Associate Researcher at the 'Laboratoire de Physique Moléculaire' (LPM) of Besançon (December 2002 - June 2005).

During my stay at the LPM, I have contributed to develop the group of Biophysics which had been initiated by Prof. Christophe Ramseyer (physicist).

The essential part of my work consisted in theoretical computational studies dealing with lipidic systems and the membrane protein KcsA as well as reactions implied in cancer, by quantum methods.

- Quantum calculations on lipidic systems and the membrane protein KcsA.

I performed ab initio calculations of the partial charge distribution on the lipid dioctadecylamine (DODA), using the suite of programs Gaussian 98. This resulted in an article published in the journal '*Chemical Physics Letters*'. Three optimized conformations of DODA were analyzed (completely stretched, slightly and strongly twisted), as well in gas phase as in presence of a solvent (dielectric continuum of Tomasi and co-workers or Langevin dipoles of Florián and Warshel). We focused on atomic charges derived from the electrostatic potential according to the Merz-Kollman-Singh scheme. After comparison of the charges obtained at different levels of theory on the stretched form of DODA, we showed that gas phase charges were sufficient to represent what appeared to be an intrinsic property of the lipid, independently from the solvent. As the molecule becomes distorted, significant partial charge fluctuations appear along the aliphatic chains. I also studied a series of DODA analogous molecules. For proteins for instance, this work shows how important it would be to develop force fields with conformation-dependent charges to correctly describe their dynamics.

This work has represented an essential step for modelling KcsA, a potassium channel whose 3D structure has been recently awarded by a Nobel price. I performed ab initio calculations of partial charges for two specific conformations of the selectivity filter of KcsA. This resulted in a publication in *Chemical Physics Letters* of an article which has been recognized as being an important contribution to the field. Other studies, more focused on electrostatic potential calculations, led to results obtained on the basis of the molecular dynamics studies of Dr M. Compoint, about the structuring role of water molecules within the protein (*Phys. Chem. Chem. Phys.*) and the behaviour of the sequence KWKWK...K (*Internet Electr. J. Mol. Des.*). We also argued about the role of partial charges for selectivity between potassium and sodium ions in this type of channel (*J. Chem. Phys.*).

- Study of important reactions for cancer mechanisms and prevention.

In collaboration with Prof. Janez Mavri, of the University of Ljubljana in Slovenia, I evaluated the chemical reactivity of ultimate carcinogens using two types of computational approaches: Linear Free Energy Relationships (LFER) or direct determination of activation energy. LFER was used to compare reactivity levels of estradiol or estrone 3,4-quinones towards guanine (*J. Chem. Inf. Comput. Sci.*), and the four benzo[*a*]pyrene diol epoxide (BPDE) stereoisomers toward guanine and adenine (*J. Mol. Struct., Theochem*). We have shown that there is no preferential reactivity of the estradiol quinone derivative compared to the estrone one towards guanine, an important result to consider as for the carcinogenic properties of estrogens. In the study of BPDE, 32 different reaction possibilities were examined, considering either cyclic or exocyclic amino group nucleophilic attack, with *cis* or *trans* adducts. The aim was to understand why only one of the four stereoisomers is generally showing very high carcinogenicity, relating this property to a difference in reactivity. This latter work was done together with a student I supervised for her Master I in Chemistry. The height of the activation energy barrier was calculated for the reaction between BPDE and the polyphenol ellagic acid, a potent chemopreventive agent active against cancers caused by polycyclic aromatic hydrocarbons. We obtained very good agreement with experimental value (*J. Chem. Inf. Model.*). In both approaches, semiempirical MO (PM3) and density functional theory (DFT) calculations were performed, whereas the effect of a polar environment was included using either the Polarizable Continuum Model or the Langevin dipoles method.

- Parallely:

- In the framework of a project on the protein ANT (Adenine Nucleotide Translocase), I developed collaborations with Dr Daniel Fau (laboratory of Histology, faculty of Pharmacy/Medicine, Besançon) and Dr Catherine Brenner (laboratory of Genetics and Cellular biology, Versailles), for the setting up of experiments on highly purified ANT-liposomes (spectroscopic measurements).

- I developed a collaboration with the pharmaceutical group "Novartis Institutes for BioMedical Research" (Basel, Switzerland, 'Profiling' group), for studying paracellular passive diffusion and modeling of this nanotransport through biological pores. In this work I supervised a student in Master II of Chemical Physics (2005).