# HOW TO USE MIKANA

MIKANA (**M**ethod to **I**nfer **K**inetics **A**nd **N**etwork **A**rchitecture) is a novel computational method to infer reaction mechanisms and estimate the kinetic parameters of biochemical pathways from time course data. This application is available for download at: http://sitemaker.umich.edu/schnell.lab/products.

## Installation

**To run MIKANA in MatLab:**

1. Decompress the zip file "MATLAB.zip". This will create the directory "MIKANA".

2. Open the MatLab environment.

3. Set the current directory to the path of the new directory "MIKANA".

4. Run the command mikana

The MIKANA Graphical User Interface (GUI) should appear immediately in your screen.

A standalone application was also generated for MIKANA. While you do not need MATLAB to run the standalone version of MIKANA, you need to have installed in your system the MATLAB Compiler Runtime (MCR).

**To run MIKANA on Windows:**

1. Extract the file MIKANA_Win.zip into a specific folder

2. If you do not have MatLab installed, download and install the MatLab runtime environment. For the purpose, we provide the file "MCRinstaller_Win.exe"

3. If you need to run the MIKANA executable in Windows 7, you need to

   a. Right click on "mikana.exe" icon,
   b. Go to "Properties". Go to Compatibility tab.
   c. Check the box saying "Run this program in compatibility mode for"
   d. Select "Windows vista" (this is the closest to windows)
   e. Apply changes.

4. Double click mikana.exe... a GUI should open

This version of MIKANA has been compiled into a standalone version using MatLab R14, 2008b. We have tested it for both windows 7 and windows vista.

**To run MIKANA on Mac OS X:**

1. Extract the file “MIKANA_Mac.zip”
2. If you do not have MatLab installed, download and extract the MatLab runtime environment. For the purpose, we provide the file "MCRinstaller_Mac.zip"
3. Open a terminal in your computer
4. Execute “./mikana.sh </MCR PATH/> IPAddress”

Where “</MCR PATH/>” corresponds to the current path of your MatLab Compiler Runtime.

This version of MIKANA has been compiled into a standalone version using the MATLAB Compiler 4.6 (R2007a).

# Example

The GUI is composed of three distinct sections: (i) the INPUT (at the top); (ii) the OUTPUT (at the bottom left); and (iii) the MAIN (bottom right). The Input is composed of five panels. At the left, the “Time Course Data” panel is used to read the input time course data from a file. The file should contain a header line followed by numeric data. The header line should contain the gene label or symbols. You should introduce as many symbols as chemical species you intend to process. The numeric data should only contain numeric characters, otherwise an invalid insertion will be reported back to you. The first column should contain the time at which the following chemical species values associate, as in the following table:

| | $Sym\_\ s_1$ | $Sym\_\ s_2$ | ... | $Sym\_\ s_n$ |
|---|---|---|---|---|
| $Time_1$ | $Species_1$ | $Species_2$ | ... | $Species_n$ |
| $Time_2$ | $Species_1$ | $Species_2$ | ... | $Species_n$ |
| | ... | ... | ... | ... |
| $Time_t$ | $Species_1$ | $Species_2$ | ... | $Species_n$ |

MIKANA’s webpage contains an example of a time course data: “example_mm.txt”. To open the file, just push the button “Read File” in the “Time Course Data” panel. The time course data of four chemical species will become visible in the panel, which should be similar to the following:

| | | | | |
|---|---|---|---|---|
| 0 | 1.86 | 1.56 | 0 | 0.07 |
| 13.23 | 0.94 | 0.64 | 0.88 | 0.08 |
| 26.46 | 0.72 | 0.55 | 1.1 | 0.16 |
| 39.68 | 0.57 | 0.49 | 0.99 | 0.15 |
| 52.91 | 0.61 | 0.47 | 1 | 0.34 |
| 66.14 | 0.49 | 0.52 | 0.96 | 0.46 |
| 79.37 | 0.46 | 0.44 | 1.04 | 0.48 |
| 92.59 | 0.35 | 0.62 | 0.92 | 0.54 |
| 105.82 | 0.31 | 0.64 | 0.83 | 0.66 |
| 119.05 | 0.32 | 0.65 | 0.79 | 0.7 |
| 132.28 | 0.28 | 0.68 | 0.89 | 0.82 |
| 145.5 | 0.34 | 0.7 | 0.86 | 0.91 |
| 158.73 | 0.2 | 0.79 | 0.8 | 1.03 |
| 171.96 | 0.3 | 0.85 | 0.62 | 1.03 |
| 185.19 | 0.25 | 0.86 | 0.63 | 1.06 |
| 198.41 | 0.06 | 0.89 | 0.6 | 1.22 |
| 211.64 | 0.05 | 0.95 | 0.58 | 1.24 |
| 224.87 | 0.09 | 0.98 | 0.51 | 1.26 |
| 238.1 | 0.1 | 0.97 | 0.45 | 1.32 |
| 251.32 | 0.1 | 1.12 | 0.44 | 1.31 |
| 264.55 | 0.13 | 1.1 | 0.49 | 1.42 |
| 277.78 | 0.05 | 1.17 | 0.53 | 1.43 |
| 291.01 | 0.04 | 1.11 | 0.39 | 1.48 |
| 304.23 | 0.06 | 1.11 | 0.34 | 1.43 |
| 317.46 | 0.06 | 1.23 | 0.36 | 1.59 |
| 330.69 | 0.07 | 1.21 | 0.28 | 1.56 |
| 343.92 | 0.1 | 1.2 | 0.38 | 1.47 |
| 357.14 | 0.08 | 1.25 | 0.32 | 1.61 |
| 370.37 | 0.04 | 1.17 | 0.18 | 1.68 |
| 383.6 | 0.07 | 1.34 | 0.19 | 1.67 |

The data above resembles the file contents. Upon successfully reading a time course data, an option to plot and visualize the data over time is made available through the button “Plot Data” in the same panel.

The other four Input panels are made available as options to select an information criterion (“Empirical”, “Akaike” or “Bayesian”), an interaction type (“Uni–molecular” or “Bi–molecular”), a maximum number of molecules (“1” or “2” molecules), and a set of reactions to remove from the final reaction solution set. MIKANA’s package includes an example reactions file (“reactions.txt”) that contains six reactions:

1. ->X
2. X->
3. X1->X
4. X->X1
5. X2->X
6. X->X2

Here, the introduction of the first two reactions could be used to produce a close

system. Reaction 3 would make it impossible to have species x1 converted to any other species with no interactions. Reversibly, reaction 4 makes it impossible to have any species converted to species x1 with no interactions. Reactions 5 and 6 stand for the same goal as the two previous reactions, but they apply it to chemical species x2. The last four reactions could be useful to introduce restrictions on chemical species interactions, such as to an enzyme or to a substrate, in an enzyme catalyzed reaction.

The user can and should use the input options presented above as he/she finds more adequate. To process the data and infer the metabolic pathway, the user should push the button "Process" (the first button in the main section).

The Output section (bottom left) of the GUI is composed of three panels. At the left, the "Used Reactions" panel shows all elementary reactions considered in the model selection process. The "Predicted Reactions" panel shows the final selection of reactions that constitute the inferred metabolic pathway. The "Differential Equations" panel shows a set of differential equations that correspond to the final mechanism. We provide three different views of the results in each of these subpanels. The first view displays all chemical species that participate in the reactions. The second view excludes from the reactions species with zero stoichiometry. The third and last view displays the chemical species by their gene name or symbol, as introduced in the input time course data file.

The Main section (bottom right) of the GUI is composed of eight buttons, each one with the following functions (from top to bottom):

1. Processes the input data ("Process").
2. Plots the chemical species changes over time from the inferred differential equations and kinetic rate constants ("Plot Output Time Course").
3. Plots the input and the output time course data in the same figure ("Plot Input/Output Time Course").
4. Shows the fit error associated with each one of the chemical species ("Show Fit Errors").
5. Saves all the results to a file ("Save Output to a File").
6. Save the output time course data to a file ("Save Output Time Course to a File").
7. Cleans all information provided in the output section of the GUI ("Clean All Output").
8. Provides information about the application ("About the Application").

Using the options "Akaike" ("Information Criteria"), "Bi-molecular" ("Interaction Type"), and "1" molecule ("Molecularity") for the time course presented here as an example, MIKANA predicts five reactions among 44 possible reactions. These predicted reactions correspond to the following differential equations:

$$
\begin{aligned}
X'(1) &= +0.0082 * X(3)^1 - 0.0478 * X(1)^1 * X(2)^1 \\
X'(2) &= +0.0103 - 0.0056 * X(2)^1 + 0.0066 * X(3)^1 - 0.0478 * X(1)^1 * X(2)^1 \\
X'(3) &= -0.0149 * X(3)^1 + 0.0478 * X(1)^1 * X(2)^1 \\
X'(4) &= +0.0066 * X(3)^1
\end{aligned}
$$

For Windows users, results saved into a file can be read properly with WordPad. For more information about MIKANA and published results, we recommend the user to consult the following publications:

Srividhya J, Crampin E, McSharry P, Schnell S: Reconstructing biochemical pathways from time course data. Proteomics 2007, 7(6):828–838.

Srividhya J, Mourao M, Crampin E, Schnell S: Enzyme catalyzed reactions: from experiments to computational mechanism reconstruction. Computational Biology and Chemistry 2010.