IN PARTNERSHIP WITH:
CNRS

Activity Report 2017

Project-Team NANO-D

Algorithms for Modeling and Simulation of Nanosystems

IN COLLABORATION WITH: Laboratoire Jean Kuntzmann (LJK)

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Numerical schemes and simulations

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Project-Team NANO-D

Creation of the Team: 2008 January 01, updated into Project-Team: 2014 July 01

Keywords:

Computer Science and Digital Science:

A6. - Modeling, simulation and control
A6.2. - Scientific Computing, Numerical Analysis & Optimization
A9.2. - Machine learning

Other Research Topics and Application Domains:

B1. - Life sciences
B1.1. - Biology
B2. - Health
B5.3. - Nanotechnology
B5.5. - Materials

1. Personnel

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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* [23], *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 [72], for neighbor search between large rigid molecules [22], and for bond-order reactive force-fields [27]. 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 [25] and over 500,000 structures of small molecules stored in the Cambridge Structural Database [18]. 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 [48]. 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 [69]. Therefore, we are developing fast search methods to perform exhaustive search.

3. Research Program

3.1. The need for practical design of nanosystems

Computing has long been an essential tool of engineering. 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, for the most part, designed and tested on computers. Digital prototypes have progressively replaced actual ones, and effective computer-aided engineering tools (e.g., CATIA, SolidWorks, T-FLEX CAD, Alibre Design, TopSolid, etc.) have helped cut costs and reduce production cycles of macroscopic systems [71].

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. The magazine Science, for example, recently featured a paper demonstrating an example of DNA nanotechnology, where DNA strands are stacked together through programmable self-assembly [37]. 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 *de-novo* computationally designed protein interface [39], a wheelbarrow molecule [51], a nano-car [76], a Morse molecule [19], etc. Typically, these designs are optimized using semi-empirical quantum mechanics calculations, such as the semi-empirical ASED+ calculation technique [20].

While impressive, these are but two examples of the nanoscience revolution already impacting numerous fields, including electronics and semiconductors [58], textiles [57], [43], energy [61], food [32], drug delivery [41], [78], chemicals [44], materials [33], the automotive industry [17], aerospace and defense [40], medical devices and therapeutics [35], medical diagnostics [82], etc. According to some estimates, the world market for nanotechnology-related products and services will reach one trillion dollars by 2015 [70]. 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 and, in Europe, Grenoble and the Rhone-Alpes area gather numerous institutions and organizations related to nanoscience.

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, such as the planetary gear designed by Eric Drexler at Nanorex. 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 and methods. Similar to what has happened with macroscopic engineering, powerful and generic software will then be employed to engineer complex nanosystems.

3.2. Challenges of practical nanosystem design

As with macrosystems, designing nanosystems will involve modeling and simulation within software applications: modeling, especially structural modeling, will be concerned with the creation of potentially complex chemical structures such as the examples above, using a graphical user interface, parsers, scripts, builders, etc.; simulation will be employed to predict some properties of the constructed models, including mechanical properties, electronic properties, chemical properties, etc.

In general, design may be considered as an "inverse simulation problem". Indeed, designed systems often need to be optimized so that their properties — predicted by simulation — satisfy specific objectives and constraints (e.g. a car should have a low drag coefficient, a drug should have a high affinity and selectivity to a target protein, a nano-wheel should roll when pushed, etc.). Being the main technique employed to predict properties, simulation is essential to the design process. At the nanoscale, simulation is even more important. Indeed, physics significantly constrains atomic structures (e.g. arbitrary inter-atomic distances cannot exist), so that a tentative atomic shape should be checked for plausibility much earlier in the design process (e.g. remove atomic clashes, prevent unrealistic, high-energy configurations, etc.). For nanosystems, thus, efficient simulation algorithms are required both when modeling structures and when predicting systems properties. Precisely, an effective software tool to design nanosystems should (a) allow for interactive physically-based modeling, where all user actions (e.g. displacing atoms, modifying the system's topology, etc.) are automatically followed by a few steps of energy minimization to help the user build plausible structures, even for large number of atoms, and (b) be able to predict systems properties, through a series of increasingly complex simulations.

3.3. Current simulation approaches

Even though the growing need for effective nanosystem design will still increase the demand for simulation, a lot of research has already gone into the development of efficient simulation algorithms. Typically, two approaches are used: (a) increasing the computational resources (use super-computers, computer clusters, grids, develop parallel computing approaches, etc.), or (b) simulating simplified physics and/or models. Even though the first strategy is sometimes favored, it is expensive and, it could be argued, inefficient: only a few supercomputers exist, not everyone is willing to share idle time from their personal computer, etc. Surely, we would see much less creativity in cars, planes, and manufactured objects all around if they had to be designed on one of these scarce super-resources.

The second strategy has received a lot of attention. Typical approaches to speed up molecular mechanics simulation include lattice simulations [84], removing some degrees of freedom (e.g. keeping torsion angles only [56], [77]), coarse-graining [83], [73], [21], [75], multiple time step methods [67], [68], fast multipole methods [36], parallelization [54], averaging [31], multi-scale modeling [29], [26], reactive force fields [28], [87], interactive multiplayer games for predicting protein structures [34], etc. Until recently, quantum mechanics methods, as well as mixed quantum / molecular mechanics methods were still extremely slow. One breakthrough has consisted in the discovery of linear-scaling, divide-and-conquer quantum mechanics methods [85], [86].

Overall, the computational community has already produced a variety of sophisticated simulation packages, for both classical and quantum simulation: ABINIT, AMBER, CHARMM, Desmond, GROMOS and GROMACS, LAMMPS, NAMD, ROSETTA, SIESTA, TINKER, VASP, YASARA, etc. Some of these tools are open source, while some others are available commercially, sometimes via integrating applications: Ascalaph Designer, BOSS, Discovery Studio, Materials Studio, Maestro, MedeA, MOE, NanoEngineer-1, Spartan, etc. Other tools are mostly concerned with visualization, but may sometimes be connected to simulation packages: Avogadro, PyMol, VMD, Zodiac, etc. The nanoHUB network also includes a rich set of tools related to computational nanoscience.

To the best of our knowledge, however, all methods which attempt to speed up dynamics simulations perform a priori simplification assumptions, which might bias the study of the simulated phenomenon. A few recent, interesting approaches have managed to combine several levels of description (e.g. atomistic and coarse-grained) into a single simulation, and have molecules switch between levels during simulation, including the adaptive resolution method [63], [64], [65], [66], the adaptive multiscale method [60], and the adaptive partitioning of the Lagrangian method [46]. Although these approaches have demonstrated some convincing applications, they all suffer from a number of limitations stemming from the fact that they are either ad hoc methods tuned to fix specific problems (e.g. fix density problems in regions where the level of description changes), or mathematically founded methods that necessitate to "calibrate" potentials so that they can be mixed (i.e. all potentials have to agree on a reference point). In general, multi-scale methods, even when they do not allow molecules to switch between levels of detail during simulation, have to solve the problem of rigorously combining multiple levels of description (i.e. preserve statistics, etc.), of assigning appropriate levels to different parts of the simulated system ("simplify as much as possible, but not too much"), and of determining computable mappings between levels of description (especially, adding back detail when going from coarse-grained descriptions to fine-grained descriptions).

3.4. Research axes

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4. New Software and Platforms

4.1. SAMSON

Software for Adaptive Modeling and Simulation Of Nanosystems

KEYWORDS: Structural Biology - Nanosystems - Simulation - Bioinformatics - Chemistry
SCIENTIFIC DESCRIPTION: Please refer to https://www.samson-connect.net
FUNCTIONAL DESCRIPTION: SAMSON is a software platform for real-time modelling and simulation of natural or artificial nanosystems. 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.).

- Contact: Stéphane Redon
- URL: http://nano-d.inrialpes.fr/software/

4.2. HermiteFit

A new docking algorithm for rapid fitting atomic structures into cryo-EM density maps
FUNCTIONAL DESCRIPTION: HermiteFit is a new docking algorithm for rapid fitting atomic structures into cryo-EM density maps using 3D orthogonal Hermite functions. HermiteFit uses the cross-correlation or the Laplacian-filtered cross-correlation as the fitting criterion. HermiteFit exhaustively rotates the protein density in the Hermite space and then converts the expansion coefficients into the Fourier space for the subsequent fast FFT-based correlation computations.

- Partners: IBS - FZJ Juelich
- Contact: Sergey Grudinin
- URL: https://team.inria.fr/nano-d/software/hermitefit/

4.3. Knodle

KNOwledge-Driven Ligand Extractor
FUNCTIONAL DESCRIPTION: KNOwledge-Driven Ligand Extractor is a software library for the recognition of atomic types, their hybridization states and bond orders in the structures of small molecules. Its prediction model is based on nonlinear Support Vector Machines. The process of bond and atom properties perception is divided into several steps. At the beginning, only information about the coordinates and elements for each atom is available :

Connectivity is recognized. A search of rings is performed to find the Smallest Set of Smallest Rings (SSSR). Atomic hybridizations are predicted by the corresponding SVM model. Bond orders are predicted by the corresponding SVM model. Aromatic cycles are found. Atomic types are set in obedience to the functional groups. Some bonds are reassigned during this stage.

- Partner: MIPT Moscow
- Contact: Sergey Grudinin
- URL: https://team.inria.fr/nano-d/software/Knodle/

4.4. RigidRMSD

A library for rapid computations of the root mean square deviations (RMSDs) corresponding to a set of rigid body transformations of a coordinate vector
FUNCTIONAL DESCRIPTION: RigidRMSD is a library for rapid computations of the root mean square deviations (RMSDs) corresponding to a set of rigid body transformations of a coordinate vector (which can be a molecule in PDB format, for example). Calculation of the RMSD splits into two steps:

Initialization, which is linear in the number of vector entities (or particles in a rigid body). RMSD computation, which is computed in constant time for a single rigid-body spatial transformation (rotation + translation). This step uses the inertia tensor and the the center of mass computed on the first step. Initialization step is performed only once. It makes RigidRMSD particularly useful when computing multiple RMSDs, since each new RMSD calculation takes only constant time.

- Contact: Sergey Grudinin
- URL: https://team.inria.fr/nano-d/software/rigidrmsd/

4.5. DockTrina

A novel protein docking method for modeling the 3D structures of nonsymmetrical triangular trimers
FUNCTIONAL DESCRIPTION: DockTrina is a novel protein docking method for modeling the 3D structures of nonsymmetrical triangular trimers. The method takes as input pair-wise contact predictions from a rigid body docking program. It then scans and scores all possible combinations of pairs of monomers using a very fast root mean square deviation (RMSD) test (see below). Finally, it ranks the predictions using a scoring function which combines triples of pair-wise contact terms and a geometric clash penalty term. The overall approach takes less than 2 min per complex on a modern desktop computer.

- Contact: Sergey Grudinin
- URL: https://team.inria.fr/nano-d/software/docktrina/

5. New Results

5.1. Incremental methods for long range interactions

Participants: Semeho Edorh, Stephane Redon.

Adaptively Restrained Molecular Dynamics (**ARMD**) were recently proposed with the purpose of speeding up molecular simulations. The main idea is to modify the Hamiltonian such that the kinetic energy is set to zero for low velocities, which allows to save computational time since particles do not move and forces need not be updated.

We continued our work on developing an extension of **ARMD** to electrostatic simulations. Therefore, we developed a fast method dedicated to the computation of the electrostatic potential in adaptively restrained systems. The proposed algorithm is derived from a multigrid-based alternative to the popular particle mesh methods. Our algorithm ,labeled as Incremental Mesh Continuum Method (IMCM),was implemented inside LAMMPS, a popular molecular dynamics simulation package. During ARMD simulations, IMCM scales with the number of active particles.

The performance of the new algorithm was accessed on various molecular systems. 1 showed that IMCM is able to outperform the well-established Particle Particle Particle Mesh (P3M) for adaptively restrained simulations. For an aqueous solution of sodium chloride, water molecules can be adaptively restrained. On this system, ARMD was able to reproduce static properties of sodium chloride (2). When a functionalized nanopore is placed at the center of the system, ARMD and IMCM were able to reproduce the ion selectivity property (3). For this benchmark, this positively charged nanopore acts like a sieve that blocks the flux of Sodium atoms, while promoting the crossing of Chlorine particles(4).

5.2. Adaptive Algorithms for Orbital-Free Density Functional Theory

Participants: Francois Rousse, Stephane Redon.

Our Orbital-Free Density Functional Theory (OF-DFT) program has been enriched and improved. Its accuracy has been demonstrated just like in he work of [79] : by comparison with the PROFESS software [47] of energies and relaxed geometries of several aluminium clusters. An incremental version has been developed and tested: it can be tuned smoothly from fast and approximative to slow and precise. We have shown that for cases where few particles positions have changed, like in an adaptively restrained dynamical [23], the update of electronic density is faster with the adaptive version.

A SAMSON App computing electronic energies through Orbital-Free DFT has been released for SAMSON 0.6.0. It is a light version, with only one optimization algorithm and no adaptive version. The parallel implementation is available for most operating systems. Another SAMSON App is being developed to generate the input files of PROFESS, our reference software for OF-DFT.

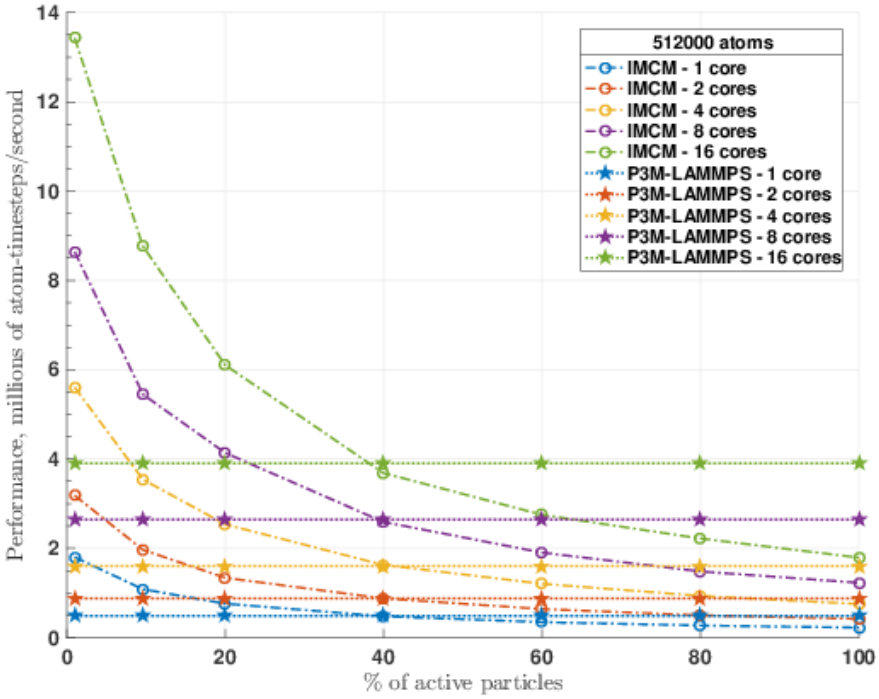

Figure 1. Performance depending on the percentage of active particles for different number of processes. Performance of LAMMPS P3M is shown as a reference (dotted lines, pentagram marker) — it does not depend on the percentage of active particles. In all cases electrostatics were computed at similar accuracy ($\sim 10^{-5}$).

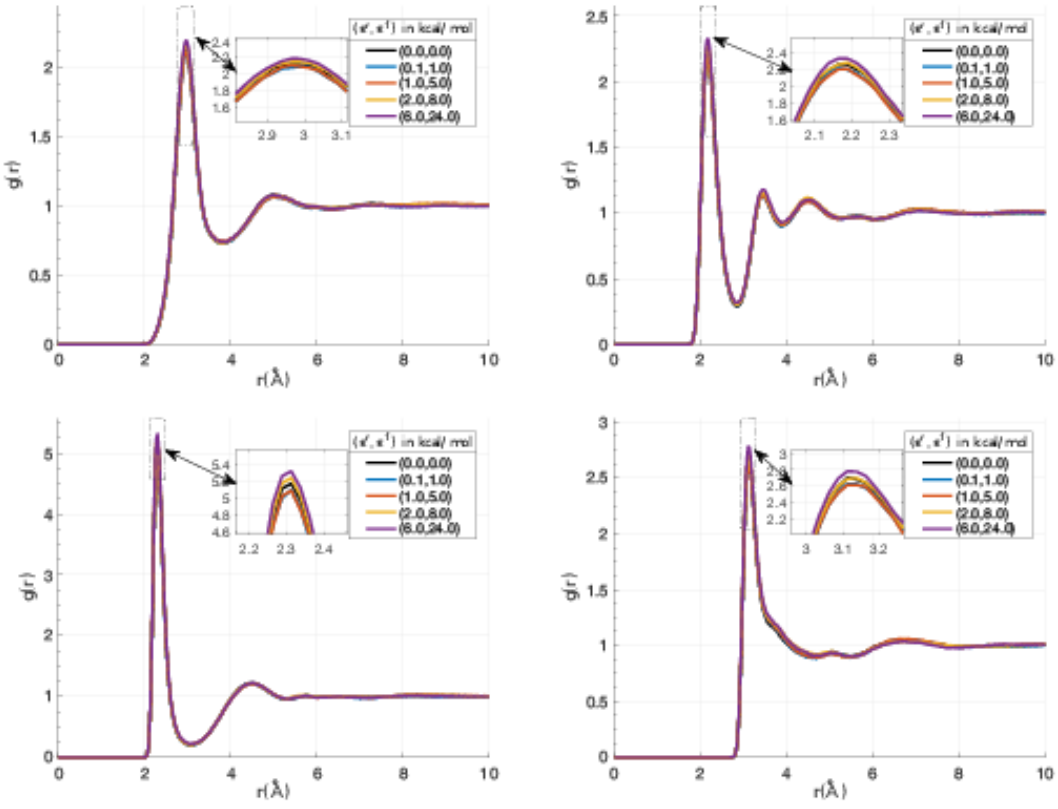

Figure 2. Ion-water pair distribution functions using armd with the NaCl/ϵ force field at 298 K the rigid water model SPC/ϵ and an ionic concentration of 10.0 molal. Different restraining parameters $(\varepsilon^r, \varepsilon^f)$ *were tested on water molecules. Na and Cl are always active. Black line corresponds to a standard molecular dynamics simulation of the system.*

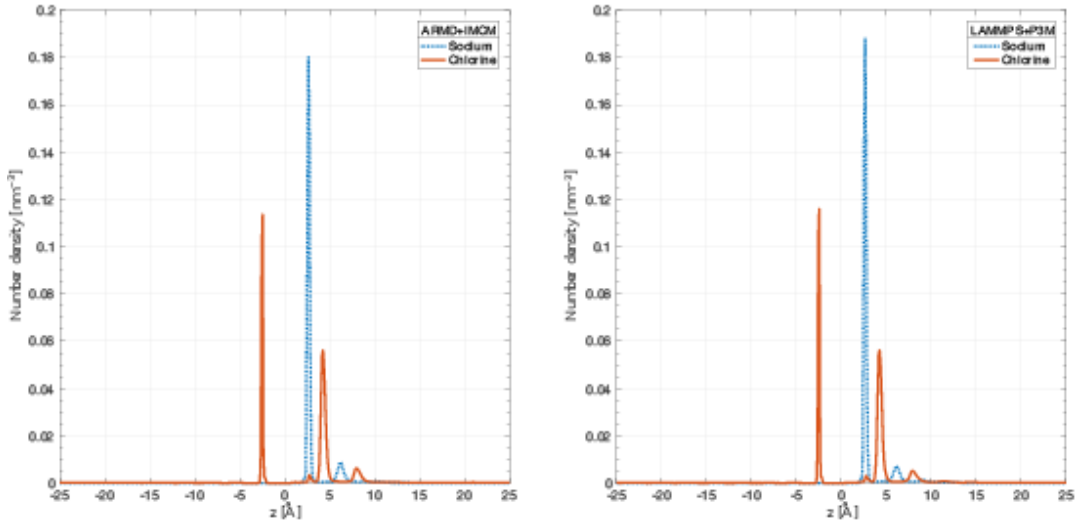

Figure 3. Number density of chlorine (red dotted line) and sodium (blue dashed line) ions along z-axis using standard ARMD (Left) and MD (Right). Both methods show the ion selectivity of the nanopore which is located at $z = 0$.

5.3. As-Rigid-As-Possible molecular interpolation paths

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

We proposed a new method to generate interpolation paths between two given molecular conformations [11]. It relies on the As-Rigid-As- Possible (ARAP) paradigm used in Computer Graphics to manipulate complex meshes while preserving their essential structural characteristics. Experiments conducted on a large set of benchmarks show how such a strategy can efficiently compute relevant interpolation paths with large conformational rearrangements.

5.4. ART-RRT: As-Rigid-As-Possible Exploration of Ligand Unbinding Pathways

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

We proposed a method to efficiently generate approximate ligand unbinding pathways (to appear in the Journal of Computational Chemistry). It combines an efficient tree-based exploration method with a morphing technique from Computer Graphics for dimensionality reduction. This method is computationally cheap and, unlike many existing approaches, does not require a reaction coordinate to guide the search. It can be used for finding pathways with known or unknown directions beforehand. The approach is evaluated on several benchmarks and the obtained solutions are compared with the results from other state-of-the-art approaches. We show that the method is time-efficient and produces pathways in good agreement with other state-of-the-art solutions. These paths can serve as first approximations that can be used, analyzed or improved with more specialized methods.

5.5. IM-UFF: extending the Universal Force Field for interactive molecular modeling

Participants: Jaillet Leonard, Svetlana Artemova, Stephane Redon.

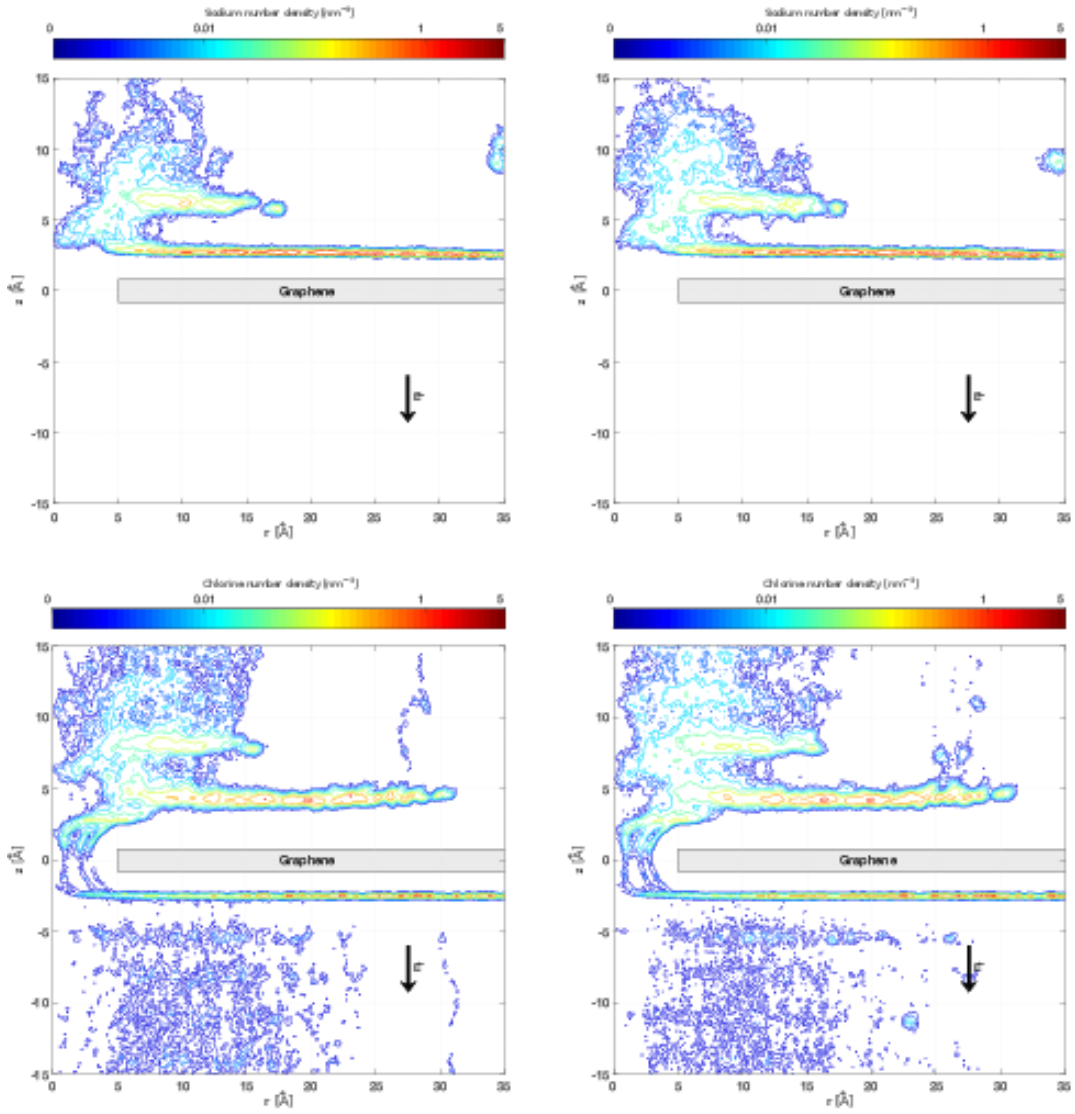

Figure 4. Nonuniform distributions of number density of chlorine (Top) and sodium (Bottom) ions driven by an external electric field (black arrow) $E = 1$ V/A using standard MD (Left) and ARMD (Right). The gray rectangles at $z = 0$ mark the graphene sheet. Both ions form concentration polarization layers.

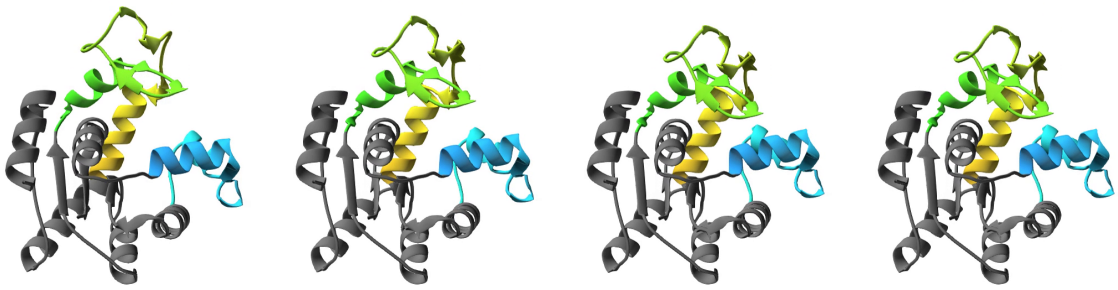

Figure 5. Motion of Adenylate Kinase from "open" to "close" state generated with the ARAP method.

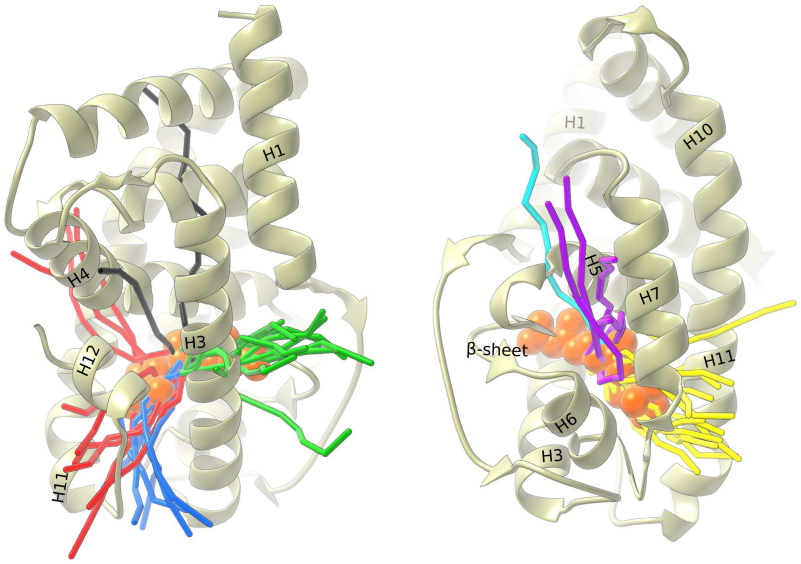

Figure 6. Paths (in colored sticks) obtained by ART-RRT for the unbinding of retinoic acid hormone from its receptor. The protein is represented by ribbons and the ligand by orange balls. Two different views are shown for clarity. The left picture shows pathways I in red, II in blue, III in green and Other in black. The right picture shows pathways IV in yellow, V in purple and VI in cyan. These main pathways are also reported by other studies by the SMD and RAMD methods for nuclear hormone receptors.

IM-UFF, the extension of UFF to interactive modeling was completed. It led to an analysis demonstrating that IM-UFF allows to obtain statistical measures that are normally only accessible to reactive force fields (cf. Figure 7). It resulted in the paper "IM-UFF: extending the Universal Force Field for interactive molecular modeling" published at the Journal of Molecular Graphics and Modelling [7]. IM-UFF will be proposed as a module available to all public in the 0.7.0 version of SAMSON that will be released soon.

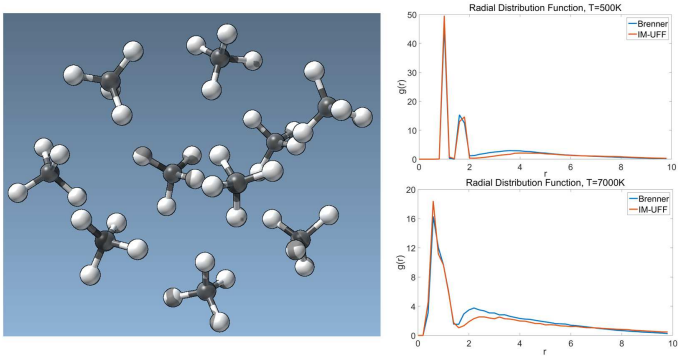

Figure 7. The interaction between 10 methane molecules restrained in a fixed volume is simulated through Monte Carlo simulation (left). The radial distribution functions (RDF) obtained with Brenner (blue curves) are qualitatively the same as those obtained with IM-UFF (red curves), in case of a 500 K temperature setup (top) as well as a 7000 K temperature setup (bottom). It means that, it might be possible to use IM-UFF to obtain statistical measures that are normally only accessible to reactive force fields.

5.6. Exploring Chemical Reaction Paths

Participant: Jaillet Leonard.

5.6.1. Context

In the past, we have developed a methodology to explore chemical reaction paths based on stochastic trees. One difficulty was the assessment of the quality of the paths found, and the comparison with existing state of the art methods.
To address these limitations, we have developed several new modules in SAMSON that propose state of the art methods and helpful tools to find and manipulate the paths and the important states of the considered systems. One can classify these modules into three categories: interpolation methods, minima and saddle point search methods and supporting tools. More details regarding these modules are provided below.

5.6.2. Interpolation methods

We have implemented the artificial force induced reaction (AFIR) method [59], that helps to find a transition path from a given initial state made of two compounds A and B, towards a goal compound X. In the futur, we would like to combine AFIR with our exploration methods.

The Linear Synchronous Transit (LST) and the Quadratic Synchronous Transit (QST) methods [42] have also been integrated in SAMSON. These methods generate paths such that each atom-pair distance in an intermediate structure is the interpolated value between those in the initial and target structures. The QST variant differs of the LST one from that the interpolated path also passes through a third intermediate point. Moreover, we have implemented the MINIMAX method as in [50] that alternates phases of minimization and QST interpolation to search for a transition path. These three methods appear to show a better behavior than a simple linear interpolation approach. In the future, we are also planning to combine them with our exploration methods.

5.6.3. Search for minima and saddle points

We have developed a SAMSON module to describe the energy basins associated to the various conformations of a given set. For this, conformations are first minimized and then clustered. This tool is also convenient when analyzing conformations along a given path to search for the states the closest to the saddle points.

In collaboration with the post doc Clément Betone, we have implemented two modules. First, the Dimer method as proposed in [45]. This method allows to find from a given point the closest saddle points in high dimensional potential surfaces, using only first derivatives. Some works remains to be done to solve the sensibility problem related to the initial orientation of the dimmer. Second, the freezing string method as proposed in [24]. This method searches efficiently for a saddle point between two given end states through a combination of interpolatoin and optimization.

To assess the various methods and obtain a visual feedback of their behavior, we have developed several 2D force fields where the energetical landscape can easily be apprehended. Such an example of landscape is illustrated in Figure 8.

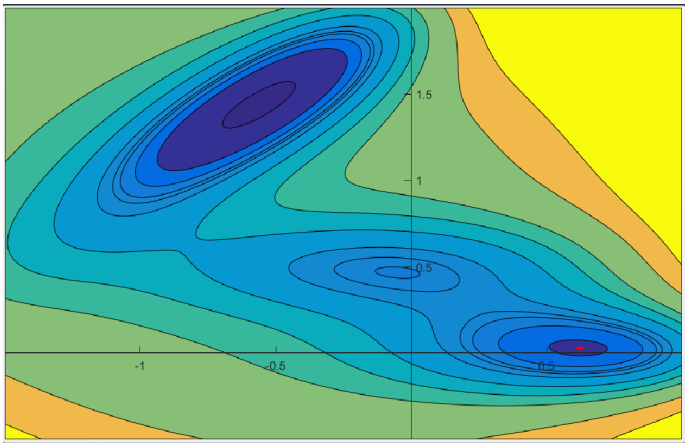

Figure 8. Example of 2D force field used to test the various methods performing force field searches. One can see at the bottom right, the current state represented by a red cross and at a local minimum

5.6.4. Supporting tools

We have proposed in SAMSON a set of tools to manipulate and perform some measures associated to set of conformations, that could potentially represent molecular paths.

A first tool was proposed to perform given measures for a given set of conformations, such as bond lengths, angle bends, or torsion angles. A second tool allows to align various conformations onto a reference on. Finally, another tool allows to compute the RMSD distance between pairs of conformations.

5.7. Combination of force fields

We have proposed in SAMSON several modules related to force fields, that can be used as soft constraints applied to a system. We have proposed a force field that sums up the contributions of two given force fields for a given system. Another force field was developed based on three force fields, where the first one concerns one part of the system, the second one an another part and the last one the interaction between these two parts. We have also added elementary force fields for the standard interactions that may be represented classical force fields: bond springs, angle bend springs, torsion springs, Steric clash and Van der Waals interactions.

5.8. Simulating nanomaterials

We have initiated an informal collaboration with Cyril Guedj, a permanent researcher of the Leti at CEA. This researcher is an expert in nanomaterials and the goal is to develop in SAMSON tools to manipulate, simulate and measure these nanomaterials. We focused in particular in crystals that appears in many new materials such as semiconductors.

So far, we have developed three versions of Keating for simulating crystals: an harmonic Keating force field for elements of type IV based on [55], an harmonic Keating force field extended to elements of type III and V based on [30] and a non-harmonic Keating force field based on [74]. An example of crystal simulated with Keating force field in SAMSON is shown in Figure 9 Currently, we are in a phase of validation of these force fields. Cyril Guedj as experts in nanomaterials is focusing on the calibration of the force field parameters and the comparison with state of the art results. In the future, we plan to extend the functionality of these force fields to address more complex scenarii.

In parallel, we have developed a set of tools to manipulate and measure these crystal: a module to rescale them, one to simplify their visualization, one to measure a set of characteristics, and finally, one to simulate constraints applied to some part of the system.

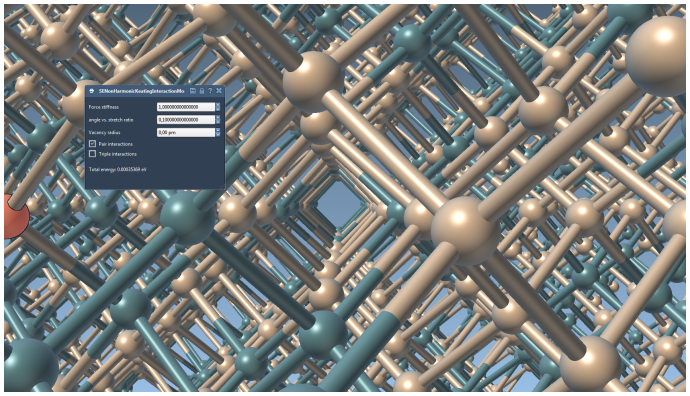

Figure 9. Example of crystal simulated in SAMSON, using one variant of the Keating force field.

5.9. Parallel algorithms for adaptive molecular dynamics simulations

Participants: Dmitriy Marin, Stephane Redon.

We worked on the development and improvement of a parallel implementation of the Adaptively Restrained Molecular Dynamics (ARMD) method in the LAMMPS molecular dynamics simulator. The parallelization was done in application to multi-core CPU and hybrid CPU/GPU systems thanks to the Kokkos package provided by LAMMPS. The ARMD can be used for decreasing computational complexity by restraining degrees of freedom for some particles in the simulated system [23], therefore allowing to gain speed-up by either decreasing precision or focusing on select subsystems. The developed parallel implementation allows us to run LAMMPS with an ARMD integrator on central processing units (CPU), graphics processing units (GPU), and many integrated core architecture (MIC). We developed a new algorithm for processing particles that switches their state from a restrained state to a full-dynamics state and vice versa. The new algorithm is modified for efficient usage of GPU and many-core CPUs (computations are performed on a computational device, communications between host and device are decreased). The results on performance and speed-up for ARMD in comparison with the non-modified LAMMPS for a standard Lennard–Jones liquid benchmark are shown in Figures 10 and 11. We showed that starting from some number of atoms in the system

and from some percentage of restrained atoms, ARMD provides better performance over classical MD. The results are published in [14].

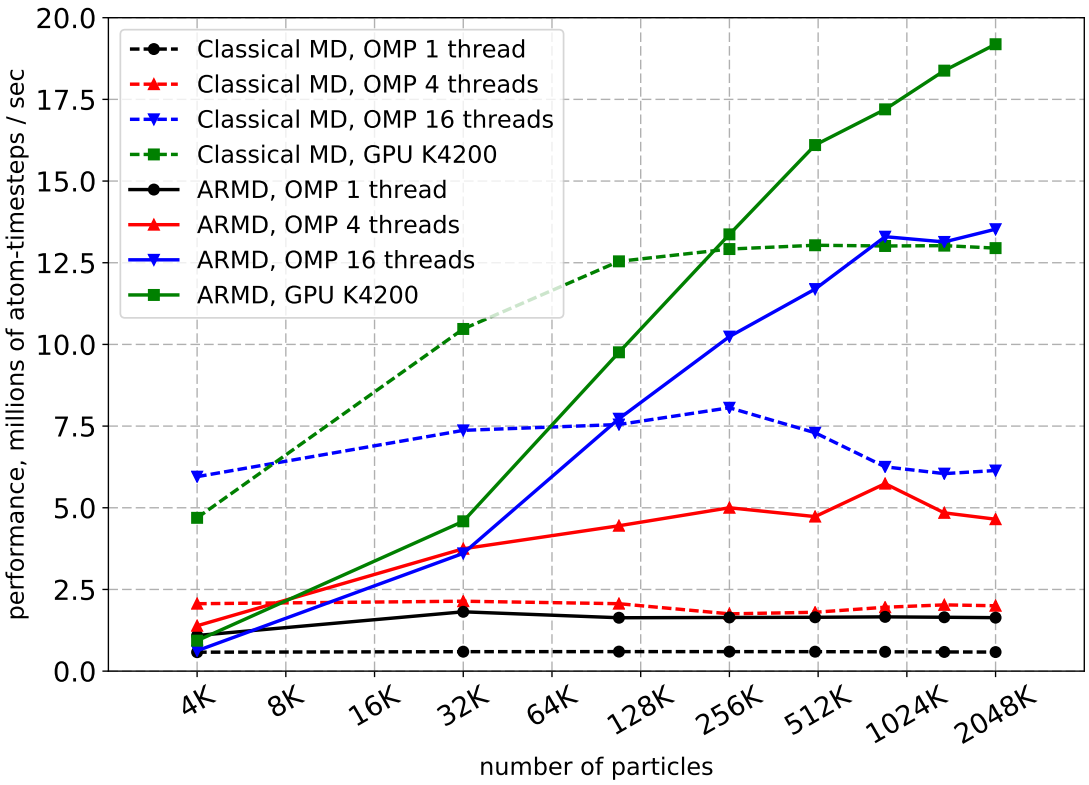

Figure 10. Performance for a system with ARMD parameters: $\varepsilon^r = 4.5$, $\varepsilon^f = 6.5$

5.10. Development of Convex-PL, a scoring function for protein-ligand interactions

Participants: Sergei Grudinin, Maria Kadukova.

We have continued developing Convex-PL, which is a knowledge-based scoring function for protein-ligand interactions. It is based on the assumption that protein-ligand interactions linearly depend on radial distributions of pairs of atoms of various types. The corresponding coefficients are deduced with a convex optimization problem from the structural data. We augmented Convex-PL with a term standing for steric clashes, ran a leave-one-out cross-validation procedure, and additionally validated it on the D3R Grand Challenge 2 user-submitted poses. The corresponding paper [8] was accepted to the Journal of Computer-Aided Molecular Design. We have also presented Convex-PL at two scientific conferences [53], [52].

5.11. Participation in the D3R Grand Challenge 2 with the Convex-PL scoring function

Participants: Sergei Grudinin, Maria Kadukova.

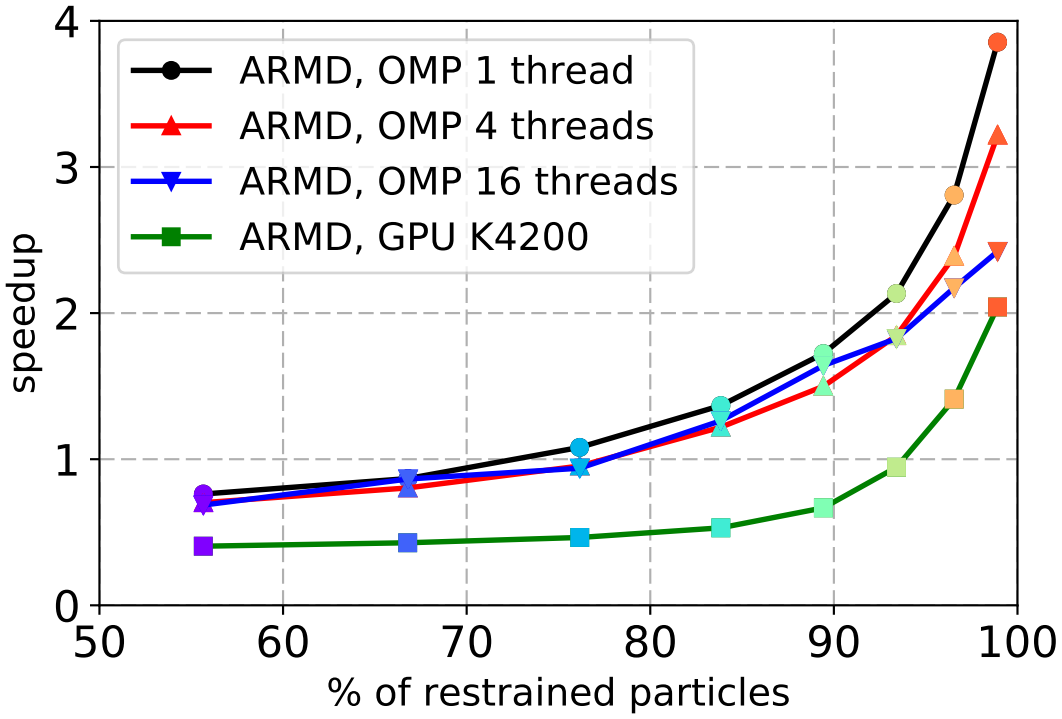

Figure 11. Speed-up for a system with 1 372 000 *atoms*

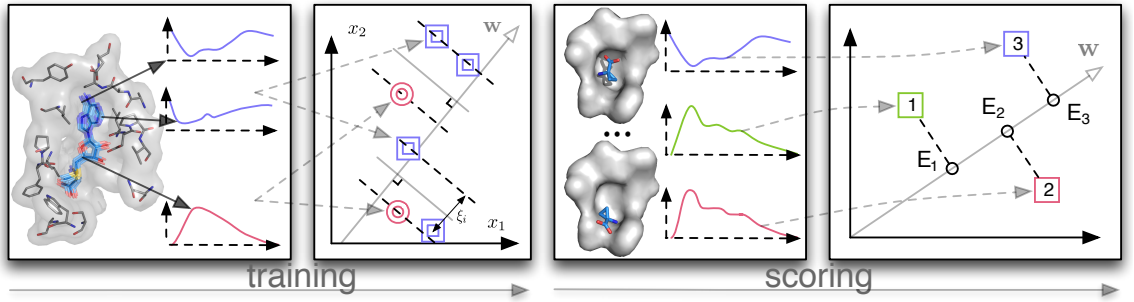

Figure 12.

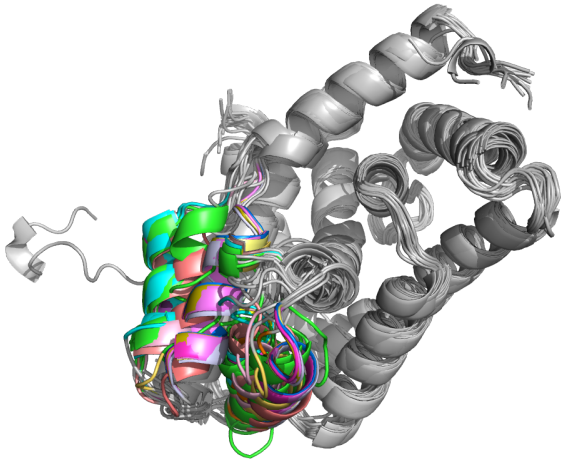

Figure 13. Structural heterogeneity of the target FXR proteins.

We have participated in the pose prediction stage of the D3R Grand Challenge 2 using Convex-PL to re-score the ligand poses obtained with Autodock Vina. The target protein of this challenge was a farnesoid X receptor (FXR). After the correct co-crystal poses were released, we carefully repeated the experiments and compared them with several other docking protocols. For these protocols we have used a modified version of Autodock Vina with Convex-PL as a built-in scoring function used in sampling. The protocols we have tried include comparison of docking to various co-crystal and mutated co-crystal FXR structures, as well as docking to the correct protein structures to evaluate the influence of receptor flexibility and docking of ligand structures generated with two different algorithms, as well as the co-crystal ones. This study was published in the Journal of Computer-Aided Molecular Design. [9]

5.12. Development of a Normal Modes Analysis SAMSON Element

Participants: Yassine Naimi, Alexandre Hoffmann, Sergei Grudinin.

We developed a SAMSON Element based on the method proposed by Alexandre Hoffman and Sergei Grudinin on Linux and Mac operating systems. This SAMSON Element was implemented in two versions, a Lite version and an Advanced version.

The first one (14) computes the nonlinear normal modes of a molecular system (protein, RNA, DNA) very quickly using the NOLB algorithm developed by Alexandre Hoffmann and Sergei Grudinin (J. Chem. Theory Comput., 2017, 13 (5), pp 2123-2134, DOI: 10.1021 / acs.jctc.7b00197.). The user indicates the desired number of modes, the interactions cutoff distance and the potential function. For now, the elastic network model potential is the one that is available but more potential functions, like the Gaussian network model, will be added in the future. In the output, each mode is represented by a slider. The user can visualize the motion of each mode independently by moving its corresponding slider manually or by checking its checkbox and then pressing on the play button. Also, the user can visualize the motion of a combination of modes selecting them before playing the motion.

The transformations used in this motion can be set to linear or nonlinear and the amplitude of the motion can be increased/decreased by changing the scaling factor. During this motion, the user can activate a real time minimization using one of the provided algorithms (steepest descent, conjugated gradient or LBGF) and defined values of minimization steps and minimization tolerance. Finally, the user can either save/export a given conformation of the structure or the entire displayed trajectory by going into the "Save Frames" tabulation of the SAMSON element.

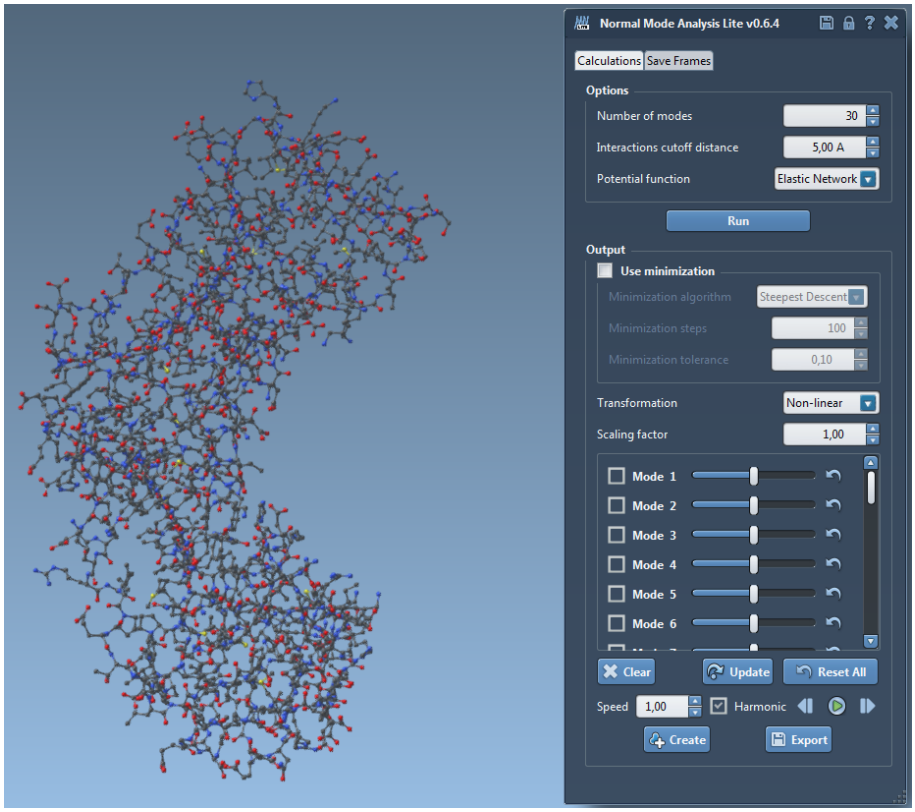

Figure 14. Normal Modes Analysis element Lite version.

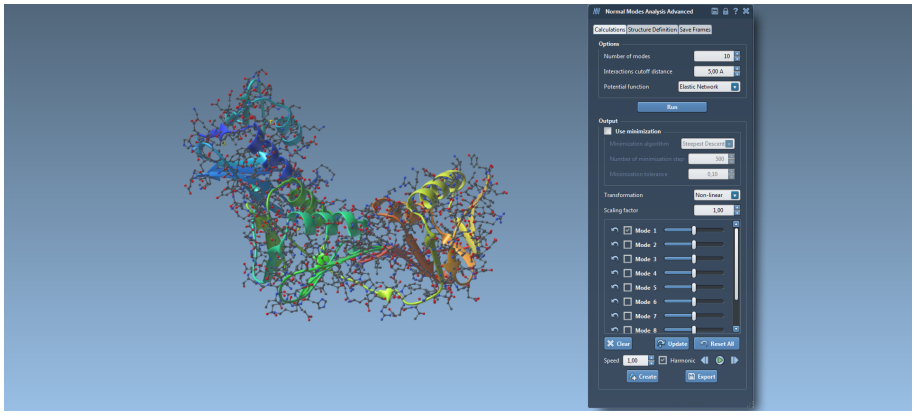

Figure 15. Normal Modes Analysis element Advanced version (A)

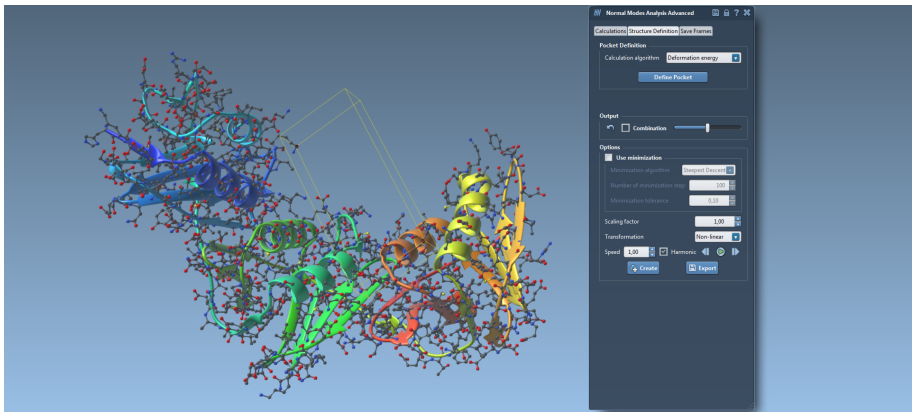

Figure 16. Normal Modes Analysis element Advanced version (B)

The second one (15) is an advanced version of the Nonlinear Normal Modes Analysis module. It computes the nonlinear normal modes of a molecular system (protein, RNA, DNA) in the same time given that it uses the same algorithm developed by Alexandre Hoffmann and Sergei Grudinin (J. Chem. Theory Comput., 2017, 13 (5), pp 2123-2134, DOI: 10.1021 / acs.jctc.7b00197.). It has the same functionalities than the Lite version of the Normal Modes Analysis element. In addition, the element has an additional tabulation called "Structure Definition" (16). In this section, users can define a pocket and ask for a combination of modes that contribute the most to the opening and closing of this pocket. Also, in the near future, another functionality will be added in the "Structure Definition" tabulation called "reference structure definition". Using this functionality, users can define the conformation of structure as a reference and the element will provide a combination of modes that will lead this structure to present this conformation.

5.13. Development of a Hex SAMSON Element

Participants: Yassine Naimi, Sergei Grudinin.

We developed a SAMSON Element to wrap Hex (17), an interactive protein docking software, written by Dave Ritchie (LORIA/Inria Nancy). With this element, users can define receptor/ligand structures displayed in the SAMSON viewport or import their PDB files. All the options available on the Hex software have been implemented in this SAMSON element.

Then, by clicking on the Run button, docking solutions will be computed and clustered in a table (18) using the Hex algorithm. Users can show the resulted docking solutions by clicking on the play button, or the solution line in the table or the next/previous buttons.

5.14. Development of RDKit Smiles Manager SAMSON Elements

Participant: Yassine Naimi.

We integrated RDKit, an open-source collection of cheminformatics and machine-learning software written in C++ and Python, in SAMSON. One of RDKit's features is the conversion of molecules from their SMILES code to a 2D and 3D structures. Therefore, it is now possible to use these features in the SAMSON platform. SMILES code files (.smi) or text files (.txt) containing several SMILES codes can be read using the import button (19).

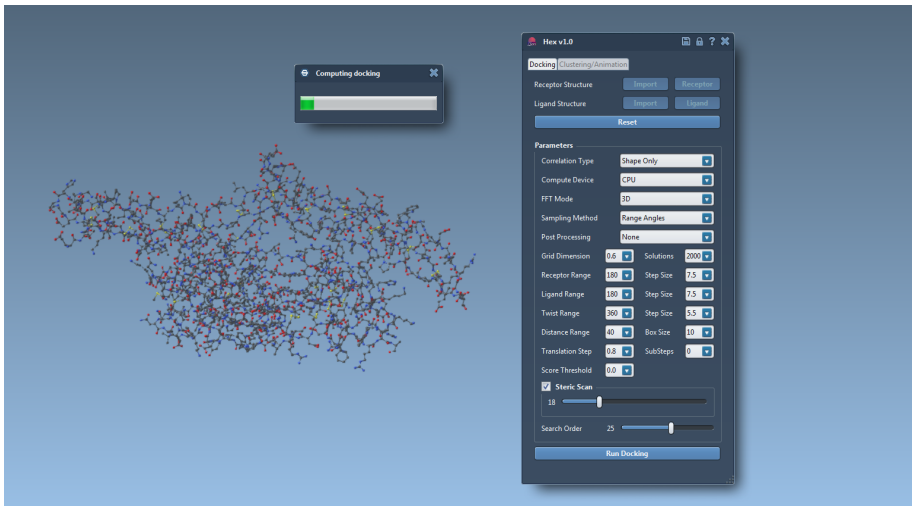

Figure 17. Hex element.

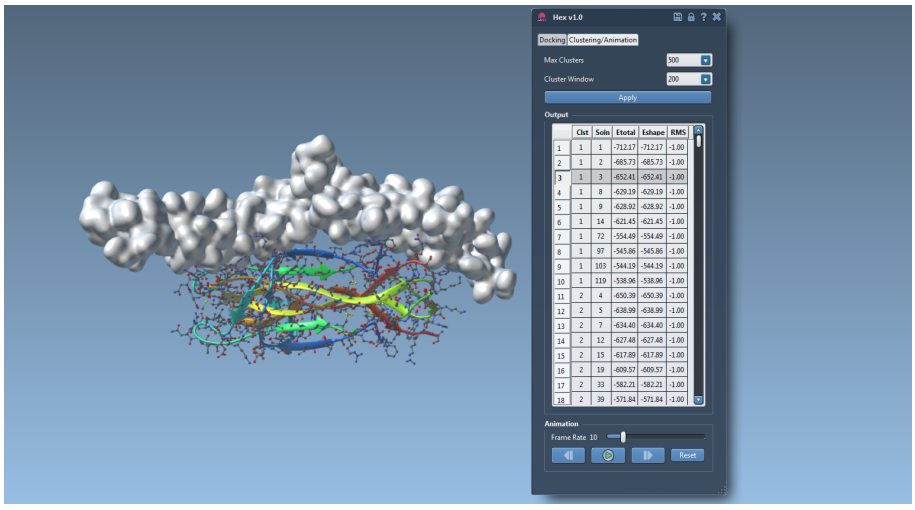

Figure 18. Hex results.

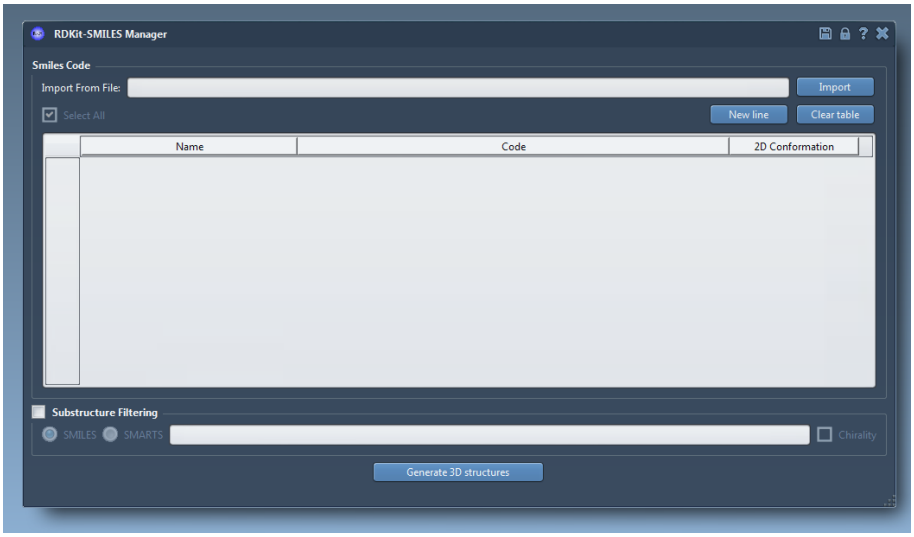

Figure 19. RDkit Smiles Manager element.

Users can manage the imported data with several manners (modify the SMILES code, add manually a new SMILES code, assign names to the molecules…). Also, 2D depictions of the SMILES code are generated on the fly (20). When a SMILES code is invalid an error image is automatically generated. By right-clicking on these images, users can open or generate the 3D structure in SAMSON or save the image as png or svg. The main feature of this element is to generate 3D structures from imported/written SMILES codes. After selecting the molecules, users can click on the Generate 3D structures button. Few seconds later, the 3D structures of the molecules (presenting a valid SMILES code) are added to the SAMSON document view. Finally, RDKit provides a feature to filter the selected molecules using a substructure pattern (SMILES or SMARTS). By default in RDKit, information about stereochemistry is not used in substructure searches but this can be changed by using the chirality. For information, the name of the molecules that did not include the given pattern are displayed in a pop-up.

5.15. Symmetry mate generator for SAMSON

Participants: Guillaume Pagès, Sergei Grudinin.

Many biological systems are composed of several identical units structurally organized in a symmetric manner. To observe the atomistic contacts in a system, one needs to replicate the asymmetric unit and apply specific rigid-body operations to it. We developed a SAMSON element that is able to read these operations from a file, and which provides a way to replicate the subunits in a user-friendly fashion.

5.16. Development of a symmetry detection software AnAnaS

Participants: Guillaume Pagès, Sergei Grudinin.

Macromolecules are generally not rigid bodies at physiological temperature and they adopt different conformational states. Thus, if one considers a macromolecular assembly made of N subunits, do we expect that all the units will be structurally identical to each other? Most probably not, since at any given moment of time, each unit may be sampling a different conformational state. For example, there are plenty of X-ray structures of homo-dimers, where the individual monomers are not structurally identical.

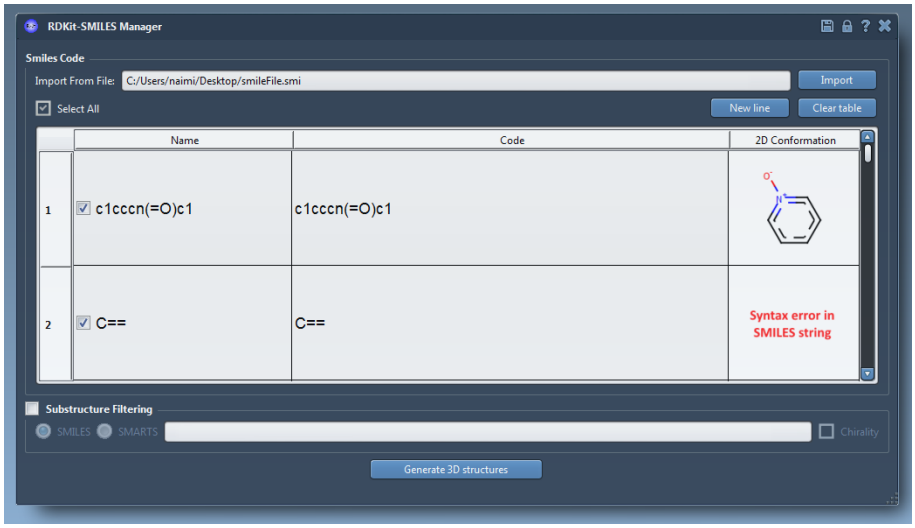

Figure 20. RDkit Smiles Manager element.

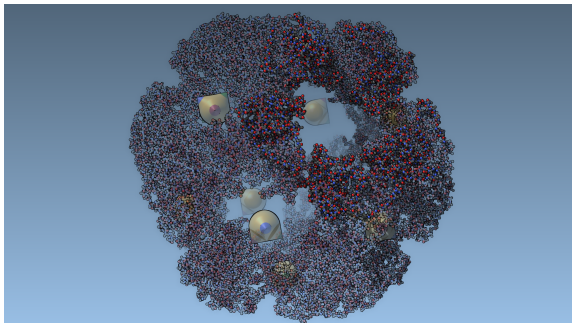

Figure 21. The Symmetry Mate element.

In order to quantitatively assess these differences, we developed a method for Analytical Analysis of Symmetries (AnAnaS) in protein complexes. The method is extremely fast, robust and accurate. Two manuscripts describing the method are currently submitted for publication. This method is available on the website of the team (https://team.inria.fr/nano-d/software/ananas/).

5.17. Integration of AnAnaS to SAMSON

Participants: Guillaume Pagès, Sergei Grudinin.

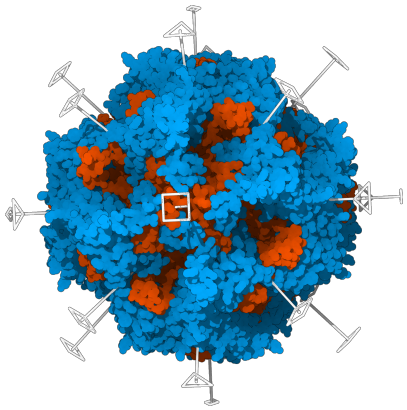

Figure 22. System with an octahedral symmetry, with the axes displayed in SAMSON.

We created a SAMSON element to make the symmetry detection and symmetry axes' visualization as easy and intuitive as possible.

5.18. Deep Learning for Symmetry detection

Participants: Guillaume Pagès, Sergei Grudinin.

We are working on a fully-structural method for detecting symmetries in molecular structures. This will allow us to detect tandem repeats, or even symmetry in density maps. We created a method based on neural network and deep learning, inspired by the advances in computer vision in the past decade. According to our first tests on simulated examples, our method is able to detect the order of a cyclic symmetry (which can be 1 for asymmetric structure) with a 92% accuracy, and guesses the direction of the axis of symmetry with an average error of 3°. We are still working on improving it and doing tests on more realistic examples.

5.19. Pepsi-SAXS calculator of small-angle X-ray scattering profiles

Participants: Sergei Grudinin, Maria Garkavenko.

We have continued the development of a new method called Pepsi-SAXS that calculates small angle X-ray scattering profiles from atomistic models [2]. The method is based on the multipole expansion scheme and is significantly faster with a comparable precision than other methods.

Our method has been highlighted in a recent SAXS-related review [49] and was one of the best performers in the recent CASP12 data-assisted protein structure prediction experiment [81].

Pepsi-SAXS is available at http://team.inria.fr/nano-d/software/pepsi-saxs. A SAMSON module will be made available at https://www.samson-connect.net.

Figure 23.

5.20. NOLB nonlinear normal modes

Participants: Alexandre Hoffmann, Sergei Grudinin.

We developed a new conceptually simple and computationally efficient method for nonlinear normal mode analysis called NOLB [4]. This is a logical evolution of the RTB-subspace method developed by Y.-H. Sanejouand and colleagues [38], [80]. We demonstrated how to physically interpret the eigenvalues computed in the RTB basis in terms of angular and linear velocities applied to the rigid blocks and how to construct a nonlinear extrapolation of motion out of these velocities. The key observation of our method is that the angular velocity of a rigid block can be interpreted as the result of an implicit force, such that the motion of the rigid block can be considered as a pure rotation about a certain center.

Overall, our method produces better structures compared to the standard approach, especially at large deformation amplitudes, as we demonstrate by visual inspection, energy and topology analyses, and also by the MolProbity service validation. Also, our method is scalable and can be applied to very large molecular systems, such as ribosomes.

Standalone executables of the NOLB normal mode analysis method are available at https://team.inria.fr/nano-d/software/nolb-normal-modes/. A graphical user interface created for the SAMSON software platform will be made available at https://www.samson-connect.net.

5.21. Applications of the NOLB NMA method to structural biology

Participant: Sergei Grudinin.

Participants: Sergei Grudinin

Using the created nonlinear normal mode analysis NMA tool, we have successfully predicted structural transitions in several protein complexes, whose structures were solved by our collaborators [6], [3].

5.22. Off-grid fitting method

Participants: Alexandre Hoffmann, Sergei Grudinin.

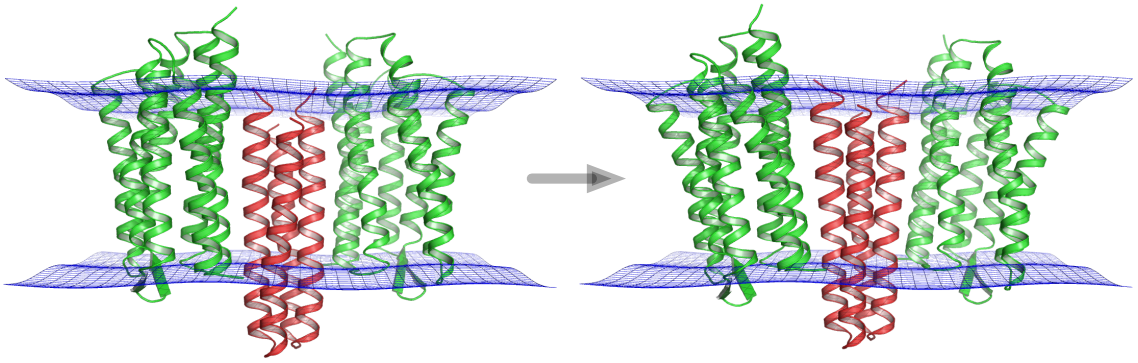

Figure 24.

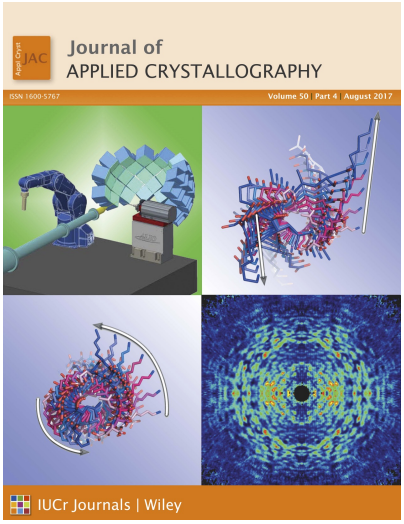

Figure 25.

We developed a novel Fast Fourier Transform (FFT)-based exhaustive search method extended to off-grid translational and rotational degrees of freedom [5]. The method combines the advantages of the FFT-based exhaustive search, which samples all the conformations of a system under study on a grid, with a local optimization technique that guarantees to find the nearest optimal off-grid conformation. The method is demonstrated on a fitting problem and can be readily applied to a docking problem.

The algorithm first samples a scoring function on a six-dimensional grid of size N^6 using the FFT. This operation has the asymptotic complexity of $O(N^6 \log N)$. Then, the method performs the off-grid search using a local quadratic approximation of the cost function and the trust region optimization algorithm. The computation of the quadratic approximation is also accelerated by FFT at the same additional asymptotic cost of $O(N^6 \log N)$. We demonstrate our method on fitting atomic protein models into several simulated and experimental maps from cryo-electron microscopy. The method is available at https://team.inria.fr/nano-d/software/offgridfit.

5.23. RapidRMSD library

Participants: Emilie Neveu, Petr Popov, Sergei Grudinin.

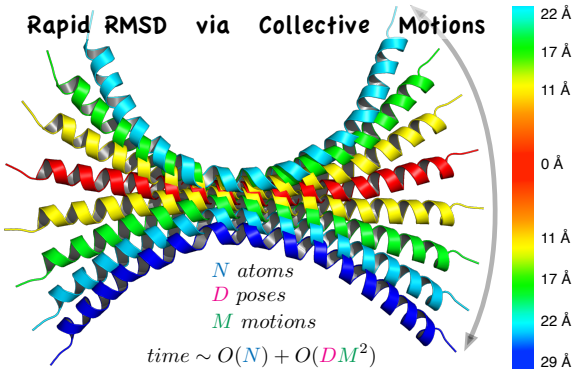

Figure 26.

The root mean square deviation (RMSD) is one of the most used similarity criteria in structural biology and bioinformatics. Standard computation of the RMSD has a linear complexity with respect to the number of atoms in a molecule, making RMSD calculations time-consuming for the large-scale modeling applications, such as assessment of molecular docking predictions or clustering of spatially proximate molecular conformations. Previously we introduced the *RigidRMSD* algorithm to compute the RMSD corresponding to the rigid-body motion of a molecule [62]. Recently, we went beyond the limits of the rigid-body approximation by taking into account conformational flexibility of the molecule. We model the flexibility with a reduced set of collective motions computed with e.g. normal modes or principal component analysis.

The initialization of our algorithm is linear in the number of atoms and all the subsequent evaluations of RMSD values between flexible molecular conformations depend only on the number of collective motions that are selected to model the flexibility. Therefore, our algorithm is much faster compared to the standard RMSD computation for large-scale modeling applications. The method can be applied e.g. to cluster flexible docking or to generate pseudo-random constant-RMSD structural molecular ensembles.

The algorithm is written in C++ as the open-source *RapidRMSD* library governed by the BSD-compatible license, which is available at http://team.inria.fr/nano-d/software/RapidRMSD/. The constant-RMSD structural ensemble application is available at http://team.inria.fr/nano-d/software/nolb-normal-modes/.

5.24. SBROD protein quality assessment method

Participants: Mikhail Karasikov, Sergei Grudinin.

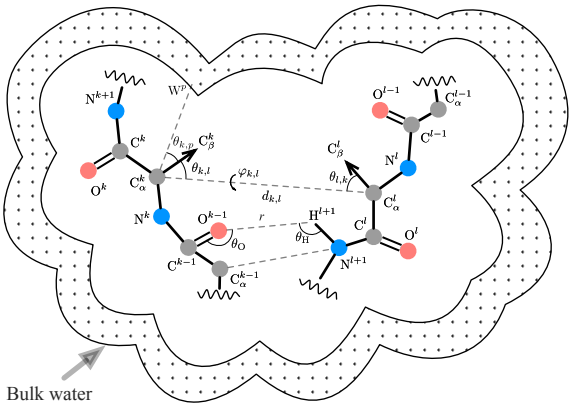

Figure 27.

Protein quality assessment (QA) is a crucial element of protein structure prediction, a fundamental but yet open problem in structural bioinformatics. QA aims at ranking predicted protein models from a set of proposed candidates. Although consensus-model QA methods often outperform single-model QA methods, their performance substantially depends on the pool of available candidates. This makes single-model QA methods a particularly important research target since these usually assist in the sampling of candidates.

We developed a novel single-model QA method called SBROD. The SBROD (Smooth Backbone-Reliant Orientation-Dependent) method uses only the conformation of the protein backbone, and hence it can be applied to scoring the coarse-grained protein models. The proposed method deduces the scoring function from a training set of protein models. This function is composed of four terms related to different structural features, residue-residue orientations, contacts between the backbone atoms, hydrogen bonding, and solvent-solvate interactions. The SBROD scoring function is smooth with respect to atomic coordinates and thus is applicable to continuous gradient-based optimization of protein conformations. Furthermore, it can also be used for coarse-grained protein modeling and computational protein design. Computational experiments conducted on diverse datasets (Stage1 and Stage2 from CASP11, and MOULDER) proved SBROD to achieve the state-of-the-art performance among single-model QA methods including meta algorithms.

The standalone application implemented in C++ and Python is freely available at https://team.inria.fr/nano-d/software/SBROD and supported on Linux, MacOS, and Windows.

5.25. Symmetry detection methods

Participants: Etienne Bamas, Sergei Grudinin.

We have developed a novel framework for the computational detection of point-group symmetries in electron density maps. The method is based on the symmetry-based reduced representation of the density using polynomial expansions.

5.26. SAXS-assisted protein docking

Participants: Gaurav Dhar, Sergei Grudinin.

We have developed an extension of the Pepsi-SAXS method [2] applicable to rescoring of rigid-body protein-protein docking predictions.

5.27. Methods for the estimation of collective motions

Participants: Robin Gullo, Sergei Grudinin.

We have studied novel ways to predict structural conformational transitions in macromolecules.

5.28. Smoothed-force energy optimization

Participants: Clement Beitone, Stephane Redon.

Many approaches have been developed during the last decades to improve the speed of convergence of optimization methods used to find minima of potential energy surfaces. We proposed to spatially and temporally smooth the force vector given by the force field. Our approach alters the deformation of the structure being minimized and makes it behave as if it was locally more rigid. We apply this filtering method to two well-known optimization methods, steepest descent and FIRE, and evaluate its efficiency on several benchmarks, including nanomaterials and biomolecules. We demonstrated that the smoothed force variants may significantly speed up energy minimization.

5.29. Adaptively Restrained Molecular Dynamics in LAMMPS

Participants: Krishna Kant Singh, Stephane Redon.

Adaptively Restrained Molecular Dynamics (ARMD) is a recently introduced particles simulation method that switches positional degrees of freedom on and off during simulation in order to speed up calculations. In the NVE ensemble, ARMD allows users to trade between precision and speed while, in the NVT ensemble, it makes it possible to compute statistical averages faster. Despite the conceptual simplicity of the approach, however, integrating it in existing molecular dynamics packages is non-trivial, in particular since implemented potentials should a priori be rewritten to take advantage of frozen particles and achieve a speed-up. We proposed novel algorithms for integrating ARMD in LAMMPS, a popular multipurpose molecular simulation package [12]. In particular, we demonstrated how to enable ARMD in LAMMPS without having to re-implement all available force fields. The proposed algorithms were assessed on four different benchmarks, and showed how they allowed us to speed up simulations up to one order of magnitude.

5.30. Single-pass Incremental Force Updates for Adaptively Restrained Molecular Dynamics

Participants: Krishna Kant Singh, Stephane Redon.

We proposed new, single-pass incremental force updates algorithms to efficiently simulate a system using ARMD [13]. We assessed different algorithms for speedup measurements and implemented them in the LAMMPS MD package. We validated the single-pass incremental force update algorithm on four different benchmarks using diverse pair potentials. The proposed algorithm allows us to perform simulation of a system faster than traditional MD in both NVE and NVT ensembles. Moreover, ARMD using the new single-pass algorithm speeds up the convergence of observables in wall-clock time.

5.31. Auto update process for SAMSON & SAMSON-SDK

Participant: Jocelyn Gate.

Since SAMSON 0.6.0, instead of manually installing the latest SAMSON updates, the existing SAMSON can keep itself up-to-date automatically. If an internet connection is established and as soon as we add a new version of SAMSON on SAMSON Connect, all users that launch SAMSON will be notified that a new version is available. The previous version will remain running until SAMSON is closed, but the updated version will be launched automatically the next time you start SAMSON. It is a one click process.

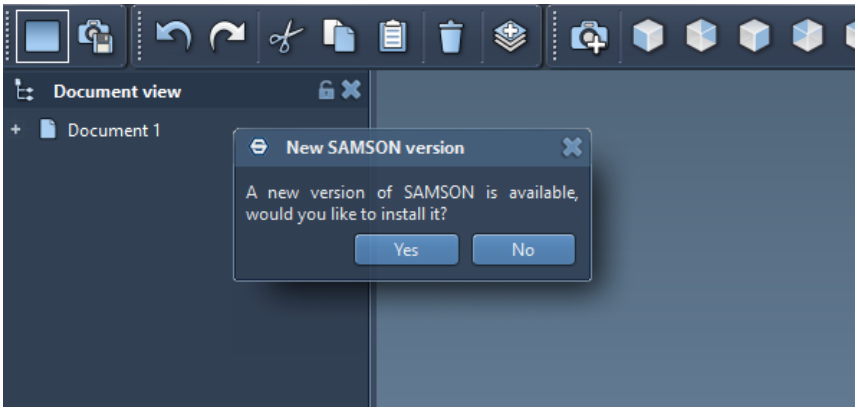

Figure 28. The update notification

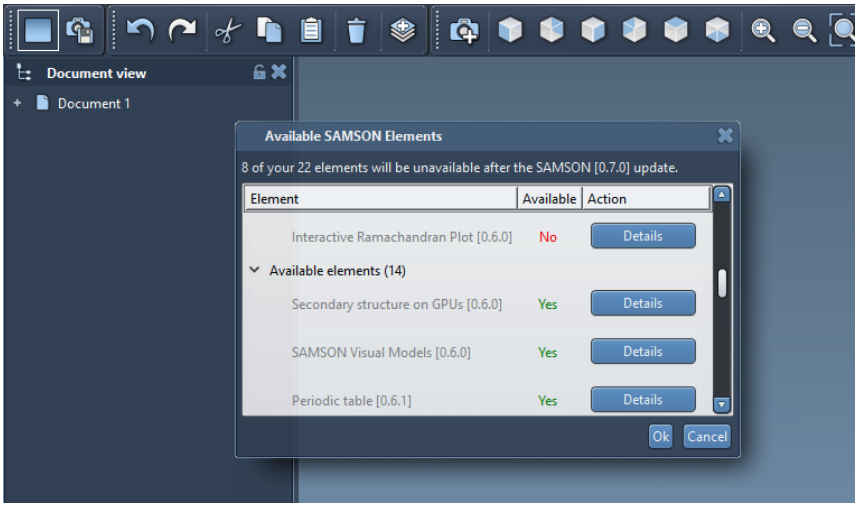

Figure 29. The available element summary

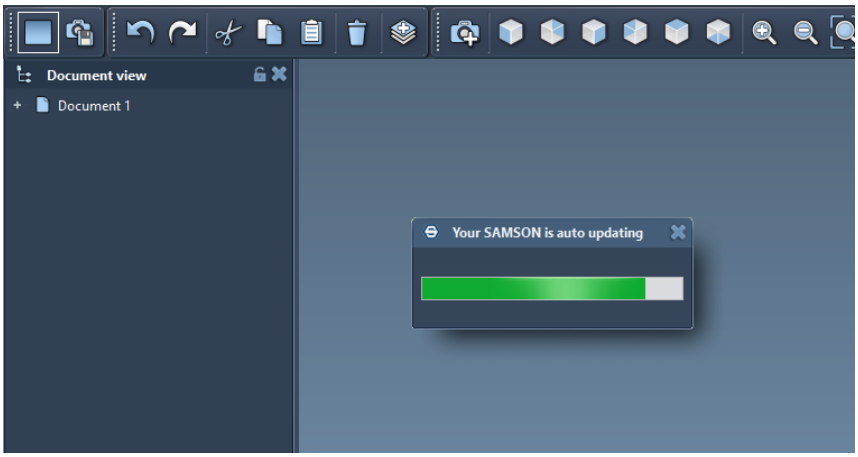

Figure 30. The update progress

5.31.1. The SAMSON auto update

When a new SAMSON is available users have a notification and a summary if all elements they use are still available in the updated version.

5.31.2. The SAMSON-SDK auto update

When a new SAMSON-SDK is available users have notification and they can install it in one click when SAMSON starts.

5.32. SAMSON Elements policies

Participants: Jocelyn Gate, Stephane Redon.

Some developers of SAMSON wanted to restrain access to their developed SAMSON Elements, hence we defined four different access policies:

- Private : only the developer and the collaborators can see and use the corresponding published element
- Public : everyone can see and use the corresponding published element
- Hidden : only users that get the corresponding hidden link can see and use the corresponding published element
- Shared : only the users that have been added to the list of shared users can see and use the corresponding published element

5.33. Improvements to our software development pipeline

Participant: Jocelyn Gate.

In order to fully automate the deployment process we increased the number of jenkins features.

- SAMSON Element packaging and deployment for every NANO-D users to samson-connect.
- SAMSON & SAMSON-SDK documentation build.
- SAMSON & SAMSON-SDK documentation upload via FTP to the new documentation website. (https://documentation.samson-connect.net/)

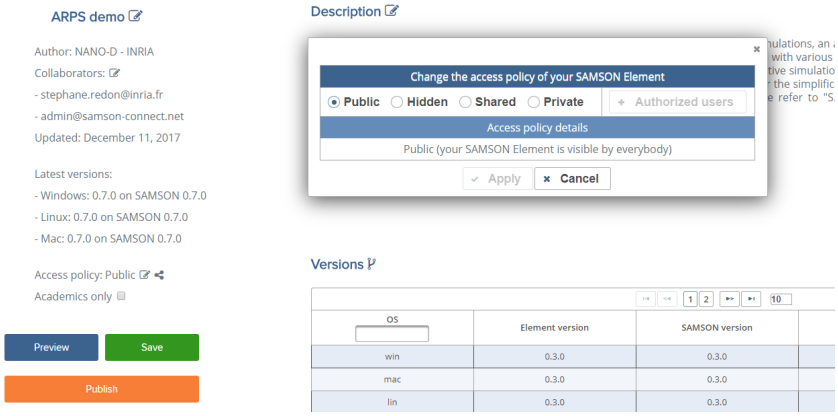

Figure 31. The policy configuration

5.34. SAMSON Connect Forum

Participants: Jocelyn Gate, Stephane Redon.

To help the community to use SAMSON and develop elements with the SAMSON SDK, we setup a forum thanks to Jean-Francois Scariot from Inria (https://forum.samson-connect.net/). Despite the fact that the samson-connect.net and forum.samson-connect.net websites are separate, the login functionality is shared, since the user logs in samson-connect.net to access the forum.

6. Partnerships and Cooperations

6.1. National Initiatives

6.1.1. ANR

In 2015, NANO-D had funding from one ANR program:

- **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. European Initiatives

6.2.1. FP7 & H2020 Projects

6.2.1.1. ADAPT

Title: Theory and Algorithms for Adaptive Particle Simulation

Programm: FP7

Duration: September 2012 - August 2017

Coordinator: Inria

Inria contact: Stephane Redon

'During the twentieth century, the development of macroscopic engineering has been largely stimulated by progress in digital prototyping: cars, planes, boats, etc. 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 needed to engineer complex nanosystems, through modeling and simulation. As a result, a major challenge is to develop efficient simulation methods and algorithms. NANO-D, the Inria research group I started in January 2008 in Grenoble, France, aims at developing efficient computational methods for modeling and simulating complex nanosystems, both natural and artificial. In particular, NANO-D develops SAMSON, a software application which gathers all algorithms designed by the group and its collaborators (SAMSON: Software for Adaptive Modeling and Simulation Of Nanosystems). In this project, I propose to develop a unified theory, and associated algorithms, for adaptive particle simulation. The proposed theory will avoid problems that plague current popular multi-scale or hybrid simulation approaches by simulating a single potential throughout the system, while allowing users to finely trade precision for computational speed. I believe the full development of the adaptive particle simulation theory will have an important impact on current modeling and simulation practices, and will enable practical design of complex nanosystems on desktop computers, which should significantly boost the emergence of generic nano-engineering.'

6.2.2. Collaborations with Major European Organizations

Partner 1: Institut Laue-Langevin, SANS platform (France)

Partner 2: European Synchrotron Radiation Facility, SAXS platform (France)

The topic of collaboration is the development and validation of novel computational methods for small-angle scattering experiments.

6.3. International Initiatives

6.3.1. Inria Associate Teams Not Involved in an Inria International Labs

6.3.1.1. PPI-3D

Title: Structure Meets Genomics

International Partner (Institution - Laboratory - Researcher):

Stony Brook University (United States) - Dima Kozakov

Start year: 2015

See also: https://team.inria.fr/nano-d/research/ppi-3d-structure-meets-genomics/

Protein–protein interactions are integral to many mechanisms of cellular control, and therefore their characterization has become an important task for both experimental and computational approaches in systems biology. Genome-wide proteomics studies provide a growing list of putative protein-protein interactions, and demonstrate that most if not all proteins have interacting partners in the cell. A fraction of these interaction has been reliably established, however, one can only identify whether two proteins interact and, in the best cases, which are the individual domains mediating the interaction. A full comprehension of how proteins bind and form complexes can only come from high-resolution three-dimensional structures. While the most complete structural characterization of a complex is provided by X-ray crystallography, protein-protein hetero-complexes constitute less than 6%Â§ of protein structures in the Protein Data Bank. Thus, it is important to develop computational methods that, starting from the structures of component proteins, can determine the structure of their complexes.

The basic problem of predictive protein docking is to start with the structures (or sequences) of unbound component proteins A and B, and to obtain computationally a model of the bound complex AB, as detailed structural knowledge of the interactions facilitates understanding of protein function and mechanism. Our current docking approaches performs ab initio docking of the two structures without the use of any additional information. The goal of this proposal is to speed up docking approaches to tackle genome-scale problems, and utilize additional information on interactions, sequences, and structures that is available for virtually any protein.

This project includes several methodological and application research directions: 1) Developing fast sampling approaches; 2) Development of new scoring functions; 3) Integrative approaches for structure determination.

Overall, during the course of the project we will (i) jointly develop new methodology and algorithms in the field of genomic-scale protein complex prediction; (ii) provide server-based applications built upon services of the Boston team; (iii) and finally develop modular applications coded inside the SAMSON software platform created by the Inria team.

6.3.2. Participation in Other International Programs

6.3.2.1. International Initiatives

BIOTOOLS

Title: Novel Computational Tools for Structural Bioinformatics
International Partner (Institution - Laboratory - Researcher):
MIPT (Russia (Russian Federation)) - Vadim Strijov
Duration: 2016 - 2020
Start year: 2016

6.4. International Research Visitors

6.4.1. Visits of International Scientists

- Dima Kozakov, Professor at the University of Stony Brook, visited Nano-D for 2 weeks in July 2017.
- Dzmitry Padhorny, PhD candidate at the University of Stony Brook, visited Nano-D for 2 weeks in July 2017.
- Mikhail Ignatov, PhD candidate at the University of Stony Brook, visited Nano-D for 2 weeks in June 2017.

6.4.1.1. Internships

Mikhail Karasikov
Date: 1/08/2016 - 30/01/2017
Institution: Skolkovo Reseach Center / MIPT Moscow (Russia (Russian Federation))
Supervisor: Sergei Grudinin

7. Dissemination

7.1. Promoting Scientific Activities

7.1.1. Scientific Events Organisation

7.1.1.1. Schools

- We organized SAMSON School 2017 in Lyon, for users and developers of SAMSON.

7.1.1.2. Member of the Organizing Committees

- Stephane Redon is a member of the steering committee of the Nanosciences Foundation in Grenoble

7.1.2. Scientific Events Selection

7.1.2.1. Member of the Conference Program Committees

Sergei Grudinin was an editorial member of the ACM–BCB'17 conference.

7.1.2.2. Reviewer

- Leonard Jaillet was a reviewer for ICRA (International Conference on Robotics and Automation), IROS (International Conference on Intelligent Robots and Systems), ISRR (International Symposium on Robotics Research) and for RA-L (Robotics and Automation Letters).
- Sergei Grudinin served as a reviewer at the ACM–BCB'17 conference.

7.1.3. Journal

7.1.3.1. Reviewer - Reviewing Activities

Sergei Grudinin served a reviewer for the following journals, several D3R assessment submissions in Journal of Computer–Aided Molecular Design; Bioinformatics, several CASP12 assessment submissions in PROTEINS: Structure, Function, and Bioinformatics; PLOS Computational Biology; PLoS One; Spectrochimica Acta Part A; Chemical Research in Toxicology; Journal of Computational Chemistry; The Journal of Physical Chemistry; Journal of Chemical Information and Modeling.

7.1.4. Invited Talks

- Sergei Grudinin gave an invited talk entitled "On the Nonlinear Normal Mode Analysis and its Applications to Structural Bioinformatics" at the Second International Conference on Computational Genomics and Proteomics, Aug 14 - 18 2017, Playa Blanca, Panama.
- Guillaume Pagès gave an invited talk entitled "Algorithms and Software for Symmetry Detection and Analysis in Large Macromolecular Assemblies" at the Second International Conference on Computational Genomics and Proteomics, Aug 14 - 18 2017, Playa Blanca, Panama.
- Sergei Grudinin gave an invited talk entitled "Some problems in computational electron–cryo microscopy" at the DROITE workshop on tomography: mathematics and applications, on the 27 Jan, 2017 in Grenoble.
- Sergei Grudinin gave an invited talk entitled "On the Nonlinear Normal Mode Analysis and its Applications to Structural Bioinformatics" at the rencontre nationales sur les modes normaux, May 30 2017, Institute Pasteur, Paris, France.
- Sergei Grudinin gave an invited talk entitled "Using machine learning and fast conformational space exploration techniques for some problems in structural bioinformatics" at the SMAI–2017 congres, June 4-9 2017, Azureva Ronce–les–Bains, France.
- Sergei Grudinin gave an invited talk entitled "Using Machine Learning and Integrative Approaches for Current Problems in Structural Biology" at the University Paris 6, Biologie Computationnelle et Quantitative lab on the 29th of May 2017.
- Sergei Grudinin gave an invited talk entitled "Application of machine learning to structural bioinformatics" on the 28th of February 2017 at the Thoth team of Inria Grenoble, France.
- Sergei Grudinin gave an invited talk entitled "Using Machine Learning and Integrative Approaches for Current Problems in Structural Biology" on the 14th of June 2017, at the ABS team of Inria Sophia-Antipolis, France.
- Sergei Grudinin gave an invited talk entitled "Using Machine Learning and Integrative Approaches for Current Problems in Structural Biology" at INRA Toulouse, France.
- Sergei Grudinin gave an invited talk entitled "On the Nonlinear Normal Mode Analysis and its Applications to Structural Biology" at LAAS CNRS, Toulouse, France.
- Sergei Grudinin gave an invited talk entitled "On the Nonlinear Normal Mode Analysis and its Applications to Structural Biology Including SAXS and Cryo-EM Experiments" at IBT Vilnius, Lithuania, on the 15th of September 2017.
- Sergei Grudinin gave an invited talk entitled "On some aspects of computational predictions of protein structure and organization" at the Institute of Bioorganic Chemistry NASB, Minsk, Belarus, on the 19th of September 2017.

- Sergei Grudinin gave an invited talk entitled "On some aspects of computational predictions of protein structure and organization" at the Interdisciplinary Laboratory Of Biological Systems Modelling, Warsaw, Poland, on the 9th of October 2017.
- Sergei Grudinin gave an invited talk entitled "Computational predictions of protein structure and organization" at the Laboratory For Biomolecular Modeling, EPFL, Lausanne, Switzerland, on the 24th of October 2017.
- Sergei Grudinin gave an invited talk entitled "On some methods for structural bioinformatics" at the Methodes Algorithmiques pour les Structures et Interactions des Macromolecules (GT MASIM) meeting on Nov. 16-17, Paris, France.
- Alexandre Hoffmann gave an invited talk entitled "On fast Fourier transform (FFT)-accelerated flexible exhaustive search for cryo-EM fitting" at the CryoEM Structure Challenges Workshop, Oct 6-8, Stanford, USA,

7.1.5. Other Talks, Presentations and Participations in the Scientific Events

- Sergei Grudinin gave a talk entitled "On the non–linear normal mode analysis and its applications" at the GGMM 2017 conference, May 9-11 2017, Reims, France.
- Guillaume Page`s, Sergei Grudinin, Alexandre Hoffmann, and Maria Kadukova presented 3 posters at the GGMM 2017 conference, May 9-11 2017, Reims, France.
- Sergei Grudinin participated in the Journees Scientifiques Inria 2017, Jun 14-16 2017, Antibes, France.
- Sergei Grudinin and Alexandre Hofmann gave a talk entitled "FFT–accelerated exhaustive flexible docking method" at the Mapping2017 conference, May 21-26 2017, Lyon, France.
- Sergei Grudinin, Guillaume Page`s, Alexandre Hoffmann, and, Maria Kadukova presented two posters at the Mapping2017 conference, May 21-26 2017, Lyon, France.
- Sergei Grudinin and Yassine Naimi gave a talk entitled "On the Small–angle X–ray Scattering modeling in SAMSON" at the SAMSON School 2017, Lyon, France.
- Sergei Grudinin gave a talk entitled "On the development of knowledge–based approaches for structural predictions of macromolecules in Nano–D team" at the seminaire d'evaluation Nano–D, Apr 15-16 2017, Paris, France.
- Sergei Grudinin gave a talk entitled "Using Machine Learning for Protein-Ligand Interactions" at the SBDD2017 conference, Sep 4-8 2017, Lausanne, Switzerland.
- Sergei Grudinin presented a poster entitled "On the Normal Modes, Small-Angle Scattering and Convex Optimization for Protein Structure Prediction" at the Coarse-graining of biomolecules and beyond workshop, on the 7th of October 2017, Warsaw, Poland.

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

- Stephane Redon is teaching INF572 (Introduction to C++) at Ecole polytechnique
- Stephane Redon is teaching INF473S (Computational nanoscience with SAMSON) at Ecole polytechnique

7.2.2. Supervision

- Leonard Jaillet is advising the PhD of Minh Khoa Nguyen
- Sergei Grudinin is advising the PhD of Alexandre Hoffmann
- Sergei Grudinin is advising the PhD of Maria Kadukova
- Sergei Grudinin is advising the PhD of Guillaume Pages

- Stephane Redon was co-advising the PhD of Krishna Kant Singh in collaboration with Jean-Francois Mehaut
- Stephane Redon is advising the PhD of Francois Rousse
- Stephane Redon is advising the PhD of Semeho Edorh

7.2.3. Juries

- Stephane Redon was a member of the PhD committee of Laurent Denarie
- Sergei Grudinin was a member of the "Suivi individuel" PhD committee of Serge Nader

7.3. Popularization

- Sergei Grudinin co-advised the team of high-school student "Cantor se Gauss d'un Poincare´" in the team competitions "Tournoi Français Des Jeunes Mathe´maticiens" (TFJM).
- NANO-D was involved in several popularization activities, including a participation to Fete de la Science, and a participation to the GameLab project in Grenoble, where SAMSON modules were developed for high school students.
- Leonard Jaillet was involved in the development of a demonstration of SAMSON in the Inria showroom. Several scenarii were proposed where the user can interact with molecular systems and test different possible applications of the SAMSON software platform.

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