ODE modelling of chemical processes in the mitochondrion

1. **Introduction to an ODE mitochondrial model**

   'A Biophysical Model of the Mitochondrial Respiratory System and Oxidative Phosphorylation' by Daniel Beard in 2005 contains an ODE-based model for the chemical action of the mitochondrion, including terms describing electron transport chain complexes, ion transporters, the different mitochondrial spaces and other important reactions.

   (a) Obtain a copy of the publication (from PLoS Computational Biology) and refer to Fig. 1 (reproduced below) and Eqns. 22, which give an overview of the model.

   (b) Obtain the MATLAB source code for the model. Observe `dCdT.m`. Locate the sections responsible for determining flux through Complex I, and verify that these sections match the expressions in the original publication.

   (c) Verify the functionality of the code by running `compute_figures` and comparing the resulting figures with Fig. 4 in the publication (ignore the first figure produced by the code). What are these figures showing?

   (d) The code works by using the MATLAB `ode15s` solver to solve the set of descriptive ODEs in the model. This set is contained in the file `dCdT.m`, which takes some arguments describing various chemical concentrations. The `ode15s` function call involves a handle to the `dCdT` function and values for these arguments. Find the first instance in `compute_figures` of such a function call. What is being varied and investigated? What is the difference between 'resting state' and 'active state'?

2. **Exploring proton leak and complex activity**

   We will now explore the effect of two key physiological factors on mitochondrial membrane potential $\Delta\Psi_m$. These two factors are proton leak (the flux of protons out of the mitochondrial matrix, affecting the electrochemical potential across the inner membrane) and the activity of complex I (the first proton pump in the electron transport chain).

   (a) The file `dCdT_prac.m` has been altered so that the parameters associated with proton leak and complex I activity appear as arguments to the function rather than constants (confirm that you can see how). Consider only the active state of the mitochondrion. Using the form of the `ode15s` calls in the original `dCdT.m` as a framework, write a loop that solves the descriptive ODEs of the system for a range of proton leak values $[100, 1000]$ mol s^{-1} mV^{-1} M^{-1} l^{-1} (the original model value is 250 mol s^{-1} mV^{-1} M^{-1} l^{-1}).

   (b) `ode15s` returns values `[t,y]`: time points t and corresponding states y of the system. We are interested in the steady state, and the outputs are terminated at this point. $\Delta\Psi_m$ is the 19th element of the returned state y. Extract values for $\Delta\Psi_m$ corresponding to each of your range of proton leak values, and plot membrane potential as a function of proton leak.

   (c) Do the same for a range of complex I activities $[0.1 - 1]$ mol s^{-1} M^{-1} l^{-1} (the original model value is 0.369 mol s^{-1} M^{-1} l^{-1}). Do these membrane potential trends behave in the way you would expect? Why? What biological processes may lead to changes in the rates of proton leak and complex I activity?