and contours, which can be superimposed on crystalline structures and interactively rotated and manipulated.

It also provides a GUI for the CRYSTAL [76] ab initio program, and a visualization system for Quantum ESPRESSO [77] and WIEN2k [78] programs.

XCrySDen possesses the major features expected from a molecular visualizer: representation of molecular-models in several display modes (wireframe, sticks, ball-and-sticks, space fill, etc.); display of forces acting on atoms; real time operations such as rotation, translation and zooming of displayed structure; and so on. In addition, XCrySDen comes with an additional set of features that are designed for visualizing crystalline structures.

### **1.5.7 Avogadro**

The Avogadro’s project [79] was initially started in 2006, when the selection of free, open-source, cross-platform molecular builders was quite limited. In fact, the Molden [80] application was also available, but it suffered of an antiquated graphical toolkit. “Avogadro is an advanced molecule editor and visualizer designed for cross-platform use in computational chemistry, molecular modeling, bioinformatics, materials science, and related areas. It offers flexible high quality rendering and a powerful plugin architecture” [81]. The application can be extended by implementing a plugin module in C++ or Python to explore different visualization techniques, build/manipulate molecular structures, and interact with other programs.

### 1.5.8 Jmol

Jmol [82] is an open source browser-based HTML5 viewer and stand-alone Java viewer for molecules, crystals, materials, and biomolecules. Among its features, there are the animation of molecular vibrations, visualization of orbitals and the possibility of measuring structural parameters.

### 1.5.9 J-ICE

J-ICE [83] is a Jmol interface for crystallographic properties. The popular molecular graphics engine Jmol, written in the portable Java language, has been combined with a specialized graphic user interface encoded in HTML and JavaScript. The J-Ice framework allows users to visualize, build and manipulate complex input or output results from a quantum chemical computation entirely via a web server, without the burden of installing complex packages.

### 1.5.10 VMS-Draw

The VMS-Draw software [84] is a GUI developed in the context of the virtual multifrequency spectrometer (VMS) [85] which provides user-friendly access to the latest developments of computational spectroscopy also to non-specialists. Depending on the kind of data to be analyzed, VMS-Draw produces different types of graphical representations, including 2D or 3D plots, bar charts, or heat maps. It is also possible to analyze and visualize, together with the structure, the molecular orbitals and/or the vibrational motions of molecular systems thanks to 3D interactive tools. VMS supports the computation of vibrational and electronic spectra, while access to electron spin resonance spectroscopy has been provided through the development of an interface to E-Spikes [86]. Very recently, it has been extended to deal with solid-state NMR spectroscopy [87] and to deal with rotational spectroscopy [88].

### 1.5.11 PyMOL

PyMOL [89] is a cross-platform molecular graphics system that takes advantage of molecular graphics packages written in C and Fortran, but is also integrates a Python interpreter that ensure features and expandability.

PyMOL was the first attempt to replicate the high quality of molecular representations of other software such as Molscript [90], but with the advantage of being open source. It supports representations for macromolecular structures and electron density, as well as molecular editing functionalities.

#### **1.5.12 VMD**

VMD [91] is a molecular graphics program designed for the visualization and analysis of biopolymers, such as proteins and nucleic acids. Besides displaying molecular structures representations, VMD is notorious for animations of molecular dynamics (MD) simulation trajectories, imported either from files or from a direct connection to a running MD simulation. VMD has been one of the first software used with a three-dimensional projection system for the display and analysis of molecules viewed simultaneously by several users. The program is freely available online.

#### **1.5.13 Chimera and ChimeraX**

Chimera [92] was developed by the UCSF Computer Graphics Laboratory, beginning with Midas system. Midas was a highly successful molecular graphics application, but it was hardly extendable. Chimera has been developed in Python. It is segmented into a core that provides basic services and visualization, and extensions that provide most higher level functionality. This architecture ensures that the extension mechanism satisfies the demands of external developers who wish to incorporate new features. Among the most important ones, there are two extensions: “multiscale”, which adds the ability to visualize large-scale molecular assemblies such as viral coats, and “collaboratory”, which allows researchers to share a Chimera session interactively despite being at separate locales.

Recently, ChimeraX [93] has been proposed to offer a wide set of features. It aims at redesigning the software interface of Chimera and comes with new tools for visualization and analysis of molecular structures, density maps, 3D microscopy, and associated data. ChimeraX supports headsets using the

OpenVR toolkit, and optimizations for graphic rendering speed and hand-controller interactions are under development.

#### **1.5.14 MDV**

Wiebrands et al. recently published a work describing MDV [94], a software made with the notorious Unity3D game engine for both desktop and stereoscopic visualization of biomolecular structures, functions and interactions. The aim of this work was to explore how to use the HIVE Cylinder display, which is a multi-user and multi-display facility, in order to investigate the possibility to enhance the visualization and interpretation of molecular structures for research, teaching and communication purposes.

As the calculation and projection of dozens of virtual cameras for the visualization scene initially had a severe impact on performance, custom software routines were developed to create highly optimized scene meshes, and demonstrated a compelling way to render detailed visualizations at acceptable speeds on large screen displays. Since the position of the users does not change, interaction is mediate through a touchscreen panel put in the center of the room.

#### **1.5.15 ChemDoodle3D**

The ChemDoodle3D [95] software is designed for editing and visualization of both small molecules and macromolecules. Among its functionalities, it reads also 3D periodic data from .CIF files and can fully resolve point groups and symmetries. Unit cells for any symmetry are also extracted.

This software is also available in the form of a pure JavaScript chemical graphics and cheminformatics library derived from the ChemDoodle® application and produced by iChemLabs. The so called “ChemDoodle Web Components” [96] produces publication quality 2D and 3D graphics and animations for chemical structures, reactions and spectra. This tool also provides a framework for creating dynamic applications through web browsers,

desktop platforms and mobile devices such as the iPhone, iPad and Android smartphones and tablets.

#### **1.5.16 Mercury**

Mercury [97] is a largely diffused tool for 3D structure visualization and the exploration of crystal packing. The free version of Mercury has a large number of options for customizing display settings, and it is widely used for the generation of publication-quality images. A Style Manager contains a number of pre-defined display styles for work, publication and presentation and also provides the option to preserve and share a customized display setting. 3D images created using Mercury can be exported in a variety of common formats.

It allows loading structural data from different formats, and supplies several options to assist the investigation and analysis of crystal structures. Simulated diffraction patterns can be calculated for any displayed crystal structure. Finally, Mercury locate and display hydrogen bonds, short non-bonded contacts, and user-specified types of contacts.

#### **1.5.17 Caffeine**

Caffeine [21] is specifically tailored for molecular representation and data visualization with VR systems, such as VR theaters and helmets. It has been developed using Qt framework and OpenSceneGraph at Scuola Normale Superiore in Pisa. Among other things it allows to visualize both static and dynamic structures using the most widespread representations, isosurfaces extracted interactively by volumetric data sets, line charts displaying additional scalar data resulting from further data analysis. Recently it has been equipped with tools supporting bond analysis [98] and vector field clustering [99]. Inside the CAVE environment, functionalities can be set both from a desktop computer connected to the CAVE and/or from a tablet.

#### **1.5.18 UnityMol**

UnityMol is a molecular viewer coded in C# with the Unity3D game engine. It has been developed by Marc Baaden's team at the Laboratoire de Biochimie

Théorique (LBT) at the Institut de Biologie Physico-Chimique (IBPC) institute of French National Scientific Research Centre (CNRS) in Paris. UnityMol can currently read .PDB, .mmCIF, .GRO, .MOL2, .XYZ and .SDF files, and XTC trajectory files. It includes the “hyperballs” representation, designed to visualize molecular structures using GPU graphics card capabilities based on shaders [101].

UnityMol implements different molecular representations, thanks to the many visualization tools offered by the Unity engine (for example triangulated spheres, triangulated cubes and lines, etc.), along with several elements in the environment, which can be modified by the user. Atom spheres can be depicted via particle systems, while Unity triangulated spheres can be used for atoms and lines for interatomic bonds. The “hyperballs” representation has been implemented as a way to use a unified algorithm to display balls, sticks and hyperboloids. Different types of molecular surfaces can be represented, with the particular addition of cut planes, which enables visualization of hidden elements in the interior of the molecular object. The use of lit sphere shading offers the production of artistic and illustrative rendering for any type of representation. Finally, several visual effects are also available [102].

The desktop version of UnityMol has been the first released version, while the VR version for HTC Vive and Oculus Rift have been introduced recently. Both desktop and VR software can be downloaded for free [103].

The current desktop version (1.0.25 beta) is the first public release of the new version with a SMCRA (Structure/Model/Chain/Residue/Atom) data structure. Other relevant features are the loading of several molecules, a python console, a selection language adapted from MDAnalysis [104], various molecular representations, and a new user interface.

The VR version of UnityMol is based on the Virtual Reality Toolkit (VRTK) to support HTC Vive and Oculus headsets.

## 1.6 WRAPPING UP

In this chapter, we have discussed how virtual reality can empower many research fields, shortening the learning process and enabling interactions with representations of phenomena of interest, whose dimensions on the time and space scales may vary greatly.

The ultimate goal of this project is to build a tool for both researchers and non-experts, who can take advantage of VR potentialities in order to improve their work and understanding of the world by putting in contact several topics belonging to heterogeneous disciplines that enrich each other.

This objective has been achieved through the development of TARDIS, a multiscale architecture built on several layers. Each layer is dedicated to a certain level of abstraction. The upper layer is the “macroscopic level”, a virtual reconstruction of a glimpse of multidisciplinary topics that we are interested in. The lower layer is the “microscopic level”, where the user enters the atomistic details of matter, or can live other experiences such as the exploration of a potential-energy surface. As it will be shown in the case studies, these layers can be adapted to all kind of disciplines and applications.

The journey between the macroscopic and microscopic worlds has been made automatic and fluid, thanks to dedicated scripts that take care of the switch between applications.

The next chapter will describe the structure of this architecture and its components.

## 2 THE TARDIS FRAMEWORK

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### 2.1 INTRODUCTION

The TARDIS architecture is based on several software components, as shown in Fig. 3. The goal of this architecture is to create multiscale virtual experiences, with seamless transitions between different scales.

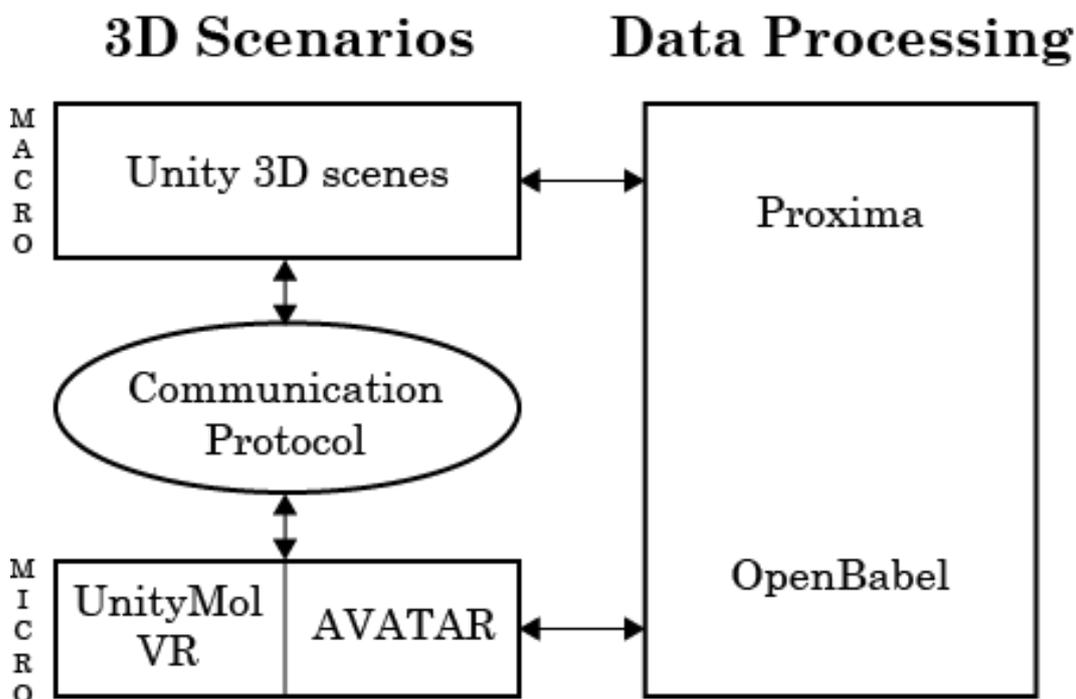


Fig. 3: the building blocks of the TARDIS architecture.

#### 2.1.1 Unity

The 3D components of the architecture have been developed using Unity [105], a well-known *cross-platform* game engine developed by Unity Technologies. The engine is widely used in the processes of creations of 2D and 3D experiences, including VR, AR and MR software. Unity includes a fully-supported .NET runtime, which includes C# 6 and the latest .NET class library.

Furthermore, the Unity editor can be customized in order to speed up application development and to execute part of code without having to run the application.

Currently, TARDIS works with HTC Vive headset [8] by Valve. The headset is integrated into the Unity environment through the “SteamVR” plugin [106], whose purpose is to ease developer’s work by managing three main aspects: loading 3D models for VR controllers, handling input from those controllers, and estimating what hands look like while using those controllers. This latter characteristic enriches the sense of presence inside the virtual experience, as it is possible to simulate visually the movement of the hands around the controllers. It is also possible to associate the touch of a button to a specific virtual hand movement: for example, when the user presses the touchpad button for teleporting, the virtual hand assumes a “pointing pose”, from whose finger comes a laser beam.

### **2.1.2 Proxima**

Proxima [107] is a Molecular Perception library under development at the SMART laboratory of Scuola Normale Superiore. The goal of Molecular Perception algorithms is to build topological models of molecular systems, starting from the minimal information conveyed by atomic symbols and coordinates, to be next used for scientific visualization purposes and/or for building initial guesses for quantum mechanical (QM) and/or molecular mechanical (MM) simulations.

The purposes of Proxima are to provide meaningful chemical information to immersive visualization software, and to be employed in workflow managers in order to exploit property calculations to prepare input files and to allow the user-friendly use of perception also by non-experts.

Proxima has been written in C++ programming language. In order to make it usable inside TARDIS, it has been necessary to develop an additional “layer” between the C++ library and the Unity software, called dynamic linked library (DLL). This layer allows the communication between the C++ library and .NET

applications developed with Unity. Proxima DLL has been developed and built with Microsoft Visual Studio [108].

Being still under development, some features of Proxima are not yet fully supported. For this reason, TARDIS is able to work also with Open Babel (see Par. 2.1.3).

In the context of the TARDIS framework, we take advantage of Proxima for the following features:

1. parsing molecular structure files to generate a visual representation of the molecule while the user navigates the macroscopic level; in particular, in the case of MD output files, it generates a simplified snapshot for the MD preview;
2. computing the Potential Energy Surface (PES);
3. extracting data from crystallographic structure files.

#### 2.1.2.1 *Snapshot generation*

During the navigation of the macroscopic level, Proxima provides the previews of the molecular structures that can be inspected in more detail at the microscopic level.

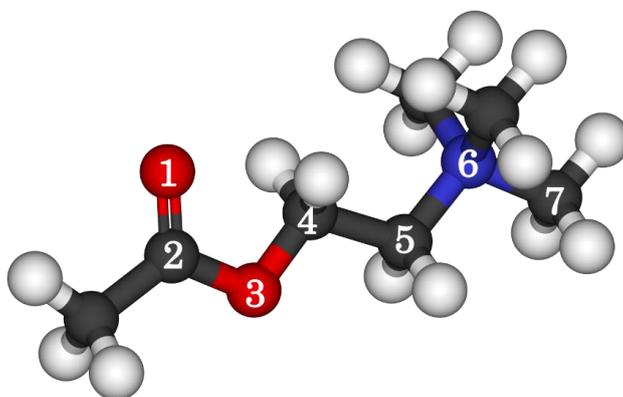
In the particular case of systems containing a solute (a molecule) surrounded by a solvent (described by explicit molecules), such preview should be simplified by reducing the number of solvent molecules in order to have a clearer view of the system. Instead of handcrafting custom snapshots for each system of interest, we have employed Proxima to automatically build such structures. Proxima automatically detects the central molecule, computes its geometrical centroid and cuts the system within a predefined radius (typically 10 angstrom). Then, we have observed that for a good quality snapshot, we should reduce the number of molecules displayed in the nearby distances of the central molecule otherwise we would have a very crowded environment. To do that, we have seen in our tests that by limiting the number of solvent molecules to 5 in the selected spherical region usually provides good visual results.

### 2.1.2.2 *PES computation and output file*

In general terms, the PES can be thought as a hypersurface describing the variation of the potential energy of a molecular system as a function of the position of its atoms. As such, it depends on  $3N - 6$  ( $3N - 5$  for linear systems) internal coordinates, where  $N$  is the number of atoms in the molecular system. Each point of the PES is associated to a specific geometry of the molecule, whose energy is the corresponding potential energy computed with some reference theoretical model. Clearly, it is impossible to visualize such hypersurface directly in a 3D environment, such as our real world. However, it is possible to reduce the dimensionality of the PES through the use of advanced clustering algorithms, or mathematical elaboration of the atomic coordinates (such as optimizing all the rigid or non-essential degrees of freedom so as to reach the lowest energy [109]).

The decision to employ a molecular perception library such as Proxima for on-the-fly PES computation, instead of relying on precomputed data, is motivated by the need for the user to customize the parameters of the PES in VR. In particular, the user might be interested in switching the angles used as variables for the PES, or change the range of values that the variables can take (such as the maximum angle value). Moreover, such approach is easier to extend to different molecular systems so to allow a more customizable software for different applications and test cases.

The molecule used in this work is Acetylcholine as shown in Fig. 4.



*Fig. 4: 2D structure of neurotransmitter acetylcholine.*

The user can select two torsion angles between the following:

- the 1-2-3-4 torsion;
- the 2-3-4-5 torsion;
- the 3-4-5-6 torsion;
- the 4-5-6-7 torsion.

The initial value for the torsion angles chosen for the scan is set to zero by default, and the maximum angle can be selected by the user. The default number of points to scan along each direction is of 50 points for each variable, and also this number can be customized.

### 2.1.2.3 *Extraction of crystallographic data*

Periodic systems, such as the ones studied in solid-state chemistry, require special care and attention since perception and visualization should both take periodicity into account. UnityMol is optimized for protein visualization, and its internal perception scheme reflects this nature, from the parsing of PDB files using standard amino acid residues names (e.g. ALA, GLY, etc.), up to the bond perception itself. The Proxima perception library does not consider periodicity yet and it is still under development. A full description of the perception algorithms employed by Proxima can be found in the original work [107].

### 2.1.3 **Open Babel**

Open Babel [110] has been defined “a full-featured open chemical toolbox”, as it presents a solution for the interconversion of chemical structures between different formats. Indeed, the need to switch between many different formats – both standard interchange and *de facto* – is a significant problem due to the availability of a large variety of software and data types. It also provides other useful utilities, such as batch conversion, filtering, and conformer search.

The Open Babel graphical user interface can be freely downloaded from the official website, and it can run on multiple platforms.

To the purpose of this project, the “OBDotNet” compiled assembly was needed, as it allows to use Open Babel functionalities from the various .NET languages. As explained in the next sections, TARDIS offers the possibility to link some molecular files in the macroscopic level, in order to show and inspect them at the microscopic level. However, it must be considered that every molecular viewer has a limit on the types of file that can be opened. In our particular case, the Open Babel conversion functionality has been useful in order to create specific types of file that UnityMol is able to parse and visualize.

#### **2.1.4 UnityMol VR**

In this architecture, a fundamental role is played by the molecular viewer. While UnityMol was initially developed only for desktop usage, its research team has recently released VR versions targeting both HTC Vive and Oculus Rift. Flexibility, expandability and modularity make UnityMol suitable for the creation of a multi-disciplinary tool, which is able to provide heterogeneous information. In the framework of an ongoing collaboration with the UnityMol team, we were able to modify the source code in order to satisfy the requirements of TARDIS. In particular, the TARDIS case studies have requested the integration of the following new functionalities:

1. normal modes loading and visualization;
2. crystal structures loading, visualization and replication;
3. visibility sphere to be applied to a MD trajectory, in order to make the graphical visualization more practical.

Moreover, in order to enable the communication between the macroscopic level and UnityMol VR, the following feature have been added:

- the possibility to launch UnityMol process with parameters, for example:  

```
> UnityMol.exe -i filename.pdb
```
- the integration of network scripts for the exchange of messages;
- the integration of functionalities for switching from/to the macroscopic level.

#### 2.1.4.1 *Normal modes visualization*

The motion of a molecule composed by  $N$  atoms can be described by  $3N$  degrees of freedom. Of these, the three coordinates representing the center of mass can be used to describe the translational motion of the whole molecule, while two or three Euler angles are needed for treating the rotational motion of linear and non-linear molecules, respectively. The remaining degrees of freedom describe the vibrational motion, hence linear and non-linear molecules present  $3N - 5$  and  $3N - 6$  vibrational degrees of freedom, respectively. In general terms, it can be thought that during a vibration all the atoms of the molecule undergo a displacement from the position they occupy in the equilibrium configuration. This complex motion, however, can be decomposed into simpler vibrations, called normal modes of vibration in which all atoms have the same frequency of oscillation and each of them carries out a harmonic motion. The number of normal modes is equal to the number of vibrational degrees of freedom [111].

For implementing the visualization of normal modes within UnityMol VR, reference has been made to the Gaussian software [72]. At the end of the computation, the output file is parsed in order to extract the molecular structure (in the so called standard orientation) and, for each normal mode, the value of the frequency, the reduced mass and the Cartesian displacement of each atom. The latter are stored as mass weighted Cartesian coordinates (MWC).

The first issue to be addressed is the extraction of the molecular structure from that file. Two possible approaches have been considered: the first one was to develop another parser specifically for the structure; the second one was to use the OpenBabel library to convert the output file into another type of file that UnityMol was already able to parse. The latter option seemed more appropriate. This whole method is integrated and automatically executed in the TARDIS framework, therefore transparent for the user.

In a second step, the standard coordinates and the frequency values are extracted and stored. At this point, for each  $j$ -th atom and for each  $i$ -th normal mode of the system, the MWC are transformed in standard Cartesian coordinates as follows:

$$x_{i,j} = \frac{x_{i,j}^{MWC}}{\sqrt{\mu_i} * a_0}, \quad y_{i,j} = \frac{y_{i,j}^{MWC}}{\sqrt{\mu_i} * a_0}, \quad z_{i,j} = \frac{z_{i,j}^{MWC}}{\sqrt{\mu_i} * a_0},$$

$$i \in [0, N), \quad j \in [0, M)$$

where  $N$  is the total number of normal modes,  $M$  is the total number of atoms, and  $\mu_i$  is the reduced mass of the  $i$ -th normal mode, and  $a_0$  represents the Bohr radius.

When the whole loading procedure is complete, the UnityMol user interface shows buttons for the selection of a normal mode by choosing its vibrational frequency, as illustrated in Fig. 5, showing the glycolaldehyde molecule absorbed on a cluster composed by 33 H<sub>2</sub>O molecules [112].

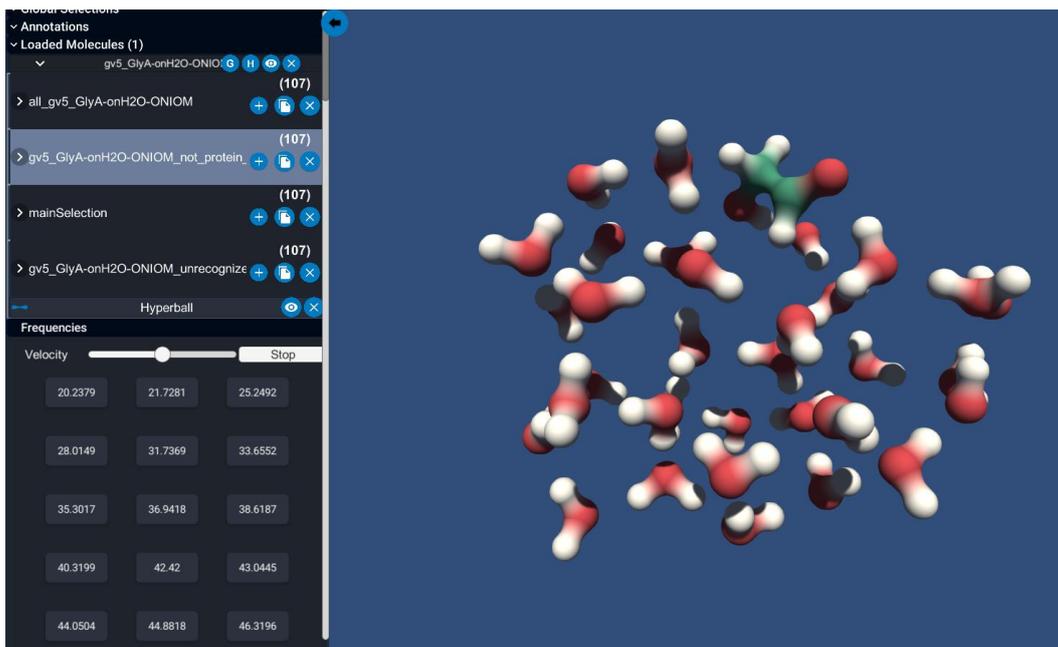
In order to compute the position of each atom at a given time during a vibration, it is necessary to combine its initial coordinates (standard orientation) with the values of the normal modes Cartesian coordinates. For the sake of simplicity, we indicate the standard orientation coordinates as  $\langle x_s, y_s, z_s \rangle$ , and the coordinates of the  $i$ -th normal mode of the  $j$ -th atom as

$$\delta = \langle x_{i,j}, y_{i,j}, z_{i,j} \rangle.$$

For each atom, the next position for a specific frequency is computed as

$$\langle x, y, z \rangle = \langle x_s, y_s, z_s \rangle + \delta * \cos(t)$$

where  $t$  indicates the time.



*Fig. 5: normal mode visualization in UnityMol showing glycolaldehyde absorbed on an ice cluster composed by 33 H<sub>2</sub>O molecules.*

#### 2.1.4.2 *Crystal structure*

The description of a crystal starts from the definition of a lattice, i.e. a collection of points repeated at intervals of length  $a$ ,  $b$  and  $c$  along three non-coplanar directions, indefinitely. The three constants  $a$ ,  $b$  and  $c$  are called lattice parameters and the vectors  $\vec{a}$ ,  $\vec{b}$  and  $\vec{c}$  oriented in the same three directions with the lattice parameters as norms are the so-called basis vectors. Lattice parameters and angles between the lattice vectors define the cell parameters.

It follows, from these definitions, that a lattice vector  $\vec{g}$ , i.e. a vector joining two lattice points, can always be described by the three coordinates  $n_1$ ,  $n_2$  and  $n_3$  in the basis vector system:

$$\vec{g} = n_1\vec{a} + n_2\vec{b} + n_3\vec{c}.$$

The basis vectors  $\vec{a}$ ,  $\vec{b}$  and  $\vec{c}$  define a parallelepiped called the unit cell. The actual shape of a unit cell depends on the lattice type. All the cells that are obtained by translation of the original unit cell, through the application of all vectors  $\vec{g}$ , fill the space completely [113]. Filling the unit cell of a lattice with particles (i.e. atoms, ions or molecules) in a well-defined geometrical

arrangement and translating it in the three dimensions allow the creation of an ideal crystal. In addition to point symmetry, crystals usually exhibit translational symmetry, which combine to form one of the possible 230 space groups [114]. The minimal set of atoms which generates the complete unit cell after application of all space group symmetry operations, is referred to as asymmetric unit. Resuming, the following information: i) space group, ii) cell parameters, iii) atom belonging to the asymmetric unit and their coordinates, are needed in order to specify the geometry of a crystal.

As for normal modes, the original source code of UnityMol did not provide any support for the visualization of crystal structures. Indeed, UnityMol's primary purpose is proteins visualization and manipulation. However, the flexibility and modularity of its source code has facilitated the integration of the necessary functionalities for dealing with periodic structures.

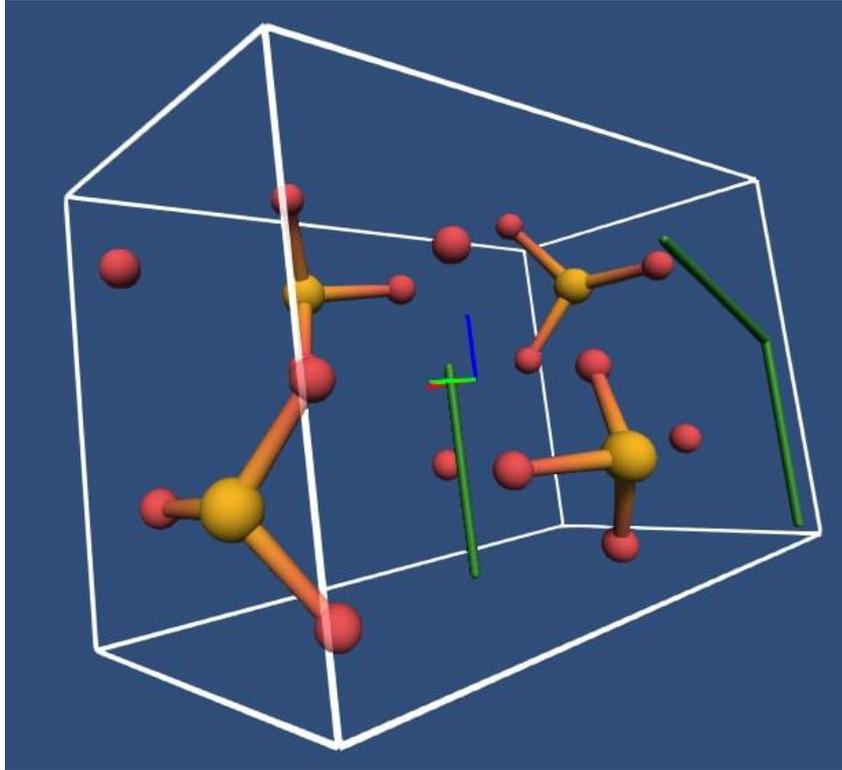
The first issue to be addressed has been to collect the various types of files that can encode a crystal structure. The types of file considered are .CIF, .mmCIF/PDBx [115] and .GUI (one of the files generated by the CRYSTAL software). Since the original source code of UnityMol already provided the parsing of .mmCIF files, its algorithm have been used for the extraction and visualization of the structure. For the other file formats, Open Babel has been used to automatically convert them. The missing part relative to the extraction of the cell parameters and the visualization of the unit cell has been integrated within UnityMol. Since UnityMol is able to parse also .XYZ file, the unit cell information have been added in the comment field.

However, the bonds of a crystal structure cannot be computed in the same way as for isolated molecules. For this reason, the Proxima library has been used to load the .XYZ and the .GUI file and to provide atoms and bonds information, without the need for UnityMol to use its bond connectivity algorithms<sup>3</sup>. This procedure applies also to the replication process, where the unit cell and its

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<sup>3</sup> Proxima converts the input file into a .MOL2 file, which UnityMol parses as it is, without computing the bonds.

atoms and bonds are cloned by translation. An example of unit cell is shown in Fig. 6.



*Fig. 6: forsterite unit cell.*

Given the lattice parameters  $a, b, c$  and  $\alpha, \beta, \gamma$  ( $\alpha$  being the angle between  $\vec{b}$  and  $\vec{c}$ , and similarly for  $\beta$  and  $\gamma$ ), it is possible to build the unit cell by defining the basis vectors. These coordinates are computed as follows:

$$\vec{a} = \begin{bmatrix} a \\ 0 \\ 0 \end{bmatrix},$$

$$\vec{b} = \begin{bmatrix} b * \cos \gamma \\ b * \sin \gamma \\ 0 \end{bmatrix},$$

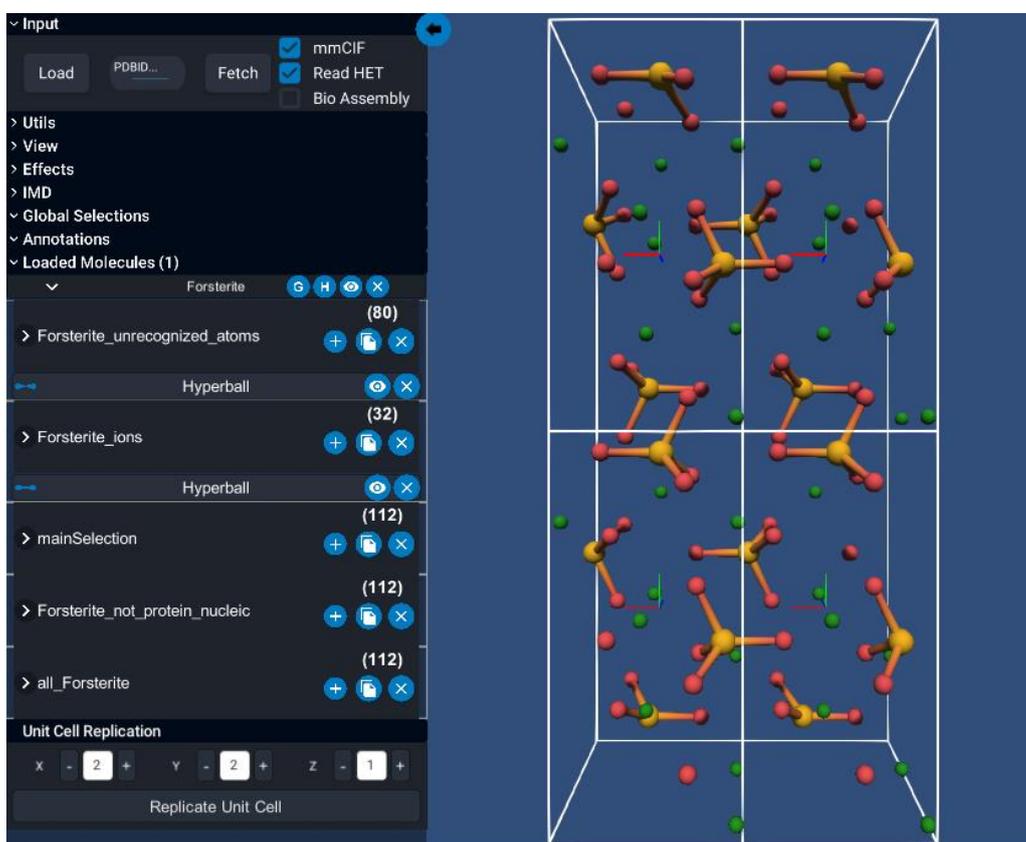
$$\vec{c} = \begin{bmatrix} c_x \\ c_y \\ \sqrt{c^2 - c_x^2 - c_y^2} \end{bmatrix},$$

where

$$c_x = C * \cos \beta, \quad c_y = C * \left( \frac{\cos \alpha - \cos \beta * \cos \gamma}{\sin \gamma} \right).$$

These coordinates allow creating a 3D mesh for the unit cell.

When the crystal structure has been loaded, the UnityMol UI shows a panel from which it is possible to set the number of replicas of the unit cell along the X, Y and Z axis. This algorithm computes the number of cells that must be eventually removed; then, it proceeds with the cloning of the atoms in the new cells. All the new atoms are then added to the structure, bonds are computed (except for .XYZ and .GUI files, as explained before) and the final model is visualized, as shown in Fig. 7.



*Fig. 7: forsterite structure loaded inside UnityMol desktop.*

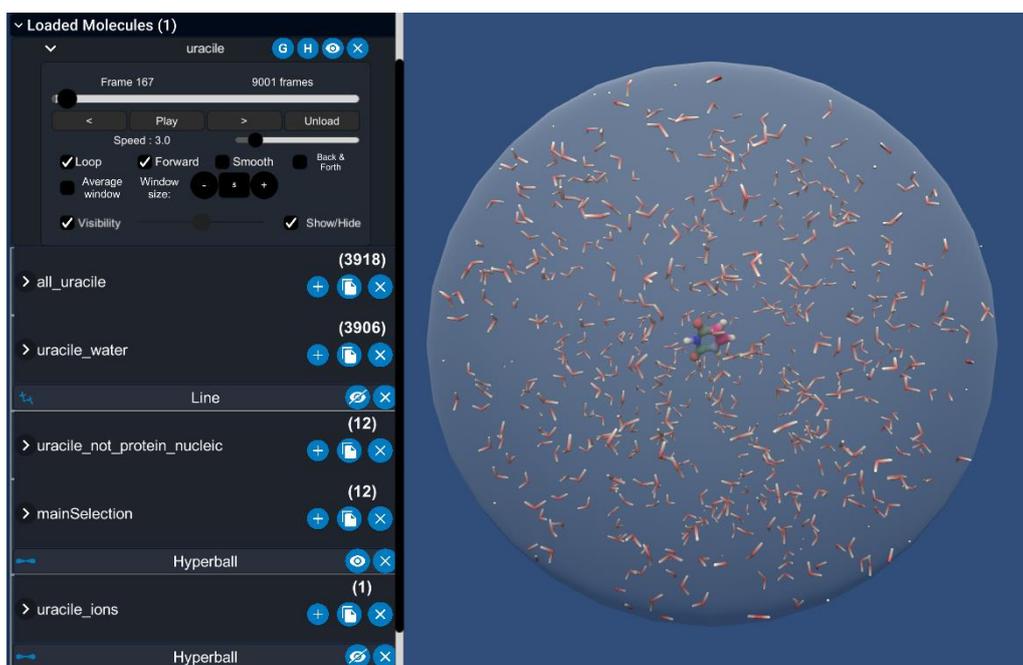
#### 2.1.4.3 **Visibility sphere for molecular dynamic trajectories**

The UnityMol code already includes the implementation for the visualization of trajectories computed by means of molecular dynamics simulations. Very often MD simulations are carried out on solvated molecules, where a large number of solvent molecules surrounds the solute. In order to favor the focus on the solute, the visualization of MD trajectories implemented within

UnityMol has been integrated with the possibility to hide molecules outside a given ellipsoid. In particular, only the set of atoms contained in the ellipsoid centered in the centroid of the molecular structure and of axis  $x_e, y_e, z_e$  are extracted and visualized.

In this version of the code, the ellipse has been simplified to a sphere, given the presence of the MDAnalysis [104] library – a tool for executing operations on trajectories – that already provided the needed functionalities. Therefore, the main objective has been to develop the functionalities for enabling the sphere and for using the MDAnalysis operations.

Once the trajectory has been loaded, the UI shows a panel from which it is possible to enable or disable the visibility sphere. When enabled, only the atoms contained in the visibility sphere are shown: this selection keeps being updated for the whole trajectory, meaning that it applies to each constituting frame. The sphere can be zoomed in and out in order to change its size with a slider. Furthermore, an additional button allows hiding and showing the contour of the sphere, maintaining however the chosen molecular visibility (see Fig. 8).



*Fig. 8: screenshot of a frame of the MD simulation of uracil in water with the visibility sphere enabled.*

### 2.1.5 AVATAR

The AVATAR (Advanced Virtual Approach to Topological Analysis of Reactivity) [116] software is a VR framework for the immersive exploration of PES designed for the HTC Vive. It has been developed by a team of the SMART Lab at Scuola Normale Superiore using the Unity software.

As previously mentioned, the computation of the PES depends on numerous variables, and it is impossible to visualize such hyper-surface directly in a 3D environment, such as our real world. Therefore, the dimensionality is reduced to two coordinates. Moreover, the surface is built following the analogy between the evolution of a chemical process on one side and a pathway through valleys (potential wells) and mountain passes (saddle points) on the other, as can be seen in Fig. 9.

In the context of TARDIS, AVATAR has needed the integration of functionalities that enable the user to switch back to the macroscopic level.

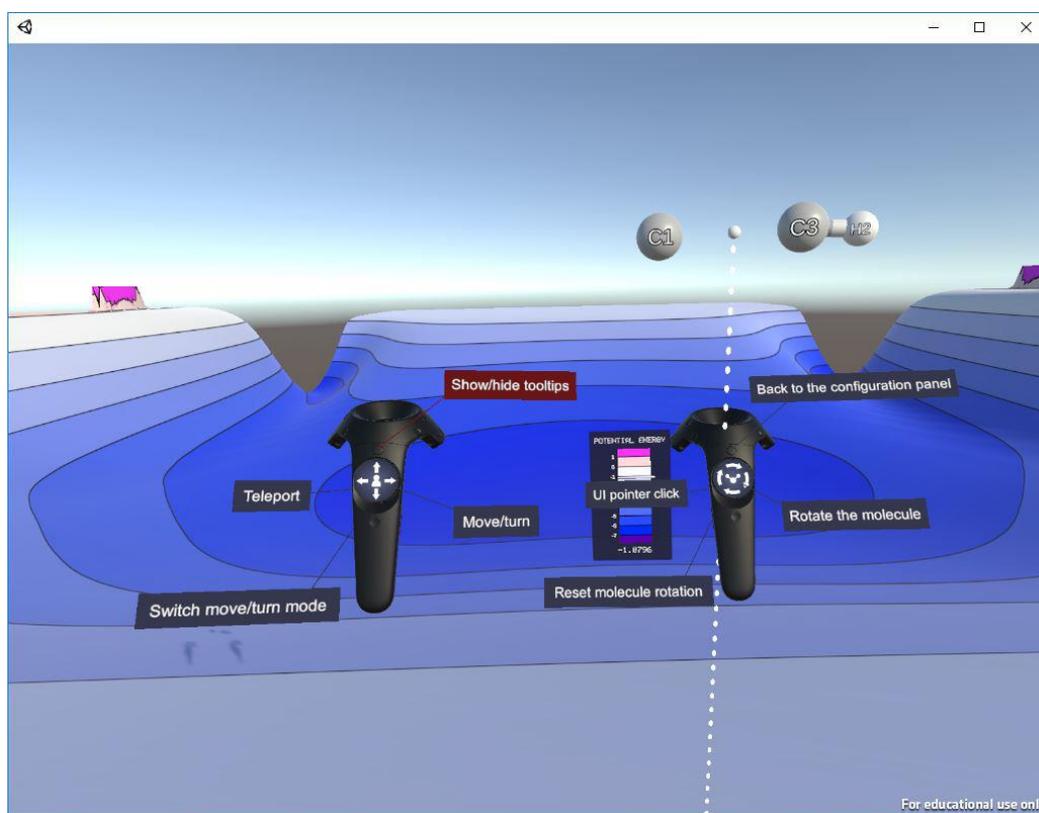
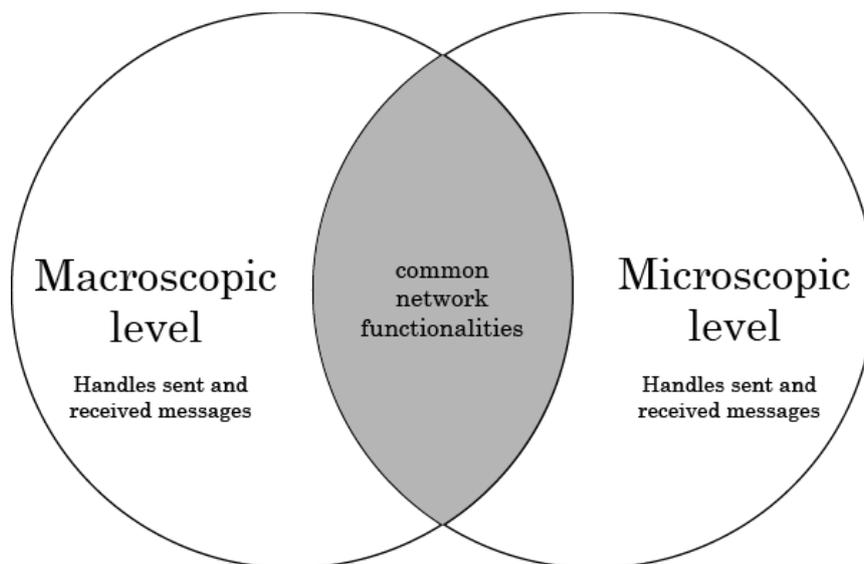


Fig. 9: a screenshot of the AVATAR application, showing an example of potential-energy surface and the different functionalities on the Vive controllers.

## 2.2 THE COMMUNICATION PROTOCOL

In order to enable the exchange of messages between the upper layer and the lower layer of the architecture, it has been necessary to implement a communication protocol. In particular, the different levels need to exchange messages via network regarding the paths of the file to be opened, and the necessary data for the automatic switching between different applications.

Ideally, the architecture can be sketched as shown in Fig. 10.



*Fig. 10: the levels of a scenario share the implementation of the sending and receiving of messages. However, the behavior is different according to the requirements.*

It has been legitimate to assume that the different applications run on the same host, which is usually referred as *localhost*. Both the macroscopic and the microscopic layers must include common network source code, in order to be able to interpret the type of incoming messages. While the Unity framework offered a high-level network solution called UNET, its use has been deprecated and substituted by a new network system. However, this new protocol was still under development and not fully reliable yet, hence for the purpose of this project the choice has fallen on synchronous Transmission Control Protocol (TCP) sockets solution.

A *socket* represents a software abstraction on which it is possible to use the standard Application Programming Interface (API) of transmission and reception of data through the network.

TCP is one of the main network protocols used for sending and receiving data on the Internet in a reliable way, meaning that all the messages sent through the network will arrive to destination in the same order they were sent, eventually causing some delay. The alternative to TCP is User Datagram Protocol (UDP), a connectionless protocol that, among other things, does not offer guarantee of delivery and ordering of the packages.

The communication protocol is composed of several scripts that are assigned to different Unity's `GameObjects` inside all the scenes of both the macroscopic and the microscopic levels. The macroscopic level acts as "listener", as it represents the entry point of the architecture. The listener waits for connections from other applications, and dispatches them among different handlers, which take care of sending and receiving messages on a specified socket from a specific application. The types of messages have been defined as follows.

- "Shared": the definition of these messages is the same for both the macroscopic and the microscopic levels. In particular, shared messages are:
  - "Init": it is the first message that the applications send to each other, can be seen as a handshake. This message contains:
    - an identifier of the sender (i.e. "Macro", "UnityMol", "AVATAR", and so on),
    - the name of the application window and the window handle (both useful for the change of focus when switching between different apps).
  - "Close": it is the last message that the applications send to each other, in order to notify the disconnection from the socket.
- "Macro": these messages are sent from the macroscopic to the microscopic level. Macro messages are:

- “MolecularStructure”: it contains the path of the file storing the molecular structure that has to be opened;
- “NormalModes”: it contains both the path of the Gaussian output file and eventually the path of the generated spectra to be visualized in the virtual scene;
- “PES”: it contains the path of the file containing the potential-energy surface that has to be opened.

## 3 CASE STUDIES

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*“So, all of time and space, everything that ever happened or ever will... Where do you want to start?”*

*– Doctor Who [117]*

### 3.1 INTRODUCTION

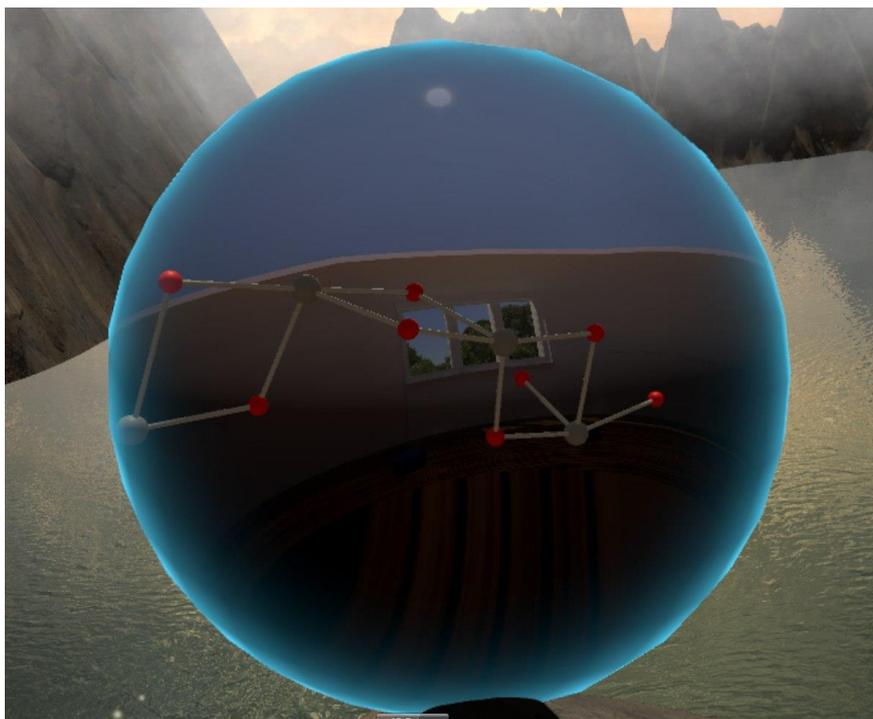
In this chapter, we describe the different case studies that have been developed to illustrate the potential of the TARDIS architecture and its general applicability to chemistry-related issues. These involves chemistry for cultural heritage, biochemistry and astrochemistry, to explore just a few of the many possible experiences than can be built within the TARDIS framework.

Before moving on with the discussion of all the scenarios, it is useful to understand how the virtual journey between macroscopic and microscopic layers has been implemented in TARDIS. All the experiences follow the same track: a human-scale 3D reconstructed environment is the entry point, and it is made available for the user to explore. Depending on the scenario, different interactive objects are highlighted through visual effects; these items are the ones that can be investigated, and that have molecular information to be further inspected with the software available at the microscopic level. Therefore, it has been necessary to design a proper expedient for the action of descending into the microscopic level and backwards.

The proposed answer is the *portal sphere*<sup>4</sup>, which is shown in Fig. 11.

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<sup>4</sup> The portal sphere solution has been inspired by “The Lab” application, a freely distributed demo developed by Valve [118].



*Fig. 11: screenshot of the portal sphere that allows the UnityMol VR environment to be spotted.*

This sphere is a special item: it contains a snapshot of the molecular structure that the user is interested in, and it behaves like a portal to another dimension, i.e. UnityMol. In order to activate it, it is necessary to bring the sphere close to the head, simulating the action of looking inside it. When the sphere is held close enough to the virtual player's head, a seamless transition changes the surroundings into the UnityMol VR environment, where the molecule is already loaded and ready to be inspected.

For what concern the return trip, a special button has being integrated in the UI of the microscopic level, which enables the user to come back to the starting macroscopic level.

### **3.2 CHEMISTRY FOR CULTURAL HERITAGE: SALA DEGLI STEMMI**

Palazzo della Carovana is the main building of the Scuola Normale Superiore in Pisa. It was built by Giorgio Vasari during the XV century for the headquarters of the Knights of St. Stephen. The name refers to the three years

long training – called “la Carovana” – that the knights had to undertake in order to enter the Order.

The palace has undergone several alterations, which led us to its current state. Vasari’s intervention was above all in the ceiling, especially in the two larger rooms prepared for group activities: the “weapons room” – today called “Sala Azzurra” – and the “fencing room” – today called “Sala degli Stemmi” – that were adorned with elegant paneled ceilings. Both these rooms and several staircases and corridors are decorated with hundreds of coat-of-arms, each of which represents the family the knights belonged to before joining the Order.

In 2012, the palace underwent a restoration process that took several months to complete. In particular, 447 coat-of-arms hanging in the historical rooms have been taken down from the walls and sampled; moreover, some samples were taken from a wooden beam of the coffered ceiling of Sala degli Stemmi. Chemical analyses were conducted in order to acquire information about the chemical composition, to understand the state of conservation, and to discover if any previous restoration on the coat-of-arms was ever conducted and how. The performed analysis were carried out by means of different physical-chemical techniques, in order to characterize both organic and inorganic molecules.

The results obtained from the chemical analysis were transcribed into files (Fig. 12 and Fig. 13 show an extract from one of these files) and not digitized in any database. This has led to the enrichment of the virtual architecture with the possibility to digitize the collected metadata directly on the 3D model of the artifacts, as will be explained in Paragraph 3.2.1.

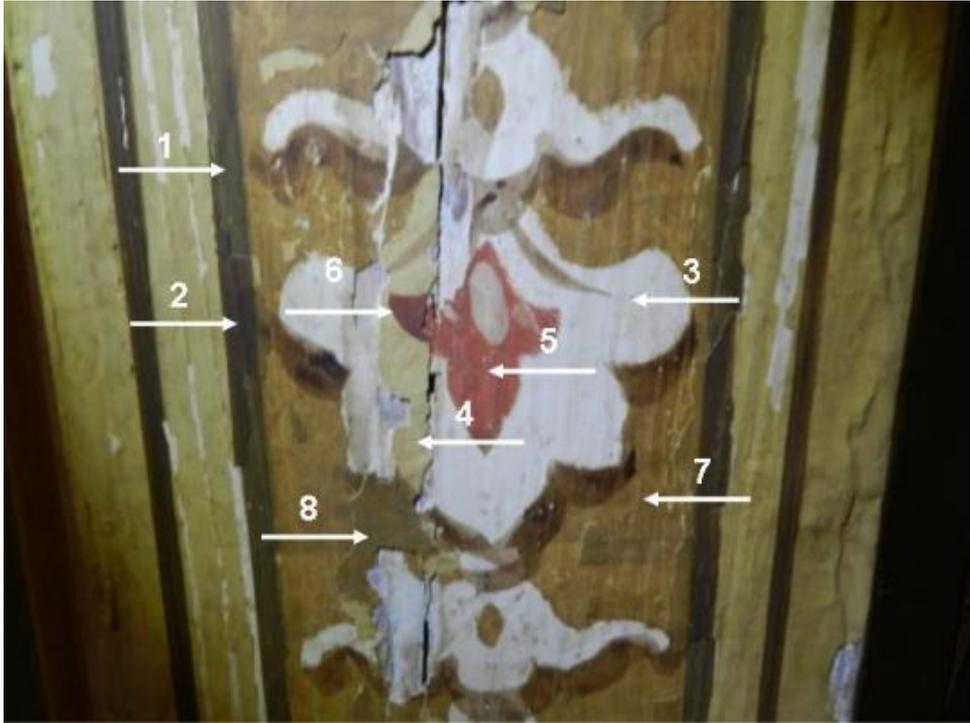


Fig. 12: the image shows the wooden beam and the numbered points from where the samples have been taken.

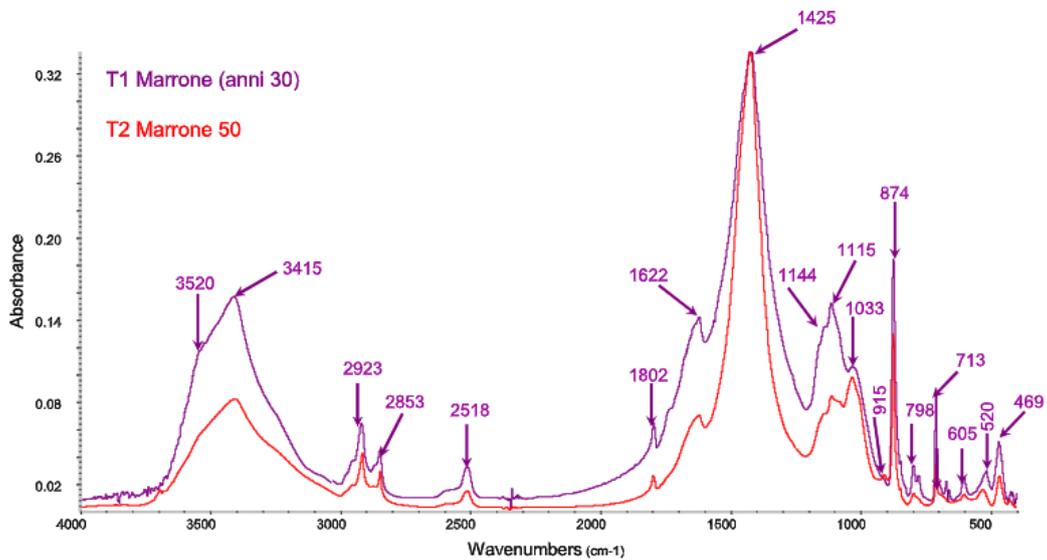


Fig. 13: comparison between the IR spectra of T1 and T2 (respectively “1” and “2” in Fig. 12).

For each sampling point, experts have inferred the molecular composition mainly on the basis of the absorption bands appearing in the vibrational spectra, an example of such spectra being shown in Fig. 13. It was possible to conclude that some of the sampling points share similar molecular compositions. For this reason, we chose to show only a few of them in the scene.

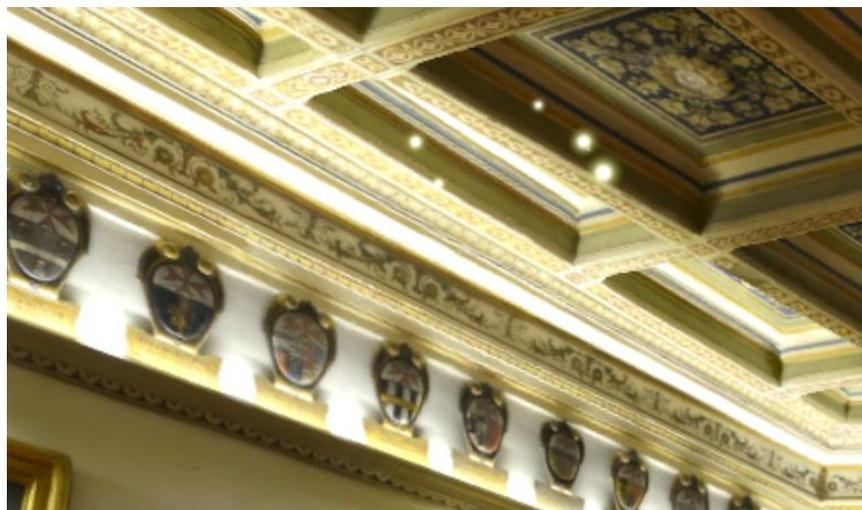
In particular, the molecular structures taken into considerations are calcium carbonate ( $\text{CaCO}_3$ ) from T3 and T6, hematite ( $\text{Fe}_2\text{O}_3$ ) from T2, T4, T5 and T6, and massicot (a lead oxide,  $\text{PbO}$ ) from T8.

The user starts the experience standing next to the entry door of the Sala degli Stemmi. It is possible to move around by physically walking (as the Vive offers positional tracking) and by using the controller for the *teleport* function. In this last scenario, the player can decide to teleport only to specific predefined spots inside the virtual room, as shown in Fig. 14.

Interactive objects are highlighted with a particle system, so they are easily visible (see Fig. 15).



*Fig. 14: the teleport action toward a specific position inside Sala degli Stemmi.*

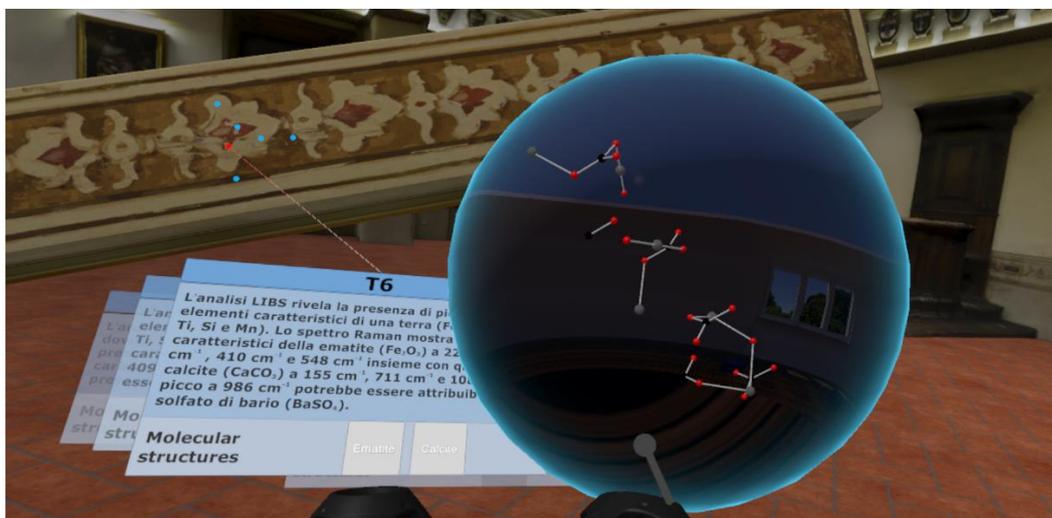


*Fig. 15: the yellow particles around the wooden beam indicates that the object is interactive.*

When the user selects the interactive object, it comes down from the ceiling and stops in front of the user. At this point, the sampling points (i.e. the points where the chemical analysis was carried out) are shown on the surface of the object as red spots. The user can grab the object with the controller, and open the metadata of each sampling point by clicking a button on the controller and pointing directly on one of them. The metadata are shown on top of the other controller (the one not used for the selection), organized inside a panel.

The panel is close enough to the player, so he is able to reach it directly with the controller. When the user selects a sampling point, all the sites of measurement and the corresponding data are opened and organized in a Cover Flow-like structure (see Fig. 16). In addition, two arrows are shown on the controller, indicating that it is possible to move between metadata by pressing the touchpad button.

The chemical species identified through the chemical analysis can be accessed by pressing a button on the panel and, when selected, the molecule appears inside the portal sphere on the controller.



*Fig. 16: the wooden beam is in front of the user. The metadata are organized in panels on the controller, and the portal sphere shows the preview of the molecular structure selected from the T6 sampling point.*

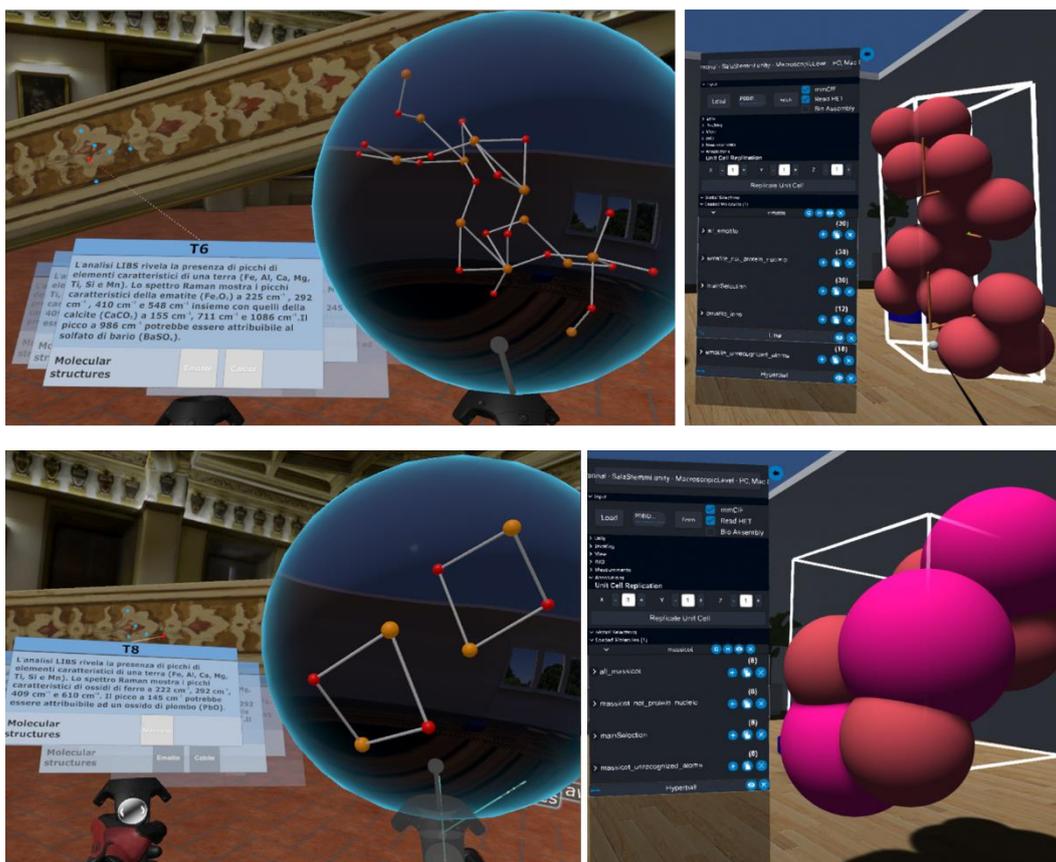


Fig. 17: on the left, the hematite and massicot molecular structures appear in the portal sphere. On the right, the same molecules (in Van der Waals radii representation) opened inside the UnityMol VR environment after the transition from macroscopic to microscopic.

By bringing the portal sphere close to the head, the virtual journey of the user moves inside UnityMol VR, where the chosen molecular structure is loaded and ready to be investigated. Fig. 17 shows the before-and-after of the virtual journey that the user is about to experience. All the molecules taken into consideration in this scenario are crystalline structures, so UnityMol VR shows their unit cell and the possibility to replicate them.

In this scenario, a particular mention is due to the 3D reconstruction of the whole room, which will be discussed in Par. 3.2.1.

### 3.2.1 Sampling operation via Unity Editor

The objective of this scenario is to add (or modify) new (or already existing) sampling points on the 3D mesh representing the interactive object. To do so, it has been necessary to setup the scene with the 3D model and the scripts that will enable the sampling operations.

First, a clarification on Unity needs to be made. Unity engine works in two different modalities: “edit mode” and “play mode”. The edit mode is for applying modifications to the virtual environment (i.e. import a 3D model in the scene, set up its behavior through scripts, and so on); the play mode is for testing its correct functioning. The import activity of a 3D model during edit mode does not require any effort from the user, as the importing functionalities are included in the Unity engine itself. However, the import activity of a 3D model during play mode needs to be handled directly by the programmer by writing appropriate source code.

The addition of sample points upon the virtual artefact surface requires the import of the 3D model inside the virtual scene. According to a research conducted some years ago [119], the total number of 3D file formats exceed 140, even though only a few of them are the most commonly used. Anyhow, every file format needs its own import algorithm. Unity, being a game engine, ensures the possibility to import different types of 3D files [120] inside the scene during edit mode, but these source codes are not public, hence they cannot be used in play mode. However, it is reasonable to take advantage of these algorithms by developing the sampling activity inside the edit mode. In this way, instead of setting up an executable, it will be possible to handle the sampling operations directly from Unity engine.

After importing the textured 3D mesh of the artefact inside the scene, the user must add the `ImportedModel` component to the game object<sup>5</sup>. This script gives different possibilities:

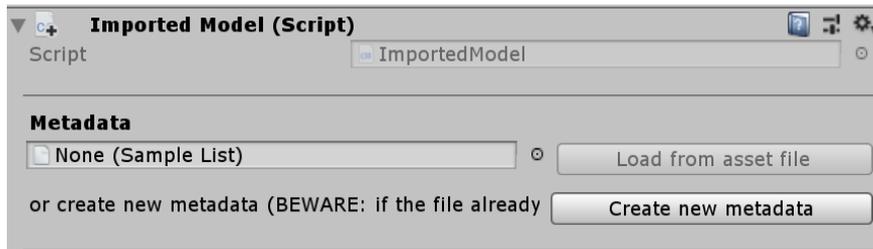
- to create a new empty data container;
- to load already existing metadata;
- to add sampling points directly on the surface of the mesh;
- to save all sampling points inside the data container;

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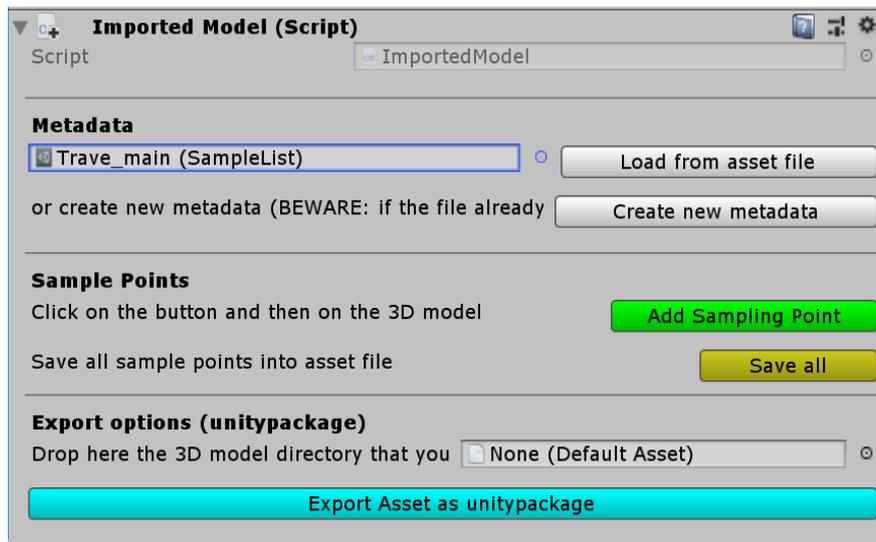
<sup>5</sup> `GameObjects` [121] are the fundamental objects in Unity that represent characters, props and scenery. They do not accomplish much in themselves but they act as containers for `Components`, which implement the real functionality.

- to export data inside a *.unitypackage* (that will contain both sample points data and all the necessary scripts that another user will need in order to reproduce the same scene in its own Unity software).

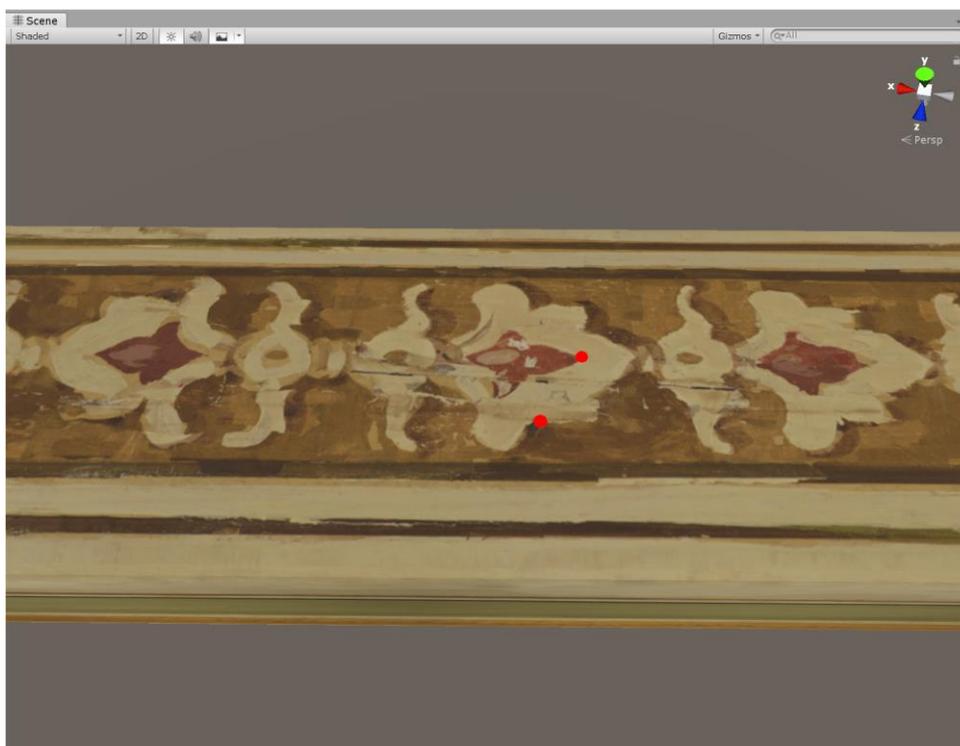
The creation of a new data container is required for the insertion of new sample points (Fig. 18, Fig. 19 and Fig. 20 show the main steps of the process).



*Fig. 18: a screenshot of the script options when no data container has been created or loaded.*



*Fig. 19: a screenshot of the script options when a data container (SampleList) has been loaded or created*



*Fig. 20: screenshot of one of the Sala degli Stemmi wooden beam mesh from Unity Editor, showing two sampling points represented as red spots on the surface of the mesh.*

Sampling points data can potentially collect all available information regarding the sampling operation, both qualitative and quantitative. In particular, each data contains:

- an identification string;
- a description of the results deriving from chemical analyses performed;
- a list of the molecular structures which can be inspected in the Visualization scene.

The molecular structures can be saved as:

- SMILES [37] string;
- path of the molecular file, if available.

SMILES notation is one of the many possible input format that Open Babel is able to read and convert into a molecular 3D structure, which will be shown in the virtual Sala degli Stemmi. Furthermore, Open Babel can convert a SMILES notation into different types of file, such as .PDB and .mmCIF, which are the requested types of input file for the UnityMol viewer.

The data container and the sampling data are saved as a Unity asset, which are written to disk and therefore persistent between sessions. Therefore, the sampling information can be directly loaded inside other Unity scenes. Moreover, the data are exportable as *unitypackage*, making it sharable within different instances of Unity.

### **3.2.2 Photogrammetric reconstruction**

“Photogrammetry comprises all techniques concerned with making measurements of real-world objects and terrain features from images. These [...] may be taken by film cameras, digital cameras or electronic scanners on tripods, airborne or space borne platforms. Applications include the measuring of coordinates, quantification of distances, heights, areas and volumes, preparation of topographic maps, and generation of digital elevation models and orthophotographs” [123]. Photogrammetric techniques use passive optical sensors to obtain three-dimensional metric information, from which it is possible to recreate a realistic virtual representation of what has been shot.

The photogrammetric reconstruction of the room and some of its artworks has required the usage of a professional Nikon D800 camera, in combination with an AF-S NIKKOR 24-120mm f/4G ED VR photographic lens.

Our objective has been to recreate the original environment as a whole, so that the user can visit and interact with the artwork in its primary spot. Hence, the first issue to be addressed has been the acquisition of the artwork and its surroundings as a 3D model. It has been realized by 3D structure from motion procedure, as a result of 359 pictures shot and given as input to the Metashape software [124]. All the pictures have been shot in manual mode, prolonging or shortening the shutter speed depending on the quality of lighting of each part of the room. In this way, it has been possible to guarantee a homogeneous colorimetric appearance overall the 3D model.

The workflow toward the VR reconstruction of Sala degli Stemmi involves the extraction of the correspondences between the images (tie points) with the Structure from Motion (SfM) algorithm, the creation of the dense point cloud

with the Dense Image Matching (DIM) algorithm. This step is called 3D survey, and it is followed by the modelling step, that is the creation of the structured polygonal surface (mesh), which is finally texturized. Metric references have been used to correctly scale the 3D model.

The acquisition of the room has required four rounds of shooting, two for the walls and two for the wooden coffered ceiling. The pictures of the walls have been shot at a different angle for the upper and the lower side, and at a fixed distance, so that the images could have an overlapping side for the Metashape software to work properly. For the coffered ceiling, it has been necessary to put the camera in a perpendicular position in respect to the ceiling itself, and also to shot diagonal pictures in order to acquire also the internal part of every coffer. On the contrary, the floor has been recreated using a 3D modelling software, since its pattern was easily replicable.

Concerning the artworks to be inspected in the virtual scenario, to start we choose a wooden beam, whose colour was restored, positioned on the coffered ceiling.

### **3.3 BIOCHEMISTRY: INSIDE THE BRAIN**

The presented scenario propose a descent into the human skull. In this scenario we focus on the spatial scale, going deep into the matter that enables us to think.

When the scene starts, the user finds himself immersed into an imaginary building made of only one big room. Inside the room, a pedestal is placed in front of a glass window overlooking the void, as reproduced in Fig. 21. A UI panel for “descending” and “ascending” between levels is placed next to the pedestal. This menu can be reached directly with the controller.

The first object presented to the user is a 3D reproduction of a real human brain, whose 3D model has been created from pictures of a computed tomography (CT) scan. Brain activity is made possible by the interconnections of neurons, electrically excitable cells that communicates with each other via

synapses: this is the reason why a 3D reproduction of a real neuron represents the “lower level” of the brain. A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. Among neurotransmitters, acetylcholine is the one that motor neurons of the nervous system release in order to activate muscles. A 3D reconstructed acetylcholine is the last object presented to the user.



*Fig. 21: the 3D models of a brain, a neuron and the acetylcholine molecule.*

These items, shown in Fig. 21, can be inspected one at a time. Following the space scale, they are placed in decreasing order of magnitude.

When the user arrives at the acetylcholine level, two possibilities are available:

to launch UnityMol VR, in order to inspect the acetylcholine molecule (see

- Fig. 22);
- to set the numeric parameters (through a virtual numeric keypad) for the computation of the PES executed by Proxima. When computed, the result file is saved on disk and its path is sent to the AVATAR application, for visualization (see Fig. 23).



sugars [125]. About 1% of the mass of the ISM is in the form of dust grains, which form in the outflows of dying stars. These eject refractory molecules, which form the aggregation nuclei for the particles collecting oxygen from the interstellar medium [126].

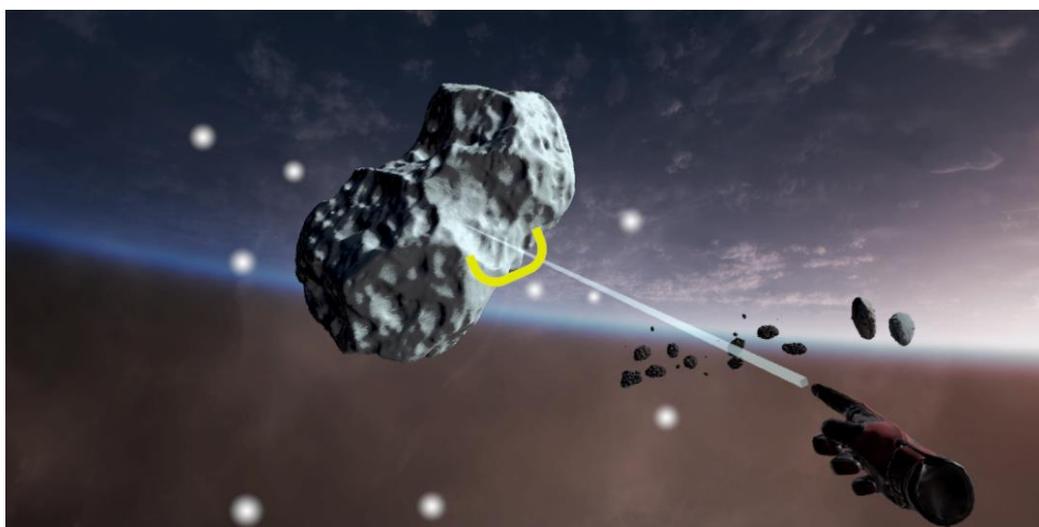
The exact composition of dust-like material is still subject of debate, however, IR spectroscopic observations reveal the presence of silicates, specifically olivines of general composition  $\text{Mg}_{2x}\text{Fe}_{2-2x}\text{SiO}_4$ . In fact, the IR features measured at 9.7  $\mu\text{m}$  and 18  $\mu\text{m}$  correspond to the Si-O stretching and O-Si-O bending vibrations, respectively. The broad appearance of the bandshape suggests that those silicates are mainly amorphous, although it has been speculated that about 5% of the grain presents a crystalline phase, a fraction that may be larger in some environments [127].

In general, comets and grains are covered by icy mantles that form through the freeze-out of gas-phase species, with water being the most abundant constituent as revealed by the vibrational signatures around 3.0 and 6.0  $\mu\text{m}$  associated with O-H stretching and H-O-H bending modes. In addition, icy mantles contain an inventory of other species, the most common being CO, CO<sub>2</sub>, CH<sub>3</sub>OH, NH<sub>3</sub>, CH<sub>4</sub> and H<sub>2</sub>CO [128], which can act as the building blocks for the formation of more complex species.

In this context, the chosen microscopic scenario involves both the icy mantle, where the glycolaldehyde molecule has been absorbed, and the inorganic silicate core. For the latter, the  $\text{Mg}_2\text{SiO}_4$  forsterite, the Mg end-member of olivines, has been chosen, being this widely used as a model substrate for the simulation of interstellar silicates (see Ref. [129] and references therein). Glycolaldehyde has been selected in view of its astronomical detection in different sources and because of its structural chemical formula  $\text{CH}_2\text{OHCHO}$ , that makes this molecule to be considered as the smallest monosaccharide, of general composition  $(\text{CH}_2\text{O})_2$ . Furthermore, this molecule is the first intermediate in the formose reaction that leads to the catalyzed synthesis of sugars up to ribose. In this process, the parent molecule is formaldehyde

( $\text{H}_2\text{CO}$ ), one of the components of icy mantles, that produces glycolaldehyde, and then successive additions of  $\text{H}_2\text{CO}$  provide a route to ribose. Hence, glycolaldehyde appears a key ingredient for the production of three-, four- and five-member sugars.

As mentioned before, virtual reality can take us into far and inhospitable places, that we would not be able to experience otherwise. In the proposed scenario, when the user enters the virtual world, he finds himself standing on a big asteroid floating in front of a planet. A swarm of small asteroids turns around the user, while a smaller one stay still. This one is highlighted (as shown in Fig. 24), meaning that is available for a deeper inspection.



*Fig. 24: the user's hand pointing to the asteroid.*

When the asteroid is selected, it approaches the user, and the sampling points are shown on the surface of the object as red spots. In particular, it is possible to explore the composition of either the surface and the core of the asteroid.

In the first case, the structure of the icy mantle represented by a  $(\text{H}_2\text{O})_{33}$  cluster can be inspected. A closer examination reveals the presence of the glycolaldehyde molecule absorbed on it, for which it is also possible to analyze the computed normal modes of vibrations, as illustrated in Fig. 25. As to the meteorite core, the crystalline structure of forsterite can be viewed and inspected at the microscopic level (see Fig. 26).

By using the controller, the user can grab the object and open the metadata of each sampling point by clicking a button and pointing directly on one of them. The metadata, organized inside a panel, are shown on top of the controller not used for the selection. The functioning of this panel is the same as in the “Sala degli Stemmi” experience.

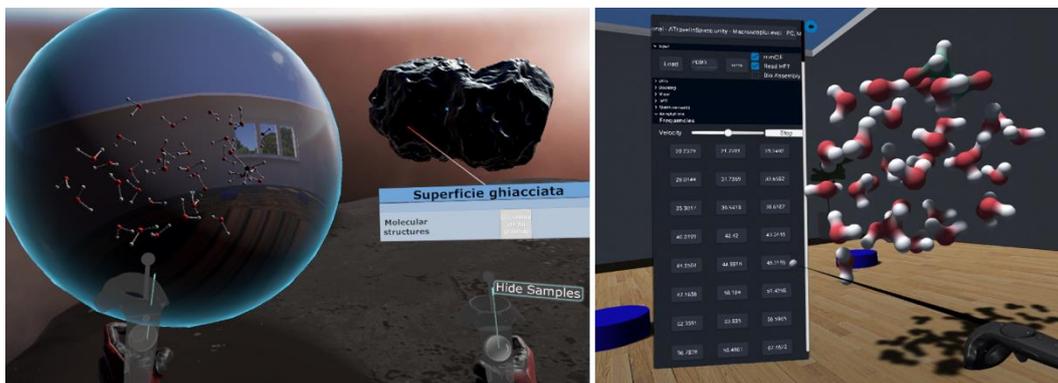


Fig. 25: on the left, the glycolaldehyde molecule surrounded by water molecules represents the icy mantle. On the right, the normal modes are shown inside UnityMol VR.

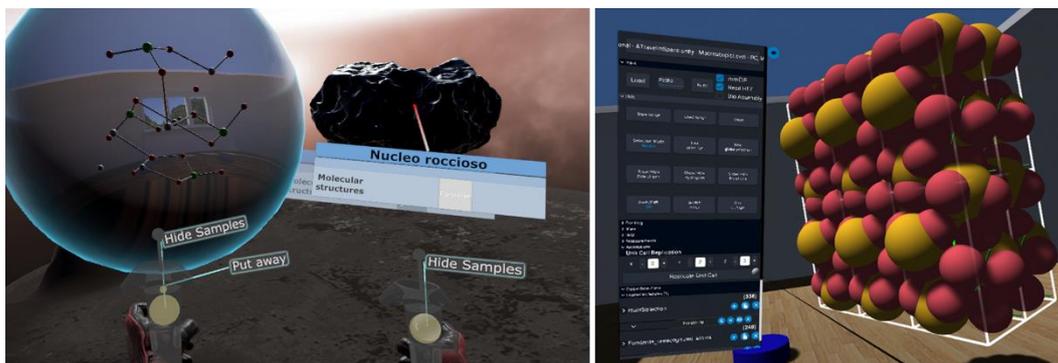


Fig. 26: on the left, the forsterite molecule representing the rocky core. On the right, in UnityMol VR, the crystalline structure of forsterite.

### 3.5 PREBIOTIC CHEMISTRY: PRIMORDIAL EARTH

The last proposed scenario puts in place a reconstruction of a hypothetical primordial terrestrial planet. The primordial Earth was formed about 4.6 billion years ago by accretion of material surrounding the sun. The early period of Earth’s history, the Hadean, featured a huge bombardment by meteors and comets. At the end of this period, about 700 million years after formation, the hot and molten Earth cooled down to temperatures around the boiling point of

water. The presence of liquid water appears one of the key factors for triggering chemical evolution and promoting life at least as we know. Hot water basins, such as lakes and lagoons, formed as a consequence of huge thunderstorms and a variety of organic molecules dissolved in them. These species might have come from the processing of atmospheric gases by some energy input (e.g. UV irradiation, volcanic thermal energy, electrical discharges). Volcanic outgassing was the main origin of gasses in the atmosphere that therefore contained carbon dioxide, nitrogen as well as traces of sulfur dioxide. Furthermore, small amounts of oxygen formed by decomposition of water and carbon dioxide promoted by UV irradiation and lightning [130]. The first fossil record of life dates from 3.5 Gyr, leaving a relatively short period, of only ~0.5 Gyr, for evolution toward the first living entities.

Either seeded to the Earth as supposed by the exogenous theory or produced locally as suggested by the endogenous paradigm, prebiotic precursors evolved, in some geochemical environmental niches, into systems capable of replication with hereditary mutation. This process is generally supposed, as pointed out previously, to have taken place in an aqueous environment and likely with the support of minerals [131]. In fact, the role of mineral surfaces in the synthesis of biologically relevant compounds is well documented, indeed they act as catalysts, concentrators and protecting agents [62], [132–136].

It follows, from the above discussion, that rocks, foggy plume and water are elements that conceal a precious treasure, the same that will slowly bring to the development of life. To emphasize this point, the following macroscopic-microscopic elements can be inspected:

- 1) a foggy plume containing molecules likely present in a rocky planet, such as sulfur dioxide ( $\text{SO}_2$ ), water ( $\text{H}_2\text{O}$ ), phosphine ( $\text{PH}_3$ ), carbon dioxide ( $\text{CO}_2$ ) and nitrogen ( $\text{N}$ ), which have all been discovered on Venus's atmosphere;
- 2) a water pool containing the RNA nucleobasis uracil ( $\text{C}_4\text{H}_4\text{N}_2\text{O}_2$ );
- 3) a rock presenting titanium dioxide among its constituent minerals.

The 3D virtual reconstructed primordial Earth is visible in Fig. 27.



*Fig. 27: the virtual reconstruction of the Primordial Earth and its active elements: rocks, water and foggy plume.*

The foggy plume, the water pool and the rock are highlighted with the usual particles, indicating their interactivity.

When the user selects the rock, the portal sphere shows titanium dioxide. The virtual journey forwards inside UnityMol VR, where the user can inspect its crystal structure, as illustrated in Fig. 28.

For the foggy plume, a UI panel gives to the user the possibility to select one of the molecules present in it (see Fig. 29). For these, beside to the possibility to investigate the geometry, it is also possible to visualize and animate the normal modes of vibration, as exemplified in Fig. 30 in the case of phosphine. For the water pool, the uracil surrounded by water molecules appears in the portal sphere, and its MD trajectory file is automatically loaded to be inspected inside UnityMol VR (see Fig. 31).

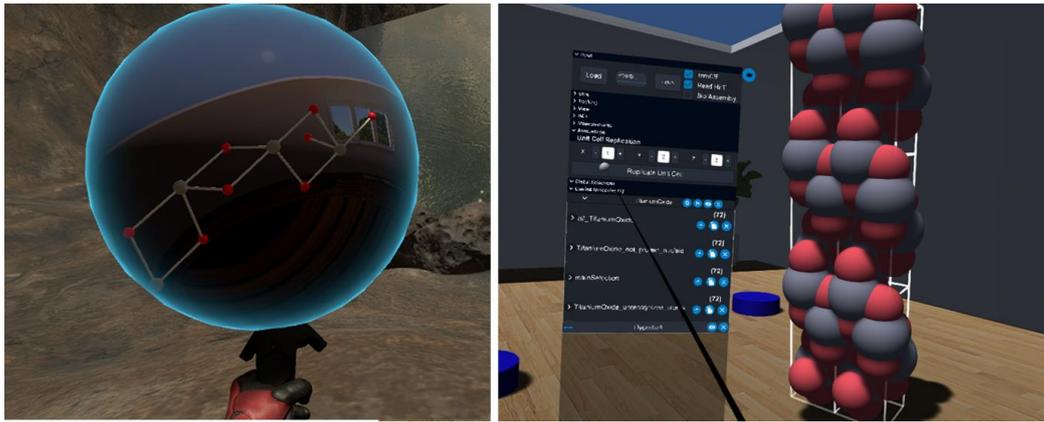


Fig. 28: macroscopic-microscopic transition for a rock containing  $TiO_2$  among the constituent minerals.

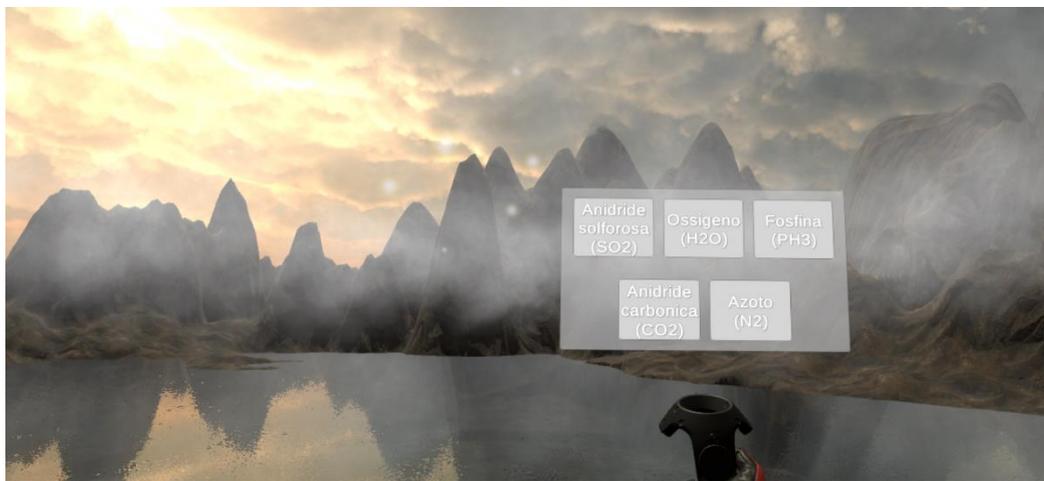


Fig. 29: when the user selects the foggy plume, a UI panel showing the molecules present in it appears on the controller.

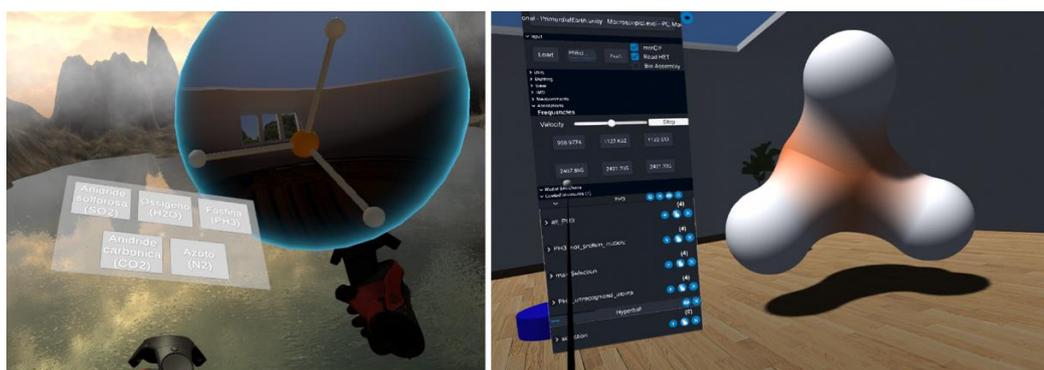


Fig. 30: the phosphine molecule has been selected from the list of Fig. 29. On the right, the normal modes (which can be played by pressing the frequency buttons) of the phosphine are loaded inside UnityMol VR.

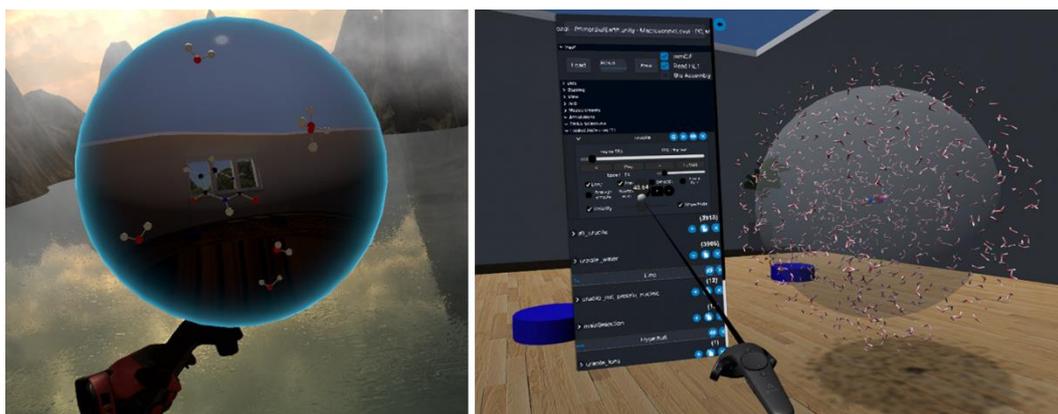


Fig. 31: the uracil molecule in the portal sphere (on the left) and inside UnityMol VR (on the right) with the loaded MD trajectory. In particular, the user is changing the size of the visibility sphere through the UI.

### 3.6 INTERACTION MODES AT MACROSCOPIC LEVEL

In the VR visualization of the macroscopic scenarios, three types of interaction modes are available:

1. *long distance*, for reaching items far from the user;
2. *natural*, for reaching items close to the user;
3. *mediate*, for interacting with the UI.

#### 3.6.1 Long distance interaction

Two approaches are viable so that user can reach far items: i) bring the user close to the item, or ii) move the item toward the user.

In the first case, a possible approach would have been to move the user's virtual camera toward the item. This would have caused motion sickness, as the user's physical body movement would not match with the one in the virtual world. It would have been likewise to move instantaneously (*teleport*) the player close to the item, resulting in he or she floating in air.

Therefore, the second solution has been considered the most suitable for our scenario. Once the player presses a button on one of the Vive controllers, a laser beam aiming in the controller direction appears. If the laser beam hits an object of interest, a circular animated timer is shown, indicating that the object will

be selected in a few seconds if the laser beam stays still on it. When the selection is engaged, the object will move in front of the player.

### **3.6.2 Natural interaction**

As for VR, the definition of “natural interaction” is not univocal. In general, natural activities are the ones where people communicates through gestures, expressions and movements, without the need of wearing device or learning instructions. For this reason, natural interaction should be intuitive, which implies a UI as transparent as possible to the eyes of the user, while the system should be able to sense what the user is trying to do [137, 138].

Given this premises, the naturalness of the interaction seems to be deeply connected to the absence of a medium, such as a mouse and keyboard, or a controller. Devices such as Microsoft Kinect [139] and Leap Motion [140] are designed to offer the possibility to interact in a natural way with the virtual environment, as the user’s body itself become the medium of the interaction.

Despite of the growing operating ability of these devices, most of VR systems are sold accompanied with fully tracked controllers. This is due to the fact that inputs from button clicking are more reliable than those coming from gesture recognition systems, which are prone to false positives issues.

The HTC Vive VR system also comes with two integrated controllers. For this reason, it is not possible to talk about “natural interaction” in the context of this project and remaining coherent with its definition. However, the SteamVR plugin gives the possibility to map a realistic 3D model of human hands instead of the controllers meshes. Moreover, hand’s poses can be adjusted in different ways when the buttons on the controller are clicked. In this way, the user can perceive the simplicity to reach for a virtual object with “his/her own hands”, enhancing even more her sense of presence. In the TARDIS framework, the hands’ poses are adjusted as follows:

- resting pose: the user is not clicking any button;

- pointing pose: the user is either indicating a position where to teleport, or is pointing towards an object of interest.

Once the object has been selected and is in front of the player, it is possible to interact with it in the most natural way, i.e. by grabbing it with one of the two controllers. This action lets the player inspect the whole object and eventually its sampling points. In order to do so, the player approach the controller close to the chosen sampling point, which will light up to indicate it is going to be selected. Its data are shown on a UI panel. The application provides a visual and a haptic feedback in order to compensate the lack of physical collision.

Natural interaction applies also to the portal sphere, as the user brings it close to the head, as to look deeply inside, which is an action that one would do with a real object.

### **3.6.3 Interaction with the UI**

The UI and the corresponding kinds of interaction changes depending on the specific scenario.

In the “Sala degli Stemmi”, “A travel in space” and “Primordial Earth” scenarios, the player can read information about the chemical composition on a panel that has a position in the virtual world, as shown in Fig. 32). Moreover, for the “Sala degli Stemmi” scenario only, it is also possible to read information about the chemical analysis. The UI panel position is the same of the controller; hence, the player is always able to read the data without moving. It is also possible to select a molecule to be displayed by putting in contact the controller with the panel. The application provides a visual and a haptic feedback also in this case.



Fig. 32: the Cover Flow-like menu shows the sampling data, in this case the T4 point from Sala degli Stemmai scenario. The molecule button highlights when the controller hovers it, showing the possibility of selection.

In the “Inside the Brain” scenario, the panel for switching between levels has a fixed position close to the pedestal. Furthermore, a numeric keyboard appears when the user has to select the numbers to be used as parameters for the PES computation executed by the Proxima library. For this type of interaction, the hand assumes a “pointing finger” pose, which indicates the possibility to select the number keys by pointing and clicking, as indicated in Fig. 33.



Fig. 33: a screenshot of the user’s hand in “pointing pose” approaching the numeric keyboard in the “Inside the Brain” scenario.

## 4 CONCLUSIONS AND FUTURE DEVELOPMENTS

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This thesis aimed at finding new ways of exploring heterogeneous fields of study through virtual reality technologies. The multiscale and multidisciplinary TARDIS framework is an attempt to create a common environment as a meeting point between experts of different fields. In particular, we aimed at creating a tool to connect the infinitely big to the infinitely small, the past and the future. We believe that the virtual journey in VR from the macroscopic to the microscopic worlds can lead to new results and insights that would have been difficult to achieve otherwise. To the best of our knowledge, this has been the first attempt to set up such a framework.

The scenarios we have proposed represent just a small part of the possibilities that can be explored with TARDIS. Thanks to the modularity and expandability of the framework, it is going to be easy to increase the number and types of case studies.

Indeed, it is our intention to keep this project going on. For example, the cultural heritage scenario could be further enriched by adding more interactive objects, such as the coat-of-arms contained in Sala degli Stemmi. We would like to add the possibility to inspect the whole set of objects by type of molecular structure. In case of restored paintings, we would like to introduce the possibility to select different areas depending on the type of pigments and/or binders. The astrochemical application could involve several exoplanet conditions, together with meteorites with different composition. Next, several networks of chemical reactions could be explored in order to compare different proposals about the interplay among different reaction channels. Analogous enhancements can be introduced in the primitive earth scenario and the interaction of different drugs with their targets can be explored along routes analogous to that already analyzed in the brain scenario.

From a more general point of view, TARDIS could become a tool not only for static but also predictive analysis. Indeed, one of the current limits of the TARDIS architecture is that the molecular structures can be only inspected and visualized. With a deeper integration of a computational or perception software, it would be possible to expand the potentialities of the framework. For example, in the Sala degli Stemmi scenario, we would be able to modify the molecular structure of a certain pigment, then to run prediction analysis algorithms and then visualize at the macroscopic level how it would appear directly on the cultural good. Analogous extensions can be introduced in the other scenarios like, e.g., exploring the formation of different DNA bases or peptides in the primitive earth scenario or replacing acetylcholine by other neurotransmitters in the brain application. In this respect, we are planning to include a full implementation of the Proxima library inside TARDIS.

Another very appealing development would be the implementation of a virtual reality viewer for solid-state chemistry capable of interfacing with quantum chemical software used to model crystals (such as CRYSTAL). This would give the possibility to visualize, in addition to the periodic structure, the properties computed for the material such as the electrostatic potential maps, eventually resorting to an augmented VR environment for the simultaneous visualization of 2D plots such as density of states, band structure and vibrational spectra. This software could be integrated in the TARDIS framework as it has already been done with UnityMol. Finally, a further development could be to create a molecular editor in VR, in order to create both isolated molecules and crystalline structures.

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## 6 PAPERS AND PUBLICATIONS

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