INTEGRATED COMPUTATIONAL APPROACHES FOR BIOSYSTEMS (AND BIOMATERIALS)

Some activities and perspectives of the Theoretical Chemistry Group in Padua - 2008-2010

antonino.polimeno@unipd.it
http://www.chimica.unipd.it/antonino.polimeno
Une ville, une campagne, de loin c'est une ville et une campagne, mais à mesure qu'on s'approche, ce sont des maisons, des arbres, des tuiles, des feuilles, des herbes, des fourmis, des jambes de fourmis, à l'infini. Tout cela s'enveloppe sous le nom campagne. (B. Pascal - Pensées)

[A town, a country-place, is from afar a town and a country-place. But, as we draw near, there are houses, trees, tiles, leaves, grass, ants, limbs of ants, in infinity. All this is contained under the name of country-place.]
Nuclear Magnetic Resonance (NMR) is a powerful tool to investigate the complex dynamics in proteins.

Macroscopic observables are the $^{15}$N, $^{13}$C and $^2$H relaxation times $T_1$, $T_2$ and NOE.

Relation of relaxation times to microscopic properties, in the Redfield limit, is given by\(^1\)

\[
\frac{1}{T_1} = \frac{\mu_0}{4\pi} \frac{\gamma_H \gamma_N}{r_{NH}^3} \left[ J^{Dip}(\omega_H - \omega_N) + 3J^{Dip}(-\omega_N) + 6J^{Dip}(\omega_H + \omega_N) \right] + \frac{2}{15} \frac{\omega_N^2}{\delta_{CSA}^2} J^{CSA}(-\omega_N)
\]

\[
\frac{1}{T_2} = \frac{\mu_0}{8\pi} \frac{\gamma_H \gamma_N}{r_{NH}^3} \left[ 4J^{Dip}(0) + J^{Dip}(\omega_H - \omega_N) + 3J^{Dip}(-\omega_N) + 6J^{Dip}(\omega_H) + 6J^{Dip}(\omega_H + \omega_N) \right] + \frac{2}{45} \frac{\omega_N^2}{\delta_{CSA}^2} \left[ 3J^{CSA}(-\omega_N) + 4J^{CSA}(0) \right]
\]

\[
NOE = 1 + \frac{\mu_0}{4\pi} \frac{\gamma_H^2}{r_{NH}^3} \frac{\gamma_N^2}{r_{NH}^3} T_1 \left[ 6J^{Dip}(\omega_H + \omega_N) - J^{Dip}(\omega_H - \omega_N) \right]
\]

Spectral densities are calculated within the framework of the theoretical model of the dynamics of the system.
Many body models / Efficient implementation
— Friction tensor properties via hydrodynamics models
— Structure & magnetic properties via QM or hybrid (QM-MM) methods
— Minimization of free (fitted) parameters

**Integrated Computational Approach**

**Quantum Mechanical** calculation pursued by Density Functional Theory (DFT) via adoption of mixed quantum-mechanical / molecular mechanical (QM/MM) methods

- **MOLECULAR GEOMETRY**
- **ELECTRONIC STRUCTURE**

Dissipative parameters, e.g. rotational diffusion tensors, can be determined via **hydrodynamic modelling**

- Principal values and orientation of **electron Zeeman** tensor and **hyperfine coupling** tensors

- Additional interactions; e.g. in double labeled systems, **dipolar interaction** based on the molecular structures beyond the point approximation

- **DIFFUSION TENSOR**
- **g, A TENSORS**
- **DIPOLE-DIPOLE TENSOR**

Interpretation based on **Stochastic Liouville Equation** (SLE) defined by the direct inclusion of motional dynamics via stochastic operators plus super Hamiltonian $H$
MD/SRLS integrated analysis of plexin-B1
Electron Spin Resonance

♦ **Labelled Peptides**


♦ **Materials**


♦ **Biological Macromolecules**

The oligopeptide is labeled with two nitroxide radicals, in the form of $\alpha$-amino acid TOAC (2,2,6,6-tetramethyl-1oxyl-4amino-4-carboxylic acid)

\[
\tilde{\Gamma} = D_{XX} \hat{J}_X^2 + D_{YY} \hat{J}_Y^2 + D_{ZZ} \hat{J}_Z^2
\]

\[
\hat{H} = \frac{\beta_e}{\hbar} \mathbf{B}_0 g_1 \hat{S}_1 + \frac{\beta_e}{\hbar} \mathbf{B}_0 g_2 \hat{S}_2 + \gamma_e \hat{I}_1 A_1 \hat{S}_1 + \gamma_e \hat{I}_2 A_2 \hat{S}_2 - 2\gamma_e \hat{J} \hat{S}_1 \hat{S}_2 + \hat{S}_1 T \hat{S}_2
\]


Simulations of cw-ESR spectra of the peptide in four different solvents. Red solid line are experimental spectra, black dashed line are theoretical spectra.

Acetonytrile  Chloroform  Methanol  Toluene
**Diego Frezzato** – attività di ricerca recente/attuale

Sviluppo di metodi per campionare l’energetica di sistemi molecolari mediante trasformazioni guidate di non-equilibrio.

- Sviluppo di protocolli di trasformazione, ad es. Monte Carlo con “configurational freezing” (in collaborazione con R. Chelli, Firenze)
- Calcolo di costanti di binding molecola-proteina (in collaborazione con R. Chelli, Firenze)
- Energie libere di stati fotoeccitati da spettri UV-Vis
- Uso computazionale dell’identità di Jarzynski: sviluppo di metodi di integrazione multidimensionale (con M. Zerbetto)

Riduzione di dimensionalità nella descrizione delle cinetiche chimiche, caratterizzazione della componente lenta (superfici “slow-manifolds”) (con P. Nicolini, Barcellona)

Studio dell’effetto paramagnetico sul rilassamento NMR in H$_2$@C$_{60}$ funzionalizzato con nitrossidi.
(con A. Bagno, F. Rastrelli, Padova, e N. J. Turro, Columbia)
Laura Orian - Mechanistic aspects of GPx-catalyzed $\text{H}_2\text{O}_2$ reduction

A state-of-the-art accurate quantum chemistry computational approach is used to investigate the mechanism of $\text{H}_2\text{O}_2$ reduction at the active site of glutathione peroxidases (GPx). In the model we consider explicitly six aminoacids surrounding the catalytic selenocysteine (SeCYS) or cysteine (CYS) residue. The aim is to investigate carefully the geometries of the plausible intermediate species.

![Diagram of reaction cycle](image)

**Figure 2:** Experimentally suggested mechanism for the catalytic cycle of GPx.

-5 Kcal mol$^{-1}$
-62 Kcal mol$^{-1}$

*L. Orian, A. Polimeno, S. Toppo, A. Ursini in preparation*
People & resources

— Antonino Polimeno
— Giorgio Moro
— Laura Orian (ab initio, DFT, QM methods)
— Diego Frezzato (stochastic modeling, advanced theoretical methods)
— Silvia Carlotto (microfluidics, GA, Md methods)
— Mirco Zerbetto (integrated approaches, MD, ESR, EPR)
— Mauro Torsello (solvation models and protein dynamics)
— Nicola Fortunati (MD, coarse-graining methods for soft materials)
— Gianpietro Sella (LICC manager)
LICC Laboratorio Interdipartimentale di Chimica Computazionale

Address
14th JULY 2009
Università degli Studi di Padova
Dipartimento di Scienze Chimiche
Via Marzolo 1 35131 Padova ITALY
Scientific coordinator: Antonino Polimeni
System manager: Gian Pietro Sella

Presentation
14th JULY 2009
LICC is a laboratory of the Department of Chemistry at the University of Padova, dedicated to computational chemistry. The facility is open to researchers of the University of Padova. Main activities are devoted to computational and theoretical chemistry through a wide range of theoretical approaches and computational techniques, all focused on the interpretation, simulation, characterization and rationalization of complex molecular systems, functionalized materials at nanoscale, biomolecular processes.

Read More >

Activities
15th JULY 2009
LICC is a computational facility dedicated to in silico description of soft- and hard materials and biosystems.

Read More >

Software repository
16th JULY 2009
A repository of software is available for diverse chemical applications, under open source license.

Read More >

A software suite for magnetic spectroscopies
25th APRIL 2006
We have recently made available new software tools aimed at the interpretation of dynamical properties of molecules in fluids from electron spin resonance (ESR) measurements and nuclear magnetic resonance (NMR). The new codes implement an integrated computational approach (ICA) for the calculation of relevant molecular properties that are needed in order to obtain spectral lines. The protocol encompasses information from atomistic level (quantum mechanical) to coarse grained level (hydromechanical), and evaluates ESR/NMR spectra for rigid or flexible single or multi-labelled paramagnetic molecules in isotropic and ordered phases, based on a numerical solution of a stochastic Liouville equation.

Read More >

http://www.chimica.unipd.it/licc
C++OPPS (COupled Protein Probe Smoluchowski) is a new tool which combines the SRLS model for the dynamics and a hydrodynamic approach to the calculation of diffusion tensor in a user-friendly program.

The new features of C++OPPS include:
- **Graphical user interface** written in JAVA
- calculation core written in the **modern object-oriented C++**
- the code is **parallelized under the MPI paradigm**
- OS-independent **web interface** to easily access to the cluster version

*M. Zerbetto, A. Polimen, E. Meirovitch Int. J. Q. Chem. 110, 387 (2009)*
C++OPPS - Graphical Interface

(A)

(B)

(C)

(D)
DiTe (Diffusion Tensor) is a program to calculate the diffusion tensor of rigid and flexible molecules.

- Algorithm written in C, graphic interface in JAVA

- Flexible molecules:
  - automatic recognition of topology
  - automatic generation of conformations
Electron Spin Resonance Simulation is a multiscale software for the ab-initio calculation of cw-ESR spectra. The core of E-SpiReS is written in C and parallelized under the MPI paradigm. The graphic user interface (GUI) is written in JAVA to ensure good portability in every operating system.

- Full diffusion tensor is calculated via a hydrodynamic model that
- Molecules can be chosen to define the stochastic Liouville operator
- Graphical definition of the stochastic Liouville equation
- All physical and calculation parameters are set here
- Non-rigid molecules can be described with internal degrees of freedom
- Quantum Mechanical calculations are employed:
  (i) Structural properties like geometry and torsional potentials;
  (ii) Magnetic properties, i.e. the magnetic tensors.

E-SpiReS automatically generates an input file for Gaussian that can be edited by the user and submitted directly from the GUI.

A number of parameters can be chosen to refine via a non-linear least squares minimization routine based on the Levenberg-Marquardt method.

Also an experimental spectrum can be loaded as reference.
AVOGADRO:
- 71 nodi Intel Wordcrest Dual Core, 4 CPU, 2.6 GHz
- 8 nodi XEON 8 Core, 2.66 GHz

CURIE:
- 5 nodi AMD OPTERON 16 Core, 2 GHz + 2 GPU nVidia Tesla M2050 per nodo
- 2 nodi AMD OPTERON 12 Core, 2.2 GHz + 2 GPU nVidia Tesla 2090 per nodo

DALTON:
- 8 nodi IBM POWER6 8 Core, 4.2 GHz
- 6 nodi XEON X5650 24 Core, 2.67 GHz