COMPUTATIONAL BIOLOGY WEBINAR @ IMSc

MODELLING APPROACHES TO UNDERSTAND THE CHALLENGES OF CANCER METABOLISM

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Cancer cells exhibit characteristic phenotypic plasticity that allows adaptive cellular reprogramming facilitating rapid proliferation, evading immunosurveillance and survival under stress. Cancer metabolism, an emerging hallmark of cancer cells, is one such adaptation that exhibit distinctive phenotypic changes and have been considered as signatures for different cancer cells. Metabolites can directly influence stress response pathways, chromatin modifications and gene expression that collectively drive tumor development. We will be discussing about the metabolic complexities in cancer with reference to a particular type of brain cancers known as glioblastomas. Metabolic alterations like the Warburg effect, Glutaminolysis, etc., help glioblastomas to survive stringent conditions. However, it is difficult to design a holistic experimental setup that could capture multiple pathways simultaneously. In recent years, this limitation is largely being handled by computational and mathematical biology study of large-scale comprehensive signaling and metabolic networks. In this lecture, we will discuss about the two broadly classified computational techniques to address this biological problem: (i) Steady-state modelling approach and (ii) Dynamic modelling approach.

In the first part of the lecture, we will discuss about a popularly used steady state approach known as Constraint-Based Metabolic Modelling. This approach makes use of linear optimization to formulate the cancer metabolic network in mathematical form. The technique provides a holistic perspective of the pathway behavior and changes in a context specific metabolic network of glioblastoma. A network consisting of 13 pathways including Glycolysis, TCA, Oxidative phosphorylation, Glycine-serine metabolism, Cysteine metabolism and Glutamate metabolism pathways was reconstructed [1]. The model was used to interpret biological questions like the differences in pathways during a normal and a glioblastoma scenario, essential metabolites for glioblastoma growth and combinations of metabolic reactions that could be used for treatment or as drug targets. The pathways were observed to be re-routed towards glutathione pathway, which is the anti-oxidant machinery of the cell. Essentiality analysis displayed that cystine and glucose were essential for glioblastoma growth in the given context. The combination of glycine-serine pathway enzymes was highlighted as combinatorial therapeutic targets.

In the second part of the lecture, we will discuss about dynamic modelling approach using ordinary differential equation (ODE). This approach requires the detailed understanding of the biological system and the knowledge of parameter values like concentration, rate kinetics, etc. We have used this approach to build an ODE model for glioblastoma to understand the effect of changing concentration of Reactive Oxygen Species (ROS) in determining the pro-apoptotic or anti-apoptotic fate of gliomas [2]. The model consists of a smaller subset of metabolic pathways that were considered in the constraint-based model, which are relevant to the anti-oxidant machinery. A total of 25 rate equations with Michaelis-Menten and modified Michaelis-Menten equations were formulated, that consisted of 35 variables and 123 parameters. Analysis of the model show that the regulation of certain parameters along with the thiol (GSH/GSSG) and redox ($NADPH/NADP^+$) ratio could determine the dual behavior of ROS in gliomas.

1. Bhowmick, R., Subramanian, A., & Sarkar, R. R. (2015). Exploring the differences in metabolic behavior of astrocyte and glioblastoma: A flux balance analysis approach. Systems and Synthetic Biology, 9, 159 - 177, DOI:10.1007/s11693-015-9183-9.
2. Bhowmick, R., & Sarkar, R. R. (2020). Differential suitability of reactive oxygen species and the role of glutathione in regulating paradoxical behavior in gliomas: A mathematical perspective. PloSOne, 15(6), e0235204. DOI: https://doi.org/10.1371/journal.pone.0235204.

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