

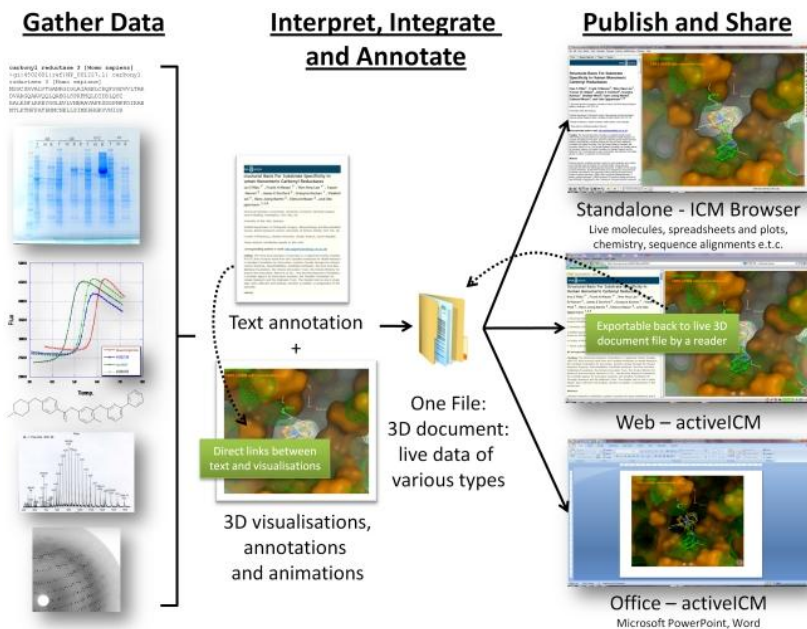
ActiveIcmJS

Eugene Raush

Molsoft LLC

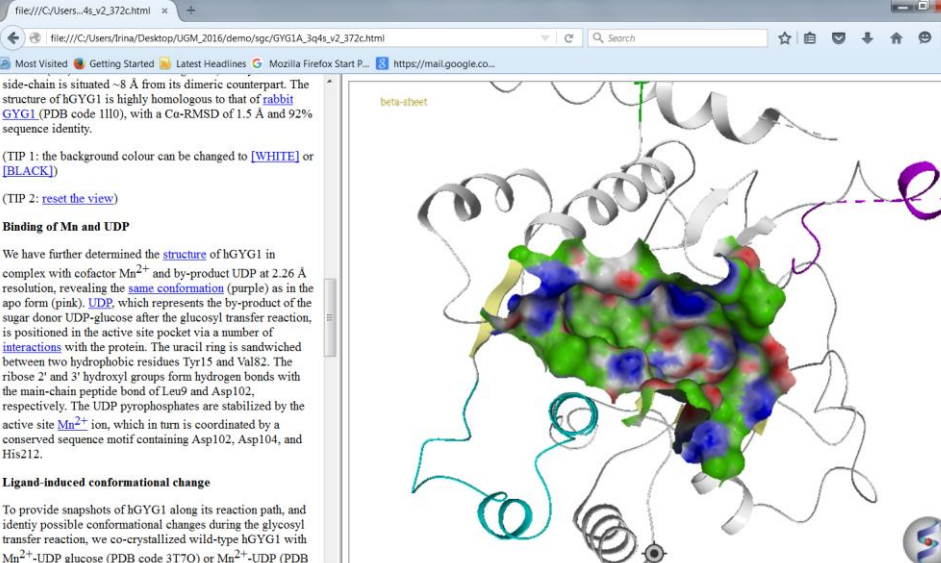
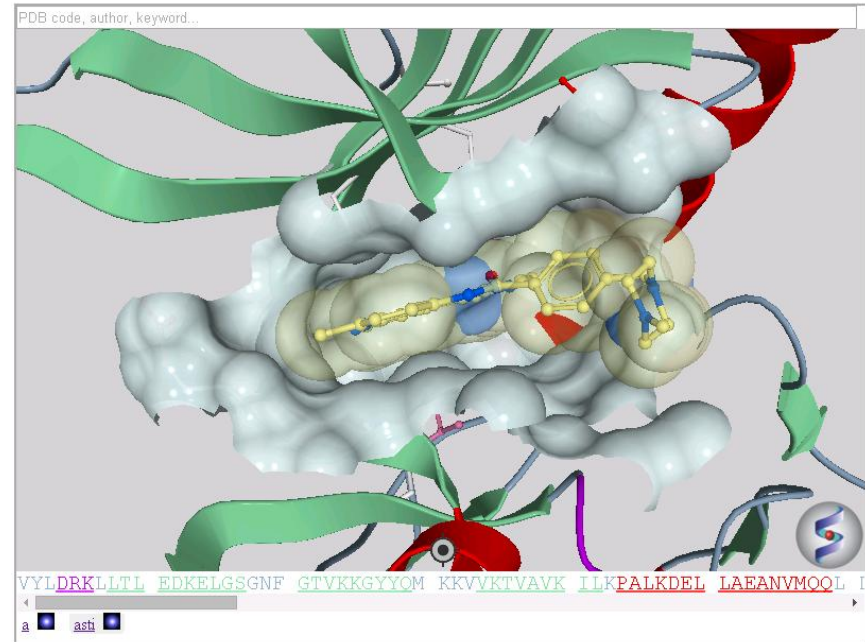
History

- ActiveICM plugin for browsers was first introduced in 2009.
- It gained a popularity for data publishing and exchange.
- Plugin was build using NPAPI interface which was supported by all major browsers.
- In early 2015 Google announced that Chrome is dropping support for native code plugins.
- We were looking at possible replacements and found a good alternative.



Introducing ActiveIcmJS.

- **ActiveIcmJS** is JavaScript port of ICM shell and 3D graphics.
- **Compatible** with all modern browsers
- **Does not require** any additional installation
- **Full access** to ICM **scripting functionality** through JavaScript object.
- **Mobile device friendly**
- **The same graphics quality** as our desktop applications.
- **Near native speed.**



file:///C:/Users/Irina/Desktop/UGM_2016/demo/sgc/GYG1A_3q4s_v2_372c.html

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side-chain is situated ~8 Å from its dimeric counterpart. The structure of hGYG1 is highly homologous to that of [rabbit GYG1](#) (PDB code 1110), with a Co-RMSD of 1.5 Å and 92% sequence identity.

(TIP 1: the background colour can be changed to [WHITE] or [BLACK])

(TIP 2: [reset the view](#))

Binding of Mn and UDP

We have further determined the [structure](#) of hGYG1 in complex with cofactor Mn^{2+} and by-product UDP at 2.26 Å resolution, revealing the [same conformation](#) (purple) as in the apo form (pink). UDP, which represents the by-product of the sugar donor UDP-glucose after the glucosyl transfer reaction, is positioned in the active site pocket via a number of [interactions](#) with the protein. The uracil ring is sandwiched between two hydrophobic residues Tyr15 and Val82. The ribose 2' and 3' hydroxyl groups form hydrogen bonds with the main-chain peptide bond of Leu9 and Asp102, respectively. The UDP pyrophosphates are stabilized by the active site Mn^{2+} ion, which in turn is coordinated by a conserved sequence motif containing Asp102, Asp104, and His212.

Ligand-induced conformational change

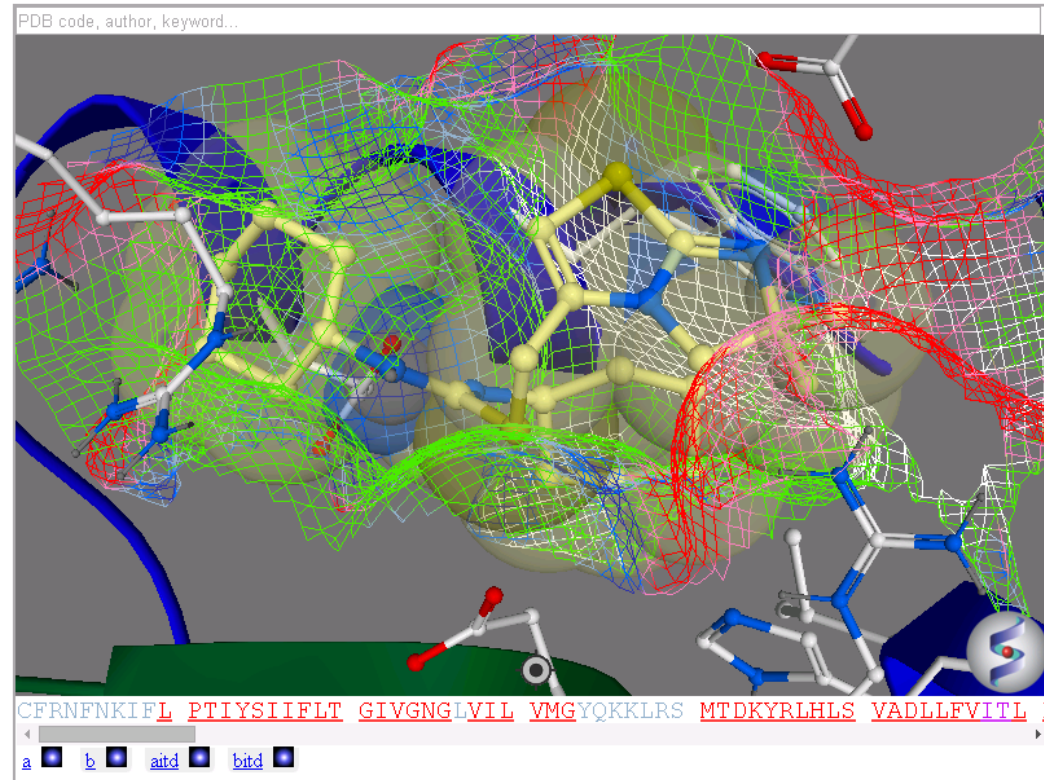
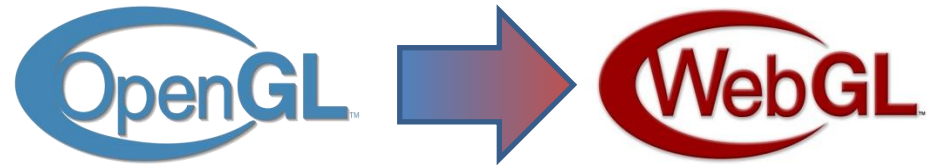
To provide snapshots of hGYG1 along its reaction path, and identify possible conformational changes during the glucosyl transfer reaction, we co-crystallized wild-type hGYG1 with Mn^{2+} -UDP glucose (PDB code 3T7O) or Mn^{2+} -UDP (PDB code 3T7M, 3T7N), and determined these structures from

Technology behind ActiveIcmJS

- **ASM.JS**
 - <http://asmjs.org/>
 - Optimizable, strictly typed, low-level subset of **JavaScript**
 - Runs inside any modern web browser with **only 1.5-3 times slower** than native code.
- **Emscripten**
 - <http://kripken.github.io/emscripten-site/index.html>
 - Compiles ICM C/C++ code into asm.js
- **ICM shell and graphics** compiled into JS code
 - 350,000 lines C/C++ code
 - Result JS library size 18M (4.7M compressed)

3D graphics and WebGL

- WebGL is a **very limited subset** of OpenGL
- We developed a **special layer** which translates OpenGL calls into WebGL
- That allows to keep the **same codebase** and deliver **highest quality graphics** to the web.

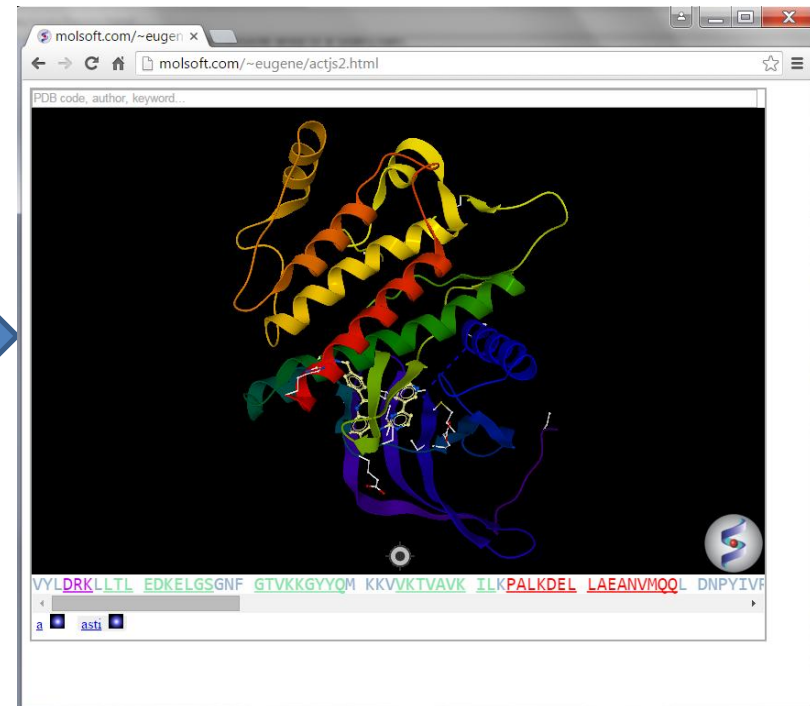
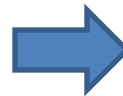


ActiveIcmJS object

- ActiveIcmJS is a JavaScript object which implements single **ICM shell and graphics** window.
- Can be **embedded** in any place in the HTML code
- API is **compatible** with old ActiveIcm

```
<html>
<head>
<script src="http://molsoft.com/lib/acticm.js"> </script>
</head>

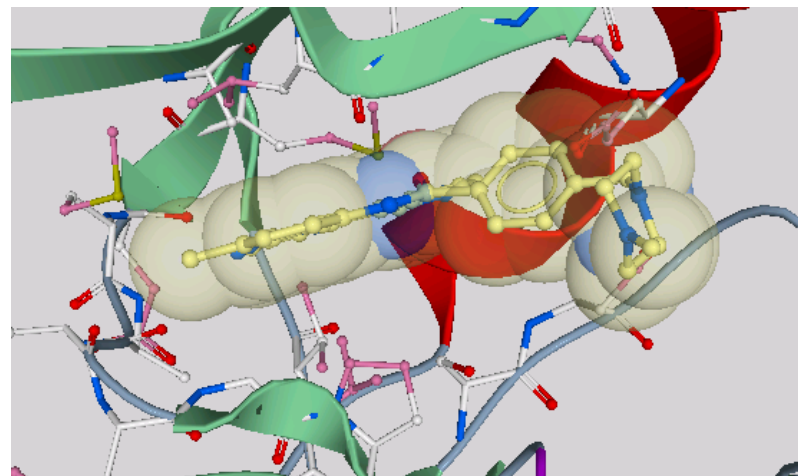
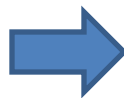
<div id="con" style="width: 800px; height: 600px;"> </div>
<script>
Function onLoadActiveIcm()
{
  act = new ActiveIcmJS("con");
  act.projectFile = "1xbb.icb"
}
</script>
</body>
</html>
```



JavaScript/ICM shell integration

- ICM shell and scripting language is **fully accessible** from within the web browser.
 - Can run **any local or remote ICM script**
 - Can run **any list of commands** from the web browser

```
act = new ActiveIcmJS("con");  
// Load standard macros  
act.CallScript( "http://molsoft.com/lib/_macro" );  
  
...  
  
// display ligand as CPK  
act.RunCommands("display cpk a_H")  
  
// display pocket residues  
act.RunCommands("display xstick Res(Sphere(a_H a_A))")
```

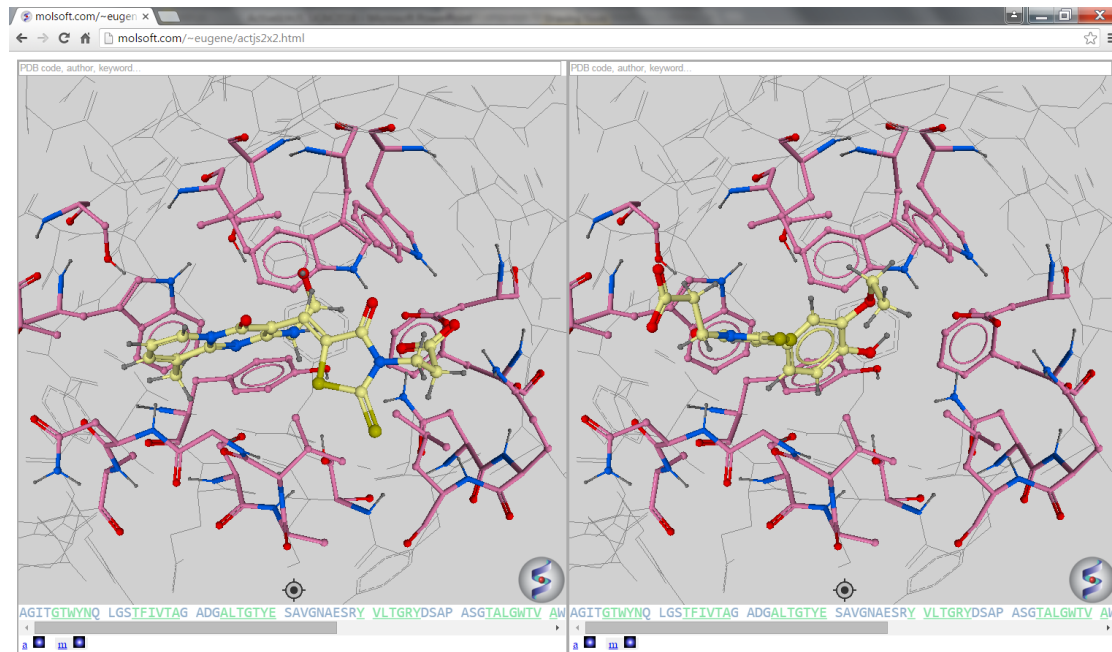


- **Multiple** ActiveIcmJS objects on the same web page are **allowed**.
- Each ActiveIcmJS object can be **controlled separately** from the UI and JavaScript.
- Can be **grouped** for synchronous rotation

```
<html>
<head>
<script src="http://molsoft.com/~eugene/lib/acticm.js"></script>
</head>

<table style="width: 100%; height: 100%;">
<tr>
<td><div id="act1" style="width: 100%; height: 100%; border: 2px solid #ABABAB"> </div></td>
<td><div id="act2" style="width: 100%; height: 100%; border: 2px solid #ABABAB"> </div></td>
</tr>
</table>

<script>
Function onLoadActiveIcm()
{
  act1 = new ActiveIcmJS("act1"); act1.projectFile = "pose1.icb"; act1.AddToGroup("grp1");
  act2 = new ActiveIcmJS("act2"); act2.projectFile = "pose2.icb"; act2.AddToGroup("grp1");
}
</script>
</html>
```



Additional features

- Interactive flexible PDB keyword search bar.
- **Sequence view** area with ability to select and mouse over
- **Full Screen** mode support
- Touch and **multi-touch** device support

gpcr

4o9r SIGNALING PROTEIN Human Smoothed Receptor structure in complex with cyclopamine HOMO SAPIENS, ESCHERICHIA COLI Wang, C., Weierstall, U., James, D., White, T.A., Wang, D., Liu, W., Spence, J.C.H., Doak, R.B., Nelson, G., Fromme, P., Fromme, R., Grotjohann, I., Kupitz, C., Zatsepin, N.A., Liu, H., Basu, S., Wacker, D., Han, G.W., Katritch, V., Boutet, S., Messerschmidt, M., Williams, G.J., Koglin, J.E., Seibert, M.M., Klinker, M., Gati, C., Shoeman, R.L., Barty, A., Chapman, H.N., Kirian, R.A., Beyerlein, K.R., Stevens, R.C., Li, D., Shah, S.T.A., Howe, N., Caffrey, M., Cherezov, V., **GPCR Network (GPCR)** cy8 C562_ECOLX,SMO_HUMAN

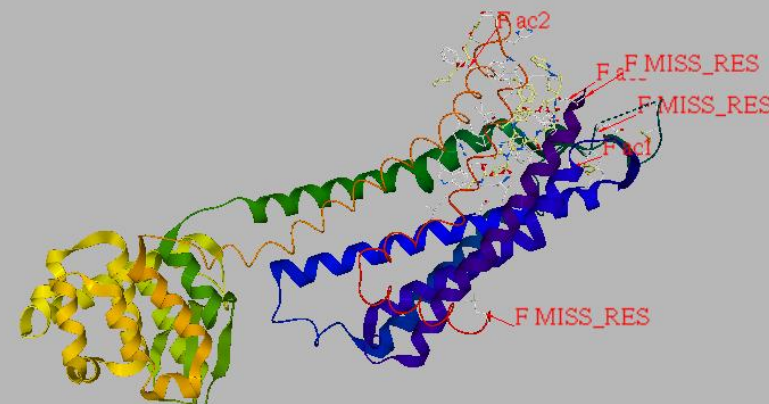
3qak SIGNALING PROTEIN, HYDROLASE Agonist bound the human adenosine A2a receptor HOMO SAPIEN, ENTEROBACTERIA PHAGE T4 Xu, F., Wu, H., Katritch, V., Han, G.W., Cherezov, V., Stevens, R., **GPCR Network (GPCR)**, Joint center for innovative membrane protein technologies (JCIMPT) uka;olc AA2AR_HUMAN,LYS_BPT4

4xt1 VIRAL PROTEIN/SIGNALLING PROTEIN a nanobody-bound viral **GPCR** bound to human chemokine CX3CL1 CYTOMEGALOVIRUS; HOMO SAPIENS; VICUGNA PACOS Burg, J.S., Jude, K.M., Waghray, D., Garcia, K.C. pca;clr;olc;unl;sin US28_HCMVA,X3CL1_HUMAN

4xt3 VIRAL PROTEIN/SIGNALLING PROTEIN a viral **GPCR** bound to human chemokine CX3CL1 CYTOMEGALOVIRUS; HOMO SAPIENS; SYNTHETIC CONSTRUCT Burg, J.S., Jude, K.M., Waghray, D., Garcia, K.C. pca;unl;po4;nag US28_HCMVA,X3CL1_HUMAN

4oo9 MEMBRANE PROTEIN the human class C **GPCR** metabotropic glutamate receptor 5 transmembrane domain in complex with the negative allosteric modulator mavoglurant HOMO SAPIENS, ENTEROBACTERIA PHAGE T4, HOMO SAPIENS Dore, A.S., Okrasa, K., Patel, J.C., Sarma-Vega, M., Bennett, K., Cooks, R.M., Frye, J.G., Izquierdo, A., Khan, S., Tobias, P., Weir, M.

PDB code, author, keyword...



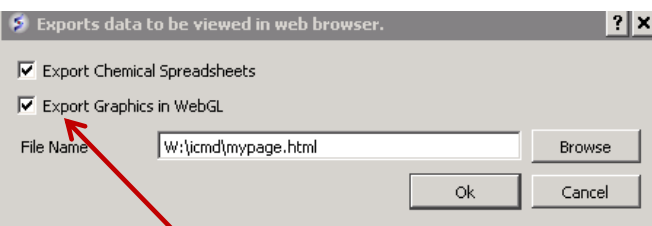
V46

W LNSNLQNVTN YFVVSLLAAAD IAVGVLAIPF AITISTGFCA ACHGCLFIAC FVLVLTQSSI FSLLA

a auka aolc aolc2

How to convert my old ActiveIcm page into a new ActiveIcmJS?

1. Open your project in ICM



molsoft.com/~eugene/sq/

Structural Features

Overall fold

We have determined the [crystal structure](#) of human glycogen-1 catalytic domain (hGYG1) in the apo form at 1.98 Å resolution. hGYG1 adopts the classic architecture of the glycosyltransferase type A (GT-A) fold, featuring a central six-stranded core [beta-sheet](#) (yellow) encompassing the [active site](#) for the glucosyl transfer reaction, flanked by helices. In addition hGYG1 contains three extension regions that are important for its glucosyl transfer and substrate specificity. These include a coil-helix segment (S4; blue), a beta sub-domain (arm; purple) that harbours the acceptor residue Tyr195, as well as a neighbouring C-terminal hairpin loop (green). In the apo form, part of the arm and hairpin are disordered suggesting their intrinsic flexibility. hGYG1 crystallizes as a [homodimer](#), with the dimer interface formed by arm sub-domain as well as a loop segment connect P5-P6 of the core (red). In this dimeric arrangement, the Tyr195 side-chain is situated ~8 Å from its dimeric counterpart. The structure of hGYG1 is highly homologous to that of [rabbit GYG1](#) (PDB code 1B0), with a Co-RMSD of 1.5 Å and 92% sequence identity.

(TIP 1: the background colour can be changed to [WHITE] or [BLACK])

(TIP 2: [reset the view](#))

Binding of Mn and UDP

We have further determined the [structure](#) of hGYG1 in complex with cofactor Mn^{2+} and by-product UDP at 2.26 Å resolution, revealing the [same conformation](#) (purple) as in the apo form (pink) [UDP](#), which represents the by-product of the sugar donor UDP-glucose after the glucosyl transfer reaction, is positioned in the active site pocket via a number of [interactions](#) with the protein. The uracil ring is sandwiched between two hydrophobic residues Tyr15 and Val82. The ribose 2' and 3' hydroxyl groups form hydrogen bonds with the main-chain peptide bond of Leu9 and Asp102, respectively. The UDP pyrophosphates are stabilized by the active site Mn^{2+} ion, which in turn is coordinated by a conserved sequence motif containing Asp102, Asp104, and His212.

Ligand-induced conformational change

To provide snapshots of hGYG1 along its reaction path, and identify possible conformational changes during the glucosyl transfer reaction, we co-crystallized wild-type hGYG1 with Mn^{2+} -UDP glucose (PDB code 3T70) or Mn^{2+} -UDP (PDB code 3T7M, 3T7N), and determined three structures from different crystal forms. They reveal a drastically [different conformation](#) of the enzyme compared to the apo-form, involving structural rearrangements in [three regions](#) of the protein that influence active site accessibility. These include a 'lid' segment (aa 60-91), a helix-turn-helix 'acceptor arm' (aa189-207) harbouring the Tyr195 acceptor residue, and the C-terminal loop ('C-loop', aa 233-243) located close to the acceptor arm.

Superimposition of the two hGYG1 conformers reveals a maximum motion in the [lid segment](#) amongst the three flexible regions. In the apo enzyme, the lid adopts an open conformation (blue) positioned away from the active site, leaving it accessible to the exterior. Upon binding the cofactor (UDP glucose), the lid adopts a closed

beta-sheet

SMTDQAEVIL TTNDAVAKGA LVLGSSLIQK RITTRRLTYLTA TFGVSDSMRK VLETFDFEVI MVDVLDSDGS AHLTLMH

1 a a1 a2 a3 a4 a5 a6 a7 a8 a9 a10 a11 a12 a13 a14 a15 a16 a17 a18 a19 a20 a21 a22 a23 a24 a25 a26 a27 a28 a29 a30 a31 a32 a33 a34 a35 a36 a37 a38 a39 a40 a41 a42 a43 a44 a45 a46 a47 a48 a49 a50 a51 a52 a53 a54 a55 a56 a57 a58 a59 a60 a61 a62 a63 a64 a65 a66 a67 a68 a69 a70 a71 a72 a73 a74 a75 a76 a77 a78 a79 a80 a81 a82 a83 a84 a85 a86 a87 a88 a89 a90 a91 a92 a93 a94 a95 a96 a97 a98 a99 a100

2. Choose File/Export and check "Export Graphics in WebGL" option

3. Your page should be fully functional And ready to use

Manual conversion for custom pages

```
<html>
<object id="ActiveIcmCtl" width="800" height="600" type="application/x-molsoft-icb" >
</object>
<script>
  act = document.getElementById("ActiveIcmCtl");
  act.projectFile = "Lab5_B2AR.icb";
</script>
</html>
```

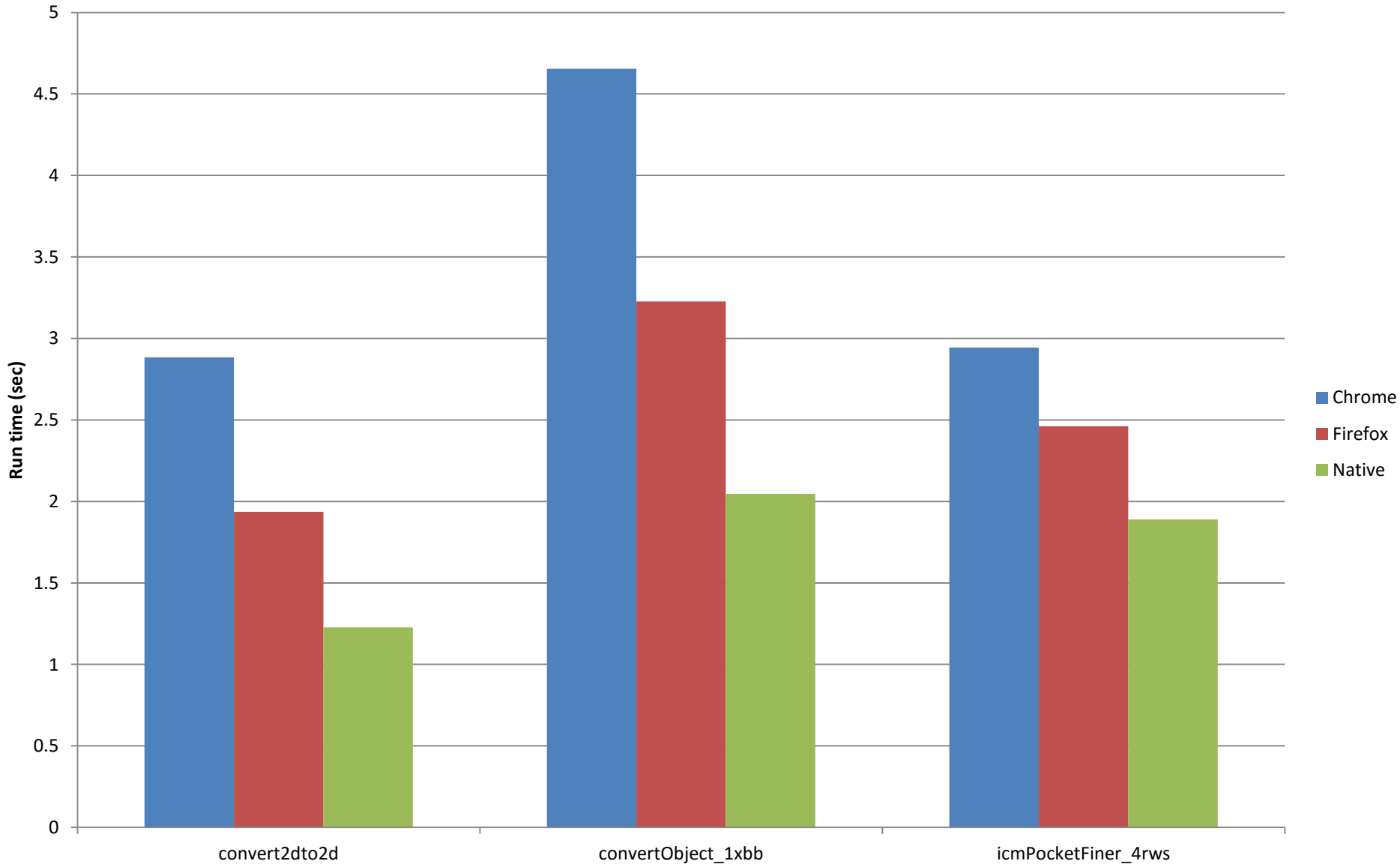


```
<html>
<head>
<script src="http://molsoft.com/~eugene/lib/acticm.js"></script>
</head>

<div id="ActiveIcmCtl" style="width: 800px; height: 600px;"> </div>
<script>
function onLoadActiveIcm()
{
  act = new ActiveIcmJS("ActiveIcmCtl");
  act.projectFile = "Lab5_B2AR.icb";
}
</script>
</html>
```

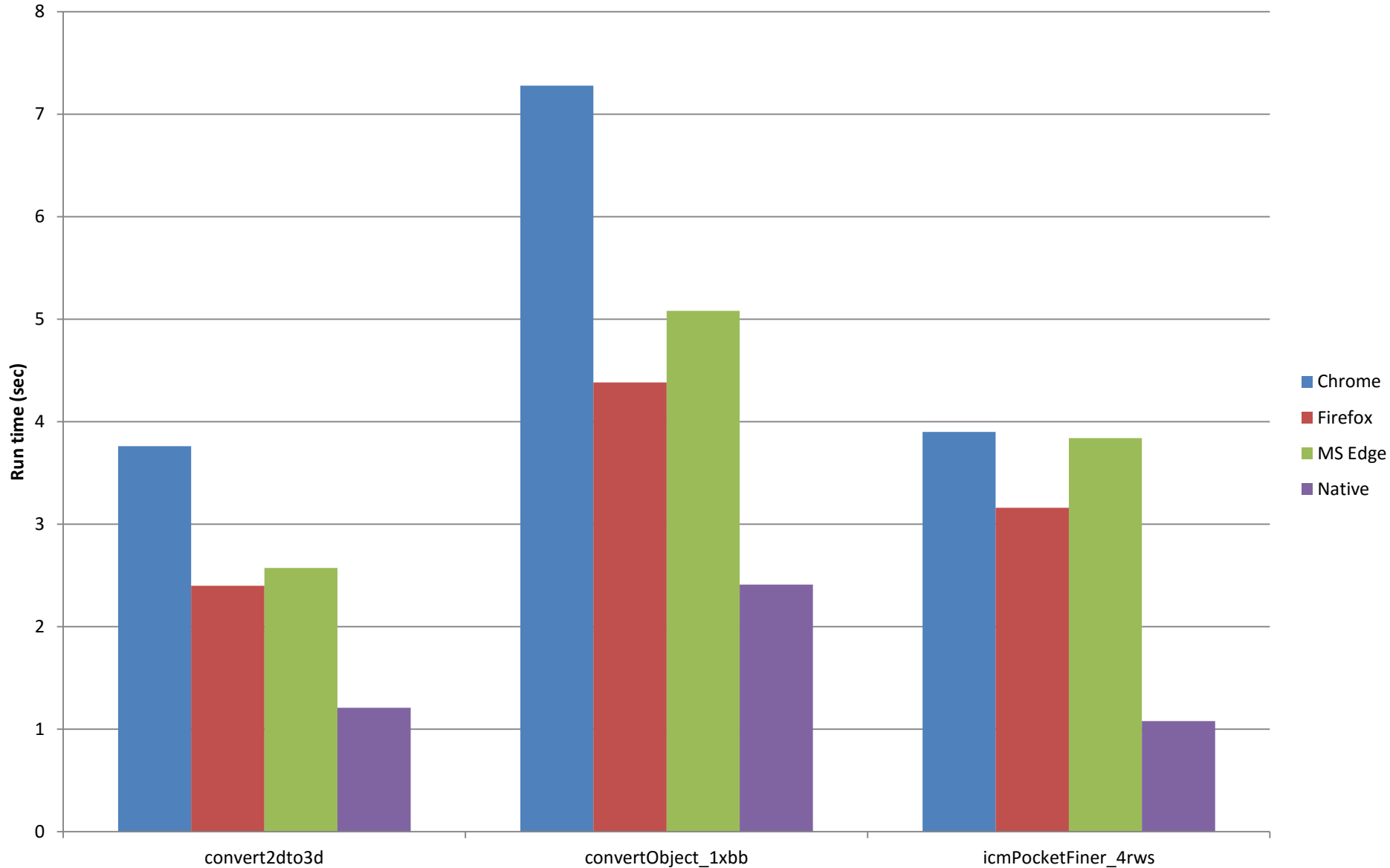
1. Replace **object** tag with **div** container
2. Create **ActiveIcmJS** object and pass container ID as an argument
3. Other API should be **compatible**.

Benchmark: PC/Win7/Intel i7 CPU 3.44GHz



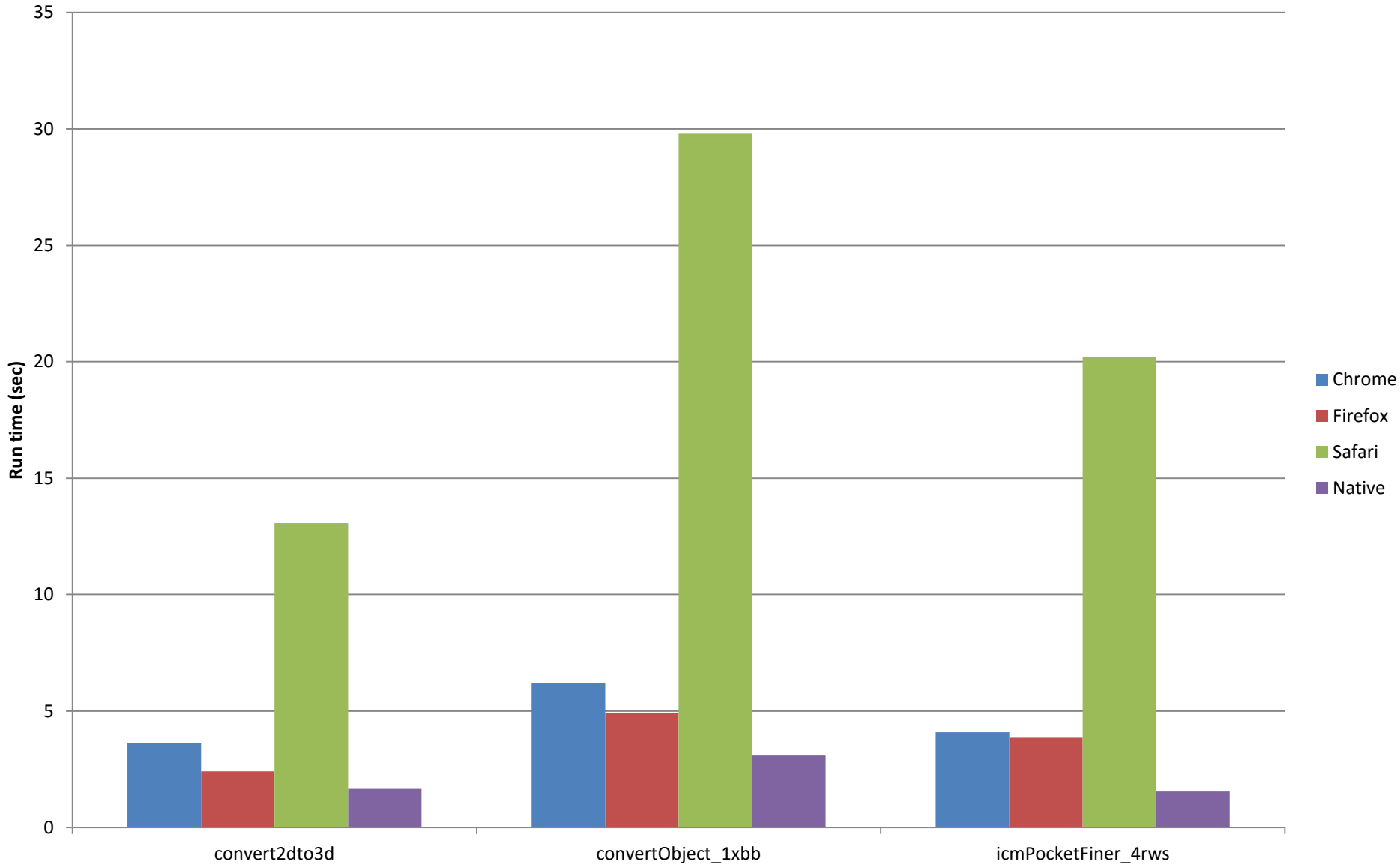
Benchmark:

MS Surface/Win10/Intel i5 CPU 2.50GHz



Benchmark:

Mac mini/OS X 10.9/Intel i5 CPU 2.30GHz



Demo

- Online services
 - pdb viewer, and 2D to 3D conversion
- HTML export demo
 - SGC data pack
 - Docking hit list export
 - APF hit list

Future work

- Develop GUI interface
 - Tool bar which toggles various graphical representations
 - Menus
- Add more objects
 - tables, plots, alignments

Links

- ActiveICMJS page
 - <http://molsoft.com/activeicmjs.html>
- Technical reference
 - <http://molsoft.com/activeicmjstech.html>

Acknowledgments

- Molsoft
 - Max Totrov, Andy Orry, Ruben Abagyan
- SGC Oxford
 - Brian Marsden, Anthony Bradley