1) Access the Plasmodium falciparum model in JWS Online

a) Point your browser to "https://jjj.bio.vu.nl"

b) Filter the database on model name: "Penkler"

c) Load the "Penkler1" model, by clicking the triangle in the green box.

2) Simulate the Penkler1 model

a) Look at the model schema, can you see the glycolytic pathway and the two branches to glycerol (gly) and pyruvate (pyr) export?

b) Click on the "Steady State" tab, and subsequently after the steady state page is loaded, the "Steady State" button. Write down the Flux values for the following reactions, and find the flux relations between the fluxes: vPFvGLCtr, vPFvLACtr, vPFvGLYtr, vPFvPYRtr

c) In the same steady state tab, click the "Flux control matrix" button to make an MCA analysis for the model. Write down the three largest Flux control coefficients (reaction and value) on vPFvLACtr.

d) Increase the parameter value of "VPFvGLCtr" with 1%, and evaluate the new steady state flux, write down the new flux value.

f) Is the flux control coefficient of vPFvGLCtr in agreement with the value determined with matrix method?

3) Simulate the infected red blood cell

a) Load the "duToit1" model.

b) Simulate a steady state. The Plasmodium falciparum variables end on "PF", and red blood cell variables end on "RBCi". Fluxes and rates for P.f. start with "vPF" and for the red blood cell with "vRBCi". Select a rate that is specific for P.f. lactate production and one that is specific for the RBC lactate production. Note that some reactions are shared by both cell types, e.g. RBC glucose transport, "vRBCivGLCTRANSPORT", and are thus not specific.

c) Check that the three reactions selected in 2c also have a high control in the duToit model, with comparable flux control coefficients (copy the values). Which reaction has the highest control coefficient in the RBC (copy the value)? Write down the RBCi flux control coefficients (FCC) for the three enzymes that have the highest control in P.f., and vice versa the FCC in P.f. for the reaction with the highest FCC in the RBCi.

d) Why is it important for drug target identification that there are reactions with a high control in the one cell type with a low control in the other cell type? Can you think of a functional difference between the two cell types that would lead to a strong difference in flux control distribution?

4) Inhibitor titrations for the glucose transport reaction

a) Download the duToit1 model in PySCeS format.

b) Load the model in PySCeS and add a multiplier to the rate equations in both cell types, for an enzyme with a high flux control in P.f. and a low control in the RBCi. Thus, you need to adapt the rate equation for the P.f. reaction, and the rate equation for the same RBCi reaction. By manipulating the multiplier you can simulate the effect of a drug that inhibits the reaction. Make such a drug titration and plot the steady state flux for a specific reaction (selected in 3b) in both cell types.

c) You can try to do the same drug titration in the JWS model, by first clicking the "details" button in the top left corner, under the model name, and subsequently clicking the "Create derivative" button. The respective sections for the model description: "Model", "Unit definitions", "Compartments", "Species", "Initial assignments", "Reactions", "Parameters", "Rules", "Function definitions", "Events", are available for editing by clicking the respective tabs. Clicking a tab can open or close the section. Start by closing the "Model" section, and open the "Reactions" section. Click the edit button (pencil icon) for the rate equation you want to edit. Add a multiplier term (e.g. drug*) for the rate equation. Do the same for the corresponding rate equation in the other cell type. Close the "Reactions" section and open the "Parameters" section. Add the multiplier name to the list of parameters and give an initial value (e.g. 1). Close the "Reactions" tab. Click the green "Simulate" button.

d) Do a steady state simulation, you should get the same steady state as before (if you chose the value of 1 for the multiplier term). Change the value of the multiplier in the "Parameters" list on the left side of the simulations interface. Analyse the steady state again, and now you should see a difference in the steady state solution.

e) Choose the "Parameter scan" option in the top of the simulation interface. Select the multiplier as a scanning parameter on the right side of the simulation engine, and chose a "Start" value of 1, and a low value as "End" (not zero as this might lead to numerical instability). Select a specific "Rates" for each of the two cell types (command click will allow for multiple selections). Click the "Go" button. You should obtain a plot showing the flux in both cell types as a function of the multiplier.