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DEVELOPING PROTEIN DOCUMENTARIES AND OTHER MULTIMEDIA PRESENTATIONS FOR MOLECULAR BIOLOGY

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Computer-based multimedia technology for distance learning and research has come of age – the price point is acceptable, domain experts using off-the-shelf software can prepare compelling materials, and the material can be efficiently delivered via the Internet to a large audience. While not presenting any new scientific results, this paper outlines experiences with a variety of commercial and free software tools and the associated protocols we have used to prepare protein documentaries and other multimedia presentations relevant to molecular biology. A protein documentary is defined here as a description of the relationship between structure and function in a single protein or in a related family of proteins. A description using text and images which is further enhanced by the use of sound and interactive graphics. Examples of documentaries prepared to describe cAMP dependent protein kinase, the founding structural member of the protein kinase family for which there is now over 40 structures can be found at http://franklin.burnham-inst.org/rcsb. A variety of other prototype multimedia presentations for molecular biology described in this paper can be found at http://franklin.burnham-inst.org.

1. Introduction

Multimedia delivery via the Internet has potential uses in both biological research and education. This paper focuses on the tools for producing multimedia materials and our limited experiments to date in using this new medium. We are encouraged enough by our informal evaluation that the goal of this paper becomes one of encouraging others to experiment with the technology. It can be argued that the bells and whistles of multimedia delivery distract the user from the content and are thus counterproductive. In many cases we believe this argument to be true and the majority of course material we have produced (see http://franklin.burnham-inst.org) does not use multimedia. Where we have used multimedia is in situations where it is useful to have multiple senses work on the problem, or it offers a unique form of delivery.

For example, consider a journal article that describes a 3-dimensional protein structure and the function of that biological macromolecule. The printed medium is a very poor means of conveying that information. Reading about a specific interaction, for example, a specific hydrogen bond between enzyme and substrate, and then shifting focus to a stereo view of the molecule in the article is counterintuitive. So is going to the Protein Data Bank (PDB), downloading a set of coordinates and loading them into a molecular graphics program to view the interaction. Both approaches require the reader to shift focus between one conceptualization of the interaction (text) and another (graphics). Ideally, the user should be able to view the protein molecule at the same time they are being told how structure components relate to function. Ideally they would be hearing this dialog spoken with enthusiasm by the original author, and 3-dimensional renderable views of the appropriate structure components would be presented in a coordinated way with the dialog. These capabilities are encompassed in what we term "protein documentaries" – multimedia presentations describing structure-function relationships. How to make a protein documentary and examples of completed documentaries will be described.

Another example where multimedia has potential is in teaching users the specifics of an interface to a program or database. While the user focuses on the interface that they will see under normal operating conditions, they are being told how to effectively use the interface to run a program or make a database query. Again, synchronization between the dialog and the view of the interface enhances the learning experience. Work in facilitating the use of the GCG package of programs, albeit from a more tutorial-based perspective, using a multimedia approach is described.

Finally, if video is available the learning experience can be enhanced in, for example, delivery of complete lectures. Experience with this media in presenting *An Introduction to Internet Resources for use in Molecular Biology* is described.

As prerequisite, we begin with a brief introduction to the available technologies to indicate that these types of development are now feasible, and follow this with pointers to the work of others. We then describe how we have specifically used the technologies and close with a discussion of future prospects for multimedia delivery.

1.1 Background – Available Technologies

Why have multimedia technologies not been used extensively to date by biologists? Rich multimedia content, such as digital video and digital/analog audio files, requires the downloading of relatively large amounts of data and ready access to significant computing power to render them on the client computer. Further, producing audio and video materials have not been as straightforward as producing text and graphics. Each of these barriers is disappearing and we believe we are at the beginning point of a new era in Internet use which will impact biology and present new opportunities and challenges for the computational biology community. This section presents new technologies to support this statement.

The response by several companies to the data transfer problem, notably RealNetworks Inc. (http://www.real.com) and Macromedia Inc. (http://www.-macromedia.com), has been two-fold. First, find ways to reduce the size of the data content that needs to be downloaded, and second, render the multimedia content in real time as the download occurs, a process known as *streaming*. Streaming obviates a potentially lengthy wait for a file to be completely downloaded before viewing begins and also the need to locally store the file. Obviously this works best when the presentation is viewed sequentially.

By far the most widely used commercial methods for disseminating audio/video content over the Internet is via RealMedia™ files. RealMedia is a proprietary technology, although RealAudio™ has published a proposal for an open Synchronized Multimedia Integration Language (SMIL) which uses this and other streaming technologies. These technologies provide a viable and efficient way to disseminate multimedia presentations by virtue of compressing the data content of a streamed file. By using different file encoding parameters (‘codecs’) the maximal data transfer rate for the data connection can be matched with the playback speed of a streaming presentation. An audio file encoded via RealAudio codecs for transmission through a 28.8 modem connection will have a relatively low data content and audio quality compared to that encoded for transmission via a much faster T1 connection (1.54 Mbits/sec). The tradeoff between data content and data transfer rate is therefore manifest in the final quality of the multimedia presentation. Low definition audio quality is rarely a problem when distributing a speech-based presentation like those developed here. Low definition video quality is a greater problem and often results in the necessity to use very small video display regions. Again satisfactory for a typical lecture like those proposed here, where there is little motion and video is more important to provide a sense of presence.

As described subsequently, animation can be effective in presenting biological concepts. Macromedia Inc. currently dominates the domain of interactive web-based animation, both through the provision of courseware authoring tools (e.g., Authorware Attain) and formats. Two widely used presentation formats are Shockwave and Flash. Though superficially similar, the two formats represent quite different content. Shockwave presentations, which can only be created by Macromedia software, are potentially quite complex interactive applications, such as are possible with Java applets, and include the use of compressed sound. Flash, on the other hand, created through the Flash3 software, is a method of creating simple vector-based animation content of extremely small download size, which can be resized with no degradation of image definition. Sound support is provided in Flash, but sound compression encoding does not appear to be as efficient as that used in a Shockwave presentation. For this reason, dissemination of even a 10-minute Flash presentation containing a synchronized sound track is currently effectively impossible except through high-speed network connectivity. Playback of a Shockwave or Flash presentation in an Internet context is through the use of a free plugin for Netscape or ActiveX control for Microsoft Internet Explorer. Unfortunately, plugins/ActiveX controls exist only for the PC and Macintosh platforms, with no plans to bring native versions to UNIX. However, the latest version (6.5) of Director software allows any project to be exported as a Java applet. The Flash player is now incorporated into new versions of the Netscape browser.

Like RealAudio, Macromedia has taken a two step approach to reducing bandwidth requirements. First, a proprietary IDE creates the compressed file for distribution at a particular data transfer rate, and second, the presentation plugin can render the presentation as it is downloaded (streaming).

Given the limitations of file sizes required for synchronized sound presentations using Flash, both Macromedia and RealMedia have collaborated to allow the RealVideo™ player to also render Flash animation files. The combination of the low bandwidth capabilities of Flash and RealAudio provides a highly acceptable solution to providing online multimedia tutorials that can be accessed by all with even low to moderate network connectivity. Examples of work using these tools are described subsequently.

1.2 Work by Others

There is considerable work being done in Internet-accessible courseware for use in biology. Georg Fuellen maintains a useful compendium of these efforts at http://www.techfak.uni-bielefeld.de/bcd/Curric/syllabi.html. As yet little of this material makes use of multimedia. Table 1 indicates some sites relevant to biology that do use multimedia.

Table 1 Example Multimedia Presentations Relevant to Biology

Resource	**Comment**
The Stanford University health library online video collection (http://www-med.stanford.edu/healthlib/catalog/realvideo.html)	Example of the conversion of existing teaching materials into a new distribution paradigm using RealAudio and MPEG
The UCLA Department of Psychiatry & Biobehavioral Sciences WebCasts (http://www.MentalHealth.ucla.edu/-webcasting/)	Live broadcasts on the Internet that can later be reviewed by students and faculty
Southwestern University Botany Tutorial(http://www.southwestern.edu/-~waittd/vbl.html)	Example use of Shockwave and Authorware Attain software
Richmond College biology quiz (http://www.rlc.dcccd.edu/MATHSCI/-Bio1406113/quiz.htm)	Typical use of Authorware Attain
The Planet Chem site designed for students at Glenbrook South High School (http://www.planetchem.com)	Example use of Flash animation and Shockwave to explain complex chemical interactions

2. Materials and Methods

Table 2 outlines the off-the-shelf software products that have been used to develop the multimedia presentations described in this paper.

Table 2 Software Products used in Developing Multimedia Presentations

Product	Function and Source URL
Microsoft Inc. Powerpoint97	Create slide presentations (http://www.microsoft.com/powerpoint/)
Microsoft Inc. Speech API SDK	Text-to-speech and voice recognition development kit (http://research.microsoft.com/srg)
Microsoft Inc. Whistler Speech Engine	Text-to-speech utility (http://research.microsoft.com/srg/ssproject.htm)
Microsoft Inc. Visual C++ 5.0 (SP3) IDE	C++ development environment (http://www.microsoft.com/visualc)
Lucent Technology Inc. Speech Applications Platform	Text-to-speech and voice recognition development kit. (http://www.lucent.com/ideas2/lsap/)
RealNetwork Inc. RealAudio and RealPresenter Plugin for Powerpoint	Powerpoint add-on to export and save applications as RealMedia (.rm) files (http://www.real.com/R/Pdtools-2R/www.real.com/-publisher/presenter.html)
RealNetwork Inc. RealAudio Intranet Server, Flash enabled	RealMedia basic server for Intranet use only (http://www.real.com/server/intranet/products/-index.html)
RealNetwork Inc. RealAudio and RealPublisher	Convert either a multimedia file (such as an AVI format file) or a captured audio/video signal into a RealMedia file (http://www.real.com/R/Pdtools-1R/www.real.com/-publisher/index.html)
RealNetwork Inc. RealAudio RealEncoder	RealMedia content creation tools (http://proforma.real.com/encoder/50.html)
RealNetwork Inc. RealAudio RMMerge events file constructer.	Merging of RealMedia files
Adobe Inc. Premiere 4.2	Non-linear digital video editor software (http://www.adobe.com/prodindex/premiere/main.html)
Macromedia Inc. Flash3	Vector graphics animation development package (http://www.macromedia.com/software/flash/)
Syntrillium Inc. CoolEdit96	Audio file editor (http://www.syntrillium.com)
Systrans Inc. Personal Translator	Software-based text translation (http://www.systransoft.com)
Elequent Technology Inc. Eloqtalk	Multi-language text-to-speech demonstration software (http://www.eloq.com/)

3. Results

The form, content and details for preparing a variety of multimedia presentations are given in this section. Readers will need at least a RealPlayer client and a VRML plugin (for sections 3.6 and 3.7) to view these presentations from the URLs specified at the beginning of each section.

3.1 GCG Tutorial - RealMedia Presentation Created using the RealPresenterPlugin for PowerPoint - http://franklin.burnham-inst.org/gcg.ram

This presentation involves overlaying an audio track on a slide presentation and provides a simple introduction to the GCG package of programs (Devereux *et al.*, 1984). The presentation was authored using the RealPresenter plugin for Microsoft's PowerPoint program. PowerPoint allows the electronic production of a slide show, which can be later played back on another personal computer or converted to 35mm-slide format using appropriate peripheral equipment. Additionally, it is possible to lay down an audio narration for the presentation. The RealPresenter plugin enables an instant conversion of a slide show, and audio narration if present, into a single RealMedia (.rm) file which can be distributed via a RealServer or from a web server. Web server distribution is less robust than using RealServer dissemination and if the RealPlayer client software detects that a file is being served from a http daemon, it requires a longer buffer time, thereby increasing download times.

The procedure to create the GCG slide show was:

1. Prepare a Microsoft PowerPoint presentation.
2. Write and add a voice narration, making sure that the configuration was set for *linked* sound files. This used the *Slide Show* and *Record Narration* menu options of PowerPoint.
3. Post-edit the sound file for each page for content and time length using CoolEdit96.
4. Access the RealPresenter plugin through the PowerPoint *Tools* menu and *Publish to RealMedia*.
5. Serve the RealMedia file from a RealAudio server running on port 7070.

3.2 Live Seminar Describing Internet Resources Available to Molecular Biologists - A RealMedia Video Presentation http://franklin.burnham-inst.org/seminar.ram

A RealMedia video presentation was made of a general seminar outlining Internet resources important to molecular biologists. The procedure used was:

1. Record the presentation using a video recorder with good dynamic sound range.
2. Convert the video to a high bandwidth RealMedia file using the RealPublisher software, at a size of 320x240 pixels.
3. Re-edit the first 5 minutes to place titles and remove seminar 'dead-space', using the Adobe Premiere non-linear editing software; the subsequent Windows format AVI file was converted to a RealMedia file using RealPublisher.

4. Use the RealAudio RMTools software to replace the initial five minutes of the full-length RealMedia file with the re-edited version.
5. Make the presentation available on a RealAudio server running on port 7070.

3.3 Live Seminar Describing Internet Resources Available to Molecular Biologists - A RealMedia Synchronized Video Multimedia Presentation of a Live Seminar in Multiple Languages with Close Captioning - http://franklin.burnham-inst.org/framework.html

The goals in developing this presentation were to: (i) investigate the viability of multimedia tutorials employing the synchronized retrieval of multiple web pages in addition to video content; and (ii) extend the audience through close captioning for the hearing impaired and through presentation in multiple languages. The 5 minute non-linearly edited version of the seminar described in section 3.2 was subject to further post-processing. The steps were:

1. Construct an HTML frame-formatted page to embed the RealPlayer plugin, and also to provide areas that could be dynamically updated during the presentation. The prototype consisted of the following:
   - Frame 1 was the frame in the top left corner of the web browser that housed the video console and controls to start/stop and set the frame position. In addition, JavaScript-enabled HTML form-tag 'radio' controls were embedded to allow switching in the frame below (frame 2) between 'closed captioning' and the menu for presentation selection (see below). The video console size was set to a 280-pixel width and 210-pixel height. An <*embed*> tag was used to include the Netscape plugin version of the RealPlayer and an <*object*> tag used for inclusion of the ActiveX control form of the RealPlayer into Microsoft Inc.'s Internet Explorer pages.
   - Frame 2 was the lower left frame that housed a menu for the selection of the desired multimedia presentation. This menu was a two-framed html page that used JavaScript to permit switching between the different menu categories (*Sequence Analysis*, *Structure Analysis* and *Live Seminars*). This same frame could also be switched to show a formatted page which contained a transcript of the seminar, with blocks of text delineated within the HTML code by <*a name*> tags, allowing a cue mechanism to display the appropriate text in a synchronized fashion.
   - Frame 3 was the large frame on the right occupying about 66% of the browser client area that dynamically displayed the seminar slides.
2. Produce video for a window size of 280x210 pixels and convert from window AVI format to RealMedia format using RealPublisher.
3. Make a manual transcript of the dialog in this short version presentation. In the future it is anticipated that this step will be automated by use of a continuous speech recognition system (e.g., Dragon Software Inc. Naturally Speaking or IBM Inc. ViaVoice).

4. Produce multi-language versions (German, Spanish, French, Italian) of the HTML transcript using the online Systrans Inc. automated translation system. Again, in the future it is anticipated that this process would be completely automated, once an automated translation software package is available for local use.
5. Make multi-language versions of the slides presented during the seminar in HTML format, again using the Systrans Inc. online service.
6. Time the video presentation in terms of speech content and also in terms of the slide presentation timeline.
7. Create a RealMedia events file. In this file, URLs could be specified that would load into specific frames of this web development framework at particular time points in the presentation. Text blocks were timed to appear at appropriate times during the presentation within the closed caption frame, corresponding to the time that those words were spoken in the video, and similarly for the slides in the larger frame area. For both the closed captioning and the slide presentation, a single HTML file would be loaded into that particular frame, with large spaces placed between the different information blocks. In this way, movement between the text blocks within the closed captioning section, or between the slides in the slides frame, was instantaneous, since no further network download beyond the initial file was required.
8. Load the main presentation description page by activating an *onLoad* JavaScript function in that page and including the location of the RealMedia file for use by the embedded RealPlayer plugin or ActiveX control.
9. Have the user make a choice on the HTML page description of the seminar between the different language versions by checking one of the radio buttons present, which through JavaScript, instantly reloaded both frame2 and frame3.
10. Use Eloqtalk text-to-speech demonstration software to convert the foreign language transcripts into wave files, using the appropriate speech font for that language. Using this procedure, different language soundtrack versions of the RealMedia presentation were created. An extra checkbox on each of the foreign language version seminar introduction pages caused, through JavaScript, the loading of the appropriate foreign language version video into the RealPlayer plugin or ActiveX control.

3.4 Description of an Institutions Basic Computing Infrastructure - An Animated Presentation using Flash - http://franklin.burnham-inst.org/flash1.htm

To investigate the viability of animated presentations, a Flash animated tutorial was produced using a beta version of the Flash3 software from Macromedia Software. The design procedure was as follows:

1. Write a broad overview that included the important concepts that needed to be conveyed.
2. Produce a detailed narrative as a Microsoft Inc. Windows wave format audio file.

3. Construct a Flash animation using a different scene for each important concept, and import the wave file narration into the movie as a synchronized sound file.
4. Export the animation in Shockwave SWF format.
5. Serve the presentation from a Web server.
6. Include <*embed*> and <*object*> tags to specify the .swf file. This would automatically load the Flash plugin/ActiveX control in the client browser, or direct the person to the appropriate site to get the Flash player, should it not be already installed.

3.5 Description of an Institutions Basic Computing Infrastructure - An Animated Presentation using RealFlash Playback - http://franklin.burnham-inst.org/flash1.ram

Additionally, a RealFlash version was created by exporting the above described Flash animation without a sound track in Flash (version 2) format, and then converting the wave file narration into a RealAudio file. The combining of these two media files is automatically performed by the RealPlayer, which renders the Flash presentation within its video display area, including some interactive capability if it is present.

3.6 Automated Protein Documentary – Medline Abstracts and VRML Rendition - http://franklin.burnham-inst.org/rcsb/

The concept of a protein documentary was introduced in section 1.0. A spectrum of documentary types can be prepared based on the degree of automation. At one extreme is an automated rendition that uses text-to-voice conversion to link the VRML representation of a PDB file to the Medline abstract describing that structure. At the other extreme is a detailed recording by a human providing a dialog at the level of detail found in a typical structural journal paper.

In the current Protein Data Bank (PDB) a significant number of entries contain a complete JRNL record. The JRNL record describes the primary citation for the protein structure. The primary citation is the publication that matches the structure for which the atomic coordinates are found in the PDB file. The goal was to automate the production of a protein documentary such that recalling a specific protein structure would play an audio file of the Medline abstract while as the same time rendering a VRML view of the molecule using the atomic coordinates present in the PDB file. The audio production and the VRML production are described separately.

A C++ program was written that accepted a URL from a CGI by using the GET method. That URL provided a direct path to the appropriate Medline abstract as defined by NCBI's Entrez system. The resulting text string was passed to a to an Eloquence system speech object whereupon a wave file was produced that could be replayed. At present, PDB files do not contain the URL for the Medline abstract and a table mapping structures to URL's must be constructed manually.

An example using the Microsoft Inc. Speech API can be found at the following URL:
http://quinn.sdsc.edu/cgi-bin/talker1.cgi?db=m&form=6&dopt=r&uid=91320112

The area of speech synthesis and recognition is the subject of intense research. To date, some of the most expressive and realistic voices have come from research within the respective countries; for example, the most realistic French language voices have been those produced by the French groups such as Elan and from the Belgium MBROLA speech project. For realistic American voice synthesis, two speech engines that stand out are the Microsoft Whistler speech engine and the Lucent Technology speech engine. Importantly, the Microsoft engine will ship in every copy of NT5.0, which brings the realistic possibility of web-based speech synthesis utilizing client-side speech engines. This obviates the need to download large audio data files.

A comparable example to that above using the Lucent speech engine can be found at:
http://quinn.sdsc.edu/cgi-bin/talk.cgi?db=m&form=6&dopt=r&uid=91320112

The VRML rendition of the molecule was produced by Per Kraulis's Molscript Program v2.0 (Kraulis, 1991). Molscript takes a PDB file as input and produces a VRML file by first running the program MolAuto. MolAuto produces the default instructions (in the form of a script) for rendering as VRML or a variety of other graphics formats. The default instructions define what can be automatically parsed from a PDB file. Additional semantics can be added via the script to better display structure-function relationships, but this requires manual editing of the script. Once rendered in VRML, provided a VRML plugin is available for the Web browser and hardware platform, the molecule can be displayed and rendered. Once rendering begins the wave file is played and sound and graphics appear to be synchronized.

3.7 Detailed Protein Documentary - http://franklin.burnham-inst.org/rcsb

The advantages of being able to manipulate the VRML rendition of the molecule while hearing an automated voice recite the Medline abstract has the potential of reducing the learning curve necessary to get a full understanding of the molecule. At present automated voices sound too mechanical and understand insufficient semantics to make long sessions pleasant, but this approach to protein documentaries should clearly be developed further since automated voices are sure to improve. A more labor intensive, yet currently more appealing approach, is for a human to lay down a detailed sound track. This has been done for a cAMP dependent protein kinase (Knighton et al., 1992) which was the first structure solved in this highly structurally conserved family of enzymes key to signal transduction. A multiple sequence alignment initially performed by Hanks (Hanks and Hunter, 1995) and updated by Gribskov (Smith et al., 1997) divides the protein structure into 11 functional domains based on sequence conservation. An audio track available as a RealAudio ram file has been recorded for each subdomain. The subdomains are color-coded and are highlighted in the VRML rendition of the molecule. Clicking on a specific domain either in an accompanying table or on the VRML rendition itself will cause the audio track for that subdomain to play, describing the relevant structure function relationships. At the same time the viewer can be manipulating the molecule to highlight features of the audio presentation. This is facilitated using the VRML construct called the *emissive light node* that is linked to the touch node. When the user *touches* the node, that is, when the cursor is over that node, the object defined by the node begins to emit light of the given RGB color value. The audio track is synchronized using the VRML *anchor node*. Upon a mouse click another URL defined by the anchor node is opened which starts the streaming audio appropriate to that node, in this instance the text of a specific subdomain.

4. Discussion

Clearly these multimedia presentations are preliminary, but we believe they illustrate the power of the technology in improving our understanding of biological concepts for both education and research purposes. However, there are problems.

First multimedia technology is evolving at a rapid rate. Though, as described in this paper, RealAudio and Macromedia currently dominate their respective areas, there are a number of well-founded ventures that will most certainly challenge this position. For example, Microsoft Liquid Motion is a web-based animation product that competes with Flash (http://www.microsoft.com/-liquidmotion/). Further, several companies are marketing streaming audio solutions, such as Echo Speech by the Echo corporations (http://-www.echospeech.com/), the Liquid Audio system (http://www.-liquidaudio.com/) and the Headspace Beatnik system (http://www.headspace.com/). Audio/Video solutions include Com One Inc.'s ViewCom system (http://www.com1.fr/uk/-demovideo/index.html) and Vivo Active from Vivo Software (http://vivo.-real.com). It is difficult to predict what will be available in even two years, however, the availability of cheap, high bandwidth connectivity is still likely to be an issue. An intriguing alternative is speech-enabled computers that are currently reaching the market and will reduce the bandwidth requirement for online presentations. A simple presentation could quite easily be envisaged in which text data were transmitted to the client computer and converted to speech in real time, at the same time as HTML, visual or video data were being downloaded and presented.

The second problem relates to form and content. While the production of multimedia materials for Internet delivery is possible by non-experts it still takes significant effort to produce compelling materials. We are currently developing tools to simplify the authoring process so that authors can focus on content. From a user's perspective the tools also provide materials with a similar look and feel. Examples of course modules that have been developed using these tools can be seen at http://franklin.burnham-inst.org/cb/tutorialsdb/.

Even with these problems to be overcome, it is not hard to imagine the journal paper describing a protein structure as the secondary form of information delivery. The primary form being a multimedia presentation maintained by the "journal" which better facilitates the understanding of structure-function relationships. As a first small step the URL http://franklin.burnham-inst.org/rcsb/ describes in a stepwise fashion the procedure for readers to produce their own protein documentaries.

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