IN PARTNERSHIP WITH:
CNRS

Activity Report 2018

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, end of the Project-Team: 2018 September 30

Keywords:

Computer Science and Digital Science:

A3.4.1. - Supervised learning
A3.4.6. - Neural networks
A5.5.1. - Geometrical modeling
A6.1.4. - Multiscale modeling
A6.1.5. - Multiphysics modeling
A9. - Artificial intelligence

Other Research Topics and Application Domains:

B1.1.1. - Structural biology
B1.1.7. - Bioinformatics
B2.6.3. - Biological Imaging

1. Team, Visitors, External Collaborators

Research Scientists

Stephane Redon [Team leader before 2018, Inria, Senior Researcher, HDR]
Sergei Grudinin [Team leader since 2018, CNRS, Researcher]
Leonard Jaillet [Inria, Starting Research Position]

Post-Doctoral Fellows

Didier Devaurs [Univ Grenoble Alpes, from Dec 2018]
Dmitriy Marin [Inria, until Sep 2018]

PhD Students

Guillaume Pages [Inria]
Maria Kadukova [Univ Grenoble Alpes]
Francois Rousse [Inria, until May 2018]
Semeho Edorh [Inria, until Jan 2018]
Alexandre Hoffmann [Inria, until Jan 2018]
Minh Khoa Nguyen [Inria, until Jan 2018]

Technical staff

Jocelyn Gate [Inria, until Sep 2018, granted by FP7 PoC SAMSON project]
Yassine Naimi [Inria, until Sep 2018]

Interns

Amal Akkari [Inria, from Jun 2018 until Nov 2018]
Loic Broyer [Univ Grenoble Alpes, from Jun 2018 until Jul 2018]
Benoit Charmettant [Inria, from Jun 2018 until Aug 2018]
Anastasia Konik [Inria, from May 2018 until Sep 2018]
Khalid Mustafin [Inria, from Sep 2018]

Administrative Assistant

Maria Immaculada Presseguer [Inria]

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* [37], *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 [80], for neighbor search between large rigid molecules [36], and for bond-order reactive force-fields [40]. 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 [38] and over 500,000 structures of small molecules stored in the Cambridge Structural Database [32]. 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 [59]. 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 [77]. 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 [79].

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 [49]. 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 [50], a wheelbarrow molecule [60], a nano-car [83], a Morse molecule [33], etc. Typically, these designs are optimized using semi-empirical quantum mechanics calculations, such as the semi-empirical ASED+ calculation technique [34].

While impressive, these are but two examples of the nanoscience revolution already impacting numerous fields, including electronics and semiconductors [64], textiles [63], [54], energy [69], food [44], drug delivery [52], [85], chemicals [55], materials [45], the automotive industry [31], aerospace and defense [51], medical devices and therapeutics [47], medical diagnostics [86], etc. According to some estimates, the world market for nanotechnology-related products and services will reach one trillion dollars by 2015 [78]. 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 [89], removing some degrees of freedom (e.g. keeping torsion angles only [62], [84]), coarse-graining [87], [81], [35], [82], multiple time step methods [75], [76], fast multipole methods [48], parallelization [61], averaging [43], multi-scale modeling [42], [39], reactive force fields [41], [92], interactive multiplayer games for predicting protein structures [46], 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 [90], [91].

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 [71], [72], [73], [74], the adaptive multiscale method [68], and the adaptive partitioning of the Lagrangian method [56]. 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. As-Rigid-As-Possible methods for molecular paths

Last year, in the scope of Minh Khoa Nguyen's PhD, we have adapted the As-Rigid-As-Possible (ARAP) paradigm used in Computer Graphics to generate paths of molecular systems. This year, we continued this line of research with new extensions of the ARAP methodology. One extension led to generate conformational transition paths with low potential-energy barriers for proteins. It was published to the Journal of Computer-Aided Molecular Design, 2018 [66]. Another extension concerned the ART-RRT method which incorporates the ARAP methodology inside tree-based exploration methods to approximate ligand unbinding pathways. This contribution was published to the Journal of Computational Chemistry, 2018 [65]. Finally, the PhD thesis

of Minh Khoa Nguyen titled *Efficient exploration of molecular paths from As-Rigid-As-Possible approaches and motion planning methods* was defended in March 2018 [67]. A brief summary of the above-mentioned contributions is presented below.

3.5. Modelling and simulation for the characterization of advanced materials

We have continued our informal collaboration with the *service de Caractérisation des Matériaux et Composants* of CEA, LETI, Minatec initiated in 2017. The collaboration with LETI will offer numerous possibilities of very precise (sub-nanometric) experimental comparisons based on the High-resolution scanning transmission electron microscopy (HRSTEM) using one of the best microscopes on the market (the FEI Titan Ultimate microscope). In this context, we have developed a set of tools tools to manipulate, simulate and measure nanomaterials, with a special focus on crystals that appears in many new materials such as semiconductors. The description of the sublines of research explored so far are detailed below.

4. Highlights of the Year

4.1. Highlights of the Year

- This year we have very successfully participated in the blind assessment of protein structure prediction methods exercise CASP13. We have evaluated the performance of several knowledge-based potentials for protein model quality and protein docking, small-angle scattering approaches Pepsi-SAXS and Pepsi-SANS, cross-linking developments, methods based on normal mode analysis and more. Our team was ranked 1st in three data-assisted CASP13 sub-challenges (SAXS, SANS, and crosslinks), and got into the top-10 predictors in the main category of the prediction of regular targets. We were also interviewed on this subject by the Le Figaro newspaper [88].
- The OneAngström startup was created this year around the development of the SAMSON software platform. Four team members have joined the startup : Stephane Redon, Jocelyn Gate, Dmitriy Marin, and Yassine Naimi.
- Our Ananas analytical symmetry detection method [70] was used in the official assessment of protein assemblies in CASP13 and was also transferred to the PDBe European resource for the collection, organisation and dissemination of data on biological macromolecular structures [30].

4.1.1. Awards

- Our paper "Analytical symmetry detection in protein assemblies. II. Dihedral and cubic symmetries" covered the September 2018 issue of the Journal of Structural Biology [20].
- Our paper "A novel fast Fourier transform accelerated off-grid exhaustive search method for cryo-electron microscopy fitting" covered the the August 2017 issue of Journal of Applied Crystallography [58].
- Our paper "NOLB: Nonlinear Rigid Block Normal Mode Analysis Method" covered May 2017 issue of Journal of Chemical Theory and Computation [57].
- Our predictions were ranked 1st in the SAXS-assisted category of the CASP13 protein structure prediction challenge (cumulative SAXS-assisted z-scores).
- Our predictions were ranked 1st in the SANS-assisted category of the CASP13 protein structure prediction challenge (cumulative SANS-assisted z-scores).
- Our predictions were ranked 1st in the X-link-assisted category of the CASP13 protein structure prediction challenge (cumulative X-link-assisted z-scores).

5. New Software and Platforms

5.1. SAMSON

Software for Adaptive Modeling and Simulation Of Nanosystems

KEYWORDS: Bioinformatics - Simulation - Nanosystems - Structural Biology - 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/

5.2. 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/

5.3. 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/

5.4. Knodle

KNOwledge-Driven Ligand Extractor
KEYWORDS: Bioinformatics - Machine learning
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.

- Participants: Maria Kadukova and Sergey Grudinin
- Partner: MIPT Moscow
- Contact: Sergey Grudinin
- Publication: Knodle: A Support Vector Machines-Based Automatic Perception of Organic Molecules from 3D Coordinates
- URL: https://team.inria.fr/nano-d/software/Knodle/

5.5. 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
KEYWORD: Bioinformatics
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.

- Participants: Petr Popov and Sergey Grudinin
- Contact: Sergey Grudinin
- Publication: Rapid determination of RMSDs corresponding to macromolecular rigid body motions
- URL: https://team.inria.fr/nano-d/software/rigidrmsd/

5.6. SAMSON-Drug-design

KEYWORDS: Algorithm - Nanosystems - Structural Biology - Bioinformatics - Chemistry - 3D modeling - Molecular simulation
FUNCTIONAL DESCRIPTION: Arap Interpolation Path : Generate interpolation path between two protein structures by the As-Rigid-As-Possible principle from computer graphics

Ligand unbinding search : Find ligand unbinding pathway with the ART-RRT method. The method uses the T-RRT method from robotics for efficiently searching low-energy paths and the ARAP modeling method from computer graphics for handling flexible motions of the ligand and reducing the number of thedimensions of the search space.

Protein Path search : Find protein conformational transition paths between two given conformations with the ART-RRT method. The method uses the T-RRT method from robotics for searching low-energy paths and the As-Rigid-As-Possible (ARAP) methods from computer graphics for handling the flexibility of the protein and reducing the number of the dimensions of the search space.

- Authors: Leonard Jaillet, Minh Khoa Nguyen and Jocelyn Gaté
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.7. DeepSymmetry

KEYWORDS: Bioinformatics - 3D modeling - Machine learning - Neural networks
FUNCTIONAL DESCRIPTION: DeepSymmetry is a method based on three-dimensional (3D) convolutional networks that detects structural repetitions in proteins and their density maps. It identifies tandem repeat proteins, proteins with internal symmetries, their symmetry order, and also the corresponding symmetry axes.

- Participants: Guillaume Pages and Sergey Grudinin
- Contact: Sergey Grudinin
- Publication: DeepSymmetry : Using 3D convolutional networks for identification of tandem repeats and internal symmetries in protein structures
- URL: https://team.inria.fr/nano-d/software/deepsymmetry/

5.8. SAMSON-ARAP-Planner

KEYWORDS: 3D - Algorithm - Nanosystems - Bioinformatics - Structural Biology - Chemistry
FUNCTIONAL DESCRIPTION: ARAP planner combines the ARAP method from computer graphics with T-RRT exploration method from robotics for efficiently finding low-energy paths in high-dimensional energy landscapes.

- Authors: Leonard Jaillet and Minh Khoa Nguyen
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.9. SAMSON-Hydrocarbons

KEYWORDS: Algorithm - Quantum chemistry - Chemistry - Nanosystems - 3D - 3D modeling
FUNCTIONAL DESCRIPTION: Interactive quantum chemistry : This SAMSON Element demonstrates interactive quantum chemistry for small molecules at the ASED-MO level of theory. Choose the ASED-MO (atom superposition and electron delocalization) interaction model when adding a simulator through the 'Simulation' menu. The SAMSON Element also includes an App that makes it possible to visualize how the electron density evolves during interactive simulation.

Brenner interction model : This SAMSON Element contains an adaptive implementation of the Brenner interaction model. Interaction models are one of the five model categories that are used to model nanosystems in SAMSON, along with structural models (for geometry and topology), dynamical models (to represent degrees of freedom), visual models (for visual representations) and property models (to represent properties). The Brenner interaction model is a reactive bond-order potential for hydrocarbon systems. This adaptive implementation makes it possible to interactively simulate large systems. Choose this interaction model when adding a simulator through the 'Simulation' menu.

- Author: Maël Bosson
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.10. SAMSON-RDKit

KEYWORDS: 2D - 3D - Chemistry - Algorithm - 3D modeling - Structural Biology - Bioinformatics
FUNCTIONAL DESCRIPTION: Based on the RDKit open-source libraries, convert and manage SMILES codes in the SAMSON platform. The RDKit-SMILES Manager element allows you to easily import files (.smi or .txt) containing several SMILES codes or add each code separately. 2D conformation of each code will then be generated and you can save them into svg or png files. Using a checkbox you will be able to select the codes that you want to convert into 3D structures and add them directly into the SAMSON data graph node as structural model. For more information about using this SAMSON Element, please visit https://documentation.samson-connect.net/using-the-rdkit-smiles-manager/.

- Author: Yassine Naimi
- Partner: Inria
- Contact: Stéphane Redon
- URL: https://samson-connect.net/app/main?key=element&uuid=ce09650a-c071-4e84-1f6a-b8706937d5c1

5.11. SAMSON-GROMACS

KEYWORDS: Algorithm - Materials - Chemistry - Bioinformatics - Structural Biology - Nanosystems - 3D modeling - 3-order

FUNCTIONAL DESCRIPTION: This SAMSON Element wraps GROMACS 5.1 force fields and setup tools. Use the "GROMACS setup" app (in the App menu), which wraps the pdb2gmx tool, to generate a structural model suitable for simulation (i.e. add hydrogens, etc.). Then, apply a simulator from the Simulation menu and choose "GROMACS force field" to add a GROMACS interaction model suitable for interactive minimization and simulation (no periodic boundary conditions). Note that, at the moment, at most one structural model should be selected (or in the document, when the selection is empty), and that bond lengths are not yet constrained in this version. This may be combined with the Twister editor to perform large-scale modifications of the structure, and the secondary structure visual model for interactively updated secondary structure prediction. Future updates of this SAMSON Element will wrap more GROMACS tools. Source code for this SAMSON Element will be made available at https://gforge.inria.fr/projects/elements/.

- Authors: Stéphane Redon, Minh Khoa Nguyen and Yassine Naimi
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.12. SAMSON-Essentials

KEYWORDS: 3D - C++ - OpenGL - Molecular surface - Molecular simulation - Structural Biology - Chemistry - 3D modeling - Bioinformatics - Nanosystems
FUNCTIONAL DESCRIPTION: A set of SAMSON Elements that adds essential features to SAMSON such as import / export of models, import / export of documents, generators, simulators, editors, scripting, app as well as software integrations (autodock vina).

- Authors: Stéphane Redon, Jocelyn Gaté, Guillaume Pages, Dmitriy Marin, Svetlana Artemova, Himani Singhal, Marc Aubert, Marc Piuzzi and Clement Beitone
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.13. Samson-base

KEYWORDS: Bioinformatics - Simulation - Nanosystems - Structural Biology - Chemistry

- Participants: Evelyne Altariba, Jocelyn Gaté, Noëlle Le Delliou and Stéphane Redon
- Contact: Stéphane Redon

5.14. SAMSON-Connect

KEYWORDS: Web Application - Software platform - Web
FUNCTIONAL DESCRIPTION: SAMSON, SAMSON Elements and the SAMSON Software Development Kit are distributed via the SAMSON Connect website.[2] The site acts as a repository for the SAMSON Elements being uploaded by developers, and users of SAMSON choose and add Elements from SAMSON Connect.

- Authors: Stéphane Redon, Mohamed Yengui and Jocelyn Gaté
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.15. SAMSON-Updater

KEYWORDS: Webservices - Web Application

FUNCTIONAL DESCRIPTION: Web service to ensure communication between SAMSON and SAMSON-Connect. Features: Add / remove new items to SAMSON if they have been added / deleted on SAMON-Connect Update SAMSON or SAMSON-Elements Authenticate users ...

- Authors: Mohamed Yengui and Jocelyn Gaté
- Partner: Inria
- Contact: Stéphane Redon

5.16. SAMSON-Various-tools

SAMSON-Various-toolsrere
KEYWORDS: 3D - 3D modeling - Chemistry - Algorithm - Bioinformatics - Nanosystems - Structural Biology
FUNCTIONAL DESCRIPTION: Cluster Game : This element has been made in order to help students discover the Lennard Jones interactions. It is a game in which the goal is to optimize the atoms' placement. Contains eight levels and five tutorial levels.

Atoms Selector : This SAMSON element allows selection of atoms in the active document according to a user-provided expression with the usage of NSL-like variables (NSL - Node Specification Language), standard mathematical and logical operations. Parsing and evaluation of expressions is done with the usage of C++ Mathematical Expression Parsing And Evaluation Library 'exprtk' by Arash Partow (https://github.com/ArashPartow/exprtk)

Simple Script : This SAMSON element allows modification of some parameters of atoms using scripting language, standard mathematical and logical operations, and NSL-like variables (NSL - Node Specification Language). The script is applied to each atom independently. Parsing and evaluation of the script is done with the usage of C++ Mathematical Expression Parsing And Evaluation Library 'exprtk' by Arash Partow (https://github.com/ArashPartow/exprtk)

Bond Angle Distribution : This App will compute the bond angle distribution of the selected atoms. The result and its image can then be exported.

Bond Distortion Visualisation : This App permits to visualize with colors the distortion of a molecular or crystalic structure. The angle distortion, the bond distortion and the projected bond distortion can be represented with colors on bonds and atoms.

Frame axis : Basic visual model to show cartesian axis. Open a new visual model and select "Frame axis" to see the frame axis as arrows, lines or both.

Radial Distribution Function : This app computes and draws the radial distribution function of a selection. - Compute the crossed-RDF by selecting 2 different sets of atoms. - Follow the evolution of the RDF by selecting a simulator.

Adaptive Lennard-Jones : An interaction model to compute the forces with an adaptive version of Lennard-Jones potential. The update of forces is done by storing all the position, and at each position update, subtracting previous pair forces, then adding new ones. If both pair particles were frozen by restraining dynamical model, the update is useless and so not done.

STL File Importer : Reads Stereolithography (.stl) binary and ASCII files. Spawns carbon atoms at the intersections of vertices to create quickly new original atomic configurations. Many STL files are avalaible online to generate thousands of new configurations.

StyleSheet Viewer : An app for internal developers to test their skin/styles ...

Animation Player : Create animation from a list of conformations in SAMSON Document view There are 3 play modes: loop, only 1 time, or continuous back-forth. The user can change the frame order by drag and drop in the frame list.

Internal Coordinate Editor : This editor rotate the molecule by defining rotation axis and rotation angle. The user define the rotation axis (represented by an arrow in the view) by clicking on one atom and drag it to the second atom. The rotation angle is defined by the small GUI windows. The editor will try to rotate all the atoms after the head of the arrow and in between the tail and head of the arrow

RMSD : This app calculates RMSD between 2 structures. If it is an amino acid chains, a sequence alignment of the structures is needed (in fasta format). The fasta format has to be obtained from external sources. If it is not a protein, the app will try to match atoms one by one in both structures.

Trajectory Importer : This app import selected pdb files (hold Ctrl + Mouse click for multiple selection) as a trajectory. The result is one single structural model and a list of conformations in SAMSON Document View

Open Babel connector : This app allows users to use Open Babel from inside SAMSON

ARPS demo : This SAMSON Element features a demonstration of ARPS: Adaptively Restrained Particle Simulations, an adaptive simulation technique able to focus computations on the most mobile degrees of freedom. In this demo, a collision cascade may be simulated with various degrees of precision by changing the restrained dynamics threshold and the full dynamics threshold. For example, 0 0 produces a classical, non-adaptive simulation, while 0.625 and 0.7 result in a 10 times speedup in this example (without the graphics overhead). Click on 2D Shock to generate the example, enter the simplification parameters, and press start to simulate the collision cascade. Undo and redo make it possible to zoom on and compare simulations. Please refer to "S. Artemova and S. Redon. Adaptively restrained particle simulations. Physical review letters, 2012" for more details.

Hydrogen bond finder : Find hydrogen bonds in a given structure. The bonds is detected by specifying a threshold distance. Bonds are displayed by yellow lines.

Lennard-Jones model : This SAMSON Element contains a Lennard-Jones interaction model that may be used for several purposes: teaching, learning about van der Waals interactions, developing optimization algorithms, looking for minimum energy Lennard-Jones clusters through interactive simulation, etc. Add this force field to a group of atoms (the atom types do not matter) via the 'Simulation' menu.

Catalogue : BETA version. Bunch of structures easy to load, with images.

Catalogue Generator : BETA. Generator for the Catalogue module.

SAMSON Basic Tutorial : Tutorial for SAMSON : Basic functionnalities. Learn how to create, move and delete an atom, and then create a basic molecule thanks to a step-by-step guide. Experiment in sandbox mode. Test your mastery of SAMSON's tools with 4 speed challenges. The following elements are required : SAMSON Editors, Periodic table, Basic importers. Currently only available in french.

SAMSON Courses : BETA. Module with a custom display, depending on the entry files

SAMSON Courses Creator : BETA. Generator for SAMSON Course module

Charts : A SAMSON Element to allow user plotting something from SAMSON datas interactively

Leap : A driver to control SAMSON with the Leap motion controller

- Authors: Mohamed Nadhir Ben Hadj Abdellatif, Svetlana Artemova, Clement Beitone, Jocelyn Gaté, Dmitriy Marin, Pierre Mehaye, Minh Khoa Nguyen, Guillaume Pages, Stéphane Redon, François Rousse and Joachim Woerly-Moussier
- Partner: Inria
- Contact: Stéphane Redon

5.17. SAMSON-Crystal-Study-Pack

KEYWORDS: Algorithm - Nanosystems - 3D - 3D modeling - Physical simulation
FUNCTIONAL DESCRIPTION: CrystalConstrainer : Constrains borders of a crystal. The crystal should be alignes on xyz axes. The margen defines the maximum distance to the bonding box border for which atoms are constrained. Can use the current positions as constrained pos or some fixed one. Can Constrain each pair of plans separately or by couples (e.g. XY)

CrystalProber : Get some statistics about a crystal. Compute for now the X, Y and Z lattice parameters. Can remove a margen to discard atoms at the border

CrystalRigidityProber : Analyze some crystal properties related to the rigidity and based on forces, such as the Young modulus, Poisson's ration, elastic constants, stiffness, etc.

Keating : Implement the Keating force field. Compute energy and forces according to positions. Follows anikin2011keating

nonharmonic Keating : Develop a nonharmonic Keating model as proposed in Rucker1995anharmonic. As parameter file it uses a .nhk extension. As parameters, it require a nu and theta0 value in addition to the equilibrium distances for each atom type. Also, it requires a0 distances for pairwise atoms, in addition to the alpha and beta parameters.

generalized harmonic Keating : Develop a generalized harmonic Keating force field as proposed in mojica2010modelisation. This model generalizes to atoms of columns III and V of the periodic table. The systems are anisotropics, with specific bond lengths and angles when involving the z direction.

CrystalCharacterizer : Provides functionalities to characterise a crystal.

CrystalVisualizer : Provides functionalities to visualize a crystal. Choose the pointing direction of the eye, according to some representative directions of the crystal mesh. Choose the orientation in the camera planer.

- Author: Leonard Jaillet
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.18. SAMSON-Materials

KEYWORDS: Algorithm - Materials - 3D - 3D modeling - Nanosystems
FUNCTIONAL DESCRIPTION: Crystal Creator : This SAMSON Elements enables to generate crystals. It contains a SAMSON App to write a unit cell and a SAMSON importer to read CIF format files. Once a unit cell is written or imported, it can be repeated in the directions of the lattice vectors to create a whole crystal. Each repetition is not a mere copy but is generated again so that the defects and the impurities are modeled. A functionality of the associated property model permits to cut the crystal with the Miller indices and expose the important crystalic planes.

Orbital Free DFT : This App computes the electron density of an atomic system. It comes with an interaction model to minimize the atomic structure and a visual model to appreciate the result of computations. The scheme used is the orbital-free DFT, and the pseudo-potential available restrains its use to only 9 elements : Li, Mg, Al, Si, P, Ga, In and Sb.

- Author: François Rousse
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.19. SAMSON-Planner-Tools

KEYWORDS: 3D - Algorithm - 3D modeling - Molecular simulation - Chemistry - Planning
FUNCTIONAL DESCRIPTION: A set of SAMSON Elements that adds planning features to SAMSON.

- Author: Leonard Jaillet
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

5.20. SAMSON-HEX

KEYWORD: Algorithm
FUNCTIONAL DESCRIPTION: Sampling and Docking using the Hex algorithm developed by Dave Ritchie in SAMSON. Docking solutions can be easily displayed and clustered.

- Authors: Sergey Grudinin, Emilie Neveu and Yassine Naimi
- Partner: Inria
- Contact: Stéphane Redon
- URL: https://www.samson-connect.net/

5.21. SAMSON-UFF

KEYWORDS: Algorithm - Bioinformatics - 3D - 3D modeling - Nanosystems - Molecular simulation
FUNCTIONAL DESCRIPTION: Universal Force Field : This SAMSON Element contains a new implementation of the Universal Force Field, with automatic structure perception. In order to use this interaction model, add a simulator to the document from the Simulation menu, and choose "Universal Force Field". The property window of the interaction model makes it possible to customize the perception and setup the interaction model (e.g. choose the cutoff), and displays the various energy types and the total energy.

Interactive Modeling Universal Force Field : It is an extension of UFF that combines the possibility to significantly modify molecular structures (as with reactive force fields) with a broad diversity of supported systems thanks to the universality of UFF. Such an extension lets the user easily build and edit molecular systems interactively while being guided by physics based inter-atomic forces.

- Authors: Leonard Jaillet and Svetlana Artemova
- Partner: Inria
- Contact: Stéphane Redon
- URL: https://samson-connect.net/app/main?key=element&uuid=8cbdc8b1-59e1-6459-d68f-b840275dd5e9

5.22. SAMSON-Normal-modes

KEYWORDS: Algorithm - Bioinformatics - Structural Biology - 3-order - 3D modeling - Nanosystems
FUNCTIONAL DESCRIPTION: Normal mode analysis advanced : This SAMSON Element 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. 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. Please visit https://blog.samson-connect.net/computing-non-linear-normal-modes-of-biomolecules/ for a tutorial.

Normal mode analysis : A light version of the previous element

- Authors: Sergey Grudinin, Alexandre Hoffmann and Yassine Naimi
- Partner: Inria
- Contact: Sergey Grudinin
- URL: http://samson-connect.net

5.23. SAMSON-SAXS

KEYWORDS: Algorithm - Bioinformatics - Structural Biology - Nanosystems - 3D - 3D modeling
FUNCTIONAL DESCRIPTION: The Pepsi-SAXS module rapidly computes small-angle X-ray scattering profiles. It is based on the spherical harmonics expansion method and interactively updates the fits if the molecular structure is modified. Multi-threading is currently only supported for Linux & macOS.

- Authors: Sergey Grudinin, Mariya Garkavenko and Mohamed Nadhir Ben Hadj Abdellatif
- Partner: Inria
- Contact: Sergey Grudinin
- URL: https://samson-connect.net/app/main?key=element&uuid=844be03b-cab2-4420-464b-6f0f9384bc4a

5.24. Ananas

Analytical Analyzer of Symmetries
KEYWORDS: Bioinformatics - Structural Biology
FUNCTIONAL DESCRIPTION: Analytical Analyzer of Symmetries is a software for detection and assessment of the quality of symmetry in a protein assembly.

This software can : Detect the best axes of symmetry for any symmetry group in an assembly containing the right amount of chains, Provide the symmetry-aware RMSD for these axes, Detect the best axis of symmetry for cyclic assemblies with missing subunits, Compute the axes of symmetry with user-provided correspondences.

- Participants: Guillaume Pages and Sergey Grudinin
- Contact: Sergey Grudinin
- Publications: Analytical symmetry detection in protein assemblies. I. Cyclic symmetries - Analytical symmetry detection in protein assemblies. II. Dihedral and Cubic symmetries
- URL: https://team.inria.fr/nano-d/software/ananas/

5.25. Pepsi-SAXS

KEYWORDS: Bioinformatics - Structural Biology - Data modeling
FUNCTIONAL DESCRIPTION: Pepsi-SAXS (PEPSI stands for Polynomial Expansions of Protein Structures and Interactions) is new implementation of the multipole-based scheme initially proposed by Stuhrmann (Stuhrmann, 1970). Overall, our method is significantly faster with a similar accuracy compared to Crysol, FoXS, and the 3D-Zernike implementation from the SAStbx package.

- Participant: Sergey Grudinin
- Partner: MIPT Moscow
- Contact: Sergey Grudinin
- Publication: Pepsi-SAXS : an adaptive method for rapid and accurate computation of small-angle X-ray scattering profiles
- URL: https://team.inria.fr/nano-d/software/pepsi-saxs/

5.26. NOLB

NOn-Linear rigid Block NMA method
KEYWORDS: Structural Biology - Bioinformatics - Elasticity - Proteins - Motion analysis

FUNCTIONAL DESCRIPTION: It's a new conceptually simple and computationally efficient method for non-linear normal mode analysis of macromolecules.

- Participants: Sergey Grudinin and Alexandre Hoffmann
- Contact: Sergey Grudinin
- Publications: NOLB: Nonlinear Rigid Block Normal Mode Analysis Method - RapidRMSD: Rapid determination of RMSDs corresponding to motions of flexible molecules
- URL: https://team.inria.fr/nano-d/software/nolb-normal-modes/

5.27. SBROD

KEYWORDS: Bioinformatics - Machine learning
FUNCTIONAL DESCRIPTION: Smooth orientation-dependent scoring function (SBROD) for coarse-grained protein quality assessment uses only the conformation of the protein backbone, and hence it can be applied to scoring the coarse-grained protein models.

The workflow of SBROD consists in two stages. First, the method extracts features from each protein model in the dataset. Then, the scoring function assigns a score to each processed protein model depending on its features extracted at the first stage. Figure above schematically shows the workflow of SBROD. Here, four types of inter-atomic interactions, described in details below, are taken into account when extracting the features. After these features have been extracted and preprocessed, a Ridge Regression model is trained on them to predict the GDT-TS of protein models.

- Participants: Mikhail Karasikov, Guillaume Pages and Sergey Grudinin
- Contact: Sergey Grudinin
- Publication: Smooth orientation-dependent scoring function for coarse-grained protein quality assessment
- URL: https://team.inria.fr/nano-d/software/sbrod/

5.28. Ornate

KEYWORDS: Bioinformatics - Machine learning - Neural networks
FUNCTIONAL DESCRIPTION: Oriented Routed Neural network with Automatic Typing is a method for protein quality assessment. Ornate is a residue-wise scoring method. It first constructs a three dimensional map representing the structure of the residue, and its neighborhood.

- Participants: Guillaume Pages, BENOIT CHARMETTANT and Sergey Grudinin
- Contact: Sergey Grudinin
- Publication: Protein model quality assessment using 3D oriented convolutional neural networks
- URL: https://team.inria.fr/nano-d/software/ornate/

5.29. SAMSON-AR-LAMMPS

KEYWORDS: Algorithm - Molecular simulation - 3D modeling

- Authors: Sémého Edorh, Krishna Kant Singh and Dmitriy Marin
- Partner: Inria
- Contact: Stéphane Redon
- URL: http://samson-connect.net

6. New Results

6.1. Generating conformational transition paths with low potential-energy barriers for proteins

Participants: Minh Khoa Nguyen, Léonard Jaillet and Stéphane Redon.
Publication: Journal of Computer-Aided Molecular Design, 2018 [66].

The knowledge of conformational transition paths in proteins can be useful for understanding protein mechanisms. Recently, we have introduced the As-Rigid-As-Possible (ARAP) interpolation method, for generating interpolation paths between two protein conformations. The method was shown to preserve well the rigidity of the initial conformation along the path. However, because the method is totally geometry-based, the generated paths may be inconsistent because the atom interactions are ignored. Therefore, we introduce a new method to generate conformational transition paths with low potential-energy barriers for proteins. The method is composed of three processing stages. First, ARAP interpolation is used for generating an initial path. Then, the path conformations are enhanced by a clash remover. Finally, Nudged Elastic Band, a path-optimization method, is used to produce a low-energy path. Large energy reductions are found in the paths obtained from the method than in those obtained from the ARAP interpolation method alone. The results also show that ARAP interpolation is a good candidate for generating an initial path because it leads to lower potential-energy paths than two other common methods for path interpolation (see Figure 1 for an example of optimized transition path).

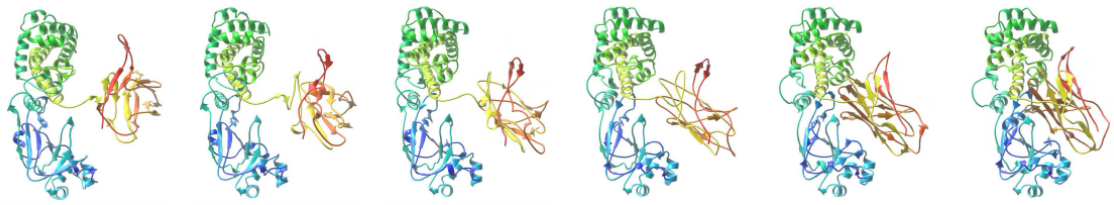

Figure 1. The path for diphtheria toxin after ARAP interpolation and NEB optimization.

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

Participants: Minh Khoa Nguyen, Leonard Jaillet, Stephane Redon.
Publication: Journal of Computational Chemistry, 2018 [65].

We have proposes a method to efficiently generate approximate ligand unbinding pathways. 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 (see Figure 2).

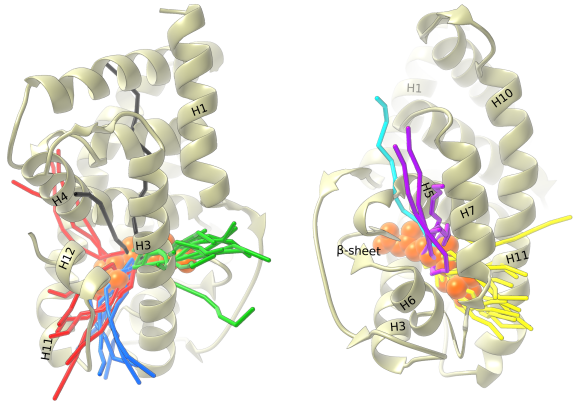

Figure 2. Families of paths (in colored sticks) obtained with ART-RRT for the unbinding of retinoic acid hormone from its receptor. The protein is represented by ribbons and the ligand by orange balls.

6.3. Atomistic modelling and simulation of transmission electron microscopy images: application to intrinsic defects of graphene

Participants: Cyril Guedj, Léonard Jaillet, François Rousse and Stéphane Redon.
Publication: Proceedings of 8th International Conference on Simulation and Modeling Methodologies, Technologies and Applications - Volume 1: SIMULTECH [53].
The characterization of advanced materials and devices in the nanometer range requires complex tools, and the data analysis at the atomic level is required to understand the precise links between structure and properties. We have demonstrated that the atomic-scale modelling of graphene-based defects may be performed efficiently for various structural arrangements using the Brenner module of the SAMSON software platform (cf Figure 3). The signatures of all kinds of defects are computed in terms of energy and scanning transmission electron microscopy simulated images. The results are in good agreement with all theoretical and experimental data available. This original methodology is an excellent compromise between the speed and the precision required by the semiconductor industry and opens the possibility of realistic in-silico research conjugated to experimental nanocharacterisation of these promising materials.

6.4. Impact of hydrogen on graphene-based materials: atomistic modeling and simulation of HRSTEM images.

Participants: Cyril Guedj, Léonard Jaillet, François Rousse and Stéphane Redon.
Oral presentation: AVS 65th International Symposium and Exhibition.
Summary: The hydrogen energy transition is highly probable, because hydrogen is the most abundant element in the universe and represents an ideal “green” source of energy. Meanwhile, the safe hydrogen production and storage remains a major challenge still in progress. To understand and optimize the device efficiency and the interface engineering, it is advantageous to perform advanced nanocharacterizations, linked to numerical modelling and simulations. This task is particularly difficult, because hydrogen is labile and prone to rapid reorganization. This structural evolution may be monitored with transmission electron microscopy (TEM) techniques, but in spite of significant progresses, the direct detection of hydrogen with High Resolution Scanning Transmission Electron Microscopy (HRSTEM) or energy-loss spectroscopy still remains a serious challenge.

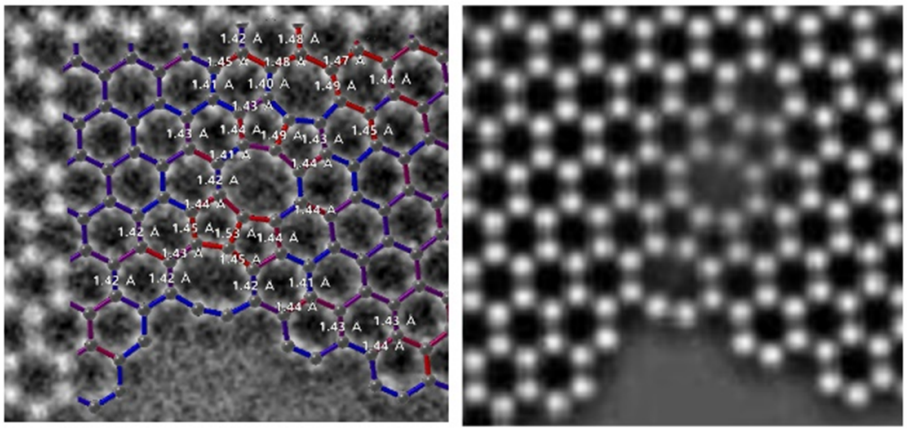

Figure 3. Left: atomistic model of the extended defect 88-7-5555 defect superimposed to the experimental HRTEM image entitled "SALVE-III-project-HRTEM-graphene-vacancy-characteristic-defects.png" (Salve, 2018). Right: corresponding simulated HRTEM image.

We investigate here the interaction of hydrogen with graphene using the Brenner module of the SAMSON software platform and we propose an original methodology to characterize its structural arrangement at the atomic scale by simulating HRSTEM images to interpret experimental results. In particular, we compare the effect of hydrogen on dark field (DF), bright field (BF), high-angle annular dark filed (HAADF) and annular bright field (ABF) images, to estimate the best technique suited to hydrogen detection. In addition, we present the effect of carbon vacancies and adatoms on the stability of hydrogen coverage, associated to the HRSTEM signatures of the most stable configurations. These results provide the necessary building blocks to analyze the structure and energetics of hydrogenated graphene-based materials at the atomic scale.

6.5. Atomistic modelling of diamond-type $Si_xGe_yC_zSn_{1-x-y-z}$ crystals for realistic transmission electron microscopy image simulations

Participants: Leonard Jaillet and Cyril Guedj.
The realistic simulations of transmission electron microscopy (TEM) images requires an accurate definition of the positions of all atoms, which are linked to the mechanical properties of the material. We are working on an approach to build optimized models to represent the lattice parameters and elastic properties of Si, Ge, diamond, alpha-tin and related diamond alloys.

In order to compute precisely the complex $Si_xGe_yC_zSn_{1-x-y-z}$ diamond crystals, a dedicated parametrization of the Keating force field has been proposed. An original periodic boundary strategy has also been provided. Our tool can be used to interpret experimental TEM with a speed several orders of magnitude higher than for ab-initio methods. The method predicts the correct lattice parameters and elastic constants for published experimental results with low deviation. Finally, we have shown that subsequent Monte Carlo simulations predict original self-ordering effects in C in good agreement with the theory. A publication is in preparation on this topic.

6.6. Analytical symmetry detection method AnAnaS

Participants: Guillaume Pagès, Sergei Grudinin, Elvira Kinzina.
Publications: Journal of Structural Biology, 2018 [21], Journal of Structural Biology, 2018 [20].

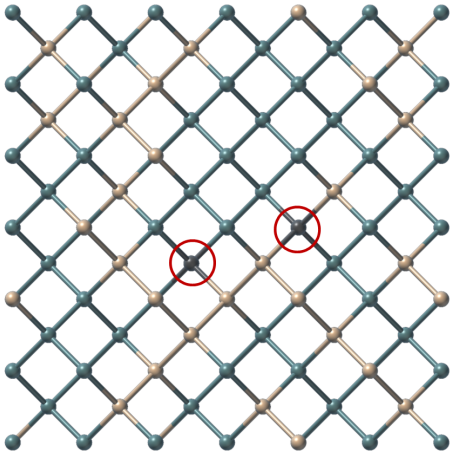

Figure 4. Crystal of $Si_{40}Ge_{60}$ where two carbon atoms (circled in red) have been inserted. The properties of the crystal such as its lattice parameter can be characterized in function of the position of the carbon atoms.

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.

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 papers describing the method were published [21], [20]. This method is available on the website of the team (https://team.inria.fr/nano-d/software/ananas/).

6.7. Deep Learning for Symmetry detection

Participants: Guillaume Pagès, Sergei Grudinin.
Publication: arXiv preprint, 2018 [29].

We worked on a fully-structural method for detecting symmetries in molecular structures. This allowed 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 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°. A manuscript describing this method has been submitted for publication and is available on arXiv [29].

6.8. New method for protein model quality assessment Ornate

Participants: Benoit Charmettant, Guillaume Pagès, Sergei Grudinin.
Publication: bioRxiv preprint, 2018 [28].

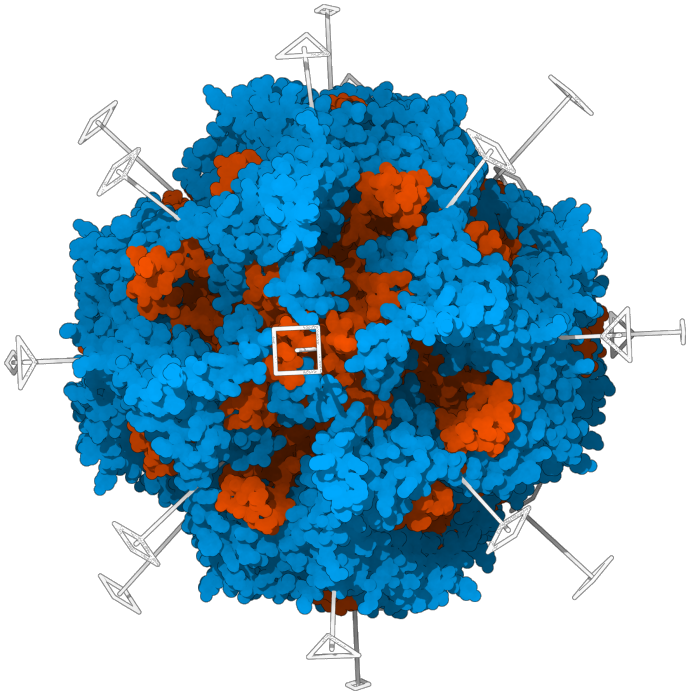

Figure 5. System with an octahedral symmetry, with the symmetry axes displayed in SAMSON.

Protein model quality assessment (QA) is a crucial and yet open problem in structural bioinformatics. It consists of estimating a score to assess whether a given three-dimensional structure is correctly folded or not. The current best methods for single-model QA typically combine results from different approaches, each based on different input features constructed by experts in the field. Then, the prediction model is trained using a machine-learning algorithm. Recently, with the development of convolutional neural networks (CNN), the training paradigm has changed. In computer vision, the expert-developed features have been significantly overpassed by automatically trained convolutional filters. This motivated us to apply a three-dimensional (3D) CNN to the problem of protein model QA.

We developed a novel method for single-model QA called Ornate. Ornate (Oriented Routed Neural network with Automatic Typing) is a residue-wise scoring function that takes as input 3D density maps. It predicts the local (residue-wise) and the global model quality through a deep 3D CNN. Specifically, Ornate aligns the input density map, corresponding to each residue and its neighborhood, with the backbone topology of this residue. This circumvents the problem of ambiguous orientations of the initial models. Also, Ornate includes automatic identification of atom types and dynamic routing of the data in the network. Established benchmarks (CASP 11 and CASP 12) demonstrate the state-of-the-art performance of our approach among single-model QA methods. A manuscript describing this method has been submitted for publication and is available on bioRxiv [28].

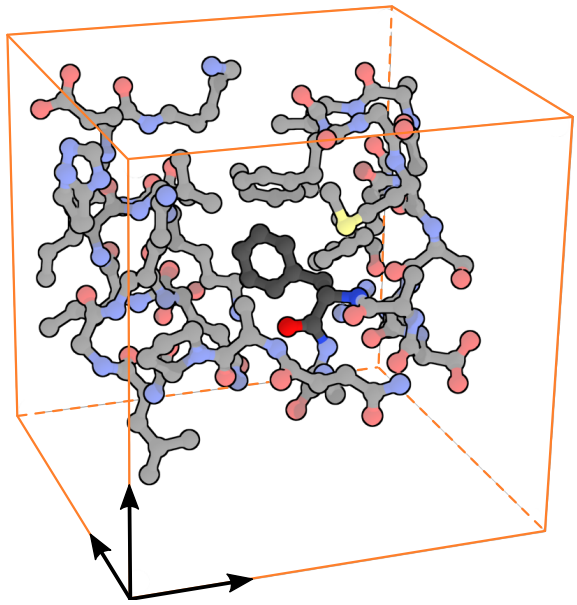

Figure 6. Example of input given to the 3D CNN Ornate.

7. Partnerships and Cooperations

7.1. Regional Initiatives

- Sergei Grudinin has obtained an IDEX UGA grant. It covers 2 years of post-doc of Didier Devaurs, starting from December 2018.
- Doctoral UGA grant covers PhD thesis of Maria Kadukova (supervised by Sergei Grudinin).

7.2. National Initiatives

7.2.1. ANR

In 2018, NANO-D had funding from one ANR program:

- **ANR PRCI**: covers PhD thesis of Guillaume Pages.

7.3. European Initiatives

7.3.1. Collaborations with Major European Organizations

Partner 1: The European Bioinformatics Institute (EMBL-EBI), Protein Data Bank in Europe (PDBe) team, Hinxton (UK)

We are collaborating on the integration of methods developed in the team into the PDBe web resource.

Partner 2: The Institute Laue-Langevin (ILL), the bioSANS team, Grenoble (France)

We are collaborating on the development of neutron small-angle scattering software.

Partner 3: The Ecole polytechnique fédérale de Lausanne (EPFL), Laboratory for Biomolecular Modeling, Lausanne (Switzerland)

We are collaborating on the integrative structural biology approaches.

7.4. International Initiatives

7.4.1. Inria International Partners

7.4.1.1. Declared Inria International Partners : BIOTOOLS

Title: Novel Computational Tools for Structural Bioinformatics

International Partner (Institution - Laboratory - Researcher):

MIPT (Russia (Russian Federation)) - Department of Control and Applied Mathematics - Vadim Strijov

Duration: 2016 - 2020

Start year: 2016

Abstract : The general scientific objectives of the forthcoming collaboration are the new developments of computational tools for structural bioinformatics. In particular, we plan to collaborate on several subjects: 1. Development of tractable approximations for intractable combinatorial problems in structural biology. 2. Development of new computational tools for scattering experiments. 3. Machine learning for structural bioinformatics.

7.4.1.2. Informal International Partners

- University of Stony Brook, lab of Dima Kozakov (USA). We have been collaborating on the development of novel protein docking methods.
- University of Vilnius, department of Bioinformatics (Lithuania). We have been collaborating on the development of novel protein docking methods.
- KU Copenhagen (Denmark), department of Chemistry. We collaborate on the integrative structural biology approaches.
- Autonomous University of Madrid (Spain), Bioinformatics Unit. We collaborate on the development of computational methods for protein flexibility.
- Francis Crick Institute, London (UK), Biomolecular Modelling Laboratory. We collaborate on the development of flexible protein docking methods.

7.4.2. Participation in Other International Programs

Our team has obtained the PHC Gilibert grant for a 2-year collaboration with the Vilnius University (Lithuania). Our partner is the Department of Bioinformatics, http://www.bti.vu.lt/en/departments/department-of-bioinformatics.

7.5. International Research Visitors

7.5.1. Visits of International Scientists

- Karina Dos Santos Machado, lecturer at the Federal University of Rio Grande (FURG, Brazil), Oct 2018 - Oct 2019.

7.5.1.1. Internships

- Amal Akkari (Mohammed V University, Rabat, Morocco), Jun 2018 - Nov 2018.
- Khalid Mustafin (MIPT Moscow, Russia), Sep 2018 - Feb 2019.

7.5.2. Visits to International Teams

Sergei Grudinin has visited and gave talks in the following research labs :

- Department of Bioinformatics, University of Vilnius, Lithuania, May 10-11, 2018.
- The team of Dima Kozakov,Stony Brook University, USA, November 12th-14th, 2018.
- The team of Simon Billinge, Columbia University, USA, November 15th, 2018.
- Department of Biology, University of Copenhagen, Denmark, November 19th, 2018.
- Department of Chemistry, University of Copenhagen, Denmark, November 22nd, 2018.
- Department of Bioinformatics, State Belorussian University, Minsk, Belarus, Dec 28, 2018.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Reviewer

- Léonard Jaillet has been reviewer for the IROS 2018 conference (International Conference on Intelligent Robots and Systems).
- Sergei Grudinin was a reviewer for the BIBM'18 conference (The IEEE International Conference on Bioinformatics and Biomedicine), and 6th International Work-Conference on Bioinformatics and Biomedical Engineering (IWBBIO 2018).

8.1.2. Journal

8.1.2.1. Reviewer - Reviewing Activities

Sergei Grudinin has reviewed submissions for the following journals : PLOS Computational Biology, Journal of Computer–Aided Molecular Design, Bioinformatics, Computational Biology and Chemistry, Journal of Computational Chemistry, Proteins, Nature, BMC Bioinformatics, The Journal of Physical Chemistry, IEEE Access, Accounts of Chemical Research, Computational and Structural Biotechnology Journal.

8.1.3. Invited Talks

- Sergei Grudinin gave an invited talk 'Algorithms for Protein–Protein Docking' at the Meet–U 2018 course on structural bioinformatics, Paris, 2018.
- Sergei Grudinin gave an invited talk 'Using Machine Learning for Structure–Based Predictions of Protein–Ligand Interactions' at the 7th French–Japanese Workshop on Computational Methods in Chemistry, Strasburg, 2018.
- Sergei Grudinin gave an invited talk 'Novel Methods for Structural Bioinformatics' at the GDR BIM / GT Méthodes Algorithmiques pour les Structures et Interactions, Paris 2018.
- Sergei Grudinin gave an invited talk 'Using machine learning to predict protein structure and interactions' at the VIth International Conference "Chemistry, Structure and Function of Biomolecules", Minsk, 2018.

- Sergei Grudinin gave an invited talk 'Predicting protein interactions with protein flexibility and small-angle scattering profiles' at the Modeling of Protein Interactions (MPI) 2018 conference, November 8-10, Lawrence, KS, USA.
- Sergei Grudinin gave an invited talk on data-assisted modeling of protein structures at the CASP13 conference, Iberostar Paraiso, Riviera Maya, Mexico December 1-4, 2018.
- Sergei Grudinin gave an invited talk 'Artificial Intelligence for Learning Protein Interactions' at the 4th International Conference on Mathematical and Computational Medicine, December 3-7, 2018, Cancun, Mexico.

8.1.4. Leadership within the Scientific Community

Sergei Grudinin with his colleagues from ILL has organized a new data-assisted (SANS) sub-challenge for the CASP13 community-wise protein structure prediction exercise.

8.1.5. Scientific Expertise

Sergei Grudinin reviewed an application for the OPUS funding scheme at the National Science Center, Poland.

8.2. Teaching - Supervision - Juries

8.2.1. Supervision

PhD : Phd thesis defence of Minh Khoa Nguyen, Université Grenoble Alpes, 2018
Title: Efficient exploration of molecular paths from As-Rigid-As-Possible approaches and motion planning methods [67].
Thesis committee: Emmanuel Mazer, Léonard Jaillet, Stéphane Redon, Juan Cortes, Charles Robert, Dirk Stratmann.
Summary: In this dissertation, we are particularly interested in developing new methods to find for a system made of a single protein or a protein and a ligand, the pathways that allow a transition from one state to another. During a few past decades, a vast amount of computational methods has been proposed to address this problem. However, these methods still have to face two challenges: the high dimensionality of the representation space, associated to the large number of atoms in these systems, and the complexity of the interactions between these atoms. This dissertation proposes two novel methods to efficiently find relevant pathways for such biomolecular systems. The methods are fast and their solutions can be used, analyzed or improved with more specialized methods. The first proposed method generates interpolation pathways for biomolecular systems using the As-Rigid-As-Possible (ARAP) principle from computer graphics. The method is robust and the generated solutions best preserve the local rigidity of the original system. An energy-based extension of the method is also proposed, which significantly improves the solution paths. However, in the scenarios requiring complex deformations, this approach may still generate unnatural paths. Therefore, we propose a second method called ART-RRT, which combines the ARAP principle for reducing the dimensionality, with the Rapidly-exploring Random Trees from robotics for efficiently exploring possible pathways. This method not only gives a variety of pathways in reasonable time but the pathways are also low-energy and clash-free, with the local rigidity preserved as much as possible. The mono-directional and bi-directional versions of the ART-RRT method were applied for finding ligand-unbinding and protein conformational transition pathways, respectively. The results were found to be in good agreement with experimental data and other state-of-the-art solutions.

PhD : Phd thesis defence of Alexandre Hoffmann, Université Grenoble Alpes, 2018
Title: Docking Flexible Proteins using Polynomial Expansions.
Thesis committee: Valérie Perrier, Slavica Jonic, Florence Tama, Sergei Grudinin, Marc Delarue, Roland Hildebrand.
Summary: This thesis focuses on two main axes. The first axis is the development of a new method that exhaustively samples both rigid-body and collective motions computed via normal mode analysis (NMA). We first present a method that combines the advantages of the fast Fourier

transform (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 and flexible conformation. The algorithm first samples a quadratic approximation of a scoring function on a 6D grid. Then, the method performs the flexible search by maximizing the quadratic approximation of the cost function within a certain search space. We then present a multi-step version of our algorithm, which finds the collective motions that maximize the docking score with respect to the rigid-body degrees of freedom (DOFs). The method exhaustively samples both rigid- body and collective motions by maximizing the soft maximum over the rigid body DOFs of the docking/fitting cost function. Both methods were applied to docking problems on both real and artificial example and we were able to design a benchmark in which the "fit then refine" approach fails at finding the correct conformation while our method succeeds.

The second axis is the development of a new extrapolation of motions computed by NMA. We show that it is possible, with minimal computations, to extrapolate the instantaneous motions computed by NMA in the rotations-translations of blocks (RTB) subspace as an almost pure rotation around a certain axis. We applied this non-linear block (NOLB) method on various biological systems and were able to, firstly, retrieve biologically relevant motions and secondly, to demonstrate that the NOLB method generates structures with a better topology than a linear NMA method.

PhD : Phd thesis defence of Semeho Prince A. Edorh, Université Grenoble Alpes, 2018
Title: Incremental Algorithm for long range interactions [11].
Thesis committee: Stephane Redon, Olivier Coulaud, Matthias Bolten, Jean-Louis Barrat, Stefano Mossa, Jerôme Mathe.
Summary: Particle simulations have become an essential tool in various fields such as physics, astrophysics, biology, chemistry, climatology, and engineering, to name few. Usually, these computer simulations produce a temporal evolution of the system of interest by describing the motion of particles. In order to perform reliable simulations, we must provide an accurate description of interaction forces undergone by each particle. In most cases, these forces mirror inter-particle interactions and depend on relative coordinates of the particles. Moreover, pairwise long-range interactions are generally the cornerstone of particle simulations, an example being gravitational forces that are so essential in astrophysics. In molecular simulations, electrostatic forces are the most common illustration of long-range interactions. Furthermore, due to their computational cost, pairwise long-range interactions are the bottleneck of particle simulations. Therefore, sophisticated algorithms must be used for efficient evaluations of these interactions. In this thesis, we thus propose algorithms which may reduce the cost of long-range interactions when the studied system is governed by a particular dynamics. Precisely, these so-called «incremental» algorithms are effective for simulations where a part of the system remains frozen awhile. In particular, our algorithms will be validated on systems whose particles are governed by the so-called Adaptively Restrained Molecular Dynamics (ARMD) which is a promising approach in molecular dynamics simulations. Although several incremental algorithms introduced by this thesis will be devoted to molecular dynamics simulations, we believe that they can be generalized to all kinds of long-range interactions.

PhD in progress : Maria Kadukova, "Novel computational approaches for protein ligand interactions", Sep 2016-, supervisors: Sergei Grudinin (France) and Vladimir Chupin (MIPT, Russia).

PhD in progress : Guillaume Pagès, "Novel computational developments for protein structure prediction", Apr 2016-, supervisors: Sergei Grudinin (Inria), Valentin Gordeliy (IBS).

8.3. Popularization

8.3.1. Articles and contents

Sergei Grudinin and Guillaume Pagès were interviewed by Le Figaro about the progress of deep learning and artificial intelligence in protein structure prediction [88].

9. Bibliography

Major publications by the team in recent years

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