MASTER « *In Silico* Drug Design »

1ère année

PROPOSITION DE STAGE

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A envoyer à Mr Pr Taboureau

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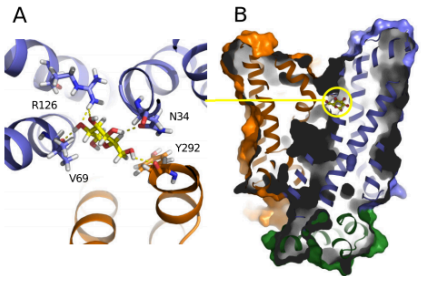
Titre du stage : Impact of point mutations on the glucose transport by GluT1

Description du sujet (quelques lignes):

Glucose is an essential source of energy for the mammalian cells. Its transport to the cell occurs as the result of the facilitative diffusion governed by membrane proteins. Human glucose transporter type 1 (GluT1) is the most rigorously characterised human solute transporter. It is primarily responsible for the cellular uptake of glucose into erythrocytes and endothelial cells of the blood-brain barrier. As the result, GluT1 deficiency or inactivating mutations lead to severe dysfunction in the central nervous system characterised by the appearance of drug-resistant epileptic seizures, psychomotor retardation and delayed development of the cranial box associated with the De Vivo disease. Previously we have described the atomistic details of glucose transfer by WT GluT1 using molecular dynamics (MD) simulations in membrane environment [1]. In the present project, we aim to elucidate the impact of pathology-related point mutations on the protein mechanics.



According to our preliminary results, GluT1 can perform glucose transport without any major conformational change thus explaining the observed inconsistencies in kinetics of glucose transition under the hypothesis of the alternating access mechanism [2]. During the internship the student will be invited to further investigate the atomistic details of the dynamics of this process. The student will perform detailed comparative analysis of MD trajectories of glucose transport obtained for WT protein as well as for on the known mutants associated with De Vivo disease (T295M, with mutation located in the extracellular cavity shown in the figure). Besides detailed analysis of GluT1 conformational behaviour, the student will investigate the interaction networks formed during glucose translocation, estimation of transport kinetics observed in our model and water behaviour during the transport. The obtained results should elucidate the mechanism of the glucose transport inhibition by the point mutations.

[1] T. Galochkina, M. Ng Fuk Chong, L. Challali, S. Abbar, C. Etchebest, New insights into GluT1 mechanics during glucose transfer, Sci Rep, 998, 2019
[2] R.J. Naftalin, Alternating Carrier Models of Asymmetric Glucose Transport Violate the Energy Conservation Laws, Biophys J, 95:9, pp 4300-4314, 2008

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