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S. Doutreligne, C. Gageat, T. Cragolini, A. Taly, S. Pasquali, et al.. UnityMol: interactive and ludic visual manipulation of coarse-grained RNA and other biomolecules. Virtual and Augmented Reality for Molecular Science (VARMS@IEEEVR), 2015 IEEE 1st International Workshop on, Mar 2015, Arles, France. pp.1–6, 10.1109/VARMS.2015.7151718 . hal-01498023

HAL Id: hal-01498023

<https://hal.science/hal-01498023v1>

Submitted on 19 Jan 2023

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UnityMol: Interactive and Ludic Visual Manipulation of Coarse-Grained RNA and other Biomolecules

Sébastien Doutréigne* Cédric Gageat† Tristan Cragolini‡ Antoine Taly§ Samuela Pasquali¶
Philippe Derreumaux|| Marc Baaden**

Lab. de Biochimie Théorique, CNRS UPR9080, Univ. Paris Diderot, Sorbonne Paris Cité, 13 rue Pierre et Marie Curie, 75005, Paris, France

ABSTRACT

We present a general software architecture to carry out interactive molecular simulations in a game engine environment. Our implementation is based on the UnityMol framework and the HireRNA physics engine. With UnityMol, we pursue the goal to create an interactive virtual laboratory enabling researchers in biology to visualize biomolecular systems, run simulations and interact with physical models and data. Similarly, UnityMol enables game designers to build scientifically accurate molecular scenarios. We discuss four case studies, from simulation setup via immersive experiments, force-induced unfolding of RNA to teaching and collaborative research applications. Visual effects enrich the dynamic and immersive aspects. We combine an appealing visual feedback with a set of analysis features to extract information about properties of the fascinating biomolecular systems under study. Access to various input devices enables a natural interaction with the simulation.

Index Terms: I.6.6 [Simulation and Modeling]—Simulation Output Analysis; J.3 [Computer Applications]: Life and Medical Sciences—Biology and Genetics

1 INTRODUCTION

Structural data for biomolecules is nowadays abundant. Yet we only start to understand the dynamical properties of these objects. Molecular simulation is key to extend our knowledge on the conformational landscape of a given static model. Interactive simulations in particular enable a scientist to directly probe and examine such properties. In our lab, we have a growing interest in studying RNA molecules, which lead to the development of original computational models. Here, we present a solution for their interactive manipulation based on the HireRNA physics engine and the UnityMol [8] visualization and interaction framework, based on the Unity3D game engine. Relevant aspects are reviewed in [6] providing a state of the art of advances in molecular simulation and visualization.

Visualization of molecular structures is commonly achieved by specialized software, among which UnityMol. It has an emphasis on real-time graphics with visual effects from the video game industry and the fast prototyping of new molecular representations, for example the HyperBalls ray-casting technique designed to render evolving atoms and bonds [1]. Among similar software figures VMD, a widespread molecular visualization software [7]. VMD inspired feature extensions that we added to UnityMol such as the

coupling with molecular dynamics simulations and the support for haptic devices.

Delalande et al. [4] used VMD together with the Gromacs molecular dynamics engine to manipulate a variety of biomolecular systems. This approach allows to interactively apply forces and investigate biomechanical effects in detail. In [5], Gao et al. used steered molecular dynamics for the study of the all-atom Titin protein II domain. Stretching the molecule and measuring its extension allowed them to correlate the resilience of the domain to specific inter-atomic interactions. This virtual setup was used to interpret experimental Atomic Force Microscopy (AFM) data.

Here, our objective is to use a dedicated user-friendly graphical environment coupled with a coarse-grained physical interaction model for a similar purpose. Our contribution then is to show how our implementation can be applied to various use cases and validate our design choices. One of Gao's unfolding experiments uses a constant force, inspiring the conditions for our Use Case 3 (Section 3.3) for RNA molecules. Particularly, we show how preliminary virtual experiments were conducted in this environment. Our work demonstrates that such investigations are feasible with a mainstream game engine.

This paper is organized as follows. We first describe UnityMol's features: the rendering methods, the coupling with molecular dynamics simulations and the use of virtual reality devices. Next, we show how these features can support research in biology with multiple use cases. Application to education and pedagogy is also addressed. The last part discusses the performance of our application, current limitations and the next additions we intend for UnityMol.

2 PRESENTATION OF UNITYMOL

UnityMol is a molecular visualization software geared towards biology. Created in 2009, it enables us to quickly prototype and validate new molecular representations. UnityMol development is based on the Unity3D video game engine, a promising new way to design research software as previously discussed [8]. The next sections describe UnityMol capacities, first pre-existing ones that were customized, then additions implemented specifically for the present contribution.

2.1 Molecular Visualization

UnityMol includes both original and more traditional implementations of molecular graphics algorithms based on polygonal static and ray-casted dynamic rendering techniques.

2.1.1 Secondary Structures, SugarRibbons and other Polygonal Mesh Representations

Common tools are provided for a static view of the system. Among them, we can cite molecular surfaces based on a Gaussian convolution kernel, secondary structure ribbon depictions of proteins as introduced by Richardson and an innovative simplified representation for complex sugar molecules.

The two first representations are standard in the field. The surface is an abstraction showing the exposed parts of the molecule, typically in contact with solvent or with a membrane. Secondary

*e-mail:doutreligne@ibpc.fr

†e-mail:gageat@ibpc.fr

‡e-mail:tristan.cragolini@ibpc.fr

§e-mail:taly@ibpc.fr

¶e-mail:samuella.pasquali@ibpc.fr

||e-mail:philippe.derreumaux@ibpc.fr

**e-mail:baaden@smplinux.de

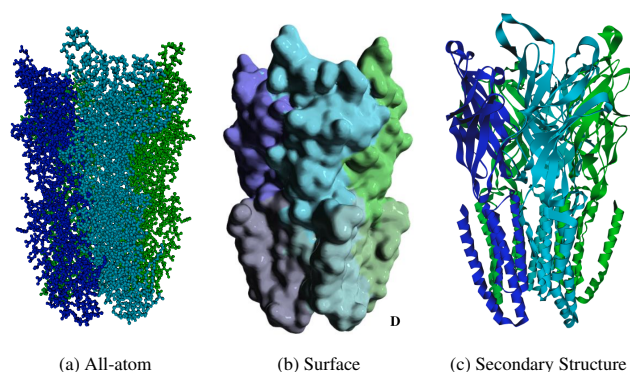


Figure 1: Three representations of the GLIC ion channel rendered in UnityMol. The five sub-units are depicted by different shades of blue and green.

structures reflect regular atom position patterns induced by aligned interatomic hydrogen bonds. These depictions are illustrated in Figure 1 for a particular molecule, a membrane-bound ion channel called GLIC rendered in UnityMol. GLIC is composed of five sub-units spread around a symmetry axis, conferring a tubular core to the assembly. Atomic interactions at the entrance conduct cations inside the structure. This way, cations are propagated from one side of the membrane to the other - from top to bottom on the figure.

In addition to such relatively common visualizations, we implemented an innovative sugar representation [11]. This extension has two main purposes. Sugar molecules feature cycles detected by our algorithm. These cycles are filled with color in accordance to the underlying chemical composition. This way, specialists can quickly determine the molecule type in 3D. On the other hand, we take advantage of this geometry to generate simplified polygonal meshes and reduce the number of triangles to render. We improve the performance for the user to navigate, but also pass from a crowded all-atom view to a useful abstraction revealing the molecular morphology (See Figure 2).

2.1.2 HyperBalls Representation and Customization for Coarse-Grained RNA Rendering

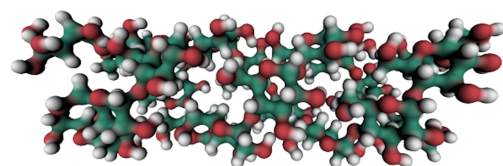
UnityMol comes with an HyperBalls GPU implementation. The heart of this ray-casting technique is the use of quadratic surface equations, perfectly compatible with a traditional rendering pipeline. HyperBalls elegantly render dynamic biomolecular events such as the formation of bonds and interactions.

To render an atom, a polygonal cube is first drawn. A fragment shader GPU program then traces a ray and solves the quadratic equation of a sphere. The normal is deduced for use in the lighting stage. The ray casting is clamped to the mesh boundaries, thus avoiding rays running toward infinity.

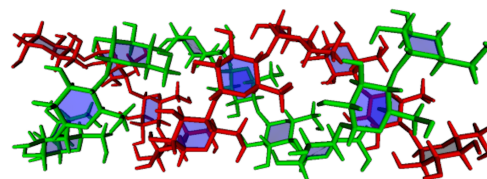
Atoms are lit using the "MatCap" shader found in Unity3D. The underlying principle is a simple texture lookup, relating the normal of each pixel to a texel. Visual feedback of molecular properties can be enhanced during this pass by using so-called "lit sphere" lighting. The procedure is the same for bonds, using a two-sheeted hyperboloid equation in this case.

UnityMol feature "metaphors". These are parameter presets corresponding to representations commonly found in the literature. An example of such a preset is the space-filling CPK representation named after the chemists Corey, Pauling, and Koltun, in which atoms are depicted as spheres.

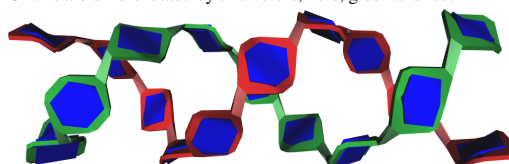
For bigger molecules, a simplified molecular representation called coarse-grained (CG) might be used. We develop such CG models for biomolecules, among which HiRE-RNA, a model for



(a) All-atom representation of a sugar double-helix. Atoms are colored according to a classic convention: white for hydrogen, red for oxygen. For convenience, carbon is green instead of black.



(b) Highlighting of cycles on top of a stick representation of the same molecule. The color denotes the sugar type; here, blue for glucose. Chains are differentiated by two colors; here, green and red.



(c) Geometry simplification where cycles have an "internal" color to show their types. They are linked together by ribbons that can be colored according to chain or type. This can be changed by the user.

Figure 2: Incremental simplification of a sugar molecule. This molecule has a double helix structure. The SugarRibbons abstraction makes this obvious.

DNA and RNA molecules [10] [3]. With such a method, several atoms are grouped together to form a pseudo-particle or grain. The amount of data to be rendered is significantly reduced, typically by an order of magnitude. The molecule parser is able to read CG models.

Furthermore, for the purposes of interactive simulations of RNA molecules, we extended the HyperBalls capabilities to render nucleobases as oriented ellipsoids instead of isotropic spheres. This is shown in Figure 3 on a tRNA molecule found in *Escherichia coli* (PDB ID 3L0U). The orientation of an ellipsoid is computed based on the plane formed by three grains constituting the nucleobase part. This geometry reflects how nucleobases must align to establish stacking interactions and form hydrogen bonded complementary pairs.

2.2 Live Simulation and Virtual Reality

To address the question of RNA and DNA folding, the HiRE-RNA physics engine computes the molecular dynamics based on a custom force field specifically developed for this model. All particles are free to move in these simulations. The next required step towards interactive visualization and manipulation of such RNA and DNA simulations was to couple UnityMol with the HiRE-RNA simulator. This coupling enables non-IT researchers to intuitively interact with the simulation and integrate their a priori knowledge about the system under study. This is a non-negligible factor to increase the precision of such simulations.

Both the HiRE-RNA in-house simulator and UnityMol now use MDDriver, a light and generic framework for bridging molecular simulators with visualization software based on the IMD protocol [4]. The HiRE-RNA simulator calculates atoms positions over

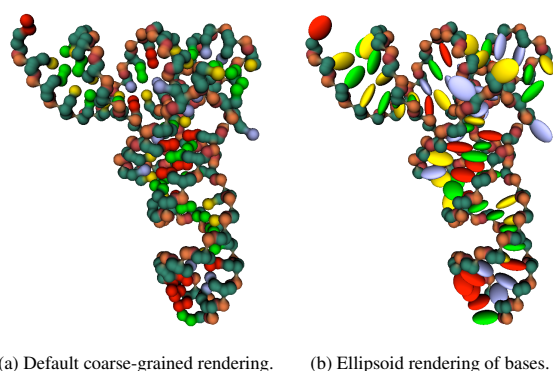


Figure 3: An RNA molecule of type tRNA in all-sphere and ellipsoid representations. Found in *Escherichia coli*, it has 73 nucleotides or 1561 atoms. With the CG HiRE-RNA model, the number of spheres to render is reduced to 475. PDB ID: 3LOU.

time. UnityMol is then fed with these new positions by the intermediary of a channel implemented in MDDriver.

The simulation transmits information related to the molecule’s energy. Among them figures the total energy of the system. The lower this energy, the more stable the molecule is. We provide this information to the user by the means of a time series plot (as shown later in Figure 5-right, subsection 3.2).

The protocol that was implemented supports sending forces to running simulations. Users are thus enabled to interact with the simulation by applying forces to atoms. Using the simplest possible interaction, with the mouse, the user can click an atom and grab it until the button is released.

To push this idea further, UnityMol supports special devices such as an haptic arm with force feedback and a 3D mouse with 6 degrees of freedom (d.o.f), three degrees of translation and three degrees of rotation, via the VRPN library. We came to implement several interaction models to obtain the best usability out of these peripherals.

When using the haptic arm, atoms act like magnets upon it. Once the arm is virtually sufficiently close to an atom, the user can feel a force attracting him toward the atom. For this purpose, we detect the closest atom. We subtract the atom position vector with the pen position vector to determine the force direction. We use a parameterized gaussian function to relate the distance between the arm and the atom to the applied force. The further the arm is from the atom, the higher is the attracting force until the gaussian peak is passed. To bypass the physical limitation of the device workspace, we implemented a clutching feature. These functionalities and more are inspired by [13].

For a team to collaborate on the same dataset, complex and large-scale data may be rendered on advanced displays such as the 33 megapixel 4,3x2,4 m display wall at Maison de la Simulation in Saclay used to validate our framework as illustrated in Figure 4.

When dealing with very large molecules, it becomes difficult to navigate in the scene. This is why we implemented an experimental guided navigation feature. The problem is to place the camera looking toward a target, while minimizing the occlusion; that is minimizing the number of obstacles between the camera and the target. For now, this feature is limited to the GLIC protein [14]. We also exploit the symmetrical architecture of GLIC. We precompute trajectories around and outside the channel to constrain the camera. To further denote the molecule structure, the five sub-units can be moved away from the center. These principles are illustrated in Figure 4.

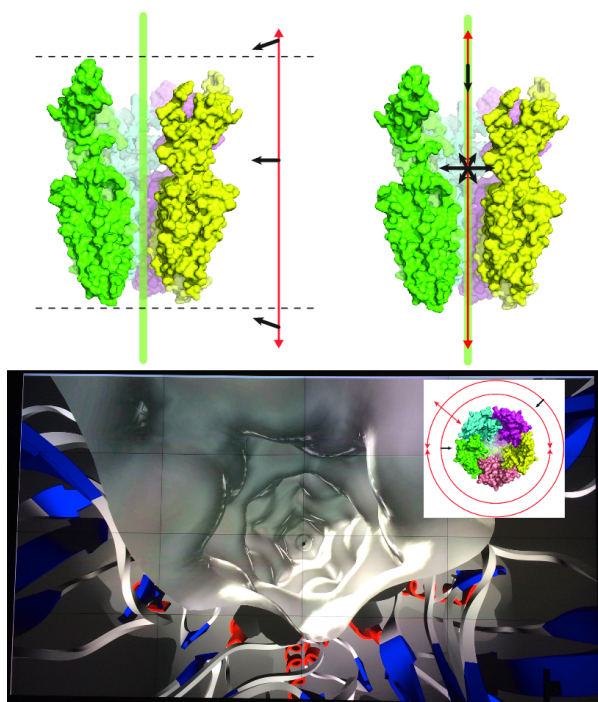


Figure 4: GLIC guided navigation through pre-computed trajectories on large-scale displays. Top: GLIC sub-units are highlighted in green, cyan, yellow, magenta and pink. The axis of symmetry is depicted as a thick green line. Red arrows show the different camera paths. Black arrows designate the camera orientation. See [14]. Bottom: a picture of UnityMol running on a display wall and rendering the GLIC surface. The camera looks inside the channel thanks to the precomputed trajectory. The image is rendered across a 4x4 tiled display matrix at 7680 x 4320 pixel resolution.

3 APPLICATIONS

Interactive manipulation of biomolecules on the computer is a very useful technique [4] to probe their mechanical properties, build complex models, explore their interactions and complement experimental investigations. In our hands, we came to the conclusion that a CG model provides an excellent compromise between simulation speed and biological fidelity, being more robust with respect to user interactions than computations carried out at an all-atom level. Enriched by special screen-space effects such as motion blur or glowing atoms, the underlying dynamic molecular behavior is highlighted visually. Important properties may augment the view to inform the user about specific features such as hydrogen bonds or overall simulation energy.

In this section, we relate four use cases of these tools that we implemented, tested on selected scenarios and so far evaluated subjectively.

3.1 Use Case 1: Simulation Setup and Preparation

UnityMol has been used in the lab to prepare and validate molecular simulations. By executing a short interactive simulation, aberrations and errors in the simulation setup are easily spotted by a trained observer, whereas they may not show up immediately upon batch execution. This visual examination of the early simulation stages avoids the loss of CPU hours for erroneous runs. Very often, available structural data does not correspond to the exact conformation a numerical experiment is supposed to investigate. An interactive simulation helps to address this issue by starting a run with a molecule in an available initial conformation. Forces are ap-

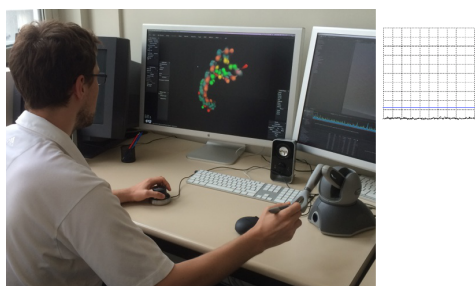


Figure 5: Left: A typical workspace. The user moves the camera with a 3D mouse (left hand) and manipulates an RNA hairpin (PDB ID 1F9L) with the haptic arm (right hand). Right: Screenshot of UnityMol with the same molecule next to an energy time plot as displayed during simulation.

plied to put the molecule in an other conformation of interest. Once ready, the user saves the resulting positions in a new file. A longer unsupervised simulation is run from the new file, commonly on a dedicated cluster. Out of the context of UnityMol, we previously described such an application for the RecA nucleofilament [12].

3.2 Use Case 2: Immersive Interactive Exploration

The interactive approach opens up perspectives to guide simulations in an intuitive way via user input, within a dedicated graphical environment providing immersion within the scene. Peripherals such as a 6 d.o.f. 3D mouse ease the navigation in the virtual space. The user can change the point of view intuitively, and focus on the relevant part of the studied molecule. Haptic devices help to render accurate molecular models more real and tangible to the scientists. Hence, the user feels an immediate force feedback by a straightforward combination of molecular modeling and virtual reality leading to an intuitive understanding of the causal relationship between the theoretical model and its biologically relevant properties. Simpler devices such as the LeapMotion (for which experimental support was tested within Unity3D) offer less features and no haptic feedback but are easier to use. They suffice for navigation and exploration tasks.

A typical biological application that we implemented in relation to experimental nanomanipulation is to stretch an RNA hairpin on two ends, controlling and monitoring the successive detachment of its base pairs. When released, the structure may either progressively return to the initial hairpin state or feature an altered conformation, for instance induced by a base shift. This numerical experiment provides insight into the hairpin's resilience, similarly to what can be probed experimentally with optical tweezers. Figure 5 depicts a typical setup.

3.3 Use Case 3: Automated Unfolding of an RNA Triple Helix

We set up an experiment in which an RNA triple helix (PDB ID: 2K96) is stretched automatically from both ends (Figure 6). We measured the distance between atoms at each side over time. This procedure is analog to what happens in AFM experiments. We performed the resilience test at constant forces of 350 pico Newtons (pN), 700pN and 1400pN and stopped once the helix was completely straight. In such simulations and throughout our tests, we used an integration time step of 4 femtoseconds. The experiment at 350pN lasted about 11,000 time steps, providing us with 44 picoseconds of simulated time.

The observed end-to-end distance time series are shown in Figure 7 and show mostly a linear relationship between time and extension. A few cases of stable distances despite prolonged force application are observed at 350pN. We can match these distance stag-

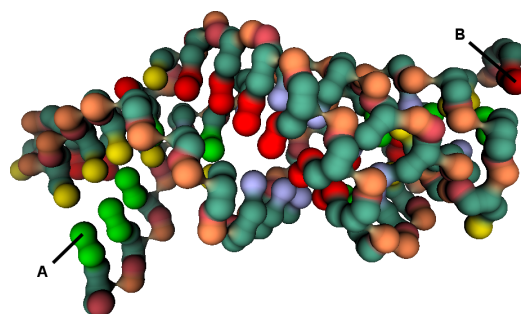


Figure 6: The triple helix and its extremities (PDB ID: 2K96). A: residue number 1; B: residue number 47

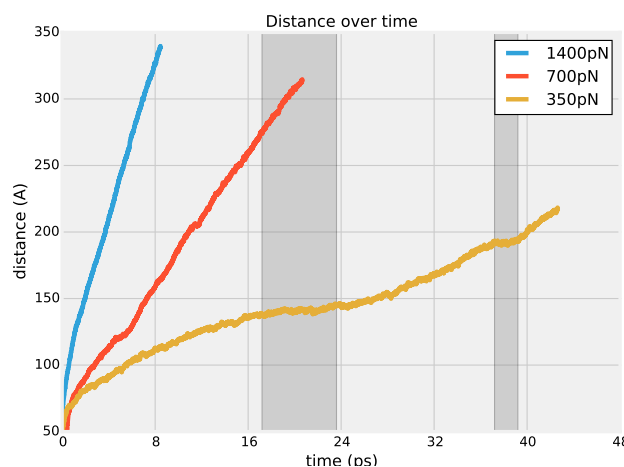


Figure 7: Distance (in Angstrom) over time with various applied forces. The yellow curve features two plateaus, meaning distance stagnation, caused by the molecule's resilience to external forces. Yellow: 350 pico Newtons (pN), red: 700pN, blue: 1400pN

nations with the resilience of hydrogen bonds between base pairs, known to favor the stability of such molecular assemblies.

Previous results are quantitative. We replicated a similar digital experiment and gathered more data. This time, a single end was pulled while the other was fixed (A is fixed, B is pulled; Figure 6). The applied force was 700pN. Measurements are reported in Figure 8.

We stored which bases formed hydrogen bonds at each timestep. Around 32 ps (marked by a red line in Figure 8), the further extension is directly related to the annihilation of the bond between nucleotides 1 and 27. We captured a video of the experiment, from which we extracted two pictures just before (Figure 9a) and right after (Figure 9b) this molecular event (Figure 9).

The applied forces are many orders of magnitude higher than in an experimental setup. This feature considerably reduces the simulation time. Furthermore, the particle of nucleotide 1, found to form an hydrogen bond with nucleotide 27, is spatially fixed in the simulation. How these simulation conditions impact the results has to be determined in the future and the numerical results should be correlated with experimental data.

3.4 Use Case 4: Education, Gamification and Ludic Research

UnityMol provides us with a ludic platform for teaching the chemistry and physics related to biomolecules. It has been used at Université Paris Diderot (Paris 7) and will be part of online courses.

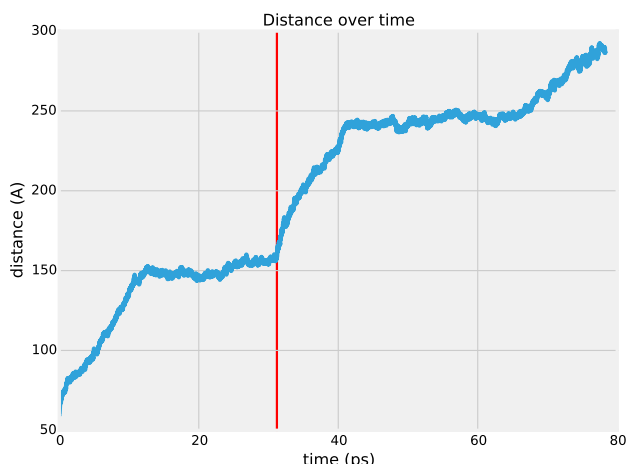


Figure 8: Distance over time with the second experiment. The bond annihilation between base pair 1/27 is marked in red. It occurs at around 32 picoseconds (8000 timesteps) of simulation.

In addition, the curriculum includes theory and practice related to molecular dynamics simulations in general, as students acquire an insight about modelling molecular behaviour. For instance, they experience hands on how the combination of weak interactions favors stable structures in such biomolecular assemblies. We already extended the idea and set up a web app so that students can send their data to a web service. The teacher can gather their results from a centralized service to further rate them. The current implementation provides a first rudimentary basis to develop serious games with molecules. In addition to posting the interaction score on a server as currently implemented, future enhancements focusing on serious gaming concern among others simplified interaction, clear feedbacks and challenge pacing. As UnityMol is integrated in a game engine many such features can easily be used to develop a game. UnityMol features different representations potentially reusable for other projects. Also, the interactive aspect is non-negligible for research and offers a ludic playground for visualizing biological data. The shape of complex molecules and their physical behavior can be difficult to comprehend. These aspects can be greatly clarified with interactive manipulations.

4 DISCUSSION

Here, we provide benchmarks under different conditions to carry out objective performance measurements. We further discuss the limitations of our application in its current state. Last but not least, we describe the focus of our future efforts.

4.1 Benchmarks

We benchmarked the performance of a compiled version of UnityMol. We measured the number of frames generated per second (FPS). The benchmarks were performed on a Mac Pro early 2009 (4.1) model equipped with 2 x 2.93 GHz Quad-Core Intel Xeon CPUs and 32 Go of memory. The graphics card features an NVIDIA GeForce GT 630 GPU with 1024 Mo of memory. The operating system is Mac OS X Yosemite 10.10.2. The selected resolution is 1920x1080 in windowed mode. Both atoms and bonds are rendered as HyperBalls.

The first test set comprises four CG RNA molecules of different structures for which we prepared simulation files. PDB-Id 1F9L is an hairpin featuring a GA mismatch. It has 22 nucleotides for 146 CG particles. PDB-Id 2K96 is the wild-type pseudoknot of human telomerase RNA. The molecule has 47 nucleotides for 303 CG par-

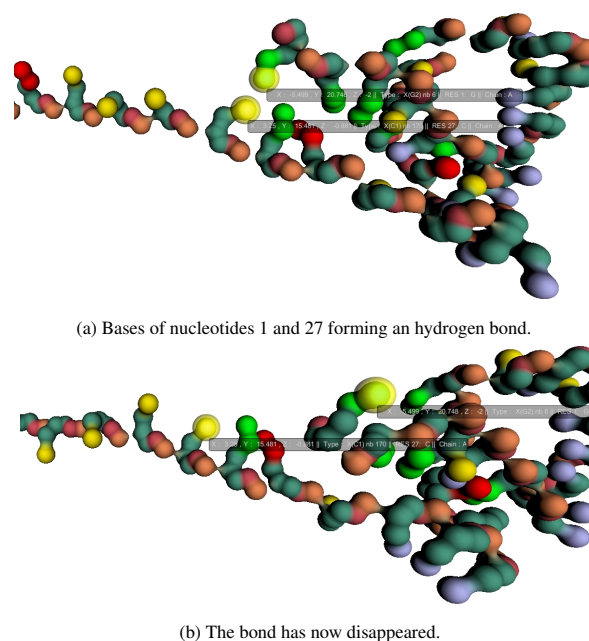


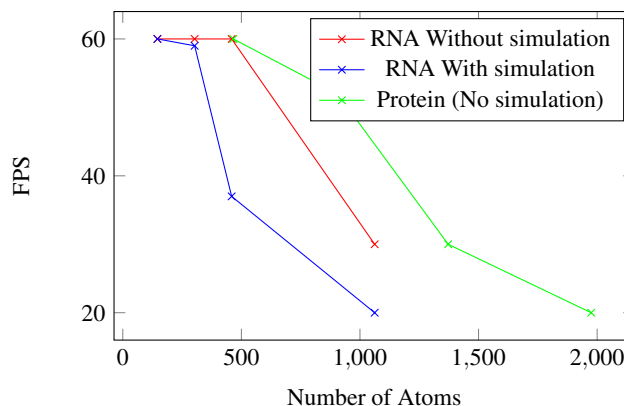
Figure 9: Snapshots of our second experiment. We selected one particle of each nucleobase forming pairs. These are highlighted by yellow spheres. The gray boxes indicate information related to our selection.

ticles. PDB-Ids 1Y26 and 3D0X are Metabolite-sensing mRNA, also referred to as "riboswitches". They respectively have 71 and 161 nucleotides for a total 459 and 1062 CG particles each.

The second test set includes four proteins, directly downloaded from the PDB website, selected based on their sizes. Values of both benchmarks are plotted in Figure 10.

We notice that the rendering rate remains acceptable for an interactive application around 1400 rendered atoms/particles (including bonds). Updating atom positions based on simulation data has a non-negligible impact on performance, and thus further limits our current implementation to relatively small biomolecules with simplified representations. The difference between RNA without simulation and protein might be due to the different bond count. To this date, we must figure out how to avoid bottlenecks for the application to scale better, but also optimize the costly bond rendering. Unlike the experiments reported in [4], it is currently not possible

Figure 10: FPS for various systems with increasing atom counts



to simulate and interact with large biomolecules in our setup.

4.2 Limitations

Currently, we are using a simulation engine initially designed for batch execution on computation farms. This design feature may limit the deployment of the application to high-end computers with sufficient resources, in particular in terms of CPU power.

Exchanging data between the Hire-RNA simulation and the UnityMol visualization is another bottleneck. The underlying MD-Driver library requires enhancements in terms of bandwidth management. More technically speaking, MDDriver integration and implementation within our simulation and visualization programs is mostly performed with mutexes. This procedure blocks the data transfer and leads to performance decrease with high simulation throughput.

Another important aspect is the user experience within interactive simulations. There is a need and much room for further improvements in UnityMol. Indeed, atoms are naturally vibrating due to thermal agitation. This relatively fast motion however impedes proper atom selection and force application, and adds jitter to the visualization. Reducing this effect visually, but also for interaction devices - in particular haptic ones - is challenging and requires further experimentation. Trivial approaches are likely to reduce the usefulness of the setup.

4.3 Feature Extension

In the next few months, we intend to organize a contest during which students will be asked to virtually interact with RNA molecules. A first set of exercises will consist in refolding molecules of known conformations. Students will pull on atoms until they obtain stable structures and then try to estimate the one of the lowest energy. They will be able to submit their structures to a web server for further evaluation and scoring, for instance using an RMSD calculation based on the known solution. A second dataset will consist in molecules of unknown structure. There, the scoring will be based on energy calculations, number of hydrogen bonds, base pair stacking etc. and it will be possible for the students to exchange and mutually improve their solution candidates. Our intention is to see how human beings may individually and collectively challenge molecular dynamics simulations in terms of time efficiency and of finding non-trivial solutions. This approach to the molecular conformation optimization problem follows a similar spirit as the Foldit puzzle game applied to protein folding [2].

Rendering massive molecular data on very high resolution display systems is challenging. Furthermore we want to be able to interact fluidly with the simulated molecule. In the future, we plan to integrate the support for various Virtual Reality devices to allow an intuitive interaction with the model through immersion. The realism of interactive immersive exploration can be enhanced by pushing the illusion to be immersed within a virtual molecular world, notably when adding 3D stereoscopic rendering of the scene and head tracking, eventually wearing a head mounted display such as the Oculus rift. These extensions are not yet implemented in UnityMol. In addition, this extension opens the way to collaborative investigations among researchers and a new era for presenting and sharing research results interactively.

We wish to extend the plotting functionalities to monitor the running simulation more exhaustively. We may watch the evolution of the mean distance between atoms, the number of weak bonds, the energy, etc., offering a visual dashboard for investigating molecular properties of biological systems.

Integrative biology takes advantage of available experimental data from various sources to accelerate simulations. Such data reduces the vast space of possible solutions to a subset of realistic ones. We want to extend the exchange protocol between simulations and visualization to manage constraints. When two parts of a

molecule exhibit a high correlation in terms of atomic movements, the researcher would force the pairing. Such a feature would allow the further behavioral study under a priori knowledge.

There are molecules for which we know the structure of fragments, but not their structure as a whole. A very useful extension is to allow the user to place fragments in space, maybe constrained to an experimentally determined envelope. Various prepared setups could then be simulated to deduce the favorable ones. We recently started to explore such techniques[9] and are eager to test them within UnityMol.

5 CONCLUSION

We presented UnityMol as a platform for a full-blown virtual laboratory featuring graphical representations of molecular data coupled with interactive visual analysis tools. UnityMol takes advantage of Virtual Reality devices to ease the interaction with the model.

We showed how this computational tool can and will be applied to research and education. We ended with a performance benchmark, current limitations and the future expected features.

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