- **Title** : Algorithms for Modeling of membrane proteins
- **MSc thesis advisor** : Sergei Grudinin, sergei.grudinin@inria.fr
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- **Laboratory** (+working place) : NANO-D, INRIA Rhone-Alpes Research Center
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- **If a PhD is forseen** : yes

Internship presentation :
Until recent time, membrane-protein interactions were underestimated and little effort was put in the development of modelling and docking algorithms for membrane embedded proteins. However, due to the recent advances in understanding the physiological role of these interactions, this situation is currently changing. The aim of this project is to advance algorithms for predicting protein structure and complexes in lipidic environments and apply these to the actual biological problems. A straightforward method to predict a binding interface of membrane proteins can be molecular dynamics simulation (Provasi et al., 2015). However, despite the methodological simplicity of this method, the accuracy of its predictions strongly depends on the exhaustiveness of the sampling and the choice of the force field. Also, as very recent docking competitions of water-soluble proteins (CASP and CAPRI) demonstrate, molecular dynamics – based predictions are far less accurate compared to other methods.

Internship objectives:
The internship project consists in modelling of membrane proteins and their complexes. In particular, it involves development of new computational tools for both automatic and user-guided modelling applications. The developed methods will be applied to a wide range of membrane proteins, starting from the systems inserted into nano discs and the rhodopsin family of proteins. The GUI interface will be developed inside the SAMSON modular platform, https://team.inria.fr/nano-d/software/samson/.
First, we will develop a method to incorporate both implicit and explicit lipidic membrane representation built on top of our previous work on prediction of crystallographic water molecules (Lensink et al., 2014). The main idea of the method is to use a machine-learning model for a convex optimization problem trained on a set of known protein interfaces. This will allow constructing a realistic scoring function for protein-protein interaction (Popov & Grudinin 2015) inside a membrane, which will ultimately help to predict the correct binding interface inside lipidic environment. Then, we will test several sampling strategies, both automatic and user-guided, to assemble membrane proteins together.
Developed methods will be employed for protein construct development for crystallization, prediction of mutations to decrease oligomerization propensity of melatonin receptors and ligands development to target dimerization interfaces.

Requirements :
We are looking for candidates from a computer science / applied math background with strong knowledge of physics and an interest in biophysics. Knowledge of C++, Python, parallel programming (e.g. multi-threading), QT, and machine learning will be an asset.

References:

D. Provasi et al. Preferred Supramolecular Organization and Dimer Interfaces of Opioid Receptors from Simulated Self-Association. PLoS Computational Biology 2015, 11(3):e1004148.

P. Popov & S. Grudinin. Knowledge of Native Protein-Protein Interfaces Is Sufficient To Construct Predictive Models for the Selection of Binding Candidates. J Chem Inf Model, 2015, doi: acs.jcim.5b00372.

F. Lensink,..., S. Grudinin,..., J. A. Wojdyla, C. Kleanthous, and S. J. Wodak. “Blind Prediction of Interfacial Water Positions in CAPRI”. Proteins 82(4):620-32, 2014.