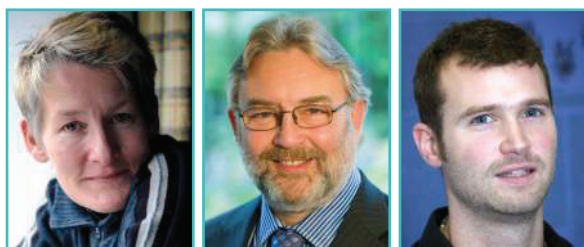


Utopia Documents and The Semantic Biochemical Journal experiment



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Introduction

Recent technological advances have led to the accumulation of data on an unprecedented scale. Adding to this information overload is the advent of desk-top sequencing, with machines capable of delivering terabytes of data per hour. The problem is, the rush to increase the amounts of information we collect does not in itself bestow a miraculous increase in knowledge. For information to be usable, it needs to be stored and organised in ways that allow us to access it, to analyse it, to annotate it and to relate it to other information. Unfortunately, to date, we have failed to store and organise much of the rapidly accumulating information (whether in databases or documents) in rigorous, principled ways, so that finding what we want and understanding what's already known become increasingly exhausting, frustrating and costly experiences.

Scientists for whom these problems have become especially acute are database curators. Today, the largest protein sequence database in the world is UniProtKB [1]. UniProtKB currently contains >9 million entries, of which ~500,000 have been contributed by its manually-annotated component, Swiss-Prot [2]. By inspecting thousands of articles and hundreds of other database entries, it has taken 23 years for the Swiss-Prot curators to annotate about half of these sequences – indeed, Bairoch estimates that this gargantuan task has involved 600 person years of effort [3]! The difficulties faced by the curators are enormous: with ~25,000 peer-reviewed journals publishing ~2.5 million articles per year, this equates to something like two new papers appearing in Medline every minute [4]. Consequently, it is impossible for curators to keep abreast of developments, and more and more difficult for them to find relevant papers, or to locate relevant facts within them. It isn't really surprising, then, that Bairoch should opine, "It is quite depressive to think that we are spending millions in grants for people to perform experiments, produce new knowledge, hide this knowledge in a often badly written text and then spend some more millions trying to second guess what the authors really did and found" [3].

The life of curators would be a lot easier if articles could become better conduits to their underlying research data. In fact, it has already been argued that the distinction between an on-line paper and a database is already diminishing [5]. Nevertheless, it is clear that much more needs to be done to make the data contained in research articles more accessible.

In this Letter, we briefly outline a new development with Portland Press Ltd., the so-called Semantic *Biochemical Journal* experiment [6]. Behind this 'experiment' is a new software tool, Utopia Documents, which builds on the Utopia suite described in previous EMBnet.news articles, and elsewhere [e.g., 7-9]. Here, we provide a sketch of these new developments, in order to provide a taster of what can be achieved through academic-journal-publisher collaboration.

The "experiment"

Utopia is a software suite that semantically integrates visualisation and data-analysis tools: its most recent component, Utopia Documents, brings document-reading and document-

The screenshot displays the Utopia Documents interface. The main window shows a PDF document titled "Volume 13 Nr. 4 EMBnet.news 29". The article text includes sections on "Druggable protein interactions" and "Inhibitors for p53-MDM2 complex". A sidebar on the right provides additional information for the term "1T4F", including its structure in complex with an optimized p53 peptide (PDB:1T4F) and a definition of "Integral membrane protein". Below the sidebar is a protein alignment tool showing the sequence of MDM2_XEN1A and other related sequences.

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Bioinformatics, which is a member of the wwPDB [21]. RCSB ensures that the PDB archive remains an international resource with uniform data.

The PDB is the single worldwide depository of information concerning the three-dimensional structures of large biological molecules, including proteins and nucleic acids. Therefore, its importance in drug designing project is indisputable.

Druggable protein interactions

Protein interactions appear in every single living cell. They are crucial for function and growth and are involved in various cellular pathways. Abnormal behavior of protein interactions and protein complexes play a key role in various diseases. Therefore, the identification of molecules preventing the formation of the complex or interaction of the proteins of the under question complex could be valuable drug targets. The inhibitor design is a very hot topic in drug discovery nowadays and one of the major goals of many drug design projects.

Below two examples are provided, a known and interesting example of a drug target and another example of a new challenging target in drug therapeutic agents. Great effort has been made in order to design an inhibitor for the interaction of the complex formed by the transcription factor p53 and the murine double minute 2 (MDM2). Our second example focuses on the new premises and challenges in applying gamma-secretase inhibitors as therapeutic agents for cancer.

Inhibitors for p53-MDM2 complex

p53 is a transcription factor known to be involved in various biological processes such as cell-cycle regulation, apoptosis, DNA repair, and differentiation [22]. The mutation or deletion of this transcription factor has disastrous consequences since such phenomena have been associated with human cancer [23]. MDM2 is a negative regulator of the p53 tumor suppressor. Overexpression of MDM2 found in several tumor cases can lead to inactivation of p53, since MDM2 constantly inhibits p53. These interactions were taken into consideration. In order to design molecules that would prevent the p53-hmd2 interaction and therefore cancer.

G-secretase - Cancer therapeutic agents

Gamma-secretase is a protease with catalytic activity, and cleaves mostly type I membrane proteins such as Notch receptor and amyloid beta peptide precursor. Several g-secretase inhibitors have been developed for the treatment of Alzheimer due to its role in clearing beta-amyloid precursor in the brain. Inhibition of amyloid β -peptide (A β) production by blocking γ -secretase activity is at present one of the most

1T4F

Structure of human MDM2 in complex with an optimized p53 peptide [pdb:1T4F]

Ubiquitin-protein ligase E3 Mdm2 (E.C.6.3.2.-), optimized p53 peptide
[View webpage...](#)

Integral membrane protein

An Integral Membrane Protein (IMP) is a protein molecule (or assembly of proteins) that is permanently attached to the biological membrane. Such proteins can be separated from the biological membranes...

[View webpage...](#)

	220	230	240	250	260	270	280
MDM2_XEN1A	E S T D S S S N S D P E R H S T N D N S E H - - D S D Q F S V E F E F E V E S V C S D D Y S P S G D E H G V S E E E E - - E I N D E V Y Q V T I Y E T E E S S						
Q6CMB_XEN1A	E S T D S S S N S D P E R H S T N D N S E H - - D S D Q F S V E F E F E V E S V C S D D Y S P S G D E H G V S E E E E - - E I N D E V Y Q V T I Y E T E E S S						
Q6P93_XEN1R	E S T D S S S N S D P E R H S T N D N S E H - - D S D Q F S V E F E F E V E S V C S D D Y S P S G D E H G V S E E E E - - E I N D E V Y Q V T I Y E T E E S S						
Q2R50_XEN1R	E S T D S S S N S D P E R H S T N D N S E H - - D S D Q F S V E F E F E V E S V C S D D Y S P S G D E H G V S E E E E - - E I N D E V Y Q V T I Y E T E E S S						
1T4F							
Consensus							

Figure 1. Composite screen-shot illustrating some of the features of Utopia Documents. Dominating the Figure is a page from EMBnet.news (volume 13, issue 4, page 29). Clicking on terms of interest in the text (e.g., 1T4F - the highlighted term half-way down the second column of text) provides definitions from various online databases, dictionaries or thesauri, and uses RDF-linked data to infer and retrieve related information. Here the reader has accumulated information about the 1T4F molecule from the PDB, a definition of 'membrane protein' from Dbpedia, and an interactive visualisation of 1T4F using Utopia's Ambrosia molecular viewer, as well as a related protein alignment, viewed using the CINEMA alignment editor. Hence, from a single page in an article, access is gained to information from databases, from online dictionaries and encyclopaedias and to interactive analysis tools, without having to leave the context of the PDF document.

management utilities to the suite. The aim of the *Semantic Biochemical Journal* (BJ) experiment was to use Utopia Documents to make the content of BJ electronic publications and supplemental data richer and more accessible. To achieve this, Utopia was integrated with in-house editorial and document-management workflows, allowing the BJ editors to mark up article content prior to publication.

The Utopia Document PDF-reader creates unique fingerprints of document contents as they are rendered onscreen, identifying key typographical and bibliometric features (authors, references, etc.). Its innovation lies in being able to turn static features of a document into objects that can be linked, annotated, visualised and analysed interactively. In so doing, the document is transformed from a digital facsimile of its printed counterpart into a gateway to related knowledge, providing readers with focused interactive access to analysis tools, external resources and the wider literature.

As part of the experiment, the journal editors have marked up papers in the December 2009 issue of the BJ using Utopia Documents. Aspects of these articles relating to protein sequence and structure analysis have been the main targets for mark-up, in the first instance, because this was the functionality built into the original Utopia toolkit. The kinds of additional mark-up currently provided by the software include: links from the text to external Websites (e.g., to databases like UniProtKB, PDB [10]) and InterPro [11]; term definitions from ontologies and controlled vocabularies; extra embedded data and materials (images, videos and the like); and links to interactive tools for sequence alignment and 3D molecular visualisation. Utopia does not itself provide any domain-specific functionality for processing or analysing data, but relies on external Web services – these are accessed via plug-ins whose appearance in the software interface is mediated by a ‘semantic core’ (which can be customised to any subject area by incorporating the relevant discipline-specific ontologies).

Reliance on external Web services is both a strength and weakness of the system: whereas it allows greater flexibility for customising the functionality of the suite, it also depends on the reliability of the external services it exploits – if these become unavailable (e.g., owing to routine maintenance or some kind of faulty opera-

tion), their functionality becomes unavailable to Utopia. These issues afflict *all* systems that rely on Web services, but are mitigated to some extent by the establishment of a Web-service registry, which systematically monitors and provides status reports on its registered services [12].

Future work

Utopia Documents is still at an early stage of development and there is much more work to be done. As the system is readily customisable, we plan to extend its scope, especially to encompass chemical biology – here, in particular, we plan to explore collaborations with the Royal Society of Chemistry, who have done pioneering work with their Prospect software (<http://www.rsc.org/Publishing/Journals/ProjectProspect/>). We are also embarking on exploratory discussions with Nature and Elsevier, and various pharmaceutical companies, in order to deliver bespoke mark-up and document-management solutions for these companies.

Another possibility that we’re keen to explore is the use of Utopia Documents to mark up issues of EMBnet.news, which could add value at a critical time, as EMBnet.news becomes a *bona fide* peer reviewed publication – see Figure 1.

Find out more

The *Semantic Biochemical Journal* was formally launched on 10 December 2009. To gain further insights into the status of the project, and to better appreciate how this might benefit EMBnet.news in future, we encourage readers to view articles in volume 424(3) of the BJ (<http://www.biochemj.org/bj/424/3/default.htm?S=0>), and especially to read the launch article, Calling International Rescue: knowledge lost in literature and data landslide! (<http://www.biochemj.org/bj/424/0317/4240317.pdf>) – a preview of this interactive paper is given in the following video: <http://www.youtube.com/watch?v=rIOgAR1Ia3E>. Utopia Documents itself is available for download from <http://getutopia.com/>.

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