PTIM GUI

User's Guide

Version 1.0

This document is to be used with the PTIM GUI Version 1.0 developed by Noah Berlow under the supervision of Dr. Ranadip Pal, both of Texas Tech University Department of Electrical and Computer Engineering..

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PTIM GUI MAIN WINDOW: To start the PTIM GUI, double click on the PTIM GUI Icon. It will take approximately 30 seconds to load, so please be patient.

When the GUI is ready to be used, this window will appear:
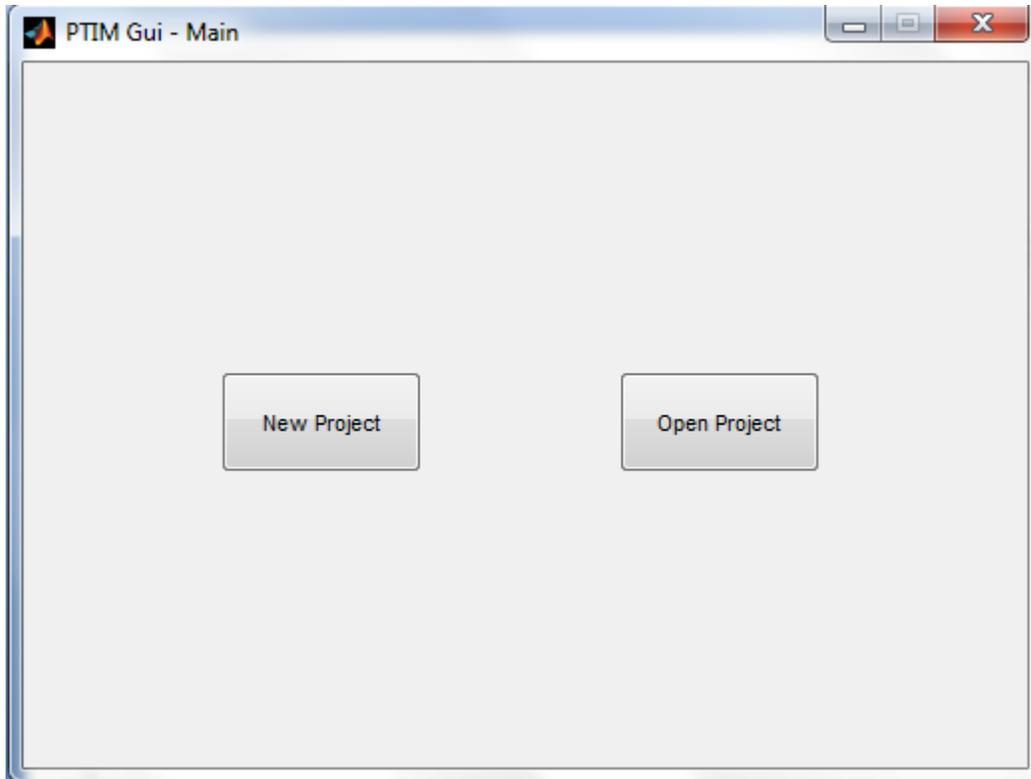

Figure 1 - PTIM GUI Main Window

A project consists of a Drug Screen Panel File (.xls or .xlsx format) and an IC50 File (.xls or .xlsx format). The PTIM GUI will only generate PTIMs in a valid project folder.

If you wish to create a new project, select the **NEW PROJECT** Button. If you wish to build or view PTIMs for an existing project, select **OPEN PROJECT.**

NEW PROJECT: When the **NEW PROJECT** button is pressed, a new window opens. This window is where parameters for the project are selected. They cannot be changed once a project is generated.

The new project window looks like this:
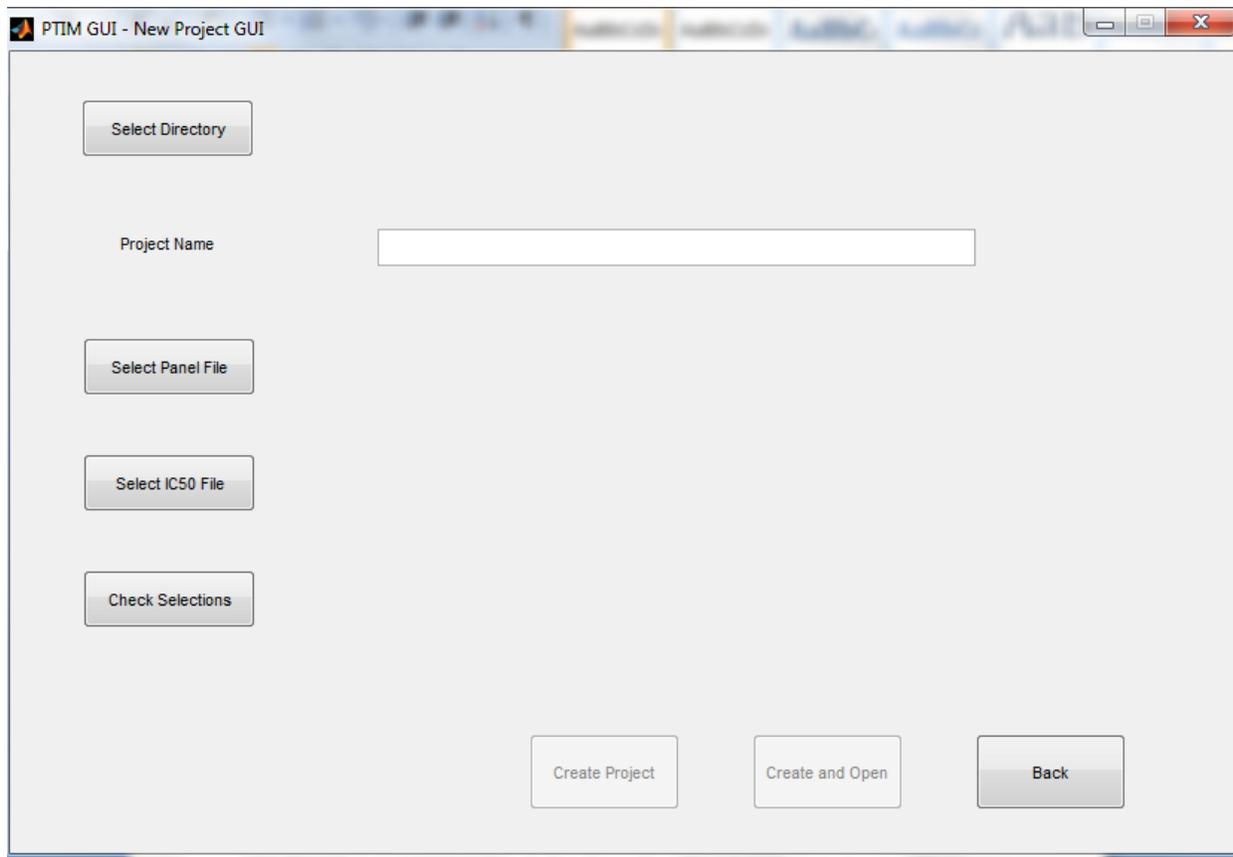
Figure 2 - New Project GUI

PROJECT NAME will be the name given to the project folder. It must adhere to standard variable name rules. (No spaces, use underscores instead. The project name must begin with a letter. No special characters.)

SELECT DIRECTORY, SELECT PANEL FILE, SELECT IC50 FILE all open up file selection windows.

SELECT DIRECTORY chooses a directory where the project file will be created. It will be created directly inside the selected directory.

SELECT PANEL FILE chooses a Drug Panel File for association with the project. This should be uniquely associated with a Drug Screen. A Panel File is a spreadsheet where the top row is the headers 'Drug Name','Csss','Cmax','Max Dose', and for every target associated with a drug in the panel, a column with the target name as the header. In 'Drug Name' column, a drug name for each drug in the screen should be added. The appropriate values for 'Csss','Cmax' (At this point, these should be identical), and 'Max Dose' should be associated with each drug. And in row for each target, the appropriate interaction value

should be entered (if there is no interaction with a target for a drug, this is left blank). The GUI will check to make sure these headers exist. If not, an error will be returned. A sample panel file is located in the same directory as this User Guide.

SELECT IC50 FILE chooses an IC50 file to associate with the project. The IC50 file should have an IC50 value associated with each drug in the panel. There should be NO HEADER for the IC50 file. The IC50 value for drug 1 should be in position A1 in the IC50 file spreadsheet. The GUI will compare the number of drugs in the panel file with the number of IC50 values listed. If there is a mismatch an error will be returned.

When all selections have been made, press CHECK SELECTIONS. If there are no errors, the CREATE and CREATE AND OPEN buttons with be enabled.
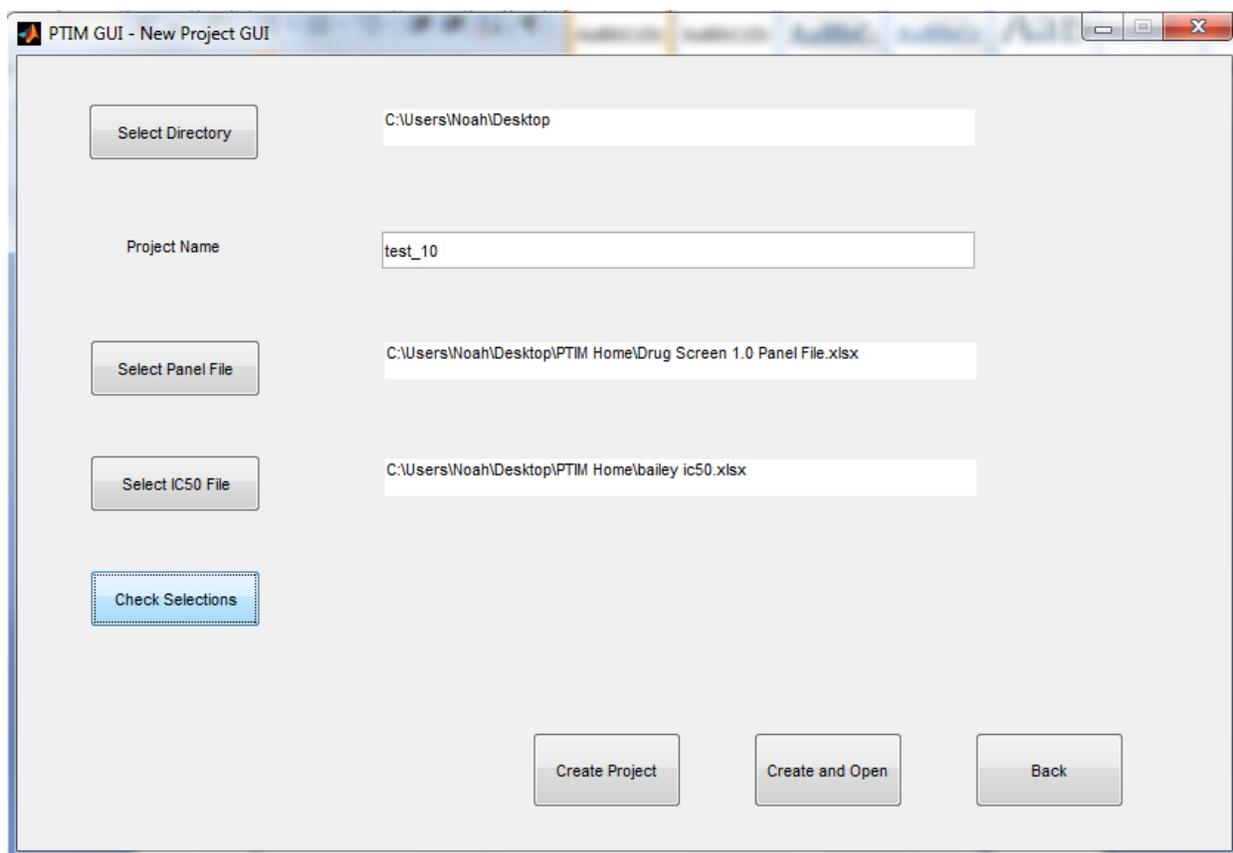
The above example has the project directory as the user's desktop. The project name is 'test_10'. The panel file is the included example panel file, same as the IC50 file. I have pressed check selections, and the CREATE PROJECT and CREATE AND OPEN buttons are now useable.

CREATE PROJECT: This selection creates the project folder and waits for further input. Use this selection is you want to create more than one project at a time.

CREATE AND OPEN: This selection creates the project folder and then opens the project directly. This is the same as selecting BACK, then OPEN PROJECT and selecting the project directory you have just created.

OPEN PROJECT: Press the SELECT PROJECT button to open up a dialogue window to select a project folder. The GUI will test to see if this folder is a valid project. If it is a valid project, the OPEN PROJECT button will become enabled.
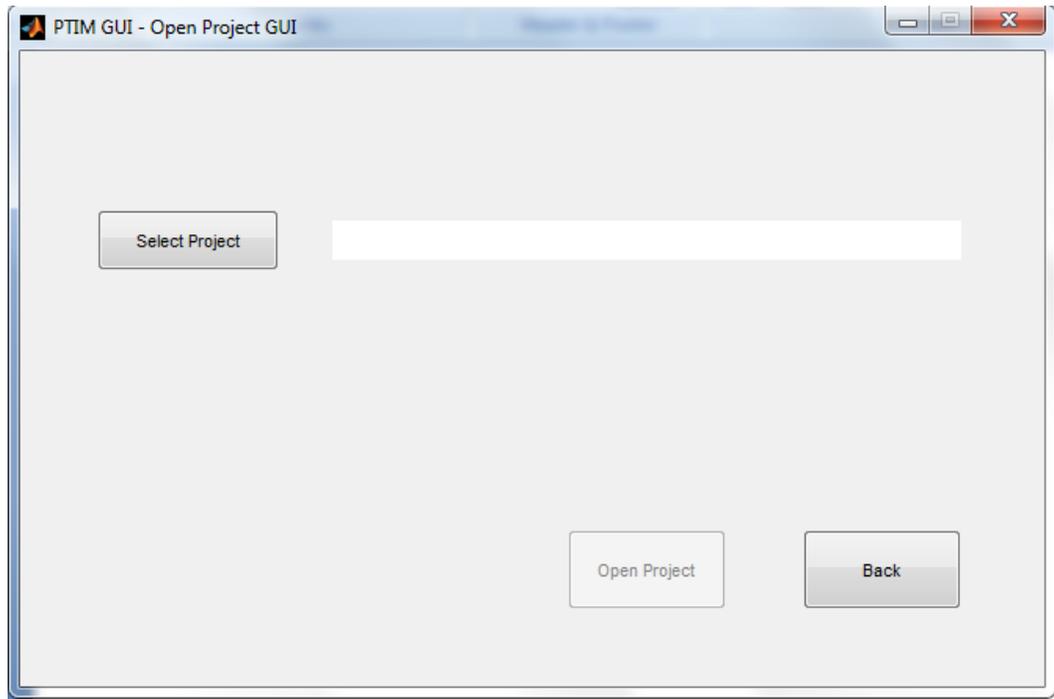
The selected project will be used for all future GUI selections following this window. If you wish to select a new project, navigate back here and select the new project in the same manner as described below.
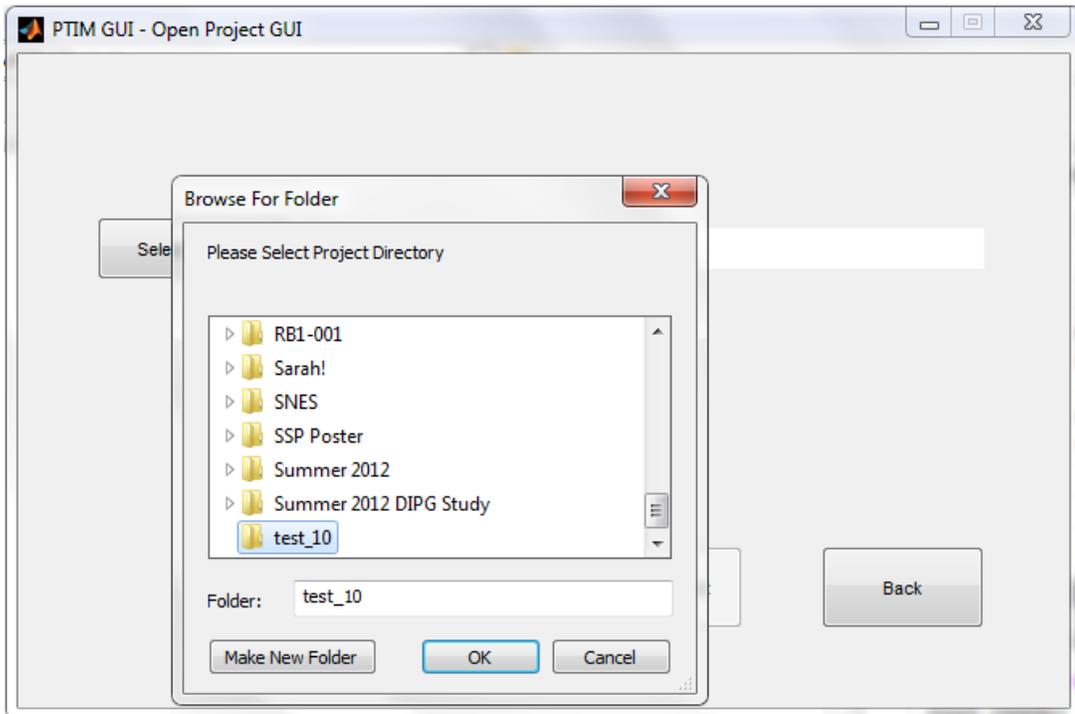
Figure 5 - Project Folder Selection

Here we have selected the project we created earlier (test_10).
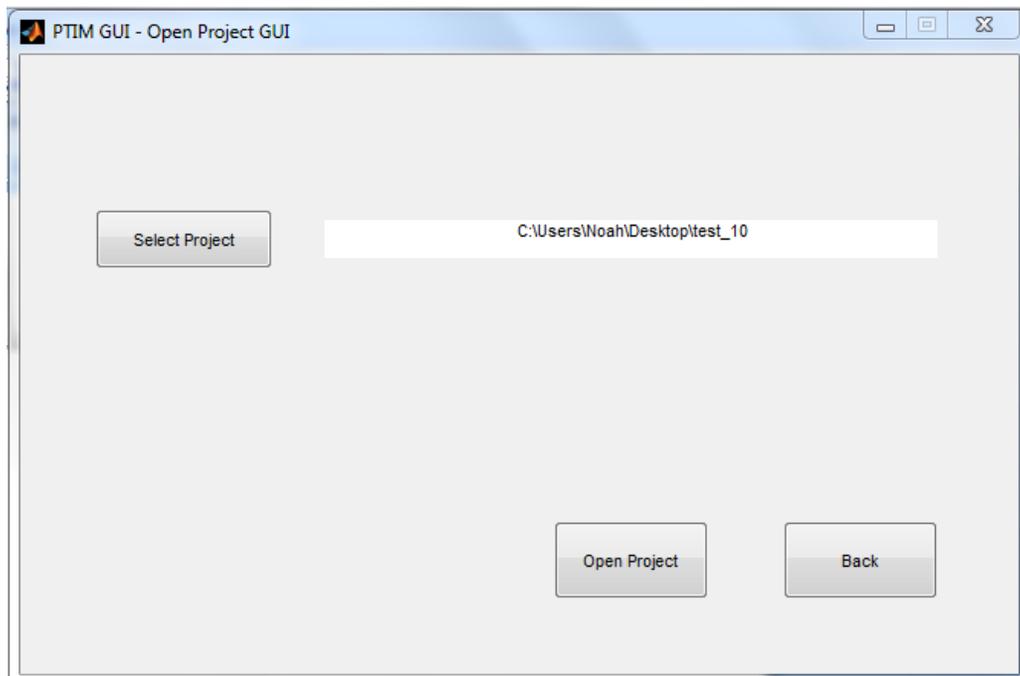

Figure 6 - OPEN PROJECT button enabled

Having selected Project test_10, the GUI has to make sure the project is valid; it is, so OPEN PROJECT is enabled. When we press OPEN PROJECT, a new GUI will appear. This is the **PROJECT MAIN GUI.**

PROJECT MAIN GUI: This window will open once a project has been selected. From here, there are three options. If you would like to select a new project to work with, press BACK here.
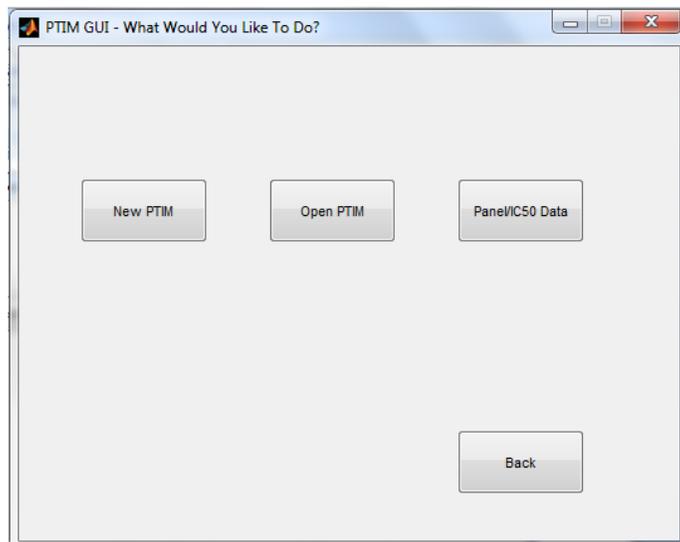

Figure 7 - Project Main Window

NEW PTIM: Press this button if you wish to generate a new PTIM for the project. PTIMs can be generated manually and automatically. As of this writing, there is currently only 1 set of filters which can be applied to the input.

OPEN PTIM: Press this button if you wish to open a PTIM. Opening a PTIM allows you to perform some analysis on the PTIM and allows you to generate PTIM maps (circuits).

PANEL/IC50 DATA: Provides a new pop-up window to show you the IC50 data and Panel data specified in the files associated with the project.

Figure 8 - PANEL/IC50 Preview Window

NEW PTIM - FILTER SELECTION GUI:

Figure 9 - Filter Selection GUI

This window allows the user to select one of multiple possible filtering methods to determine the values of the input to the PTIM algorithm. As of this writing, only one filtering method is available. Selecting the filtering method will take you to the associated next GUI.

NEW PTIM - KELLER FILTER: This filter implements 4 layers of filtering to determine the final input the PTIM generating algorithm will see. The PTIM algorithm expects to see: a set of drug names and associated scaled sensitivities and binarized inhibition profiles for each drug associated with each protein kinase target in the screen. The first later of the filter allows for direct removal of drugs and targets.
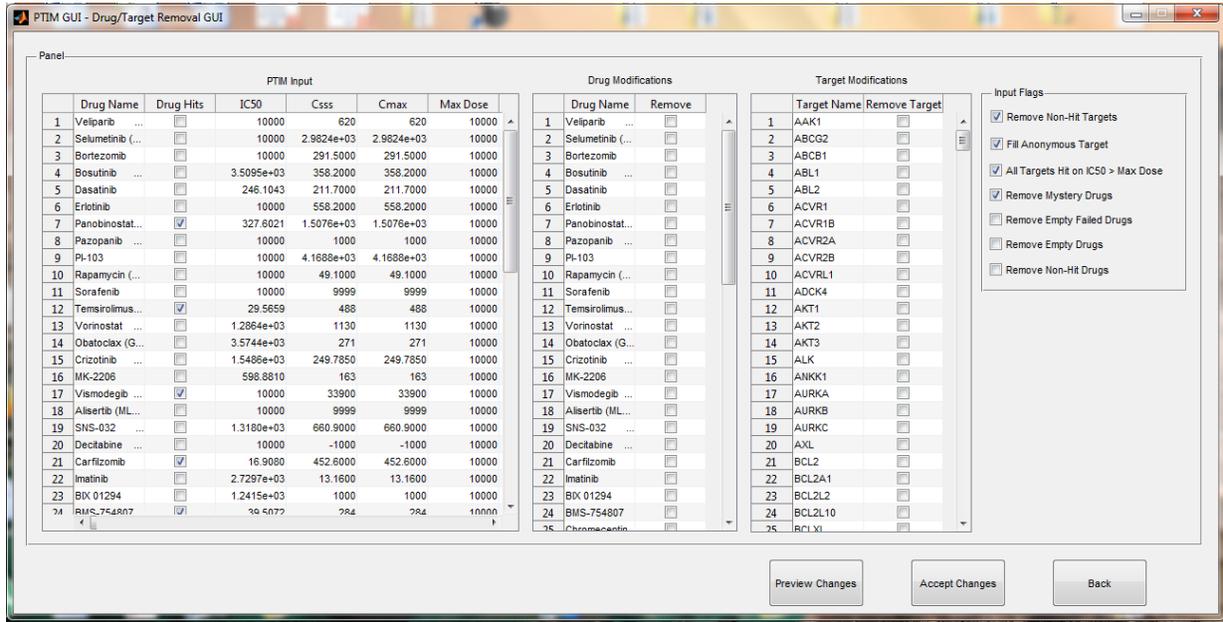

Figure 10 - PTIM Drug/Target Filter GUI

Let's suppose, for example, that drug 1 (Veliparib) originated from a old batch which had lost its efficacy. As such, the results from that drug are unreliable. In addition, suppose that prior information has shown that target 4 (ABL1) is unimportant in this particular dataset. By selecting the check boxes to the right of each and pressing PREVIEW CHANGES, we will see that the drug and target are removed.

Figure 11 - PREVIEW with Veliparib and ABL1 Removed

In addition, there are a set of 7 boolean flags on the right side of the filter.

Figure 12 - Set of filter 1 flags

The flags have the following behaviors:

REMOVE NON-HIT TARGETS: If a protein target has no drugs which successfully inhibit it, it will be automatically removed from the input set.

FILL ANONYMOUS TARGET: If a successful (IC50 < max dose) drug has no inhibited protein targets according to the filter coefficients selected later, the drug will have an anonymous protein target associated with it. These targets will be Target_X1, Target_X2, etc.

ALL TARGETS HIT ON IC50 > MAX DOSE: When a drug is unsuccessful in the drug screen, all protein targets with EC50 below the maximum dosage are hit for that unsuccessful drug.

REMOVE MYSTERY DRUG: If a drug in the drug screen has no available information concerning its protein targets, the drug is removed from the dataset.

REMOVE EMPTY FAILED DRUGS: If a an unsuccessful drug has no protein targets hit, it is removed from the dataset. This is mutually exclusive with **ALL TARGETS HIT ON IC50 > MAX DOSE.**

REMOVE EMPTY DRUGS: Removes from the input set any successful drugs which to not have any protein targets hit as per the selected parameters. This is mutually exclusive with **FILL ANONYMOUS TARGET.**

REMOVE NON-HIT DRUGS: Removes from the dataset drugs which were not "hits" in the drug, screen, in this case defined as a drug which has IC50 below a selectable constant times the Cmax/Csss value.

Once the changes are satisfactory, press ACCEPT CHANGES To move to the second filter.

NEW PTIM - DRUG HIT FILTER: This is the second filter that will be applied to the input data. Here, a hit is determined by the IC50 of a drug being less than the Cmax value of the drug multiplied by a constant. The constant is selectable one of two ways. By selecting the "Uniform Filter" radio button, two coefficients are used. The low hit coefficient will be a lower bound on the IC50, and the high hit coefficient will be the upper bound. The result is that any drug which has its IC50 fall between the low bound and the high bound will be termed a drug hit. However, unless the "**REMOVE NON-HIT DRUG"** flag is set, this will not have any lasting effect on the input set.
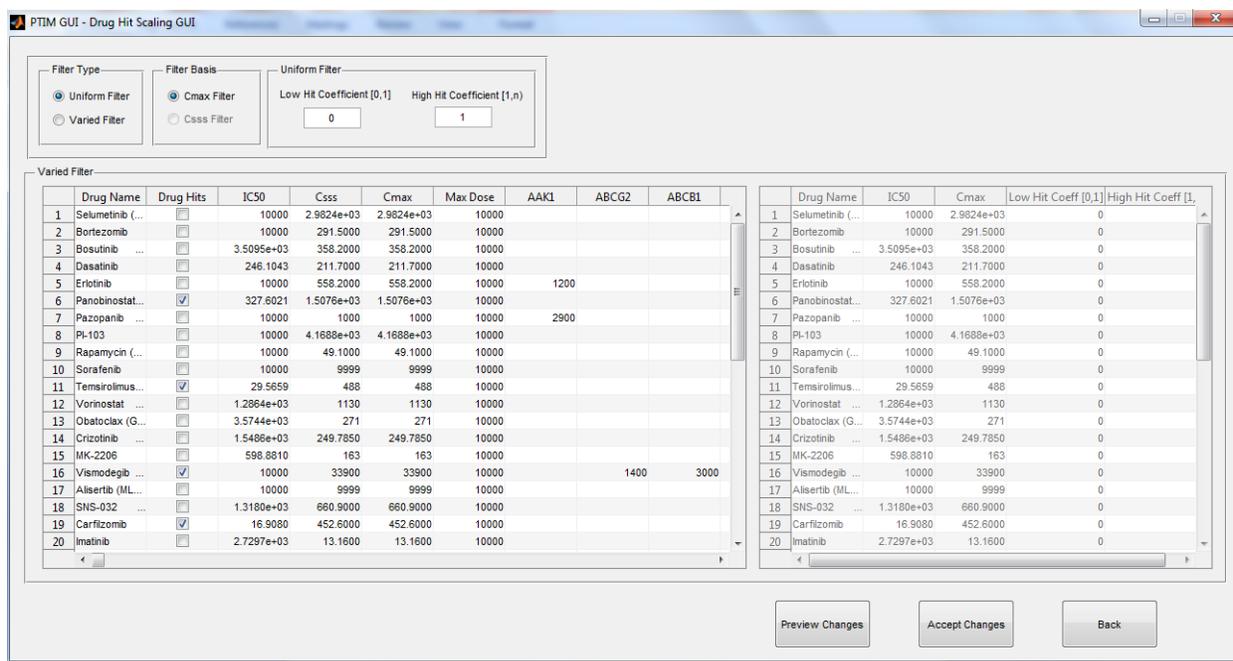

Figure 13 - Drug Hit GUI

For example, suppose we set the High Hit coefficient to 2. When we preview the changes, we find that drug 12 (Vorinostat) becomes a hit.

			IC50	Csss	Cmax	Max Dose			
9	Rapamycin (...	☐	10000	49.1000	49.1000	10000	0	98.2000	
10	Sorafenib	☐	10000	9999	9999	10000	0	19998	
11	Temsirolimus...	☑	29.5659	488	488	10000	0	976	
12	Vorinostat ...	☑	1.2864e+03	1130	1130	10000	0	2260	
13	Obatoclax (G...	☐	3.5744e+03	271	271	10000	0	542	
14	Crizotinib ...	☐	1.5486e+03	249.7850	249.7850	10000	0	499.5700	

Figure 14 - New Drug hits for High Hit Coefficient of 2

Once the changes are satisfactory, press ACCEPT CHANGES to move to the third filter.

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NEW PTIM - Target Hit GUI: This GUI serves to convert the continuous-valued EC50 and Kd values (drug-protein interaction values) and classify the targets as inhibited (1) or not inhibited (0) based on bounding regions selected by coefficients associated with the EC50 values and the IC50 values.

When selecting EC50 coefficients, the bounding is done as Low*EC50 < IC50 < High*EC50. If this inequality is true for a drug-protein interaction value, the drug is considered to inhibit the protein.

When selecting IC50 coefficients, the bounding is done as Low*IC50 < EC50 < High*IC50. If this inequality is true for a drug-protein interaction value, the drug is considered to inhibit the protein.
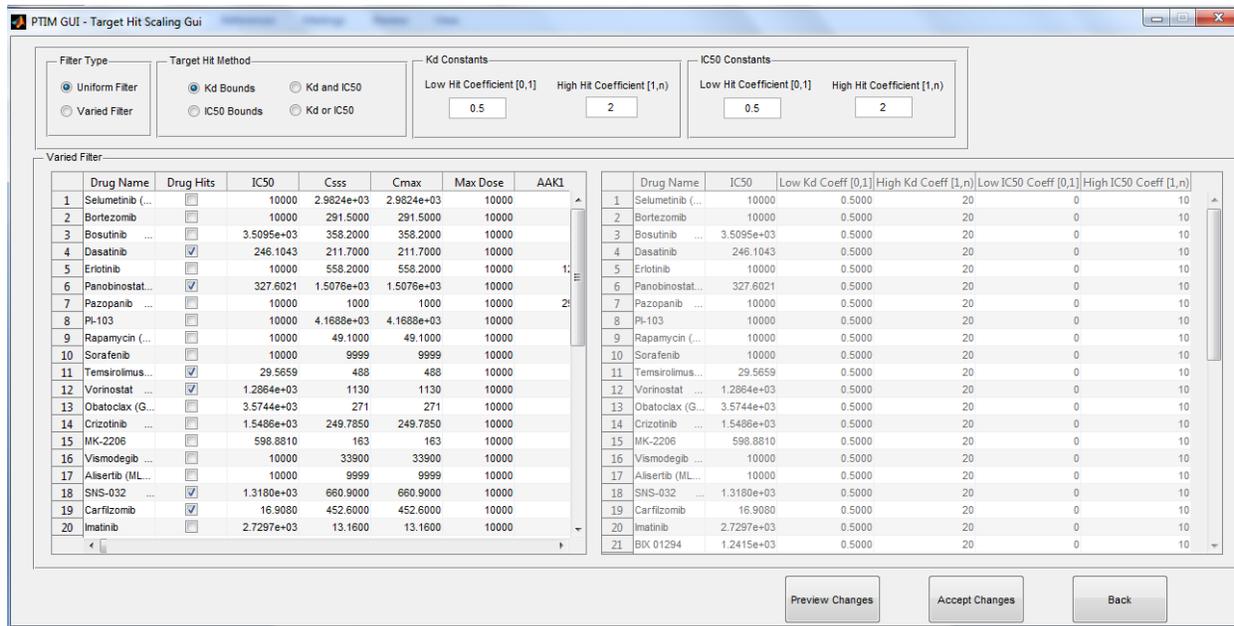

Figure 15 - PTIM Target Hit Filter GUI

There is, once again, a uniform and varied coefficient entry method. There is an additional radio button selection to be made in the box denoted **TARGET HIT METHOD.** This is the method by which targets are selected.

Kd BOUNDS: This choice uses the EC50 and Kd values and the associated coefficients to create the inequality.

IC50 BOUNDS: This choice uses the IC50 values and the associated coefficients to create the inequality.

Kd and IC50: This choice uses the associated bounds for the EC50/Kd values and the IC50 values to set up the two simultaneous inequalities. With this selection, a drug hits a target only if it satisfies BOTH inequalities. This is a much stricter criterion.

Kd or IC50: This choice uses the associated bounds for the EC50/Kd values and the IC50 values to set up the two simultaneous inequalities. With this selection, a drug hits a target if it satisfies EITHER inequality.

In addition, if the **FILL ANONYMOUS TARGET** flag was selected previously, this stage is where the anonymous targets would be added.

For example, suppose we leave the parameters as is, but select the radio button **KD or IC50**.
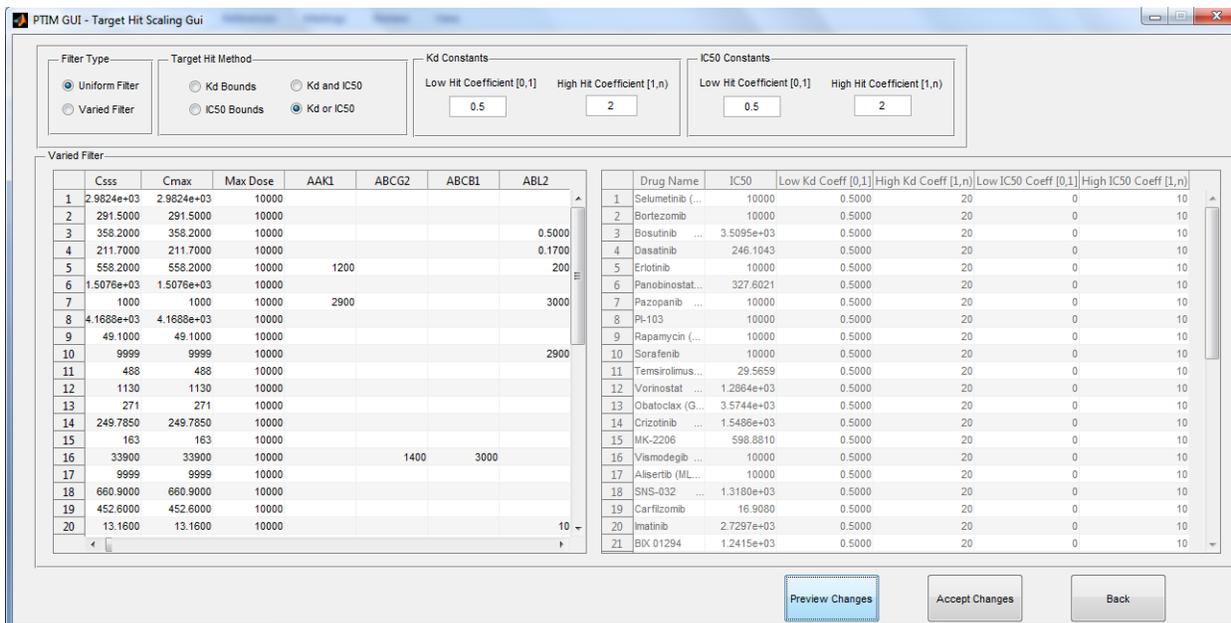
Figure 16 - Target Hit Gui Example

When we preview the changes, we find that 1) Six effective drugs had no explained targets and, as such, are filled with anonymous targets. In general, the fewer unexplained targets, the more relevant the resulting PTIM will be.
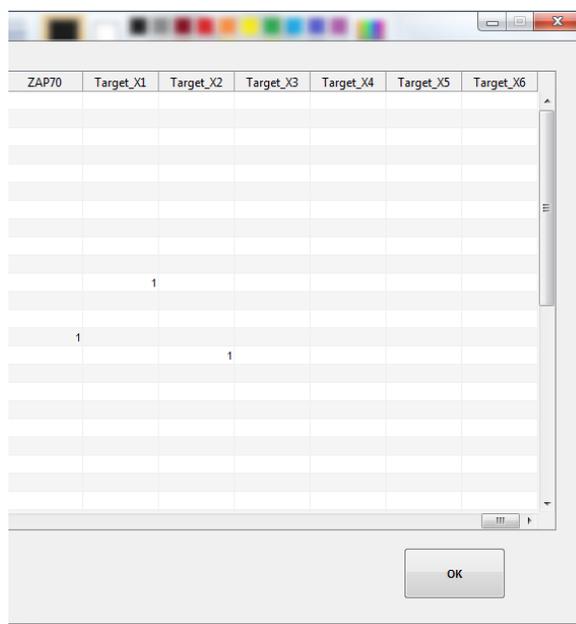
Figure 17 - Anonymous Targets for Successful Drugs

	Drug Name	Drug Hits	IC50	Csss	Cmax	Max Dose	AAK1	ABCG2	ABCB1	ABL2	ACVR1B	ACVR2A	AC
1	Selumetinib (...	☐	10000	2.9824e+03	2.9824e+03	10000							
2	Bortezomib	☐	10000	291.5000	291.5000	10000							
3	Bosutinib ...	☐	3.5095e+03	358.2000	358.2000	10000							
4	Dasatinib	☑	246.1043	211.7000	211.7000	10000						1	1
5	Erlotinib	☐	10000	558.2000	558.2000	10000	1				1		
6	Panobinostat...	☑	327.6021	1.5076e+03	1.5076e+03	10000							
7	Pazopanib ...	☐	10000	1000	1000	10000	1				1		
8	PI-103	☐	10000	4.1688e+03	4.1688e+03	10000							
9	Rapamycin (...	☐	10000	49.1000	49.1000	10000							
10	Sorafenib	☐	10000	9999	9999	10000					1		
11	Temsirolimus...	☑	29.5659	488	488	10000							
12	Vorinostat ...	☑	1.2864e+03	1130	1130	10000							
13	Obatoclax (G...	☐	3.5744e+03	271	271	10000							
14	Crizotinib ...	☐	1.5486e+03	249.7850	249.7850	10000							
15	MK-2206	☐	598.8810	163	163	10000							
16	Vismodegib ...	☐	10000	33900	33900	10000		1	1				
17	Alisertib (ML...	☐	10000	9999	9999	10000							
18	SNS-032 ...	☑	1.3180e+03	660.9000	660.9000	10000							
19	Carfilzomib	☑	16.9080	452.6000	452.6000	10000							
20	Imatinib	☐	2.7297e+03	13.1600	13.1600	10000							
21	BIX 01294	☑	1.2415e+03	1000	1000	10000							
22	BMS-754807	☑	39.5072	284	284	10000							
23	SJ-172550	☐	10000	1000	1000	10000							

Figure 18 - Binarized Drug-Protein Interactions for above parameters

Once the changes are satisfactory, press ACCEPT CHANGES to move to the fourth and final filter.

NEW PTIM - DRUG SENSITVITY GUI:
This GUI is the last GUI before development of a PTIM. In this GUI, scaling methods are used to determine the scaled sensitivity of the drugs used in the drug screen. Ideally, a highly effective drug should have a sensitivity of 1 and an ineffective drug (IC50 > max dose) should have sensitivity of 0. Here, there are 3 methods to scale the IC50 values into sensitivity values.

CMAX/Max Dose Scaling: Here, the user selects two coefficients, Cmax coefficient and Max Dose coefficient. The scaling for a drug is based on the following rule: if IC50 < Cmax coefficient * Cmax, the drug sensitvity is 1. If IC50 > max dose, the drug has sensitivity 0. Between that, the drug sensitivity is scaled logarithmically based on log(IC50)/log(Max Dose Coefficient * Max Dose). This is recommended to reward drugs based on a more realistic performance metric.

THRESHOLD/Cmax Scaling: Here, the user selects two values, a threshold value and a Cmax coefficient value. The scaling for a drug is based on the following rule: if IC50 < threshold, the drug sensitvity is 1. If IC50 > Cmax coefficient*Cmax, the drug has sensitivity 0. Between that, the drug sensitivity is scaled logarithmically based on log(IC50)/log(Cmax Coefficient * Cmax). This will likely lead to very low sensitivity values.

THRESHOLD/Max Dose scaling: Here, the user selects two values, a threshold value and a Max Dose coefficient value. The scaling for a drug is based on the following rule: if IC50 < threshold, the drug sensitvity is 1. If IC50 > Max Dose, the drug has sensitivity 0. Between that, the drug sensitivity is scaled logarithmically based on log(IC50)/log(Max Dose Coefficient * Max Dose). This will likely lead to higher sensitivity values.

Figure 19 - Drug Sensitivity Scaling GUI

For example, we will use **Cmax/Max Dose Scaling.** We will leave the Max Dose coefficient as 1 and set the Cmax coefficient to 0.2.


Figure 20 - Drug Sensitivity Scaling Example

Now let us preview the changes we have made.
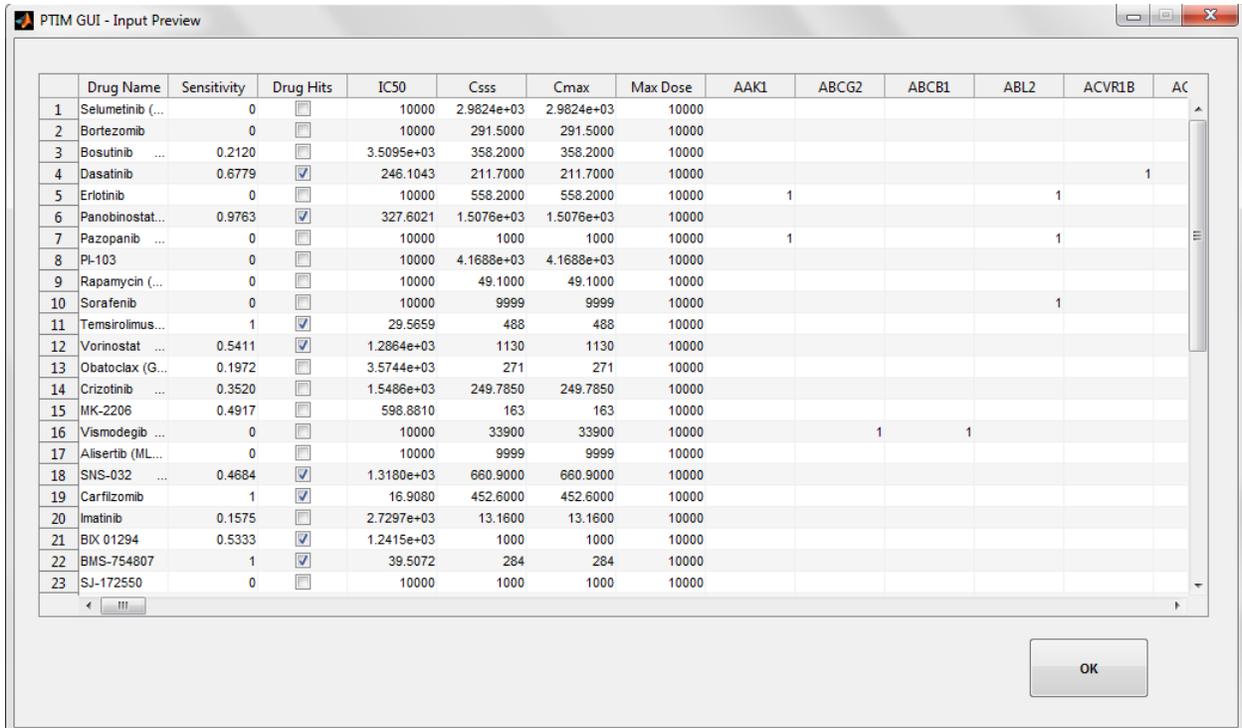
Figure 21 - Scaled Sensitivity Preview

Here, we can see that unsuccessful drugs have had their sensitivities (the second column) scaled to zero, while most other drugs have sensitivity 1 or sensitivity less than 0.5. With a low Cmax coefficient, the sensitivies will be generally lower.

Once the changes are satisfactory, we will be able to generate a PTIM as we now have a complete input set. We have two choices on methods to generate PTIMs. The standard choice is **AUTOMATIC,** which automatically generates a set of targets and builds a PTIM. The other choice is **MANUAL** where the user will select a set of targets to use to build the map.

NEW PTIM - AUTOMATIC PTIM GUI: This GUI will automatically generate a set of targets for a PTIM using a Sequential Floating Forward Search approach. No initial state is needed to generate this set of targets. However, an initial state can be set by the **TARGET SELECTION** subwindow. Inside this window are three different columns of selectable boxes which can change the starting state of the target search.

INITIAL TAR: If you wish for a target to be selected in the initial list of targets used in the PTIM, check the box in this column next to the desired target.

PROTECTED TAR: If you wish for a target to NEVER be removed once it has been added to the target set, select the box next to the target that should not be removed.

IGNORE TAR: If you wish for a target to not be considered for addition to the PTIM target set, then select the box next to the target that should not be included. This option is mutually exclusive with the other two for a single target.

In addition, the GUI requires one more input: a name for the PTIM. This is entered in the editable text box with the **CHECK NAME** button. When a name has been entered, press **CHECK NAME** to make sure the name is unused and is valid. The names require a similar convention as project names.
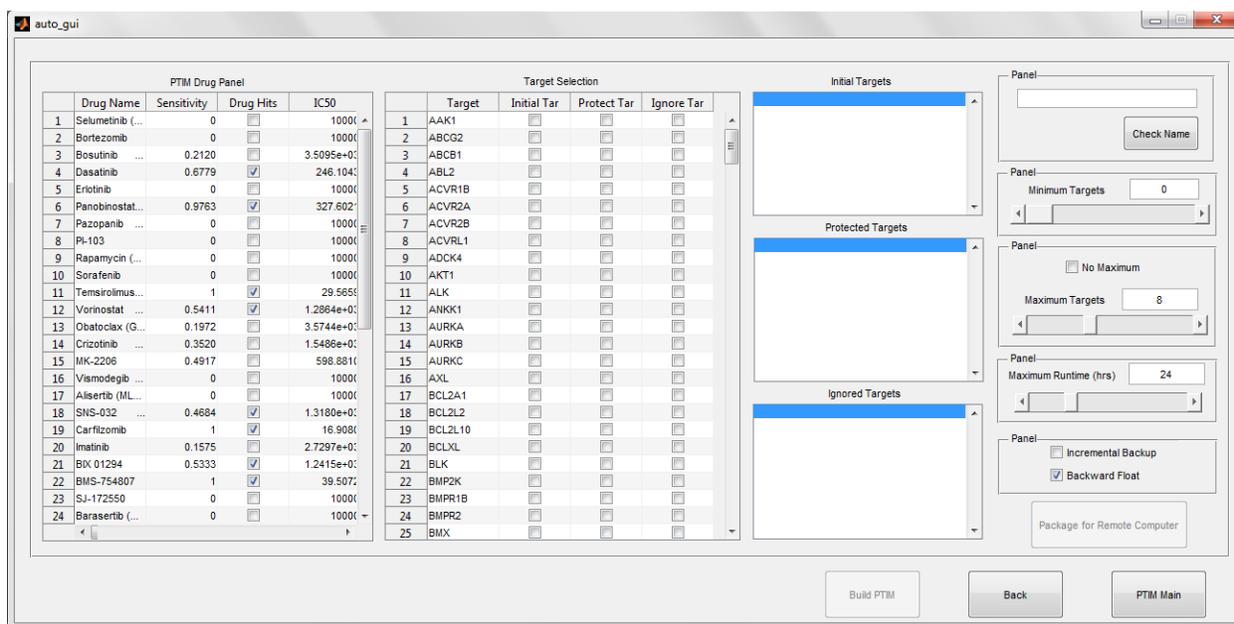

Figure 22 - Automatic PTIM Generation GUI

The GUI has 3 additional selectable options. Ignore those listed beyond these.

MINIMUM TARGETS: In the situation where the PTIM has found that no additional targets will improve the PTIM score during target selection, this will force the GUI to add additional targets to the PTIM until the minimum number of targets is satisfied. This will have no effect if the PTIM error reaches 0.

MAXIMUM TARGETS: Due to the high computational cost associated with some of the later PTIM GUI operations, the maximum number of targets which can be selected is 20, and is scalable with the **MAXIMUM TARGETS** sliding value. However, **NO MAXIMUM** can be selected, which will create no limit on the number of targets which can be automatically added.

BACKWARD FLOAT: This option allows for targets to be removed from the target set consistent with the SFFS algorithm. This increases runtime but will provide equal to or better results than a straight Forward Search. This is a highly recommended option.

For example, lets select targets AURKA and BLK as both initial and protected. Set the name of the PTIM as test_ptim. The **CHECK NAME** button has been pressed, so the resulting GUI has this form.
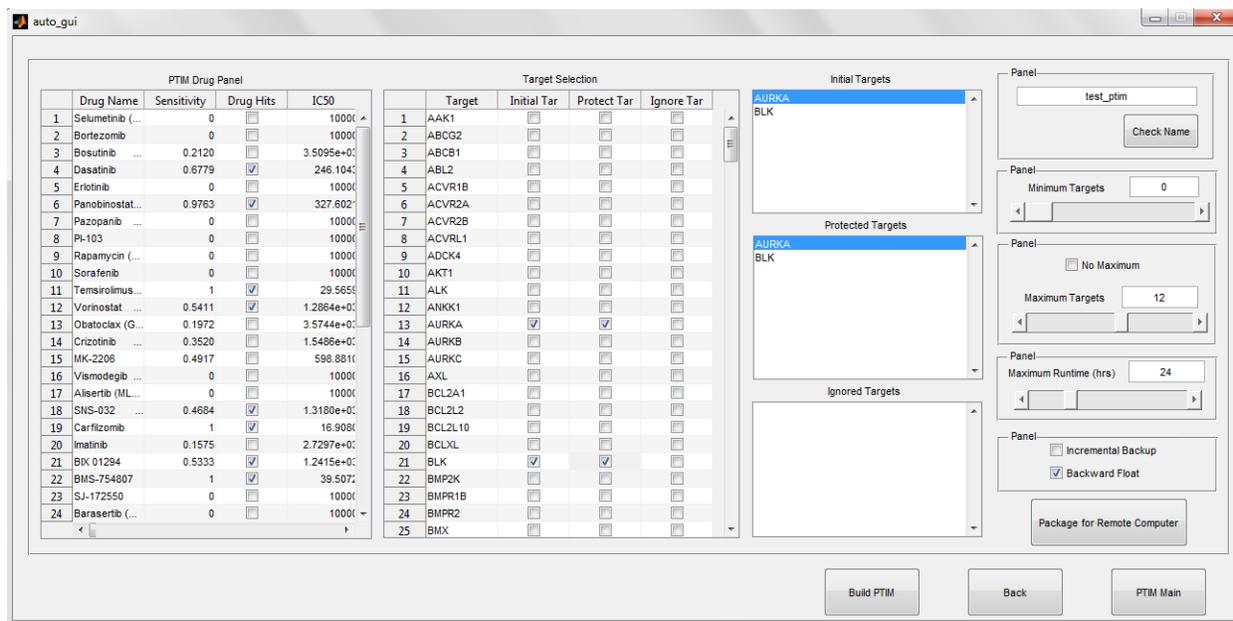
Figure 23 - PTIM Automatic GUI Setup

The targets with modifications as per the **TARGET SELECTIONS** window will appear in the three corresponding windows beside the **TARGET SELECTIONS** subwindow.

Next, I press the **BUILD PTIM** button. FIrst, this window will appear, signifying opening of a parallel computation setup to speed up generation of results.
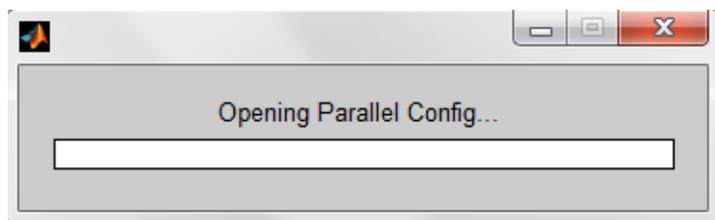
Figure 24 - Opening Parallel Configuration Warning

Next, as targets are added to the PTIM the following progress bar will fill towards conclusion.
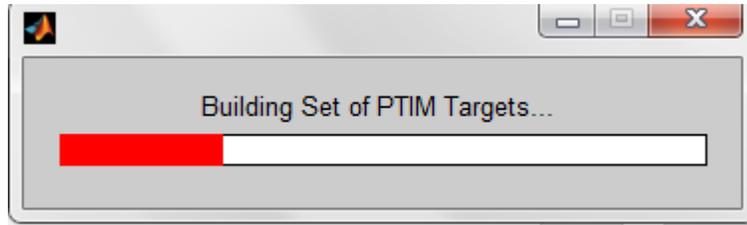
Figure 25 - PTIM Target Set Progress Window

When the complete target set has been generated, a window will appear showing the set of selected targets that have been added to the PTIM.
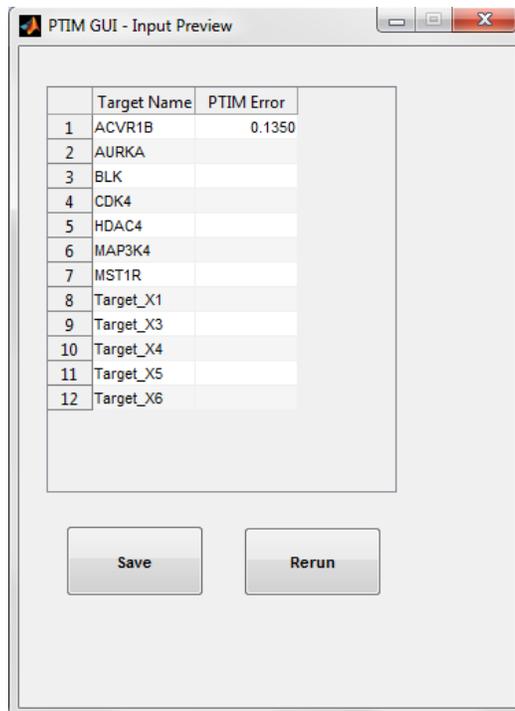
Figure 26 - Added PTIM Targets for Current Setup

At this point, there are two options.

SAVE: If the selected set of targets is satisfactory, the PTIM will be saved under the current name.

RERUN: If the set of selected targets is unsatisfactory, the PTIM will not be saved and changes can be made to the PTIM parameters.

For this example, we will select **SAVE.**

To return to where a PTIM Map can be generated, press **PTIM MAIN.**

MANUAL PTIM: The other option in building a PTIM is to build one manually. Here, in the **TARGET SELECTION** subwindow, there is a checkbox next to each target. To add a target to a PTIM, select the box next to the desired target. These targets will appear in the **TARGETS IN PTIM** subwindow.
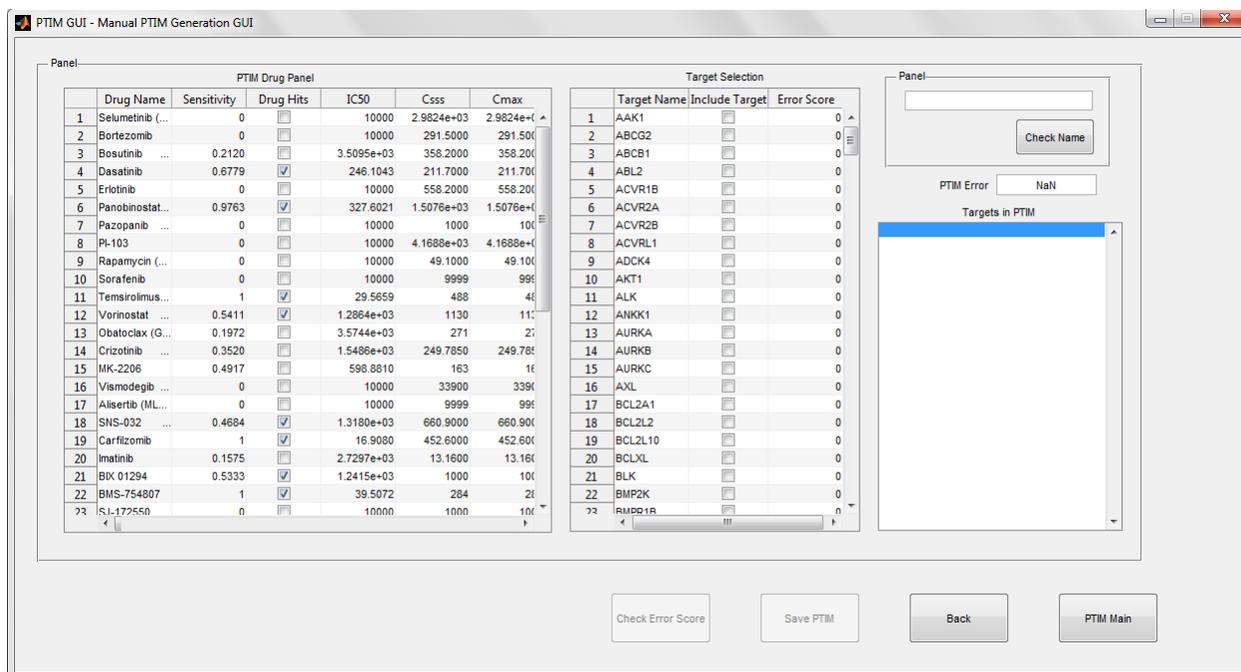
After entering a name and pressing **CHECK NAME** as in the **AUTOMATIC PTIM GUI**, two options will be enabled.

CHECK ERROR SCORE: This will assist in selection of additional targets. After pressing this button, each target not currently in the target set will be added to the PTIM target set and the resulting PTIM error will be tested and displayed next to the target name in the **TARGET SELECTION** window. In addition, each target already in the target set will be temporarily removed from the PTIM target set and the resulting error will be displayed next to the target. Additionally, the error for the current PTIM target set will be displayed in the **PTIM ERROR** textbox.

Once you are satisfied with the PTIM target set, press **SAVE PTIM** to save the PTIM.

For example, I have added three targets to the PTIM: AURKA, AXL, and CDK4. I have pressed the **CHECK ERROR SCORES** button and have found that the PTIM error is 0.28551. Having generated this PTIM, I elect to save it.
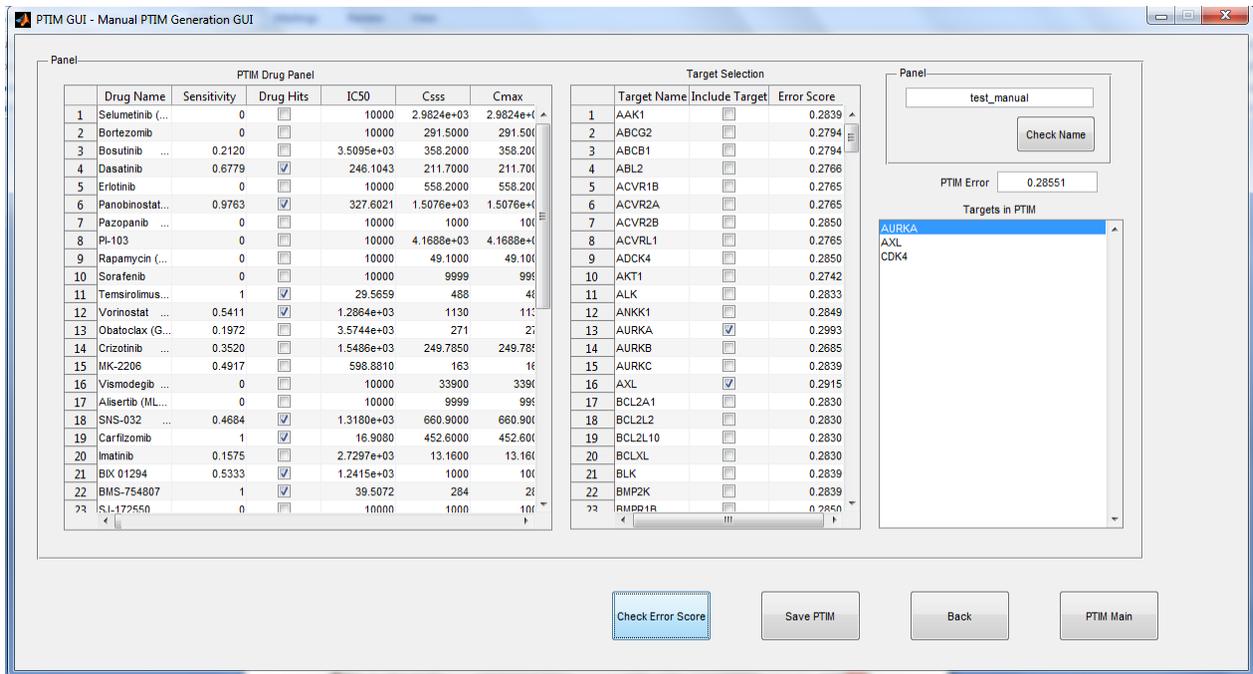
Figure 28 - Manual PTIM Gui Example

To return to where a PTIM Map can be generated, press **PTIM MAIN.**

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OPEN PTIM: Once a PTIM has been generated for a project, it can be opened to generate a PTIM Map/PTIM Circuit.
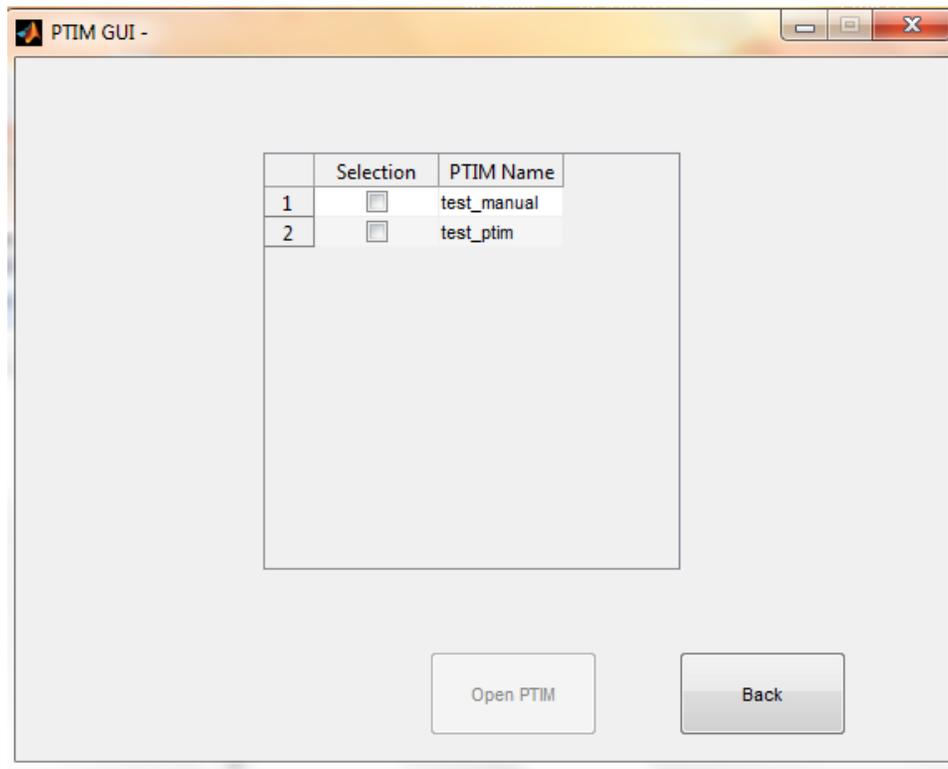
To open a PTIM, select the PTIM you wish to open and press **OPEN PTIM** to move to the next window. We will open **TEST PTIM.**

OPENED PTIM GUI: Once a PTIM has been opened, a new GUI will appear with 5 options to perform with the selected PTIM.
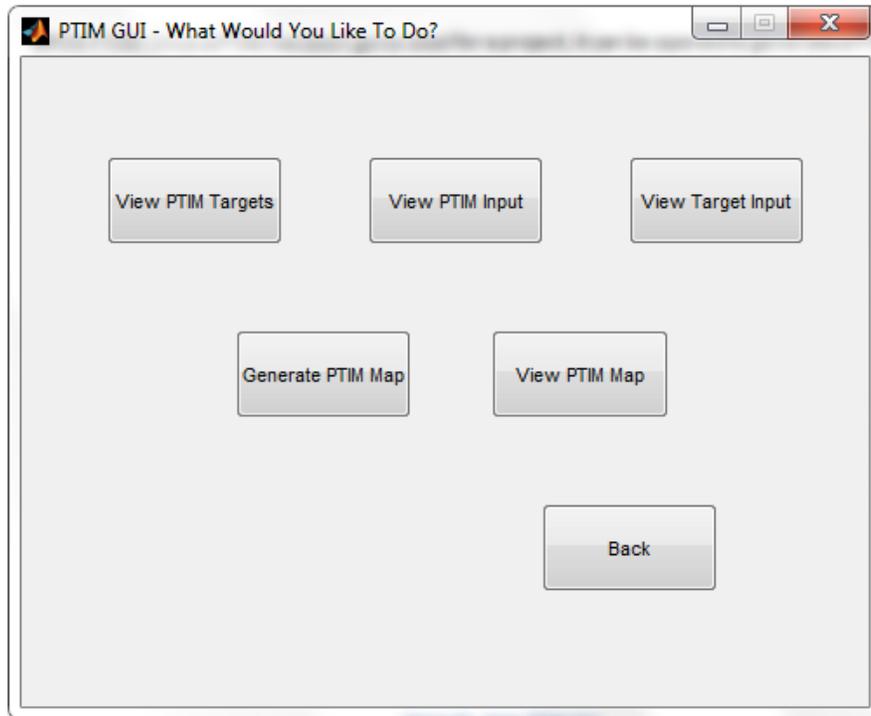
Figure 30 - Opened PTIM GUI

VIEW PTIM TARGETS: This will display a pop-up window with the set of targets in the opened PTIM. In this instance, the following window will appear:
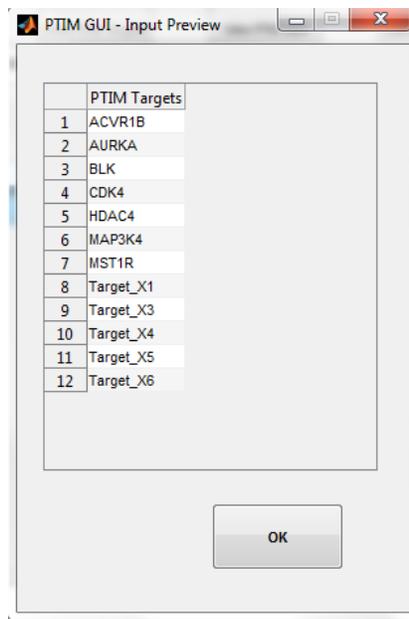
Figure 31 - PTIM Added Targets Window for PTIM test_ptim

VIEW PTIM INPUT: This selection will display the input given to the PTIM generation algorithm. This includes drug names, target names, sensitivity, etc.

Figure 32 - PTIM Input for PTIM test_ptim

VIEW TARGET INPUT: This window will display a reduced PTIM input consisting of all the input data with all targets NOT in the PTIM removed. This way, the user can see the equivalent drug inhibition profile within the current PTIM to get a visual explanation of the PTIM.

Figure 33 - PTIM Target Input Window for PTIM test_ptim

PTIM GENERATE MAP GUI: This GUI is used to generate a PTIM Matrix (a numerical matrix consisting of sensitivity scores for all combinations of targets in the PTIM) and a corresponding PTIM Map (PTIM Circuit) that gives a binarized and imaged equivalent of the PTIM.
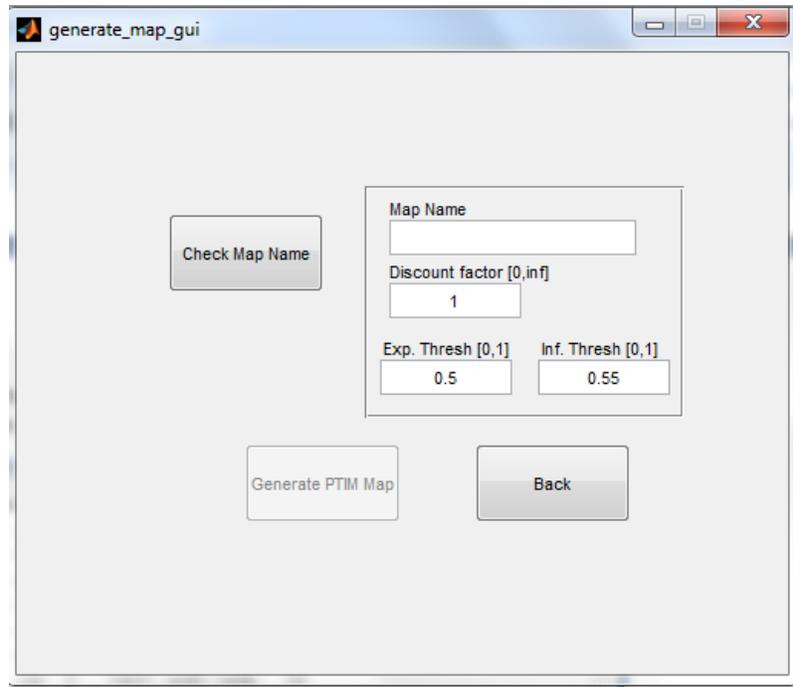

Figure 34 - PTIM Generate Map GUI

First, a name must be selected for the PTIM Map. A single PTIM can have multiple associated Matrices and Maps. The naming must be consistent with the previous naming conventions.

DISCOUNT FACTOR: This is a value associated with making inference steps in the PTIM. When the sensitivity of a combination is unknown, an inference is made based on the known combination sensitivities. Essentially, the higher the discount factor, the lower the inferred sensitivity values will be. Leaving this value at 1 is recommended. If the user feels that the data is less reliable, or that the cancer may be particularly difficult to treat, increasing the discount factor can be used to represent this.

EXP(ERIMENTAL) THRESHOLD/INF(ERENCE) THRESHOLD: These two values are used in PTIM Map generation. It is a binarization point for combination sensitivities in the PTIM Matrix used to generate the PTIM Map. **EXP. THRESHOLD** is the value above which an experimental combination sensitivity value is considered to be a 1. **INF. THRESHOLD** is the value above which an inferred combination sensitivity value is considered to be a 1. These two values can be equal if desired. As the values increase, the PTIM becomes more selective in which combinations are considered "hits" (1s). As such, increasing these values should create more complicated circuits. The PTIM Map which is generated represents the minimal target sets which should be effective in the tumor.

Once these values have been selected and a name has been entered, press the **CHECK MAP NAME** button to enable the **GENERATE PTIM MAP.**

First, the GUI opens a parallel configuration to speed up PTIM Map generation.
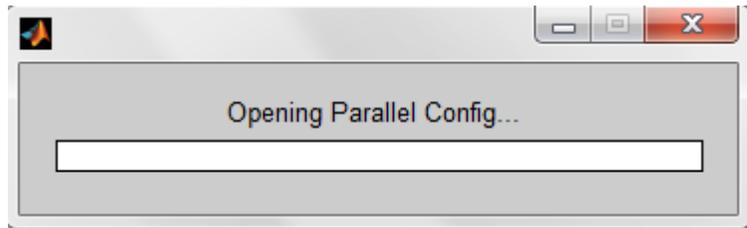
Figure 35 - Opening Parallel Configuration Warning

Once the parallel configuration has been opened, the PTIM Matrix is generated.
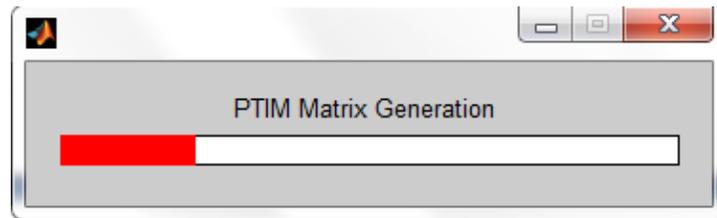

Figure 36 - PTIM Matrix Generation Progress Bar

Once the PTIM Matrix has been generated, the resulting PTIM Map will be displayed on the screen.

For example, we will set the PTIM name to be map1, the discount factor will be 1, the Exp. Thresh value will be 0.8, and the Inf. Thresh will be 0.3.
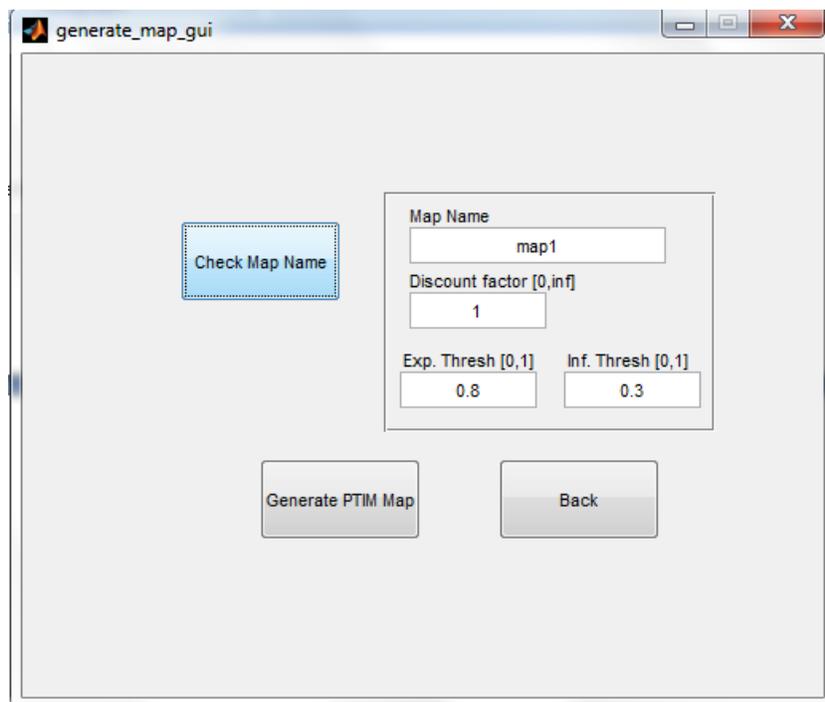

Figure 37 - Example PTIM Generation GUI

The PTIM generated from these parameters is shown below.
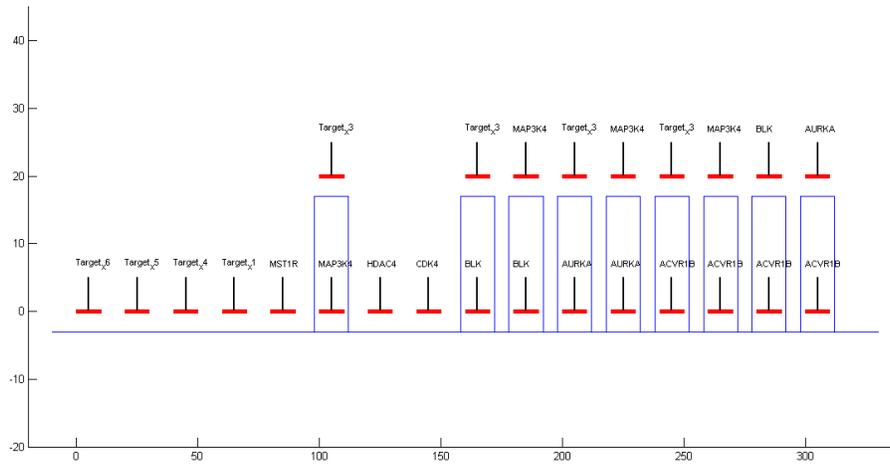
Figure 38 - PTIM Generated from PTIM test_ptim

The generated PTIM Matrix and PTIM map is automatically saved in the project folder.

VIEW PTIM MAP: Once a PTIM Map has been generated, this window will allow you to view the generated Matrices and Maps within a PTIM. Working with test_ptim after generation of the PTIM Map, the following window will appear.
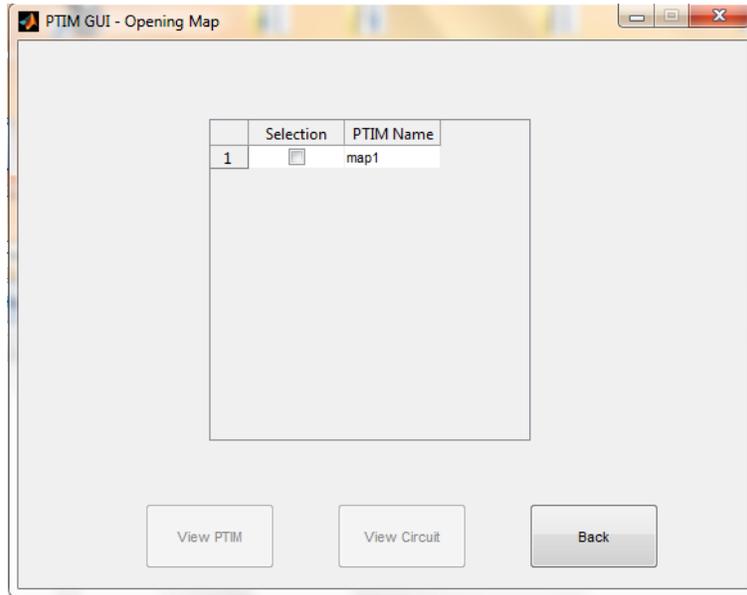

Figure 39 - View PTIM Map for PTIM test_ptim

To view the PTIM Map or PTIM Matrix for map1, select the box next to map1.

VIEW PTIM: This will display the PTIM Matrix associated with the selected PTIM.

Figure 40 - PTIM Matrix for map1

VIEW CIRCUIT: This will display the PTIM Map (Circuit) associated with the select PTIM. This is the same Map that was displayed when the PTIM Matrix and PTIM Map was generated.
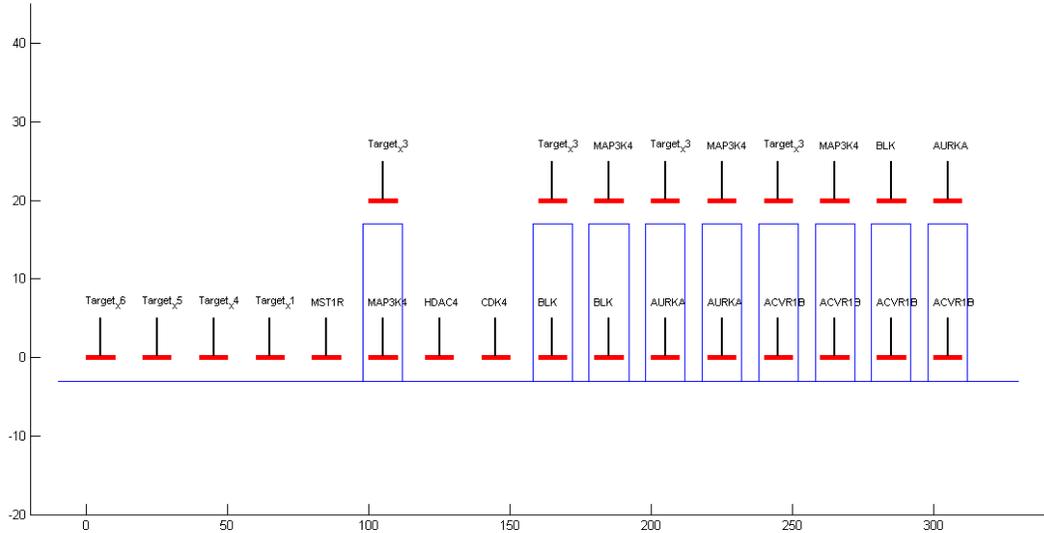

Figure 41 - PTIM Map Associated with map1