APIC : A Generic Interface for Sequencing Projects

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Abstract

In this paper, we describe the APIC graphical interface that aims at displaying the results produced by the genomic sequence analysis methods and at helping a comparison of these results. The major feature of APIC lies in its genericity. As a matter of fact, this interface can obviously be used to visualise genetic or physical maps but it also able to display other kinds of information such as curves or pictures. On the one hand, APIC provides the biologist who builds a new sequence analysis method with a standard interface allowing to display his results. Thus, he can avoid implementing a specific visualisation tool. On the other hand, even when the methods already have their own interfaces, using APIC has the advantage of giving a homogeneous way to compare several results coming from different analysis tools. Moreover, it provides some powerful functions for navigating and browsing into the results.

1 Motivations

To handle the large amount of data and knowledge produced by the sequencing projects, the approaches using a standard data base schema can no longer be used. As a matter of fact, as shown by (Durbin, Mieg 93) the management of these data and knowledge involves some specific problems that do not come down to a simple problem of information storage. On the one hand, the elaboration of new knowledge through the sequencing project involves a fast modification of the biological paradigms. Thus, one needs to be able to modify incrementally the modelling schema used in the knowledge bases. On the other hand, the information contained into the knowledge bases bring the ground fact helping the research of new knowledge. Thus, we need to supply some suitable and efficient interface to the biologist to access to the content of these knowledge bases. The system ACeDB (Durbin, Mieg 92), which has been initially implemented in the frame of the project for obtaining the genomic sequence of the nematode *C. Elegans*, is one of the most popular knowledge base management system currently used by the sequencing projects. Its success is partially due to its powerful graphical interface allowing the biologists to visualise the data in the form of a biological map (genetic, physical, ...) and to navigate from map to map.

In the frame of a project (Médigue *et al.*, 95) supported by the GREG[1] we are developing the generic mapping interface APIC[2]. Here, the word generic have three different meanings. Firstly, this interface is not dedicated to a specific organism. Secondly, this interface is able to display in a homogeneous way many kinds of genomic maps (cytogenetic, genetic, physical, ...). Finally, APIC is not limited to the display of biological entities but is also able to display the graphical objects (curves or pictures) produced by the sequence analysis methods.

Before detailing more precisely the functionalities of APIC and its specificities with respect to the other existing products such as ACeDB (Durbin, Mieg 93), SIGMA (Cinkosky, Fickett 92) or GnomeView (Douthart *et al.* 94), it is necessary to express the context in which this product has been implemented. Currently, the study of a genomic sequence of an organism involves two different requirements. On the one hand, one needs to manage a set of biological and bibliographical information about this genome. On the other hand, one needs to implement some specific analysis methods to deal with this genome (for instance, the search of coding parts, of homologies, ...). Therefore, two kinds of knowledge must be handled in the course of a sequencing project :

- *descriptive knowledge* that are used to define the biological entities of the genome, to describe the relationship between these entities and finally to indicate the related bibliographical references.

- *methodological knowledge* that are made of two parts. Firstly, a set of general purpose sequence analysis methods, such as BlastX (Altschul *et al.*, 90), whose algorithms are rather independent of the genome under study. Secondly, a set of analysis strategies more related to the genome under study. Each analysis aims at dealing with a particular task, each task being solved by calling a

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[1] From french acronym: “Groupement de Recherches et d’Etudes sur les Génomes”. This project have four partners: Curie Institute in Paris, Laboratory of Biometry, Genetic et Biology of Populations in Lyon, L’INRIA Rhône-Alpes in Grenoble and the ILOG company in Paris.

[2] From french acronym “Aide à la Présentation des Interfaces Cartographiques”

sequence of general purpose methods with some specific parameters. For instance, the biologist can look for the coding part of a sequence by successively running BLASTX, searching for the ORF (Open Reading Frames), and searching for the CDS (CoDing Sequences). It is worth noting that the structure of an analysis strategy can be very complex and involves several iterations, tests and calls for other more elementary strategies.

Until now, the sequencing project managers have mainly focused on the problem of modelling the descriptive knowledge. Obviously, it is generally possible to introduce in these systems some new methods to analyse the genome, unfortunately these additions involved the use of programming tools. Our project aims at providing the biologists with a cooperative workbench allowing (1) to manage both descriptive and methodological knowledge (2) to reuse as far as possible the existing analysis methods (3) to implement new strategies without programming. The descriptive knowledge is managed with the object-oriented modelling tool TROPES[3] (Mariño *et al.* 90) and the methodological knowledge is managed with SCARP (Willamowski 94 ; Médigue *et al.* 93) that allows a declarative definition of the solving strategies. The final system will focus both on ergonomy and extendibility.

- *Ergonomy.* Thanks to the explicit definition of the solving strategies, the system can give some advices to the biologist about the general method to use for solving a given analysis task, or it can indicate the right strategies to apply for solving a complex analysis task. In this framework, the graphical interface APIC allows to compare easily the results produced by the different analysis methods and provides some powerful functions for navigating and browsing into these results.

- *Extendibility*. Obviously, the final system will be able to store and manage the sequences produced by the sequencing tasks and the new data and knowledge created by the analysis of these sequences. However, neither the set of the biological entities defined in the system nor the analysis methods and strategies used to deal with these entities are fixed. It is always possible to add new analysis strategies or to improve the existing ones. Similarly, the system can be adapted to some specific application contexts by adjoining new sequence analysis methods.

As previously said, one of the major features of a sequencing project manager is its ability to display the information known about the genome in a comprehensive form and to supply some high level tools for browsing and navigating in the knowledge base. In our project, as it is possible to introduce new analysis techniques, we absolutely need to provide the biologist with a generic tool allowing to visualise and compare the results generated by these new methods (figure 1). As a matter of fact, it is worth noting that these methods have not always a built-in display interface, especially when they are totally new. The advantages of using such a generic approach are threefold. First, APIC brings a standard interface displaying the information in an homogeneous way, therefore, the comparison of the results is make easier. Moreover, the user's task is simplified since he has to manipulate only one general interface instead of a set of dedicated interfaces. Finally, by separating the visualisation interface from the sequence analysis methods, one obtains a more modular system whose further evolution will be made easier.

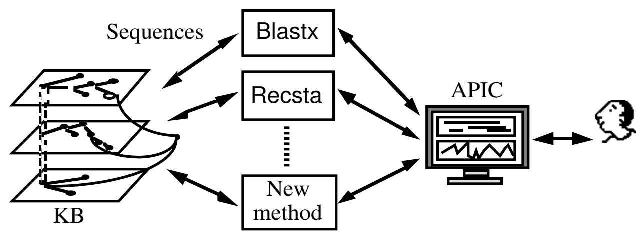


Figure 1 : a generic tool for displaying and comparing the results produced by the analysis methods

In this paper, we are going to present the general functionalities of APIC and the underlying concepts used (section 2). Next, in the sections from 3 to 7 we will detail the main features of the system such as zooming, synchronised scrolling, surimposing of curves and customisation of the interface. Finally, we will provide some information about the implementation (section 8).

2 A generic approach

2.1 Introduction

The different sequence analysis methods produce a great diversity of results such as new entities, sequence, genomic map, curves, drawings ... whose biological meaning are different. Therefore, to specify the features of our generic interface we are temporarily going to forget the biological aspects and we are going to analyse this problem from a strictly graphical standpoint (figure 2).

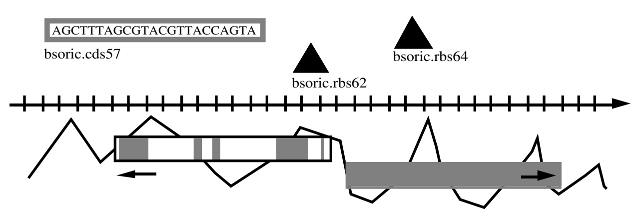


Figure 2 : a graphical point of view of the interface

Practically, in most of the situations the problem comes down to representing a set of graphical objects on an oriented and graduated axis (horizontal or vertical). These graphical objects can be points, segments, curves or pictures and can be seen as the display of a set of boxes

[3] In the final release of the project. Currently we use the modelisation tool Shirka (Rechenmann, Uvietta 91).

containing various patterns. Finally, several annotations can be linked to these graphical objects such as their name, their sequence of nucleotides or their orientation in the axis. In conclusion, we see that an interface comes down to a small amount of graphical concepts.

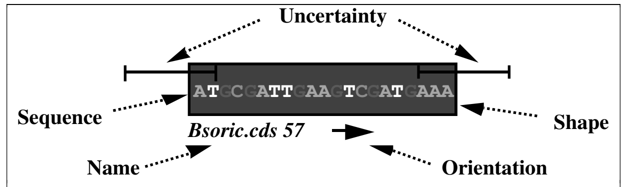
However, an interface is not restricted to the display of a graphical representation. It must also provide several manipulation functions allowing the user to browse and to navigate into these representations. Again, the set of useful functions is relatively small and can be defined independently of the biological problem. Here are a list of some of the relevant functions :

- Displaying simultaneously several kinds of maps showing different set of information.
- Easy and quick selection of the types of objects we want to display in the maps.
- Possibility of accessing (read/write) to the information contained in the KB through the interface.
- Zooming (in and out) into the maps until the sequences of nucleotides become visible.
- Providing multiple methods to navigate in the maps and to memorize the relevant sites.
- To be able to synchronised the scrolling between maps having different scales and different units.
- Possibilities of surimposing different kinds of information on the same display.
- Customisation of the interface by the user (choice of the colors, settings of the layout, ...).

2.2 Basic notions

In the interface APIC, a map is an oriented and graduated window containing a set of graphical objects. Each map is described by its name and its unit[4] (Kb, CentiMorgan, ...), however the list of these units is not fixed and the user can easily define a new unit. Each graphical object is typed and have a beginning and ending positions in the sequence, both positions are expressed in the unit of the corresponding map (figure 3). The notion of type is very important since the display settings are performed according to the type of the objects. In other words, all the objects belonging to a given type will be displayed in the same way in a map. Several optional attributes can be associated to an object such as its name, its shape (plain pattern, curve or picture), its uncertainty concerning its position in the sequence, its orientation into the map (3' or 5') and the sequence of nucleotides. Finally, other attributes can be freely provided to the interface, for instance to express some biological data. These last attributes are not directly used by the interface but can be viewed by the user by clicking on the object.

In the current implementation of APIC, the description of a map is given to the interface in the form of a read only text file using the format TINA. This format consists of a non-ordered sequence of records. Each records describes one entity of the map whose features are summerized by a non-ordered set of attributes (figure 3).




```
Type      {CDS}
Name      {Bsoric.cds 57}
Frame     {2}
Begin     {100}
End       {121}
Sequence  {ATGCGATTGAAGTCGATGAAA}
```

Figure 3 : graphical representation of an object in a map and its description in the TINA format

Thanks to this general definition of the notion of object, the system can easily take into account some specific graphical data such as curves or pictures since they just consist in objects filled with particular patterns.

However, a problem remains : all these objects cannot be placed anywhere within the map and we can stated several requirements. Generally, it is necessary to avoid any kind of overlapping between the objects. However, when the interface displays an object such as a curve, it can be very interesting to surimpose this curve above (or under) the other entities of the map. In other respect, we need to be able to group the related biological entities into the same area of the map. For instance, if there are some objects on the map standing for the codons STOP of the six reading frames of a sequence, it is relevant to organize these codons frame by frame in the map.

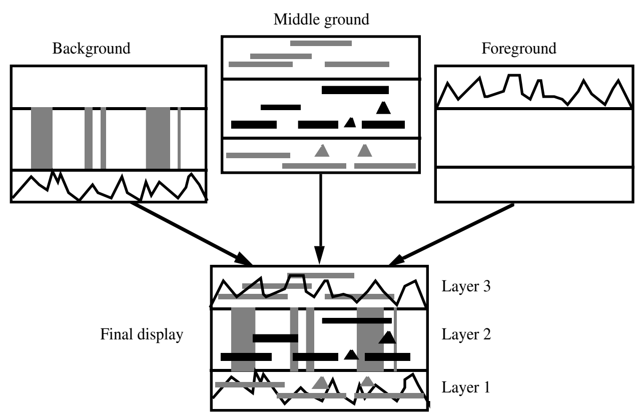


Figure 4 : in APIC a map is structured following the notions of layers and levels

Thus, in order to fulfil all these requirements, we have introduced in APIC the notion of layers and the notion of level (figure 4). Layers are a horizontal structuration of the map, each map can contain up to ten different layers. In each layer the user can put one or several types of objects.

[4] Some other attributes exist such as the accurracy or the origin of the map. There will not be detailed here.

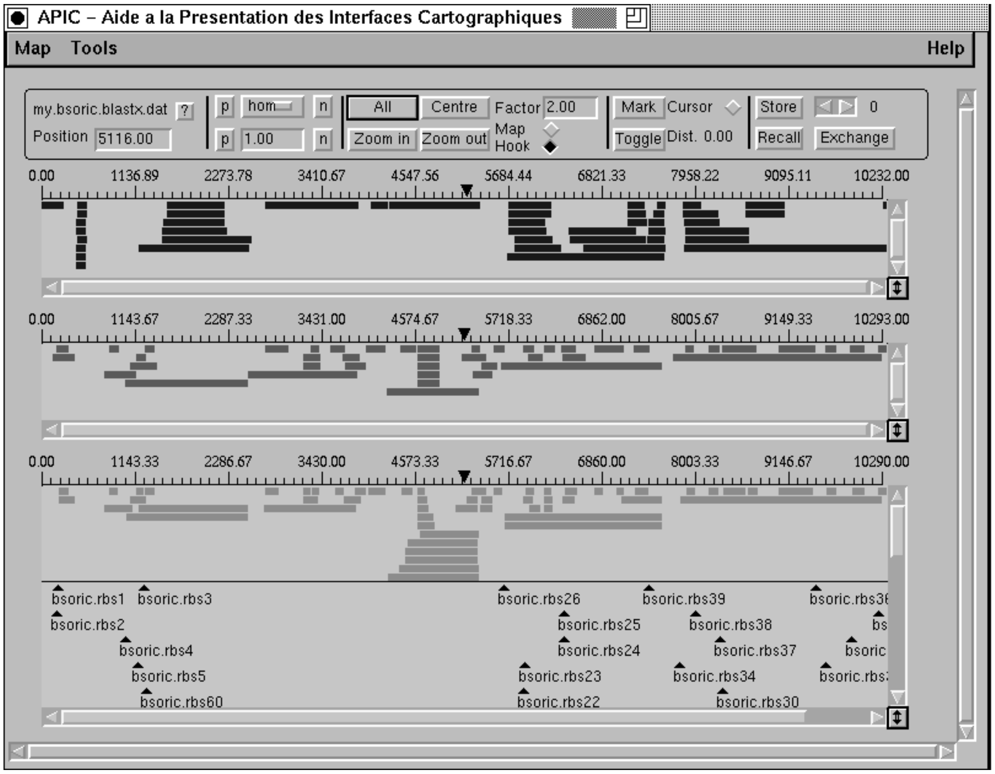


Figure 5 : general aspect of the interface

For instance, in the case of the codons STOP, the user could assign each frame to a specific layer : in this way, the 6 frames are displayed into 6 raws as in the interface of RECSTA (Fichant *et al.* 87). The height of a layer is dynamically computed by APIC according to the objects hold in this layer. This notion of layer is roughly equivalent to the notion of "tiers" used by SIGMA.

The notion of level is more original. In practice, each layer of APIC can have three different levels of display : foreground, middle ground, background. The types of objects that are placed in the middle ground level are automatically shifted on the Y-axis so that there is no overlapping between the different objects belonging to this level. In other respect, the types of objects that are placed into the two other levels are displayed without taking care of the overlapping problem. In that case, the user can provide, in the description of an object, the absolute Y-position (in pixels) of this object in the level.

The final display is performed by merging the three levels (figure 4). Thanks to this mechanism, the user can structure the maps and he can create rather complex displays (section 6). For instance, he can easily surimpose some cytogenetic bands, a list of genes and a set of curves on the same screen. Finally, it is worth noting that the structuration of a map is performed by the user after the loading of this map in the interface and by interacting through a set of dialogue boxes. Therefore, there is a clear separation between the biological knowledge which is described in the TINA file and the representational choices done in the interface. Obviously, all these choices can be saved in a resource files and reused on some other maps containing the same types of objects.

3 General aspect of APIC

The APIC interface consists in a X11 window (figure 5) in which one or several maps can be simultaneously loaded. The maps loaded by the user can express different kinds of knowledge (physical, genetic, ...). Each map is topped (1) by a scale whose graduations are expressed in the units of the map and (2) by an optional command panel providing some basic functions allowing to navigate into the map (zoom, scrolling, ...). These functionalities are described in section 5. Finally, the user can change the order of the maps and can hide the command panel.

In the example figure 5, the three maps visualise the results found by three sequence analysis methods for all the reading frames of a sequence. Top-down, we find the map of the homologies found by a BlastX into a protein database, the entities found by an ORF research (Open Reading Frames) and the entities found by an RBS/CDS research (Ribosome Binding Site/CoDing Sequence). In the third map, the RBS and CDS has been splitted by the user into two different layers. This structuration into layers increases the readability of the map. The possibility of loading several maps in the interface makes easier for the biologist the comparison of the content of these maps. For instance, we can see that there is a close similarity between the structure of the ORF and the CDS (second and third maps) in the right part of the window.

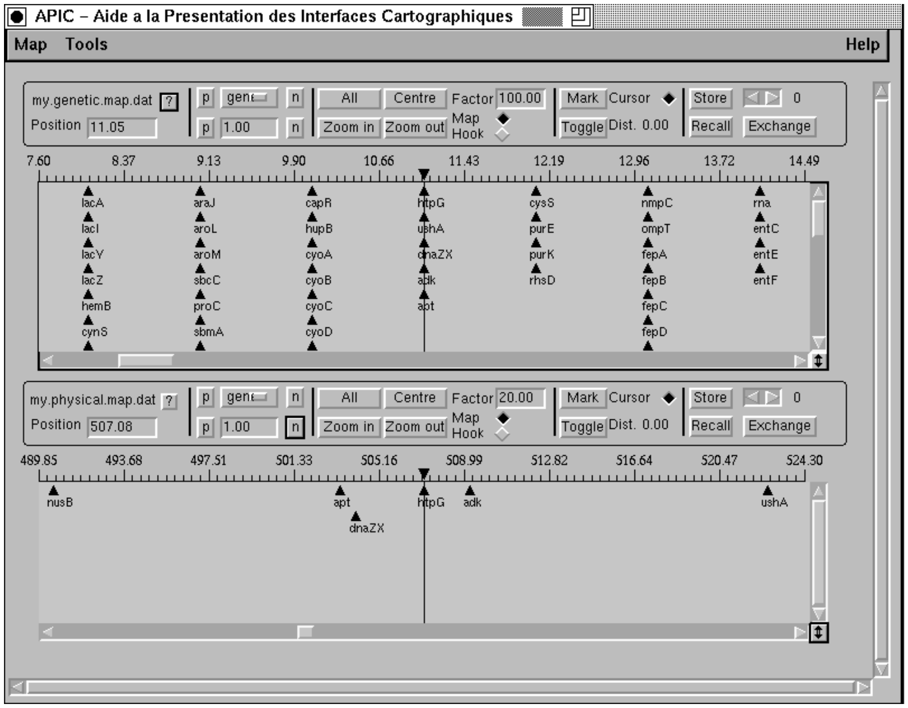


Figure 7 : synchronised scrolling between a genetic and a physical map

4 Scrolling and navigation

The quality of a mapping interface strongly depends on the quality of the navigation functions provided to the user such as the scrolling and the zooming. In practice, when we work on a set of related maps in a window, it is interesting to group these maps together such that they have the same behavior with respect to the navigation functions. For instance, in figure 5 when we move the scroll bar of the first map, it would be nice to move automatically the scroll bar of the second map from a distance corresponding to the scales ratio between these maps. This possibility has been implemented in APIC through the notion of *hook*. When two or several maps have been hooked in the interface, all scrolling or zooming actions performed on one map of the hook are automatically applied to the other maps of this hook.

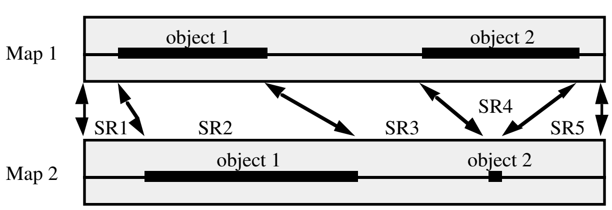


Figure 6 : computation of the scale factors between the shared objects of two maps

Obviously, this function is easy to implement when all the maps use some similar scales, the interface just need to have the conversion table between the different units. However, the situation can be also more complex: for instance in figure 7 we have loaded a genetic map whose scale is expressed in minutes and a physical map whose scale is expressed in Kilobases. Here, the two scales are not linearly correlated, moreover the objects do not always occur in the same order in the two maps. Therefore, to synchronise the scrolling between these two maps, APIC uses a special algorithm based on the notion of shared objects (figure 6) ; the idea is the following. When several maps $\{M_1, ..., M_n\}$ have been hooked together, for each pair of map M_i and M_j, the system builds a table in which each cell corresponds to the interval between two consecutive *anchorage points*. An anchorage point corresponds either to the beginning of a shared object[5] or the end of a shared object.

Next, each cell of this table is set to the scale ratio between the segment in M_i and the segment in M_j. A negative scale ratio is generated when there is an inversion between the positions of two objects in the sequences and thus the two maps will be moved in an opposite way during the synchronised scrolling. Here is the table generated for the example in figure 6 :

Map origin	-	Begin object 1	SR_1
Begin object 1	-	End object 1	SR_2
End object 1	-	Begin object 2	SR_3
Begin object 2	-	End object 2	SR_4
End object 2	-	Map end	SR_5

[5] Two objects are considered as being identical is they have the same type and name in the two maps.

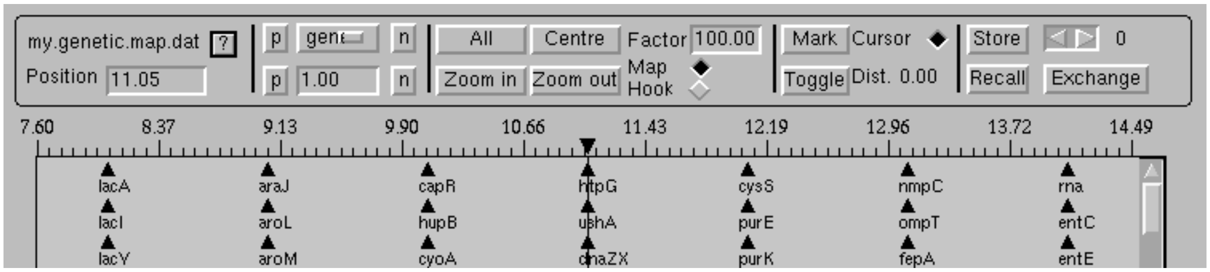


Figure 8 : the command panel of APIC

Thanks to the previous table, it becomes possible to synchronise the scrolling of the maps. In this way, in figure 7, when the user moves the scroll bar of the physical map, the genetic map is scrolled too and when the cursor (which corresponds to the vertical line) points at a common object in the physical map (here HtpG) it always points at the same object in the genetic map.

Concerning the navigation in the sequence, our interface provides a large set of functions to the biologist. These functions can be used through the command panel placed above the map (figure 8).

• The left part of the command panel indicates the current position in the sequence. This current position is materialised in the map through the medium of a small triangle placed in the scale. The user can change this position by introducing by hand a new value in the field position. When a new position is given the current map is scrolled and the hooked maps are scrolled too.

• The second part of the panel allows the user to shift the genomic map from left or right. There are two different kinds of moves. On the one hand, the user can specify a type of object and move the map from object to object. For instance, by clicking on the upper right button (next), the user will move the map toward the next gene at the right of the current position. On the other hand, the map can be scrolled following a given step that the user can edit. In figure 8, this step equals 1minute in the genetic map and 1 Kb in the physical map.

• The third part of the panel controls the zoom functionalities. The user can increase or decrease the scale of the map by clicking on the button Zoom-Out or Zoom-In. During a zoom, the user can decide if a zoom concerns the current map only or all the maps that have been hooked to this map. The increase/decrease factor of the scale is defined in the field "factor" that can be edited. The button ALL allows to select a scale factor allowing to see all the current genomic map, and the button CENTER allows to center the map on a given position.

• The fourth part of the panel concerns the cursor. This cursor allows to visualize the current position in the map in the form of a thin vertical line and it can be shown or hidden. The user can also put a *mark* into the current map ; once the mark is set the field "dist" visualises the distance between this mark and the current position of the cursor. In this way, the biologist can easily measure the distance between any two objects of the map.

• Finally, the right part of the interface allows the user to memorise some "views" of the current map. The mechanism is closely related to the one used in the handheld computers. When the user stores a view in the

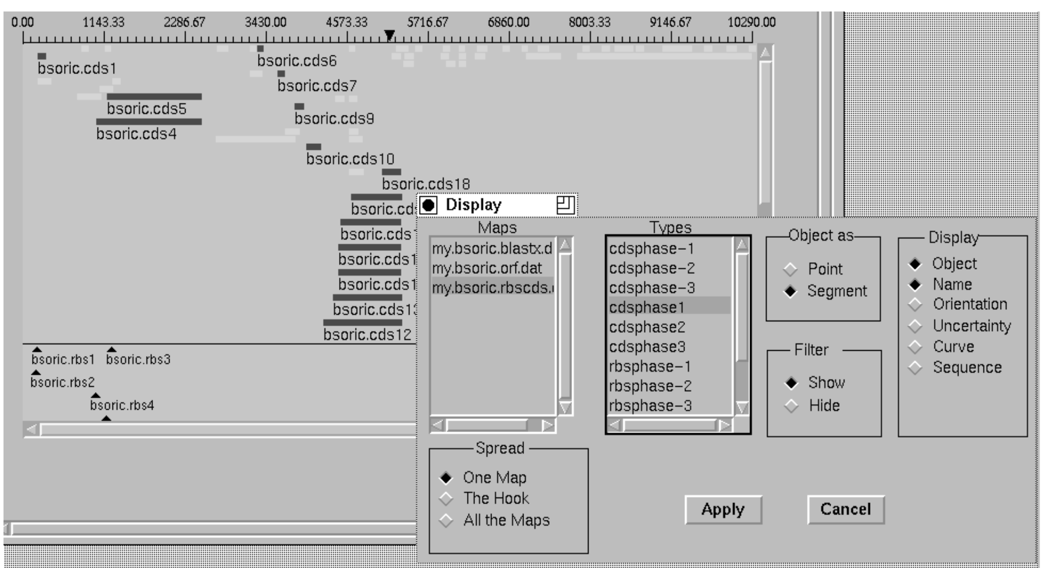


Figure 9 : display settings for the different types of objects

memory number M, the interface memorises the position and the scale factor of the current map. When the content of the memory M is recalled, the interface restores the position and the scale previously memorised. In this way the user can easily toggle between different parts of the map without doing any scrolling. When the content of a memory is recalled all the maps that have been hooked to the current one are automatically scrolled.

5 Information to display

According to the problem under study, the visualisation of the all the information associated to the objects such as their names or their orientations in the sequence, are not always relevant.

APIC allows the user to set the display for each type of objects through a dialogue box (figure 9). The spread of a display setting can concern either the current map, all the maps hooked to the current one or all the maps of the interface. For instance in figure 9 we only display the names of the CDS belonging to the frame 1. In other respect, the user can temporarily show or hide a given type of object through the buttons occurring in the field “filter”. Finally, with the field “object as” the user can choose if an object is always displayed as a point (independently of the scale) or as a scaled segment.

6 Curves and sequences

As emphasized in the section 2, the visualisation of the results produced by the sequence analysis methods are not always restricted to the display of a set of objects. Figure 10 shows an example of a more complex display. This figure displays the results of a contig analysis on three reading frames. The arrows stand for the CDS, the rectangles stand for the homologies found by BlastX and the curves have been produced with GenMark (Borodovsky, McIninch 93) to predict the coding parts of the sequence from a statistical analysis of the codons. As shown in the bottom part of this figure the user can easily display the information associated to an object by clicking on it. Here, the selected object is “ak2_bacsu” which occurs in the second reading frame.

To obtain this screen, the biologist has performed two operations. First, he has translated the output of the analysis methods into a text file (in the TINA format) containing the list and the description of the objects to display and the coordinates of the points of the curves. Second, he has loaded this file in the interface and assigned the different types of objects to three different layers (one for each reading frame) ; next he has put the CDS and the homologies into the middle ground level and the curves into the foreground level. Therefore, once the translation procedures between the output of the sequence analysis methods into the TINA format are written, the display of these results can be automatically achieved without any programming.

The map in figure 11 shows how our interface displays the sequences of nucleotides. In APIC, the sequence of nucleotides associated to an object becomes automatically visible as soon as the scale factor is sufficient. However, from a practical point of view the letters ATGC which compose a sequence become easily readable only when the size of the font is greater than 8 points. Therefore on a screen having 1000 points it is only possible to display a sequence up to 120 nucleotides. To overcome this problem APIC proposes another representation mode in which the nucleotides are represented as *colored strips*. In this way, the interface can display larger sequences since the minimal size for a nucleotide is now 1 pixel. This

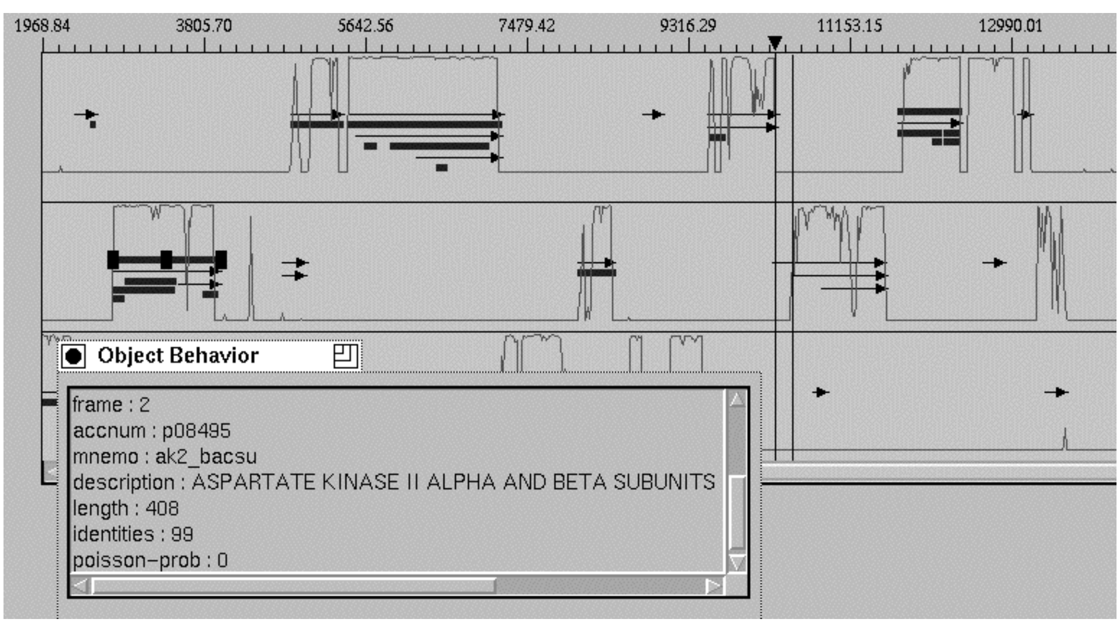


Figure 10 : curves and other biological entities

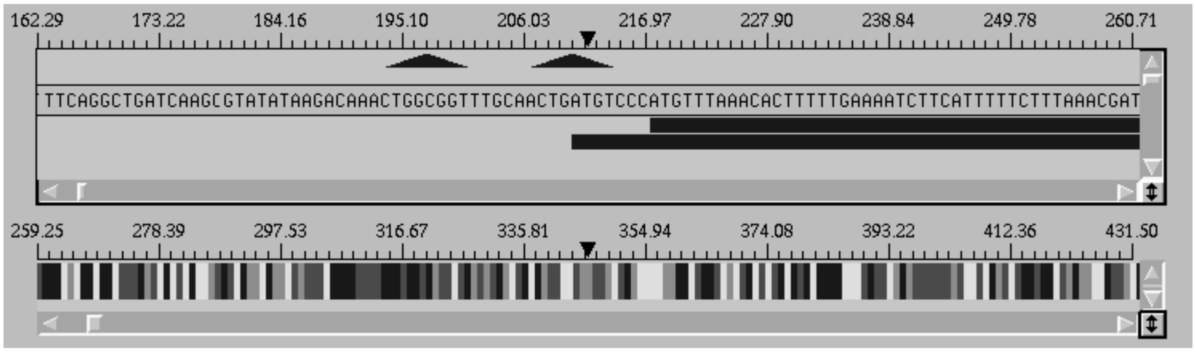


Figure 11 : APIC proposes different modes to display the sequence of nucleotides

new representation is also interesting because it is well-adapted to the research of regularities into a sequence.

7 Customisation of the interface

As shown in section 5, APIC allows the user to select the information to display in the maps. But it is also possible to change the overall aspect of the entities thanks to the dialogue box shown in figure 12. In this way, the biologist can modify the representation associated to each type of objects according to the kind of knowledge he wants to bring to the fore.

For instance, in the field "object" of this dialogue box, the biologist can modify the shape, the color, the size and the layout (offset and height) of the different types of object. As in the display settings (section 5) the modifications performed on a type of object can concern either a map, all the maps hooked to the current map or all the maps of the interface. In the field "sequence", the user can modify the color associated to each nucleotide in the colored strip mode and the minimal size of font to use to display the letters of the sequence. It is worth noting that all these settings can be saved and reused on another map containing the same types of objects.

8 Conclusion

In this paper we have presented the main characteristics of APIC, a generic interface allowing to visualise genomic information. Genericity is the main strength of this interface since it allows the system to deal with a large panel of information without involving any programming from the user standpoint. Clearly, the major difference between APIC and the other existing interfaces lies in the fact that APIC is just a visualisation interface and not a database manager, nor a sequence analysis tool.

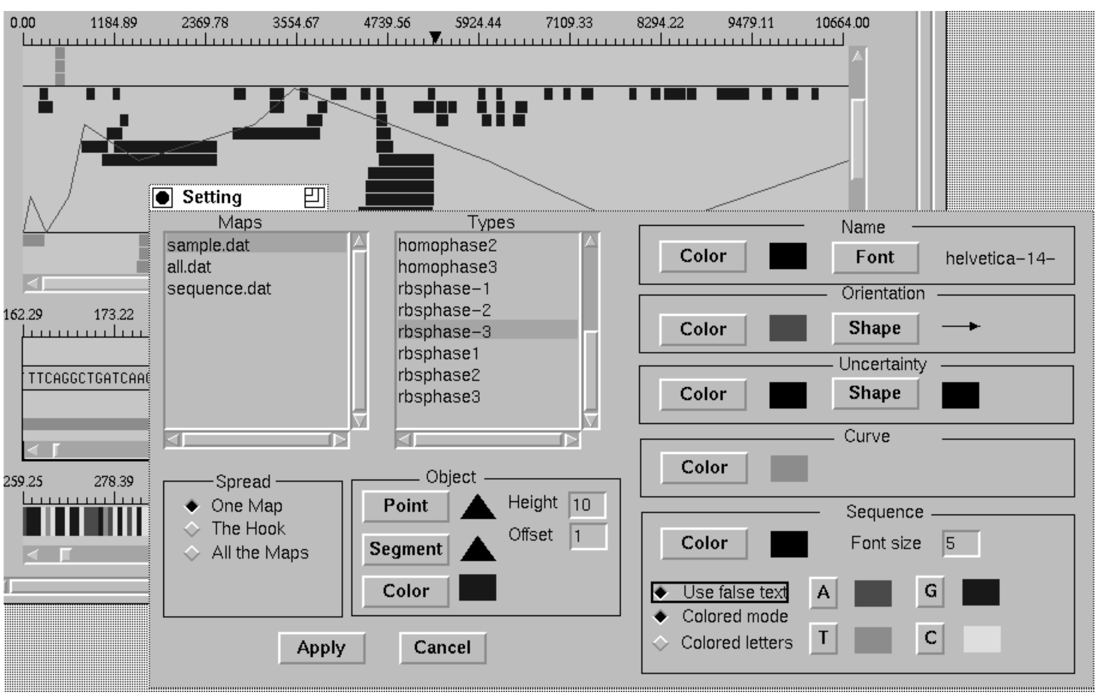


Figure 12 : customisation of the interface by the user

However, in the project supported by the GREG all these features exist but there are managed at the level of the object-oriented modelling tool TROPES and the level of the sequence analysis manager SCARP. Thanks to this modular architecture, the system has the advantage to provide an homogeneous interface allowing to display many kinds of information (biological and graphical) in a structured way through the notions of layer and level. Furthermore, the navigation facilities (synchronised scrolling, ...) provided by APIC and its ability to structure the display makes the comparison of the results produced by the sequence analysis methods easier.

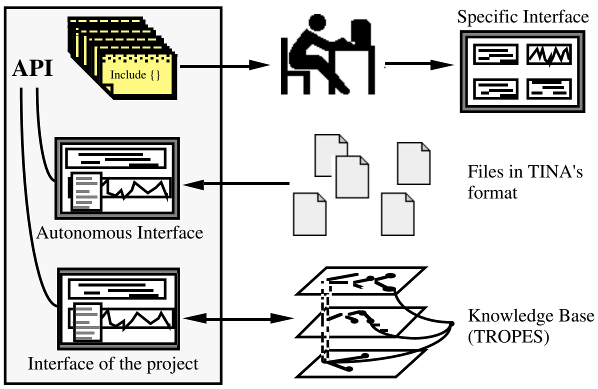


Figure 13 : the different implementations of APIC

From a technical standpoint, APIC has been developed in C++ with the help of the interface builder ILOG-VIEWS (Ilog 94). In the current version of APIC, the communication between the sequence analysis manager and the interface is done through a read only text file in the TINA format. In the next release the communication will be directly ensured through a set of functions allowing to modify "on-line" the content of the KB. Moreover, this release will integrate some new features such as the possibility of doing some queries in the interface and storing the selected entities in a new map.

At the end of our project (in 1996), there will be three versions of APIC (figure 13). Basically, it will consist in a library of functions allowing to display genomic sequences and to navigate in these sequences. This library will be organised in the form of an API (Application Programming Interface) allowing the other programmers to develop their specific interfaces. From this API, we will implement two specific applications. First, an autonomous application that will be usable by all the biologists ; this application (as the one presented in this paper) will communicate with the user through a set of files in the TINA format. Secondly, APIC will be a module, fully integrated in our GREG project, allowing to visualise and to modify the content of the KB.

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References

ALTSCHUL S.F., GISH W., MILLER W., MYERS E.W., LIPMAN D.J. 1990. Basic local alignment search tool. *Journal of Mol. Biol.*, 215. 403-410.

BORODOVSKY M., MCININCH J.D. 1993. GENMARK: Parallel gene recognition for both DNA strands. *Computers & Chemistry*, 17(2).123-133.

CINKOSKY M. J. FICKETT J.W. 1992. SIGMA: System for Integrated Genome Map Assembly, User's Manual. Los Alamos. NM 87545. See also on the WWW, URL http://www.ncgr.org/

DURBIN R., MIEG J.T. 1993. The ACeDB Genome Database. WWW document, URL http://probe.nalusda.gov:8000/acedocs.

DURBIN R., MIEG J.T. 1992. - ACeDB - A C. Elegans Database 1. User's Guide 2. System manual.

DOUTHART R.J., PELKEY J.E, THOMAS G.S. 1994. Data Integration and Visualization of Maps of Human Genome Using the GnomeView Interface. Proceedings of 27th Annual Hawaï International Conference on System Sciences. 49-57.

FICHANT G., GAUTIER C. 1987. Statistical Method For Predicting Protein Coding Regions In Nucleic Acid Sequences. CABIOS vol.3. no.4. 1987. 287-295

ILOG 1994. Ilog Views Reference Manual. Version 2.1

MARIÑO O., RECHENMANN F., UVIETTA P. 1990. Multiple Perspectives and Classification Mechanism in Object-Oriented Representation. Proceedings of 9th European Conference on Artificial Intelligence (ECAI). Stockholm. 425-430.

MÉDIGUE C., VERMAT T, BISSON G., VIARI A., DANCHIN A. In proceedings of ISMB 95. Cooperative computer system for genome sequence analysis.

MÉDIGUE C., WILLAMOWSKI J., CHEVENET F., RECHENMANN F. 1993. Modeling tasks for problem solving in molecular biology. Proceedings of the IJCAI'93 Workshop *Artificial intelligence and genome*. Chambéry (France). pp 67-76.

RECHENMANN F., UVIETTA P. 1991. Shirka - An object-centered knowledge base management system. In *Artificial Intelligence in Numerical and Symbolic Simulation*, ALÉAS Publ, Lyon.

WILLAMOWSKI J. 1994. *Modélisation de tâches pour la résolution de problèmes en coopération système-utilisateur.* Ph.D. Thesis, Université Joseph Fourier, Grenoble 1.