Molecules for the masses

Dear biochemists:

Over a year and a half since I took this section in my hands, the opportunity comes of addressing a commentary about recent advances in a field which, as many of you will know, is my passion: the use of molecular models in the computer. This is the matter that started me into the realm of web page editing, back in 1998, to be able to work with my students on manipulation of models of DNA and RNA structure, in which we used to call "informatics practicals" –a name that has never looked proper to me–. There Biomodel was born, which has kept growing up to now in the web hosting provided by my university[1] and which, in parallel, a couple years later was integrated in a communal project you may know, BioROM.[2]

Molecules jump out of the paper

Undoubtedly, the rendering of molecular structures is essential for an efficient analysis of both structure and function of biomolecules, drugs, etc. While in some fields like the organic chemistry formulas drawn with lines and wedges solve the issue quite satisfactorily –even though improvable–, in biochemistry the need for a three-dimensional representation is more critical, as well as the possibility of simplified renderings for the structure of macromolecules (such as ribbons, spirals or other styles for the polymeric chain). No one would think of trying to explain the structure of haemoglobin by drawing all its atoms and bonds!

All this leads to so-called molecular visualisation being an essential element to be included in numerous presentations and discussions of results. Fortunately, advances in the experimental resolution of macromolecular structures[3] (X-ray diffraction on crystals, NMR, neutron diffraction, electron (cryo)microscopy...) (fig. 1) have markedly improved our understanding of the organisation and interactions of molecules, and allow to much better appreciate the fundamentals for many biological activities of both proteins and nucleic acids. To have this asset of information available demands our displaying of biomolecules in a much more realistic way, not so much simplified into basic shapes –even though these also fulfil their role in certain circumstances. This will help our students to perceive proteins, for instance, as complex entities, flexible and adaptable but at the same time unique and specific, and not so much as a ball with a slot.

You will indubitably have some experience on this issue of visualising three-dimensional structures, at least as occasional users of structure databases, textbook ancillary material or educational material available in the web. However, many of you will possibly not be familiar enough as to be up to date with somewhat technical issues related to accessibility of this kind of material. This is the scope where the approach of this article fits.

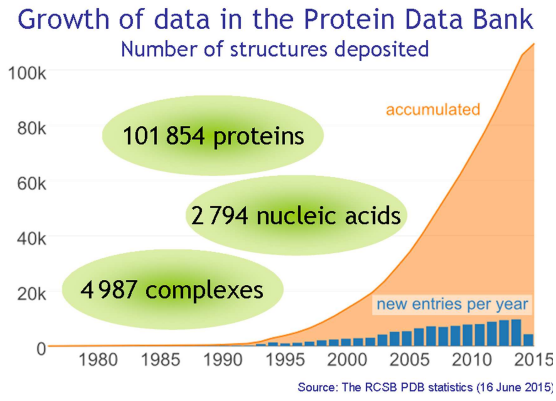

Figure 1.

Rise and fall of Java

For many years we have been enjoying software for the interactive display of molecular structures in non-specialised computers. Up to recently, this typically required installing a specific program or including a plug-in in the web browser. For the first case we may cite RasMol or the more sophisticated PyMOL.[4-5] For the second, MDL Chime was prominent, later followed by several alternatives using Java to allow pages including the viewer applet, such as Jmol, Marvin, PDBjViewer or Chemis3D.[6-9]

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These solutions have been satisfactory for several years, although they required some configuration in the user's device (with the resulting need for providing instructions) and could be restricted to some operating systems. When developing teaching activities in computer rooms, a far from negligible task of setup and maintenance was needed, as many of you may have endured. Along the last years, certain risks associated to the chance of malicious Java applets being used for intrusion have lead to the enforcement of security policies both in Java itself and in the web browsers, resulting in increasing restrictions on the execution of Java applets within the web pages. You have likely experienced this, even suffered it with marked frustration, by way of successive and changing dialogs warning about the blockade, asking for an updated installation, just to repeatedly keep requiring permissions to execute the content. If one is not specially persistent or gets worried before obscure warnings and instructions, one finally gives up the attempt. Does it ring a bell for you?

To put the icing on this overly sweet cake, some web browsers are fully removing support for the plug-in format[10] employed not only by Java, but also by movie players and other software that integrates into the browser. All this has posed a risk of loosing functionality developed in hundreds of websites, particularly when they come from an amateur and voluntary effort, and there is no company behind them able to assume the needed remodelling and update for keeping the materials operational.

Motivated by this technical evolution and by that risk, along the last two years a team of enthusiasts on molecular visualisation[11] has developed a powerful alternative: JSmol[12], a solution that does not use Java but only the features belonging to the web browser (HTML5 and JavaScript). JSmol derives from the Jmol Project and, hence, shares all features with the Jmol applet, which is widely established among databases, online services and educational sites in biochemistry, chemistry, crystallography and other fields. As a result, web pages –including many database portals– may now display molecular structures without requiring any additional software, but just the web browser.[1]

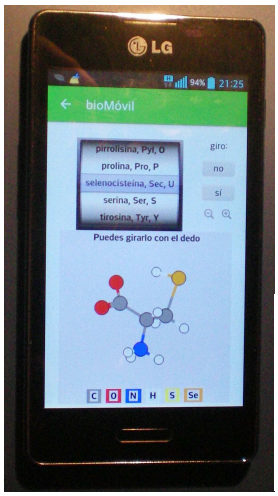

Figure 2. The structure of the 22 amino acids may be experienced with 3D models in a smartphone. (Ref. 13)

A world without keyboards

We are all experimenting every day this social revolution on the use of communication media and the prominence of extremely portable digital media: smartphones and tablets are now a must, and those who develop contents of any kind are strongly urged to adapt to these formats.

The above commented restrictions on the use of Java in computers have converged with the proliferation of portable media which mostly lack the ability to play contents in the Java format.

In addition to sidestepping the commented restrictions, the abandoning of dependence on complements like Java in favour of an HTML5 format, self-contained in the browser, opens at the same time the door to the portable devices. It is hence feasible for tablets and even phones (fig. 2) to use materials built on tools such as JSmol.[13] As you may foresee, there are some limitations imposed by both the processing power and the screen size, but not a material or technical inability to access the contents. We can, therefore, speak about a truly multiplatform solution: compatible with several browsers, operating systems and devices.

A noticeable progress

As a conclusion of all that, several sites across the internet have already adapted their content in order to display molecular structures using interactive molecular models without any software requirements. As a prominent example we may cite the Protein Data Bank (PDB) which now displays the models by default using JSmol or offers the user a choice of other viewers, like Jmol with Java and the new PV (Protein

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Viewer[14]). PV also uses the browser resources without plug-ins, but in this case takes advantage of WebGL technology (hardware-accelerated graphics, available on reasonably modern graphic cards); this is an alternative with swifter graphics, although less sophisticated that JSmol with regard to possibilities of structure investigation and of customising the rendering style.

Figure 4. Alternative use of the modalities of the Jmol object: either Java applet or HTML5 object (JSmol). This example is taken from the ancillary website for the book (in Spanish only) *Texto ilustrado e interactivo de biología molecular e ingeniería genética, 2ª ed*. (http://StudentConsult.es)

As a second, closer, example, all the material in the Biomodel site has been updated (in Spanish and English) along the last year and a half and may now be visited without the need for Java. For modules that deal with bigger molecules and complexes, there is still the option for the user to choose the Java modality and so obtain better performance in model manipulation, provided his device is properly configured. The power of the JavaScript included in browsers does not yet reach the swiftness provided by Java, although improvements are coming fast. On the other hand, with respect to image quality, results provided by JSmol are comparable to those from Jmol (fig. 3).

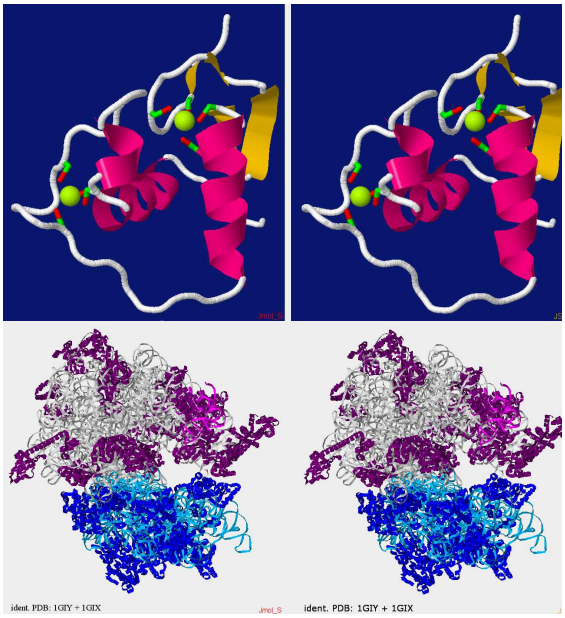

Figure 3. (top) Detailed rendering of the structure of two zinc fingers in the oestrogen receptor (screenshots from http://biomodel.uah.es/en/model1/dna-prot/zincfing.htm). On the left panel, the Java modality of Jmol; on the right panel, JSmol without Java.
(bottom) Rendering of the structure of the ribosome from an archaea (screenshots from http://biomodel.uah.es/model1j/rna-prot/ribosoma.htm). On the left panel, the Java modality of Jmol; on the right panel, JSmol without Java.

Since the code base in JSmol is the same as in Jmol, when we edit web pages we can enjoy the full wealth of features developed for the latter along the years, which constitutes the *JmolScript* command and scripting language. You only need to adapt that part of the code dealing with insertion of the *JmolApplets* so that, instead, the *Jmol objects* are now inserted in the page; these objects mat adopt either the Java modality as before or the new HTML5 modality characteristic of JSmol[15] (fig. 4).

To conclude, we may offer this summary: although specialists will keep relying on the dedicated and sophisticated software such as PyMOL, the molecular scientists al large can enjoy molecular visualisation without trouble – even though rich in features– for their needs of analysis, presentation, etc. without requiring specific programs or limitation to certain computing platforms.

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3. H. Khatter *et al.* (2015) *Structure of the human 80S ribosome*. doi:10.1038/nature14427 and doi:10.2210/pdb4ug0/pdb A recent and outstanding example, formed by 81 chains and nearly 219 thousand atoms located with a resolution between 2.9 and 3.6 Å.
4. H. J. Bernstein. *RasMol and OpenRasMol: Molecular Graphics Visualisation Tool.* http://openrasmol.org/
5. *PyMOL: A molecular visualization system on an open source foundation*. http://pymol.org/
6. *Jmol: an open-source Java viewer for chemical structures in 3D*. http://jmol.org and http://wiki.jmol.org/
7. *Marvin: Intuitive applications and API for chemical sketching, visualization and data exploration.* https://www.chemaxon.com/products/marvin and https://www.chemaxon.com/marvin/examples/applets/view/configure3.html
8. *PDBjViewer (jV): a program to display molecular graphics of proteins and nucleic acids*. http://pdbj.org/jv/
9. *Chemis 3D: Integration within an HTML document.* http://www.mol3d.com/integration.html
10. Since spring 2015, Chrome does no longer allow execution within web pages of complements like Java applets, QuickTime movies, Shockwave animations, Microsoft Silverlight, etc., all of them based on plug-ins with the NPAPI technology. At the time of writing this article, this browser supports an alternative technology only for Flash animations and movies and for pdf documents.
11. Within the developers team of the Jmol open-source project, we must highlight the effort of Bob Hanson, Organic Chemistry Professor at St. Olaf College in Northfield, Minnesota. To him we owe the majority of innovations in Jmol as well as the conversion into JSmol.
12. *JSmol: JavaScript-based molecular viewer from Jmol.* http://jsmol.sourceforge.net/ For a more complete description, visit also http://wiki.jmol.org/index.php/JSmol
13. By way of example, you may use your tablet to visit the different modules in Biomodel (ref.1); for smartphones, a specifically designed module at http://biomodel.uah.es/m/
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