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BE21B004

BT4110 – Computational Biology Lab

Dynamic Modelling Assignment

1a

The differential equation $\frac{dy}{dt} = y + 1$ was integrated over the time interval $[0.01, 1]$ with a time step of $h = 0.1$ and boundary condition $y(1) = 0.1$. Since we have the final value a backward integration approach was used, integrating from $t = 1$ to $t = 0.01$ in steps of $h = 0.1$.

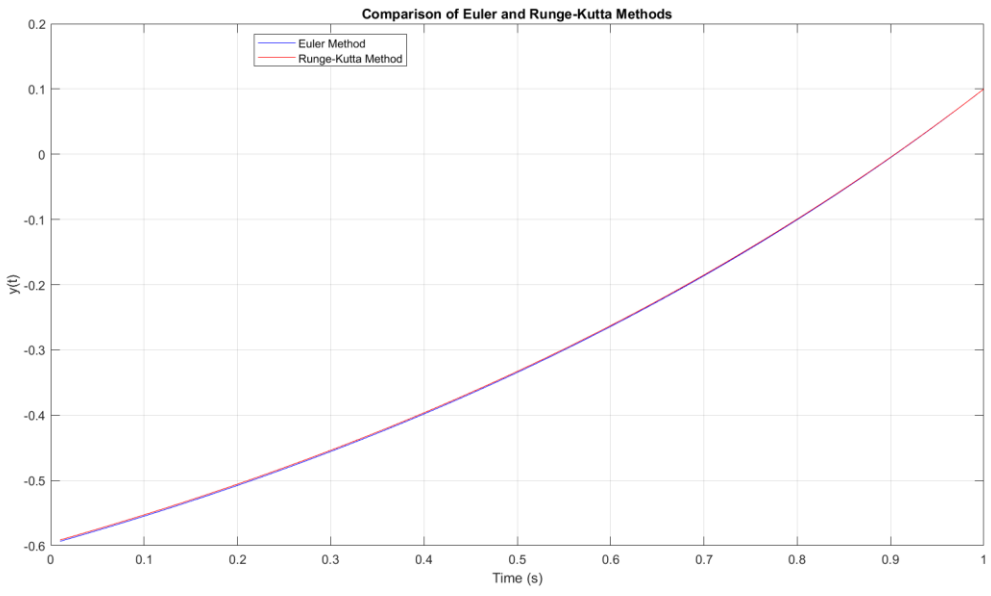
Using the Euler method, the integration was performed as

$$y_{t-h} = y_t - h\left(\left.\frac{dy}{dt}\right|_t\right)$$

$$= y_t - h(y_t + 1)$$

MATLAB's inbuilt `ode45` solver was used to implement the Runge-Kutta method for solving the differential equation. It uses adaptive time stepping while performing integration.

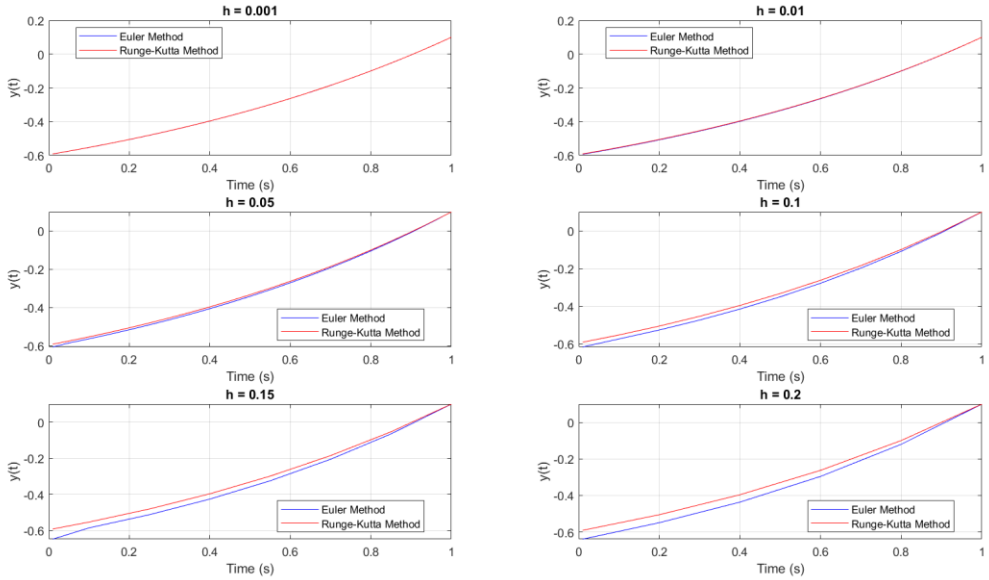
After using both methods, the following solutions were obtained:



Both methods yield a similar solution. They slightly deviate as they approach $t = 0.01$.

1b

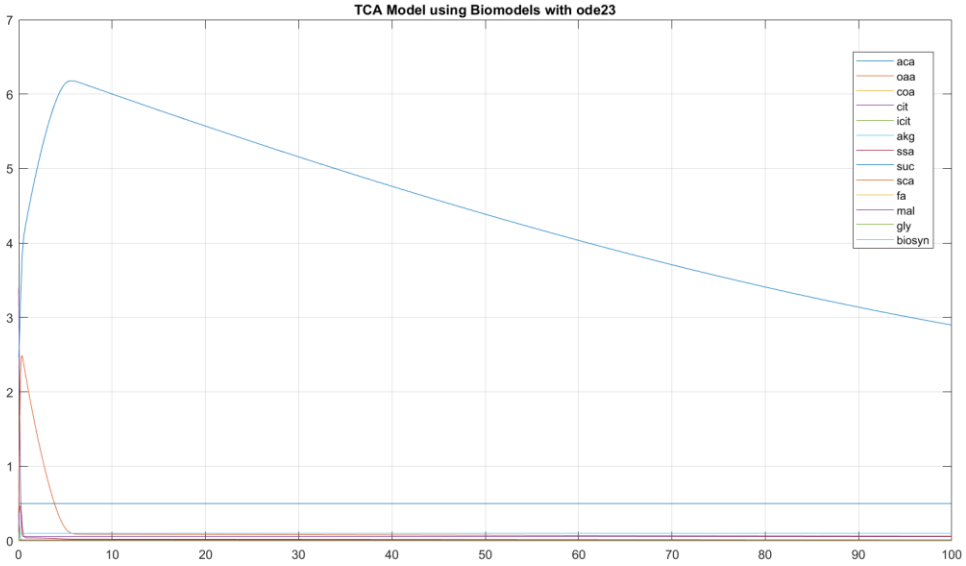
Five different time steps, 0.001, 0.01, 0.05, 0.1, 0.15, and 0.2, were used to integrate the above differential equation using both methods. The following results were obtained:



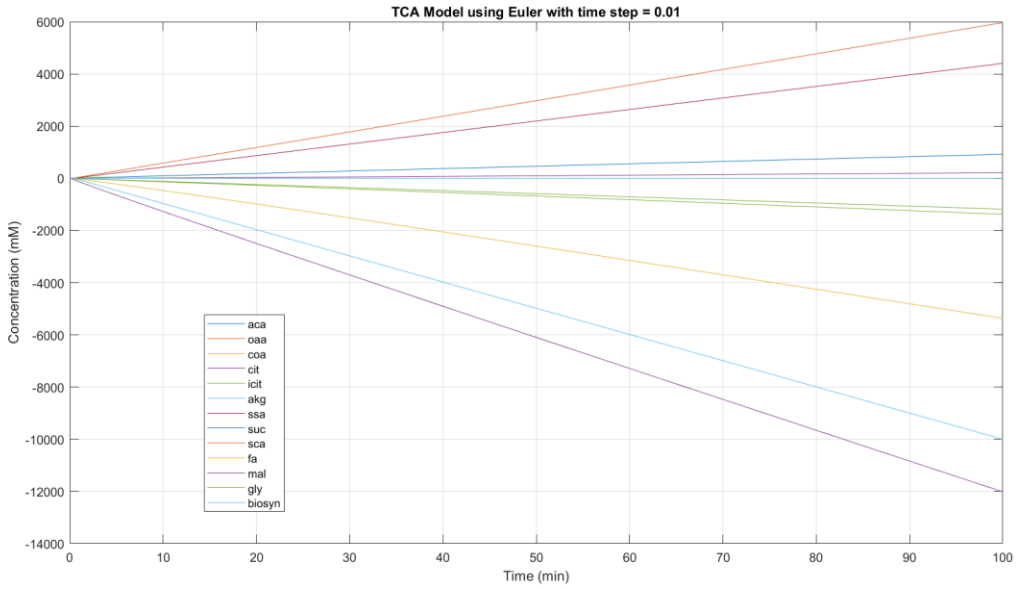
It was observed that the Runge-Kutta solution remains stable for different time steps as its implementation naturally uses adaptive time stepping. However, the Euler solution starts deviating from the true solution as the time step is increased, but still maintains the same qualitative behaviour. Thus, the Euler method is sensitive to changes in time step while the Runge-Kutta method is not. Since the general behaviour of the solution to the differential equation does not vary wildly with varying time step, it must be a non-stiff system.

2a

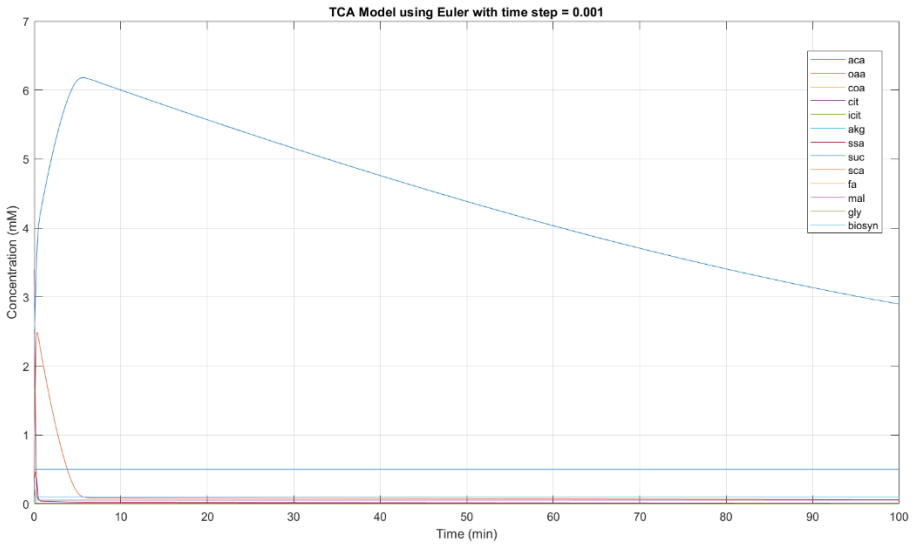
The differential equations in the dynamic model for the TCA cycle in *Mycobacterium tuberculosis* were first integrated using the MATLAB code provided in the Biomodels repository. This makes use of the inbuilt `ode23` solver that uses adaptive time stepping. The following solution was obtained:



Next, the Euler method was used with a time step of 0.01 to integrate the differential equations. A very drastic change was observed in the solution, leading to negative concentrations.



The time step for the Euler method was then reduced to 0.001. A solution comparable to the `ode23` solution was obtained.

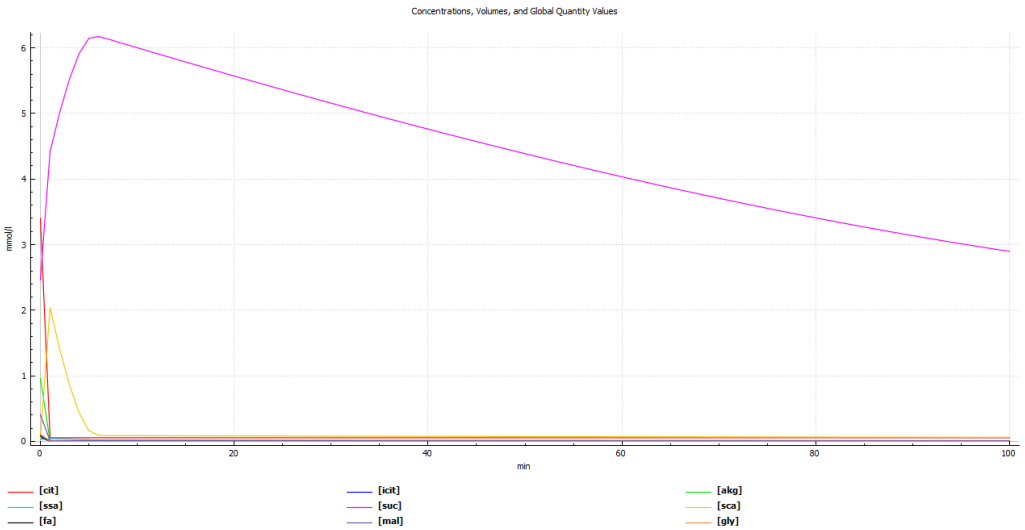


2b

As the solution for the system of differential equations became stable after reduction of time step, it is a stiff system. A stiff system requires very small time steps for numerical stability, often leading to instability when solved with larger time steps. In contrast, a non-stiff system evolves more smoothly and can be solved accurately with larger time steps without stability issues.

2c

COPASI was then used to run the model's .xml file. The following solution was obtained:



The solution is qualitatively and quantitatively similar to that obtained by running the MATLAB code. However, it only plots the time course for 9 of the 13 chemical species involved in the system of differential equations. Based on the information given in the model's PDF file, the 4 species that were not plotted (`aca`, `oaa`, `coa`, `biosyn`) have rates of change equal to 0. Thus, COPASI does not plot them.

2d

We wish to investigate the roles of isocitrate dehydrogenase (ICD-1, ICD-2) and isocitrate lyase (ICL-1, ICL-2) on the switch from the TCA cycle to the glyoxylate bypass by *M. tuberculosis*, which uses the bypass to survive on fatty acids and stay persistent in the lungs. This phenomenon occurs because ICD kinase deactivates the ICDs, causing the TCA cycle to switch off and the flux to get diverted through the glyoxylate bypass.

We can design 3 strains of the bacterium – (i) wildtype, (ii) overexpressed ICD kinase, (iii) knocked-down ICD kinase. The growth of these bacteria on glucose-based media and fatty acid-based media can be studied. We would expect that the overexpressed ICD kinase strain would grow better on the fatty acid-based media as it can divert flux through the glyoxylate bypass. This is similar to the persistent tuberculosis-causing strain. The knocked-down ICD kinase strain can be expected to grow better on the glucose-based media as its TCA cycle is active. This strain will not cause persistent tuberculosis. Thus, ICD kinase inhibition is a good strategy to prevent *M. tuberculosis* resistance.

A similar experiment can be carried out *in silico* using the dynamic model. The flux through the ICD reactions can be made higher to simulate ICD kinase inhibition. We would expect the growth of the bacterium (`biosyn`) to reduce. Alternatively, the flux through the ICL reactions can be set to 0 to simulate the inhibition of the glyoxylate bypass.