Manual for webANIMO

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1   Introduction

webANIMO contains many functions to aid the user in analysing their biological signaling pathways. These features are explained one by one in section [4]. But, while each feature on its own is very powerful, webANIMO is more than the sum of its parts. Therefore various simple and complex use-cases are walked through in sections [2] and [3].

2   Basic tasks

In this section of the manual basic tasks like loading examples and creating simple networks are described. It is assumed that the user has a good understanding of the user interface of webANIMO and the various graphical elements it is composed of. If this is not the case the user is advised to have a look at section [4] before proceeding further in the manual.

2.1   Loading an example

The most straightforward way to learn to work with webANIMO is by loading a built-in example. These examples can be used to test various webANIMO features and learn how the interface works. First, click the "Examples" menu, as described in section [4.1.2]. Then pick one of the displayed options. Within a second an example network should be loaded and displayed in the network view.

2.2   Creating & analyzing a simple ANIMO network

Here the process to create a simple network with two reactants and one interaction connecting them will be explained. First create a reactant by right clicking on an empty location in the network view or selecting the "Add reactant" button in the toolbar. The property panel should change to "Add reactant" mode. Give the reactant a clear and recognizable name and click the "Save" button to add the reactant to the network view.

The reactant should now be visible somewhere in the network view. If not, click the "Zoom to fit" shortcut in the toolbar to find it. Now add another reactant to the network view in the same way as before. There should now be two reactants visible in the network view. If this is not the case, it might be the case that two reactants are located on top of each other, the first reactant hiding behind the second. To resolve this, locate one of the reactants and then click and drag the reactant to a different place in the network graph view. This should reveal the reactant hiding behind the other reactant.

Now click the "Add new interaction" button in the toolbar. The property panel should change to the "Add interaction" mode. As the source reactant, select the reactant that was first created. As the target reactant, select the reactant that was created after that. Make sure the "K" slider is positioned on the "Slow" position. Now click save.

A network with two reactants and one interaction should now be visible in the network view. However, to get an interesting analysis result, one more thing has to be done. Click on the source reactant of the interaction. The property panel should change to the "Edit reactant" mode. Change the "Initial activity level" slider to the highest level. Now click close.

The network is now ready to be analysed. Click on the "Analyse" button in the property panel. If the property panel is not in normal mode, click on an empty location in the network view. The property panel should then switch to normal mode. Once the "Analyse" button is clicked a "Loading, please wait" dialog will appear. The analysis of the network is now being done on the webANIMO server. Once the analysis is complete the dialog will disappear and the analysis result will be displayed in the plot view. The red vertical bar in the plot can be used to display the activation levels of the reactants at that point in the simulation.

2.3   Complex webANIMO features

Some of the advanced graph creation features will be addressed in this section. It is assumed that the user has already completed section [2.2] and already has a simple network available.

2.3.1   Self-interactions

When an interaction is added to the network view, the property panel requires that two reactants are indicated as source and target for the interaction. However, these two reactants need not be different. If required, a "self-interaction" can be created. This is an interaction where the source is the same as the target. To see this in practice, add an interaction to the existing network view. In the property panel, select any reactant as source and target, but make sure that the source and target fields are identical. After clicking save an edge should be visible that starts at a reactant but also ends at that same reactant. This way nodes can be created that when activated activate themselves even more.

2.3.2 Scenarios

A "scenario" is useful when a relation needs to be expressed between two reactants that is not linear, but depends on both ends of the interaction, or maybe even an arbitrary other node. First add another reactant besides the two already existing reactants. Then add an interaction to the network view. In the property panel at the "Reaction kinetics" field select scenario 3. Two extra fields should appear below the "Reaction kinetics" field. Here you can specify which two other reactants the interaction should depend on. When scenario 2 or 1 is selected these extra fields will disappear. Scenario 2 can be used if the interaction is related to the activity levels of both the source and the target.

3 Advanced tasks

3.1 Importing & exporting CSV data

Open a network, for example the Chrondrocyte network found under "Examples" and press "Analyse". You can export the data of the plot on the right by clicking "Plot > Export data as CSV". This will open a file dialog window. Find a suitable directory to save the file and open it with a spreadsheet editor such as Excel. You are now able to make a plot of the data in for Excel or analyse the data further.

If you want to compare experimental data with webANIMO results you can import that experimental data into the plot. This is done by pressing the "Plot > Import CSV data" button. This will open a file dialog which you can use to select a CSV file containing the experimental data. If you selected properly formatted data additional lines describing the data will be added to the plot window.

3.2 Saving analysis data as a PNG image

If you want to include an image of your plot in your report or paper it is possible to download an image of the results. To do this, first ensure that there is data present in the plot by pressing the "Analyse" button. Then press "Plot > Download plot as Image" and save the image to some place on your computer. If you want to inspect the image before downloading it you can press the 'Open plot as Image' button, which will open the image in a new browser tab. You might get a message informing you that a pop-up is blocked. In this case you can enable pop-ups for the site and try again.

3.3   Importing Cytoscape ANIMO networks

It is possible to work directly with Cytoscape files in webANIMO. To open a desktop file, simply press "Network > Open" and select a .cys file. It is possible that files made with an old Cytoscape version are loaded incorrectly, whereby all reactants are in the same spot. To fix this, press the "Reorganize network" button on the toolbar to move the reactants around.

3.4   Exporting ANIMO networks to Cytoscape format

If you save a file using "Network > Save" it is saved to the .cys format and made available to download for the user. This means that you can open your webANIMO networks in Cytoscape without any hassle.

3.5   Revisions

A revision in a webANIMO network is a set of changes a user performed on the network. These revisions are stored in the network file and thus are saved to the server whenever editing a shared network, or to your browser when editing a non-shared network. The revisions can be shown when pressing the "show revision list" button, [figure 3.1].

Figure 3.1: Show revision list toggle button

From the revision list view the user can select a revision to view changes from, by clicking on a revision in the list. The buttons also show a textual representation of important changes in the network.

Legend
Added Deleted Modified Unchanged

Revision #4 (current)

Revision #3
63 MoleculeType: mRNA→Cytokine
Initial activity level: 37→55
Plotted: false→true
Name: EGFR 2→EGFR
removed Edges: ele2 ele0
Nodes: ele1
ele1 Created
ele2 Created
ele3 Created

Revision #2
63 Initial activity level: 0→37
Plotted: true→false
MoleculeType: Receptor→mRNA
Name: EGFR→EGFR 2
ele1 Created
ele2 Created

Revision #1
64 Name: EGFR internalization→EGFR
Initial activity level: 0→61
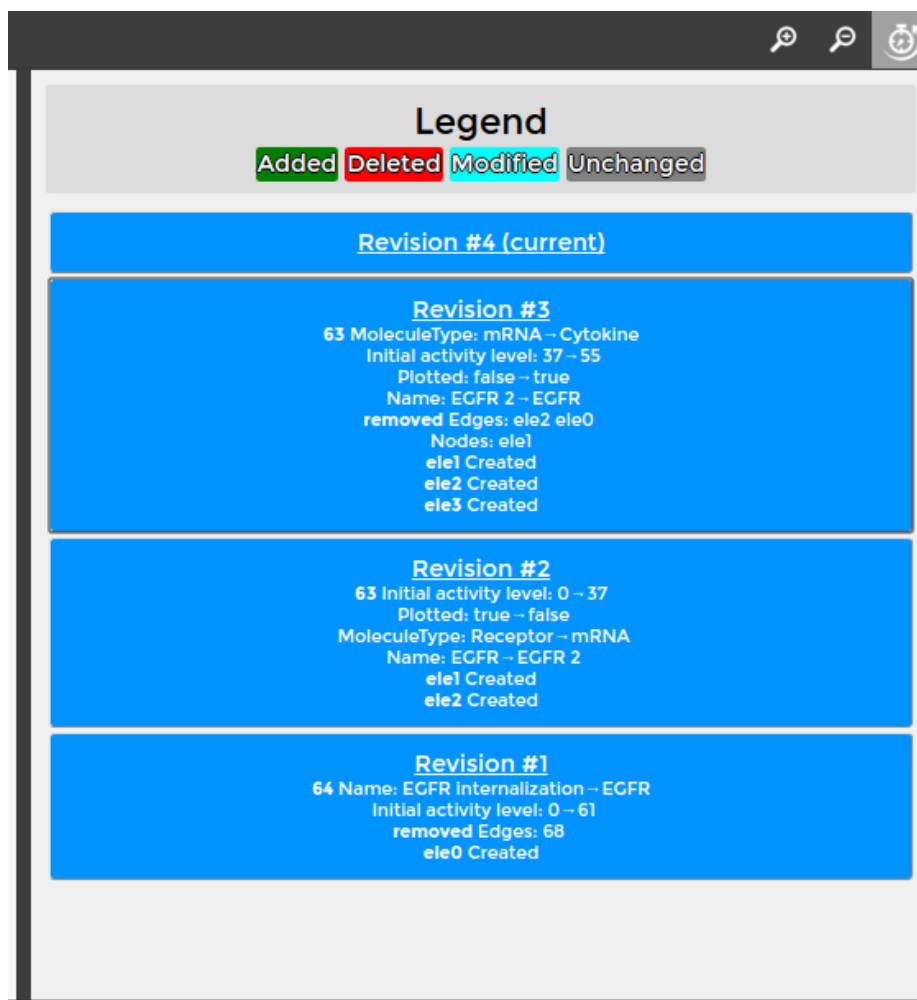**removed** Edges: 68
ele0 Created

Figure 3.2: Opened the revisions list.

When a revision is selected, the network is loaded onto the screen, and changes are highlighted according to the following rules:

- Green: Added

- Red: Deleted

- Light Blue: Modified

- Grey: Unchanged

The nodes and edges receive these colors to quickly visualize where changes were made in the network.
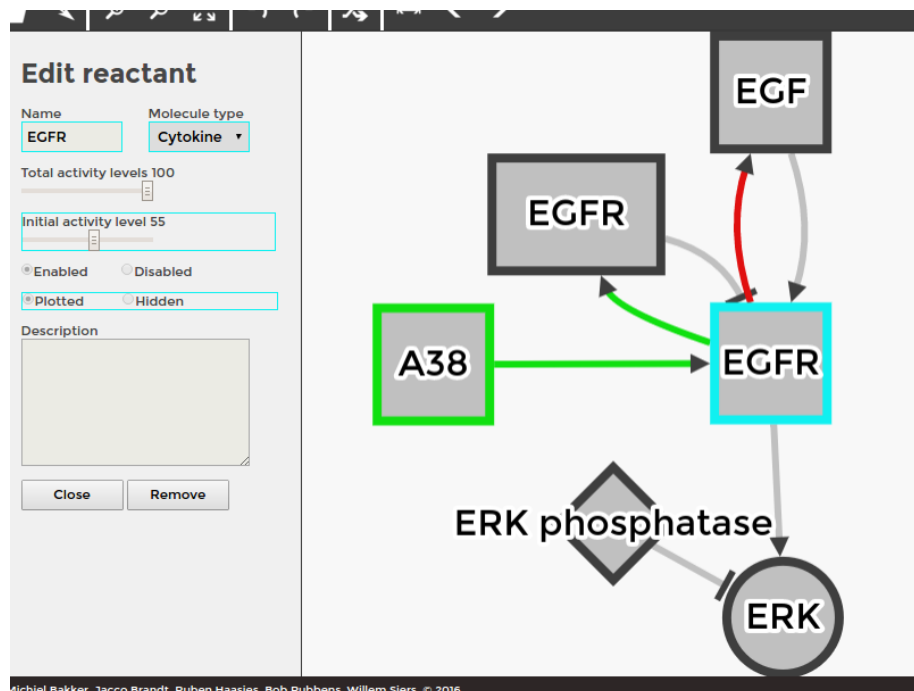

Figure 3.3: Opened revision #3, and selected EGFR

The user can also click a node or edge to display the changes that were made. These changes are then highlighted (light blue) in the left panel. When exiting the revision list view, the old network is restored (i.e. the network that the user was editing before opening the revision view).

3.6 ONLINE NETWORK SHARING

To save a network on the server, a user can click menu item "Network -> Get Shareable Link". A message will be displayed indicating that the network will be saved to the cloud. When pressing "Ok" webANIMO reloads and the new link in the address bar can be opened by anyone at any time, and the network will be loaded. The link will always contain "?network=X", where X is the identifier of the network.

When editing a shared network the changes are automatically saved to the server. A message will be displayed about the status of saving to the server is shown, for example "All changes saved to the cloud (14:16:24)" indicates up

until which time the changes are saved. Multiple users editing the same network simultaneously is not possible, and trying to do so will cause only one of the users to be able to save their changes to the server. If the other user wants to edit the network, the user editing the network must first close the page and wait approximately 30 seconds for the network to become available to the other user.

4 USER INTERFACE

The user interface of webANIMO was design for ease of use and simplicity. Therefore the interface of webANIMO was design with a small amount of components: the menu bar, the toolbar, the property panel, the network view, the plot view, and the notification toasts. Each component and its subcommands will be displayed and discussed separately.
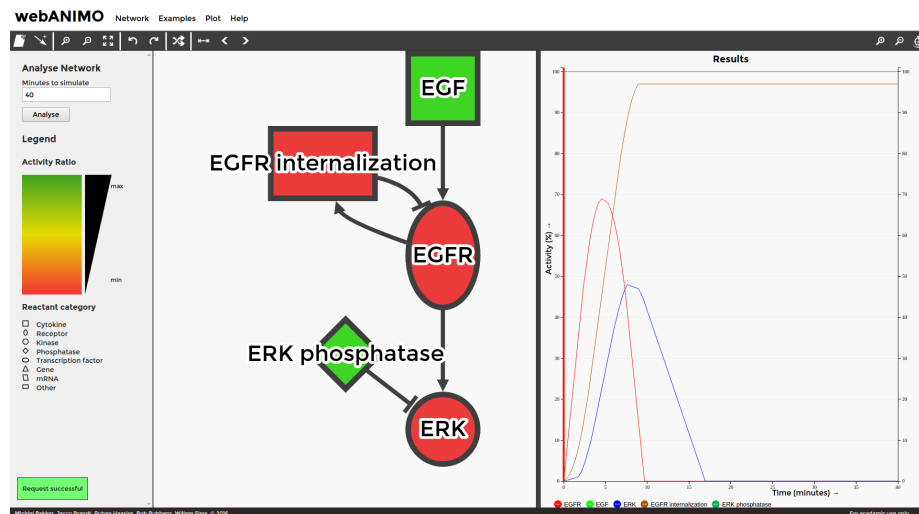

Figure 4.1: Screenshot of webANIMO

4.1 MENU BAR

The menu bar is start and ending point of webANIMO: the place where networks are opened and saved, and where plots are imported and exported. The menu bar contains four menus: the "Network" menu, the "Examples" menu, the "Plot" menu, and the "Help" menu.

Figure 4.2: Screenshot of the menubar, located in the top left of webANIMO

4.1.1 Network menu

The network menu generally concerns management of the currently loaded network. It has five subcommands.

New   The "New" command clears the currently loaded network, allowing the user to start with a blank slate. This command is useful if the currently loaded network is outdated or no longer needed, and the user wants to start over.

Open   The "Open" command allows the user to load a network stored on the local disk. This network can be either a Cytoscape JS file (with the extension `.cyjs`) or a Cytoscape session file (with the extension `.cys`). While `.cyjs` files can only contain one network, Cytoscape session files can possibly contain any number of network. Therefore when a Cytoscape session file with multiple networks is loaded, a dialog appears in which the user can specify which network from the Cytoscape session has to be loaded. This is necessary because webANIMO can only edit one network at a time. webANIMO supports Cytoscape session files from both Cytoscape 2 and Cytoscape 3.

Save   The "Save" command converts the current network into a Cytoscape session file and downloads it to the local disk of the user. The user can then open this file in both Cytoscape 2 and Cytoscape 3. This feature can be useful if the user wants to store a network locally for later use. However, for sharing networks between peers the use of the Revisions feature is recommended (see section [3.5]).

Export as Image   The "Export as Image" command exports the current ANIMO network as a PNG image and downloads it to the local disk of the user. This can be useful for embedding a webANIMO network in a document, or sharing it with a user who does not have access to web- or desktop ANIMO.

Get shareable link   The "Get shareable link" command generates a link which can be sent to a peer. This peer can then view and interact with his

own version of the network. This allows for easy and lightweight sharing of the network, but does require the peer to have access to webANIMO. This is part of the Revisions feature. An in-depth explanation of this feature can be found in section [3.5].

4.1.2 Examples menu

This menu allows the user to easily load various example networks to test cytoscape functinonality. The menu contains 3 networks:

- Model base

- Chrondrocyte

- ECHO

These networks are sorted according to size in ascending order. Particularly interesting is the ECHO network which contains more than 90 reactants. Be warned however that a network of this size usually takes more than 10 seconds to analyse.

4.1.3 Plot menu

This file allows the user to interact with the analysis result, the plot, in various ways. See section [4.5] for an in-depth explanation of the plot view. The menu contains five commands.

Set initial activities When "Set initial activities" is clicked all the activity levels indicated in the plot view are set as initial activity ratios of their respective cells. This is useful if the user wants to offset the analysis plot to the left, or wants to start the analysis from the point indicated by the analysis bar.

Import CSV data The "Import CSV data" menu item allows the user to import their own data in the plot view. See section [4.5.1] for a more detailed explanation of the expected CSV format.

Export data as CSV The "Export data as CSV" functionality allows the user to export the lines in the plot view as a CSV file. This way the user can process webANIMO results in any way they prefer. The format of this exported CSV file is the same as the format accepted by the "Import CSV data" feature. See [4.5.1] for a more detailed explanation of the expected CSV format.

DOWNLOAD PLOT AS IMAGE   "Download plot as Image" converts the plot view to a PNG image and downloads the resulting image to local disc. This can be useful if the user wants to embed webANIMO analysis results in a document without having to interpret the webANIMO CSV format.

OPEN PLOT AS IMAGE   "Open plot as Image" does exactly the same as "Download plot as Image", except instead of downloading the PNG file to local disc it opens the image in a separate window.

4.1.4   HELP MENU

The help menu is there when the user needs help with something. It contains two sub menus: the "Manual" sub menu, and the "Contact" submenu. When "Manual" is clicked a PDF file of the manual is opened for the user to read and download. When "Contact" is clicked some information about the tool is displayed, together with an address the user can contact if the user needs help.

4.2   TOOLBAR

The toolbar allows the user to manage and interact with the currently loaded network. It has eleven buttons, allowing you do things like adding reactants, zooming in or out, undoing or redoing changes. When the user hovers the mouse over each button a tooltip appears that tells the user the name of the button and if available a keyboard shortcut for the button. The buttons will be discussed from left to right.

Figure 4.3: Screenshot of the toolbar, located in the top left of webANIMO

ADD NEW REACTANT   When "Add new reactant" is clicked the property panel changes to the "Add reactant" panel. The user can set properties of the new reactant here. When the user clicks "Save" the reactant will be added to the network with the specified properties. Interesting properties in this panel are the "Total activity levels" property and the "Initial activity level" property, which indicate how active the reactants are by default.

ADD NEW INTERACTION   When "Add new interaction" is clicked the property panel changes to the "Add interaction" panel. The user can set properties of the new interaction here. There are a few interesting properties in this panel. The "Source" and "Target" properties indicate from which reactant to which reactant the interaction goes. The "Reaction kinetics" property allow the user to specify that the reaction should depend on more than one reactant. Take care that when scenario 3 is selected, two properties "E1" and "E2" appear below the "Reaction kinetics" property which allow you to choose two other reactants for the interaction to depend on. Lastly there is the "K" property which can be set in two ways. The user can either use the slider above the "K" property to set the intensity of the reaction relatively in terms of "slower" and "faster", or the user can set it absolutely by specifying a certain value in the text field.

ZOOM IN   The "Zoom in" button simply zooms in the network view.

ZOOM OUT   The "Zoom out" button simply zooms out the network view.

ZOOM TO FIT   The "Zoom to fit" button zooms and position the network in such a way that is optimally display in the network view.

UNDO CHANGES   When "Undo changes" is clicked the network reverts back to the network before the last change. All changes can be undone, including changes to properties of reactants, moving reactants, or loading a new network.

REDO CHANGES   Does exactly the same as "Undo changes", only the other way around.

REORGANIZE NETWORK   When a network is cluttered with many reactants it can be nice to layout the network in an orderly fashion. When you click the "Reorganize network" button webANIMO tries the layout the network in such a way that each reactant and its interactions is easily visible. While this usually works fine, if this is not possible (as is the case with networks that contain 100 or more reactants) webANIMO will fail and the resulting layout will be as incomprehensible as the previous layout.

RESET WINDOW SIZES   When the "Reset window sizes" button is clicked, the display area is divided between the network view and the plot view.

SET PLOT VIEW FULL WIDTH   When "Set graph window full width" is clicked, the display area is completely used for displaying the plot view.

SET NETWORK VIEW FULL WIDTH   When "Set network view full width" is clicked, the display area is completely used for displaying the network view.

4.3 PROPERTY PANEL

The property panel is the main workhorse of the webANIMO user interface. It is the place where analysis of the network is initiated and where network elements such as reactants and interactions are edited. When nothing is selected it resides in "Normal mode". When a reactant or an interaction is added it switches to "Add reactant" or "Add interaction" mode respectively. How the panel works in "Add reactant" and "Add interaction" mode is explained in section [4.2] and section [4.2]. When an existing reactant or interaction is clicked the panel switches to "Edit reactant" or "Edit interaction" mode respectively. These modes work in the same way with the only difference being that changes made in editing mode are saved immediately, while changes made while in adding mode are only saved when the "Save" button is clicked.
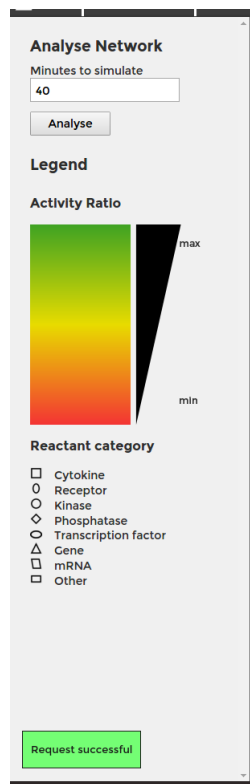

Figure 4.4: A screenshot of the property panel, located on the left of webANIMO

4.3.1 Normal mode

"Normal mode" is the mode the panel is in by default, as displayed in [figure 4.4]. While the property panel is in this mode it contains a text field where the user can enter the duration of the analysis, and a button "Analyse" that the user can click to invoke analysis. Below those elements two legends are displayed. The first legend indicates the correlation between colors of the reactants and the activation level for quick reference. The second legend indicates the correlation between the shape of a reactant and what type of reactant it is (e.g. cytokine, receptor). Note that these "types of reactants" are merely for visual purposes; the actual type of a reactant has no impact on the analysis of the network or the behaviour of the reactant in the network.

4.3.2 Notification toasts

The notification toasts are part of the lower section of the "Property panel". In [figure 4.4] a notification toast is visible in the bottom; it is bright green and contains a piece of text.

Notification toasts in general are used by webANIMO to tell the user when various events occur. For example, when a network is loaded successfully, when a network is analyzed successfully, or when something goes wrong. A notifcation toast always looks similar to the one depicted in [figure 4.4]: rectangular, filled with a certain color, and a text commenting on something that just happened. Notification toasts come in three flavors:

Green This toast generally indicates that something succeeded, and can be perceived a "good news". They can possibly contain interesting information, but if one is not interested they can be skipped.

Gray A gray toast is a toast that only brings information; it is neither malign or benign. The world will keep turning if these toasts go by unread, but it is advised that the users do take a second to look at these toasts.

Red Finally, a red toast is very bad news. It almost always indicates something has gone horribly wrong, and sometimes even requires the user to refresh the page. While during development an effort has been made to keep the occurrences of these toasts to a minimum, it cannot be guaranteed that they have all been eliminated.

4.4 Network view

The network view displays the currently loaded network and allowes the user to explore and modify the network. The user can move the network view around

by clicking on an empty location in the network view and dragging the mouse. Scrolling with the mouse wheel or clicking on the "Zoom in" or "Zoom out" buttons in the toolbar (as explained in section [4.2] and [4.2]) zooms the network view in our out respectively. When either a reactant or an interaction is clicked the property panel (see section [4.3]) changes to the respective edit mode of the clicked element. When the right mouse button is clicked on an empty location in the network view a menu appears containing the options "Add reactant" and "Add interaction". When the user clicks either of these options the property panel changes to the proper mode such that either a reactant or interaction can be added (as explained in section [4.2] and section [4.2]).
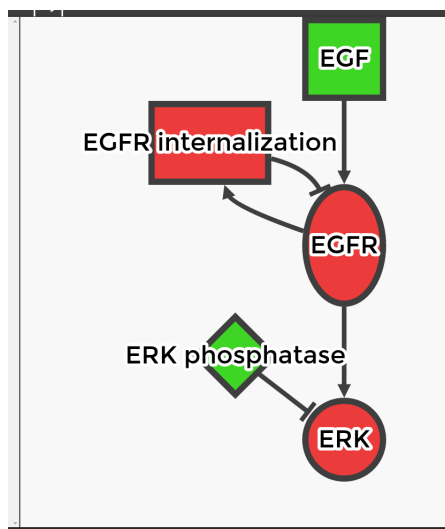

Figure 4.5: A screenshot of the network view, located in the center of webANIMO

4.5   Plot view

The webANIMO "Plot view" consists three components. First there is the actual plot view. It is displayed in the center of the plot view area and shows the analysis results as colored lines. The width of the plot is determined by the analysis time filled in in the "Property panel". Below the plot view is a legend, indicating which color correlates with which reactant. Lastly, there is a 3-button toolbar above the plot view. These buttons are, from left to right, "Zoom the plot in", "Zoom the plot out", and "Show or hide the revision list". The "Zoom the plot in" and "Zoom the plot out" do exactly what one would expect. Additionally the plot can be zoomed in our out by scrolling with the mouse scroll wheel. The last button "Show or hide the revision list" is used to

enable the "Revision" functionality. This is further explained in section [3.5].
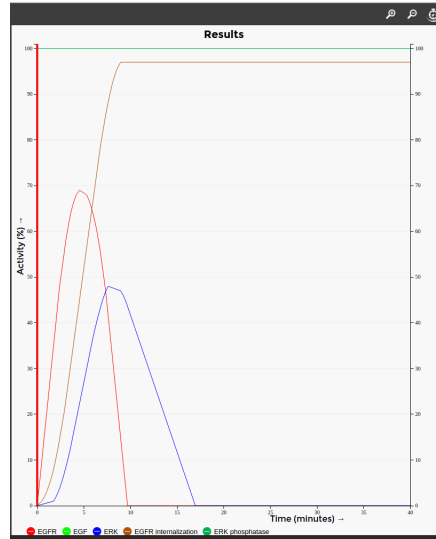

Figure 4.6: A screenshot of the plot view, located on the right of webANIMO

4.5.1 CSV DATA FORMAT

The CSV format is simple and widespread, which is why it was chosen as the default format for importing and exporting analysis data. Figure [4.7] shows an example CSV file, which will be used as an example for the explanation.

```
Time (min),      EGFR,    EGF,    number_of_levels,
0,               0,       100,    100,
0.05,            1,       ,       ,
0.1,             2,       ,       ,
0.15,            3,       ,       ,
0.2,             4,       ,       ,
0.25,            5,       ,       ,
0.3,             6,       ,       ,
0.35,            7,       ,       ,
0.4,             8,       ,       ,
0.45,            9,       ,       ,
0.5,             10,      ,       ,
```

Figure 4.7: CSV data format example

The text represents a table. Every line in the text file represents a row in the table. Every value between two commas represents a table cell. Therefore the example above has exactly 4 columns. The first row of the CSV table represents the header of the table. Therefore each of the 4 columns has a name. The first

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column is called "Time (min)", the second "EGFR", and so forth. The expected layout of the CSV table is as follows: the first column should contain the time steps in minutes. Then the CSV can contain any amount of other columns where each column represents one data series. Then the last column is special, because the first value represents the maximum value of each data point. Of the last column only the first value indicates the maximum value. The other values in that column are irrelevant. If a CSV value is empty (e.g. when there is only whitespace between two commas or after a comma) a CSV value simply repeats the value of the cell above it.