Description of Codes for Catalytic Coupling of Oxidative Phosphorylation, ATP Demand, and Reactive Oxygen Species Generation [Bazil et al., 2016]

This package represents a version of the model of the mitochondrial respiratory chain and ATP synthesis published in Bazil et al. [1]. Please cite this paper in all applications that use these codes, which are freely distributed for use for non-profit and academic purposes. The original version of these codes used to generate the results published in Ref. [1] can be found here:

http://virtualrat.org/models/catalytic-coupling-oxidative-phosphorylation-atp-demand-reactive-oxygen-species-generation

The purpose of this alternative set of codes is to distribute a version of the model that is implemented in a framework for integration with other biochemical models, such as models of the tricarboxylic acid cycle and β-oxidation. Toward that end, the model of Bazil et al. has been reproduced using the BISEN simulation environment [2], and coordinated with the biochemical database of Li et al. [3]. Making the model consistent with the BISEN package introduces slight modification to thermodynamic parameters, and also requires addition of new reaction modules to the BISEN package. Thus, this distribution includes updated BISEN codes and databases. A description of components and how to use the follows below. For full details on BISEN see Vanlier et al. [2].

List of Files and Folders in the Package

Folder `Databases`: This folder contains the three databases that specify the chemical reaction and property data necessary to construct a biochemical kinetic model.

`ReactantDatabase.xls`: This spreadsheet list all thermodynamic data compiled for species in the Li et al. [3] database. These data include free energies of formation, enthalpies, charge, and data on dissociation constants. Detailed information is found in Li et al. [3].

`ReactionDatabase.xls`: This spreadsheet defines the stoichiometry of reference reactions for which models may be constructed.

`TransportDatabase.xls`: This spreadsheet defines the stoichiometry of reference transport processes for which models may be constructed.

Folder `BiochemicalReactions`: This folder contains the text files that define the rate laws (reaction flux expressions) for the reactions in the model. For example, the file `ATPASE.txt` defines the kinetic model used to simulate the apyrase reaction used in the experiments simulated below.

Folder `Transporters`: Similarly, this folder contains the text files that define the rate laws (reaction flux expressions) for the transport processes in the model. For some transporters, such as ANT, multiple alternative models are listed in the text file. Either ANT model may be specified in the integrated model construction.

Folder `BuilderFiles`: This folder contains all of the codes used to construct biochemical systems models. The main function is `BuildDXDT.m`, which generates a MATLAB-file that computes the right-hand side of an ordinary differential equation-based model. How this function is used is described below.

Folder `Warnings`: This folder contains scripts that generate error warnings.

Folder `Examples`: This is the folder that includes the scripts to build and simulate the model. The user can run the model and generate plots of model variables similar to those in Bazil et al. by running the script `mod_DSK_JB_OXPHOS_1.m` in MATLAB. (The model is similar to, but not identical to the published Bazil et al. model because of small differences in thermodynamic data. For the identical model, see the URL provided at the beginning of this document.)

The first major function call in the the script `mod_DSK_JB_OXPHOS_1.m` is to the function `BuildDXDT.m`, with the syntax:

```
modelInfo = BuildDXDT('mod_DSK_JB_OXPHOS.bsl','dXdT_DSK_JB_OXPHOS.m');
```

This script reads the input argument `'mod_DSK_JB_OXPHOS.bsl'` and generates the matlab code `'dXdT_DSK_JB_OXPHOS.m'`. The input file specifies the content of the model with the following syntax.

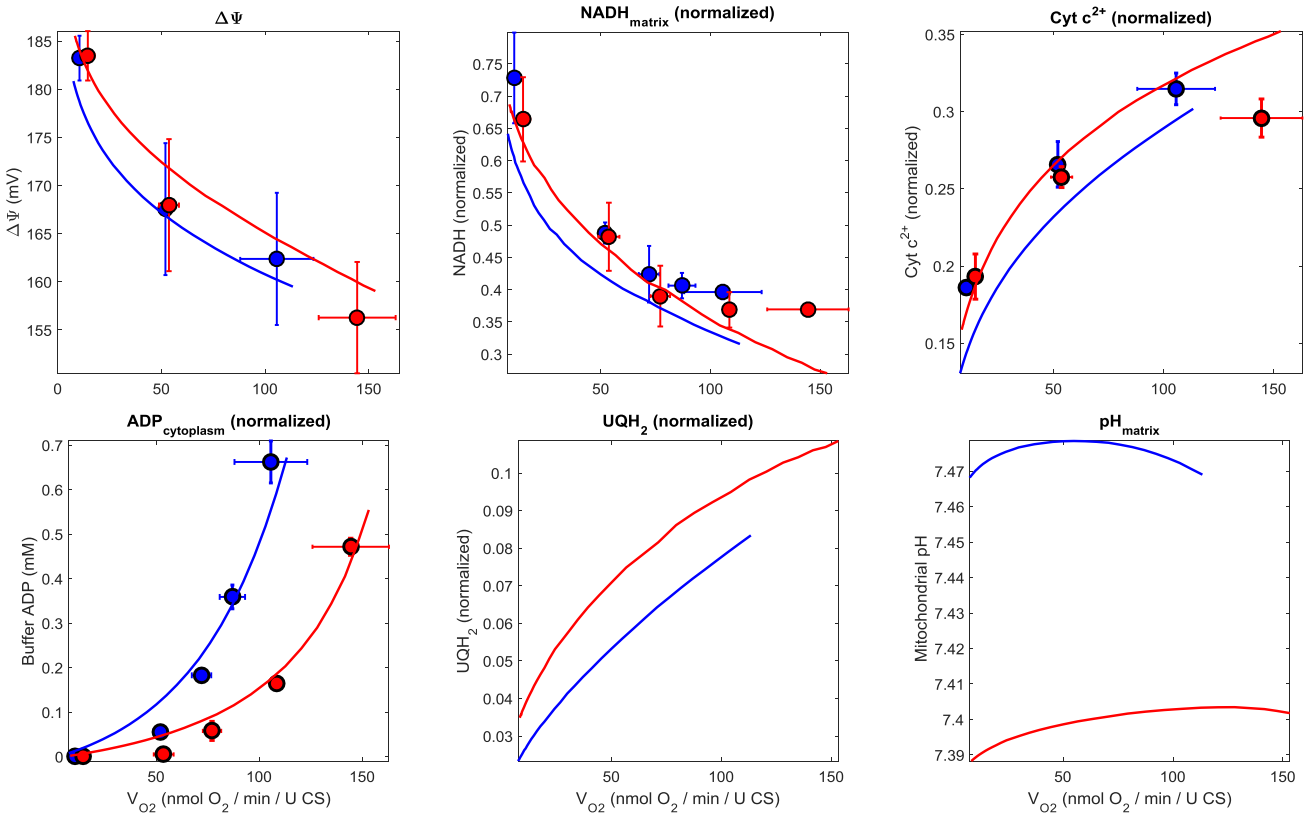
```
temperature 37

% Global experimental values
% mito membrane area per cell volume micron^{-1};
      gamma  = 5.99;
% minimal parameter value
      MinCon = 0;
compartment       matrix       0.6514     1/4541
    DH         E.DH.0
    SDH_BBV    E.SDH_BBV.0

compartment     cytoplasm     1     4540/4541
    ATPASE      E.ATPASE.0

compartment     im      0.0724      1/4541

transport   im matrix
    F1F0ATPASE      T.F1F0ATPASE.1
    ETC1            T.ETC1.1
    ETC3            T.ETC3.1
    ETC4            T.ETC4.1
    HLEAK           T.HLEAK.1
    PIH             T.PIH.2
    ANT             T.ANT.1
    KH              T.KH.0
    clamped O2aq

transport   cytoplasm im
    ADPPERM       T.ADPPERM.0
    ATPPERM       T.ATPPERM.0
    PIPERM        T.PIPERM.0
    HPERM         T.HPERM.0
    KPERM         T.KPERM.0
    MPERM         T.MPERM.0
EOF
```

This input function invokes three compartments, “matrix”, “im”, and “cytoplasm”, representing mitochondrial matrix, intermembrane space, and external space. The matrix is defined to have a water space of 0.6514, meaning that 65.14% of total mitochondrial volume is made up of water. The total mitochondrial volume is specified to be 1/4541, meaning that this fraction of the experimental system is made up mitochondria, corresponding to the experiments simulated below. The buffer/cytoplasm space has a water fraction of 1, for a dilute solution, and makes up 4540/4541 of the experimental system.

Transporters and reactions within and between compartments are indicated by listing the reactions/transporters to be built in the system.

Execution of the script `BuildDXDT` produces the computer-generated file `dXdT_DSK_JB_OXPHOS.m`, with approximately 1000 lines of MATLAB code to represent the model.

The remaining commands in the script `mod_DSK_JB_OXPHOS_1.m` set parameter and initial variable values, simulate the model, and plot the results. Initial conditions and parameter values correspond to the model of Bazil et al. For reference, the user should produce the steady-state simulations illustrated below.



References

1. Bazil JN, KC Vinnakota, DA Beard. Catalytic Coupling of Oxidative Phosphorylation, ATP Demand, and Mitochondrial Reactive Oxygen Species Generation. *Biophys J*. 110:962-71, 2016.
2. Vanlier, J, F Wu, F Qi, K C Vinnakota, Y Han, RK Dash, and DA Beard. BISEN: Biochemical simulation environment. *Bioinformatics* 25:836-837, 2009.
3. Li, X, and DA Beard. A database of thermodynamic properties of the reactions of glycolysis, the tricarboxylic acid cycle, and the pentose phosphate pathway. *Database* (Oxford) 2011:bar005.