Modelling Absorption Spectra of Furimamide-Nanoluciferase System

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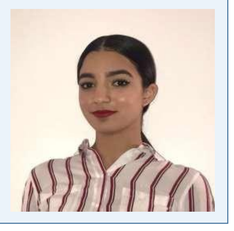
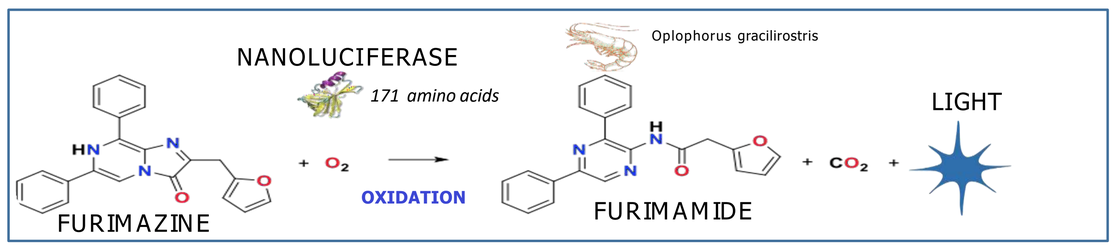


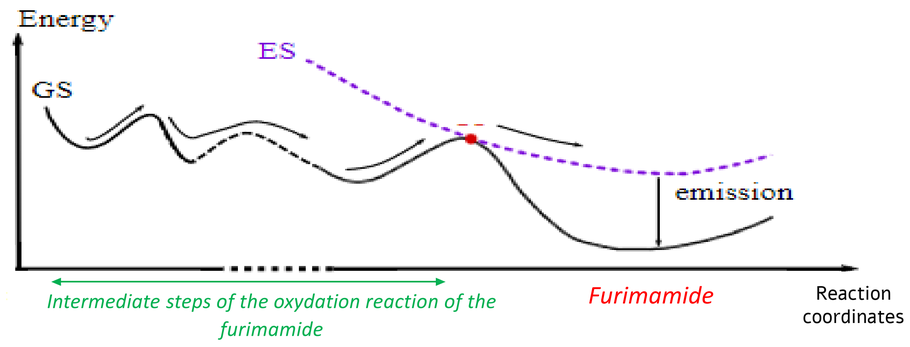
Bioluminescence is a biological phenomenon of light production by living species with many applications[1], notably for the detection of cancer cells[2]. The present study deals with a ligand-protein bioluminescent system (furimazine – Nanoluciferase) derived from a shrimp called *Oplophorus gracilirostri* with a very high luminescence intensity[3]. A better understanding of this system will provide insights to tailor new devices with emission of a photon with a red color, and thus a light signal more easily detectable inside the human body. Simulations of the emission and absorption spectra are relevant tools to comply this goal[4]. We focus here on the absorption spectra of the light emitter system furimamide – Nanoluciferase. In order to take into account the protein environment and the system flexibility, we carry out classical molecular dynamics (MM) with AMBER software. Furimamide is a flexible molecule: standard force fields such as GAFF[5] (General Amber Force Field) are unable to reproduce correctly potential energy along torsion angles when compared to in vacuo DFT computations. Thus, we perform a multidimensional fit using 1D and 2D potential energy surface scans with several torsion angles of the molecule in order to parameterize a new force field. Then, we compute electronic transitions at a QM/MM level of theory on a set of 100 snapshots extracted from MM trajectory. As a perspective, we plan to use the same methodology to simulate emission spectra.

Nanoluc/Furimamide system:

This system derives from a bioluminescent complex of a shrimp species.

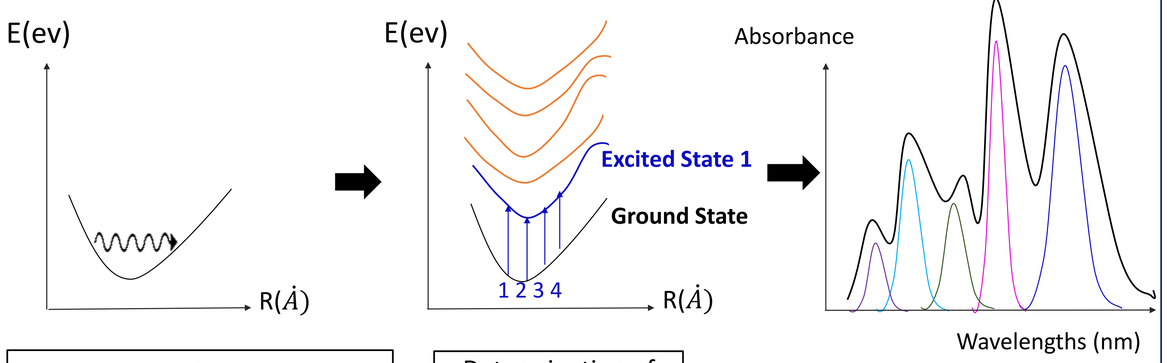


The oxidation of the furimazine, in the cavity of the protein called nanoluciferase, leads to furimamide in its excited state : by fluorescence, it emits light.



Methodology / Spectra simulation:

In order to simulate the absorption spectra, we need to carry out the following steps:



Sampling of the ground potential energy surfaces and determining relevant molecular conformations

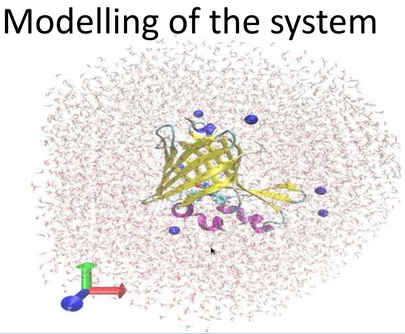
Determination of the electronic transitions and oscillator strengths between two states

Theoretical Absorption Spectra for five excited electronic transitions

How to explore the complex configuration space?

Molecular dynamics allow to calculate the trajectories of a system, the evolution of the positions of each atom of the system over time using Newton's equations of motion.

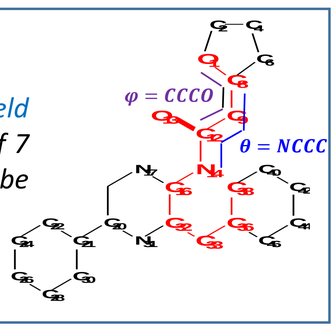
1. Modelling of the system



2. The force field

- FF14SB (Force Field 14 Stony Brook) for the protein
- TIP3P for water molecules
- GAFF2 for the ligand ?

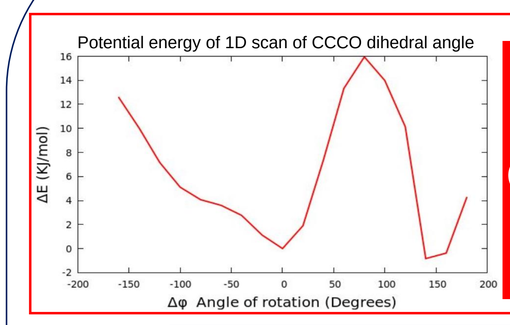
The potential energies calculated using the GAFF2 force field doesn't match with the ones calculated using DFT scans of 7 dihedral angles of the molecule. The force field needs to be adjusted.



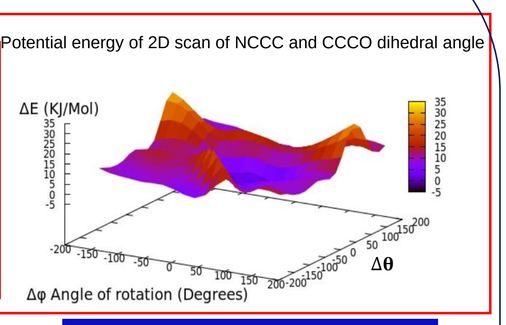
References:

[1] A. J. Syed et J. C. Anderson, Chem. Soc. Rev. 50 (2021) 5668-5705.
[2] M. A. Paley et J. A. Prescher, Medchemcomm 5 (2014) 255-267.
[3] M. P. Hall et al., ACS Chem. Biol., 7 (2012) 1848-1857.
[4] M. Sahihi, J. Sanz García, et I. Navizet, J. Phys. Chem. B 124 (2020) 2539-2548.
[5] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, et D. A. Case, Journal of Computational Chemistry 25 (2014) 18.

Adjusting the force field (FF): MDGX program



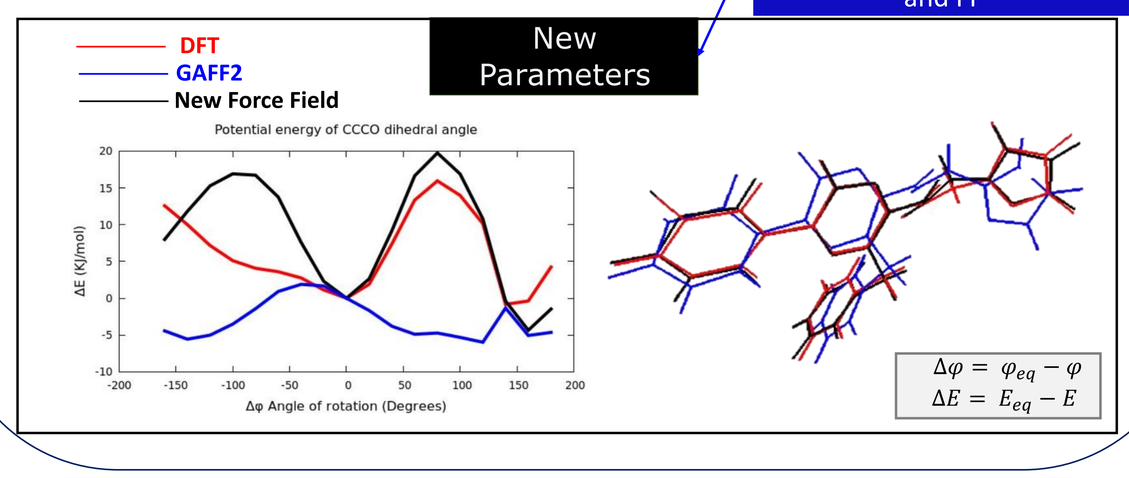
Reference set of conformations (**1D et 2D DFT SCANS on 7 dihedral angles**)



Initial guess of parameters (GAFF2)

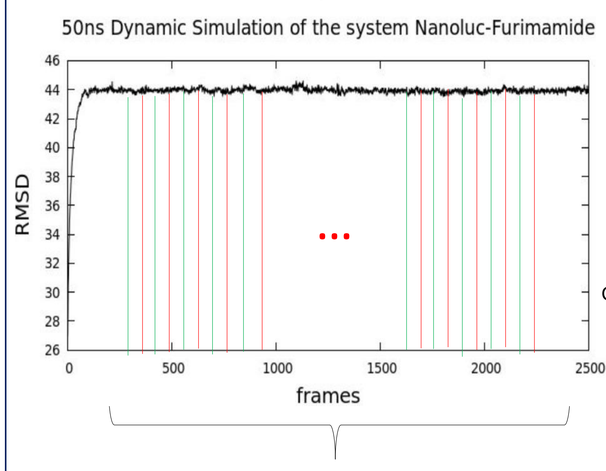
Least-square fitting to minimize the energy difference between DFT and FF

New Parameters



MD simulation: *(Amber20)*

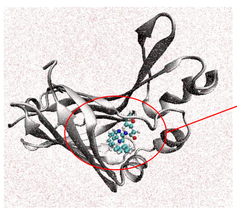
50ns Dynamics



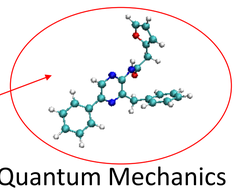
First set : 101 Snapshots

Second set : 100 snapshots

QMMM simulation: *(Amber20/Gaussian16)*

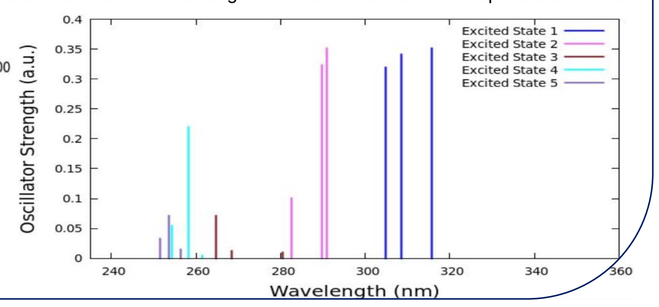


Molecular mechanic subsystem
Protein + WATER



Quantum Mechanics subsystem
Ligand
DFT Method : CAM-B3LYP/6-311G(2d,p)

Calculated oscillator strengths of excited states for 3 snapshots of furimamide

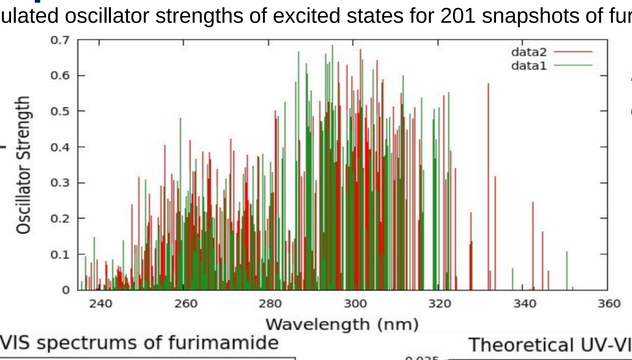


Absorption spectra simulation:

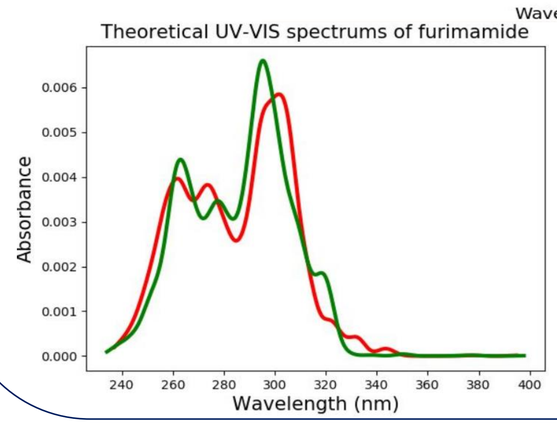
Calculated oscillator strengths of excited states for 201 snapshots of furimamide

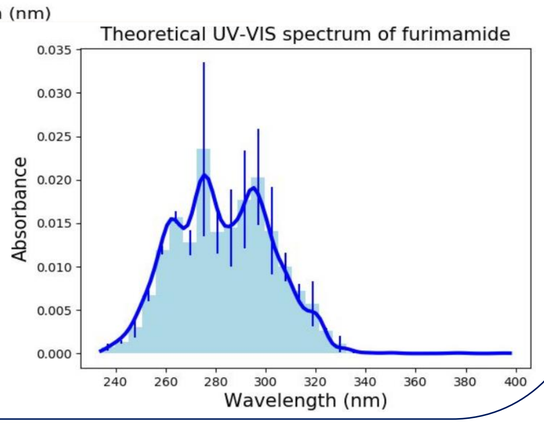
Gaussian Convolution

Set 1
Set 2



Histogram and errorbar calculations





Conclusion and perspectives:

We have automatized the absorption spectra simulation, we need to compare our results with experimental data. The emission spectra are yet to be simulated in order to modelize the color of emission of this system.