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Activity Report 2014

Project-Team NANO-D

Algorithms for Modeling and Simulation of
Nanosystems

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Numerical schemes and simulations

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Project-Team NANO-D

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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. The nanoscience revolution is already impacting numerous fields, including electronics and semiconductors, textiles, energy, food, drug delivery, chemicals, materials, the automotive industry, aerospace and defense, medical devices and therapeutics, medical diagnostics, etc. According to some estimates, the world market for nanotechnology-related products and services will reach one trillion dollars by 2015. Nano-engineering groups are multiplying throughout the world, both in academia and in the industry: in the USA, the MIT has a “NanoEngineering” research group, Sandia National Laboratories created a “National Institute for Nano Engineering”, to name a few; China founded a “National Center for Nano Engineering” in 2003, etc. Europe is also a significant force in public funding of nanoscience and nanotechnology.

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.

2.2. Research axes

The goal of the NANO-D group is to help current and future designers of *nanosystems*, i.e. systems studied or designed at the atomic scale (whether natural or artificial, independently of the application domain, including structural biology, material science, chemistry, etc.) by developing the **foundations of a software application which will run on a desktop computer, and will allow for efficient analysis, design, modeling and simulation of nanosystems**.

To achieve this, we will be developing a series of **adaptive methods and algorithms** that allow users to focus computational resources on the parts of the models that they want to simulate, and that allow to finely trade between speed and precision.

In parallel, we will develop the architecture of a new desktop application for virtual prototyping of nanosystems, and will integrate all our algorithms into this application. Furthermore, the architecture of this platform will be open, so that independent developers may add modules, for **multiple application domains** (physics, biology, chemistry, materials, electronics, etc.). With this open platform, we will attempt to federate the research performed in computational nanoscience throughout the world.

This application is called **SAMSON: “Software for Adaptive Modeling and Simulation Of Nanosystems”**.

Our two research axes are:

1. Developing adaptive algorithms for simulating nanosystems

- **Defining adaptive Hamiltonians:** In order to be able to perform simulations with good mathematical properties, we are expanding on our recent work on *adaptively restrained Hamiltonians*[15], i.e. modified Hamiltonian representations of molecular systems that are able to switch degrees of freedom on and off during a simulation. These will allow us to finely trade between precision and computational performance, by choosing arbitrarily the number of degrees of freedom. Even though we have already obtained some promising results in this domain, our goal is to develop several different simplification methods.

- **Developing algorithms for incremental potential update:** In order to benefit from performing adaptive particle simulations, we need to develop a series of algorithms that will take advantage of the fact that some (potentially relative) atomic positions are frozen. We have already demonstrated how this is possible for torsion-angle quasi-static simulation of classical bio-molecular force-fields [22], for neighbor search between large rigid molecules [14], and for bond-order reactive force-fields [17]. We are developing new algorithms for incremental neighbor search, energy and force updates corresponding to the adaptive Hamiltonians that we are defining.

2. Developing algorithms for modeling molecular interactions

- **Developing knowledge-driven methods, potentials and algorithms:** Over time, more and more experimental information becomes available. One can use this information to predict and discover new types of molecular interactions and various mechanisms or molecular organization. For example, currently there are more than 50,000 protein structures of a high resolution stored in the Protein Data Bank [16] and over 500,000 structures of small molecules stored in the Cambridge Structural Database [13]. We are developing algorithms for protein-protein interactions and protein-ligand interactions.
- **Developing parametrization algorithms for interaction potentials:** Molecular models typically require their own potential energy function (or a *forcefield*) to be assigned. However, the development of a new potential function is a very difficult and sometimes challenging task [18]. Therefore, we are developing algorithms for automatic parametrization of new potential functions for some particular representations of a molecular system.
- **Developing algorithms for exhaustive sampling:** Some application domains, such as computational docking, cryo-EM rigid-body fitting, etc., require sampling in a low-dimensional space. For such applications it is advantageous to perform an exhaustive search rather than accelerated sampling [20]. Therefore, we are developing fast search methods to perform exhaustive search.

3. Application Domains

3.1. 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. Thanks to the development of algorithms to efficiently simulate reactive force fields, as well as to perform interactive quantum mechanical calculations, however, we now have the possibility to address problems in chemistry, and physics.

3.2. 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.

3.3. Pharmaceuticals 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.

3.4. Nano-engineering

The magazine Science has recently featured a paper demonstrating an example of DNA nanotechnology, where DNA strands are stacked together through programmable self-assembly. In February 2007, the cover of Nature Nanotechnology showed a “nano-wheel” composed of a few atoms only. Several nanosystems have already been demonstrated, including a wheelbarrow molecule, a nano-car and a Morse molecule, etc. Typically, these nanosystems are designed in part *via* quantum mechanics calculations, such as the semi-empirical ASE+ calculation technique.

Of course, not all small systems that currently fall under the label “nano” have mechanical, electronic, optical properties similar to the examples given above. Furthermore, current construction capabilities lack behind some of the theoretical designs which have been proposed. However, the trend is clearly for adding more and more functionality to nanosystems. While designing nanosystems is still very much an art mostly performed by physicists, chemists and biologists in labs throughout the world, there is absolutely no doubt that fundamental engineering practices will progressively emerge, and that these practices will be turned into quantitative rules

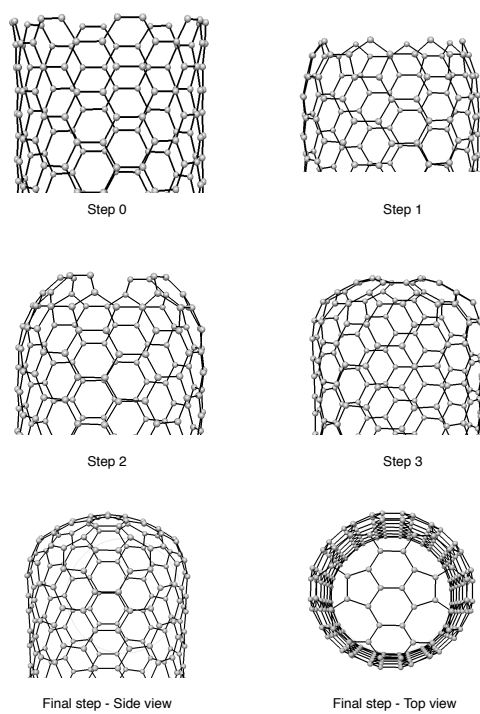


Figure 1. Snapshots of a nanotube capping process with the adaptive interactive modeler. Thanks to the adaptive methodology, this operation can be done in a few minutes.

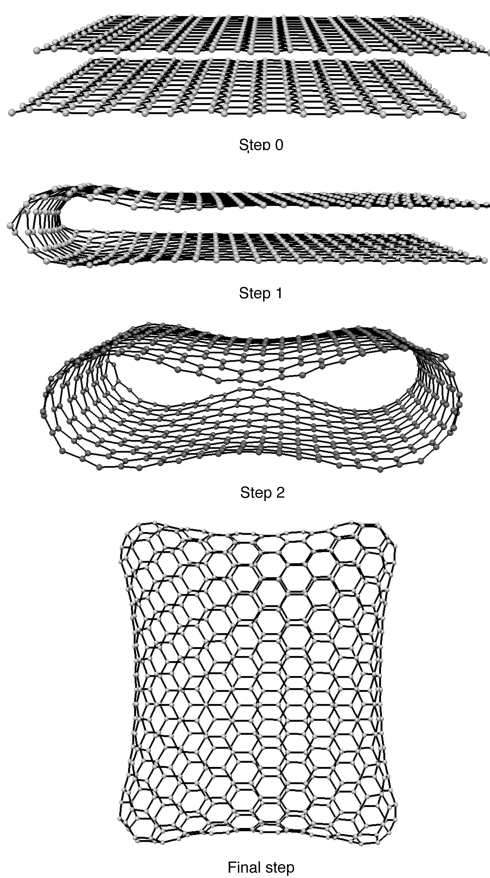


Figure 2. Different steps to prototype a “nano-pillow” with the adaptive interactive modeler.

and methods. Similar to what has happened with macroscopic engineering, powerful and generic software will then be employed to engineer complex nanosystems.

We have recently shown that our incremental and adaptive algorithms allow us to easily edit and model complex shapes, such as a nanotube (Fig. 1) and the “nano-pillow” below (Fig. 2).

4. New Software and Platforms

4.1. SAMSON

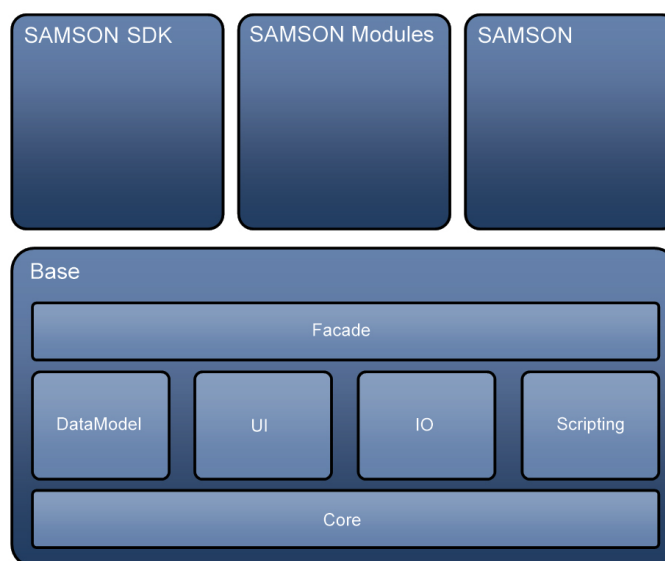


Figure 3. SAMSON's architecture.

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.).

The current architecture of SAMSON is visible in Figure 3. 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.

5. New Results

5.1. Variance Analysis of ARPS-Langevin dynamics

Participants: Zofia Trstanova, Gabriel Stoltz, Stephane Redon.

In order to analyze statistical convergence speed-up that can be achieved by using Adaptively Restrained Particle Simulations (ARPS) dynamics, we proposed a formula that combines the variance of the sampled process and the algorithmic speed-up:

$$S_\sigma = S_A \frac{\sigma_0^2}{\sigma_\epsilon^2} \quad (1)$$

where S_σ is the convergence speed-up, S_A is the algorithmic speed-up, σ_0^2 is the variance of the original system and σ_ϵ^2 is the variance of the ARPS-Langevin system. This led to a need of a detailed analysis of the variance of ARPS-Langevin process. We performed many numerical simulations, from the simple one-dimensional case up to more realistic dimer-solvent models, in order to observe the behavior of the variance and the quantitative dependence on the ARPS coefficients. For the one-dimensional case we managed to compute by using Galerkin approximations the numerical approximation of the variance. We are also studying analytically by use of standard techniques the properties of the ARPS-Langevin dynamics such as the existence of an invariant measure. We are also interested in the relationship between the variance of the Langevin dynamics and the ARPS-Langevin dynamics. We showed that for small ARPS coefficients the ARPS-Langevin process can be seen as a perturbation of a standard Langevin process by a perturbation operator that depends on the ARPS coefficient ϵ .

5.2. Parallel adaptively restrained particle simulations

Participants: Krishna Kant Singh, Stephane Redon.

We have continued our work on the development of *parallel* adaptively restrained particle simulations. We have integrated the ARPS algorithm in LAMMPS (Large-scale Atomic/ Molecular Massively Parallel Simulator). LAMMPS is a computationally efficient simulator, which contains a wide range of potentials and force fields for simulating systems like solid-state materials (metals, semiconductors), soft matter (biomolecules, polymers) and coarse-grained or mesoscopic systems.

In order to verify our implementation of ARPS in LAMMPS, we have generated a trajectory of 1 ns by simulating 108 Argon particles using the ARPS algorithm and the NVE ensemble (constant Number of particles, Volume and Energy). All the particles were placed in an orthogonal box with a side length of 17.158 angstrom. We used periodic boundary conditions with 8.5 angstrom cut-off for the Lennard-Jones potential. We used a threshold $\epsilon_r = 0.0000001$ for applying restraints and a threshold $\epsilon_f = 0.005$ for releasing restraints. The system was simulated at different step sizes: using 0.5, 1, 2, 3, 4, 5, 10, 50, 60, 70, 80 and 90 femtoseconds.

Our results show that ARPS in LAMMPS preserves the total energy during simulation (Figure 4) as well as the radial distribution function (Figure 5). We are now in the process of modifying the parallel force calculation algorithms in LAMMPS to make them incremental, i.e. make their cost proportional to the number of active particles in the simulation at a given time.

5.3. Molecular Modeling

5.3.1. The CARBON method

Participants: Sergei Grudin, Stephane Redon, Petr Popov.

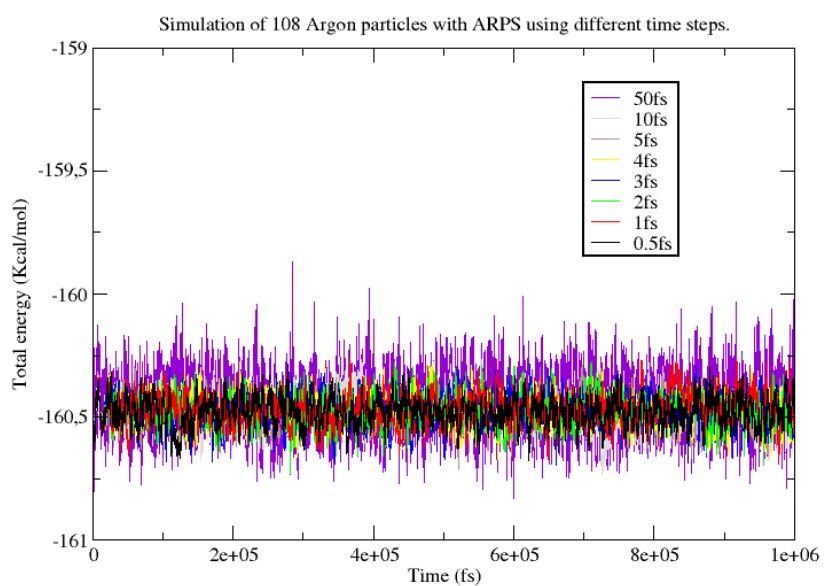


Figure 4. Energy conservation in LAMMPS using ARPS.

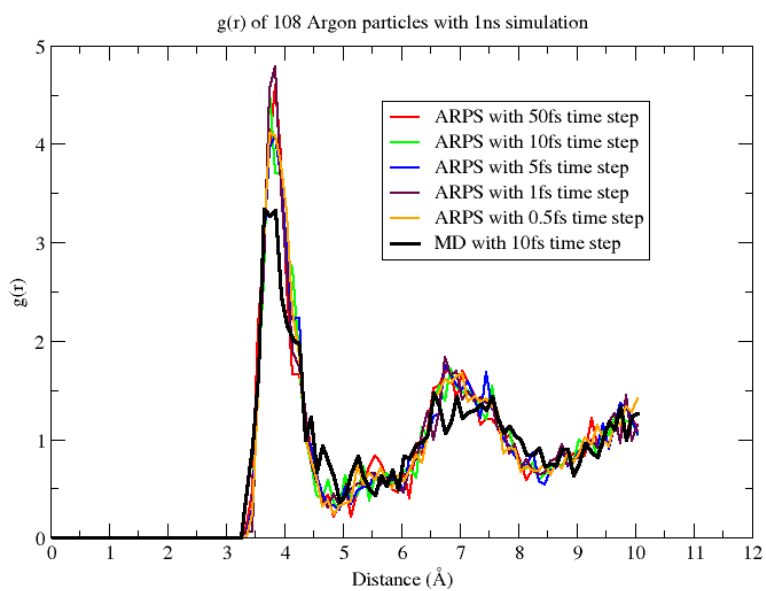


Figure 5. Preservation of the radial distribution function in LAMMPS using ARPS.

In molecular docking, various refinement algorithms are implied either to take into account flexibility of molecular complexes or to get rid of the docking artefacts, e.g. steric clashes. To address the latter problem, one possibility is to continuously minimize the energy of the complex with respect to the affine transformations, i.e. rigid transformations. Petr Popov developed a fast and efficient method called CARBON, where one considers the rigid-body optimization problem as the calculation of quasi-static trajectories of rigid bodies influenced by the inverse-inertia-weighted energy gradient. In order to determine the appropriate step-size in the direction of the net generalized force, we introduce the concept of advancement region, which is the interval of step-sizes that provide movements of the rigid body within a certain range of root mean square deviation from the initial conformation. We tested and validated CARBON on several benchmarks using both a classical force-field and a knowledge-based scoring function and demonstrated that CARBON significantly improves the quality of docking predictions and also remains stable when monomers of a molecular complex significantly overlap. CARBON will be made available as a SAMSON Element for the SAMSON software platform at <http://www.samson-connect.net>.

5.3.2. *The KSENIA method*

Participants: Petr Popov, Sergei Grudinin.

Molecular docking as an integral part of the drug discovery involves the scoring stage, where one selects the best binding candidates from the set of ligand poses. The scoring stage incorporates sophisticated scoring functions based on the empirical force-fields or the information derived from known structures of protein complexes. The latter type of scoring functions belongs to the family of the knowledge-based or statistical scoring functions. Typically, for the training of a knowledge-based scoring function, modern methods require an ensemble of generated non-native decoy structures and a computation of the reference state, which is challenging. Petr Popov developed a method that does not require neither the computation of the reference state nor the ensemble of non-native complexes. Furthermore, the developed approach fully relies on the structures of protein complexes in their native configurations. More precisely, Petr trained the knowledge-based scoring function based on sets of near-native conformations. These are composed using the fluctuations along the direction of low-frequency normal modes computed at the native configurations. The obtained scoring function is capable to distinguish the native and near-native protein-protein interactions from the non-native ones. The robustness of the method was verified on several protein-protein docking benchmarks. Our methodology can be easily adapted to the recognition of other types of molecular interactions, such as protein-ligand, protein-RNA, etc. KSENIA will be made publicly available as a part of the SAMSON software platform at <http://www.samson-connect.net>.

5.3.3. *Optimization solvers*

Participants: Petr Popov, Anatoli Juditsky, Sergei Grudinin.

To derive a knowledge-based scoring function, we map non-native and near-native molecular complexes to the vectors of descriptors in a high-dimensional space. In this space, we formulate an optimization problem to construct the scoring function in such a way, that the projection of a descriptor vector onto the scoring vector corresponds to the score of a molecular complex. The formulated problem contains the regularization term and the penalty term and might vary depending on the method applied to solve the optimization problem. Different methods provide different convergence rates and cost per operation. We implemented several modern first- and second-order optimization techniques and explored which one works the best on the given data. Namely, we tested the standard gradient descent method, the conjugate gradients method, the Nesterov method, the Fista and Fista-descent methods, and the proximal gradient method.

5.3.4. *Novel Docking Criterion*

Participants: Petr Popov, Sergei Grudinin.

Generally, to assess the prediction capabilities of a scoring function for protein- protein interactions, one evaluates the success rate of the scoring function on widely used protein-protein benchmarks. The percentage of correctly predicted complexes is taken as the characteristic of the scoring function. However, all existing benchmarks nowadays consists on many non-native and only few near- native conformations. However, the ability of the scoring function to distinguish a particular near-native conformation from the non-native decoys does not guarantee that the scoring function is able to distinguish another near-native conformation. The same is applied if the scoring function fails on a particular molecular complex. Thus, the success rate is not a robust criterion, since it depends on the near-native and non-native conformations presented in the benchmark. We proposed the new robust method to evaluate the predictive capability of a scoring function, which does not suffer from such drawback. The method uses the probability density function of the score computed from the set of the near-native conformations and complementary empirical distribution function of the score computed from the set on non-native conformations. We tested the criterion on the previously derived scoring functions and showed that the criterion also provides an insight on some limits and restrictions of the atom-atom distant-dependent knowledge-based scoring functions.

5.4. Flexible molecular fitting

Participants: Alexandre Hoffmann, Sergei Grudinin.

We have started a PhD on flexible molecular fitting. The first part of the PhD aims at developing a new method for non-rigid molecular fitting. The problem is the following : We have two proteins \mathcal{P}_1 and \mathcal{P}_2 and we know $d_1 : \mathbb{R}^3 \rightarrow \mathbb{R}$, the electron density of \mathcal{P}_1 and $(Y_k)_{k=0 \dots N_{atoms}-1}$, the average positions of the atoms of \mathcal{P}_2 . Assuming we can generate an artificial electron density $d_2 : \mathbb{R}^3 \rightarrow \mathbb{R}$ from $(Y_k)_{k=0 \dots N_{atoms}-1}$, our problem is to find a transformation of the atoms $T : \mathbb{R}^3 \rightarrow \mathbb{R}^3$ that minimizes the L^2 distance between d_1 and d_2 .

In image processing this problem is usually solved using the optimal transport theory, but this method assumes that both densities have the same L^2 norm, which is not necessarily the case for the fitting problem. To solve this problem, one instead starts by splitting T into a rigid transformation T_{rigid} (which is a combination of translation and rotation) and a flexible transformation $T_{flexible}$. Two classes of methods have been developed to find T_{rigid} :

- the first one uses optimization techniques such as gradient descent, and
- the second one uses Fast Fourier Transform (FFT) to compute the Cross Correlation Function (CCF) of d_1 and d_2 .

We have already developed several algorithms based on the FFT to find T_{rigid} and we now want to develop an efficient algorithm to find $T_{flexible}$.

The majority of algorithms first finds the best T_{rigid} and then use Normal Mode Analysis (NMA) to improve their fitting, the problem with such a method is that one can miss the optimal solution. We aim at developing a method that uses convex optimization to find the best $T_{flexible}$ for each T_{rigid} sampled on a grid, and therefore find the best T possible on a grid.

The rest of the PhD will be focused on the improvement of the modeling of the atom's motion, by using machine learning algorithms and methods that go beyond linear NMA. We hope that such an improvement can improve the quality of the fitting method.

5.5. PEPSI-Dock : Fast predictions of putative docking poses using accurate knowledge-based potentials functions to describe interaction between proteins

Participants: Emilie Neveu, Sergei Grudinin, David Ritchie, Petr Popov.

Many biological tasks involve finding proteins that can act as an inhibitor for a virus or a bacteria, for example. Such task requires knowledge on the structure of the complex to be formed. Protein Data Bank can help but only a small fraction of its proteins are complexes [16]. Therefore, computational docking predictions, being low-cost and easy to perform, are very attractive if they describe accurately the interactions between proteins while being fast to find which conformation will be the most probable. We have been developing a fast and accurate algorithm that combines the FFT-accelerated docking methods with the precise knowledge-based potential functions describing interactions between the atoms in the proteins.

Docking methods can be described as a two ingredients recipe. First, a certain approximation for the binding free energy needed to describe the interactions between the proteins. Second, an efficient sampling algorithm is used to find the lowest-energy conformations. Commonly, as going through all the possibilities with a realistic energy function is very costly, it is approximated with a very simple energy function. Then, a much more precise energy function is typically used to re-score the most promising predictions. Considering the numerous local minima that can be found, it is important to use the most accurate free energy from the beginning not to miss some important docking solutions. In the *Hex* code, an exhaustive search combined with a spherical polar Fourier representation enables the fast exploration of all the conformations. By now it is still the most efficient and reliable search algorithm [21]. However, only a few types of energies have been accelerated using this technic (shape complementarity and electrostatics, for example). Knowledge-based potential functions are much more precise but have been used only at the re-scoring stage of the protein docking predictions pipeline. Thus, our aim is to take advantage of the fast exhaustive search by integrating the very-detailed knowledge-based potentials into the *Hex* exhaustive search method.

We have demonstrated that we can adapt the machine learning process so that the knowledge-based potentials describing atom interactions can be translated into the polynomial basis used in *Hex*. Then, the knowledge-based scores are calculated in *Hex* using the fast polynomial expansions accelerated by the fast Fourier transform. The current evaluations of the knowledge-based scores takes more time than a shape+electrostatic representation but is still fast. More precisely, docking predictions for a single complex takes on average 5-10 minutes on a regular laptop computer. The preliminary results on the data set used for training shows significant improvements in accuracy of the method. Indeed, considering the prediction is correct if its Root Mean Square distance from the true solution is smaller than 5 Å, we currently obtain more than 50% of correct predictions rank first.

5.6. Extended Universal Force Field

Participants: Svetlana Artemova, Leonard Jaillet, Stephane Redon.

In parallel with the implementation of a Universal Force Field module in SAMSON (see Section 5.10.3), we have developed an extension of this force field to allow soft transitions for both topologies and atoms' typizations. In classical UFF topologies and atoms' typizations are set in the initialization phase and remain fixed for the entire simulation. In the proposed extension, they can vary continuously to allow the transition from one given topology to another (see Figure 6). This extended UFF combined with the interaction modeling tools already present in SAMSON allows to interactively build and modify molecules while being driven by UFF forces to ensure the relevance of the corresponding structures. The validity of this extended version of UFF was also tested on the same type of benchmarks as those used to test UFF.

5.7. Incremental Algorithms for Orbital-Free Density Functional Theory

Participants: François Rousse, Stephane Redon.

We have started a new PhD to develop incremental algorithms for electronic structure calculation.

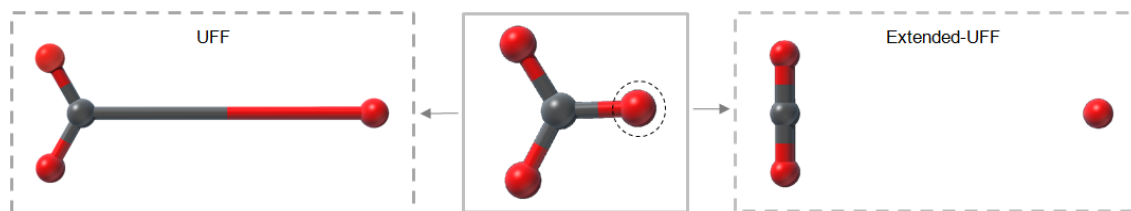


Figure 6. An oxygen atom (dashed circle) of the carbonate ion CO_3^{2-} is displaced using the interactive simulation framework in SAMSON (center). With standard UFF, the topology remains unchanged which leads to unrealistic geometries (left). With extended UFF, the covalent bond is broken forming a Carbon dioxide CO_2 and an isolated Oxygen (right).

Density Functional Theory (DFT) permits to simulate the electronic structure of a molecular system without solving the Schrödinger equation, but by finding incrementally the electronic density that minimizes the system's energy. The most used method is based on the determination of molecular orbitals. It has been shown to be an accurate method but the computation of the energy makes it too slow for the study of big systems ($> 10^3$ atoms) or dynamical ones. The Orbital-Free DFT, although less precise, is faster and can simulate the electronic density of systems up to 10^6 atoms. The aim of the PhD research is to develop new algorithms for Orbital-Free DFT that are *incremental*, i.e. whose complexity depends on the atoms that are adaptively simulated.

5.8. Robotics-inspired methods for large nanosystems

Participants: Minh Khoa Nguyen, Leonard Jaillet, Stephane Redon.

We have started a new PhD to develop robotics-inspired methods for modeling and simulating large nanosystems. Several motion planning methods issued from robotics have been successfully applied to solve problems in the field of biological molecular systems such as, including probabilistic roadmap and rapidly-exploring random trees [12]. However, large systems are still challenging due to the high number of degree of freedom. Our aim is to apply dimensionality reduction methods and/or smart conformational-space exploration techniques inspired from robotics to overcome this difficulty. The PhD topic has started since 1 Oct 2014. Reviews of the state of art and preliminary implementations have been done.

5.9. Incremental algorithms for long-range interactions

Participants: Semeho Edoth, Stephane Redon.

We have started a PhD to develop incremental algorithms for calculating long-range molecular interactions. Numerical simulation of molecular dynamics are very expensive in terms of CPU resources, especially because of the evaluation of the interaction potential. In large crystalline ionic systems, *Ewald summation* is the most popular method for computing Coulombic interactions. It rewrites the interaction potential ϕ as the sum of two terms: $\phi(r) = \phi_{dir}(r) + \phi_{rec}(r)$. The so-called “short-range” contribution ϕ_{dir} can be easily calculated in a direct space, where as the “long-range” contribution ϕ_{rec} is calculated using a Fourier transform.

Direct evaluation of the Ewald summation is an order N^2 computational problem. Over the past three decades, many techniques were developed and reduced the evaluation of the potential to an order $N \log(N)$ problem. We want to develop a new approach that can reduce the computational cost by using incremental algorithms. The key idea is to use, at each time step of the simulation, information that has been computed in previous steps.

5.10. Software development of SAMSON

5.10.1. Development of SAMSON Connect

Participants: Mohamed Yengui, Jocelyn Gate, Stephane Redon.

We have continued the development of SAMSON Connect, the web site that will contribute to the diffusion and promotion of SAMSON and SAMSON Elements (modules for SAMSON).

SAMSON Elements are adapted to different application domain and help users build new models, perform calculations, run interactive or offline simulations, visualize and interpret results, etc. The goal of SAMSON Connect is to bring together a set of users and developers of SAMSON Elements in all areas of nanoscience (physics, biology, chemistry, electronics, etc...). It offers a set of features available depending on the user role:

- Developers (who have obtained the SAMSON-SDK) can develop SAMSON Elements and upload them to SAMSON Connect through the tools provided.
- Users (who have obtained the SAMSON Core application) can add SAMSON Elements to their instance of SAMSON Core in one click. The download process is performed during startup of SAMSON and without outside intervention.

All users can give feedbacks, review and rate SAMSON Elements after adding them to their SAMSON Core (Figure 7).

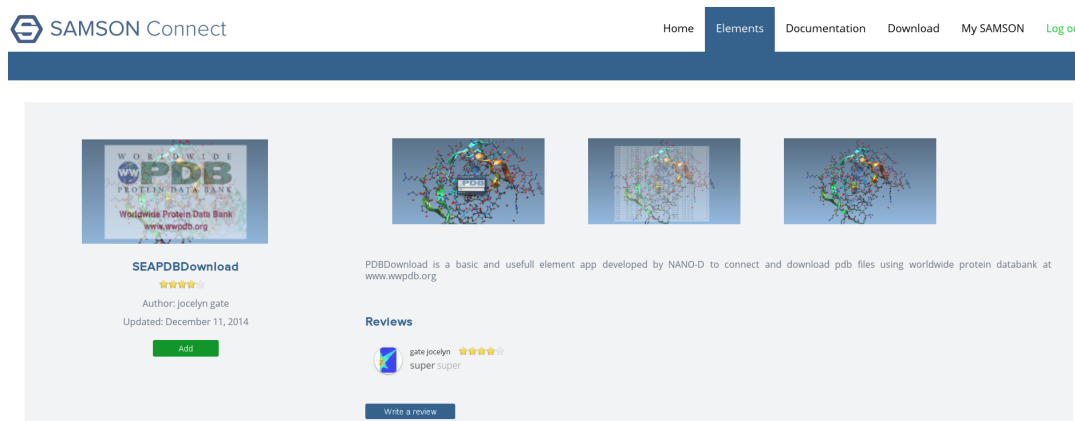


Figure 7. Screenshot of a SAMSON Element on SAMSON Connect.

SAMSON Connect also features some documentation to develop new elements for SAMSON (Figure 8).

SAMSON Connect will be available at <http://samson-connect.net>.

5.10.2. Deployment of SAMSON and the SAMSON SDK

Participants: Jocelyn Gate, Mohamed Yengui, Stephane Redon.

The SAMSON installer has been split in two parts: SAMSON-setup (installation of the SAMSON application, Figure 9) and SAMSON-Developer-setup (installation of the SAMSON SDK). internet. It is very useful to increase security.

Several helper tools related to SAMSON Elements management were developed to facilitate Element deployment. For example, the element packager is a tool useful for developers who want to distribute a new SAMSON Element on the SAMSON Connect platform. With this packager we can control many things: check whether the file is valid, if the SAMSON Element is readable with SAMSON, add a description file that contains useful information (name, author ID, checksum, element version, SDK version, operating system, etc.).

The screenshot shows the SAMSON Connect website. At the top left is the SAMSON Connect logo. To the right are navigation links for Home, Elements, and Documentation. Below the logo is a navigation bar with 'Users' and 'Developers' tabs. Under 'Users', there are links for 'Main Page', 'Related Pages', 'Classes', and 'Files'. The main content area is titled 'SAMSON's Software Development Kit' and is divided into sections: 'Getting Started' (with links for installing SAMSON, Quick Start, The Element Generator, and Tutorials), 'Fundamentals' (with an 'Overview' section containing links for SAMSON's architecture, SAMSON Documents, SAMSON Elements, and Adaptive Modeling and Simulation in SAMSON), 'Key mechanisms' (with links for Signals and slots, Editors, The referencing system, Rendering, and Units), 'Advanced topics' (with a link for Serialization), and 'Reference'.

Figure 8. Screenshot of documentation on SAMSON-Connect.

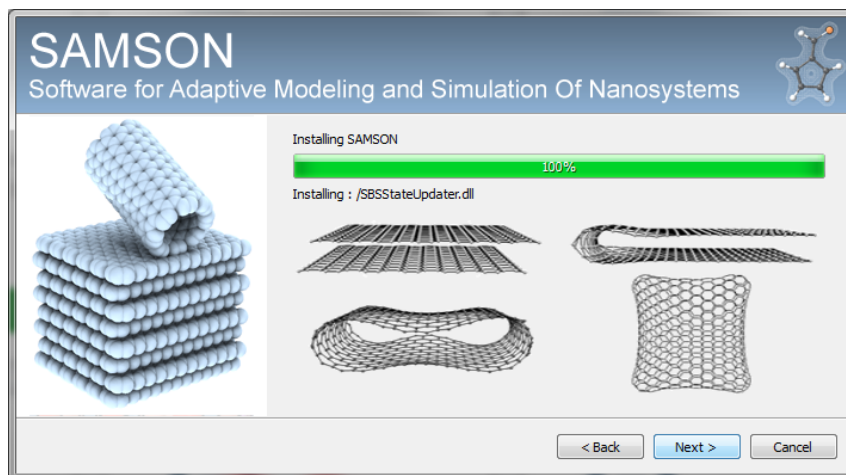


Figure 9. The SAMSON Installer

We added a service requester to SAMSON to communicate with SAMSON Connect and

- Check users/developers status
- Easily download new SAMSON Elements
- Be notified about updates

5.10.3. Universal Force Field

Participants: Svetlana Artemova, Leonard Jaillet, Stephane Redon.

We have implemented a version of the Universal Force Field (UFF) [19] in SAMSON, as a SAMSON Element embedding an interaction model. UFF is a classical force field, which can take as input almost every atom of the periodic table. Such flexibility allows to potentially use UFF on a large spectrum of systems and since its introduction, it has been applied to simulate problems involving main group compounds, organic molecules, metal complexes and has even been recently extended to MOF (Metal Organic Framework) [11]. The general energy expression for UFF as described in [19] is:

$$E_{UFF} = E_R + E_\theta + E_\phi + E_\omega + E_{vdw} + E_{el},$$

where E_R stands for bond stretching, E_θ describes angle bending, E_ϕ is dihedral angle torsion term, E_ω represents inversion, E_{vdw} stands for van der Waals interactions and E_{el} represents electrostatics (this last term is rarely considered for UFF, we do not study it neither). Forces involved in the atoms interactions can then be derived from the previous expression. Each energetic term in UFF can be computed based on simple rules deduced from a set of parameters. This set is based on the atoms' elements, their hybridization, and the overall connectivity of the molecular system.

In our implementation, we took into account several corrections and refinements that have been lately proposed in the literature for Universal Force Field. Our contribution also concerns the development of algorithms to automatically perceive the system's topology (covalent bonds and bond orders assignments). Moreover, we have introduced a method to automatically find the correct typization of the atoms. Precisely, atoms' hybridizations and oxidation states are computed, and resonance groups within or out of cycles are detected and treated. The implementation provided is computationally efficient enough to allow interactive simulation in SAMSON. The validity of the force field was tested on several groups of molecules proposed as benchmarks in the literature.

5.10.4. Integration of existing tools

Participants: Nadhir Abdellatif, Svetlana Artemova, Stephane Redon.

We have obtained funding from the Nanosciences Foundation in Grenoble to integrate in SAMSON some tools developed and used by the Grenoble community, in the form of SAMSON Elements, i.e. modules that integrate into SAMSON and may interact with SAMSON's main data graph. In particular, we have been meeting with some biologists and physicists to determine which tools and methods used (or developed) in Grenoble would be most appropriate for integration.

We integrated our first Element which is Babel, a chemical toolbox designed to "speak the many languages of chemical data", i.e. read, write and convert data files (over 110 chemical file formats) from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas (see <http://openbabel.org>). The corresponding SAMSON element is an *app* that delegates all calculations to the Babel external executable. The app also makes it possible to import the data files to SAMSON to visualize the molecular data and proceed with other SAMSON elements.

We have also integrated Clustal, a tool for multiple sequence alignment. Thanks to Clustal's license, all source code is wrapped into the SAMSON Element (whose source code will be made available as well), and SAMSON users do not need to install Clustal separately.

5.10.5. Various

Participants: Stephane Redon, Svetlana Artemova, Marc Aubert.

- Units management was added to SAMSON. The mechanism relies on C++ template meta-programming techniques to perform dimensional analysis and automatic conversions at compile time, and has no runtime overhead. This was a significant undertaking, but one that will be very helpful to integrate in SAMSON different domains of nanoscience that have come to use different units for identical dimensions (e.g. kilocalories per mole in biology, electron volts in chemistry, etc.).
- SAMSON's reflection mechanism was improved to perform type registration and casting, and facilitate scripting and pipelining of SAMSON Elements.
- SAMSON now handles multiple documents.
- SAMSON has its own file format, which allows it to save the data graph information.
- More data graph nodes are now visible in SAMSON's data graph view.
- The split between classical and quantum interaction models was abandoned, for simplicity.
- SAMSON now handles multiple cameras.
- Selection methods have been improved, and selection is now undoable. Selections may be saved, retrieved, have boolean operations performed onto them, etc.
- The documentation of the SAMSON SDK has been improved.
- Controllers, a new type of data graph nodes, were added to SAMSON. Controllers are used to act on other data graph nodes (e.g. translate and rotate models).
- The object lifecycle of SAMSON was improved.
- SAMSON now has a mechanism for serialization.
- SAMSON now has preferences (e.g. for rendering).
- Existing parsers for input and output of molecular information in SAMSON have been improved and accelerated, and property windows for these parsers have been added.
- The Lennard-Jones potential has been added as an interaction model to SAMSON.
- A new editor for adding atoms corresponding to a chemical formula (in disorder) has been created.
- The work on a new editor containing functional groups and frequently-used molecular patterns has been started.
- Periodic Boundary Conditions (an important concept in molecular simulations) were implemented in SAMSON.
- General code debugging and improvement has been performed
- We decided to use the Qt5 framework for shaders management, for some maintenance reasons especially. This structure implied some other type changes to adapt to Qt5, such as the vertex buffers.
- We changed the way viewports display text. It is now possible to run SAMSON on every platform (Windows, Linux and Mac) and display text, and it provides Elements programmers a simple way to add text where they want in the 3D view.

6. Partnerships and Cooperations

6.1. Regional Initiatives

We have funding from the Rhone-Alpes region through an ARC6 grant for the development of parallel algorithms for adaptively restrained particle simulations. This grant is funding Krishna Kant Singh's PhD project.

6.2. National Initiatives

6.2.1. ANR

In 2014, NANO-D had funding from two ANR programs:

- **ANR Jeunes Chercheurs Jeunes Chercheuses (JCJC)**: 340,000 Euros over three years (2011-2014). This grant has been provided to S. Redon 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 Modeles Numeriques (MN)**: 180,000 Euros over four years (2011-2015). This project, coordinated by NANO-D (S. Grudinin), gathers biologists and computer scientists from three research groups: Dave Ritchie at LORIA, Valentin Gordeliy at IBS (total grant: 360,000 Euros).

6.2.2. PEPS

Sergei Grudinin participates in the Cryo-CA PEPS project. Cryo-CA (Computational algorithms for biomolecular structure determination by cryo-electron microscopy) is a 2-years project, supported by the Projets Exploratoires Pluridisciplinaires (PEPS) program in the panel Bio-Maths-Info provided by CNRS (French National Centre for Scientific Research). The project started on the 01/09/2012. Its main goal is to develop computational algorithms for cryo-electron microscopy (cryo-EM).

The partners of the Cryo-CA project are: Inria Nancy / Team Orpailleur (David Ritchie); Inria Grenoble / Team NANO-D (Sergei Grudinin); and INSERM IGBMC/ Team Integrated structural Biology (Annick Dejaegere, Patrick Schultz, and Benjamin Schwarz).

The main scientific aim of this cross-disciplinary project is to develop computational algorithms to help experimentalists and molecular modelers to solve more rapidly and accurately the structures of macromolecular complexes using cryo-electron microscopy (cryo-EM) and integrative structural biomolecular modeling techniques. More specifically, this PEPS initiative aims to address two important challenges in single particle cryo-EM, namely particle picking and multi-dimensional structure fitting. In the longer term, a further driving aim of this project is to develop strong collaborations amongst the participating teams to position ourselves for a larger project proposal to ANR or ERC.

6.3. European Initiatives

6.3.1. FP7 & H2020 Projects

6.3.1.1. ADAPT

Type: IDEAS

Defi: NC

Instrument: ERC Starting Grant

Objectif: Theory and algorithms for adaptive particle simulation

Duration: September 2012 - August 2017

Coordinator: Stephane Redon

Inria contact: Stephane Redon

6.4. International Initiatives

6.4.1. Inria International Partners

6.4.1.1. Informal International Partners

- We have a collaboration with Boston University on the development of docking algorithms (Dima Kozakov).
- We have a collaboration with ETH Zurich on the development of interactive algorithms for quantum chemistry (Markus Reiher).

6.5. International Research Visitors

6.5.1. Visits of International Scientists

Prof. Dima Kozakov visited the group in 2014. Dima Kozakov is a Research Assistant Professor at Boston University (<http://www.bu.edu/bmerc/people/affiliated-faculty/>). Proteomics revolution provided blue-print of molecular interactions in the cell, however, full mechanistic understanding of how molecules interact comes only from three-dimensional structures. As was shown by Protein Structure Initiative (PSI), it is much more difficult to obtain structures of the protein complexes using high resolution experimental approaches, such as an X-ray or NMR, rather than structures of its individual components. Our groups (at Boston University and Inria / LJK Grenoble) have developed highly efficient protein docking approaches, which were successful in the CAPRI protein docking competition, and thus our next goal is to apply these to genome scale studies. We hope that structural modeling can not only provide potential complex structures, but also clean up uncertainty of the data obtained from high-throughput approaches.

7. Dissemination

7.1. Promoting Scientific Activities

7.1.1. Scientific events selection

7.1.1.1. Reviewer

- Leonard Jaillet was reviewer for the International Conference on Intelligent Robots and Systems (IROS).
- Leonard Jaillet was reviewer for the International Conference on Robotics and Automation (ICRA).
- Stephane Redon was reviewer for the Workshop on Virtual Reality Interaction and Physical Simulation (VRIPHYS).

7.1.2. Journal

7.1.2.1. Reviewer

- Sergei Grudinin was reviewer for the FEBS Journal.
- Sergei Grudinin was reviewer for Proteins: Structure, Function, and Bioinformatics.
- Sergei Grudinin was reviewer for the Journal of Bioinformatics (JBI).
- Leonard Jaillet was reviewer for Transaction on Robotics (T-RO).
- Stephane Redon was reviewer for the Journal of Computational Chemistry (JCC).

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

Licence : Stephane Redon, "Introduction to C++ Programming", INF585, 36h, Ecole Polytechnique, Paris, France

Licence : Stephane Redon, "Algorithms and Programming", INF431, 40h, Ecole Polytechnique, Paris, France

E-learning

Stephane Redon was involved in the creation of a video explaining adaptively restrained particle simulations for Inria's Mooc Lab (direction Jean-Marc Hasenfratz): <https://www.youtube.com/watch?v=RYFSdWy3DcE>.

7.2.2. Supervision

- PhD : Georyy Derevyanko, Algorithmes appliqués aux structures pour l'étude des interactions protéines-protéines, defended on October 15, 2014, advised by Valentin Gordeliy and Sergei Grudin
- PhD : Ivan Gushchin, Etudes structurales des rhodopsines microbiennes et des autres protéines membranaires au moyen de la cristallographie aux rayons X et de la modélisation informatique, defended on September 5, 2014, advised by Valentin Gordeliy and Sergei Grudin
- PhD in progress : Sémého Edoh, advised by Stephane Redon
- PhD in progress : Alexandre Hoffmann, advised by Valérie Perrier and Sergei Grudin
- PhD in progress : Khoa Minh Nguyen, advised by Leonard Jaillet and Stephane Redon
- PhD in progress : Petr Popov, advised by Sergei Grudin, Anatoli Juditsky and Stephane Redon
- PhD in progress : François Rouse, advised by Stephane Redon
- PhD in progress : Krishna Kant Singh, advised by Jean-François Méhaut, Benjamin Bouvier and Stephane Redon
- PhD in progress : Zlatomir Todorov, advised by Michel Vivaudou, Christophe Moreau and Sergei Grudin
- PhD in progress : Zofia Trstanova, advised by Gabriel Stoltz and Stephane Redon

7.2.3. Juries

- Stephane Redon was in the PhD committee of Didier Devaurs (LAAS)
- Stephane Redon was in the PhD committee of Aude Giard (Montpellier University)

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- [10] S. REDON. *Modélisation et simulation adaptatives pour les nanosciences*, in "Modéliser & simuler. Epistémologies et pratiques de la modélisation et de la simulation", F. VARENNE, M. SILBERSTEIN (editors), Éditions Matériologiques, November 2014, vol. 2, <https://hal.inria.fr/hal-01085275>

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