ABSTRACT **Index No.: 73/18/Maths./25**

Title of the Thesis: Understanding the role of metabolic perturbation in disease condition through mathematical modelling

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Understanding metabolism is crucial for comprehending the phenotypic nature of all living things, including humans. Metabolism is essential for life and good health, any dysregulation in metabolic processes can be detrimental and involved in various diseases, including cancers, diabetes, cardiovascular diseases, etc. Therefore, exploring metabolic alterations is essential to comprehend the underlying mechanism behind disease development. Additionally, it offers a unique opportunity to identify potential drug targets and design new therapeutic strategies. Due to the complexity and high dimensionality, mathematical modelling-based approaches have been used to study metabolic perturbations in various conditions like human diseases. Although numerous mathematical modelling-based studies have been performed, there still exists a lacuna of metabolic perturbations in several diseases such as diabetes, cancer, nonalcoholic fatty liver disease, etc. The present thesis aims to explore metabolic perturbations in disease to understand the underlying mechanism and develop therapeutic strategies.

Here, we explored the application of genome-scale metabolic models (GSMM) and small-scale kinetic models in studying the role of metabolites and associated pathways in disease progression. We start by applying GSMM to identify the altered metabolic flux state of pancreatic β-cells under type 2 diabetes (T2D). We identified seven secreted metabolites from β-cell associated with cardiovascular disease (CVD) pathogenesis. Additionally, GSMMs were applied to identify critical regulatory points through *in silico* knockout approaches. . In total, 13 genes were obtained whose knockout reduced the growth rate of all cancer models but were inactive across all nine normal cell models. We later validated two of these genes (SOAT1 and CYTB) experimentally on four cancer cell-lines. Finally, the combination of these two applications of GSMM, i.e., identifying metabolic alterations and regulatory points through *in silico* gene knockout, was used to identify potential targets for nonalcoholic steatohepatitis (NASH). We elucidated the possible mechanism of action of these identified targets using GSMM. Our analysis identified three potential targets for NASH. Their inhibition attenuate hepatic steatosis by promoting higher flux rates for the altered reactions involved in fatty acid activation and mitochondrial beta-oxidation pathways.

The current thesis is not limited to the application of GSMM. We have also used small-scale kinetic models to capture the underlying disease mechanism. We have proposed and analyzed a six-dimensional model on glucose-stimulated insulin secretion (GSIS) to identify the crucial factors whose impairment can either lead to hyperglycemia or hypoglycemia. Our analysis uncovers the potential therapeutic strategies for preventing the progression of T2D during these alterations. We have also proposed another seven-dimensional model for insulin synthesis and secretion to understand the pathophysiology of T2D and hyperinsulinemic hypoglycaemia. The model analysis revealed that the defects in the insulin granules dynamics hamper first- and second-phase insulin secretion. In contrast, abnormal insulin synthesis takes a long time to exert the effect and might also be one of the reasons for fasting hypoglycemia in insulinoma patients. Our study also suggests that targeting insulin synthesis could become a potential therapeutic strategy for controlling impaired insulin secretion.

Overall, the work discussed in this thesis explores the application of GSMMs and small-scale kinetic models in understanding metabolic perturbations in human disease. The identified crucial factors responsible for impaired metabolism will enrich our understanding of disease pathogenesis. The proposed drug targets or therapeutic strategies have the potential to control the disease progression, and thus opens door for further exploration.

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