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REVIEW

Virtual resource development in the glycosciences

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The development of Internet-based virtual resources is a relatively new area of scientific and technical activity that is currently undergoing rapid expansion. Major factors fuelling recent growth include the emergence of multimedia capabilities through the rapid evolution of the World Wide Web, the reduction in cost of high quality personal computers and graphics workstations and the provision of mass-marketed provider services. Prior to 1995 the presence of Internet resources in the glycosciences was virtually non-existent. Existing scientific knowledge was primarily made available on the Net through the provision of databases from gopher and ftp sites. A particular example in the glycosciences is the Carbbank database of biological carbohydrate sequences. We will describe here our efforts in 1994–95 in establishing The Glycoscience Network (TGN, http://bellatrix.pcl.ox.ac.uk/TGN/). These activities included the establishment of a newsgroup, mailing lists, Web resources and the running of the First Electronic Glycoscience Conference (EGC-1, http://bellatrix.pcl.ox.ac.uk/egc/). EGC-1 included many novel initiatives in the glycosciences including electronic posters and papers, a Virtual Conference Centre, a Web-based hyperglossary, Virtual Trade and Employment Centres, refereed electronic publishing, and the creation of a Virtual Reality Gallery. We would like to look towards the near future and discuss several initiatives in virtual resource creation that we believe will have significant scientific impact on the glycosciences including the development of bioinformatics-based servers, sophisticated interactive databases, and videoconferencing. Furthermore, we cherish the belief that these resources will foster international scientific collaboration and progress of an extent never previously possible. Finally, we indulge in speculation and make some suggestions on the form and long-term impact of Glycoscience Virtual Resources. We predict that their development may completely reconstruct the scientific environment that we work in as scientists and we reflect on the probable benefits and pitfalls to be encountered.

Keywords: virtual resources, the glycoscience network, electronic conference, newsgroup, World Wide Web, database, virtual reality

Introduction

Most of the electronic resources in the biological sciences are available for molecular biology and protein structure applications. The Genbank [1], European Molecular Biology Laboratory (EMBL) [2], Swissprot [3], Protein Information Resource (PIR) [4] and Brookhaven databases [5] are well documented and easily accessible via the Internet for those who do not subscribe directly (via CD-ROM) or indirectly (via local computer services). The Internet-accessible forms of these databases are fully hyperlinked to each other as well as to enzyme nomenclature and literature databases. The same is not true for carbohydrate structure, but the non-linearity of carbohydrate primary structure adds to the difficulties involved with Carbbank, the one carbohydrate database that does exist (either on CD-ROM or downloadable via FTP [6]). Perhaps the very lack of Internet resources has meant that glycoscientists have seen no reason to familiarise themselves with the Internet. However, this may be starting to change with the formation of The Glycoscience Network (TGN) [7], the advent of an electronic newsgroup [8], creation of a number of glycoscience-related World Wide Web (www) pages and the First Electronic Glycoscience Conference (EGC-1) [9].

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In this perspective we would like to describe these recent developments and discuss some promising areas of virtual resource development in the glycosciences.

The glycoscience network

The Glycoscience Network (TGN) [7] is not a formal organisational structure but instead describes a distributed group of scientists interacting through the Internet who share a common interest in glycoscience. The group is not solely based on a single field such as glycobiology or carbohydrate organic chemistry but instead covers a broad range of disciplines including chemical, physical, biological and medical areas using theoretical, experimental and computational approaches. We formed TGN for the following purposes:

(a) to encourage the participation of scientists interested in developing and participating in Internet-based activities in the glycosciences;
(b) to develop and support high quality scientific events on the Internet in the glycosciences;
(c) to foster interdisciplinary activity between different glycoscience fields;
(d) to promote the glycosciences to the general scientific community.

TGN activities have included the formation of the bionet newsgroup discussed below and the holding of the First Electronic Glycoscience Conference (EGC-1) [9]. Distributed Web resources have been created which can be linked into from The Glycoscience Network Home Page [7]. Here we would like to describe several of the content areas that have been developed:

Directory of glycoscientists [10]

A directory of glycoscientists is maintained by Laura Morris (laura@gsu.edu) of Georgia State University, USA, and provides an alphabetical list of glycoscientists' names, addresses, email addresses, phone and fax numbers, and interests.

Meetings list [11]

A list of glycoscience-related meetings is maintained by Jerry Thomas (J.Thomas@cs.ucl.ac.uk) of the University of London, and provides a form for automated submission of conference information.

Glycosyltransferase guide [12]

Iain Wilson (wilson@edv1.boku.ac.at) of Institut fuer Chemie der Universitaet fuer Bodenkultur, Vienna, maintains a guide to eukaryotic glycosyltransferases involved in glycoprotein and glycolipid biosynthesis. The entries contain references (first author, year, etc.), database references, Genbank (gb:) and Swissprot (sw:) accession numbers, literature citations, and where possible links to the GenBank/EMBL/DDBJ database and the Swissprot/Expasy database in Geneva.

Carbhyd [13]

Carbhyd, developed by Pedro Coutinho and Artem Evdokimov at Iowa State, USA, provides an information resource on carbohydrate nomenclature, sugar stereochemistry and carbohydrate biochemistry.

Proteoglycans and glycosaminoglycans resource [14]

Robert Lauder (R.Lauder@Lancaster.ac.uk) of the University of Lancaster, UK maintains an information resource on Proteoglycans and Glycosaminoglycans.

Polysaccharide structure [15]

Vicktoria Finkenstadt (vicki@kiwi.foodsci.purdue.edu) maintains an information resource on Polysaccharide Structure.

N-glycans [16]

Christian Frosch (frosch@mzdmza.zdv.uni-mainz.de) at the Institute of Toxicology, University of Mainz, Germany describes the structure and processing of N-glycans in the biosynthetic pathway.

Monosaccharide browser [17]

The monosaccharide browser allows you to view space filling Fischer projections of monosaccharides. It was written by Jon Maber (j.r.maber@leeds.ac.uk) at the University of Leeds, UK.

Mechanistic enzymology in glycobiology [18]

This enzymology guide is being developed at the University of Alberta, Canada.

Structural resource [19]

A glycoscience structural resource is under development by Barry J. Hardy (barry@bellatrix.pcl.ox.ac.uk) and includes a guide to carbohydrate conformational structure and molecular modelling force fields. A virtual gallery [20] is being created for the display of molecular images and for the interactive creation of biomolecular structural complexes involved in protein-carbohydrate and membrane interactions.

The above list is not exhaustive; rather it outlines some of the diverse information resources that have already been created on the World Wide Web in the glycosciences.

Formation of the Glycoscience Newsgroup – a bit of history

In the past 2 years, low levels of carbohydrate-related questions on bionet newsgroups [21] such as bionet.molbio.methds-reagents showed that non-specialists did

have questions that perhaps would be best answered in a more specialist forum. The bionet.molbio.methds-reagents is a good example of a newsgroup that has a tangible benefit to research since it enables molecular biologists worldwide to ask each other questions on experimental techniques and to publicly discuss the merits or pitfalls of techniques in a manner which is only possible otherwise through personal contact and would not be possible with traditional publications. Additionally, carbohydrate researchers in different disciplines of research such as organic chemistry, molecular modelling or Nuclear Magnetic Resonance (NMR) often had only limited contact with carbohydrate researchers in other disciplines. Until the creation of bionet.glycosci late in 1994, there was no dedicated electronic forum for questions related to carbohydrate research.

Occasionally glycoscientists like ourselves would encounter each other on the network, due to replying to queries in bionet newsgroups or posting messages such as 'is there a newsgroup for people like me?' and use electronic mail as a subsequent means of communication; but otherwise the glycosciences had no newsgroup presence. It was through such contact that we initially conceived of promoting the formation of an electronic newsgroup in the glycosciences as a first step towards promoting the use of the Internet in the field. Bionet newsgroups require that a proposal be written and promoted and that sufficient potential demand for the newsgroup be identified through a voting procedure. Since all this takes place electronically, electronic mail addresses had to be found, either amongst our professional acquaintances or by using gopher or WWW servers to find addresses of people we had heard were in the field. Perhaps 200 messages later, we found support for a newsgroup and so proceeded to the formal stages of newsgroup proposition using gathered electronic mail addresses as the basis for the Glycoscience Interest Group mailing list. Once the voting had come to a successful conclusion, the newsgroup was made ready by the Bionet newsgroups manager. Announcements and scientific queries were posted to the group and we hope that the effort in setting up the newsgroup has proven useful for scientists in the field and is facilitating interactions that would not otherwise occur. Postings to the newsgroup are archived at the bionet.glycosci WWW site [22].

We initially maintained the Glycoscience Interest Group (GIG) mailing list as a subscribed mailing list which was not open like the bionet newsgroup. This list was used to post specific informational messages on The Glycoscience Network [7] and The First Electronic Glycoscience Conference [9]. The GIG mailing list has now been superseded by the TGN mailing list (tgn@bellatrix.pcl.ox.ac.uk) which is hypermailed [23]. A subscription to this list may be obtained by contacting egc2org@bellatrix.pcl.ox.ac.uk.

The present conference

The idea for the First Electronic Glycoscience Conference (EGC-1) [9] sprang from the participation of one of us, Barry Hardy, in the First Computational Chemistry Conference late in 1994 [24]. Some carbohydrate-related posters did appear in ECCC-1, but for most glycoscientists EGC-1 offered the first opportunity for them to use electronic means for presenting results (via WWW pages) and discussion (via electronic mailing lists and virtual conference centre sessions in a multiple-object oriented (MOO) environment) in a manner which attempted to mimic a normal 'real' conference. Since most electronic conferences in the past were held in computer-related sciences, the EGC-1 conference was one of the first of its kind in a traditionally experimental biological/chemical field. The bionet.glycosci newsgroup and the Glycoscience Interest Group mailing list were used as the basis for publicity which encouraged registration and preparation of papers and posters. EGC-1 was divided into 16 sections, each with a section convener who screened incoming abstracts for suitability.

EGC-1 improved the knowledge of conference participants about tools for using the Internet since WWW and MOO-based virtual discussion as well as the ubiquitous electronic mail were used. It also involved conference participants in creating WWW documents and so writing HTML and converting files to GIF format were skills that some exercised for the first time. As a result EGC-1 was probably quite a demanding starting point for a group of scientists who often were not at all exposed to the use of the Internet. There were obvious and justifiable concerns about electronic means of publication, since this was new in the field. However we believed that the cultural taboos on this subject would rapidly disappear in subsequent years due to cost-effectiveness, content variety, and interactivity of presentation, rendering electronic publication a compelling form of scientific presentation. The fact that EGC-1, the first electronic conference in this area, received over 100 submitted titles and over 550 registrants hinted that there was considerable interest and enthusiasm in this form of scientific communication. Over two-thirds of the presentations were in poster format which provided authors the ability to discuss work-in-progress in an international setting. Access to the conference required registration and the use of a user-specific password so that material presented at EGC-1 was to a limited registered audience. Additionally, ca. 30 papers were submitted and refereed through in conference and were used for publication in *Glycoconjugate Journal*.

EGC-1 probably went further than many electronic conferences to date in trying to re-create in a virtual setting a number of other events that are normally only happening in 'real' life. These included a Trade Centre

(where companies advertised using WWW pages); refereeing of some of the submissions to the conference; a complete Virtual Conference Centre MOO (based on that at BioMOO); and an Employment Centre listing vacancies and offering the possibility of private interviews. Interactive discussions took place in the MOO, and ongoing mailing list discussions were processed into threaded hypermail Web pages. A Hyperglossary project which aimed to create an electronic dictionary, a Virtual Gallery providing biomolecular images, and virtual reality constructs were ongoing projects which evolved material throughout the conference. We hoped that EGC-1 would prove a sound basis for a series of annual electronic glycoscience conferences and would be seen as a model for similar conferences in other fields. One major barrier to be overcome for this kind of event is the acquisition of technical knowledge by participants. The speed of the Internet and current computer platforms also limits the type of presentation at the conference. Depending on time of day and computer platform, considerable access time may be required to reach conference material on the Web. It is not practically possible at present to provide face-to-face interaction through video-conferencing on the Internet and inevitably the type of social interaction of a real conference is not approached.

BioMedComm – a supporting structure

In 1995 The Biological and Medical Virtual Communications Trust (BioMedComm) was founded. The first trustees of the trust were Barry J. Hardy of Oxford University, Iain Wilson of the Universitaet fuer Bodenkultur, Vienna and Robert Lauder of the University of Lancaster. The purposes of the trust are:

(a) to further the improvement of worldwide health and reduction of disease through the enhanced global communication of information in the biological and medical sciences and related basic and applied sciences;

(b) to improve the efficiency and clarity of communication between scientific and medical communities and the general public by virtual means;

(c) to establish and support international virtual resources in cyberspace including but not limited to electronic conferencing, electronic publishing, information databases and networked environments;

(d) to support the high quality career development and career guidance of young scientists in the fields covered by Trust activities;

(e) to raise and distribute finances to support these activities.

BioMedComm is supporting the activities of the new interdisciplinary growth area of the Glycosciences which has involved the formation of The Glycoscience Network. The Trust administered the financial activities of the EGC-1 conference. It is anticipated that the Trust will support subsequent virtual events and resource creation in other appropriate scientific areas. The technical areas of activity will include World Wide Web content development, CD-ROM production, interactive 3D databases, videoconferencing, bioinformatics servers and virtual reality environments. The trust will also support the establishment of new groups and add to the support of existing groups who are undertaking these activities. This support may be of a financial, organisational, consulting or technical nature. It is also envisaged that commercial sector developments will have a significant role to play in the information sector that will be strengthened by their effective communication with non-profit groups such as BioMedComm in moulding mutually beneficial roles.

The medium-term future

The range of Internet-accessible informational services for the glycosciences is, at present, limited. As mentioned above, a number of WWW pages of interest to glycoscientists have appeared in the last year, but no major initiatives have been possible since development of resources is dependent on the 'free time' of research scientists. A first question that many may have is whether Internet-accessible services are of any routine benefit. It must be admitted that the Internet has led to the propagation of material of dubious reliability, but in some fields the benefits of easy access to information are tangible. For instance, the contents of an increasing number of journals are now available on bionet.journals.contents and recently the *Journal of Biological Chemistry* has become available 'on-line', at least presently free-of-charge, but unfortunately the slowness of the Internet may make reference to the on-line version of the journal limited to really significant new papers that one otherwise would have to wait a month or two for. A number of literature and molecular biology databases are also available on-line and these present a definitely useful and speedy resource. As mentioned above, Carbbank [6] is at present the only database available for carbohydrate primary structures but its lack of graphical sophistication and informatics tools, and its availability only on CD-ROM or as a set of files totalling 70 megabytes, makes its utility limited as an informational springboard. One has to look elsewhere for models of how a modern 'Hypertext-Carbbank' may function, even though the Complex Carbohydrate Structural Database upon which Carbbank is based could become the backbone of any such resource.

A good example of an integrated biological database is Swissprot which is a curated protein sequence database [3]. This can be accessed via the Internet and is fully usable on the WWW. Simple search strings are possible and these retrieve a number of hypertext-linked accession

numbers. In turn these entries include links to the EC database, GenBank/EMBL database, the PIR database, a two-dimensional SDS-PAGE gel database, abstracts from Medline, and the Brookhaven three-dimensional protein database (where links exist). Thus starting from a query on say antitrypsin one can select, for instance, the A1AT_HUMAN entry and accumulate literature references (albeit only those directly related to sequencing the DNA or protein) and a three-dimensional structure with little effort. It is alsc possible via a swiss-BLAST search to find the nearest matches to your query sequence and examine hypertext database entries which in turn link to all those databases mentioned above. With Carbbank, there is a skeleton of such information available –

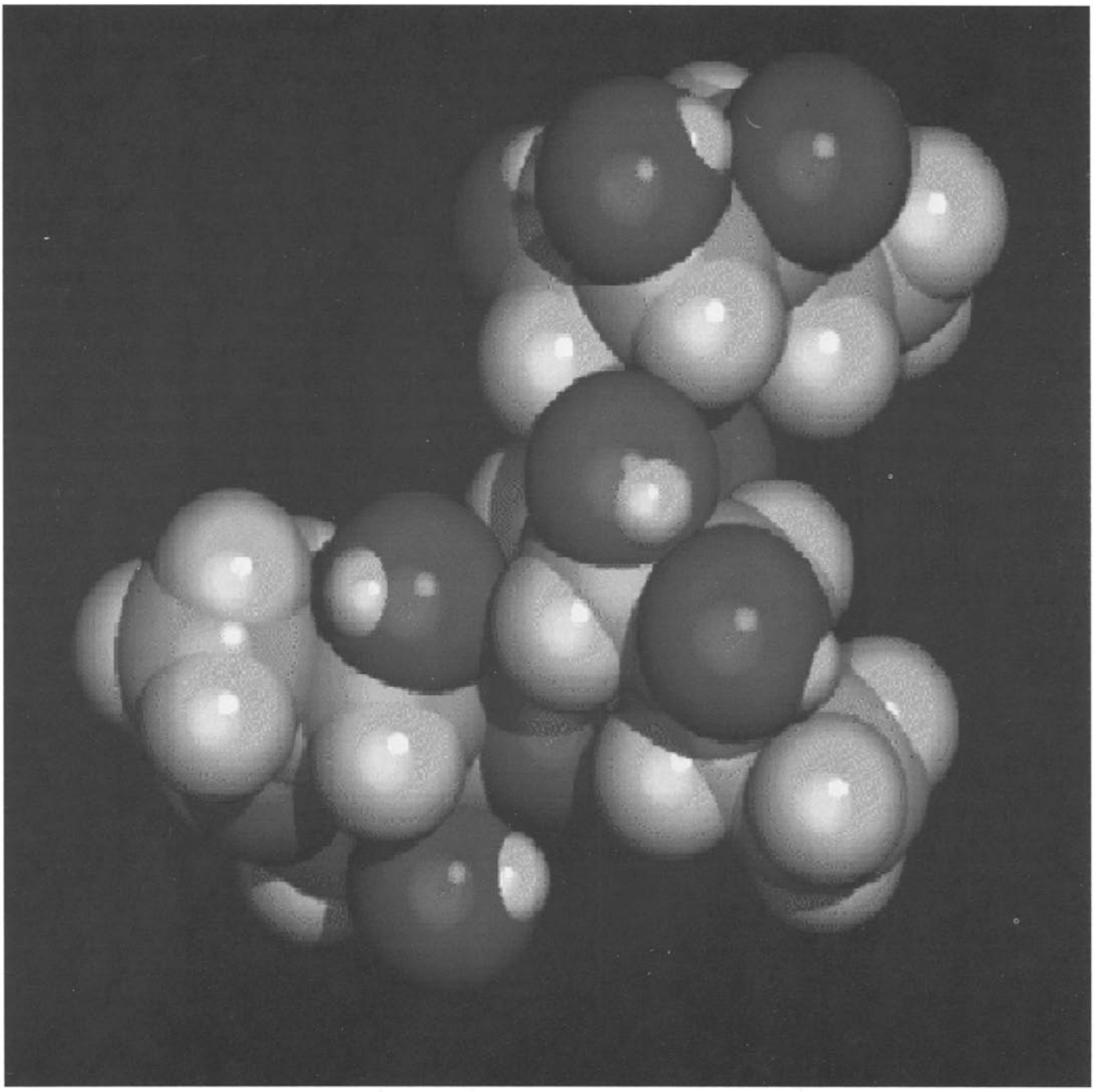

Figure 1. Picture of a conformation of the trisaccharide structure α-L-Rhamnose p-(1 → 2)-α-L-Rhamnose p-(1 → 3)-α-L-Rhamnose(1 → OMe).

searching by author and sequence is possible, but the syntax is difficult and clumsy. Certainly access to three-dimensional structures is not currently possible.

TGN, BioMedComm and other groups will, hopefully, begin to allow a filling of the 'glycoscience gap' in hypertext databases, by being a channel for the organisation and development of electronic resources useful for those in the glycosciences and beyond. A joint public-private venture could be initiated to explore the possibilities of a fully integrated hypertext-based carbohydrate primary structure database.

In addition it would be valuable to coordinate a database of simulated, proposed or proven three-dimensional structures of carbohydrates, which at present are held on computers in different laboratories throughout the world. For instance, at present if you wanted a diagram indicating what sort of conformation a biantennary N-linked oligosaccharide may adopt you may have to refer to a journal or ask a relevant laboratory whether you could have a copy of their model. In the future one could conceive that it may be as simple as clicking 'transferrin asialo-oligosaccharide' within our proposed hypertext version of Carbbank in order to have a diagram of the proposed solution conformation. In Fig. 1 we show an example GIF file of a simulated solution conformation of the trisaccharide α-L-Rhamnose p-(1 $\rightarrow$ 2)-α-L-Rhamnose p-(1 $\rightarrow$ 3)-α-L-Rhamnose (1 $\rightarrow$ OMe) that can be directly hyperlinked to. In addition, the user can examine the PDB file using a viewing program such as Rasmol, rotate the structure to a desired position and ruminate on the possible steric hindrances and the subsequent biological effects (Fig. 2).

Longer term

The above example provides sequence retrieval and structural visualisation to the user but scientific enquiry in this situation demands us to develop more sophisticated tools than the mere rendering of a three-dimensional picture. Information on the structure queried could be obtained by a keyword-directed search of experimental databases. Information returned from a distributed network could include a crystal structure, NMR data, CD spectra or binding constants for a specific protein. Upon return of this information, the recipient should be able to perform an interactive investigation. For example, the recipient could impose a set of experimental NOE constraints on a structure, examine the constraints superimposed on a model, send the combined information off to a calculation facility for refinement and retrieve and examine results. If the structure is unknown, it might be desirable to send a trial structure off to a spectral simulation utility to obtain CD or mass-spectrometric theoretical spectra which could be compared against known spectra from databases or recent experimental data on the structure obtained by the investigator themselves. Proposed mimics to a carbohydrate ligand could be transmitted for calculation of binding constants based on either protein docking protocols or Quantitative Structure Activity Relationship prediction utilities. Whereas these activities could be performed locally a considerable amount of effort and expertise is required to maintain, operate and understand a diverse variety of software. In comparison, access to distributed specialist facilities via the Internet and Web, would allow the accomplishment of a scientific task without the required considerable investment in local facilities. Such Net-based tools in the glycosciences will probably include both freely-available academic-based utilities and also robust commercials sites which will levy a subscription or query-based downloading fee.

The recent development of Virtual Reality Markup Language (VRML) has brought a practical virtual reality tool to the Web and consequently opens up many exciting possibilities. VRML activities presented at EGC-1 demonstrated the building of model cell membranes and the glycosylation of proteins [20]. These capabilities allow an investigator to explore a structure in an interactive virtual reality environment on the Web accompanied by the advantages of hyperlinks. This activity combined with bioinformatics servers opens the possibility of combining sequence and structure information to remotely create a virtual construct through which the user can explore. This provides an unprecedented opportunity for the remote exploration of experimental data. It is tempting to speculate on the potential of further development of VRML-based tools to the glycosciences. Currently VRML primarily allows the exploration of a single static object through which the viewer moves. The development of multiple object environments accompanied by user object control will allow the interactive combination and interaction of structural objects. This could be used for example, to glycosylate a protein or to present a carbohydrate at a membrane surface. If the information used to construct the objects is obtained from remote databases the remarkable conclusion is that a scientist with no other software than a sophisticated Web browser could move from a query on a protein-carbohydrate complex to an interactive virtual reality-based docking experiment. The combination of VRML with force-field approaches will allow the inclusion of physical forces in the virtual reality. For example, in the docking experiment, it will be possible for the Web-browser to assume the structure and potential energy surface of the carbohydrate ligand themselves and to experience the approach and entry into the protein cavity. A drug designer with an inappropriately designed carbohydrate mimic may suffer with dispiriting but useful experience of rejection from which they may move on to more compatible designs.

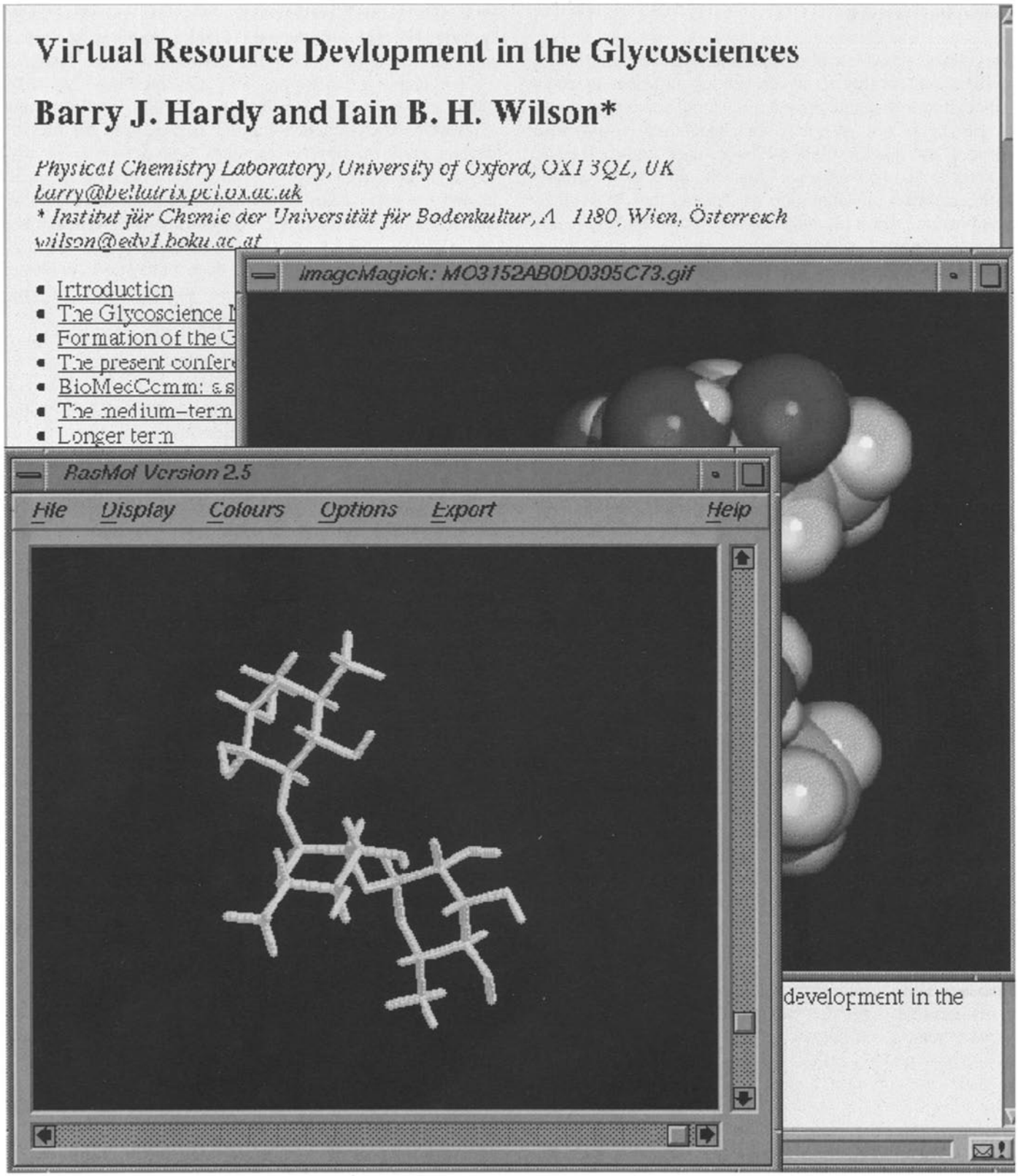

Figure 2. Interactive viewing with Rasmol of the pdb file of the trisaccharide structure α-L-Rhamnose *p*-(1 → 2)-α-L-Rhamnose *p*-(1 → 3)-α-L-Rhamnose(1 → OMe).

Concluding remarks

One advantage of extending the database revolution to the glycosciences is that it makes gaining information about carbohydrates that much easier, not only for those trained in the field, but also for non-specialists from other sciences, to quickly find out structures and references related to carbohydrates. This should foster greater interdisciplinary collaboration or insights than may otherwise occur, since non-specialists may find standard literature searches unrewarding or may just stumble on the glycoscientific possibilities due to netsurfing. It may be possible for the accumulated knowledge in the field to become Internet-accessible: protocols, bibliographies and novel reviews could be made accessible that otherwise would not be published in a traditional way due to the lack of a suitable forum. On-line images that can be manipulated by the user or hypertext-linking are obvious examples where WWW documents can be used to do things not possible on paper.

There is no point in the Internet merely duplicating traditional means of publication, unless there are distinct advantages in time. Keyword searching can improve the efficiency of a flick through a paper journal, since interesting items can be found which otherwise would be missed. The new hobby of Web-surfing provides for the discovery of unexpected information as might have been gained previously from an undirected casual stroll in the local bookstore. Electronic publication is probably going to become more frequent, and collectively the scientific community has to arrive at a framework within which electronic publication is generally accepted and adequately controlled. Electronic publication may mean a reduction in the number of paper journals as small-circulation journals become superseded by, or adopt the status of, electronic journals. Larger and more prestigious journals will, presumably, follow the example of the *Journal of Biological Chemistry* and produce an on-line edition, presumably on subscription in the not-to-distant future. Similarly the proliferation of specialist conferences may be partially replaced by virtual conferences, but of course these lack the face-to-face aspect that can make attending conferences worthwhile. However, virtual conferences do save on travel and hotel expenses. It is probable that a balance will eventually be hit whereby real and virtual conferences exist in complementary fashion. Virtual discussion should become a more pleasant social prospect if the networks become faster.

Our hope is that the The Glycoscience Network activities we have described here and The First Electronic Glycoscience Conference will act as a catalyst for further development of virtual resources and activities in the Glycosciences. We believe that such undertakings will provide a solid base for scientific communication and collaboration involving the widest possible participation of different individuals and diverse scientific groups. These developments should contribute and enhance significantly the activities and achievements of the community involved in carbohydrate research.

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