

# User Manual for MitoModel, A Graphical User Interface for Mitochondrial Modeling

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## Introduction

This application is a standalone tool for optimizing mitochondrial function models, provided as an executable file. No installation of MATLAB is required. The app enables users to estimate model parameters, load experimental data, adjust model settings, and visualize results through an intuitive graphical user interface (GUI). The app supports advanced features such as model selection, weighted analysis, and comprehensive data analysis.<sup>1</sup>

## 1 User Interface Overview

The application's user interface is structured into two primary sections, as depicted in Figure 1:

- **Left Panel:** This section facilitates parameter initialization and problem customization. It includes tools for loading and editing data, setting the time unit, selecting the model type and weights, and accessing a data analysis hub. The hub comprises three drop-down menus for identifying the optimal fit for the selected model and for visualizing and analyzing results.
- **Right Panel:** This section is dedicated to result visualization and analysis. It displays graphs, tables of optimized parameters along with associated details, correlation analysis, and error analysis, providing comprehensive insights into model performance.

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<sup>1</sup>This GUI was originally developed by Chris Cadonic using GUIDE; and it was subsequently developed, revised, edited, and extended by Marzieh Eini Keleshteri using App Designer, MATLAB

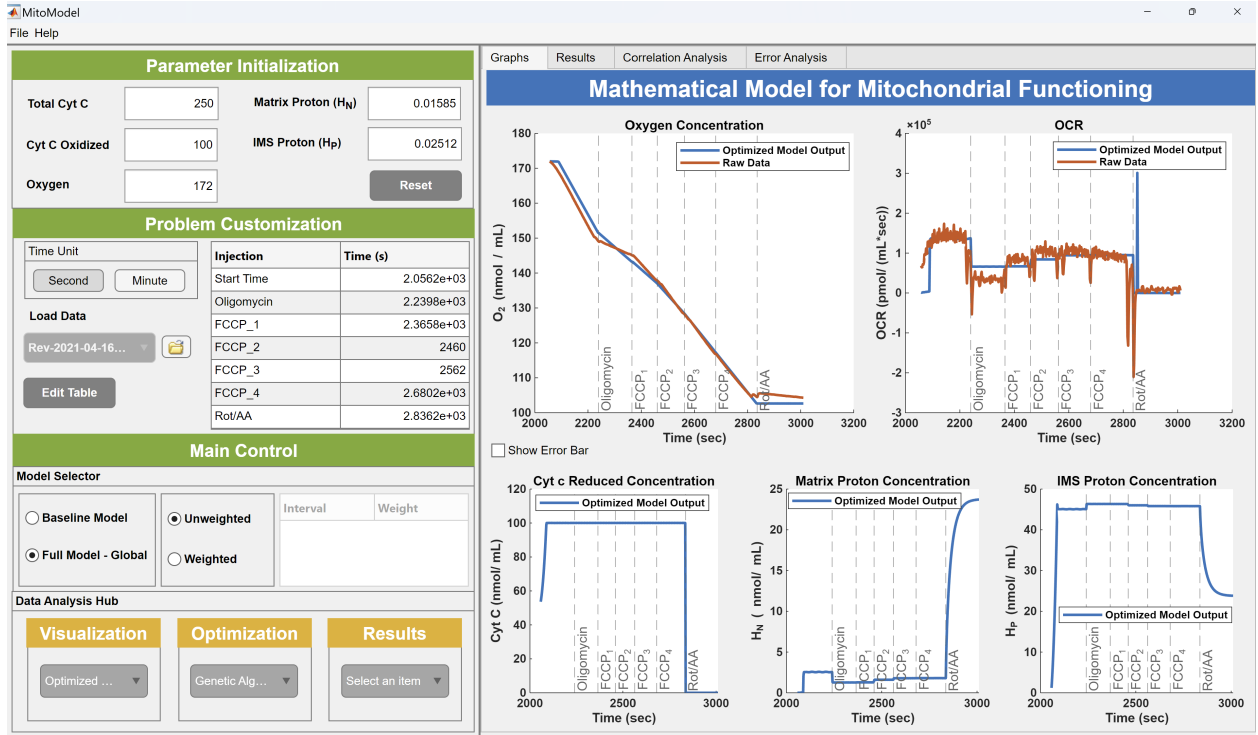


Figure 1: An overview of the GUI.

## 2 Left Panel: Setup and Customization

The left panel consists of four sub-panels to manage the setup, data input, and customization options.

### 2.1 Parameter Initialization Panel

As illustrated in Fig. 2, this section allows users to configure the initial values of key parameters, including:

The 'Parameter Initialization' panel contains the following fields and controls:

- Total Cyt C:** Input field with value 250.
- Cyt C Oxidized:** Input field with value 100.
- Oxygen:** Input field with value 180. A tooltip '(nmol/mL)' is visible below this field.
- Matrix Proton ( $H_N$ ):** Input field with value 0.01585.
- IMS Proton ( $H_P$ ):** Input field with value 0.02512.
- Reset:** A button located at the bottom right of the panel.

Figure 2: Parameter initialization panel.

- **Total cytochrome  $c$  concentration** ( $c_0$ ).
- **Oxidized cytochrome  $c$  concentration** ( $cyt\ c_{ox}(0)$ ), from which the initial reduced cytochrome  $c$  concentration is calculated as  $r(t)(0) = c_0 - cyt\ c_{ox}(0)$ .
- **Oxygen concentration** ( $o(0)$ ).
- **Matrix protons** ( $H_N^+$ ).
- **Intermembrane space protons** ( $H_P^+$ ).

The default values of these parameters are displayed in Fig. 2 and can be reset at any time using the **Reset** button, which reverts the parameters to their original defaults. Additionally, hovering the mouse over a parameter provides a tooltip displaying its unit, enhancing usability.

It is important to note that the initial value of the oxygen concentration ( $o(0)$ ) will automatically be replaced by the first element of the oxygen column in the dataset once the data is loaded.

These parameter values serve as initial conditions for fitting the model to experimental data and can be further adjusted during the optimization process.

## 2.2 Problem Customization Panel

After determining the initial values of the model, the user can customize the model by fitting it to a desired experimental data set with different numbers of bioenergetics assays involving the injection of four chemical reagents: *oligomycin*, *FCCP*, *rotenone*, and *antimycin A*. The number of *FCCP* injections can vary up to 4 injections.

- **Time Unit Selection:** As can be seen in Fig 3, users can specify the unit of time used in the analysis by selecting either seconds or minutes.
- **Load Data:** The user can load experimental data by uploading an Excel file. Once the file is loaded, a summary of its contents is displayed in a table on the right side of the panel, including the name and time of the bioenergetics assays injected during the
- **Edit Table:** This section allows users to edit the content of the Excel file directly within the app. Users can modify experimental data or parameters as needed.

Injection	Time (s)
Start Time	2.0562e+03
Oligomycin	2.2398e+03
FCCP_1	2.3658e+03
FCCP_2	2460
FCCP_3	2562
FCCP_4	2.6802e+03
Rot/AA	2.8362e+03

Figure 3: Problem customization panel.

## 2.3 Model Selector Panel

In this panel, users can choose the type of model and define specific characteristics for the analysis:

- **Model Selection:** Users can choose between two model types:
  - **Baseline Model**
  - **Full Model - Global**
- **Weighting Option:** Users can select whether the model is weighted or unweighted.
- **Weight Input (if weighted):** If weighted analysis is selected, the user can input weight values for different time intervals, allowing for custom importance to be given to certain periods of the data.

## 2.4 Data Analysis Hub

The final section of the left panel is the **Data Analysis Hub**, which includes three dropdown menus for various functionalities:

- **Visualization:** Allows users to visualize different aspects of the model and compare the simulation with experimental data.
- **Optimization:** Users can run optimization algorithms to estimate the best-fit parameters based on the model and data.
- **Results:** Displays the results after running the optimization, including optimized parameters and error metrics.

## 3 Right Panel: Results and Analysis

The right panel is dedicated to displaying results, with four main tabs:

### 3.1 Graphs Tab (Default View)

The default tab in the right panel is the **Graphs** tab, which contains five axes to visualize different parameters of the model:

- **Oxygen Concentration vs Time:** Displays the change in oxygen concentration over time.
- **Oxygen Consumption Rate (OCR) vs Time:** Shows the oxygen consumption rate as a function of time.
- **Cytochrome C Reduced Concentration vs Time:** Visualizes the concentration of reduced cytochrome C over time.
- **Matrix Protein Concentration vs Time:** Shows the concentration of matrix proteins over time.
- **IMS Proton Concentration vs Time:** Displays the concentration of protons in the intermembrane space (IMS) over time.

### 3.2 Results Tab

The **Results** tab provides a detailed table of the optimized parameters. This includes the parameter names, their optimized values, and confidence intervals.

### 3.3 Correlation Analysis Tab

The **Correlation Analysis** tab offers tools to analyze the correlations between the different model parameters. This is useful for understanding parameter dependencies and potential redundancies.

### 3.4 Error Analysis Tab

The **Error Analysis** tab visualizes the error between the model's output and experimental data, helping the user evaluate the model's fit to the data. Various error metrics and plots are provided.

## 4 Using the App

### 4.1 Adjusting Parameters

- Go to the **Parameter Initialization Panel** to set the initial values for model parameters.
- If needed, adjust the time units from the **Parameter Customization Panel**.

### 4.2 Loading Data

1. In the **Data Loading Panel**, click **Load Data** to upload your experimental data as an Excel file.
2. Review the summary of the uploaded data and, if necessary, modify it in the **Parameter Customization Panel**.

### 4.3 Selecting the Model and Weighting

1. Navigate to the **Model Selector Panel** to choose the model type (Baseline or Full Model - Global).
2. If you choose a weighted model, enter the appropriate weight values for different time intervals.

### 4.4 Running Optimization

1. In the **Data Analysis Hub**, open the **Optimization** dropdown and select the optimization algorithm you wish to use.
2. Adjust the optimization settings (if necessary) and click **Run Optimization**.

### 4.5 Visualizing Results

1. Navigate to the **Graphs** tab to visualize the key parameters of the model.
2. If optimization has been run, the graphs will display the optimized model outputs versus the experimental data.

## 4.6 Viewing Additional Results

- Go to the **Results** tab to view the optimized parameters and their confidence intervals.
- Visit the **Correlation Analysis** and **Error Analysis** tabs for more in-depth analysis of the optimization results.

# 5 Saving and Loading Results

## 5.1 Saving Results

1. Once the optimization is complete, click **Save Results** in the **Results** dropdown menu.
2. The results will be saved as a **.mat** file for future reference.

## 5.2 Loading Previous Results

1. Select **Load Previous Results** from the **Results** dropdown menu.
2. Choose the appropriate **.mat** file to load previously optimized parameters and results.

# 6 Visualization Dropdown Option

The "Visualization" dropdown in the MATLAB GUI provides options for displaying different types of plots and analyses based on the current state of the model and data. This section describes the functionality of each option available in the dropdown menu.

- **Raw Data**

- Selecting *Raw Data* will display the raw experimental data for Oxygen Concentration (O<sub>2</sub>) and Oxygen Consumption Rate (OCR).
- The plots will show:
  - \* **Oxygen Concentration (O<sub>2</sub>)**: The raw data is plotted against time with grey dashed lines.
  - \* **Oxygen Consumption Rate (OCR)**: The raw data is plotted against time with grey dashed lines.
- The axes for the plots will be cleared before displaying the data.

- **Non-Optimized Model**

- This option displays the model predictions based on the non-optimized parameters.
- The model is solved using the solver with current parameter settings, and the results are plotted alongside the raw data.
- The plots include:
  - \* **Oxygen Concentration (O2)**: Model output and raw data are plotted with different colors.
  - \* **Oxygen Consumption Rate (OCR)**: Model output and raw data are plotted with different colors.
  - \* **Cyt C Reduced**: The concentration of Cyt C Reduced over time is plotted.
  - \* **Hn and Hp Concentrations**: Concentrations of Hn and Hp over time are plotted.
- The axes will be cleared and updated with the new model outputs and raw data.

- **Optimized Model**

- This option displays the model predictions using the optimized parameters obtained from the optimization process.
- If the model has been optimized, the following plots will be updated:
  - \* **Oxygen Concentration (O2)**: Optimized model output and raw data are plotted with different colors.
  - \* **Oxygen Consumption Rate (OCR)**: Optimized model output and raw data are plotted with different colors.
  - \* **Cyt C Reduced**: Concentration of Cyt C Reduced over time is plotted based on the optimized model.
  - \* **Hn and Hp Concentrations**: Concentrations of Hn and Hp over time are plotted based on the optimized model.
- Error bars will be displayed if the corresponding checkbox is enabled.
- If the model has not been optimized, a message will prompt the user to optimize the model first.

- **In Silico Prediction**

- This option generates predictions based on previously loaded optimized results.
- If previous results are loaded, the model will be solved using those parameters, and predictions will be plotted.
- The plots include:
  - \* **Oxygen Concentration (O2)**: Predicted O2 and raw data are plotted with different colors.



- \* **Oxygen Consumption Rate (OCR):** Predicted OCR and raw data are plotted with different colors.
  - \* **Cyt C Reduced:** Predicted concentration of Cyt C Reduced over time.
  - \* **Hn and Hp Concentrations:** Predicted concentrations of Hn and Hp over time.
- If previous results are not loaded, a message will prompt the user to load results before performing in silico predictions.

## 7 Optimization Dropdown Options

The Optimization DropDown function allows users to choose and customize optimization algorithms for fitting the model parameters. This document provides detailed instructions on how the function operates and how users can interact with it.

## 8 Functionality

The Optimization DropDown function handles three types of optimization algorithms:

- Genetic Algorithm
- Enhanced GA (Bootstrap)
- Enhanced GA (Hybrid Function)

## 9 Initialization Options

Upon selecting an optimization algorithm, the user is prompted to choose how to initialize the parameters:

1. **Use Solved Model Values:** The parameters are initialized with values obtained from a previously solved model.
2. **Keep Initial Values:** The parameters are kept unchanged from their initial state.

## 10 Algorithm-Specific Instructions

### 10.1 Genetic Algorithm

1. **Clear Axes:** Clears the plots in the GUI to prepare for new optimization results.
2. **Custom GA Options:** The user is prompted to enter the following custom options:
  - Number of Iterations
  - Maximum Number of Generations
  - Population Size
  - Crossover Fraction (0-1)
  - Mutation Rate (0-1)
3. **Progress Dialog:** Displays a progress dialog to inform the user about the ongoing optimization process.
4. **Optimization Execution:** Runs the Genetic Algorithm with the specified options and updates the model parameters based on the optimized values.
5. **Result Notification:** A message box notifies the user of the successful completion of the optimization.

For more details, see the **Genetic Algorithm** documentation: <https://www.mathworks.com/help/gads/genetic-algorithm.html>

### 10.2 Enhanced GA (Bootstrap)

1. **Clear Axes:** Clears the plots in the GUI to prepare for new optimization results.
2. **Bootstrap Parameters:** The user is prompted to enter the following parameters:
  - Number of Bootstrap Samples
  - Maximum Number of Generations
  - Population Size
  - Crossover Fraction (0-1)
  - Mutation Rate (0-1)
3. **Progress Dialog:** Displays a progress dialog to inform the user about the ongoing optimization process.
4. **Optimization Execution:** Runs the Enhanced GA with bootstrap sampling and updates the model parameters based on the optimized values.

5. **Result Notification:** A message box notifies the user of the successful completion of the optimization.

For more details on Enhanced GA with Bootstrap, refer to the **Bootstrap Method** section in the documentation: <https://www.mathworks.com/help/stats/bootstrapping.html>

### 10.3 Enhanced GA (Hybrid Function)

1. **Clear Axes:** Clears the plots in the GUI to prepare for new optimization results.
2. **Maximum Generations:** The user is prompted to enter the maximum number of generations.
3. **Progress Dialog:** Displays a progress dialog to inform the user about the ongoing optimization process.
4. **Optimization Execution:** Runs the Hybrid Function GA and updates the model parameters based on the optimized values.
5. **Result Notification:** A message box notifies the user of the successful completion of the optimization.

For further details on Hybrid Function GA, consult the **Hybrid Optimization** documentation: <https://www.mathworks.com/help/gads/hybrid-function-optimization.html>

## 11 Error Handling

In case of invalid inputs or errors during optimization:

- An error dialog will prompt the user to enter valid inputs.
- If an error occurs during optimization, an error message will be displayed to inform the user.

The Optimization DropDown function provides users with flexible and customizable optimization options for fitting model parameters. By following the instructions provided, users can efficiently set up and execute different optimization algorithms based on their needs.

## 12 Results Dropdown Options

The "Results" dropdown in the MATLAB GUI provides multiple options to display and analyze the optimization and simulation results from the model. This manual explains the purpose and functionality of each option available in the dropdown menu.

- **Display**

- Selecting *Display* allows the user to view the optimized parameters in a table format.
- The table includes two columns:
  - \* **Parameter** – the name of the parameter, represented using LaTeX notation for readability.
  - \* **Optimized Value** – the value of the parameter after optimization.
- Example of displayed parameter names:
  - \*  $V_{max_{c_0}}$
  - \*  $C_{yt} c_{tot}$
  - \*  $K_{m_{c_0}}$
- Additional details about the Genetic Algorithm (GA) process will also be displayed in the *GAInfoTable*, such as:
  - \* Optimization Success
  - \* Number of Iterations
  - \* Population Size
  - \* GA Error
  - \* Duration (seconds)

- **Markov Chain Monte Carlo (MCMC) Analysis**

- This option allows the user to run a Markov Chain Monte Carlo (MCMC) analysis using custom input parameters provided through a dialog box.
- The dialog prompts the user to input:
  - \* Number of MCMC iterations
  - \* Thinning factor
  - \* Step size for the proposal distribution
  - \* Confidence level for the calculated intervals
- After running the MCMC analysis, the results will be displayed in the table with the following columns:
  - \* **Parameter** – parameter name in LaTeX format
  - \* **Optimized Value** – value after GA optimization

- \* **Mean Value** – mean value obtained from the MCMC analysis
- \* **Confidence Interval (CI)** – the calculated confidence interval for each parameter.
- Log-prior, log-likelihood, and acceptance rates will be displayed in the *mcmcInfoTable*.
- For more information on MCMC methods and their implementation in MATLAB, please refer to the **Markov Chain Monte Carlo (MCMC)** documentation: <https://www.mathworks.com/help/stats/markov-chain-monte-carlo.html>
- **Bootstrap Confidence Intervals**
  - This option is available only if the model has been optimized using the Enhanced Genetic Algorithm (GA) with Bootstrap.
  - Confidence intervals are calculated based on bootstrap samples, and the following columns are displayed in the table:
    - \* **Parameter**
    - \* **Optimized Value**
    - \* **Mean Value** (if available)
    - \* **Confidence Interval (CI) by Bootstrap**
- **Correlation Analysis**
  - Selecting *Correlation Analysis* switches the view to the *Correlation Analysis* tab.
  - The user can view a filtered correlation matrix based on MCMC samples.
  - The user can define upper and lower limits for the filtering, and only the correlations within this range are displayed.

## 13 LaTeX Representation of Parameters

The table below summarizes the LaTeX formatting of the parameters displayed in the Results Table:

Parameter Name	LaTeX Representation
Vmax_c0	$V_{max_{c_0}}$
cyt c_tot	$Cyt\ c_{tot}$
Km_c0	$K_{m_{c_0}}$
Vmax_cIV	$V_{max_{c_{IV}}}$
Km_cIV	$K_{m_{c_{IV}}}$
Kc_IV	$K_{c_{IV}}$
Vmax_cV	$V_{max_{c_V}}$
Kc_V	$K_{c_V}$
Km_cV	$K_{m_{c_V}}$
P_leak	$P_{leak}$
cyt c red_prop	$Cyt\ c_{red_{prop}}$

Table 1: LaTeX Representation of Parameters

## References

## 14 Troubleshooting

### 14.1 Data Loading Issues

Ensure the Excel file is formatted correctly with appropriate time points and parameter values. Missing or incorrect data may prevent successful data loading.

### 14.2 Optimization Issues

If optimization results appear incorrect or the process stalls, consider adjusting the initial parameter values or selecting a different optimization algorithm.

## 15 Contact and Support

For any issues or inquiries regarding the application, please contact the developer at [marzieh.eini@gmail.com](mailto:marzieh.eini@gmail.com).