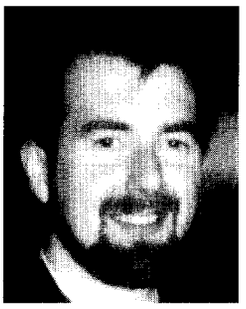
Virtual molecules!



'What could be better than using a WWW browser to "surf" through a library of compounds?'

The recent explosion in combinatorial chemistry has created an evident need for management of the compound libraries being generated. It appears that the classic 2D models of pharmacophores will soon be pushed aside by the 3D representation of compounds. What could be better than using a Worldwide Web (WWW) browser to 'surf' through a library of compounds?

Those readers familiar with the WWW will probably have heard of HTML (hypertext markup language), but probably not of VRML (virtual reality markup language). Recent advances are increasingly allowing the visualization of VRML 3D models within browsers. For example, the Volkswagen group has adopted virtual reality for dealership training using computer-generated 3D models of vehicles. The 3D world of VRML has been thoroughly underexploited by scientists and is just now coming into its prime thanks to recent advances in WWW browsers. The latest versions of Netscape and Microsoft Internet Explorer have plug-ins that allow users to do this (see Box 1). Those who do not use either of these browsers yet should switch now; they dominate the market and are the most advanced in their class.

'Those who do not use either of these browsers yet should switch now'

How can we use these browsers for *work*, instead of wipeing out on a wild surf? By building a small intranet (an in-house network of computers with a web server) access to a relational database containing compound data can be provided readily. Using search criteria the user will be 'catapulted' into a 3D world of potential lead molecules. He or she will be able to walk through the library manipulating molecules and spinning them on their axes to see if they fit the criteria.

Clicking on a specific molecule will bring the user down to earth with a textual representation of the molecule and information on synthesis, applications and related compounds and patents. An interesting article entitled 'Chemical collaboratories using Explorer EyeChem-CCI-VRML' can be found on the WWW (Box 1).

Another way to view 3D drug libraries interactively is by using MDL Information Systems' Chemscape Chime (see Box 1). This is a plug-in that works with either Netscape Navigator or Microsoft Internet Explorer and allows scientists to view chemical information including MDL Information Systems, Inc. Molfile and many of the popular 3D display formats such as the Brookhaven Protein Databank (PDB) format. Minor modifications to a web page will allow users to embed a 3D molecular

Box 1. Web sites for 3D applications and VRML discussed in the text plus additional sites

- Netscape and live-3D plugin: http://www.netscape.com/comprod/products/navigator/version_3.0/multimedia/live3d/index.html
- Microsoft Internet Explorer and 3D plugin: http://www.microsoft.com/msdownload/ieadd/05000.html
- Browserwatch – 3D section: http://browserwatch.iworld.com/plug-in/plug-in-vr.html
- Silicon Graphic's VRML site: http://vrml.sgi.com/
- The VRML forum: http://vag.vrml.org/www-vrml/
- Yahoo's section on VRML: http://www.yahoo.com/Computers_and_Internet/Internet/World_Wide_Web/Virtual_Reality_Modeling_Language__VRML_/
- 'The easy VRML tutorial' (highly recommended): http://www.mwc.edu/~pclark/vrmltut.html
- 'Chemical collaboratories using Explorer EyeChem-CCI-VRML': http://www.ch.ic.ac.uk/talks/acs/
- Chemscape Chime (MDL Information Systems): http://www.mdli.com/chemscape/chime/chime.html
- WebLab Viewer (Molecular Simulations Inc.): http://www.msi.com
- Comprehensive list of molecular modeling software: http://cmm.info.nih.gov/modeling/software_list/sw_index_document.html

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  1359-6446/97/$17.00. PII:S1359-6446(96)20012-1

structure within a web page that can then be manipulated and modified by the viewer. This software is currently in prototype for Mac, PC and SGI machines. A commercial version of this software, called Chemscape Chime Pro, is available from MDL and allows rendering of 2D and 3D chemical and biological structures within a Web browser. This is used in conjunction with the Chemscape Server which provides full ISIS (their proprietary integrated chemical database search) structure and text search capabilities within a Web browser.

'The 3D-world of VRML...is just now coming into its prime'

An interesting tool called WebLab Viewer was recently released by Molecular Simulations, Inc. (see Box 1). Upon filling in a tracking form, users can freely download a molecule-viewing application program that opens several popular file formats, including PDB (protein database). Interestingly, this program will convert a file into VRML format from one of the other 3D formats it supports. Using a simple macro the user could convert a whole drug library into a 3D world, viewable with a web browser. This and many other programs can be used in a less elegant fashion as 'helper applications' that work in conjunction with WWW browsers.

A comprehensive list of molecular modeling software can be found on the WWW (see Box 1).

Agreed, *for now*, some of the software available may still be a little fragile or difficult to use productively for day-to-day applications. Nevertheless, the 3D world of VRML has been thoroughly underexploited by scientists and it will soon be coming into its prime thanks to recent advances in WWW browsers.

Martin Leach

Automated discovery – faster and cheaper, but better?

About 600 scientists and automation specialists attended the *International Symposium on Laboratory Automation and Robotics (ISLAR '96)* in Boston in late October, which was opened by Dr Walter Moos (Figure 1). Dr Moos joined Chiron Technologies, a division of Chiron Corporation (Emeryville, CA, USA), as Vice President of R&D in 1991 following his pioneering work in combinatorial chemistry at Parke-Davis (Ann Arbor, MI, USA). His keynote address highlighted the drug discovery technology advances of the 1990s. He outlined the paradigm shifts in discovery from affinity chromatography and radioligand receptor binding (1970s), through biotechnology and structure-based design (1980s) to combinatorial chemistry and molecular diversity (CCMD) in the 1990s. Into the next millennium, nucleic acid therapies and the delivery and targeting of natural and unnatural molecules will lead the way.

Using illustrations from the evolution of Chiron's discovery technologies, Moos showed how CCMD had enabled drug discovery to proceed 'faster and cheaper' against a difficult background of increasing costs and regulatory controls for the industry. But is it 'better'? Moos says that only time will tell. Nevertheless, the application of CCMD in discovery is already creating bottlenecks in exploratory development; Moos suggests that this has increasingly forced many laboratories to look toward the application of combinatorial principles and automation in preclinical development.

One interesting statistic to emerge from this keynote presentation was that, on the same basis that the 20 standard amino acids could yield 8,000 tripeptides, the theoretical number of all possible organic compounds has been calculated to be 10^{250}, which apparently represents many more orders of magnitude than there are particles in the universe.

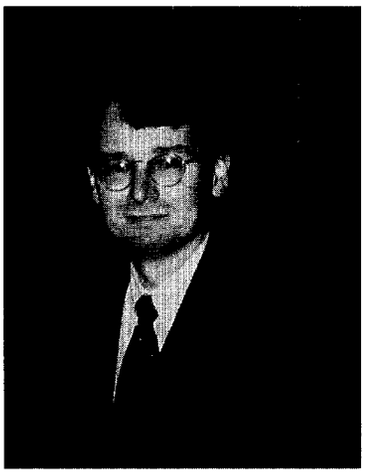

Figure 1. *Dr Walter Moos, Vice President of R&D, Chiron Technologies, gave the opening address at* ISLAR '96.

Application of 384-well plates

The main reason that scientists and automation specialists attend this meeting is to share experiences, both good and bad, and outline how they have reached solutions to their discovery problems, in terms of strategy, technology and logistics. Some companies offered 'case histories' of the theory and practice behind their approach to automated systems for HTS and combinatorial chemistry. One that attracted particular attention was that of the Glaxo Wellcome group (Stevenage, UK) represented by Dr Martyn Banks. Dr Banks argues that HTS is now entering the production era, with 'screening factories' incorporating integrated automated solid and liquid compound stores and automated combinatorial synthesis.