Computational Biology Lab

Practical 8: Dynamic Modeling (BE21B037)

Part A

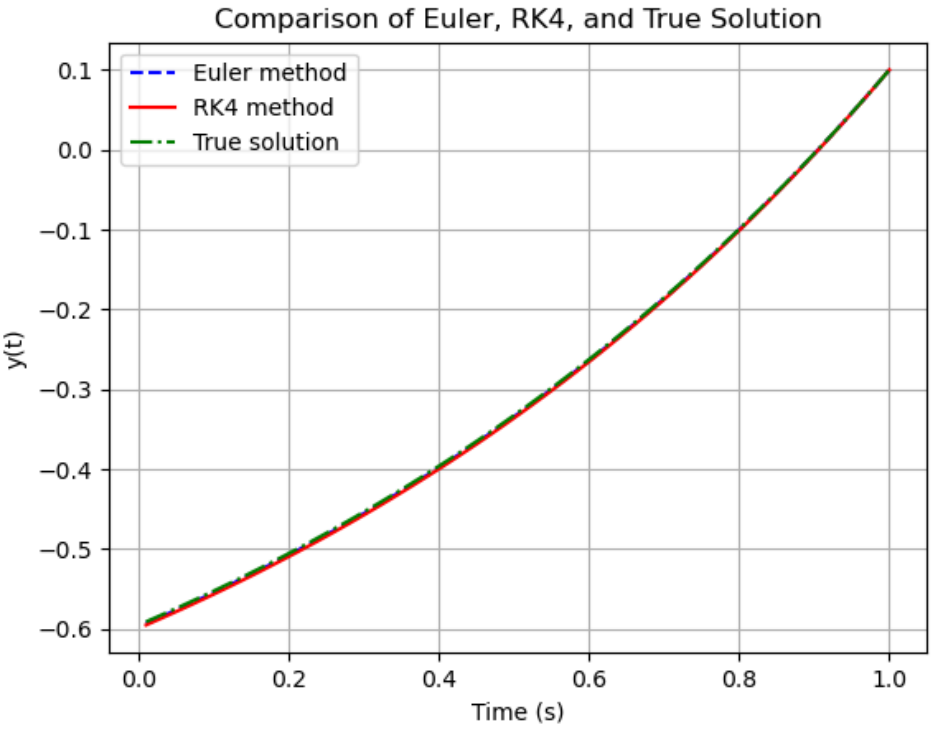
1. Integrate the given differential equation from 0.01s to 1s with a time interval of 0.01s with the following methods:

   a) Simple Euler method

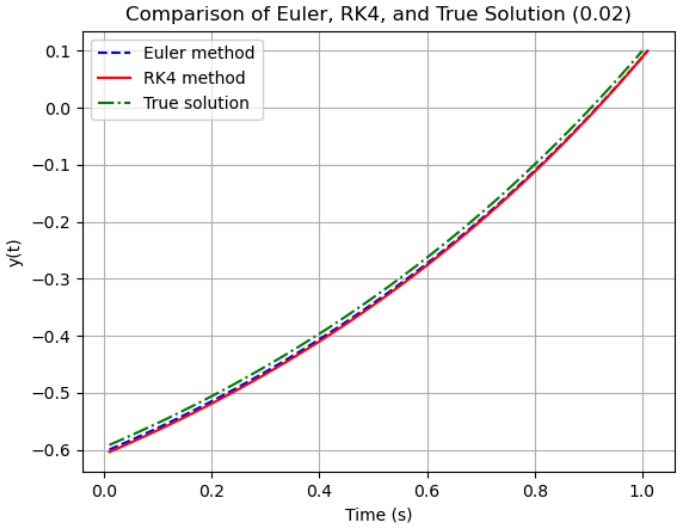
   b) Runge - Kutta method (fourth order method)

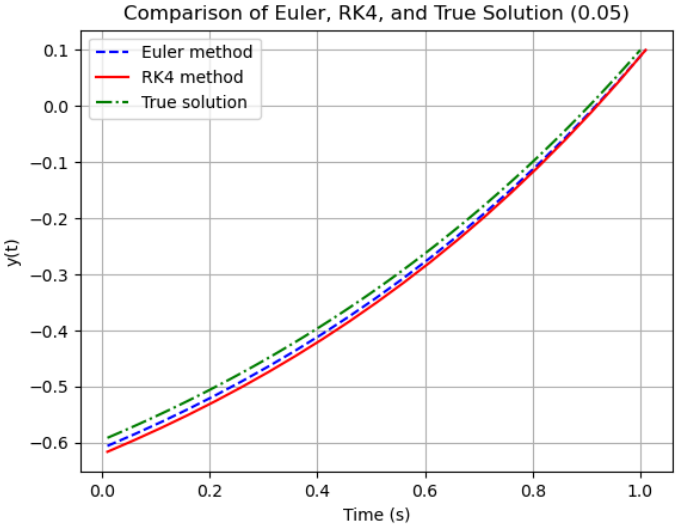
$$y(1) = 0.1 \text{ and } dy/dt = (y+1)$$

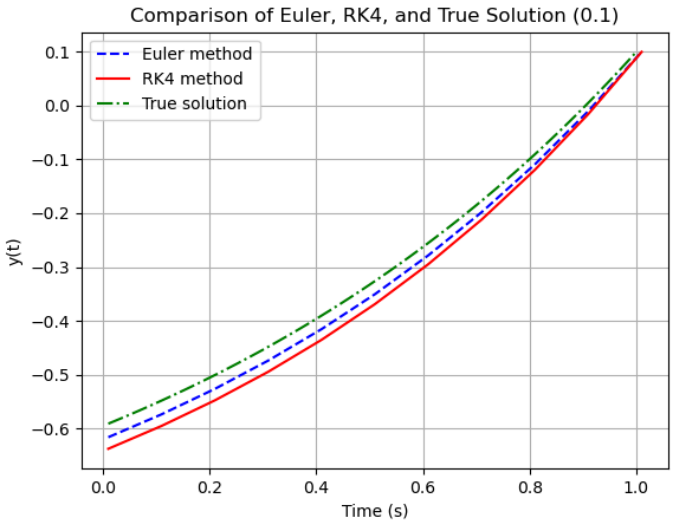
a) Plot the solution over time for these two methods in a single plot

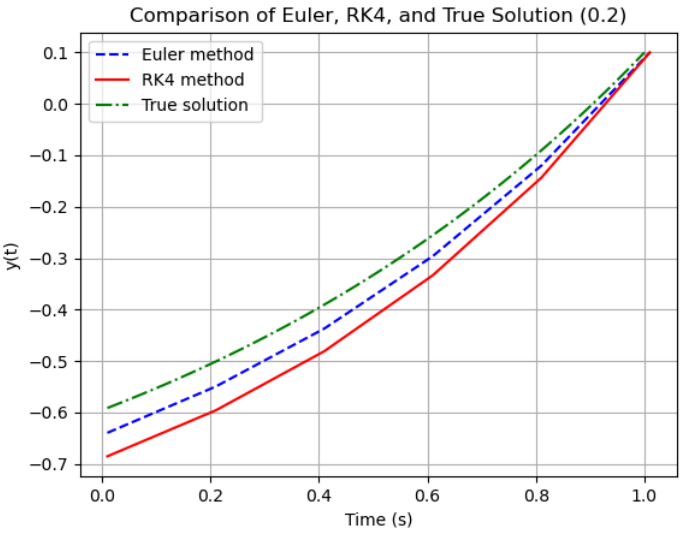


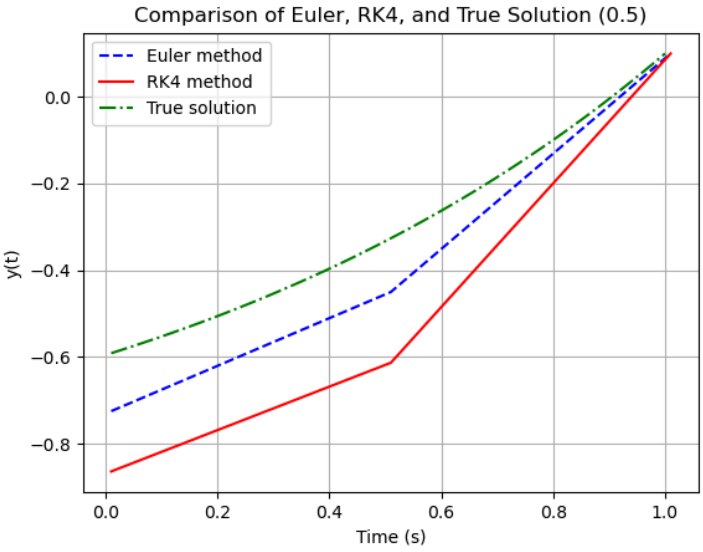
b) Experiment with five different ranges of time intervals and comment on your observations. What happens in each of the solving methods as the interval is increased?











The time intervals are mentioned in the titles for each graph

We started the integration from 1 till it reaches zero, as we are provided the initial value of y(1) = 0.1. The Euler performs better as its much more tuned to linear differential equations, than Runge-kutta, which works better in the case of nonlinear differential equations

As the time step increases, the error in the estimation also increases for both RK and Euler methods.

Part B

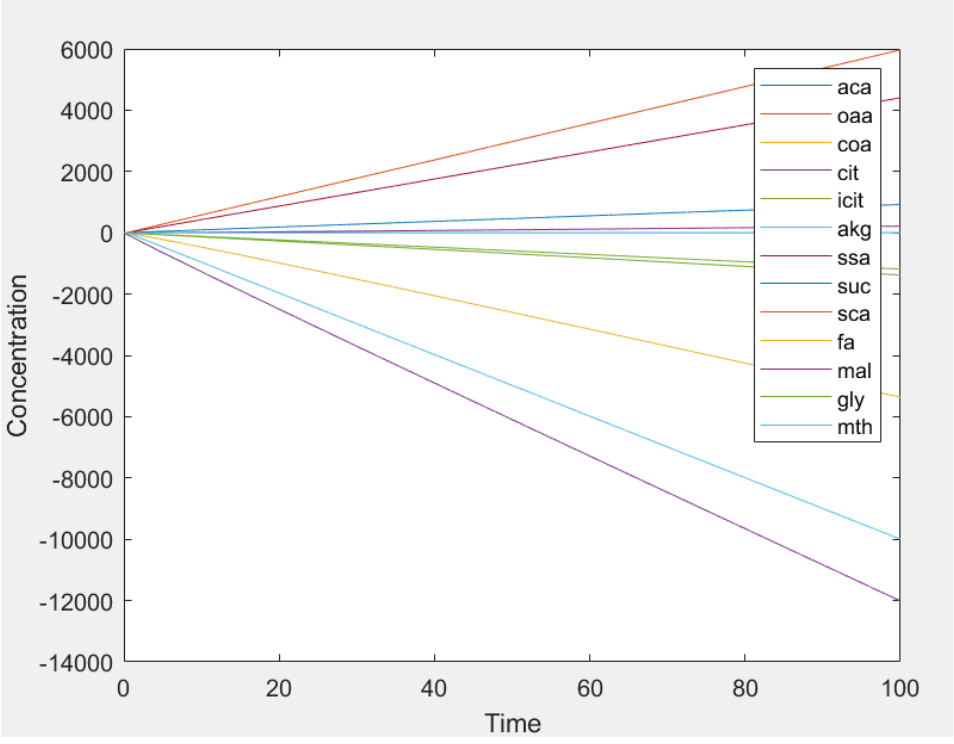
2. Download the dynamic model (both .m and .xml format) of TCA cycle in M. tuberculosis from this site: (https://www.ebi.ac.uk/biomodels/BIOMD0000000219#Files)

The central idea: Persistent tuberculosis bacteria survive on fatty acids, through the glyoxylate bypass. The flux through the bypass is aided by isoform enzymes (Isocitrate lyase) (ICL - 1) and (ICL - 2), and the objective in this paper is to reduce the flow through this pathway, and for the bacteria depend only on the main TCA cycle. This is involved with (Isocitrate dehydrogenase) (ICD -1) and (ICD-2), and these enzymes are deactivated by ICD kinase (so that the glyoxylate bypass is activated). The reduction in the deactivation of ICDS will serve as a possible strategy for targeting drug resistant M. tuberculosis.

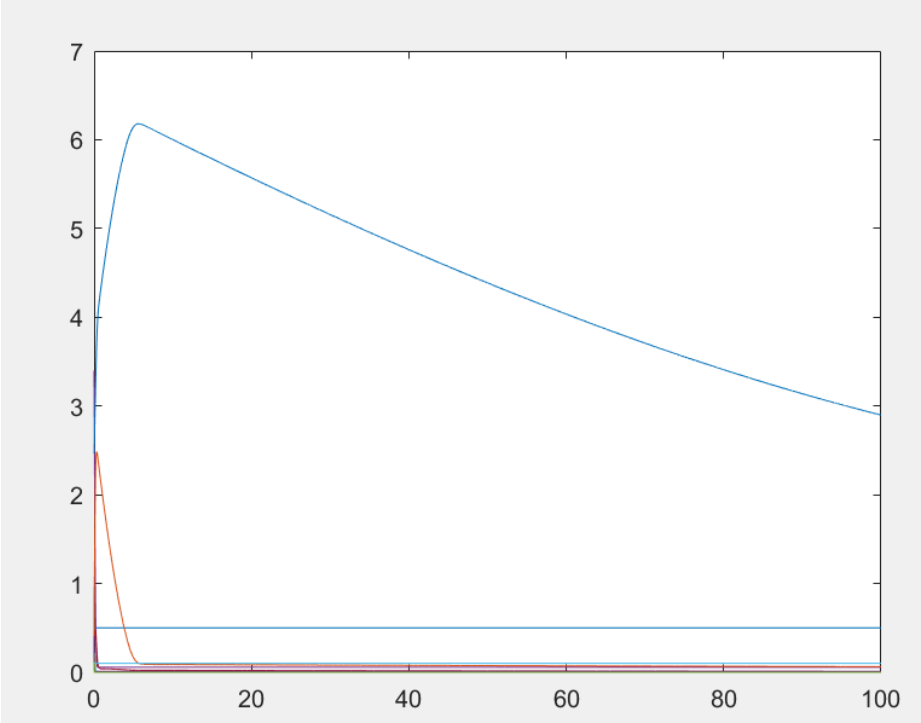
a) Can you use the equations given in the pdf (given on the website, same link), but use a simple euler method to integrate the same? Observe what happens if you use the code as compared to the euler method.

Using the Euler method causes all the concentration values to strictly decrease on increase linear with each time step.

After altering the matlab code to solve the differential equations using the Euler model, we get the following output



Using the inbuilt differential equation solver, we get



There is a stark difference in the output based on the method used.

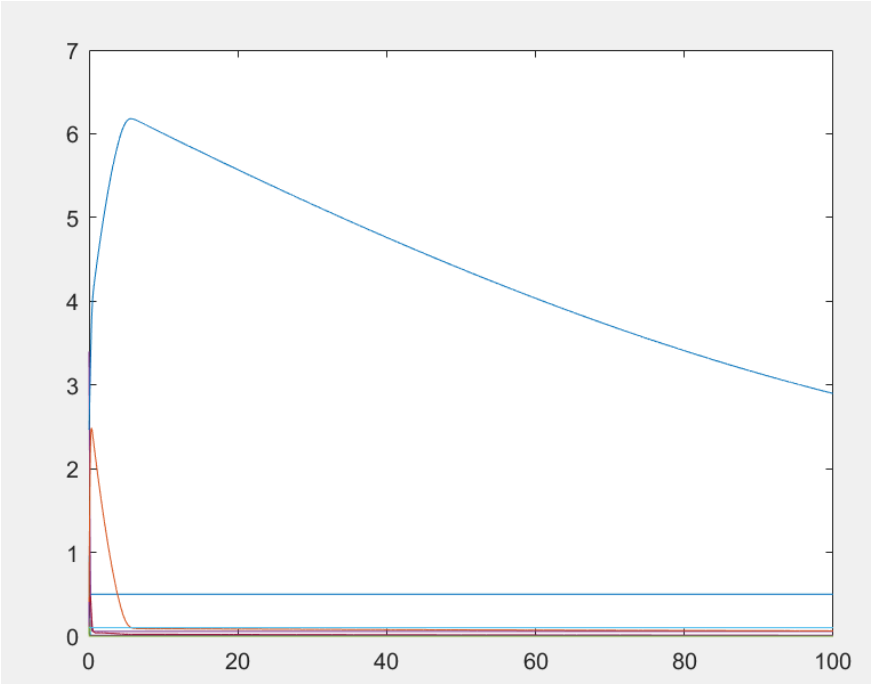
b) Based on the above results, can you differentiate between a stiff system and a non - stiff system?

“Stiffness” refers to the difficulty of the equations while solving a differential equation.

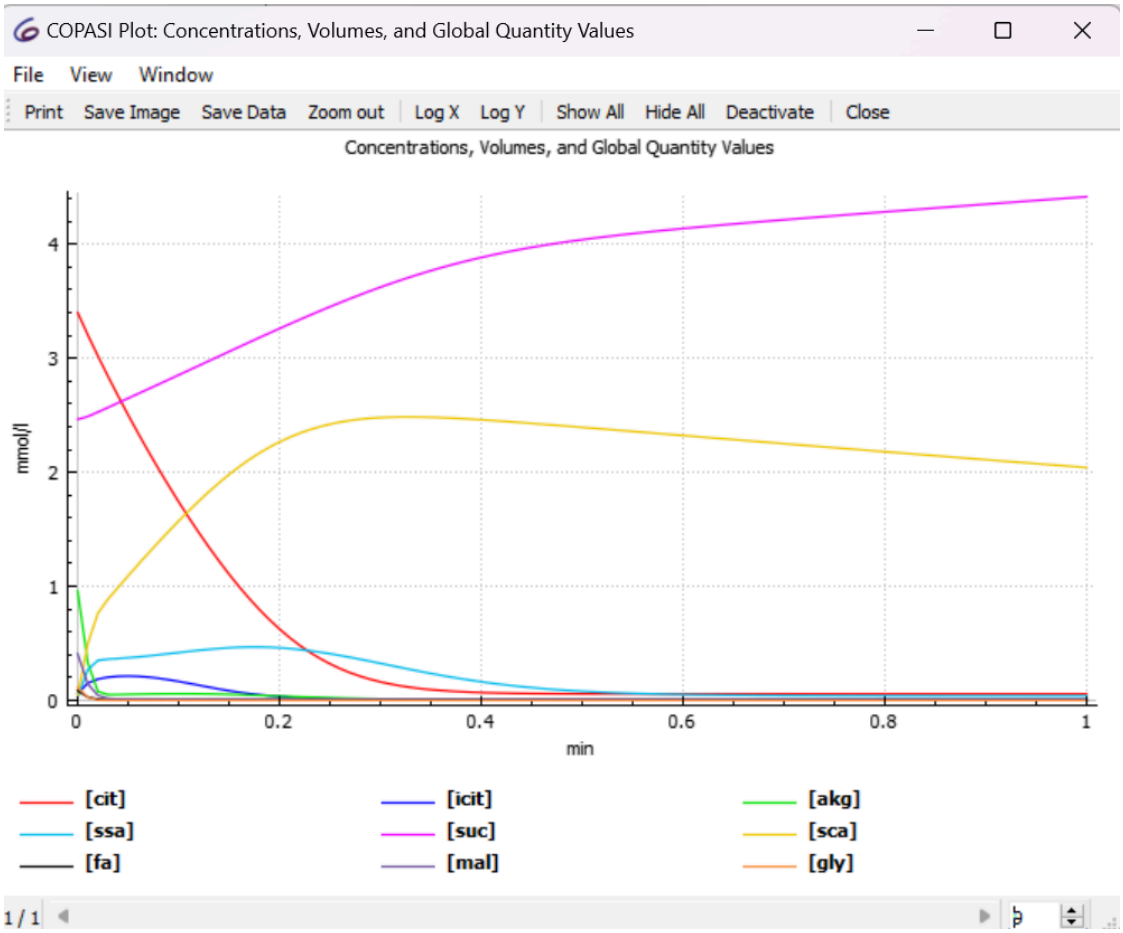
The equations for the following experiment can be described as a stiff system, and it is more logical to use a more complex solver than a simple euler integrator, While non-stiff systems are considered very simple and easier to solve.

c) Run the code in MATLAB as well as COPASI (.xml) , are there any differences between the Results?

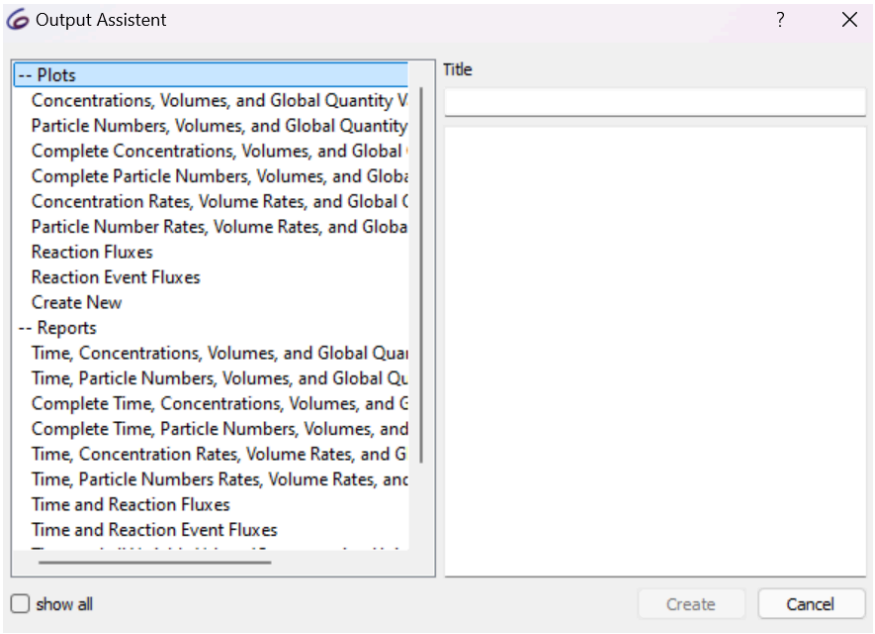
Matlab Output



COPASI output



The COPASI output is more accurate and detailed than the matlab output, which only shows a clear variation in only one of the reaction molecules, While COPASI can easily show the variation in concentration. COPASI also provides a chance to analyze other factors as well



The graphs in both the cases are different due to the fact that they use different solvers to solve the differential equation.

Matlab uses the Ode23tb solver while the COPASI uses the LSODA solver.

d) Can you come up with an interesting experiment to determine the effect of corresponding enzymes on the pathway, and how to possibly prevent bacteria from taking up the path of resistivity?

To determine the effects of inhibiting ICL–1 and ICL– 2, and ICD Kinase on the metabolic flux through the glyoxylate bypass and the TCA cycle, we evaluate if inhibition of these drugs will lead to the bacteria adopting a persistent, drug resistant state.

We perform metabolic flux analysis for 4 different cases

1) Control group, untreated
2) ICL inhibited group (inhibit both ICL–1 and ICL–2)
3) ICD Kinase inhibited (inhibit both ICD–1 and ICD–2) and
4) The combined ICL and ICD inhibition

The Flux analysis should help determine the effect of corresponding enzymes on the pathway
Preventing the bacteria from utilizing the glyoxylate bypass or disabling ICD kinases would force them to use the TCA cycle