INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team NANO-D

Algorithms for Modeling and Simulation of Nanosystems

Grenoble - Rhône-Alpes

Theme : Computational models and simulation

Table of contents

1. Team

Research Scientists

Sergei Grudinin [CNRS Junior Researcher]
Stéphane Redon [Team leader, INRIA Junior Researcher]

Technical Staff

Jocelyn Gaté [Software Engineer]

PhD Students

Svetlana Artemova [INRIA PhD Student]
Maël Bosson [PhD Student - Université Joseph Fourier]

Administrative Assistant

Françoise de Coninck [Assistant]

Other

Georgy Derevyanko [Intern]

2. Overall Objectives

2.1. Overview

During the twentieth century, the development of macroscopic engineering has been largely stimulated by progress in numerical design and prototyping : cars, planes, boats, and many other manufactured objects are nowadays designed and tested on computers. Digital prototypes have progressively replaced actual ones, and effective computer-aided engineering tools have helped cut costs and reduce production cycles of these macroscopic systems.

The twenty-first century is most likely to see a similar development at the atomic scale. Indeed, the recent years have seen tremendous progress in nanotechnology - in particular in the ability to control matter at the atomic scale. Similar to what has happened with macroscopic engineering, powerful and generic computational tools will be employed to engineer complex nanosystems, through modeling and simulation.

Modeling and simulation of natural or artificial nanosystems is still a challenging problem, however, for at least three reasons: (a) the number of involved atoms may be extremely large (liposomes, proteins, viruses, DNA, cell membrane, etc.); (b) some chemical, physical or biological phenomena have large durations (e.g. the folding of some proteins); and (c) the underlying physico-chemistry of some phenomena can only be described by quantum chemistry (local chemical reactions, isomerizations, metallic atoms, etc.). The large cost of modeling and simulation constitutes a major impediment to the development of nanotechnology.

The NANO-D team aims at developing efficient computational methods for modeling and simulation of complex nanosystems, both natural (e.g. the ATPase engine and other complex molecular mechanisms found in biology) and artificial (e.g. NEMS - Nano Electro-Mechanical Systems).

In particular, the group develops novel multiscale, adaptive modeling and simulation methods, which automatically focus computational resources on the most relevant parts of the nanosystems under study.

3. Scientific Foundations

3.1. Adaptive molecular mechanics

In the current adaptive molecular mechanics framework, a molecular system is recursively defined as the assembly of two molecular systems connected by a joint (when connecting two subassemblies which belong to the same molecule) or, more generally, by a rigid body transform (to assemble several molecules).

Thus, the complete molecular system is represented by a binary tree, in which leaves are rigid bodies (a rigid body can be a single atom), internal nodes represent both sub-assemblies and connections between sub-assemblies, and the root represents the complete molecular system (see Figure 1 on the right, which shows an assembly tree associated to a short polyalanin). This hierarchical representation handles any branched molecule or groups of molecules, since the connections between two sub-molecular systems can be a rigid body transformation. In this representation, the positions of atoms are thus represented as superimposed rigid transformations: the position of any atom is obtained from the position of the whole set, to which is "added" the transformation from the complete set to the sub-set the atom belongs to, and so on until we reach the leaf node representing the atom. Similarly, the atomic motions are superimposed rigid motions.

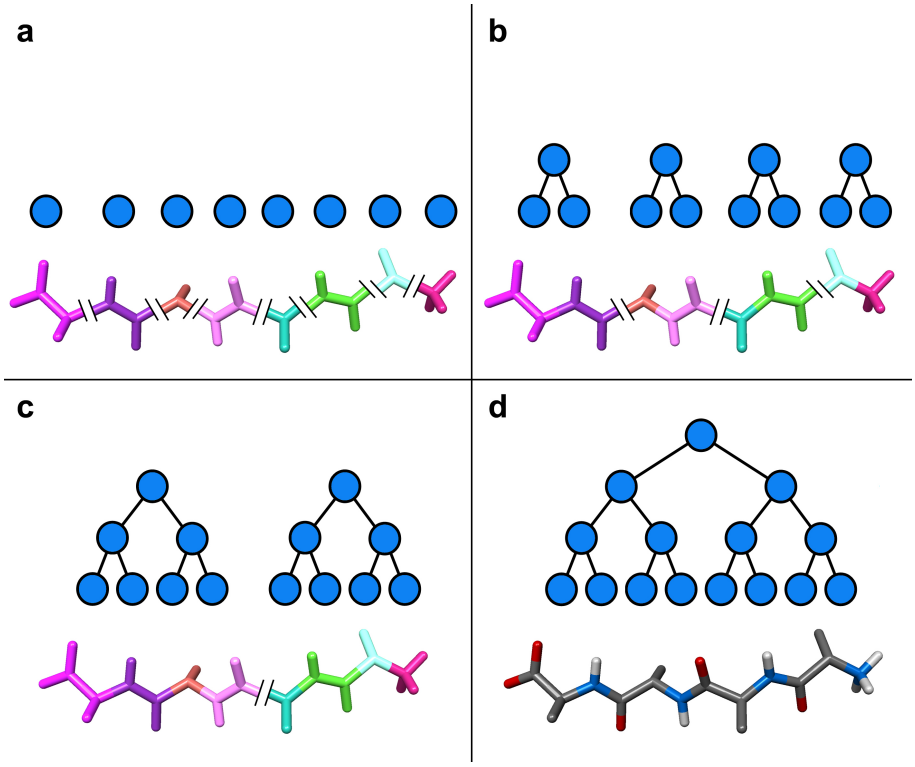

Figure 1. The assembly tree associated to a short polyalanin.

Our adaptive framework relies on two essential components. First, we associate a hierarchical set of reference frames to the assembly tree. Precisely, each node is associated to a local reference frame, in which all dynamical coefficients are expressed. This allows us to avoid updating these coefficients when a sub-assembly moves rigidly. Second, we have demonstrated that it is possible to determine a priori, at each time step, the set of joints which have the largest accelerations. Precisely, when going down the tree to compute joint accelerations, we are able to compute the weighted sum of the (squared) norms of joint accelerations in a sub-assembly C before computing joint accelerations themselves:

$$\mathcal{A}(C) = (\mathbf{f}^C)^T \Psi^C \mathbf{f}^C + (\mathbf{f}^C)^T \mathbf{p}^C + \eta^C, \tag{1}$$

where the right part is a quadratic form of the spatial forces applied on the "handles" of node C. This allows us to cull away those sub-assemblies with (relatively) lower internal accelerations, and focus on the most mobile joints. Thus, at each time step, we can thus predict the set of joints with highest accelerations without computing all accelerations, and we simulate only a sub-tree of the assembly tree (the green nodes in the assembly tree, as in the figure above), based on an user-defined error threshold or computation time constraints. This sub-tree is called the active region, and may change at each time step.

We have exploited these two characteristics - hierarchical coordinate systems and adaptive motion refinement - to develop data structures and algorithms which enable adaptive molecular mechanics. The key observation in our approach is the following: all coefficients which only depend on relative atomic positions do not have to be updated when these relative positions do not change. We can thus store in each node of the assembly tree partial system states which hold information relative only to the node itself.

Precisely, each time step involves the following operations:

1. Adaptive acceleration update
    1. Determination of the acceleration update region: we determine the acceleration update region, i.e. the subset of nodes of the full articulated body which matter the most according to the acceleration metric, as indicated above. The union of the previous active region and the acceleration update region is the transient active region, i.e. the region temporarily considered as the active region.
    2. Joint accelerations projection: the acceleration is projected on the reduced motion space defined by the transient active region (to ensure that joint accelerations are consistent with both motion constraints and applied forces).
2. Adaptive velocity update
    1. Determination of the new active region: we update the joint velocities and the velocity metric values of the nodes in the transient active region. We then determine the set of nodes which are considered to be important according to the velocity metric (which is similar to the acceleration metric). This set becomes the new active region.
    2. Joint velocities projection: if one or more nodes become inactive due to the update of the active region, we determine a set of impulses that we must apply to the transient hybrid body to perform the rigidification of these nodes. This amounts to projecting joint velocities to the reduced motion space defined by the new active region.
3. Adaptive position update
    1. Position update: we update joint positions based on non-zero joint velocities in the active region.
    2. State update: once joint positions have been updated, we update the rest of the system's state: inverse inertias, acceleration metric coefficients, partial neighbor lists, partial force tables, etc.

Again, each of these steps involves a limited sub-tree of the assembly tree, which enables a fine control of the compromise between computation time and precision.

We have showed that our adaptive approach allows for a number of applications, some of which that were not possible for classical methods when using low-end desktop workstations. Indeed, by selecting a sufficiently small number of simultaneously active degrees of freedom, it becomes possible to perform interactive structural modifications of complex molecular systems.

4. Application Domains

4.1. Overview

NANO-D is *a priori* concerned with all applications domains involving atomistic representations, including chemistry, physics, electronics, material science, biology, etc. Historically, though, our first applications have been in biology, as the next two sections detail.

As NANO-D is now expanding into computational methods for quantum chemistry, however, more application domains, with more collaborators, will be studied.

4.2. Structural Biology

Structural biology is a branch of molecular biology, biochemistry, and biophysics concerned with the molecular structure of biological macromolecules, especially proteins and nucleic acids. Structural biology studies how these macromolecules acquire the structures they have, and how alterations in their structures affect their function. The methods that structural biologists use to determine the structure typically involve measurements on vast numbers of identical molecules at the same time, such as X-Ray crystallography, NMR, cryo-electron microscopy, etc. In many cases these methods do not directly provide the structural answer, therefore new combinations of methods and modeling techniques are often required to advance further.

We develop a set of tools that help biologists to model structural features and motifs not resolved experimentally and to understand the function of different structural fragments.

- Symmetry is a frequent structural trait in molecular systems. For example, most of the water-soluble and membrane proteins found in living cells are composed of symmetrical subunits, and nearly all structural proteins form long oligomeric chains of identical subunits. Only a limited number of symmetry groups is allowed in crystallography, and thus, in many cases the native macromolecular conformation is not present on high-resolution X-ray structures. Therefore, to understand the realistic macromolecular packing, modeling techniques are required.
- Many biological experiments are rather costly and time-demanding. For instance, the complexity of mutagenesis experiments grows exponentially with the number of mutations tried simultaneously. In other experiments, many candidates are tried to obtain a desired function. For example, about 250,000 candidates were tested for the recently discovered antibiotic Platensimycin. Therefore, there is a vast need in advance modeling techniques that can predict interactions and foresee the function of new structures.
- Structure of many macromolecules is still unknown. For other complexes, it is known only partially. Thus, software tools and new algorithms are needed by biologists to model missing structural fragments or predict the structure of those molecule, where there is no experimental structural information available.

4.3. Pharmaceutics and Drug Design

Drug design is the inventive process of finding new medications based on the knowledge of the biological target. The drug is most commonly an organic small molecule which activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. In the most basic sense, drug design involves design of small molecules that are complementary in shape and charge to the biomolecular target to which they interact and therefore will bind to it. Drug design frequently relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design.

Structure-based drug design attempts to use the structure of proteins as a basis for designing new ligands by applying accepted principles of molecular recognition. The basic assumption underlying structure-based drug design is that a good ligand molecule should bind tightly to its target. Thus, one of the most important principles for designing or obtaining potential new ligands is to predict the binding affinity of a certain ligand to its target and use it as a criterion for selection.

We develop new methods to estimate the binding affinity using an approximation to the binding free energy. This approximation is assumed to depend on various structural characteristics of a representative set of native complexes with their structure solved to a high resolution. We study and verify different structural characteristics, such as radial distribution functions, and their affect on the binding free energy approximation.

5. Software

5.1. SAMSON

A major objective of NANO-D is to try and integrate a variety of adaptive algorithms into a unified framework. As a result, NANO-D is developing SAMSON (Software for Adaptive Modeling and Simulation Of Nanosystems), a software platform aimed at including all developments from the group, in particular those described below.

The objective is to make SAMSON a generic application for computer-aided design of nanosystems, similar to existing applications for macrosystem prototyping (CATIA, SolidWorks, etc.).

6. New Results

6.1. Algorithms for molecular modeling

6.1.1. Modeling of Molecular Systems With Symmetries

Participants: Sergei Grudinin, Stéphane Redon.

We have developed a method for efficient modeling of macromolecular systems with symmetries. The method is based on a hierarchical representation of the molecular system and a novel fast binary tree-based neighbor list construction algorithm. The method supports all types of molecular symmetry, including crystallographic symmetry.

Testing the proposed neighbor list construction algorithm on a number of different macromolecular systems containing up to about 200,000 of atoms shows that (1) the developed binary tree-based neighbor list construction algorithm scales linearly in the number of atoms for the central subunit, and sublinearly for its replicas, (2) the overall computational overhead of the method for a system with symmetry with respect to the same system without symmetry scales linearly with the cutoff value and does not exceed 50% for all but one tested macromolecules at the cutoff distance of 12 Å, (3) the method may help produce optimized molecular structures that are much closer to experimentally determined structures compared to the optimization without symmetry, (4) the method can be applied to models of macromolecules with still unknown detailed structure.

These results have been *published in the Journal of Computational Chemistry*[3].

6.1.2. Fast construction of assembly trees for molecular graphs

Participants: Svetlana Artemova, Sergei Grudinin, Stéphane Redon.

A number of modeling and simulation algorithms using internal coordinates (e.g. adaptive torsion-angle molecular mechanics) rely on hierarchical representations of molecular systems. Given the potentially complex topologies of molecular systems, though, automatically generating such hierarchical decompositions may be difficult.

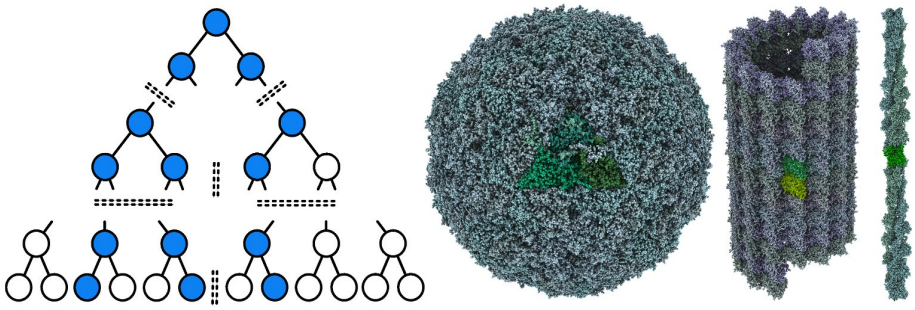

Figure 2. Symmetrical macromolecules modeled with a tree-based approach

We have developed a fast, general algorithm for the complete construction of a hierarchical representation of a molecular system. This two-step algorithm treats the input molecular system as a graph in which vertices represent atoms or pseudo-atoms, and edges represent covalent bonds. The first step contracts all cycles in the input graph. The second step builds an assembly tree from the reduced graph. We analyze the complexity of this algorithm and show that the first step is linear in the number of edges in the input graph, while the second one is linear in the number of edges in the graph without cycles, but dependent on the branching factor of the molecular graph. We demonstrate the performance of our algorithm on a set of specifically tailored difficult cases, as well as on a large subset of molecular graphs extracted from the Protein Data Bank. In particular, we experimentally show that both steps behave linearly in the number of edges in the input graph (the branching factor is fixed for the second step).

These results have been *accepted for publication in the Journal of Computational Chemistry*[1].

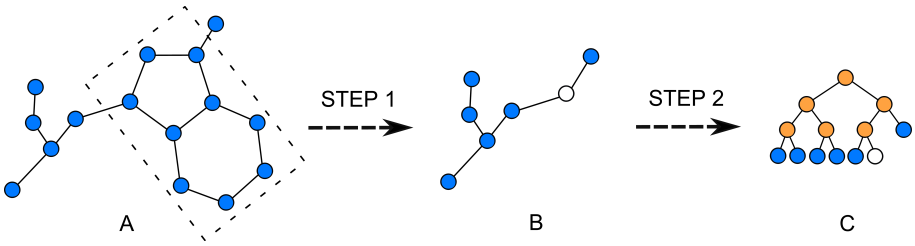

Figure 3. Workflow of the algorithm for construction of an assembly trees for a molecular graph, overview. Step 1 contracts cycles in the input graph, Step 2 builds a tree for a connected component. Blue nodes represent vertices of the input graph and tree nodes, corresponding to them; white nodes stand for group vertices; yellow nodes describe internal nodes of the assembly tree.

6.1.3. Interactive molecular modeling with a reactive potential

Participants: Mael Bosson, Sergei Grudinin, Stéphane Redon.

We have developed an incremental algorithm to update the Brenner potential, i.e. an algorithm able to update only the terms which have changed in the expression of the Brenner potential and forces. Our adaptive algorithm may be integrated into several modeling and simulation methods, for instance we have presented two main applications of our incremental algorithm.

The first one is a modified steepest descent algorithm, which may allow for an important speed up when the energy gradient is non-uniform. However, we have mentioned that the overhead resulting from the incremental update and the marginal cost of a relative motion may make our approach slower than the classical one in some cases. This suggests the need for hybrid minimization algorithms which would be able to switch between the classical and the adaptive approach at runtime based on the distribution of forces in the system.

The second application is the use of the Brenner potential as an efficient guide for digital prototyping of hydrocarbon structures. In the interactive modeler proposed, interactivity is guaranteed by the adaptive minimization algorithm, which focuses the computational resources on the regions that are the most affected by the user actions. Furthermore, when user actions have a local impact, the adaptive approach appears to be an effective way to rapidly reach neighboring energy minima, which helps the user build realistic structures. The results of this methodology are illustrated in Figures 4 and 5.

These results have been *submitted for publication*.

6.1.4. A comparison of neighbor search algorithms for large rigid molecules

Participants: Svetlana Artemova, Sergei Grudinin, Stéphane Redon.

Fast determination of neighboring atoms is an essential step in molecular dynamics simulations or Monte Carlo computations, and there exists a variety of algorithms to efficiently compute neighbor lists. However, most of these algorithms are not specifically designed for a given type of application and, although their average performance is satisfactory, they might be inappropriate in some specific application domains. We have been studying the case of detecting neighbors between large rigid molecules, which has applications in e.g. rigid body docking, Monte Carlo simulations of molecular self-assembly or diffusion, and rigid body molecular dynamics simulation. Precisely, we have compared the traditional grid-based algorithm to a series of hierarchy-based algorithms that use bounding volumes to rapidly eliminate large groups of irrelevant pairs of atoms during the neighbor search. A paper will be submitted shortly.

6.1.5. Divide-and-conquer quantum chemistry

Participants: Mael Bosson, Sergei Grudinin, Stéphane Redon.

A quantum mechanical treatment of molecular interactions is sometimes necessary. This can be the case in many situations encountered in both nano- and bio- applications, including simulating chemical reactions, enzymatic reactions, isomerizations, electron transport in nanotubes, etc. Efficient simulation of quantum mechanical phenomena is thus an essential part of a generic tool for nanosystem design, and designing effective algorithms for quantum mechanics simulation is thus an important component in the overall strategy of the NANO-D group.

To make a first step in this direction, we have designed a divide-and-conquer extended Hückel method. In the extended Hückel method, off-diagonal components of the Hamiltonian matrix are computed using the Wolfsberg-Helmholz approximation:

$$H_{ij} = K\frac{I_i + I_j}{2}S_{ij} \tag{2}$$

where I_i is the ionization energy of the atomic orbital ϕ_i. This efficient scheme provides a good initial guess of the electronic structure but fails at describing the energy of the two bodies long range electrostatic interactions. To be able to compute a more accurate geometry for a molecule by minimizing the energy of the system, Anderson developed the Atom Superposition and Electron Delocalization Molecular Orbital (ASED-MO) method [6].

In this model, two essential characteristics have allowed us to design the divide-and-conquer algorithm. First, the Hamiltonian matrix is sparse for large systems, since overlap integrals may be considered to be zero when atoms are sufficiently far apart. Second, and most important, overlap integrals only depend on relative positions of atoms. As in the Newtonian dynamics case with locally-dependent position-based force fields, we can use this property to incrementally update the Hamiltonian matrix: only off-diagonal blocks corresponding to non-rigid blocks have to be updated.

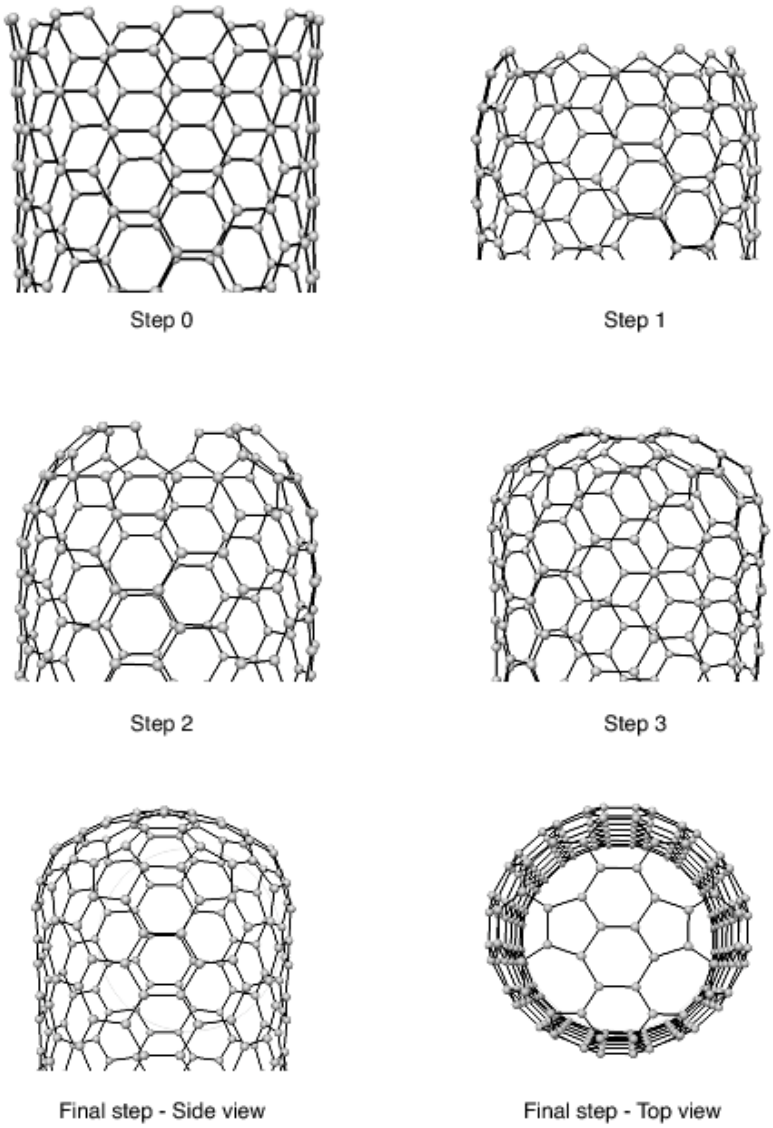

Figure 4. Snapshots of a nanotube capping process with the adaptive interactive modeler. Thanks to the adaptive methodology, this operation can be done in a few minutes.

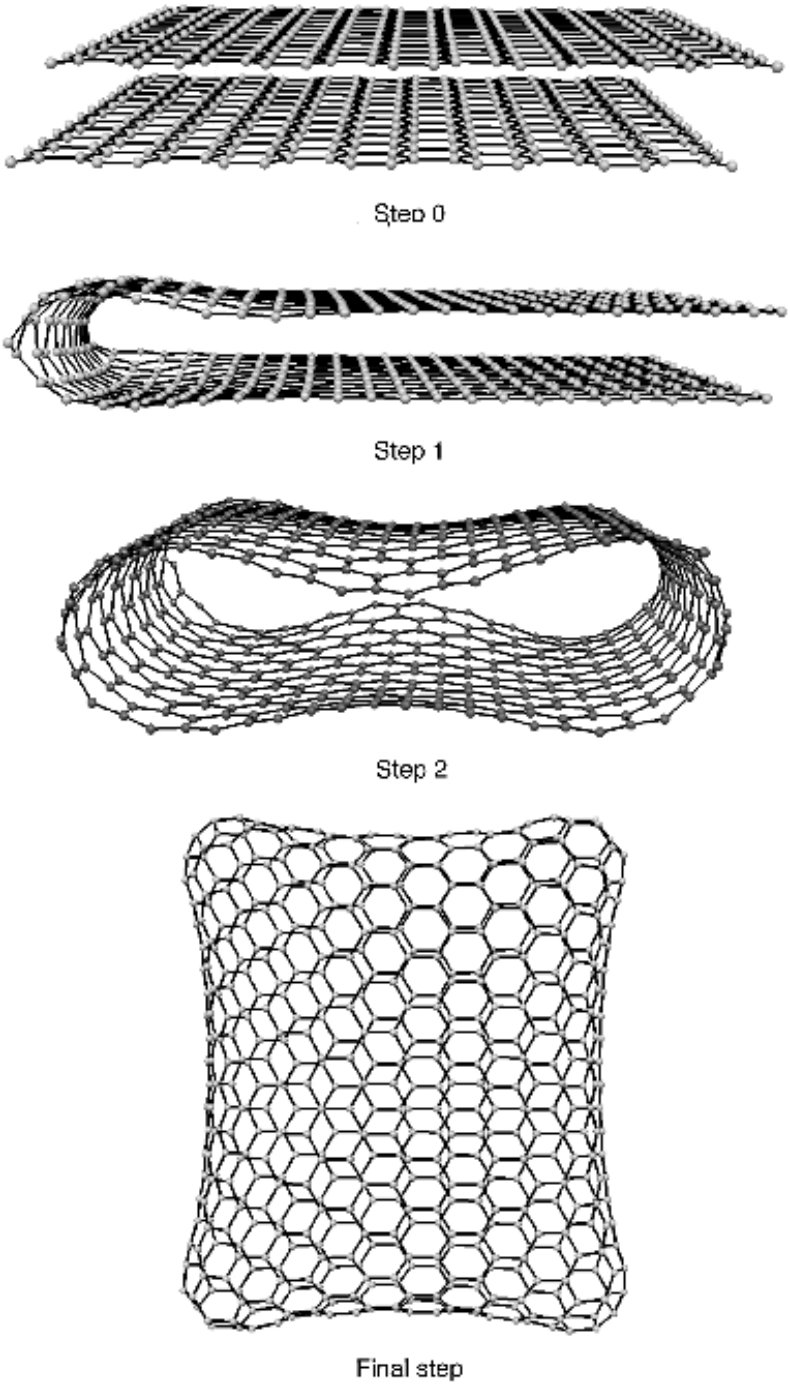

Figure 5. Different steps to prototype a "nano-pillow" with the adaptive interactive modeler.

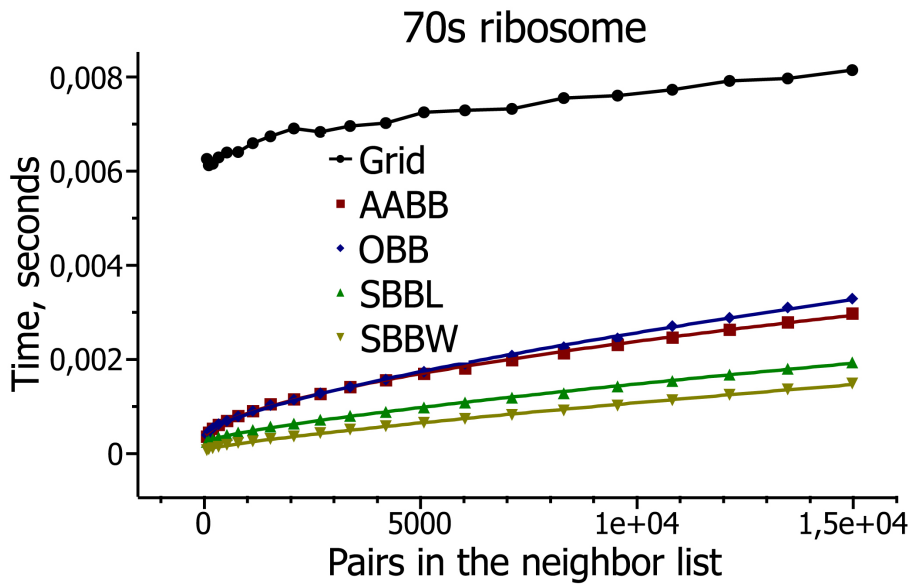

Figure 6. Computational performances of several neighbor-search algorithms as functions of the number of pairs in contact for the 70s ribosome.

Methods to cut the computational cost of the electronic structure calculation is of huge interest because many systems cannot be simulated with the classical approach in a decent time. At a first glance, it seems difficult because even if semi-empirical methods are used to save time for expressing the generalized eigenvalue problem, the complexity is still $O(n^3)$ with the number of basis functions n. The main difficulty comes from the fact that quantum physics is non-local in space. However, in some cases, interesting decay observations of the density matrix suggest some locality property, and that a linear scheme should exist in these cases. As a result, some divide-and-conquer approaches have emerged. The general idea is to split the system in many subsystems, then determine the density matrix for each subsystem and then sum their contributions to get the total density and the energy of the system. Such a method was first developed for DFT (Density Functional Theory) on a grid and then extended to work with a finite set of basis functions and the density matrix [8]. We have implemented this scheme for the semi-empirical ASED model (the resulting electronic structures of the model are illustrated in Figure 7.). The quasi-linear complexity in the size of the system and the parallel implementation enable an important simulation speed-up.

6.1.6. Fast approximate matching of molecular graphs

Participants: Ahmad Shahwan, Sergei Grudinin, Stéphane Redon.

Typically, a molecular *model* involves both a description of the possible *topology* of the molecular system, as well as possible *interactions* between parts of the molecular system (in terms of potential energies and forces). In order to apply a model to a nanosystem, it must thus be ensured that the topology of the nanosystem is compatible with the one prescribed by the model. For example, some models might choose to explicitly include all hydrogen atoms, while other models will completely remove hydrogen atoms in the geometric description of the molecule. These *coarser* models will implicitly include the effects of missing hydrogens on other atoms by modifying the types of other atoms (e.g. the molecule in the coarser description will contain "CH3 pseudo-atoms" which represent a carbon atom attached to a three hydrogen atoms by a single particle), as well as modifying the potential energy function.

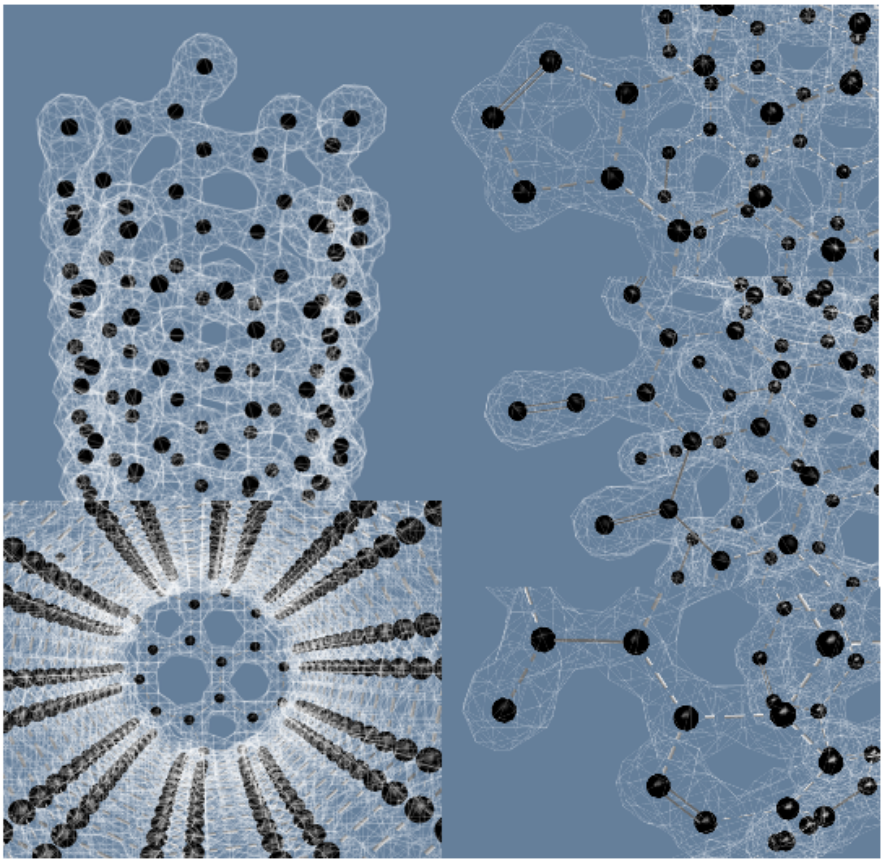

Figure 7. ***Electronic density from the ASED model illustrations***

In general, because the topology of a nanosystem might have been arbitrarily defined by the user, or might come from a predefined system (e.g. the Protein Data Bank, an online repository of protein structures), there must exist a method to automatically convert a molecular topology to another one. In particular, there must exist a method to convert a "raw" model to a model that may be simulated. To do this, the first task is to *detect* which parts of the raw model correspond to patterns of a simulation-ready model.

We have thus developed an algorithm to perform "pattern matching" of molecular graphs. In this algorithm, the input is a raw molecular graph and a simulation-ready model (e.g. the CHARMM19 model specifies that an alanine amino-acid should contain six pseudo-atoms). The output of the algorithm is a list probabilities that a given atom belongs to a specific pattern in a simulation model.

Figure 8 shows an example of an imaginary nano-train data graph being matched against different patterns: the railway engine, the coal trailer, the carriage wagon, and the passengers wagon. Although the coal trailer matches carriage wagon and passengers wagon perfectly, as it is an exact subgraph of both, the passenger wagon and carriage wagon patterns are prior to that of coal trailer, as they contain more vertices, thus they had the chance to choose their matches first, leaving only one choice to the coal trailer pattern.

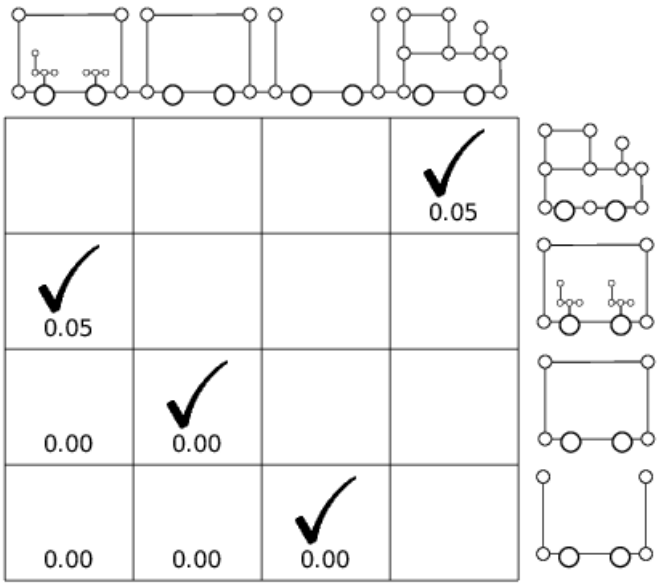

Figure 8. Matching a "nano-train" (top) graph to "train parts" (right). The approximate graph matching algorithm has been used to assign simulation models to raw molecular systems.

This algorithm will be integrated to SAMSON to allow users to easily convert raw molecular systems to systems that may be simulated using a give force-field, as well as to convert in-between models.

6.1.7. Molecular Docking

Participants: Sergei Grudinin, Georgiy Derevyanko.

In the field of molecular modeling, docking is a method which predicts the preferred location of one molecule with respect to the second when bound to each other to form a stable complex. Knowledge of the preferred location in turn may be used to predict the strength of association or binding affinity between two molecules

using for example scoring functions. These predicted quantities are further used in experimental studies to produce stable molecular complexes or to block trans-membrane ion channels.

Recently, molecular docking has made a big progress. There are currently several algorithms that produce high quality predictions of molecular complexes. In order to assess the quality of different predictions, CAPRI, The Critical Assessment of Prediction of Interactions, has been established.

We developed a set of knowledge-based scoring function, along with several structure refinement algorithms. Since then we have participated in the CAPRI competition Round 23 for structure prediction and structure refinement.

6.2. Interactive molecular modeling with haptic feedback

6.2.1. Force control

Participants: Aude Bolopion, Barthelemy Cagneau, Stephane Regnier, Stéphane Redon.

In collaboration with ISIR in Paris, we have proposed and analyzed *force control* to connect a molecular simulator (SAMSON) to a haptic device. Most of the works dealing with this kind of simulators use position control to manipulate the molecule, with major concerns of stability. Force control is compared to position control in terms of adequacy with the molecular simulator. Stability with respect to the scaling coefficients introduced to connect the macro and the nanoworlds is also considered. It is demonstrated by theoretical results and confirmed by the experiment carried out that position control is sensitive to the gain tuning. Force control enables to get stable force feedback for varying gains, and is thus a promising coupling to perform manipulations on complex molecular systems. Thanks to the accuracy of the simulator used, haptic feedback greatly improves the users understanding of molecular interactions. Figure 9 shows the structure of the force control coupling method. This result has been published in the proceedings of the IEEE/ASME International Conference on Advanced Intelligent Mechatronics[5].

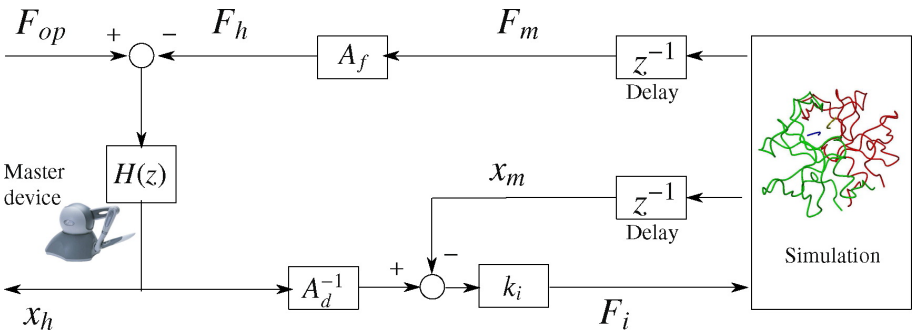

Figure 9. The structure of the force control coupling.

6.2.2. Comparing position and force control for haptic feedback

Participants: Aude Bolopion, Barthelemy Cagneau, Stephane Regnier, Stéphane Redon.

We have performed an extensive comparison of position and force control for the analysis of new molecular structures using haptic feedback. Precisely, we have compared the two control modes in terms of adequacy with molecular dynamics, transparency, and stability sensitivity with respect to environmental conditions. Several experiments have highlighted the usability of the tool for different steps of the analysis of molecular structures, including the global reconfiguration of a molecular system, measurement of molecular properties, and the understanding of nanoscale interactions. Compared to most existing systems, the one developed in this

paper offers a wide range of possible experiments. Figure 10 compares the haptic force rendered to the user depending on the coupling mode that has been chosen. Force control allows for a more stable haptic feedback. This result has been published in the Journal of Molecular Graphics and Modelling[2].

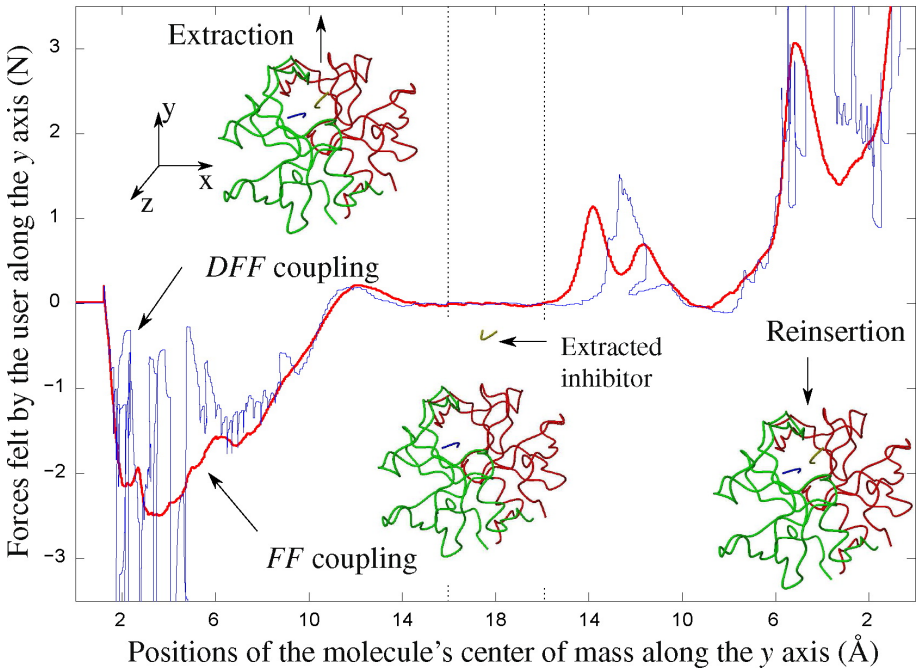

Figure 10. Comparison of position (DFF) and force control (FF) when the user extracts an inhibitor of the HIV protease. Force control is smoother and more stable than position control.

6.3. Software engineering

6.3.1. SAMSON's architecture

Participants: Evelyne Altariba, Stéphane Redon.

We have been developing SAMSON over the past months, and the current architecture is visible in Figure 11. The code is organized into four main parts: a) the Base (in which "Core" contains, in particular, the heart of the adaptive algorithms: signaling mechanisms specifically designed for SAMSON), b) the Software Development Kit (SDK: a subset of the base that will be provided to module developers), c) Modules, and d) the SAMSON application itself.

Similar to the concept of Mathematica *toolboxes*, for example, the goal has been to make it possible to personalize the user interface of SAMSON for potentially many distinct applications. For example, we may want to personalize the interface of SAMSON for crystallography, drug design, protein folding, electronics, material science, nano-engineering, etc., by loading different modules at startup, depending on the user application domain.

6.3.2. Graphical User Interface design

Participants: Noelle le Delliou, Jocelyn Gate, Stéphane Redon.

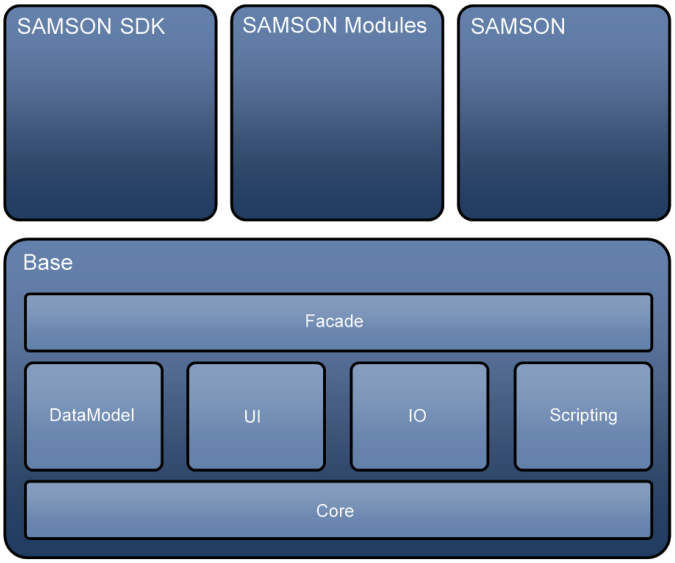

Figure 11. SAMSON's architecture.

As discussed above, an objective of the NANO-D team is to develop SAMSON (Software for Adaptive Modeling and Simulation of Nanosystems), a generic application for nanosystem analysis and design. As any CAD application, SAMSON has to have a Graphical User Interface (GUI), which includes menus, icons, windows, etc., as well as interfaces that are specific to the application domain, e.g. building and editing complex molecular systems, visualizing the results of computations (e.g. electronic densities, etc.).

We have chosen to develop a specific GUI style for SAMSON using Qt, a multiplatform GUI building library. The current interface already integrates several widgets:

- The menu widget
- The title bar widget
- Personalized windows
- Personalized window groups
- A Dock Area to contain windows and window groups
- An OpenGL viewport
- The tool box widget

Figure 12 represents a custom SAMSON window. As can be seen, each window contains a central widget, a title bar, rounded corners, custom buttons which appear with an animation when the user's mouse enters the title bar.

Qt's animation framework has allowed us to include specific animated behaviors. For example, when a user minimizes or maximizes a window, the change is continuous. Moreover, when the window is closed, there is an effect on the shadow (which decreases) and on the opacity (which reaches zero), then the window is hidden. All of these particularities help give SAMSON its own style.

Because the architecture of SAMSON will be open, and developers will be able to add modules to it (e.g. structural models, visual models, computational tools, etc.), an important goal is to design a simple and effective API that will allow developers to effortlessly add interfaces to their modules. In particular, we have designed the GUI so that SAMSON modules automatically get the SAMSON GUI style.

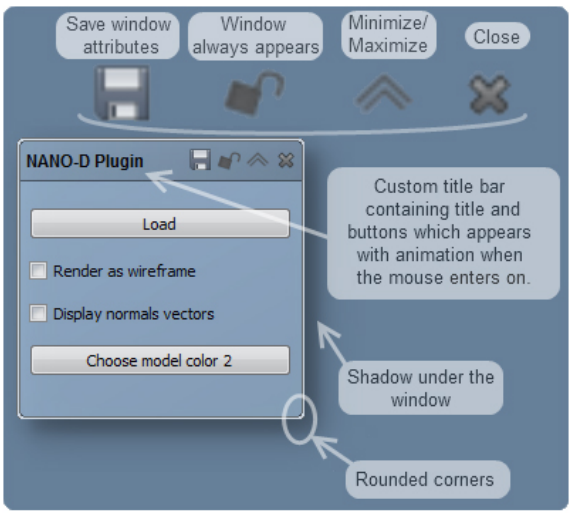

Figure 12. SAMSON's GUI style

6.4. Applications

Methods and tools developed in our group have been used in the following studies:

6.4.1. Role of HAMP domain region of sensory rhodopsin transducers in signal transduction

Participant: Sergei Grudinin.

Archaea are able to sense light via the complexes of sensory rhodopsins I and II and their corresponding chemoreceptor-like transducers HtrI and HtrII. Though generation of the signal has been studied in detail, mechanism of its propagation to the cytoplasm remains obscured. The cytoplasmic part of the transducer consists of adaptation and kinase activity modulating regions, connected to transmembrane helices via two HAMP (Histidine kinases, Adenylyl cyclases, Methyl binding proteins, Phosphatases) domains. The inter-HAMP region of Natronomonas pharaonis HtrII (NpHtrII) was found to be alpha- helical [7]. In [4] we studied the inter-HAMP regions of NpHtrII and other phototactic signal transducers by means of molecular modeling and dynamics. Their structure is found to be a bistable asymmetric coiled coil, in which the protomers are longitudinally shifted for about 1.3 Å. Free energy penalty for the symmetric structure is estimated to be 1.2-1.5 kcal/mol depending on the molarity of the solvent. Both flanking HAMP domains are mechanistically coupled to the inter-HAMP region, and are also asymmetric. The longitudinal shift in the inter-HAMP region is coupled with the in-plane displacement of the cytoplasmic part by 8.6 Årelative to the transmembrane part. The established properties suggest that 1) the signal may be transduced through the inter-HAMP domain switching; 2) the inter-HAMP region may enable cytoplasmic parts of the transducers to come close enough to form oligomers.

6.4.2. Crystal Packing of NpSRII/NpHtrII Complex in Different Spacegroups

Participant: Sergei Grudinin.

The question of the signal transduction through the HAMP domain still remains open [9]. Thus, it would be very beneficial to obtain the structure of the junction between the transmembrane part of the transducer and the HAMP domain. Unfortunately, the HAMP domain is not observed in the crystal structures from different spacegroups, though it is present in the construct used for crystallization. To analyze possible reasons for that, we modeled the HAMP domain at the position, where it could be present in NpHtrII, assuming that the NpHtrII

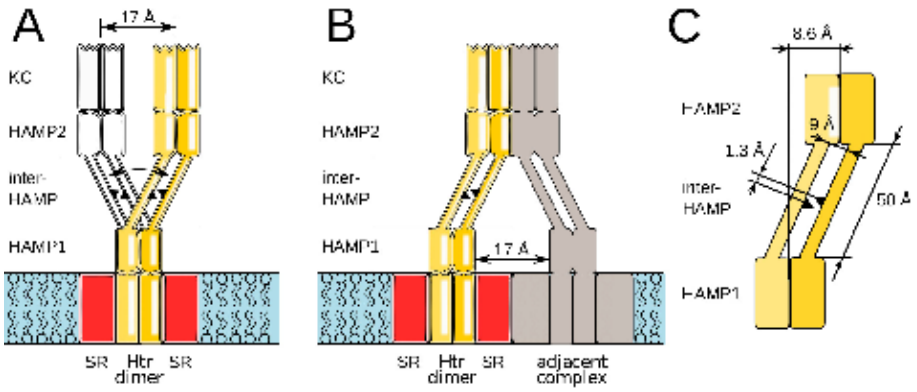

Figure 13. Proposed role of the HAMP domain region

HAMP domain has the same folding as observed for other HAMP domains and that the HAMP domain is connected to the transmembrane helices via a helical linker. In order to deeper understand the influence of the crystal packing of the NpHtrII structure, we performed the modeling in two different spacegroups.

From our modeling studies we concluded that the proposed folding of the HAMP domain is not allowed in the P212121 space group because of steric clashes between two subsequent crystal layers. Interestingly enough, the proposed folding seems feasible in the I212121 spacegroup, as there is sufficient room between two subsequent crystal layers to accommodate the folded HAMP domain. This spacegroup allows the HAMP domain to preserve the proposed folding throughout the whole sequence of the HAMP domain except two regions.

6.4.3. Mechanism of Signal Transduction in Sensory Rhodopsin and Bacteriorhodopsin

Participant: Sergei Grudinin.

Sensory rhodopsin II from Natronobacterium pharaonis is a photosensitive membrane protein. In complex with its cognate transducer NpHtrII it mediates phototaxis of archea, allowing them to avoid UV-light. In the absence of the transducer NpSRII function switches to proton pumping. It is striking that single A215T mutation of the proton pump bacteriorhodopsin (bR) is sufficient to convey bR the ability to generate photophobic signal. The molecular mechanisms of such functional interconversion are still unknown.

We modeled the A215T mutation in bacteriorhodopsin and based on the modeling studies proposed a mechanism of signal transduction from the receptor to the bound transducer.

6.5. National Initiatives

NANO-D is currently receiving funding from three ANR programs:

- **ANR JCJC**: 340,000 Euros over three years (2011-2014). This grant has been provided by the French Research Agency for being a finalist in the ERC Starting Grant 2009 call, and is for two PhD students and an engineer.
- **ANR COSINUS**: 85,000 Euros over three years (2009-2011). This project, coordinated by NANO-D, gathers physicists, biologists and computer scientists from five research groups: Xavier Bouju and Christian Joachim at CEMES, Martin J. Field at IBS, Serge Crouzy at CEA/LCBM, Thierry Deutsch and Frederic Lançon at CEA/SP2M (total grant: 380,000 Euros for five partners over three years - an average of 25,000 Euros per partner, per year).

- **ANR PIRIBio**: 25,000 Euros over four years (2010-2013). We are participating in this project coordinated by Michel Vivaudou at IBS, with Serge Crouzy at CEA/LCBM and Frank Fieschi at IBS.

7. Dissemination

7.1. Animation of the scientific community

7.1.1. Program Committees

Stéphane Redon was a member of the following program committees:

- Workshop on the Algorithmic Foundations of Robotics (WAFR 2010)
- ACM Solid and Physical Modeling Symposium 2010 (SPM 2010)
- Robotics: Science and Systems 2010 (RSS 2010)
- Computer Animation and Social Agents 2010 (CASA 2010)

7.1.2. ANR Reviews

Stéphane Redon was a reviewer for the French National Research Agency (ANR) in the following programs:

- ANR Blanc (2010)
- ANR CONTINT (2010)

7.1.3. Popular Science

Mael Bosson, Svetlana Artemova and Stéphane Redon participated to the "Fete de la Science 2010" (booth "Comment simuler l'infiniment petit").

7.2. Participation to conferences, seminars

- S. Grudinin gave a talk "Computer Modeling of Proteins for Fundamental Studies and Drug Design" at the International School on Modern Fundamental, Medical and Biotechnological Aspects of the Biological Membranes, Moscow, 3-7 October 2010
- S. Redon gave a talk "Adaptive Algorithms for Modeling and Simulating Nanosystems" at RTRA Nanosciences in Grenoble, November 4, 2010.
- S. Redon gave a talk "Manipuler l'infiniment petit" in "Lycée du Grésivaudan", March 18, 2010.
- S. Redon gave a talk "Towards adaptive simulation of molecular systems" in Rice University, February 25, 2010.
- M. Bosson, S. Grudinin and S. Redon attended the CEA-EDF-INRIA School "Simulation of hybrid dynamical systems and applications to molecular dynamics".

7.3. Teaching

- UJF, Grenoble, France: M. Bosson, Basic Linear Algebra, 30h
- ENSIMAG, INPG, Grenoble, France: M. Bosson, Analysis (Lebesgue's theory, Fourier transform, distribution theory) (36h), Advanced Numerical Methods (12h)
- INRIA Grenoble, France: M. Bosson, Mobinet, 6h
- MIPT, Moscow, Russia: S. Grudinin, "Modeling and Simulations of Macromolecules", 10h (May 17 - 31 2010)
- Ecole Polytechnique, Paris, France: S. Redon, INF311 and INF321, 80h

- MOSIG, Grenoble, France: S. Redon, “Introduction to rigid, articulated and molecular dynamics”, 6h

8. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journal

[1] S. ARTEMOVA, S. GRUDININ, S. REDON. *Fast construction of assembly trees for molecular graphs*, in "Journal of Computational Chemistry", 2011, To appear in 2011.

[2] A. BOLOPION, B. CAGNEAU, S. REDON, S. RÉGNIER. *Comparing position and force control for interactive molecular simulators with haptic feedback*, in "Journal of Molecular Graphics and Modelling", 2010, vol. 29, n^{o} 2, p. 280 - 289 [*DOI :* DOI: 10.1016/J.JMGM.2010.06.003], http://dx.doi.org/10.1016/j.jmgm.2010.06.003.

[3] S. GRUDININ, S. REDON. *Practical modeling of molecular systems with symmetries*, in "Journal of Computational Chemistry", 2010, vol. 31, n^{o} 9, p. 1799-1814.

[4] I. GUSCHIN, I. GORDELIY, S. GRUDININ. *Role of the HAMP domain region of sensory rhodopsin transducers in signal transduction*, in "Biochemistry", 2011, To appear in 2011.

International Peer-Reviewed Conference/Proceedings

[5] A. BOLOPION, B. CAGNEAU, S. REDON, S. RÉGNIER. *Haptic molecular simulation based on force control*, in "IEEE/ASME International Conference on Advanced Intelligent Mechatronics", 2010.

References in notes

[6] A. B. ANDERSON. *Electron density distribution functions and the ASED-MO theory*, in "International Journal of Quantum Chemistry", 1994, vol. 49, n^{o} 5, 581589.

[7] K. HAYASHI, Y. SUDO, J. JEE, M. MISHIMA, H. HARA, N. KAMO, C. KOJIMA. *Structural Analysis of the Phototactic Transducer Protein HtrII Linker Region from Natronomonas pharaonis*, in "Biochemistry", 2007, vol. 46, n^{o} 50, p. 14380-14390.

[8] T. S. LEE, J. P. LEWIS, W. YANG. *Linear-scaling quantum mechanical calculations of biological molecules: The divide-and-conquer approach*, in "Computational Materials Science", 1998, vol. 12, n^{o} 3, 259277.

[9] J. PARKINSON. *Signaling Mechanisms of HAMP Domains in Chemoreceptors and Sensor Kinases*, in "Annu. Rev. Microbiol", 2010, vol. 64, p. 101- 22.