Visualization and modelling of moving biomolecules: a new approach based on professional 3D animation software

Yuri Porozov[1,2], Raluca Andrei[1,2], Susanna Monti[3] and Monica Zoppè[1]

[1] Lab. of Gene and Molecular Therapy, Inst. of Clinical Physiology CNR, Pisa, Italy.

Introduction and objectives

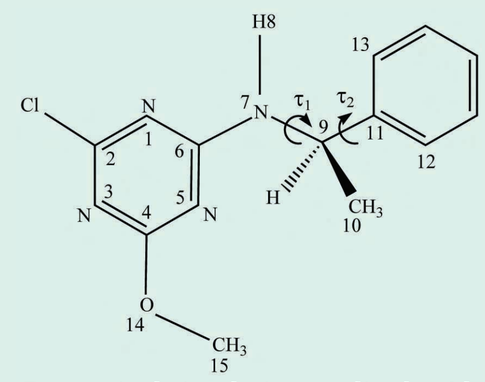
While the structural biology community widely appreciates the wealth of structural information, the vast majority of experimental biologists still have difficulties in figuring the actual structures and, especially, the dynamical movements that constitute the core of life's inner working. We suggest that this is due to the fact that, even with the newest visualization tools, the 3D shapes of proteins are not easily grasped, and that many aspects considered important are related to the activity of proteins, which is difficult to visualize.

We have taken advantage of the professional 3D instruments (Maya/Autodesk) which were developed for the entertainment industry, to visually deliver biological information through the representation, modelling and animation of biomolecules. The possibility of seeing molecules at work in a reconstructed environment will facilitate the use of structural information by the experimental biologists (1), and will foster advancements in biological science through several mechanisms:

- better understanding of biological phenomena
- enabling the formulation of new hypothesis
- ameliorate teaching by delivering messages in a more direct way

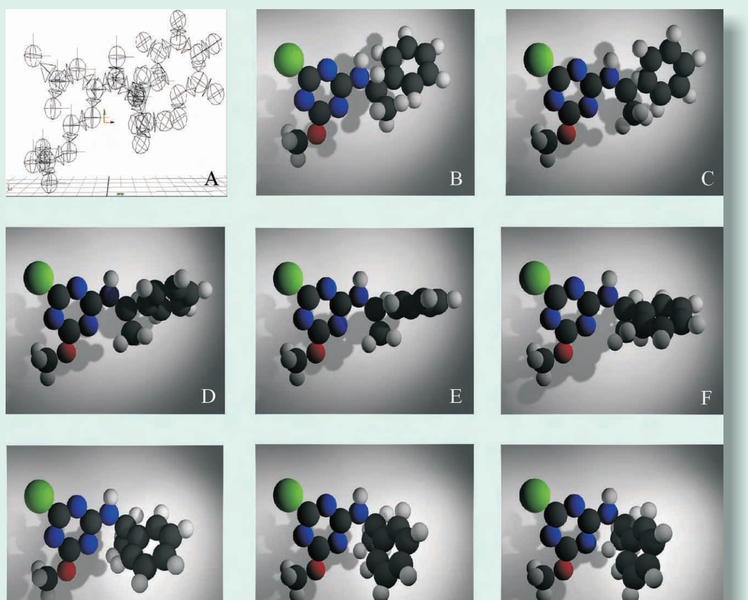
In this report, we describe the initial results obtained with three different models: the small molecule Triazine (C12, N4, O, H13, Cl) , the V3 peptide from HIV-1 surface protein gp120 (35 aa, ~500 atoms), and the entire gp120 glycoprotein of about 400 aminoacids.

Triazine



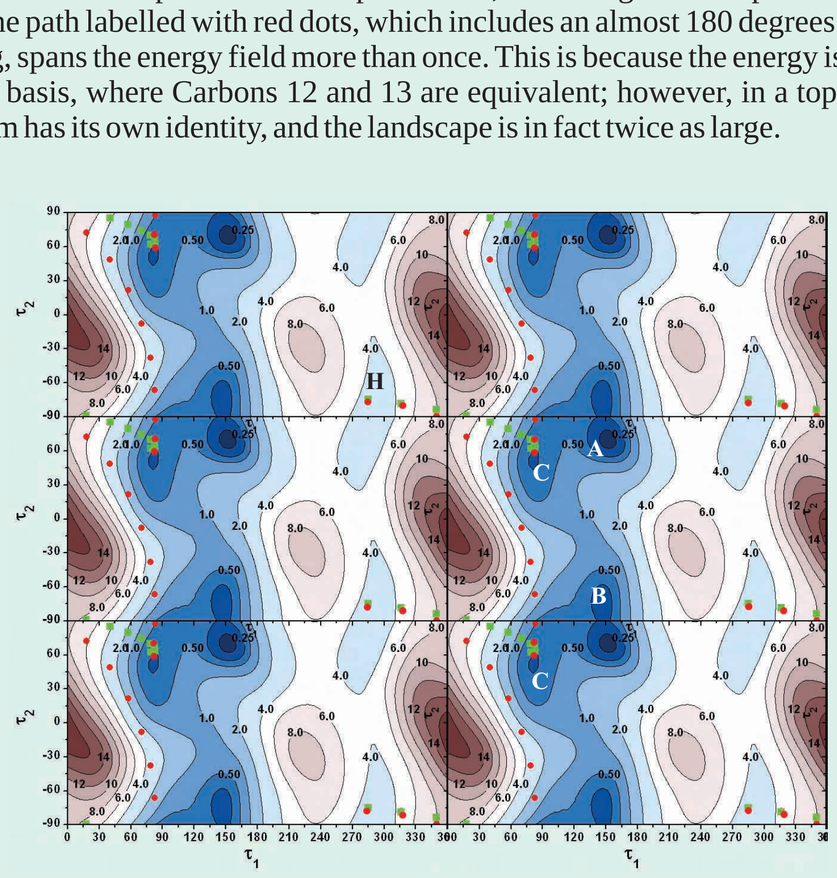
Triazine (2-chloro-4-methoxy-6-[(R)-1-phenylethylamino]-1,3,5-triazine) is a small molecule composed of 31 atoms, with a relatively simple structure of two rigid disks connected by a C-N bridge (see figure). The different conformational positions that Triazine can assume are basically variations of τ1 and τ2, i.e. rotations around the two chemical links that connect N7, C9 and C11.

Dynamical simulation studies by Alagona et al (2), have revealed the energy landscape for all possible conformations that Triazine can assume. For this reason we chose it as the initial test molecule of our chemical Maya system. The program we developed to import chemical data into Maya assigns every atom to a position. Atoms are linked through bones, which behave like chemical bonds, have fixed length, and are constrained by codified rules.



Four different conformers, three minimal energy positions (A-B-C) and one intermediate (H) were imported, and assigned to different time points in the animation (key-framed). Coordinates for all atoms in the intermediate positions (reported as snapshots from the animation in the figure) calculated by Maya along two possible pathways between C and H were retrieved, fed back into pdb-like files and entered into Origin software, allowing for physico-chemical evaluation of the path calculated by Maya.

In the following figure is reported the energy landscape, with the paths calculated by Maya for transition between position C and position H, following the two possible trajectories. Note that the path labelled with red dots, which includes an almost 180 degrees rotation of the phenyl ring, spans the energy field more than once. This is because the energy is calculated on a chemical basis, where Carbons 12 and 13 are equivalent; however, in a topological view, each of them has its own identity, and the landscape is in fact twice as large.



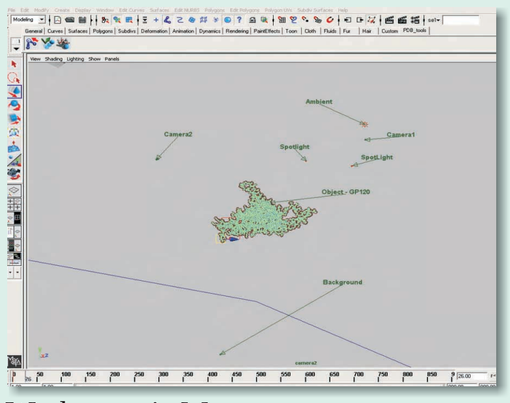
These results show that Maya can calculate paths avoiding the energy peaks, i.e. describing a movement that is chemically acceptable, flowing naturally in the 'valleys' of the landscape.
Further work is ongoing on different molecules.

HIV-1 gp120 and its V3 loop

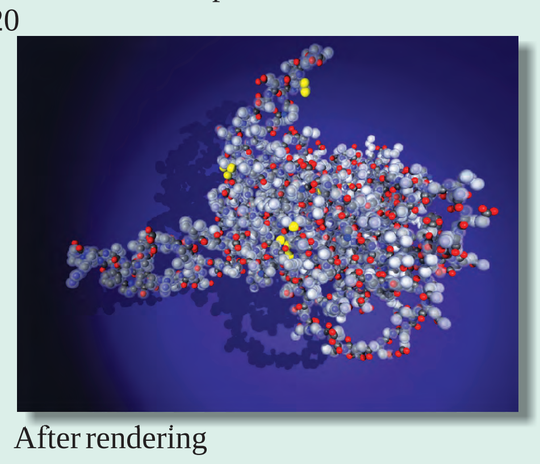
Gp120 structure of Human Immunodeficiency Virus 1 (HIV-1) has been solved in different conformations either unbound or bound to Cd4 (3, 4). Its interaction with the receptor CD4 triggers a major movement of parts of the protein, in particular the V3 loop. V3 loop is implicated in the selection of co-receptor and in the subsequent step of co-receptor binding.

The entire gp120 protein is shown below in the Maya workspace to illustrate handling tools (left) and in a final rendered image with atoms represented in standard colors, except Hydrogen, which is shown as semi-transparent spheres around the parent atom.

Gp120



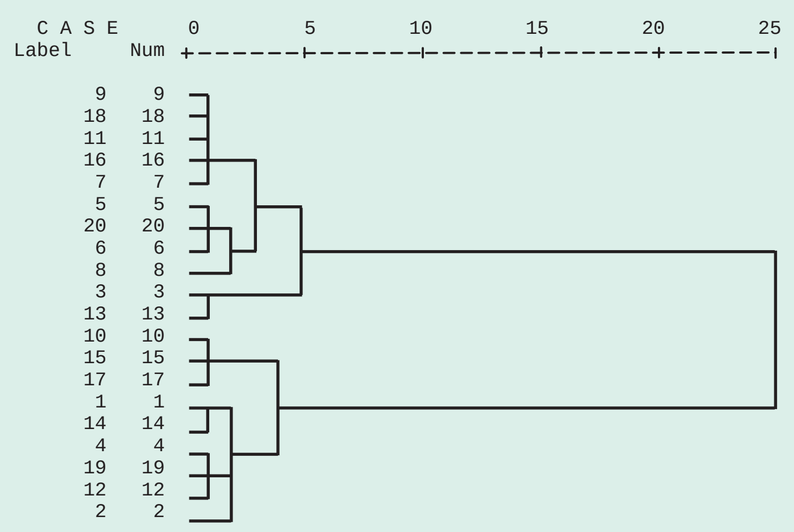
Workspace in Maya

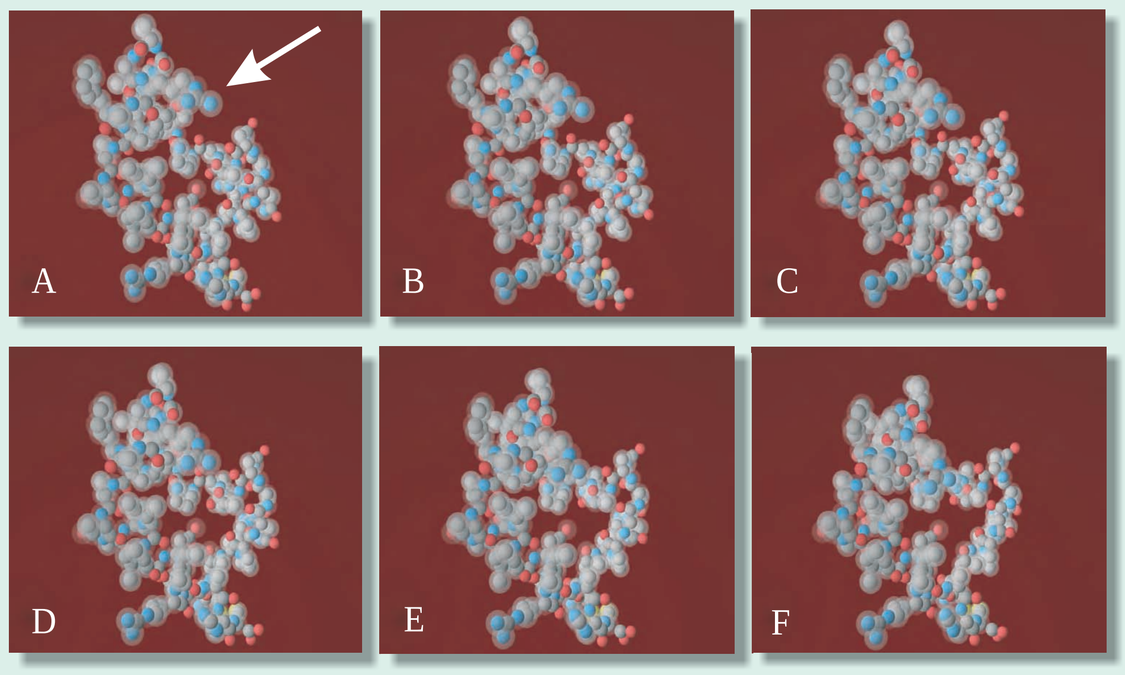


After rendering

V3 loop

Twenty conformers of V3, derived from NMR studies and available from the public database (PDB entry 1CE4 (5)) were imported into Maya and animated by means of newly developed software. The order of average models for animation was chosen with the aim of facilitating calculations during realtime pathway. For this we performed cluster analysis, using ϕ and ψ angles as inputs, and selecting residue ASN7, which exposes a very fast and large range of movement.





Six frames from the animation, showing the major movements of the peptide. Panel A is from NMR position 6 moving towards position 8. Images are taken at intervals representing about half way between the two NMR conformations. Please note the movement of the the loop indicated by the arrow and the widening gap in the lower part of the molecule.

Conclusions

The possibility of producing realistic (in biological and chemical terms) virtual scenes with objects, environment, interactions, and behavior derived from our increasing knowledge of cellular and molecular biology can be used for obtaining a better understanding of the processes that underlie life, as it may offer a dynamic representation of bio-processes.

The results reported here are a first glimpse of how biological molecules can be represented and animated. By introducing physical and chemical principles encoded as mathematical procedures as well as statistical preliminary analysis of input, we can visualize how single molecules move from one stable conformation to another. By entering information from experimental biology, it is possible to represent the relative interactions of biomolecules (with each other and with the environment) in order to understand and deliver 'scenes' from the complex picture of life processes. This will increase our understanding of biological processes, and will enable experimental scientists to design and evaluate their experiments from a different viewpoint.

The versatility of Maya is well suited for use at several levels of complexity: from creation of simple molecules to highly complex intermolecular dynamics. These features allow step by step construction of complicated scenes, in order to explain the many different aspects of cellular and molecular biology in university or high school classes

1. Breithaupt, H. (2006). *Seeing is understanding. Improvements in computer software and hardware are revolutionizing three-dimensional imaging in biology.* EMBO Rep **7**(5): 467-70.
2. Alagona, G., C. Ghio, et al. (2006). *A Test Case for Time-Dependent Density Functional Thepry Calculations of Electronic Circular Dichroism: 2-Chloro-4-Methoxy-6-[(R)-1-Phenylethylamino]-1,3,5-Triazine.* Theor. Chem. Acc. ***(in press)***.
3. Chen, B., E. M. Vogan, et al. (2005). *Structure of an unliganded simian immunodeficiency virus gp120 core.* Nature **433**(7028): 834-41.