Glycolytic flux control of glyceraldehyde-3-phosphate dehydrogenase in *Lactococcus lactis* and *Plasmodium falciparum*

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Introduction: Plasmodium falciparum, the parasite that causes severe malaria, has the highest prevalence in Africa, and its resistance to current treatment options is rapidly increasing. There are ongoing efforts to identify novel drug targets in the parasite's metabolism, and Lactococcus lactis is a bacterium with similar glycolytic properties to P. falciparum. Thus, it may serve as a model organism, given that there is a need to develop new drug targets, and glycolysis is an important source of energy and carbon for both parasite and bacterium.

Methodology: This study aims to investigate whether iodoacetic acid (IAA) influences the flux in *L. lactis* and *P. falciparum* to identify novel drug targets in the metabolism of the malaria parasite by determining the control of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) on the glycolytic flux. This project uses experimental enzyme kinetics, mathematical modeling, and metabolic control analysis to analyze published detailed models of glycolysis within both species to elucidate the flux control of GAPDH under titrations of IAA.

Results: An observable decrease in both lactate production and glucose consumption was established after IAA exposure in both *L. lactis* and *P. falciparum*, and the GAPDH activity was affected as well. Low GAPDH control was observed experimentally and was accurately predicted by the *L. lactis* model. The GAPDH of *P. falciparum* has greater flux control than that of *L. lactis* as predicted by the *P. falciparum* model.

Discussion and Conclusion: Metabolic control analysis performed on detailed enzyme kinetic models of *L. lactis* and *P. falciparum* was successful in predicting the experimentally observed flux controls of GAPDH. This approach could be used to identify other enzymatic drug targets and quantify drug effects on the metabolism of pathogens.

Keywords: glycolysis, *P. falciparum*, *L. lactis*, MCA, GAPDH, IAA, flux control, mathematical modelling, enzyme kinetics

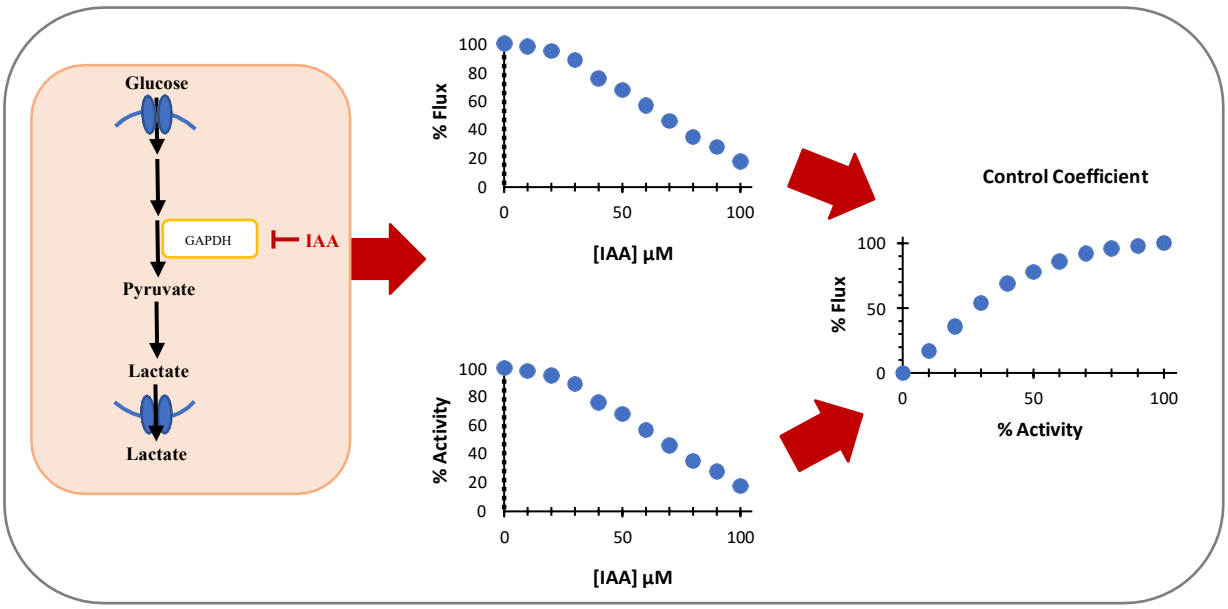

Figure 1:*The workflow of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inhibition by iodoacetic acid (IAA).* ***A)*** *GAPDH is targeted by IAA in glycolysis.* ***B)*** *The percentage flux and percentage activity versus IAA concentration curve is quantified.* ***C)*** *The flux control coefficient is derived using the percentage flux versus the percentage activity.*