SIMULATOR OF MECHANISMS OF TOXICITY
INSTRUCTION MANUAL

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1) INTRODUCTION

This project started as a request from the Pharmacology Faculty of Yeditepe and developed by the Computer Science Engineering Department of Yeditepe with the collaboration of the Pharmacology Faculty of Yeditepe. The purpose of this project was to develop a desktop application that would provide tools for the user to design and simulate simulations of mechanisms of toxicity of a living cell. The resulting application is capable of providing both design and simulation tools for the user. In order to accomplish such tasks this application consists of complex mechanisms, therefore this instruction manual is written for the application in order to make the application easy to use for the users.

2) MAIN WINDOW

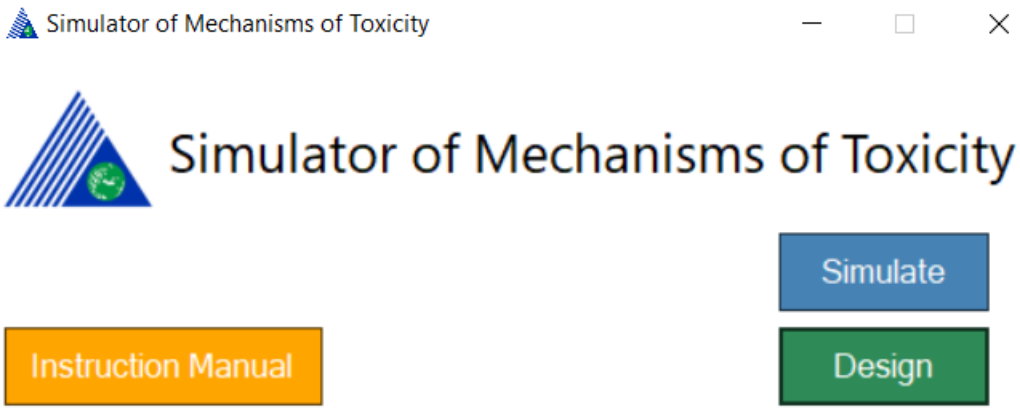

Figure 2.1 Welcome Screen

Upon start, the application meets the user with a welcome screen. This screen consists of 3 buttons. The user can navigate through the application using these buttons.

1) **Design Button:** Opens the “Design Window” of the application.
2) **Simulate Button:** Opens the list of saved simulations.
3) **Instruction Manual Button:** Opens the instruction manual document.

3) DESIGN WINDOW

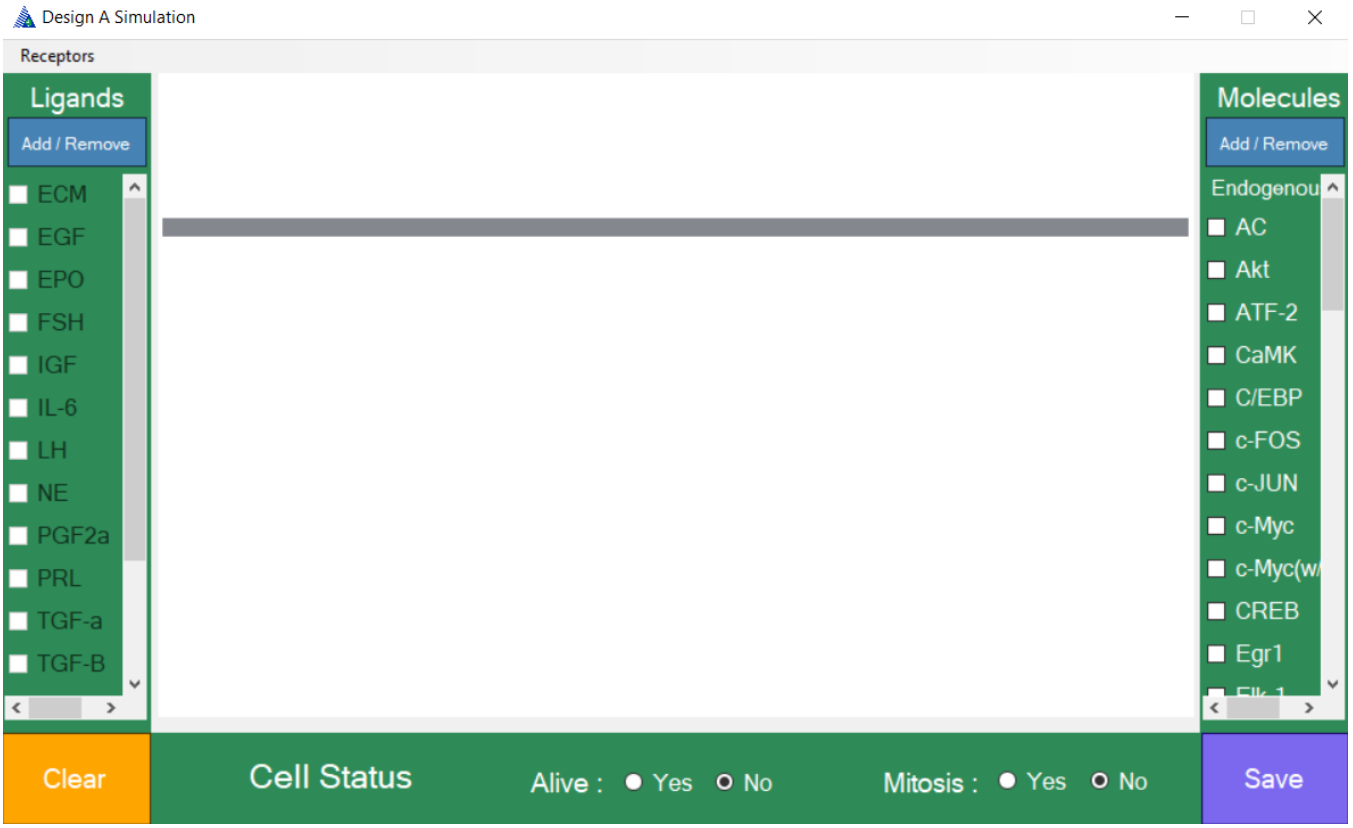

Figure 3.1 Design Window

The design window provides simulation designing tools for the user. This window can be examined under five sections:

1) Ligands
2) Molecules
3) Receptors
4) Simulation Draw Panel
5) Simulation Options Panel

3.1) LIGANDS

3.1.1) LIGANDS PANEL

The ligands panel is the lefmost panel inside the design window. Users can select the ligand they want to add to the design using ligand checkboxes inside the ligands list. The checkboxes are disabled and can only be enabled by the selected receptors. If a ligand can connect and activate a receptor's pathway, than the ligand's checkbox is enabled to use. Users can use the Add / Remove button to open the Ligands Window.

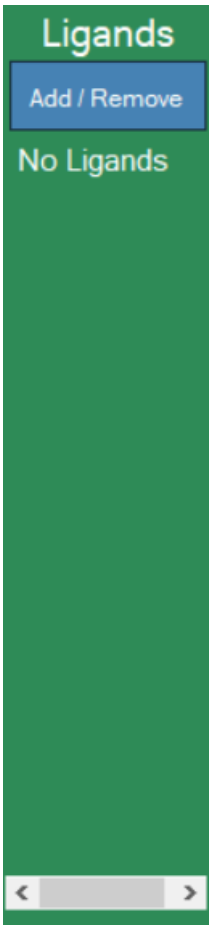

Figure 3.2 Empty Ligands Panel

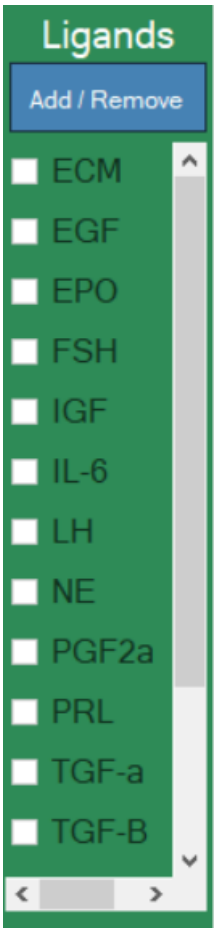

Figure 3.3 Ligands Panel with a list of ligands

3.1.2) LIGANDS WINDOW

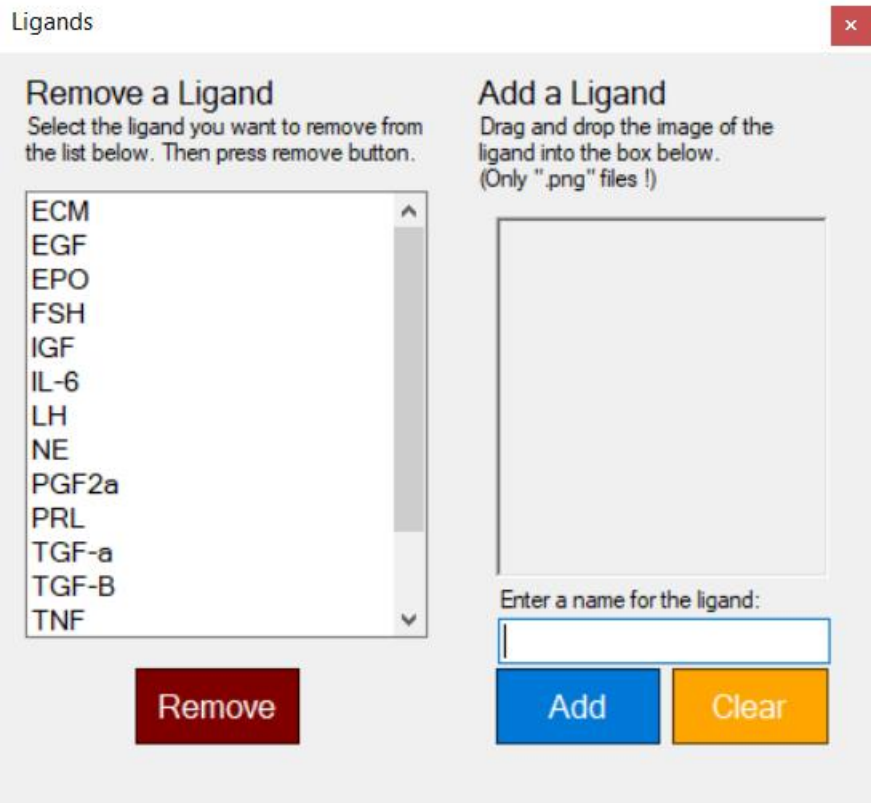

Figure 3.4 Ligands Window

The Ligands Window can be used for defining new ligands to the system or removing defined ligands from the system. This window provides a list of defined ligands. In order to remove a ligand from the system, first the user must select a ligand from the list. Then by pressing the “Remove” button the user can remove the selected ligand from the system.

In order to define a new ligand to the system, the user must provide a picture of the ligand to the system. User can drag&drop the picture of the ligand from any file to the application. After providing the picture, the user must enter the ligand’s name. When everything is ready the user can use the “Add” button to save the new ligand to the system. Note that a ligand can only saved once to the system.

To start defining the ligand from the scratch at any point the user can use “Clear” button to clear name textbox, and ligand picturebox.

3.2) MOLECULES

3.2.1) MOLECULES PANEL

The molecules panel is the rightmost panel inside the design window. Users can select the molecule they want to add to the design using molecule checkboxes inside the molecules list. The checkboxes of the molecules are enabled all the time since they do not depend on receptors. The list of molecules is split to two parts: Endogenous Molecules and Exogenous Molecules. Users can use the “Add/Remove” button to open the Selection Window. Depending on the selection of the user Molecules Window will be opened with the selected type of molecules loaded.

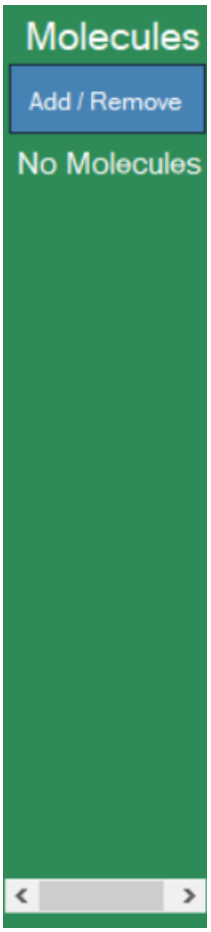

Figure 3.5 Empty Molecules List

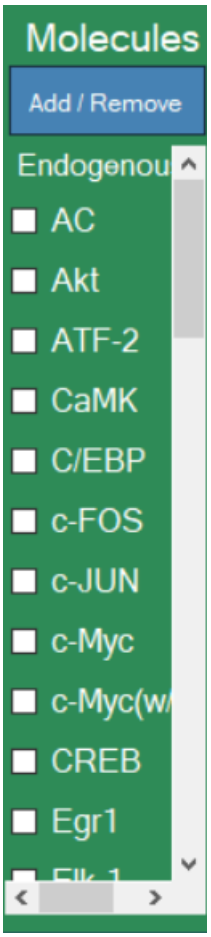

Figure 3.6 Molecules List with a list of molecules.

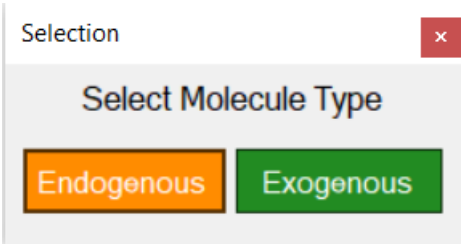

Figure 3.7 Selection Window

3.2.2) MOLECULES WINDOW

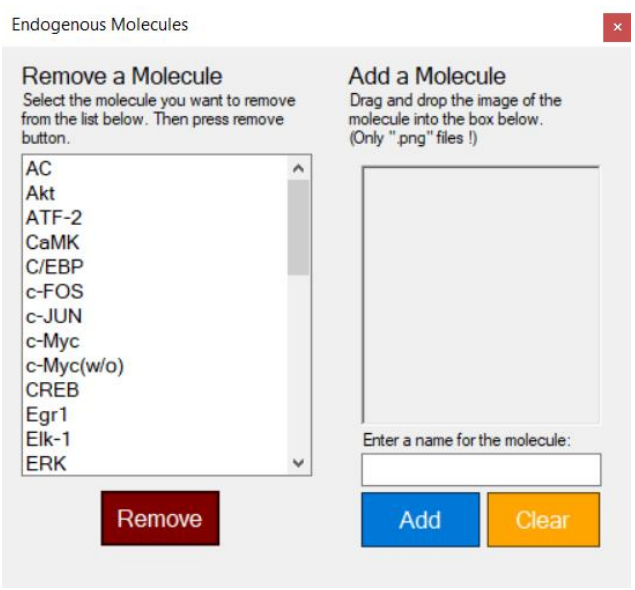

Figure 3.8 Molecules Window with Endogenous molecules loaded.

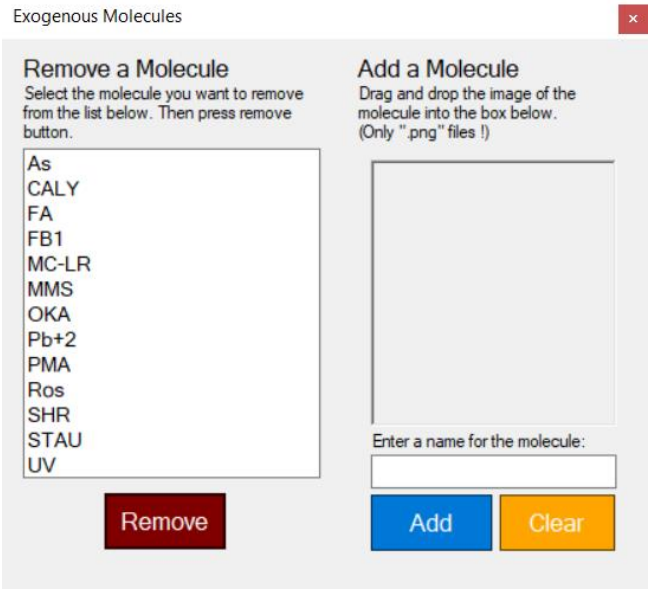

Figure 3.9 Molecules Window with Exogenous molecules loaded.

The Molecules Window can be used for defining new molecules to the system or removing defined molecules from the system. This window provides a list of defined molecules. This list depends on the selection on the Selection Window.

In order to remove a molecule from the system, first the user must select a molecule from the list. Then by pressing the “Remove” button the user can remove the selected molecule from the system.

In order to define a new molecule to the system, the user must provide a picture of the molecule to the system. User can drag&drop the picture of the molecule from any file to the application. After providing the picture, the user must enter the molecule’s name. When everything is ready the user can use the “Add” button to save the new molecule to the system.

Note that a molecule can only saved once to the system. To start defining the molecule from the scratch at any point the user can use “Clear” button to clear name textbox, and molecule picturebox.

3.3) RECEPTORS

3.3.1) RECEPTORS MENU

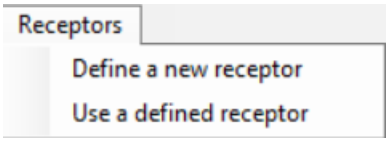

Figure 3.10. Receptors Menu

The receptors menu can be opened by pressing “Receptors” button on the topmost panel inside the design window. Users can select “Define a new receptor” option to open “Define a new receptor” window where they can define a new receptor to the system or “Use a defined receptor” option to open “Receptor Options” window.

3.3.2) DEFINE A NEW RECEPTOR WINDOW

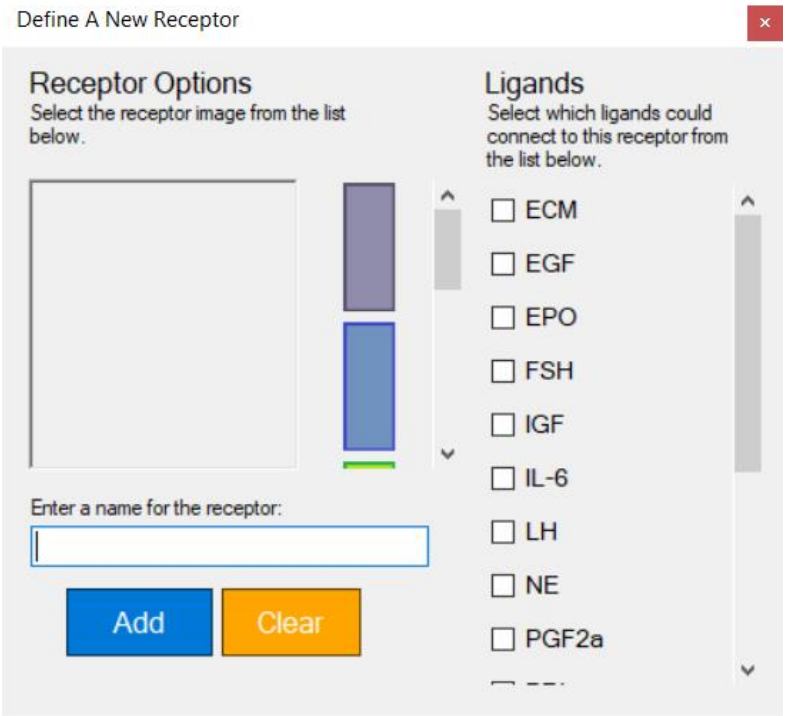

Figure 3.11 Define A New Receptor window.

The Define A New Receptor Window can be used for defining new receptors to the system. This window provides a list of ligands saved in the system and list of receptor pictures with different colors. In order to define a new receptor to the system, the user must select a receptor image from the list. After selection, the user must enter the receptor's name. Lastly the user must select which ligands can connect to this receptor from the ligands checkbox. Note that at least one ligand must be chosen and a receptor can only saved once to the system.

When everything is ready the user can use the "Add" button to save the new receptor to the system. To start defining the receptor from the scratch at any point the user can use "Clear" button to clear name textbox, selected receptor image and selected ligands.

3.3.3) RECEPTOR OPTIONS WINDOW

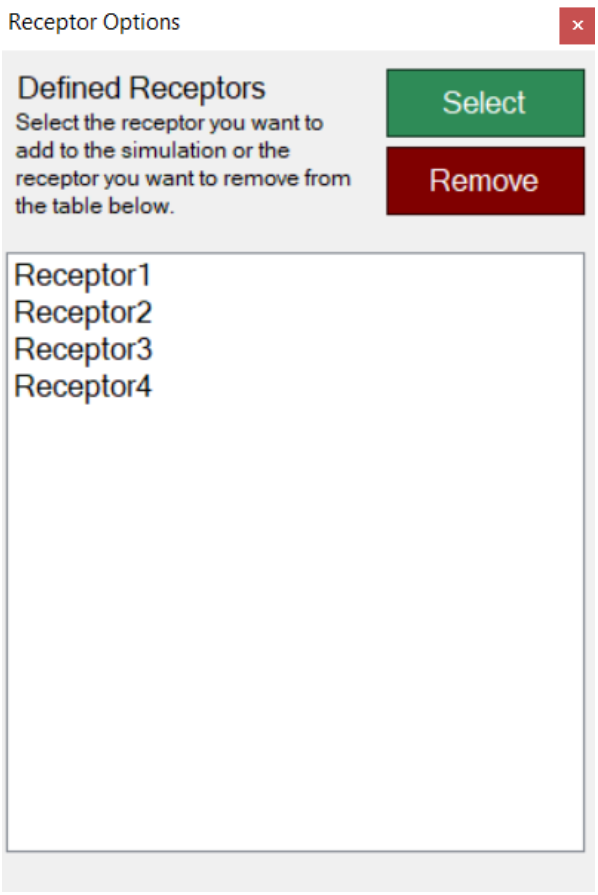

Figure 3.12 Receptor Options window

The Receptor Options window can be used using the defined receptors in the design or removing defined receptors from the system. This window provides a list of defined receptors. In order to remove a receptor from the system, first the user must select a receptor from the list. Then by pressing the “Remove” button the user can remove the selected receptor from the system.

In order to use a defined receptor in the design, the user must select a receptor from the list. Then by pressing the “Select” button the receptor will be added to the Design Window. According to the number of receptors present in the design window the applications splits the design panel to areas in order to make the pathways work properly in the simulation. Since we don’t want to narrow the workspace for the user a maximum of four receptors can be used in a simulation.

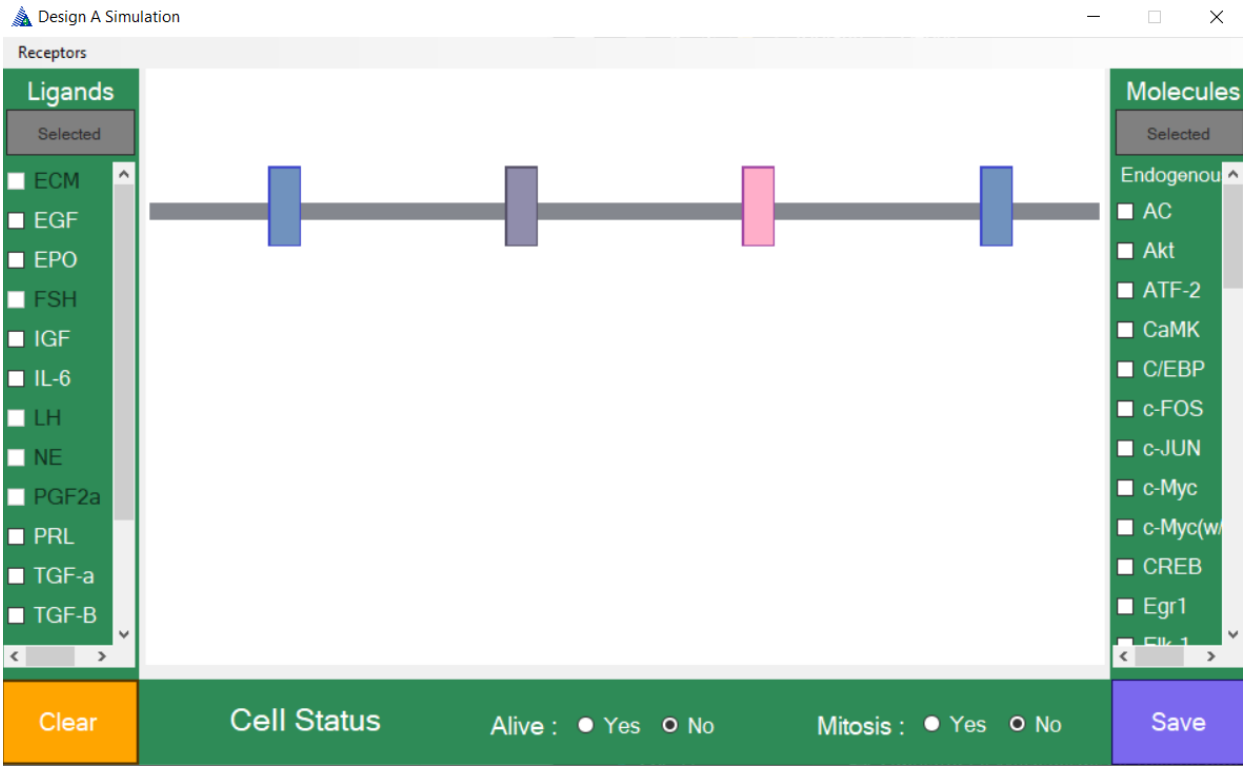

Figure 3.13 Design Window with four receptors.

3.4) SIMULATION DRAW PANEL

Simulation draw panel is the center panel of the Design Window. The design of the simulation is done in this panel using the features of the panel. The features of the Simulation Draw Panel can be defined in four sections:

1) Adding objects to the panel
2) Simulation Draw Panel Menu
3) Moving/Re-sizing objects on the panel
4) Defining Events

3.4.1) ADDING OBJECTS TO THE PANEL

In the beginning of every design, it's advised to users that they should start with adding defined receptors to the design since every time a receptor is added to the design window, the simulation draw panel will be reset and split into areas. Adding, removing or using receptors in the design is defined in the section 3.3.

In order to add ligand objects to the design, the user could select the desired ligand's checkbox from the ligands list in the ligands panel. When a ligand checkbox is checked, the image of the ligand will appear above the cell wall on the draw panel. The ligands list and ligands panel are defined in the section 3.1.

In order to add molecule objects to the design, the user could select the desired molecule's checkbox from the molecules list in the molecules panel. When a molecule checkbox is checked, the image of the molecule will appear under the cell wall on the draw panel. The molecules list and molecules panel are defined in the section 3.2.

In order to add arrows or "+P" or "-P" objects to the design, the user could use the "Simulation Draw Panel Menu". This menu will be defined in the section 3.4.2.

Note that in running the simulation the objects will be animated according to the order of their addition to the design panel. Therefore users are advised to pay attention to the order of adding objects to the design panel.The moving/re-sizing features of added objects on the draw panel will be defined in the section 3.4.3.

3.4.2) SIMULATION DRAW PANEL MENU

The simulation draw panel menu is used for adding objects to the design such as straight arrows, dotted arrows, inhibitor arrow, “+P” etc.

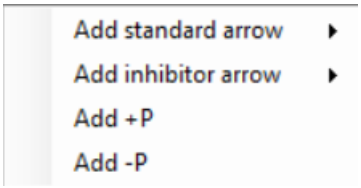

Figure 3.14 Simulation Draw Panel Menu

Users could navigate through the menu to add the desired object to the design. When the object is selected from the menu, the image of the object is will appear under the cell wall on the draw panel. The user cannot rotate these images of the objects, therefore in order to cover all points both standard and inhibitor arrows are defined for all directions Up - Down - Left - Right. Also all arrows can be selected as “Straight” form or “Dotted” form. The moving/re-sizing of these objects will be defined in the section 3.4.3.

Some example figures of draw panel menu objects are shown in the Figure.

Figure 3.15 Objects of the draw panel menu

3.4.3) MOVING/RE-SIZING OBJECTS ON THE PANEL

Users could move or re-size every object added to the draw panel except the receptors. By clicking and using drag&drop features the users can move objects to their desired location on the design panel. Note that the ligands can only move outside the cell which means above the cell wall and other objects such as molecules or arrows can only move inside the cell which means under the cell wall on the draw panel.

In order to re-size the objects the users must bring the mouse cursor to the edges of each object. When the re-sizing cursor appears the user can re-size the objects using mouse button. Note that the ligand objects cannot be re-sized.

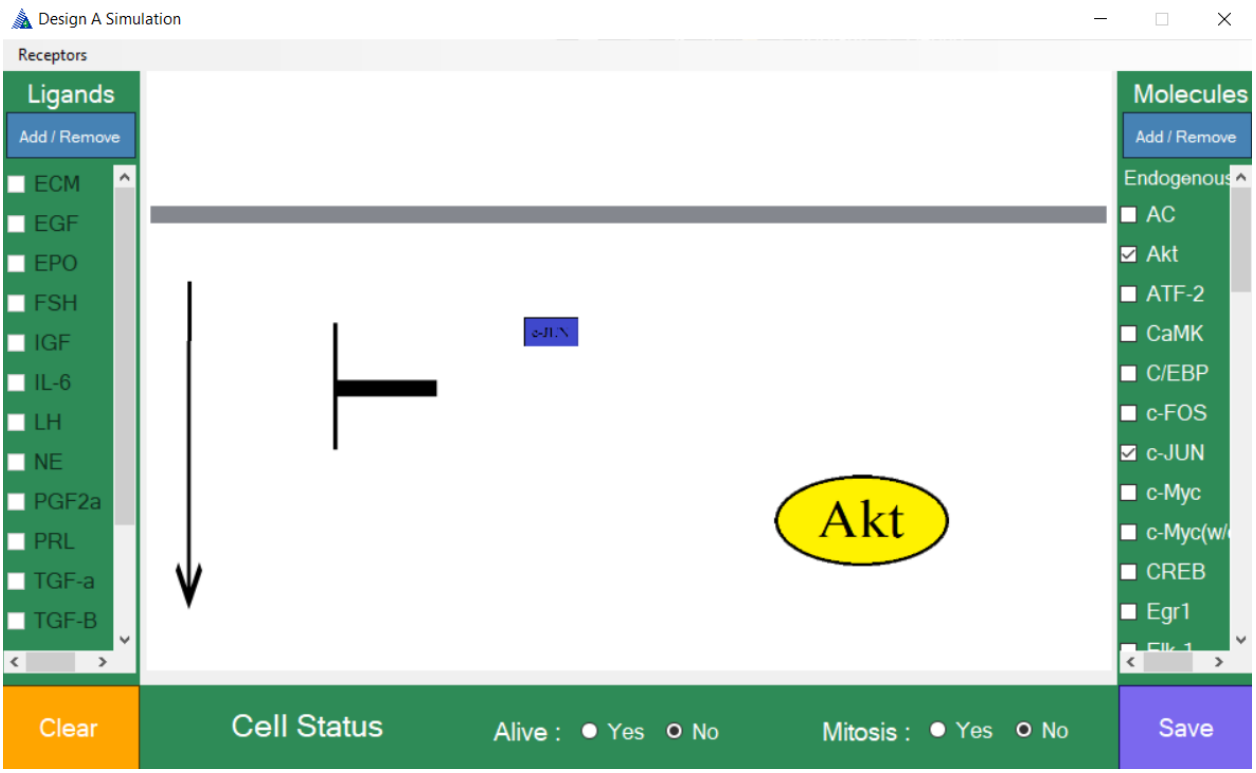

Figure 3.16 Design Window with moved, re-sized objects.

3.4.4) DEFINING EVENTS

If a molecule's presence effects the pathway of any receptor and relatively the simulation then the user must define that molecule as an event to the system. Defining an event provides the user a selection in the simulation whether the molecule should present in the simulation and affect the pathways or not. In order to define an event the user must right click on a molecule object on the simulation draw panel and select "Add event". This option will open "Define An Event" window. Note that before defining an event the users must add all the necessary objects to the simulation draw panel since they will be making all their operations on the current state of the design window.

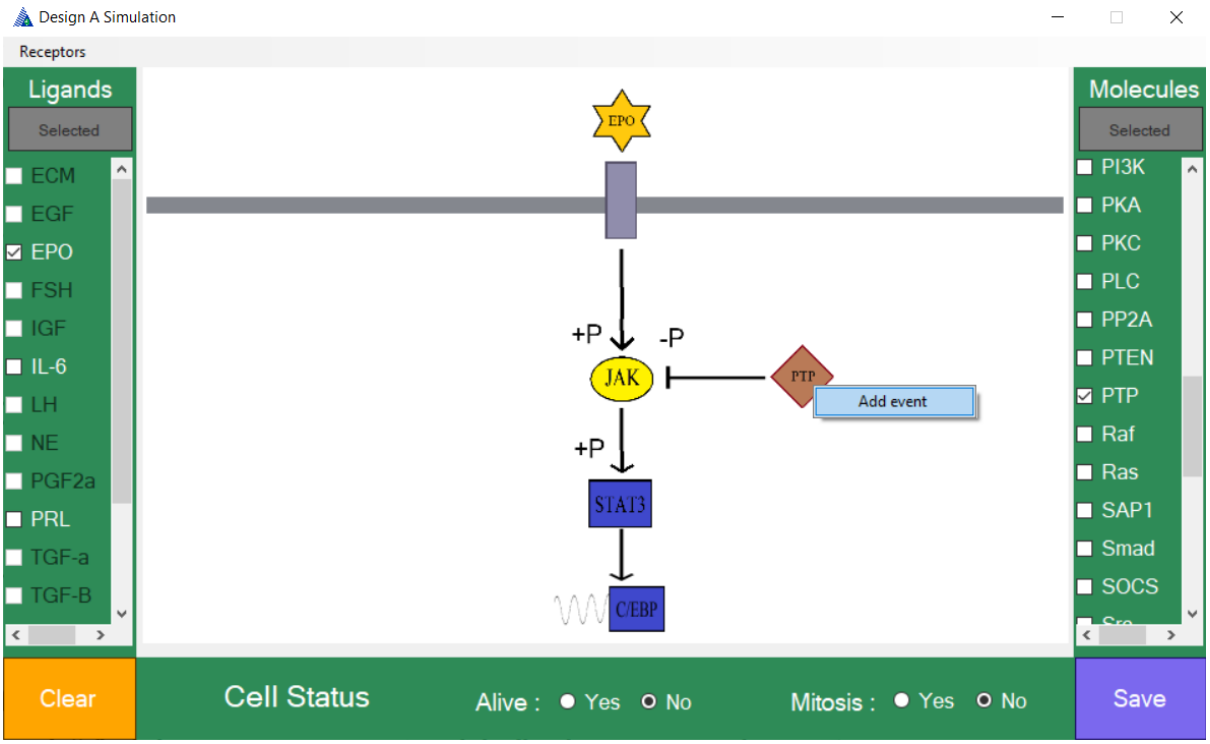

Figure 3.17 Adding an event to the molecule "PTP".

In the Define an Event window the users must define in the presence of the molecule which objects should be displayed or removed. In order to select objects the users must right click to each object. This will open a menu with "Display", "Remove" and "Inhibit" selections.

If the user selects “Display” for any object, that object will only be shown in the simulation in the presence of the event’s defined molecule.

If the user selects “Remove” for any object, that object will be removed from the simulation in the presence of the event’s defined molecule.

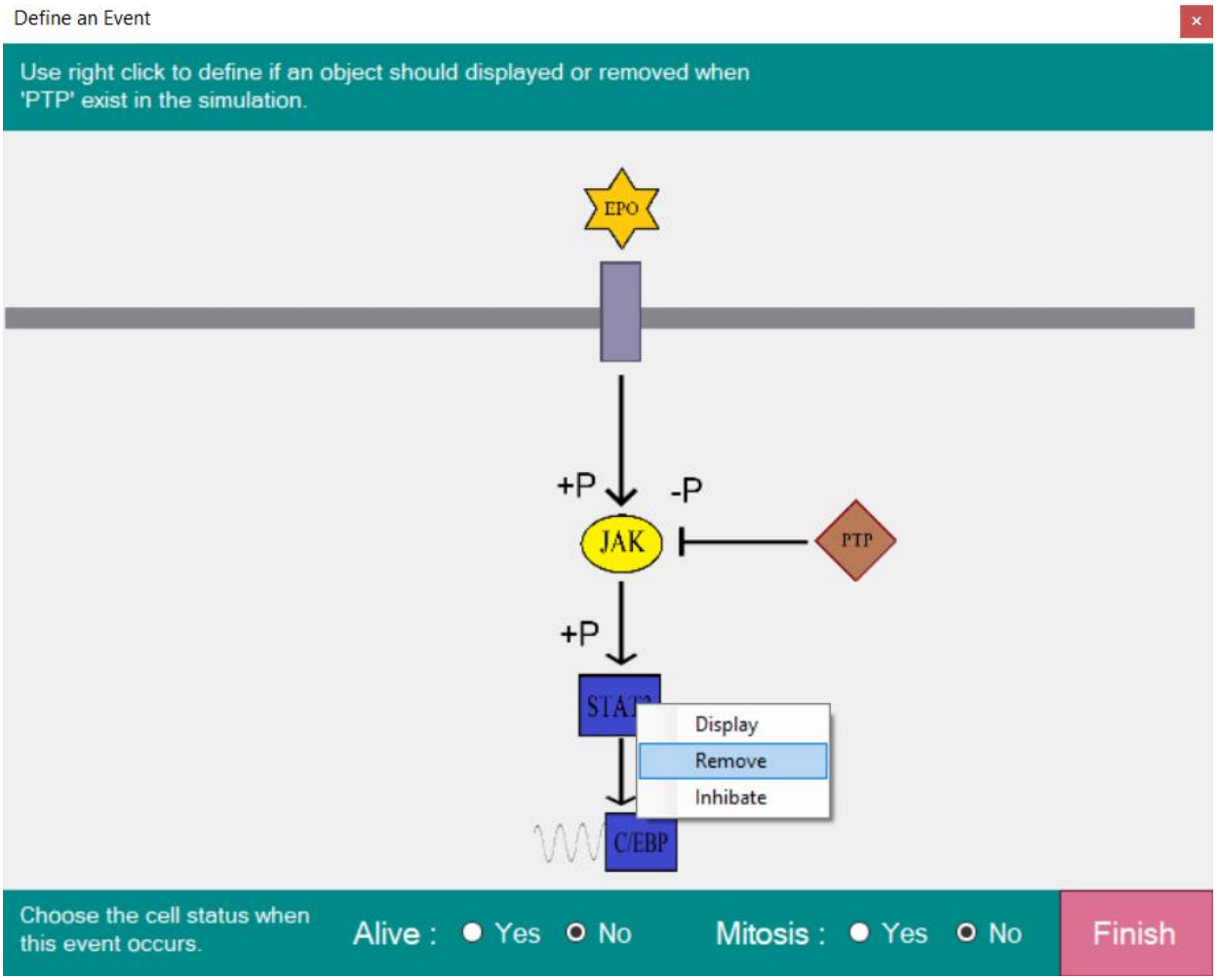

Figure 3.18 Define an Event window with “STAT3” right clicked.

For example in order to display “when PTP is present, the pathway of the JAK should stop and inhibitor arrow and “-P” molecule of PTP should be displayed.” according to the above figure following steps must be applied:

- The user must right-click the left-straight-inhibator arrow and “-P” objects and select “Display” respectively.
- To make the “JAK” molecule pathway disappear, the user must right-click and select “Remove” for all the objects under the “JAK” pathway respectively.

Lets say we defined an event for a molecule “B” but we have another molecule “A” in the simulation which inhibits the effects of the molecule “B”. In that case in the define event window we could right-click to molecule “B” and select “Inhibit”. This definition means that in the simulation, the presence of molecule “A” will inhibit and reverse all the effects of the molecule “B”.

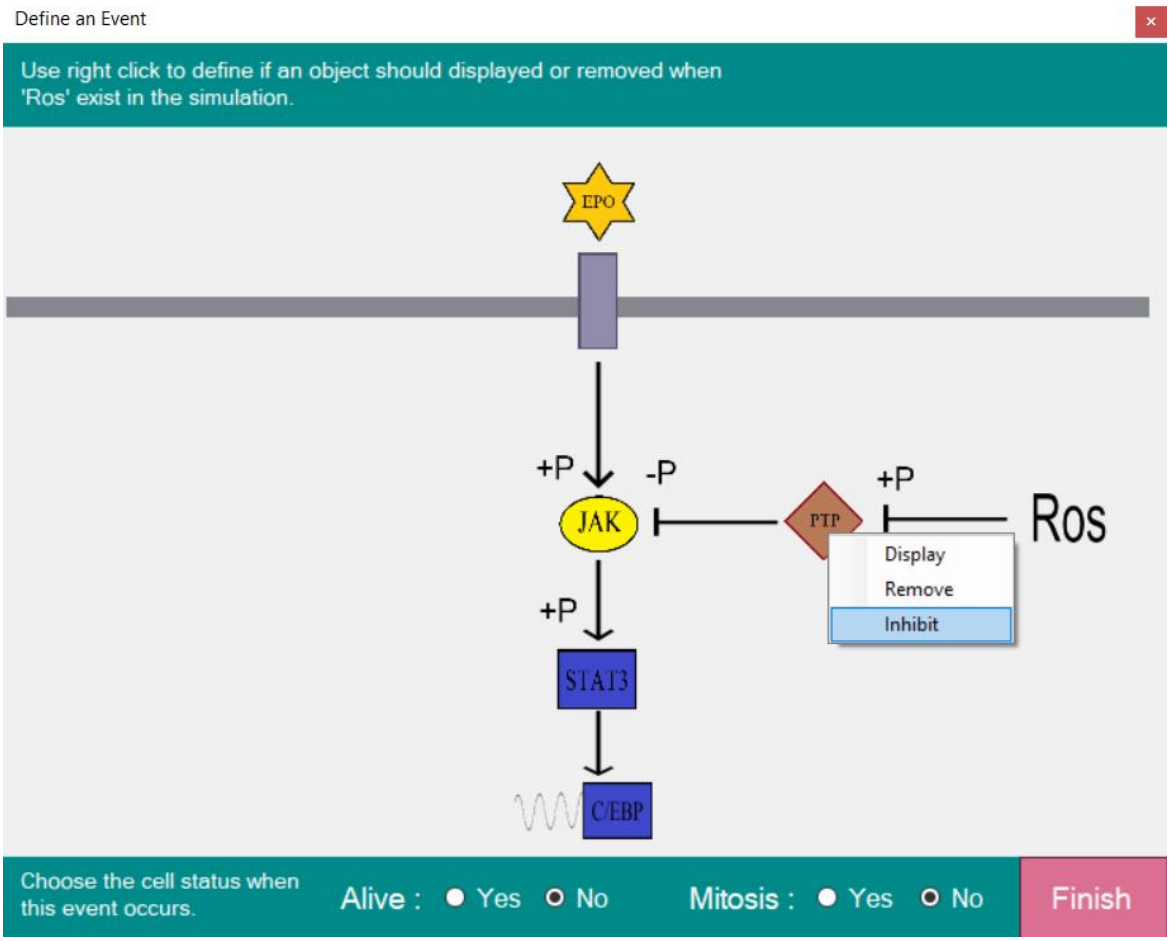

Figure 3.19 Define an Event window with “PTP” object right clicked and Inhibit selection highlighted.

For example in order to display “when ROS is present, inhibit PTP and reverse all it’s effects” according to the above figure following steps must be applied:

- The user must right-click the left-straight-inhibator arrow and “+P” of left side of the“ROS” molecule and select “Display” respectively.
- In order to inhibit and revers the effects of PTP, the user must right-click to PTP object and select “Inhibit”.

If the presence of the defined molecule affects the Alive and Mitosis states of the cell then the user must select the Alive and Mitosis states after the presence of the molecule using the radio buttons on the bottom panel. To finish the event definition the user must use “Finish” button.

3.5) SIMULATION OPTIONS PANEL

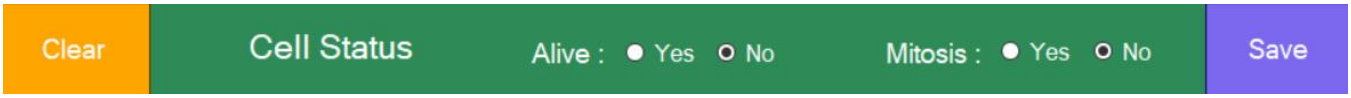

Figure 3.20 Simulation Options Panel

The simulation options panel is the bottom panel inside the design window. Users can select the cell status using the radio buttons on the panel. If the user wants to start the design from scratch, the user can use “Clear” button to reset the design window.

After finishing the design the user can use “Save” button to finish designing the simulation. The “Save” button opens a window where the user can name the simulation. After naming the simulation the user can press “Save the simulation” button to save the simulation to the system.

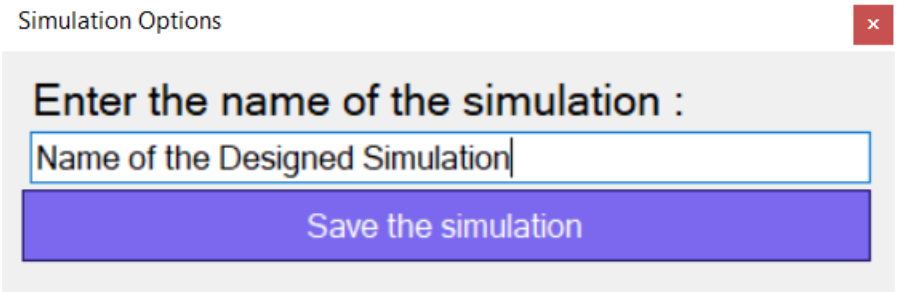

Figure 3.21 Simulation Options Window

4) SIMULATION SELECTION AND RUNNING

4.1) SIMULATION SELECTION WINDOW

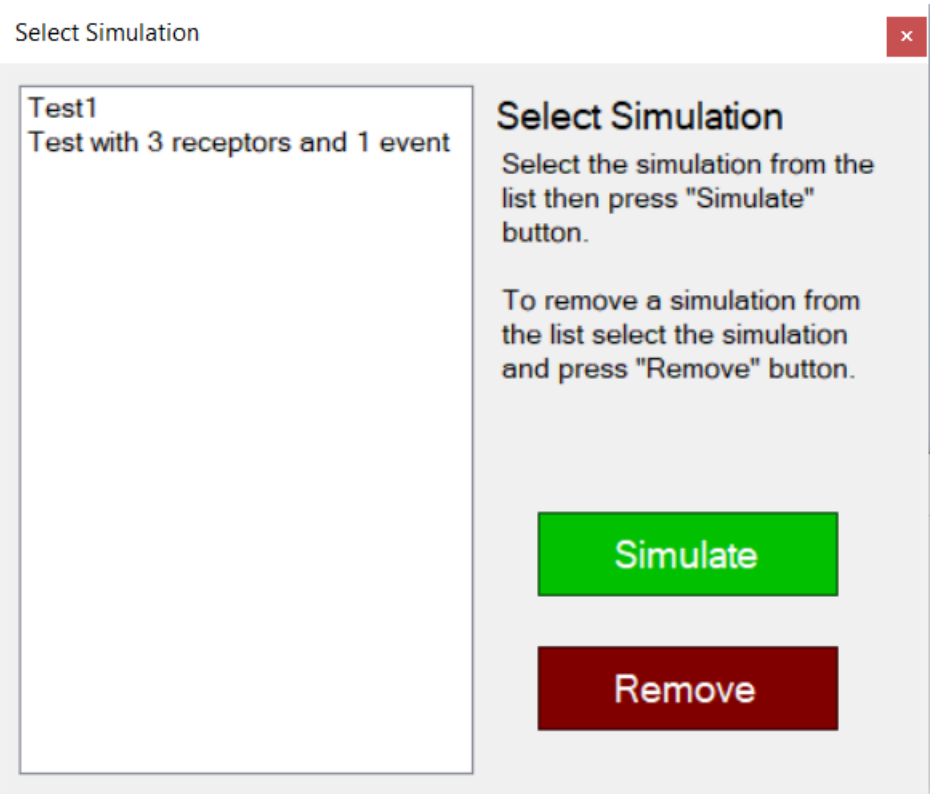

Figure 4.1 Select Simulation window

The Simulation Selection window can be used for opening or removing saved simulations in the system. This window provides a list of saved simulations. In order to remove a simulation from the system, first the user must select a simulation from the list. Then by pressing the “Remove” button the user can remove the selected simulation from the system.

In order to open and run a simulation the user must select a simulation from the list. Then by pressing the “Simulate” button the application opens the “Simulate a Simulation” window with the selected simulation loaded.

4.2) SIMULATE A SIMULATION WINDOW

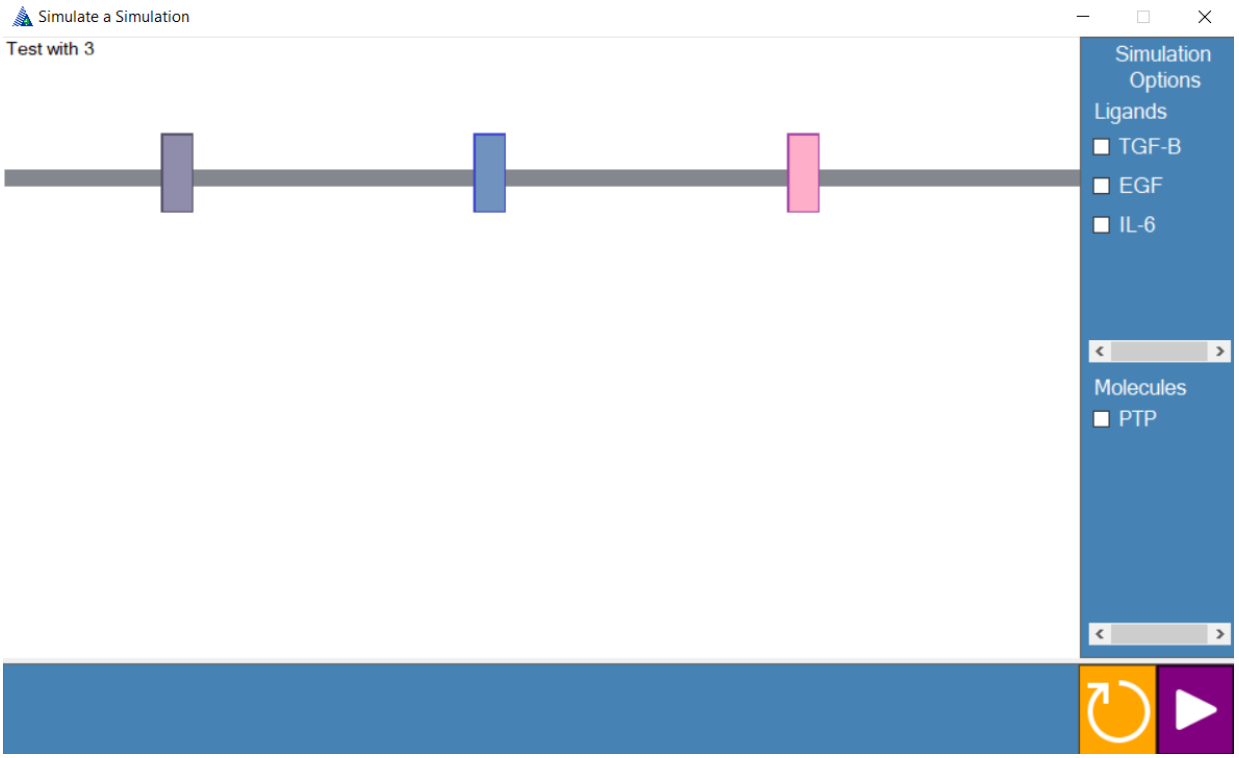

Figure 4.2. Simulate a Simulation window

Simulate a Simulation window provides tools for the user to simulate a designed simulation. The features of the Simulate a Simulation window can be defined in four sections:

1) Simulation Options Panel
2) Simulation Main Panel
3) Simulation Status Panel

4.2.1) SIMULATION OPTIONS PANEL

Simulation options panel is the rightmost panel on the Simulate a Simulation window. This panel provides list of molecule presence options for the user. These molecules could be ligands or event defined molecules. Event defining to molecules and their effect on the simulation is defined in the section 3.4.4.

Simulation options panel provides a purple colored “Run” button and orange colored “Reset” button. After selecting the desired simulation options using the lists on the simulation options panel, the user can use the “Run” button to start the simulation. If the user wants to reset the simulation, the user can use the “Reset” button to reset the simulation window.

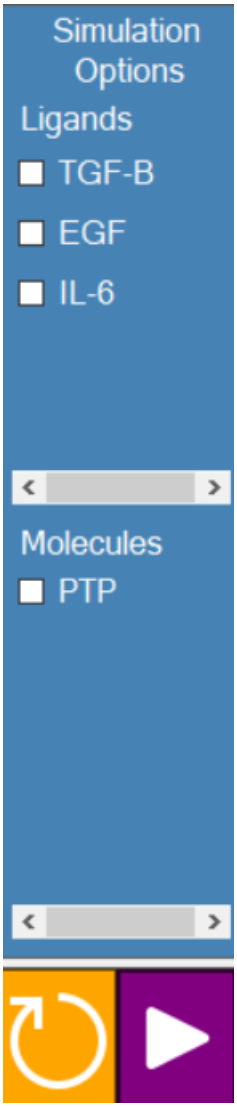

Figure 4.3 Simulation Options Panel

4.2.2) SIMULATION MAIN PANEL

Simulation Main panel is the center panel on the simulate a simulation window. The running simulation animations and events are displayed on this panel. According to the selected simulation options the designed receptor pathways will be animated on this panel.The name of the simulation can be seen on the top-left corner of this panel.

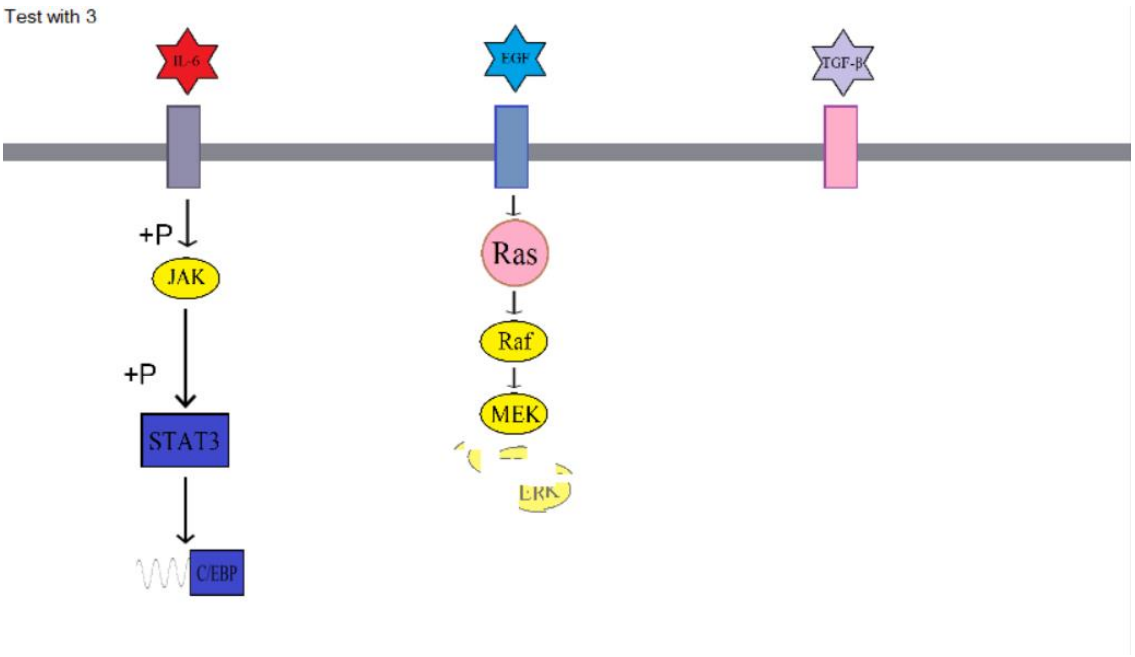

Figure 4.4 Simulation Main Panel animating a simulation

4.2.3) SIMULATION STATUS PANEL

Simulation Status panel is the bottom panel on the simulate a simulation window. In the beginning of the simulation this panel will be empty. After the finish of the animations of the simulation, alive and mitosis status of the simulated cell will be displayed on this panel. An alive cell will be display with a cell image with green color. A dead cell will be display with a skull image with red color.

If the simulation leads the cell into a mitosis then the mitosis status will be displayed with an arrow image with green color. If the simulation does not lead to a mitosis status than the mitosis status will be displayed with a gray sign.

Figure 4.5 Simulation Status Panel in the beginning of a simulation

Figure 4.6 Simulation Status Panel showing the cell status. (Alive with mitosis)

Figure 4.7 Simulation Status Panel showing the cell status. (Dead with no mitosis)

5) DEPENDENCIES

- This application works only on Windows OS. Minimum recommended version for this application is Windows 8.0 . This application have not been tested on the versions lower than Windows 8.0 therefore lower versions may cause unexpected errors.

- This application works with the Microsoft .NET Framework. Therefore .NET Framework (version 4.7.2 or higher) must be installed on your computer in order to use this application. An online installer for .NET Framework version 4.7.2 will be provided with this application. If that does not work you could use this link to download .NET Framework from Microsoft's official website:

  https://dotnet.microsoft.com/download/dotnet-framework/net472