UNIVERSITÉ PARIS DESCARTES
MEMBRE DE
USPC Université Sorbonne Paris Cité
LABORATOIRE DE CRISTALLOGRAPHIE ET RMN BIOLOGIQUES
U M R 8 0 1 5
Faculté de pharmacie
4, avenue de l'Observatoire
75270 Paris cedex 06

Master 2 internship proposal

Modeling G-quadruplexes, their intrinsic polymorphism and folding properties

G-quadruplexes (GQ) are non-canonical structures of DNA or RNA that are formed by sequences rich in guanine. In the cell these sequences are found in genes regulatory regions and in the telomeres, the terminal portion of chromosomes, regulating the cell's life cycles. Because of their effects on the regulation of the telomerase enzyme, GQs have become an important in subject field of cancer research, with the hypothesis that the stabilization of their structures could have favorable repercussions in anti-cancer therapies.

The various structures of GQ that have been determined experimentally by NRM and by crystallography show a significant structural polymorphism for these small molecules. Measurements of folding times are also in support of the existence of a large variety of possible conformations for a given sequence, which can impair folding and lead the molecule to stable conformations other than the experimental native state. In order to understand the folding mechanism and stabilization of certain structures, it is necessary to understand folding at the structural level.

In this internship we propose to use molecular modeling to shad light on the polymorphism of GQ sequences. The main questions we will address are how many structures are compatibles with a given sequence, what is their relative stability and how does the plurality of stable or metastable states impacts the folding pathway.

To address these questions we will focus on the sequence of the human telomere quadruplex which is the most studied experimentally and that we already started studying in recent years. We will use a combination of atomistic and coarse-grained models for nucleic acids (that we develop) and that have shown the ability to fold GQs.

The work will be supervised by Pr. Samuela Pasquali at the Laboratoire de Cristallographie et RMN Biologiques (LCRB), UMR 8015 CNRS, Université Paris Descartes. The project will benefit from the environment at LCRB, where different biophysical techniques are used to study nucleic acids, and from the collaboration with professors David Wales (University of Cambidge) and Jiri Sponer (Czech Academy of Science). The student will receive an allowance of 550 euros/month to cover local expenses. Duration of the internship will depend on the applicant's master program requirements.

If interested, please send your CV including a copy of your undergraduate records and one recommendation letter to Samuela Pasquali: samuela.pasquali@parisdescartes.fr

S. Pasquali, P. Derreumaux, « HiRE-RNA: a high resolution coarse-grained energy model for RNA », J Phys Chem B., 114, 11957-11966 (2010)

T. Cragnolini, Derreumaux, S. Pasquali, Ab initio RNA folding, Journal of Physics: Condensed matter, 2015, 23, 233102 T. Cragnolini, Y. Laurin, P. Derreumaux, S. Pasquali (2015), « Coarse-grained HiRE-RNA model for ab initio RNA folding beyond simple molecules, including noncanonical and multiple base pairings », JCTC, 11, 3510-5322

P. Stadlbauer, L. Mazzanti, T. Cragnolini, D. J. Wales, P. Derreumaux, S. Pasquali, J. Sponer, «Coarse-Grained Simulations Complemented by Atomistic Molecular Dynamics Provide New Insights into Folding of Human Telomeric G-Quadruplexes», *J. Chem. Theory Comput.*, in press. DOI: 10.1021/acs.jctc.6b0066

Cragnolini T, Chakraborty D, Šponer J, Derreumaux P, Pasquali S, Wales DJ, "Multifunctional energy landscape for a DNA G-quadruplex: An evolved molecular switch", Journal of Chemical Physics 147, 152715 (2017)