Easy DNA Modeling and More with GraphiteLifeExplorer

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Abstract
The GraphiteLifeExplorer tool enables biologists to reconstruct 3D cellular complexes built from proteins and DNA molecules. Models of DNA molecules can be drawn in an intuitive way and assembled to proteins or others globular structures. Real time navigation and immersion offer a unique view to the reconstructed biological machinery.

Introduction
Thanks to structural biology and -omics technologies, biologists have now collected large amounts of data regarding individual biological molecules. In order to build a system view of living organisms, new engineering tools like large scale 3D modeling software are required.

The GraphiteLifeExplorer 3D modeling tool is being developed with the ultimate goal to reconstruct a complete bacterial cell from its individual parts. In addition to the 3D reconstruction of protein arrangements, one of its main features is the ability to model, in an intuitive manner, any DNA molecules of arbitrary length and shape at the resolution of one base pair. It is intended to help biologists to formulate and test hypothesis on some unavailable shape at the resolution of one base pair. It is intended to help biologists to formulate and test hypothesis on some unavailable shape at the resolution of one base pair.

This paper describes the process and the tool to achieve 3D modeling of cellular complexes with the ability to add DNA. The program architecture is then presented as well as technical details about the DNA representation.

The 3D Modeling Process
Bacterial cells are internally organized [1–3]. Figure 1 gives an illustration of the spatial organization for a bacterial cell. Figure 2 shows at a glance the potential of the GraphiteLifeExplorer tool to virtually rebuild a bacterium.

A Global View
The modeling process carried out with GraphiteLifeExplorer is made of the following steps (see also [4]):

- The first step is the collection of structural data on the complex or the process of interest.
- The 3D shape of DNA molecules is generally unconstrained but can be generated using geometry modeling. The atomic structure of a protein can also be transformed into a surface representation that allows an immediate and intuitive understanding of its shape. Some regions can be distinguished with different colors to highlight residues involved in protein-protein interaction for instance.

Geometry Modeling with GraphiteLifeExplorer
Since no fixed structure is available, some macromolecules have to be modeled de novo (DNA, linkers, membrane...). Modeling DNA is intuitive and easy in GraphiteLifeExplorer as explained Figures 3 and 4. The DNA strand is built by modeling its helical axis as a curve in space. Currently, GraphiteLifeExplorer allows the edition of quadratic and cubic Bezier curves [7]. The Bezier curves are modifiable: their control points can be created, moved, deleted and duplicated to model DNA strands of arbitrarily complicated shape, open or closed. At any time during the interactive modeling session, the curve can be visualized using different representations: as a plain line, as a tube or as an atomic representation. The visualization can be partially transparent to allow editing the curve while seeing the DNA model move and transform in real-time. When the overall shape of the DNA has been fixed, it is possible to fine tune the position of its base pairs: the user can force the angular position (the twist) of any chosen base pair around the curve. This angular constraint is then automatically propagated to the neighboring pairs to get as close as possible to the canonical DNA helix. For example, DNA can be locally untwisted, as illustrated in Figure 5. Unwinding the helices can lead to chemically impossible structures without inappropriate molecular dynamics refinement. This functionality allows the user to find a DNA structure that is intermediate between the untwisted...
helices and the expected structure. By exporting the DNA structure to a PDB file format, it is possible to perform a further refinement step.

3DNA [8] or Nucleic Acid Builder (NAB) [9] are powerful programming environments dedicated to the chemically rigorous structural building of nucleic acids but cannot be used to create arbitrary DNA shapes in an interactive manner. A portion of DNA

Figure 1. Realistic illustration of the interior of an E. coli bacterial cell by D.S. Goodsell (TSRI). It shows the spatial organization of the cell and its crowding: 1/The nucleoid (in yellow/orange) is made of DNA containing the genetic information and of proteins interacting with the DNA (to repair it for instance) 2/Some of these proteins read the genetic information and transfer it (see the red circle) into the cytoplasm (in blue/purple) where it serves to build new proteins performing most of the tasks inside the cell 3/Some of these proteins go back to the nucleoid, others remains in the cytoplasm, still others go to the membrane (in green). Other elements of this organization are the cytoskeletons (the blue filament in the upper left corner of the illustration), long and filamentous “molecular motorways” that track various proteins from one pole of the cell to the other one. About genome organization in E. coli, the DNA is condensed into a compact structure called the nucleoid and is organized into macrodomains [25]. However the fine spatial organization of the DNA inside a macrodomain is still largely debated. This illustration is an original photograph of David Goodsell’s painting. It differs from the version published in [26–27]. With kind permission of David S. Goodsell.

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Usefulness and Limitations: Shapes vs. Structure

By using simple geometric shapes for DNA, GraphiteLifeExplorer helps biologists to study and discriminate between the global shapes likely taken by DNA in contact with proteins. Information like protein-protein or DNA-protein crosslinks [11–12] or tomograms might provide further proofs of the model.

Powerful for studying shapes, GraphiteLifeExplorer is not designed for detailed local structure studies. Single/double nicks, mismatches, kinks or interbase stretches cannot be created by using the tool exclusively. Moreover a few structural deficiencies can subsist such as O3’ – P bond abnormal stretches between adjacent residues of the same chain. Clashes between atoms can also occur at the apex for severe curvatures. The user needs to be aware that cyclized DNA can be created (figure 3) but closing of DNA whose length is not a multiple of 10.4 requires the pitch to slightly differ from 10.4 base pairs per turn. Refinement can be done by exporting the model in the Protein Data Bank (PDB) file format (see § Export capability) and by performing an Amber based-molecular dynamics [13].

Associated with a tool like Web 3DNA [10] GraphiteLifeExplorer can nevertheless help the structural study of interaction with proteins. In the example of figure 8, GraphiteLifeExplorer is used to create the missing part between two nucleosomal particles. The connection with the experimental DNA structures is carried out with Web 3DNA. Obviously, molecular dynamics is mandatory at the end of the process as the connecting DNA portion must mechanically and structurally accommodate with the structural constraints on each side.

Enhanced Real-time Navigation

Real-time navigation (coupled with scene composition) is a valuable experience to inspire new questions. Rendering is enhanced in GraphiteLifeExplorer by real-time ambient occlusion, providing a better perception not only of the protein shape [14] but also of the relative position of the components in the scene (figure 9). Various effects (like cartoon rendering, figure 2) can be used for illustration purpose.

Export Capability

GraphiteLifeExplorer relies on its export capabilities coupled with well-established tools for physics-based animation or minimization computations. A scene can be exported either as a set of full atom representations in the Protein Data Bank (PDB) file format or as a set of geometric shapes.

**PDB export.** Each component of a scene (DNA and proteins) can individually be saved in the PDB format in which new atomic coordinates account for the spatial transformation that occurred during the composition of the scene. Figure 10 shows an example of a scene initially made with GraphiteLifeExplorer and visualized in Maya and Blender. Exporting in PDB thus allows the user to perform any task requiring a full-atom description of the components in an external tool.

**Geometry export.** As shown Figure 10, tubular shaped linkers and molecular surfaces can be exported as geometric objects (surfaces) in a common 3D format called Virtual Reality Markup Language (VRML). Doing so, any connection to the atomic description is definitively lost. This geometric export is useful when the user wishes to explore the scene in another tool with no PDB import capability, the user does not wish to lose the high-quality multi-colored surfaces generated with GraphiteLifeExplorer once in Maya, Blender or UCSF Chimera, or the user wishes to keep a geometric object like a tube representing an unstructured linker for which no atomic structure does exist.
Implementation Details

Graphite

Graphite (http://alice.loria.fr/index.php/software.html) is the program hosting the GraphiteLifeExplorer plugin. It is a research application, written in C++ and Python, developed with the goal to simplify the development of new geometry processing algorithms (e.g., for computing surface parameterizations or for re-meshing surfaces). Since the techniques involved are generic, they can be used for other purposes such as the development of our GraphiteLifeExplorer plugin.

Graphite provides compile-time introspection that is used to automatically generate user-interfaces for C++ functions. That way, the selected functions in a plugin automatically become commands in the graphics interface (available in menus). Graphite offers similar helpers for implementing tools relying on mouse events.

A particularly useful feature of Graphite is its ability to dynamically (at run-time) attach any kind of attribute to elements.

Figure 3. The DNA modeling process. To create DNA the user draws a path which can be adjusted in the three directions of space thanks to control points. The whole atomic structure is built upon the path. Closed structures can be created as shown by the circular A-DNA model. doi:10.1371/journal.pone.0053609.g003
of a geometric object. For example, we can load a PDB file as a set of points in space, and attach the radius and the name of each atom as attributes to the points, without having to declare new C++ data-structures.

All these features make Graphite a very developer-friendly environment for implementing innovative geometric algorithms. Furthermore, the graphical user interface (GUI) is sufficiently simple to be accessible to the casual user.

Implementation of the DNA Tool

We choose to use a smooth curve $C$ to model DNA: at any point on the curve, the tangent vector must be well defined. So must be the arc-length from the start of the curve to that point.

We use two point samplings of $C$. An adaptive sampling of $C$ consists of a sequence of point on $C$ that forms a linear approximation of the curve by straight line-segments such that the angle between two consecutive segments is below some threshold. This adaptive sampling is used to display a visually smooth curve with a minimal number of line-segments. It is used
solely for visualizing the helical axis (or DNA itself when it is far from the viewpoint).

We also use a uniform sampling $S_u$ of $C$, in which all sub-curves between consecutive sample points have the same arc-length. We use a spacing close to 3.4 Å to obtain a uniform sampling $S_u$ in which the samples can serve as anchor points for base pairs of DNA.

A rigidly moving frame. From the above, we have obtained a uniform sampling $S_u$ of the curve together with the tangent vector at every sample point. In order to coherently orient the base pairs along the curve, we need to augment this data with a normal vector, so as to obtain an orthonormal frame at each sample point. Many simple methods to do so result in a sequence of frames exhibiting discontinuities or strong torsion (e.g., the Frenet frame [15]). But ideally, we would like the frames in the sequence to

Figure 5. Twisting DNA. From top to bottom: 1/The initial DNA strand 2/A base pair is selected and 3/Twisted. All pairs follow the twist 4/Another pair is selected and 5/Twisted. The DNA is unwound between the two selected pairs 6/More pairs have been twisted. doi:10.1371/journal.pone.0053609.g005
Figure 6. Visualization of DNA simulation results. The comprehension of the (dynamic) configuration adopted by the DNA, of its packing into the cell is one of the major goals of biology. Numerical simulations address the topology of longer and longer DNA structures like plasmids. Here is shown the compaction of 28,000 DNA base pairs resulting from the action of fifty transcription factors (data shown courtesy of Ivan Junier; see [28] for details about the self-avoiding worm-like chain numerical simulation). Left image: The DNA is displayed as a thick line. Middle image: The DNA is displayed as a helicoidal double ribbon when the user zooms in. Right image: A transition between the helicoidal double ribbon rendering and the atomic rendering occurs when the user brings the camera closer to the object.

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Figure 7. Reconstruction process of a complex in GraphiteLifeExplorer. Case of the bacterial DNA repair protein MutL: (a) the N-terminal (NTD) and the C-terminal domain (CTD) of MutL are imported under the form of a full-atom representation from their respective PDB file. (b) The CTD is moved manually relatively to the NTD. (c) A surface appearance is given where residues 331 of the NTD and 432 of the CTD are colored in blue to help the modeling of two 40 nm long amino-acid linkers connecting the two domains. Although their amino-acid sequence is known, the linkers are disordered and therefore missing in the attempts to experimentally solve the 3D structure of the whole MutL. Here, the linkers have been built as a simple tube of fixed length and in agreement with AFM images [29]. Some residues at the surface of the N-ter domain have been colored in red to show where another repair protein called MutH interacts with MutL. PDB code N-ter: 1B63, PDB code C-ter: 1x9z (both subunits have been reconformed as suggested in [30]).

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transform as rigidly as possible from one to the next (i.e. without discontinuities and minimizing torsion). Indeed, such a rotation minimizing frame sequence allows to model a DNA strand at rest, without torsion. Obtaining a rotation minimizing frame sequence is not an easy task, but Wang et al. [16] show how one can obtain an extremely good approximation at a very low computational cost. After computing a normal vector at each sample point of \( S_u \) in this way, we store the sequence of triplets \( F_u = \{ f_i = (o_i, t_i, n_i), i \in [1, N] \} \) where \( t_i \) is the tangent vector and \( n_i \) is a normal vector to the curve \( C \) at the sample point \( o_i \) (Figure 11). The uniform sampling \( S_u \) and the frame sequence \( F_u \) are recomputed from scratch whenever the user modifies the control points of the curves. Our optimized implementation is sufficiently fast for interactive modeling.

**The DNA strand model.** GraphiteLifeExplorer does not support a specific sequence of nucleotides yet, and thus assumes a generic one: \((ACTG)^n\). We keep in RAM an atomic model centered at the origin for each four possible base pairs AT, TA, CG and GC. In order to model or draw the full DNA strand, we instantiate the atomic (3D) model at each sampling point \( o_i \) of \( S_u \) in the local frame \( f_i \). To reproduce the DNA helix, the model is rotated by \( \sim \frac{2\pi}{10.4} \) rad around the tangent \( t_i \). In this way, memory cost is kept to a minimum and DNA strands of several millions base pairs easily fit in an average PC RAM.

When exporting the DNA strand to a PDB file, the instantiation of a base pair corresponds to the writing of the PDB records for each atom in the base pair, with proper position in space.

When drawing the DNA strand to the screen, the instantiation is performed by the GPU (graphics processing unit), driven by the OpenGL API: For each base pair \( i \), the local-to-global coordinate transformation for frame \( f_i \) is loaded into GPU memory. Then, the centers, colors and radii of the base pair atoms are streamed to the GPU. Each atom center is transformed (by a geometry shader) into a square, tangent to the atom ball and facing the viewpoint. Further, a pixel shader is set to cast a ray from each rasterized pixel away from the viewpoint towards the atom ball (Figure 12). In this way we obtain the same results as a ray-traced image, but at a much lower cost, thus retaining interactivity.

**Twisting strands.** It is crucial for the user to be able to fine tune the position of the DNA atoms individually; at least locally when there is a strong interaction with, say, a protein residue. Allowing independent atom placement, while most powerful, would destroy the curve abstraction that we use to make DNA modeling easier. Instead, we allow the adjustment of the twist of

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**Figure 8. Connecting nucleic acid structures.** Missing DNA between two nucleosomal complexes containing DNA (PDB code 1KX5) is modeled with GraphiteLifeExplorer (upper image). The “welding” between modeled DNA and DNA from crystallography is carried out in a simple manner with Web 3DNA [10]. Whole DNA is shown as an isosurface in GraphiteLifeExplorer (lower image). Molecular dynamics would then be necessary to take relaxation effects into account.

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each base pair around the curve. That is, at each frame \( f_i \), the base pair is rotated by angle \( \sim i \times 2\pi /10.4 + a_i \), where \( a_i \) is specified by the user. More precisely, \( a_i = 0 \) initially, and the user can then modify the angle of each base pair individually. The values are interpolated where they are not specifically defined: Suppose that the user has defined the values \( \{a_{i_1}, a_{i_2}, \ldots, a_{i_k}\} \) with \( i_1 < i_2 < \ldots < i_k \). If \( i_j > 1 \) we artificially set \( i_0 = 1 \) and \( a_1 \leftarrow a_{i_j} \) and similarly beyond \( i_j \). Then for all \( i \), there exists \( j \) so that \( i_j \leq i < i_{j+1} \), and the value \( a_i \) is a linear blend of \( a_{i_j} \) and \( a_{i_{j+1}} \), interpolating the twisting constraints at positions \( i_j \) and \( i_{j+1} \) (Figure 5).

**Real-time Visualization**

The previous section explained how the atomic model of a DNA strand is drawn on the screen. When the strand is very long, many base pairs are sufficiently far away from the viewpoint so as to cover only a small part of the screen. The atomic model is thus not appropriate since the atoms have a size comparable to that of a pixel, leading to objectionable flickering. For this reason, strands in the distance are drawn with simplified models: a ribbon model for moderately far strands, and a simple line for very far ones. In this way, we retain a pleasing and interactive visualization of long strands. We use a hierarchical decomposition to select a display model for each part of the strand, as detailed below.

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**Figure 9. Sophisticated rendering.** Top: Simple lighting from the viewpoint. Bottom: Ambient occlusion without lighting. doi:10.1371/journal.pone.0053609.g009
A hierarchy for interactive visualization and base pair selection. We build a binary hierarchy over the sequence of frames $F_n$. The root node consists of the entire sequence. The subsequence at one node is split in two sub-subsequences of equal length to form the two child nodes. At each node, a sphere bounding all the sampling points in the subsequence of the node is computed. We stop splitting a node when it contains about ten base pairs.

**Figure 10. 3D model export.** Upper left image: This 3D scene has been made in GraphiteLifeExplorer and exported (upper right image) in Maya thanks to Molecular Maya (http://www.molecularmovies.com/toolkit/) and (lower images) in the Blender 3D tool thanks to the ePMV plugin [31]. In Blender, a script written by L. Autin (Scripps) superimposes an inverse kinematic armature to the linkers. This mechanical articulation greatly helps and facilitates the animation of the proteins from a first position (right figure) to a second position (left figure): thanks to the IK chain, moving the pink and green domains results in a reconformation of the linkers, pushed or pulled like a chain, in the deformation of the geometry (the tubes representing the linkers) attached to the linkers, and in the displacement of the CTD domain (green-blue/yellow). The model can serve as an interactive data-constrained thinking tool to help a lab contemplate plausible dynamics for this system. Note that the inverse kinematic joints of such an armature can be set at each alpha-carbon of any backbone if the linkers is no more a tube but an aminoacid based linker modeled with tools like Phyre2 [32] and be combined with physics solvers hosted in the high-end 3D packages. doi:10.1371/journal.pone.0053609.g010

**Figure 11. A rigidly moving frame.** A uniform, rotation minimizing frame sequence along a cubic Bézier curve. The normal and binormal vectors are shown yellow. doi:10.1371/journal.pone.0053609.g011
When drawing a long DNA strand, the hierarchy is traversed top-down. If the bounding sphere of the node is sufficiently far away, we use the alternative, simpler display models for that node’s subsequence.

The hierarchy is also used to quickly determine which base pair the user has clicked on when he wants to twist the DNA.

**Protein surface meshing and visualization.** GraphiteLifeExplorer provides a tool for computing a mesh of the surface of a molecule (Figure 13). We use the ESBTL library for parsing and writing PDB files [17]. We use the surface model proposed by Grant et al. [18] and compute a linear approximation of it using the algorithm of Boissonnat and Oudot [19] as implemented in the CGAL library (Computational Geometry Algorithms Library http://www.cgal.org). The algorithm ensures that the mesh triangle size adapts to the local curvature of the surface, leading to high quality surface, even for low triangle budget.

More importantly, the tool allows for selecting subsets of a protein residues and coloring the parts of the protein (or DNA) surface that are closer to these residues than to others. In this way, one can visually locate selected residues on the molecule surface, in order to ease subsequent modeling.

**Conclusions**

3D modeling has proved its use beyond education and illustration as it helps to build our understanding [4] by formulating hypotheses and new avenues of research [20]. With the constant flow of new information regarding the spatio-temporal organization of living systems, the development of integrative tools [21] linking architecture, genetic information and metabolism is a key step to understand how processes are performed inside the spatially structured cells. At the current stage, GraphiteLifeExplorer enables to build spatial arrangements of proteins and nucleic acids representing cellular processing, while looking for a complete bacterium in the future. To our

![Figure 12. Casting a ray towards an atom.](doi:10.1371/journal.pone.0053609.g012)

![Figure 13. Surface meshing. The structure corresponding to the PDB code 2IUU is imported and an isocontoured surface is created showing its shape. This shape is shown at three different precision levels from coarsed-grain (A, B) to molecular skin (C). Specific residues at the surface are highlighted in red to help the connection of this hexameric protein with six linkers.](doi:10.1371/journal.pone.0053609.g013)
knowledge, GraphiteLifeExplorer is the first interactive tool with the capability to freely model the shape of DNA strands, and is far easier to use than previous approaches using generic 3D modeling software.

In addition to providing new integrative tools, the lack of common biological scene repositories needs to be addressed. The use of a standard format for macromolecular assemblies would favor its adoption in the scientific community. Such standard would drive future developments of software with a high potential to foster research and discovery processes in biology [22–23]. The establishment of the “Working Group on Theoretical Structural Models Validation” [24] is a step in this direction.

Availability

GraphiteLifeExplorer supports Windows Seven, Linux and Mac OS X (Lion). The pre-compiled program is freely available at http://www.loria.fr/~shornus/FFG/gle.html. The source code can be downloaded from http://gforge.inria.fr/frs/?group_id=1465. Tutorials are available from http://www.lifeexplorer.eu/3d-models/tutorials.

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Author Contributions

Designed the GraphiteLifeExplorer software: DL EF. Developed the GraphiteLifeExplorer plugin: SH. Developed the Graphite software: BL. Wrote the paper: SH DL EF.

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