ADN_Viewer

A Software Framework Toward

3d Modeling and Stereoscopic Visualization of Genome

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Abstract

At present, the biologists in genomic study the genomic sequences in textual form. Unfortunately, this representation does not offer a global vision of these sequences. Our goal was then to develop a tool allowing a representation and a three-dimensional visualization of the sequences. The interaction with the user is appreciably increased by multiples functionalities such as rotations and translations of the molecule, zoom, extraction, etc. From the Computer Science point of view, the major interests of this work are, on the one hand, the management of complex scenes (genetic information is conveyed by several tens, even several hundreds, of million atoms) and, on the other hand, the interaction within a virtual environment. In addition, the representation of this information must be multiple to allow various types of biologic analysis. ADN_Viewer is an useful tool for the specialists in genomic for the *in silico* analysis of the DNA 3d structures. It can also provide 3D databases to the biologists. ADN_Viewer represents a first stage towards more advanced work for the management and interaction of virtual objects of huge size and carrying rich information. And finally, this tool makes it possible to produce genomic multimedia documents for teaching or entertainment purpose.

Keywords:

Stereoscopic Visualization, Navigation, 3d Representation, Human-Computer Interaction, Scientific Data, Genome, DNA

1. INTRODUCTION

This paper describes the functionalities of a software tool named ADN_Viewer. This software was developed within the framework of Bioinformatics activity of GI team (Gesture and Image) of CHM department (Human-Computer Communication) of the LIMSI (Laboratoire en Informatique pour la Mécanique et les Sciences de l'Ingénieur). ADN_Viewer allows the modeling and the stereoscopic visualization of genomic sequences. This tool is developed using standard programming tools such as C, C++, Tcl-Tk and uses the graphic library OpenGL [9].

Within the framework of collaboration between Computer Science specialists of the LIMSI and biologists of the IGM (Institut de Génétique et de Microbiologie) of Orsay, we started to study and analyze the three-dimensional structures of the genomic sequences [2][6][7]. Indeed, it appeared interesting to us to work directly on the 3D modeled molecules.
From the biological point of view, the principal interest of this approach, compared to a textual study, is the visual and global representation of the studied living organisms. In addition, the interaction with the user is appreciably increased by multiple functionalities: rotations and translations of the molecule, zoom, extraction, etc.
This multi-disciplinary work is at the interface of two innovative fields: genomic one (Biology) and virtual reality [13][14] (Computer Science). In this context, three principal objectives are pursued.

On the one hand, ADN_Viewer is a useful tool for the specialists in genomic for the *in silico* analysis of the three-dimensional structures of the DNA.
In addition, it represents a first stage towards more advanced work. In particular for the management and interaction of huge virtual objects that carrying rich information.
And finally, this tool makes it possible to produce multimedia documents at teaching or entertainment ends.

2. GENERAL PRESENTATION OF ADN_VIEWER

2.1 Some Genomic Definitions [11][12]

The nucleic acids are the fundamental components of the alive cell, carrying genetic information. They are polymers made up of very many units of nucleotides. The nucleic acids were initially highlighted in the cellular core; it is with this circumstance that they owe their name. These acids are of two according to the type of ooze (sugar) that uses their composition:

- deoxyribonucleic acid (DNA), especially localized in the core,

- and the acids ribonucleic (RNA), more abundant in the cytoplasm.

The DNA is a double strand formed by the 4 nucleotides A, C, G, and T. The succession of thousands, even of millions, nucleotides constitute the molecule of DNA. The two strands are anti-parallel and complementary: with each nucleotide A of a strand corresponds to him one T of the other, and vice versa, and to each C corresponds one G, and vice versa.

Figure 1: The DNA is a double strand

In the following, we will speak about nucleotide when one strand is read; but if two bound nucleotides are considered, we will speak about plate.

2.2 ADN_Viewer Functional Architecture

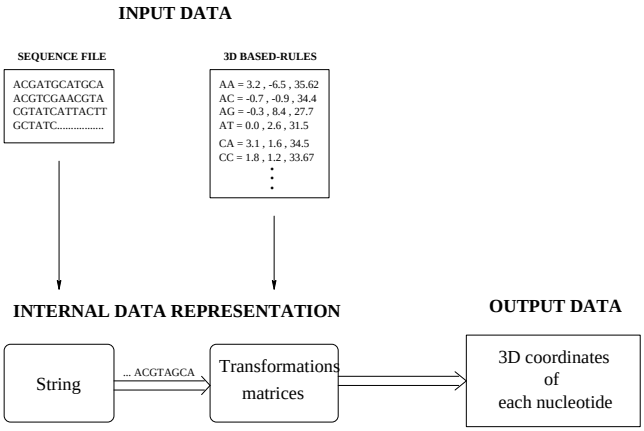

Figure 2: Functional architecture of ADN_Viewer

2.3 Input Data

2.3.1 The DNA Sequence

A file sequence contains all the nucleotide continuation in the form of letters (ACGT) as well as other information such as the name of the organism, the numerical indexing of the sequence, or of the gene names. The structure of such a file depends on the format in which it was seized. The most widespread formats are:

- FASTA format, used by GenBank, http://www2.ncbi.nlm.nih.gov/genbank/query_form.html),
- and GCG format, used by the university of Stanford, http://www.stanford.edu).

The size of the sequences is very variable, but we can divide the whole of the known sequences into 3 categories:

- the sequences of small size, which do not exceed about fifteen nucleotides and often represent the vicinity close to a start codon (or a stop codon) of a gene,
- sequences of middle size, several hundreds even a few thousands of nucleotides, which are generally genes,
- and finally the sequences of huge size (≥ 10 000), which are complete molecules (largest sequence being the chromosome n° 22 of the human genome which enters 4 938 732 nucleotides).

2.3.2 3D rule-based construction of DNA

The rules of 3D construction [5] provide geometrical information on the DNA molecule. These rules are generic with any sequence, and any modification of one of these rules amounts changing the geometrical model of the molecule. Indeed, they are composed of a table of rotations and a translation. The table of rotations contains 3 values of angles (one by axis) for each succession of two nucleotides; these values represent relative rotations between the current plate and the previous plate. The translation represents the vertical distance between two successive plates.

Figure 3: Sequence + rules = 3D visualization

2.4 Input Data

By reading a letter representing a nucleotide, we apply the rules of construction corresponding to the couple **(previous**

letter, current letter). By reiterating this method on whole the sequence, we gradually calculate the absolute 3D coordinates of each nucleotide and, finally, we obtain the three-dimensional structure of the DNA molecule (cf. **Figure 3**).

3. REPRESENTATION, VISUALIZATION AND INTERACTION

3.1 Modeling and Representation

3.1.1 Genomic Representation

To visualize a whole DNA molecule, it is advisable to adjust its distance according to its size. The larger the distance is, the less the details of the molecule are perceptible. And beyond a certain distance, it becomes useless to display more details than the two strands (**Watson** and **Crick**). This representation is suitable on molecules of huge and middle sizes (cf. **Figure 4**).

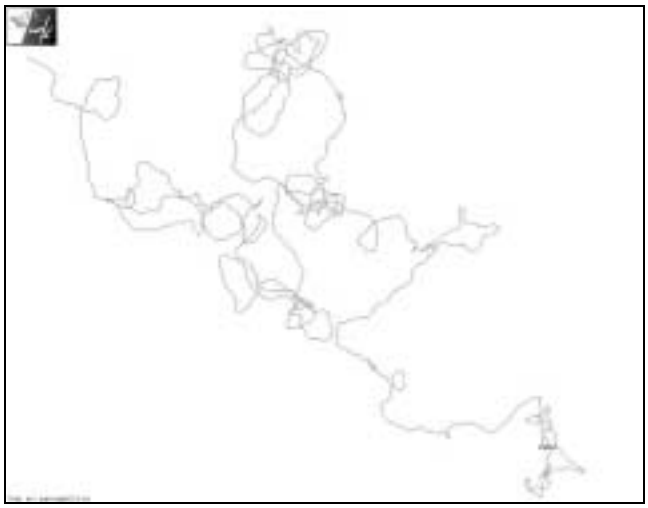

Figure 4: Genomic representation of a sequence including 80.000 nucleotides.

3.1.2 Genic representation

On parts of molecules such as genes, it is useful to have information on the placement of nucleotides the ones compared to the others. A sphere models each nucleotide, and each type of nucleotide (A, C, G or T) has a different color. This representation applies to sequences of middle size (cf. **Figure 5**).

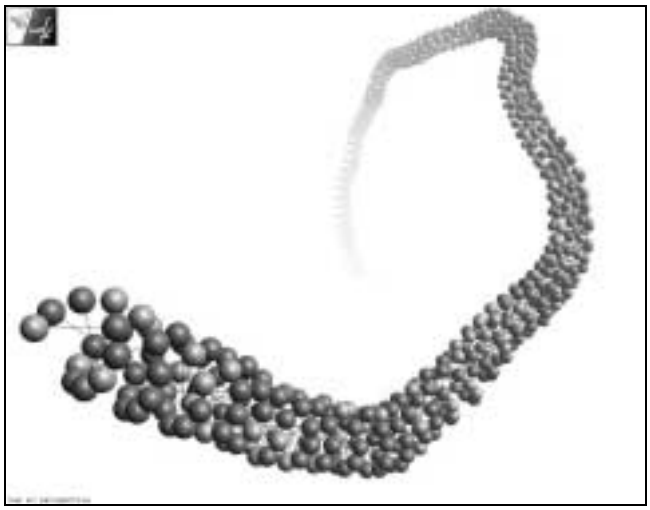

Figure 5: Genic representation of a sequence including 500 nucleotides

3.1.3 Nucleic representation

To observe the vicinity close to a key part such as a start codon (3 successive nucleotides), it then should become necessary to have all information on the atomic structure and links of each nucleotide. A sphere models each atom composing a nucleotide, and each atom has a single color. This level of representation is biologically and visually relevant only on sequences not exceeding about fifteen nucleotides (cf. **Figure 6**).

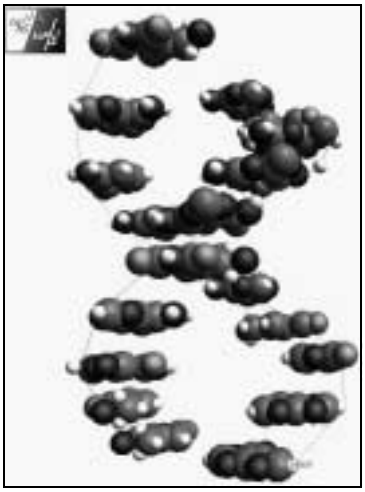

Figure 6: Nucleic representation of a sequence including 11 bases

3.2 Visualization

To study the molecule of D.N.A., the user has several modes of visualization: various points of view and of full-screen modes.

3.2.1 The Multi-View Mode

The **perspective view** (cf. **Figure 7**, Top-Left) is the main view; it has the major functionalities of interaction, navigation and stereoscopic visualization.

At any moment, the user must have information on the spatiality of the molecule without needing to carry out movement. In order to satisfy this, 3 other views were represented (cf. **Figure 7**):

- view of lower part (Top-Right),
- view on the side of the Watson strand (Bottom-Left),
- and view on the side of the Crick strand (Bottom-Right).

These views use orthogonal projection and propose a complementary view to the perspective one. They make it possible to have a more precise idea on spatiality of the molecule without carrying out movement. In addition, and for a better precision of orientation of the molecule, they are limited in terms of interaction with the mouse.

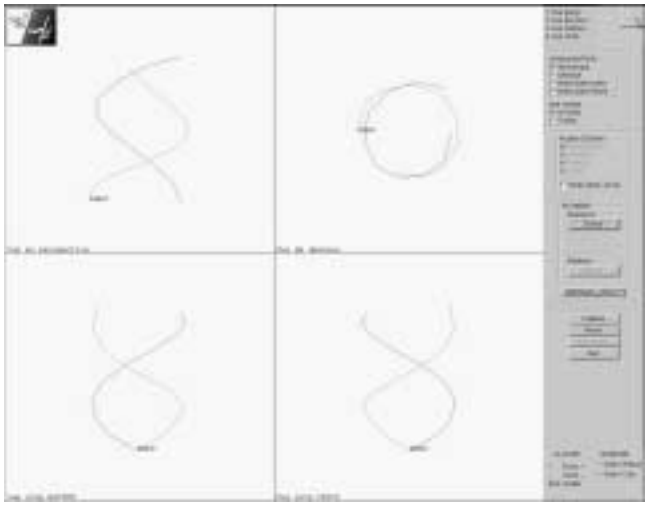

Figure 7: Visualization according to 4 views

3.2.2 The Full-Screen Mode

For a comfort of visualization, it is pleasant to be able to visualize a scene out of full-screen. Two types of full-screen are available with ADN_Viewer :

- full-screen type with menu (cf. **Figure 8**),
- and full-screen type without menu (cf. **Figure 9**).

The first gives a fast access to the databases (sequences and tables of rotations) and allows carrying out various actions such as the extraction, the reset and modification of the values of angles and distance, etc.
The second offers a true type of full-screen, but the user does not have then menu but the keyboard and the mouse like interfaces with the application. This type is necessary to separate the interface from the graphical views, especially in the context of immersion-based virtual reality plate-forms.

Figure 8: Full-screen with menu

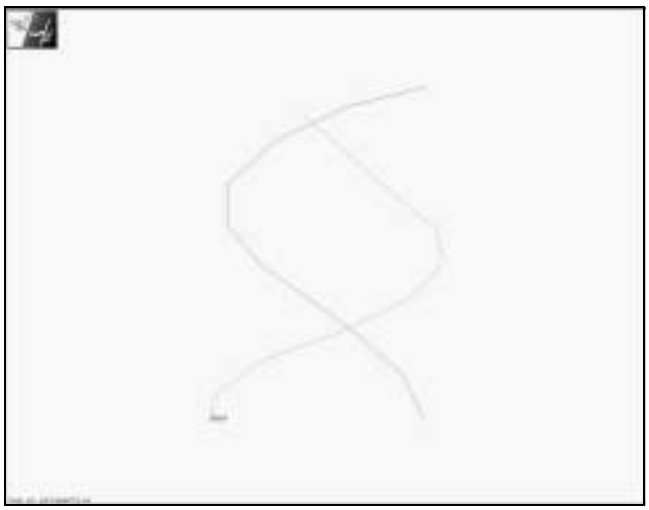

Figure 9: Full-screen without menu

3.3 Stereoscopic visualization

The user has the possibility of visualizing the DNA molecule in relief; the spatiality of the molecule is perceived much better.

3.3.1 Description of the process

If the human being perceives the world in which it moves in relief, it is that he sees the objects from two different points of view (eyes). To have a same relief vision with computers, there are two main technical solutions:

- active stereoscopy,
- or passive stereoscopy.

These two solutions differ as well by the hardware used as by the result obtained. However, they use the same approach.

Active stereoscopy requires particular material device. The computer must be equipped with a suitable card and the user must carry glasses that are synchronized with the screen. Then, from the display point of view, it is necessary to calculate the object under two different points of view (eyes) and to display the two images one after the other at 60Hz frequency. The

glasses synchronized with the displaying frequency of the screen make it possible each eye to have its own point of view (unfeasible thing if the two images are displayed simultaneously on the 2d screen). This frequency being too high so that the brain perceives the phenomenon, the object appears in relief.

Passive stereoscopy or anaglyph requires only one pair of colored glasses. The colors (one for each glass) are two complementary colors (in general, red and cyan). As for the active stereoscopy, one calculates the object under two different points of view, but instead of displaying the two images one after the other, one displays only one image made up of the two objects which have each one a different color. These colors are those of the glasses and in conformity with the projective geometry of the stereoscopy. In fact, colored glasses play the role of chromatic filters and thus offer to each eye its own point of view.

Unfortunately, we cannot illustrate the powerful of stereoscopic visualization in this paper, but the lecturer can see some anaglyph images at our web site: http://www.limsi.fr/Individu/gherbi/ADN_Viewer.

3.4 User Interaction with DNA Structures

3.4.1 The mouse

The mouse manages the rotational movements around the molecule. These 2d movements are interpreted as being three-dimensional ones around a sphere (cf. **Figure 10**).

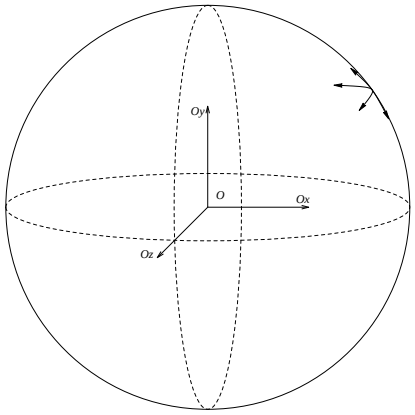

Figure 10: Rotations are carried out according to a sphere model

The mouse also gives access to the contextual menu that manages the levels of details and the output of the application.

3.4.2 The keyboard

The keyboard manages all the functionalities that can be controlled by the mouse, the vertical and horizontal adjustments, as well as the zoom in and out. It also takes again the majority of the functionalities that offers the menu.

3.4.3 The Extraction

When observing a whole molecule, the user should want to study only a part of the molecule (for example a gene or a start codon). In this case, he can isolate this part using the functionality of extraction. This option makes it possible to represent only the selected part, thus eliminating any disturbing elements such as the remainder from the sequence in background. The size of the visualized sequence having decreased, the user can possibly increase the level of detail to obtain more information on this selected part.

3.4.4 Reference Axis

As shows the **Figure 11**, the reference axis is a line segment with length equal to the vertical height of the sequence and which passes by the center of first nucleotide of the sequence.

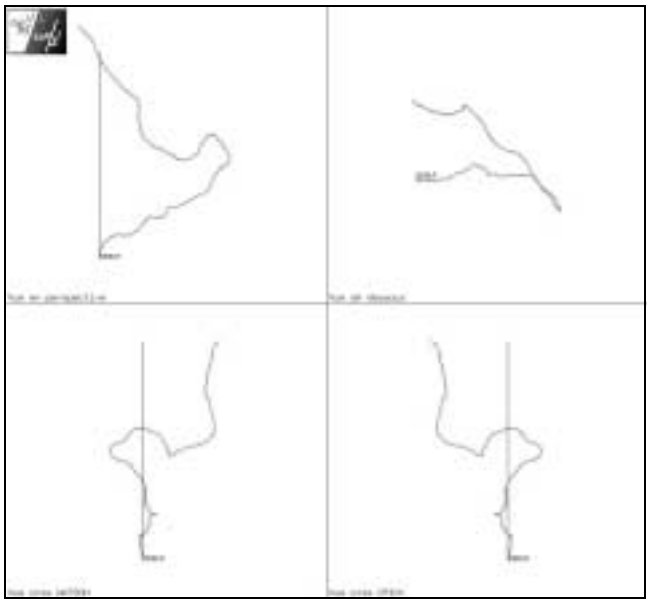

Figure 11: Reference axis

This line is inserted in the three-dimensional representation of the sequence, which provides additional information on spatiality: orientation and distribution of the molecule in space.

3.4.5 Documents produced by ADN_Viewer

DNAtoStillImage is a function that produces a still image (JPEG format) of all information displayed on the screen. These snapshots can be useful during the visualization of a molecule allowing the spatial comparison of several sequences. It is also essential to be able to compare the virtual molecule with the real molecule, would be this only for the validation of the application in its first use. The majority of the images of this paper were thus obtained by this functionality.

DNAtoVideo is also implemented, knowing the precise scenario of the video (digital film) which one wants to carry out, and writing some lines of code. This film can be documentary and/or multimedia (presentation document of the software with mixing of voice or music).

4. GENOME-DATA PROCESSING

4.1.1 The table of rotations

Each line read in the table of rotations including the 3 values of angles is transformed into a geometrical matrix of transformation that also includes the vertical adjustment between two successive plates. Then 16 matrices corresponding to the 16 combinations of couples within alphabet {A; C; G; T} are stored in a two-dimensional table. Thus, having the letter of previous nucleotide and that of the current, and establishing a relation between the letters and the indices of the table, one reaches directly the matrix of corresponding transformation (cf. **Figure 12**). This process of pre-computing appreciably decreases the calculating time of the points constituting the sequence. Indeed, to apply a rotation or a translation to an object amounts exactly carrying out a product of matrices. Here, a matrix contains 3 rotations and 1 translation, i.e. we gain a factor 4 with each time a sequence is computed.

4.1.2 The Sequences

The letters of a sequence file representing nucleotides are stored in a mono-dimensional table. Then, by applying the matrices of transformations computed above, we calculate the absolute 3D coordinates of each nucleotide, which they are also stored in a mono-dimensional table (cf. **Figure 12**).

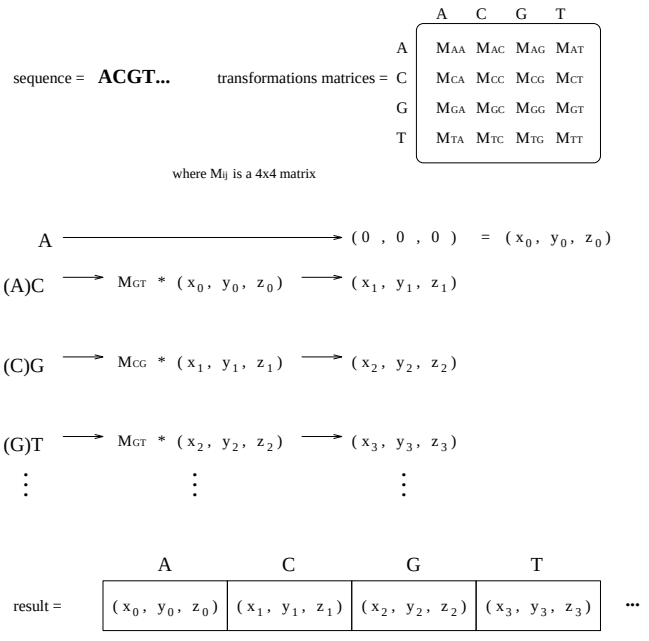

Figure 12: Principe of coordinates computing

There still, this phase of pre-computing saves to us an invaluable time, because, with each movement of the scene, the latter must be entirely recomputed. In the present case, it is enough to traverse the table in which are stored the coordinates of the points and to display the graphic objects according to the level of desired detail (genomic or genic). Once these coordinates computed, we deduce the coordinates from nucleotides forming the other strand.

For the nucleic representation, we must propagate the matrices of transformations to each scene display. Indeed, for a nucleotide plate given, we computed the coordinates of the two points modeling each nucleotide; we propagate well three rotations and the translation by the office plurality of the matrices of transformations, but, for a given plate, the third rotation (that around axis *Ox*) is not represented. On the points of the genomic representation where the spheres modeling all nucleotide of the genic representation, rotation around axis *Ox* does not intervene in the representation of the plates. Indeed, a dumbbell (genic representation) that rotates around axis *Ox* remains identical to itself (cf. **Figure 13**).

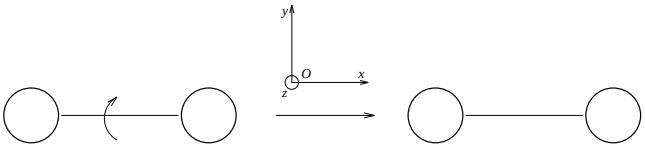

Figure 13: Alter turning around *Ox* axis

On the other hand, in the nucleic representation where the layout of the spheres modeling the atoms creates a parallelepiped structure, rotation around *Ox* axis causes slopes of the plate that it must absolutely represented (cf. **Figure 14**).

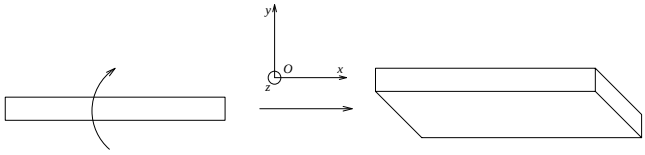

Figure 14: Parallelepiped turning around *Ox* axis

4.2 Visualization of a Sequence

It was known as previously that the manner of displaying a sequence was a simple course of table. Actually, we make evolve dynamically this course according to the complexity of the scene, we sample it. I.e. if the molecule represented is of big size and moved away, we will not display all the points but perhaps one on twenty. The granularity of the scene thus is managed. This process applies to all the levels of details. For the representations utilizing spheres, we also manage the precision of these spheres according to the distance from the object.

4.3 The Bounding Box

We thus chose to compute a bounding box adjusted with the treated sequence. It is a question of parameterization of this box so that it includes (since it is its role well there) the molecule whatever its orientation. Then we parameterize the cone of visualization according to this box. When a zoom is carried out, the box moves with the sequence.

5. SOME PRESENT ENHANCMENT AND FUTURE WORK

5.1 3d Object Clipping

For the moment, we do not carry out a clipping on the 3d objects of the scene. That has as a consequence an increase of the computation time, losing hence some real time interactivity. This is more visible when ADN_Viewer displays a complete huge sequence, which is fluid in its movements thanks to the sampling, but when the user performs a zoom action until the interior of the molecule, the granularity of the scene becoming finer, we have more details to display.

There exist two approaches of clipping:

- downstream clipping,
- and upstream one.

Downstream clipping is carried out after the matrix of modeling, i.e. the objects are calculated but are not displayed. This process is intended to display only part of an object while placing a plan of clipping which intersects this object. It is very useful, for example, to represent an object partly immersed in water. There is no saving of time of calculation.
Upstream clipping is carried out before the matrix of modeling, i.e. only the objects or parts of the visible objects in the scene will be calculated. Here, the economy of time of calculation is sensitive.
It is this last approach of clipping which interests us since it will enable us to solve the problem stated higher.

5.2 Visualization close to en offset part

When a rotation is carried out, the scene turns around a pre-computed fixed point that is the center of the bounding box (we can assimilate this point to the center of gravity of the molecule). On a sequence of small size or an overall visualization of an unspecified molecule, no problem of ergonomics arises. But, when, on a sequence of huge size, we visualize part of the molecule which is far away from the center of rotation, the movements undergo an arm of lever such as it becomes very difficult to control the least small movement.

5.3 Simultaneous Visualization of Several Sequences

It proved to be useful, at meetings of work with biologists, to be able to visualize several sequences simultaneously. It will be necessary of course to place them in the same reference mark (but in distinct windows) and to synchronize the movements (i.e. to make undergo the same movements with the various molecules).

5.4 Curve computation and analysis

All the genomists who analyze the geometrical structures of DNA work rather on the corresponding cards of curve. These cards are with two dimensions that provide information partial on the 3D curve of DNA. This is why it is necessary to integrate a curve maps generator [4] within ADN_Viewer. These data will be useful like *corpus* of training in systems of pattern recognition applied to the genome.

5.5 From DNA to Genes Visualization

In certain files of sequences, are indicated the positions of genes within the sequence. It would be wise to be able to graphically visualize genes on a molecule.

5.6 Proteins Visualization [8]

A protein is a sequence of units which one calls amino acids. The proteins adopt, because of their molecular structure, a three-dimensional conformation. These molecular sets are directly related to genes. It is thus essential to be able simultaneously to visualize gene and corresponding protein.

5.7 From Stereo-Workstation to Virtual Reality Plate-Form

In the case of a standard graphical workstation, the user interface can be included in the graphical window of the application itself; it is preferable solution for the ease of use. But in the case of a platform of virtual reality, for example of *HoloBench* type (cf. **Figure 15**) that is a semi-immersion type, it becomes infeasible to integrate a small 2d menu in the stereoscopic scene. This problem is more critical in full-immersion type (cf. **Figure 15**) such as CAVE (Cave Automatic Virtual Environment)

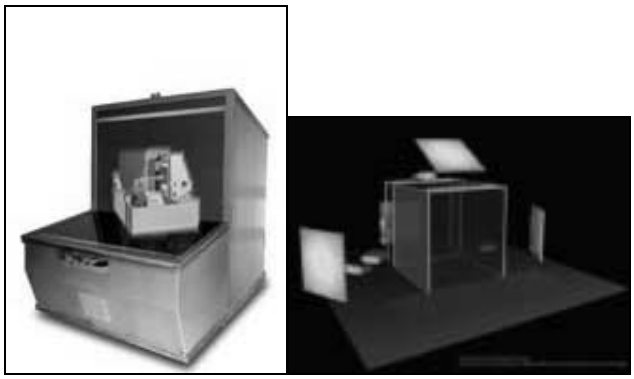

Figure 15: HoloBench and CAVE plate-forms

The most widespread solution at the present time and most adaptive (on workstation and plate-form) is to create a stereoscopic 3d menu. That known as, it can be useless to interact with such a menu when a stereoscopic scene is observed, especially if the plate-form allows a full-immersion

It would be necessary that the user can interact with the scene by keeping a maximum of natural interaction. It is thus advisable to dissociate the part interface part from display part of the scene. However, it is good to keep a user interface part as controller of the application. One will use for that the ***multi-display***, i.e. which is able to send the interface on a screen of control (workstation) and the graphic scene on one or more other screens (local station or platform).

Besides, the major functionalities accessible by the menu can be favorably handled by ***vocal commands*** [3]. These functionalities are those particularly concerning the levels of representation, the changes of views, the extraction, etc.

Immersion-based navigation [1] makes it possible to eliminate all the classical input devices (3d mouse, Joystick, Keyboard, etc.) used for navigation within a virtual scene. For instance, with a tracking system of the stereoscopic glasses, it is enough to perform head movements in order to navigate in the virtual scene (cf. **Figure 16**).

Figure 16: Shutter-Glass + Headphone + Tracker (CrystalEyes, Inc.)

The ***gesture interaction*** [10] can be very useful when the user wants to manipulate, to describe or to point a whole molecule or a part of it. It is much more ergonomic to consider then the molecule more as one object that as a navigation scene.
A data glove would be perfectly appropriate for these interaction types. One can also think of a device with tactile feedback, as shows it the **Figure 17**.

Figure 17: CyberGrasp with feedback (Virtual Technologies, Inc.)

6. CONCLUSION

This paper described a software framework focused on 3d modeling and stereoscopic visualization of scientific information dealing with genomic data. This work is basically bi-disciplinary; its evolution must be carried out on as well computer science field as biological one. Even if the ADN_Viewer tool has already an added value compared to what was already made for this type of genomic applications, it is necessary to augment its functionalities. On one hand, the tool will be integrated to the LIMSI new virtual reality plate-form; on the other hand, the biologist should use this tool using their standard graphical workstation. Biologists' colleagues of Orsay are using ADN_Viewer, in its present version, in order to analyze the 3d structures and curves of DNA of various organisms.

7. REFERENCES

[1] P. Bourdot and M. Dromigny and L. Arnal", "Virtual Navigation Fully controlled by Head Tracking", in proc. of international scientific symposium on Virtual Reality, June 1999, Laval, France.

[2] E.S. Shpigelman and E.N. Trifonov and A. Bolshoy, "CURVATURE~: software for the analysis of curved DNA", CABIOS journal, Oxford University Press, 1993, pp. 435-440.

[3] P. Bourdot and M. Krus and R. Gherbi, "Cooperation between Reactive 3D Objects & a Multimodal X Window Kernel for CAD", in Multimodal Human-Computer Communication, Lecture Notes in Artificial Intelligence 1374, Subseries of Lecture Notes in Computer Science, H. Bunt & RJ. Beun & T. Borghuis Eds. Springer-Verlag, 1998, pp 188-212.

[4] L. Sicaud and R. Simermann and R. Gherbi, "Algorithmes de segmentation et de calcul de courbures~: application au génome", Technical Report, LIMSI-CNRS, to appear.

[5] P. Pasero, "L'organisation du chromosome eucaryote et ses implications dans le contrôle de l'activité génique et la transmission des patrons d'expression", PhD thesis in cellular Biology and Microbiology, University of Aix-Marseille II, Luminy", 1993, France.

[6] M. Roux-Rouquié and M. Marilley, "Modeling of DNA local parameters predicts encrypted architectural motifs in Xenopus laevis ribosomal gene promoter", 2000, Nucleic acids research.

[7] M. Marilley and P. Pasero, "Common DNA structural features exhibited by eukaryotic ribosomal gene promoters." Nucleic Acids Res. 1996 Jun 15;24(12):2204-11.

[8] R. Sayle, "RasMol : software tool for protein visualization", http:://www.chemie.fu-berlin.de/chemnet/use/rasmol.html, 1995.

[9] Silicon Graphics, "OpenGL Reference Manual", http://shiva.missouri.edu:88/SGI_Developer/OpenGL_RM/6300.toc\#X", Silicon Graphics publication.

[10] A. Braffort and R. Gherbi and S. Gibet and J. Richardson and D. Teil (Eds.), "Gesture-Based Communication in Human-Computer Interaction", Lecture Notes in Artificial Intelligence, number 1739, Springer, 1999.

[11] JM. Lackie and JAT Dow, "The dictionary of cell and molecular biology", Academic Press, London, 1999.

[12] J-P. Boden and J-N. Cloarec and all, "Biologie Terminale D", collection Tavernier, Bordas editor, 1989.

[13] P. Fuchs, "Les interfaces de la Réalité Virtuelle", AJIIMD", 1996.

[14] H. Rheingold, "Virtual Reality", Touchstone Books, 1992.

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Joan Hérisson is a master student in computer science at Paris-Sud University. He will start a PhD work, at LIMSI, on virtual reality that is focused on management of complex and rich graphical data and applied to genomic information.