PathWhiz User Manual

I. Account Types

PathWhiz can be accessed either as a guest user or by signing up for a private account. Both guest users and users with accounts have access to identical pathway drawing functions, the only difference is pathway access and privacy.

Guest users can edit all public pathways, and likewise, all pathways created by a guest user are public and can be edited by other guest users. Guests also have the ability to "lock" public pathways, preventing them from being further edited (see section IIIc).

Private accounts are free and allow users to create their own collection of pathways. Pathways created in a user account are publically viewable but editable only by the logged in user. Logged in users have the option of making any of their pathways private, meaning no other users (guest or otherwise) can see them.

II. Elements and Processes

a. Types

PathWhiz houses a large public database of pathway components. Users are welcome to use any existing component, or create new ones, for their pathways.

PathWhiz contains 6 mains element types:

- **Compound**: Any small molecule
- **Protein**: An amino acid macromolecule, corresponding to a singular entry in UniProt
- **Protein Complex**: A combination of one or more proteins, along with any modifications and cofactors
- **Nucleic Acid:** DNA or RNA
- **Element Collection**: Represents a general class of compounds, protein complexes, or nucleic acids (i.e. alcohols, bacterial ribosomes, etc.)
- **Bound Element**: A protein or nucleic acid bound to one or more compounds, protein complexes, elements collections, or nucleic acids

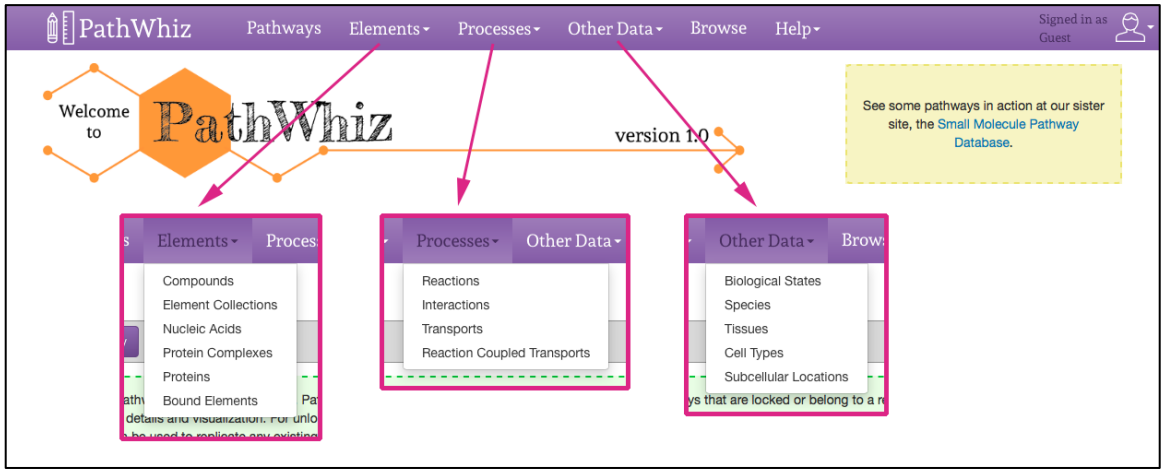
And 4 main process types:

- **Reaction**: Contains at least one left and right element, and zero or more enzymes
- **Reaction Coupled Transport**: Contains at least one left and right element with their respective biological states, and zero or more enzymes
- **Transport**: Contains up to three elements that are transported simultaneously and zero or more transporters
- **Interaction**: Contains two elements where the first either activates or inhibits the second

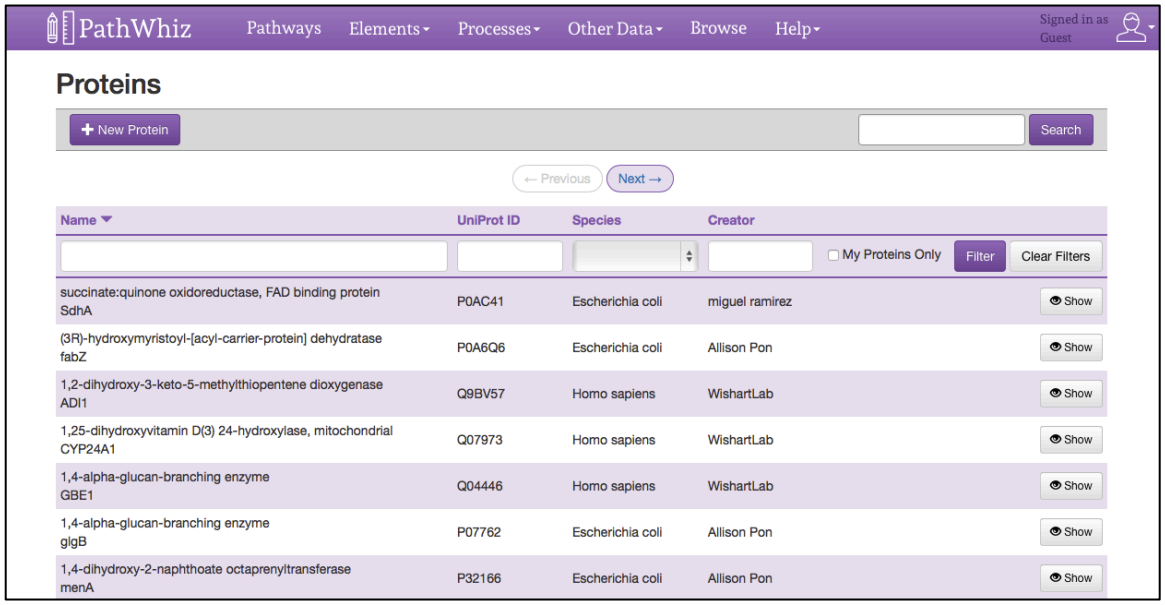
Some elements also have an associated Biological State, indicating the biological location where it's found (in the context of the pathway). Biological States are composed of up to four components:

- Species
- Tissue
- Cell Type
- Subcellular Location

All elements and processes can be browsed via their respective links in the PathWhiz menu bar.

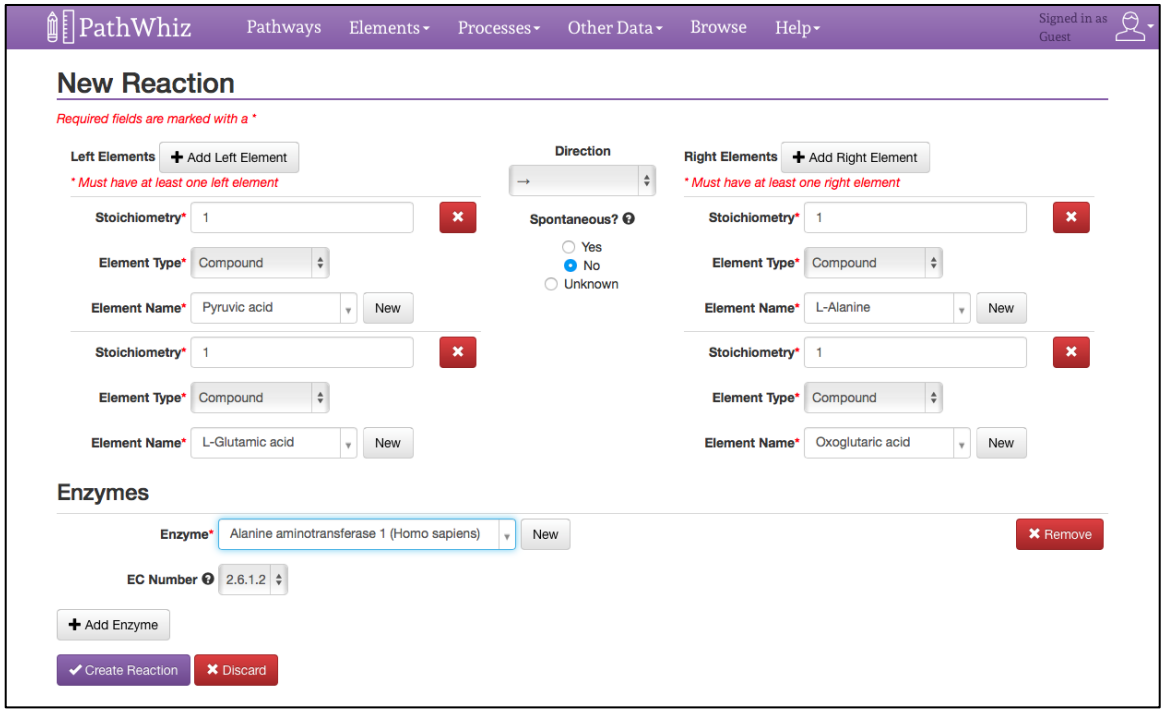


Each component has its own index page, where you can browse, filter, and search what's currently in the database.



b. Creating and Editing

You can also add you own elements and processes if needed, by selecting the “New” button on the index page. When adding new elements to the database, required fields are marked with a red *.



Compounds – Require only a name, but it is strongly recommended that they also have a structure. Structures can be drawn or imported from various formats (SMILES, InChI, Mol file, etc.). These structures can be displayed in pathway diagrams. Compounds can also have various external reference ids, allowing them to be linked to other databases.

Proteins – Require a name, species, and a UniProt ID. A gene name is recommended to allow for simplified visualization. Other data such as sequences (protein or gene) and descriptions can also be added; these are stored and can be accessed as meta data but will not be seen in the visualization. Filling in the UniProt ID will automatically annotate some fields (name, species, gene name, description, EC numbers, protein sequence).

Protein Complexes – Require a name, species, and at least one protein. Protein complexes can also have cofactors (which are compounds) and protein modifications (which are a compounds associated with specific proteins in the complex). The proteins and compounds that make up a protein complex must also exist in the database.

Element Collections – Require a name and the element class they represent (compounds, protein complexes, or nucleic acids). Element collections can also be given an example element; if present, that element can be rendered in visualizations as a representative of the element collection.

Nucleic Acids – Must have a name and a type (DNA or RNA). Can also have sequences and external reference ids, allowing them to be linked to other databases.

Bounds Elements – Must consist of at least two bounds elements, one of which is a protein complex or a nucleic acid.

Reaction - Must have at least one left element and one right element (of any type), but can have as many as necessary. It is recommended that they also have a specified direction. Reactions not marked as spontaneous also must have at least one enzyme, but can have as many as necessary. Enzymes may be any protein complexes from the database. NOTE: When rendering a reaction in a pathway, you are able to choose which enzymes are displayed. Thus, if multiple enzymes catalyze the same reaction, they should all be listed with that reaction (not as separate reactions).

Reaction Coupled Transports - Must have at least one left element (of any type), one right element (of any type), and one enzyme, but can have as many as necessary. Enzymes may be any protein complexes from the database. It is recommended that they also have a specified direction. NOTE: When rendering a reaction coupled transport in a pathway, you are able to choose which enzymes are displayed. Thus, if multiple enzymes catalyze the same reaction, they should all be listed with that reaction (not as separate reactions).

Transports – Must have at least one and up to three elements (of any type) that are transported simultaneously (i.e. as part of the same process). Must also have a left and right biological state specified. Transporters can also have a type and as many transporters as necessary. Transporters may be any protein complexes from the database. NOTE: When rendering a transport in a pathway, you are able to choose which transporters are displayed. Thus, if multiple transporters enable the same transport, they should all be listed with that transport (not as separate transports).

Interactions – Must have a left and right element (of any type) and an action (activation or inhibition).

Biological States – Must have at least one of Species, Tissue, Cell Type, or Subcellular Location. Can have all four.

Species – Must have a name (scientific name preferred) and taxonomy id (from NCBI).

Tissue – Must have a name and ontology id (from NCBI).

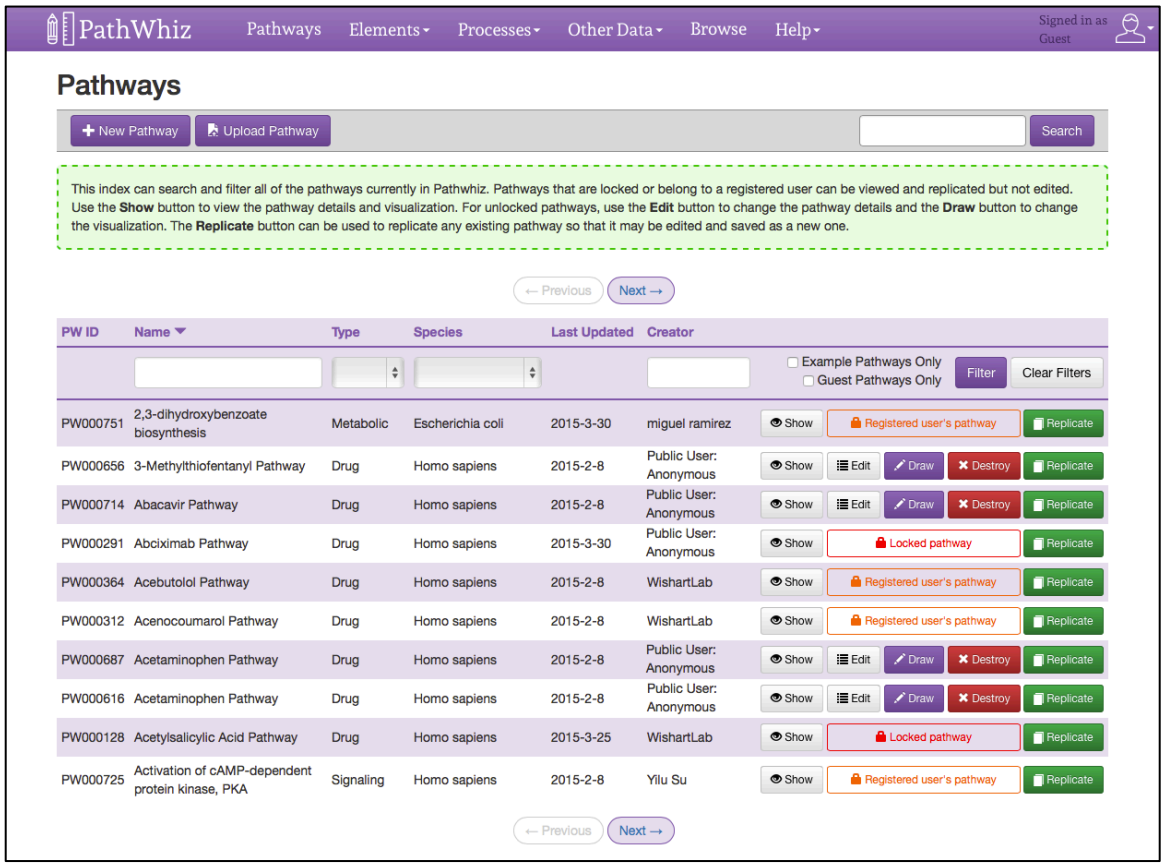
Cell Type – Must have a name and ontology id (from NCBI).

Subcellular Location – Must have a name and ontology id (from NCBI).

Check out the legend (http://smpdb.ca/pathwhiz/legend) to see the elements.

III. Pathways

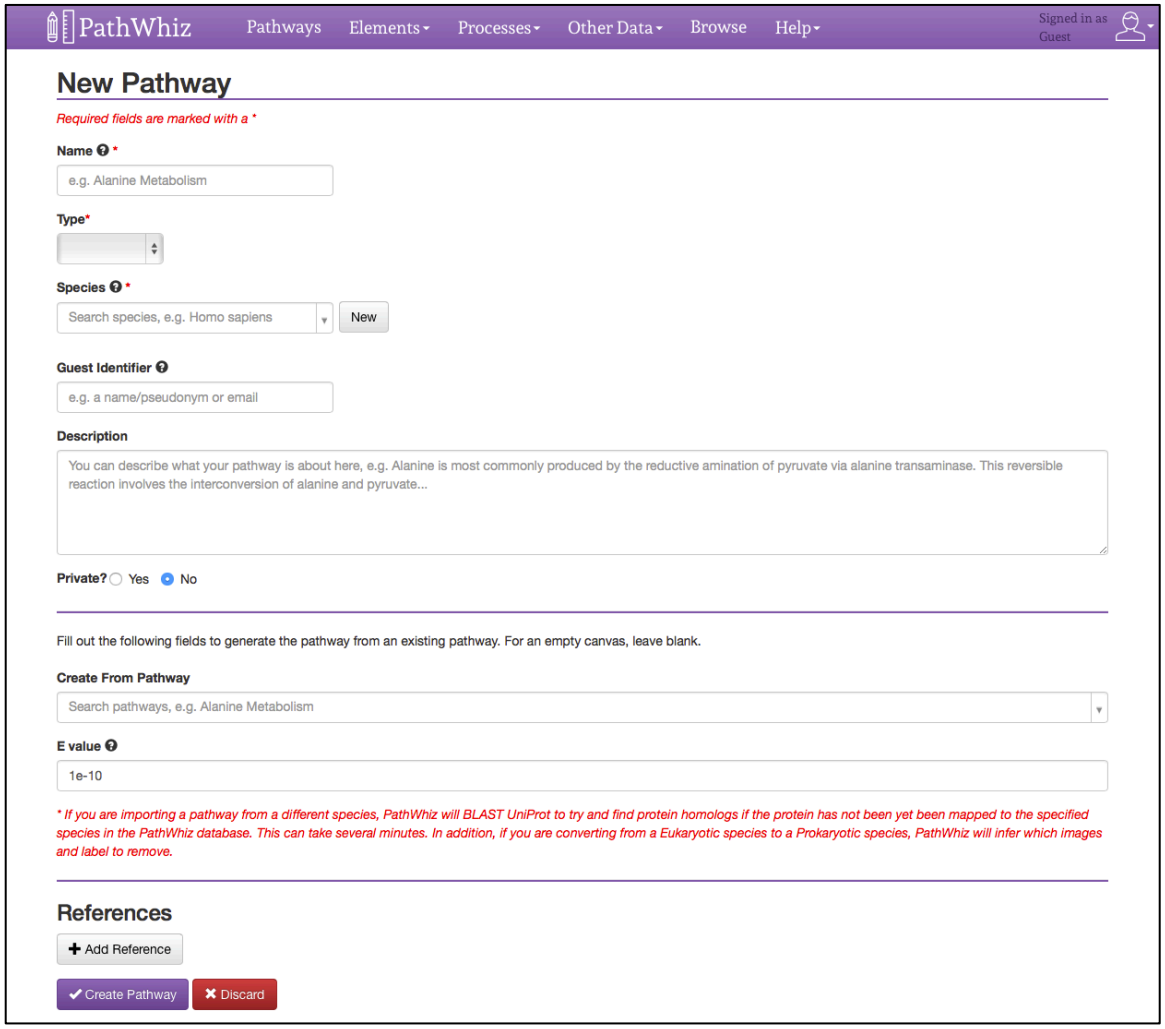
a. Creating a New Pathway



On the pathway index you can view all the pathways currently in PathWhiz. If you are a guest user, you will be able to edit all other unlocked public pathways (pathway locking is discussed in section IIIc below). Guest pathways can be filtered using the “Guest Pathways Only” checkbox. If you log into your own account, you can only edit your own pathways. These can be filtered using the “My Pathways Only” checkbox. Registered user’s pathways and locked pathways are marked accordingly.

NOTE FOR GUEST USERS: When using PathWhiz as a guest, any pathways you create will be public and can also be accessed and altered by other guest users. To create your own private pathways that can't be edited by other users, sign up for your own account. It's free!

To create a new pathway from scratch, use the "New Pathway" button on the top left and enter your pathway details. You can also use the "Replicate" button next to an existing public pathway if you wish to use it as the basis for your new pathway (replication and propagation are discussed in further detail in section IIIb below).



The name, type, and species are required fields. Guest users can optionally add their name if they wish to be associated with the pathway. If you have your own account, marking a pathway as private means other users will not be able to see it.

Filling out the “Create From Pathway” and “E-value” fields will generate the basis of your pathway from an existing pathway in the database. The E-value is used by BLAST to find protein homolog if the species is different. Leave these blank if you wish to start from scratch.

References can also be added if desired. If a PubMed ID is given, the annotation will be filled automatically.

Once your pathway has been created, you will be taken to the pathway drawer.

b. Replication and Propagation

From the index, existing pathways can be replicated using the “Replicate” button beside each listed pathway. This will bring you to the New Pathway form, where you can enter and edit the remaining pathway details. If the chosen species for your new pathway is different from the species the pathway was originally drawn for, PathWhiz will use BLAST to try and find protein homologs for the original pathway proteins. If BLAST cannot find a suitable homolog, an “Unknown” protein will be put in its place.

Pathway propagation works similarly. To propagate a pathway, go to the pathway details page (clicking the “Show” button from the index). The “Propagate” link is in the top right corner. On the propagate page, multiple species may be chosen. Propagation will then convert the chosen pathway for each of the specified species. Please note that BLAST may take several minutes or more to search for protein homologs, depending on the number of proteins and species specified.

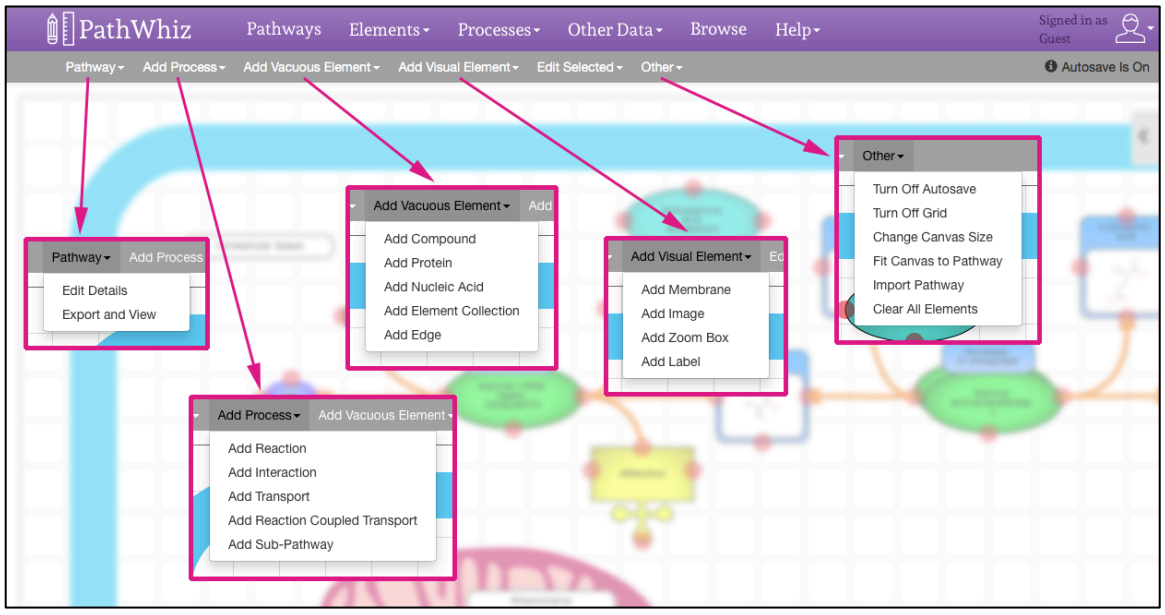
BLAST requires an E-value, which is used to determine if a candidate protein is similar enough in sequence to be considered a homolog

c. Locking Pathways

At any point during the editing process, users have the ability to lock a pathway. This is done from the pathway edit page (clicking the “Edit” button from the index, or the “Pathway”-> “Edit Details” link from the drawing system). Locked pathways can no longer be edited by any type of user. NOTE: Once locked, a pathway cannot be unlocked (though it can be replicated and propagated). Pathway locking is meant to prevent completed public pathways from being further edited, thus should only be done when a pathway is completely finished.

IV. Building a Pathway Visualization

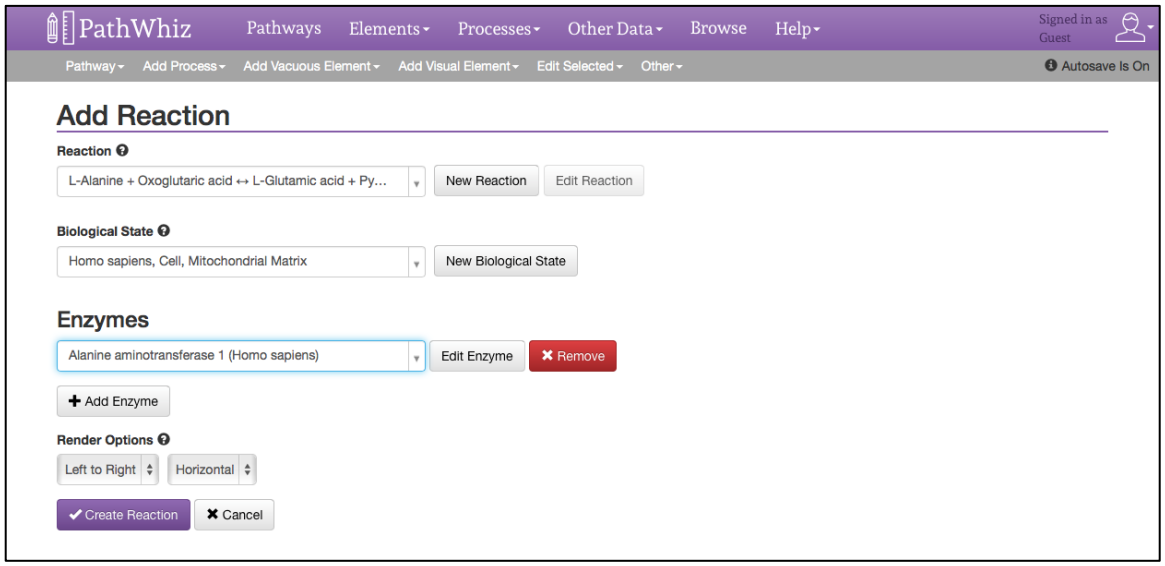
Pathway visualizations can be accessed and edited via the "Draw" link on the index or the "Draw Pathway" link on a pathway show page. This will take you to the pathway drawing system. The pathway drawing system has a second grey menu bar containing the different drawing functionalities explained below.



As you work on your pathway visualization, it will be automatically saved anytime you make a change. Autosaving can be turned off and is discussed in section IVf below.

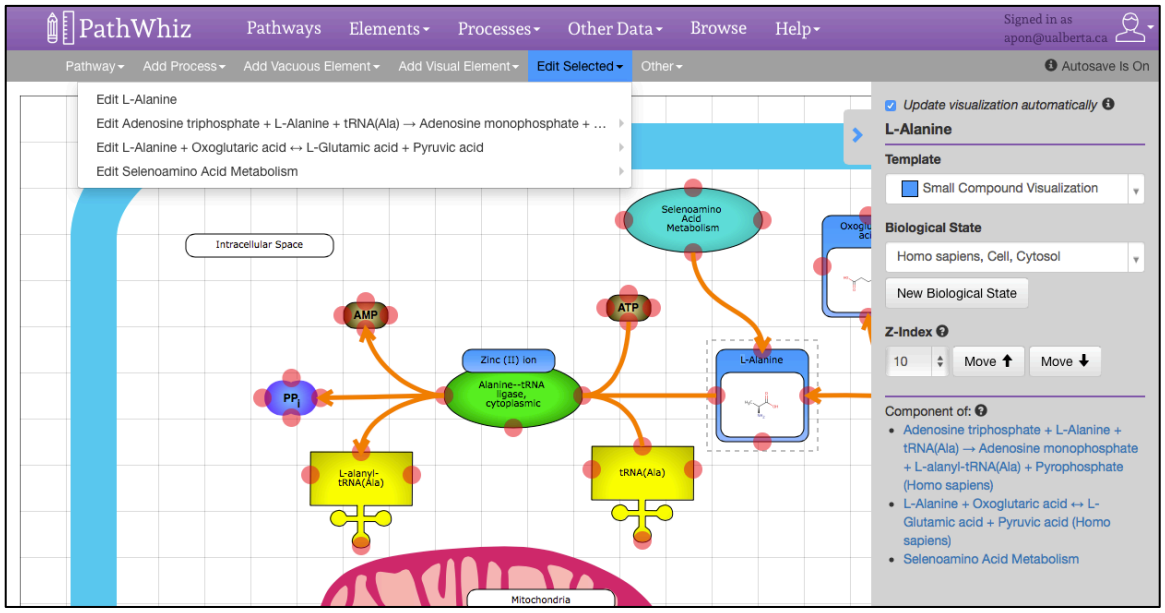
a. Adding Processes

To add new processes, use the "Add Process" link in the menu bar. Processes include reactions, reaction coupled transports, transports, interactions, and sub-pathways. You will be prompted to either select an existing process from the database or create your own. Search the database by entering text into the associated text box. Processes can be searched by their respective PathWhiz IDs or by the names of their components.



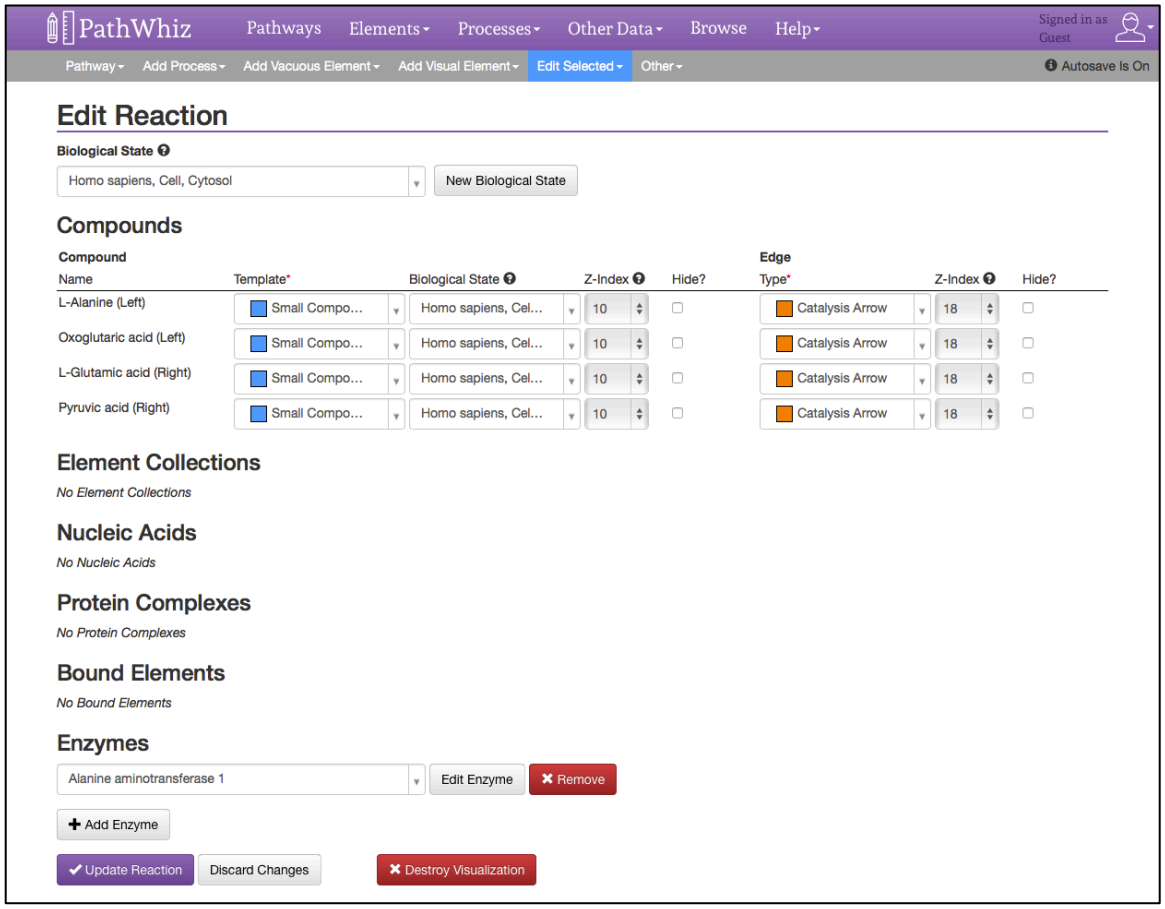
Once you've selected a process, and added its details, the "Create" button will add it to the visualization.

When adding processes, new processes can be built onto existing ones by first highlighting the element you wish to build from, then selecting the desired process from the menu. This will cause your new process to be rendered attached to the existing process. If you've highlighted one or more elements before attempting to add a new process, you will only be able to add processes that can be connected to the highlighted elements.



A process's visualization details can be edited by double-clicking any element in the process, which activates the "Edit Selected" menu and sidebar (explained in further

detail in section IVd). The process can then be found in the "Edit Selected" menu or on the bottom of the sidebar and selected. When a process is selected for editing you will be presented with a page where you can edit the visualization details. Here you can change the templates used for each element, the z-indexes of each element, and show/hide the different elements if necessary. Saving the visualization will return you to the full pathway view.



b. Adding Vacuous Elements

To add new vacuous elements use the "Add Vacuous Element" link in the menu bar. Allowed vacuous elements are compounds, element collections, nucleic acids, proteins, and edges. Once added, you can edit the details of a vacuous element on the sidebar. To change the element, search the database by entering text into the associated text box. You can also change the template used for the element and the z-index of the element.

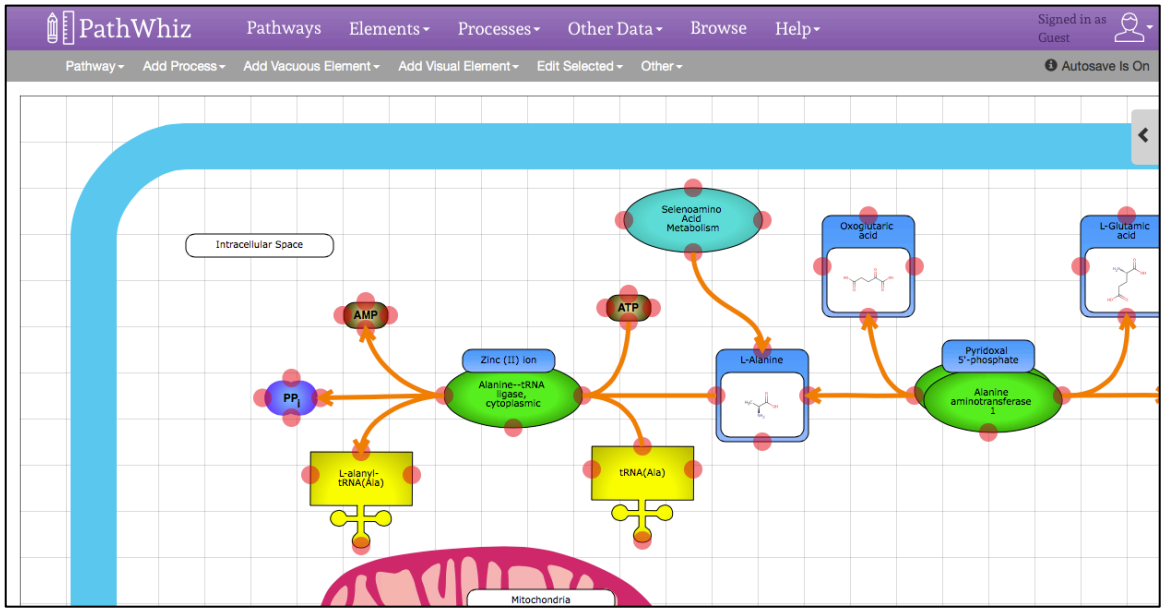
NOTE: Though processes can theoretically be depicted by combining vacuous elements instead of rendering a process stored in the database, it is always preferable to visualize a process from its corresponding database model. This is because otherwise the pathway cannot be properly converted to other data

exchange formats (BioPAX, SBML, SBGN, PWML) because it will not have the required process meta data.

c. Adding Other Visual Elements

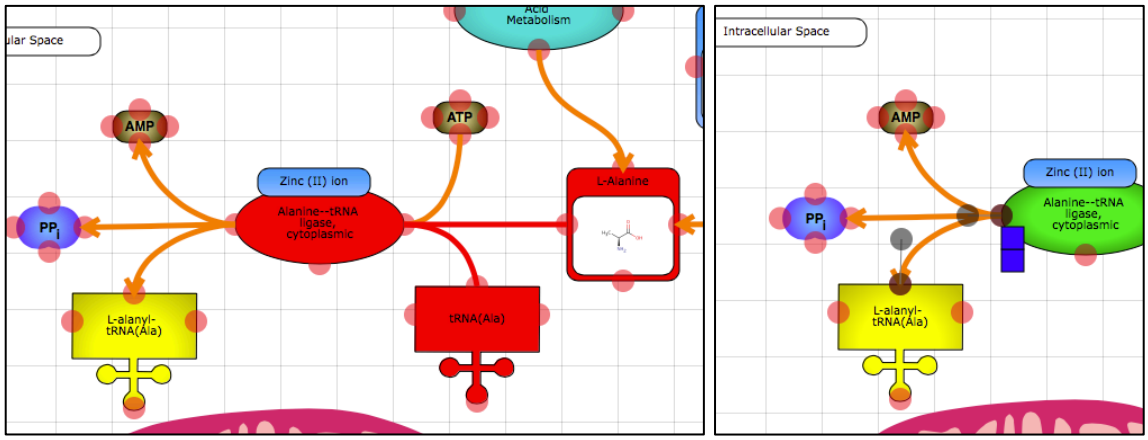
To add other visual elements use the "Add Visual Element" link in the menu bar. These include membranes, images (including cellular components, tissues, organs), labels, and zoom boxes. Once added, you can edit the details of a visual element on the sidebar. Options for visual elements include the template, z-index, size, and rotation.

d. Moving and Connecting Elements and Edges



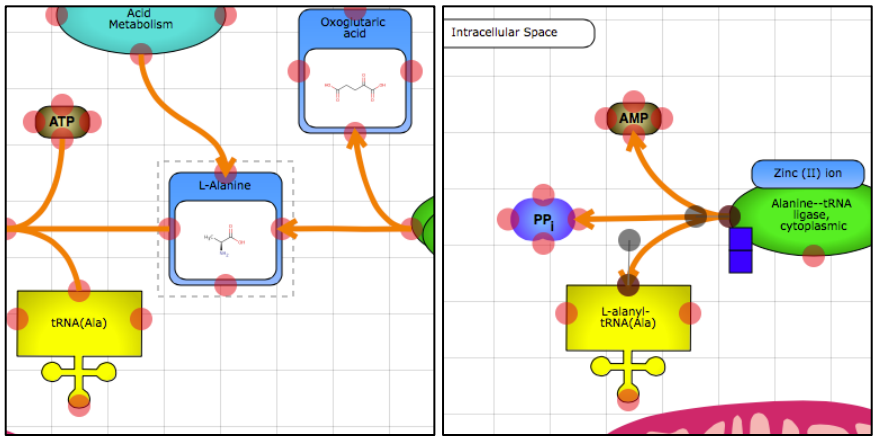
Moving Elements: Click and drag elements to move them around. Multiple elements can be selected using single clicks. Elements selected for moving are highlighted in red. Unselect them by click on them a second time.

Editing Edges: Double click an edge to select it. Selected edges are marked by grey circles on their start and end points. Click and drag these circles to move the start and end points or adjust the curve of that edge segment. Edge segments can be added and removed from the edge using the blue boxes (clicking the upper box will add a segment, while clicking the bottom box will remove one). Double clicking an end point of a selected edge will allow you to cycle through the different types of end points – arrow, flat, or none.



Snap Points: Snap points on elements are indicated by red circles (these do not appear in the final visualization). To snap an edge to an element, double click to select the desired edge. Then click the end point you wish to snap (indicated with a grey circle), followed by the snap point of the element you wish to join it to.

e. Editing Existing Elements

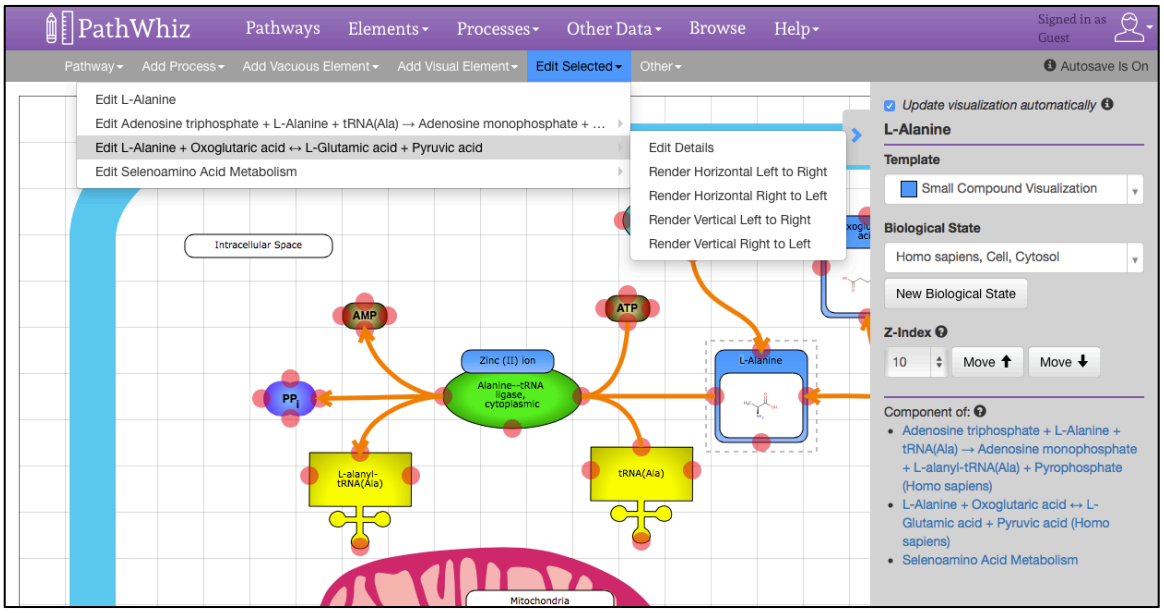


To edit an existing process/element, double click that element (or an element in that process). A dashed line will appear around the selected element. Lines can also be selected, and will be marked by grey circles at the start and end points.

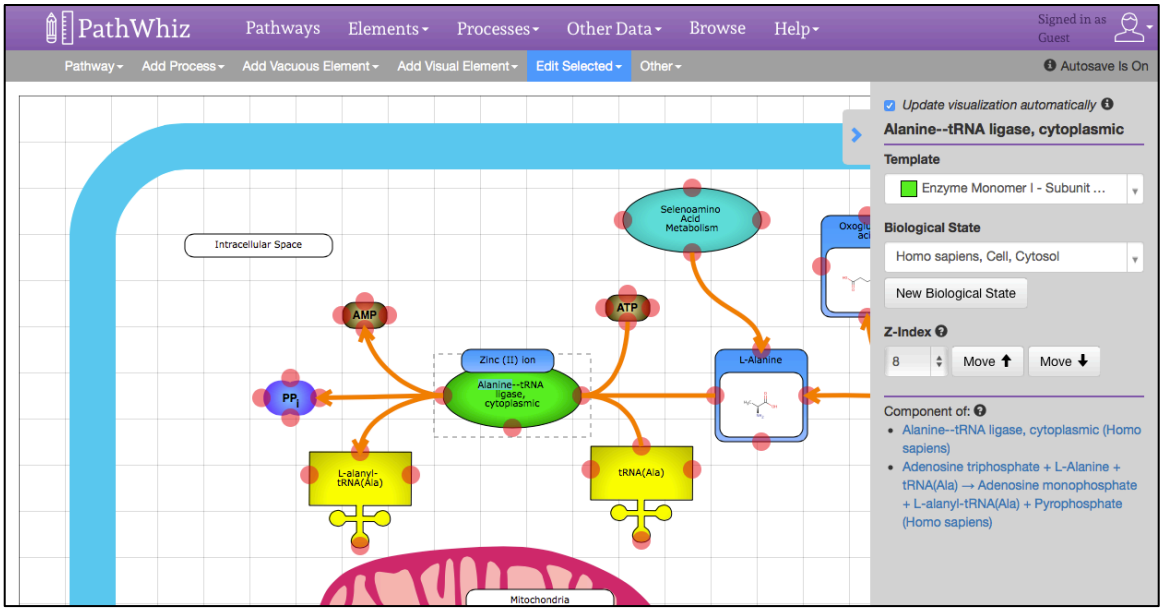
Once an element is selected, the “Edit Selected” menu item and sidebar will become active. On the sidebar you can edit the appearance of individual elements, including the template used and z-index. On the “Edit Selected” menu or bottom of the sidebar, processes and complexes that this element belongs to can be accessed, edited, and re-rendered. Selecting a process will bring you to the process editing screen described in section IVa above.

From the “Edit Selected” menu, processes may be re-rendered horizontally or vertically (the direction of a layout) and left-to-right or right-to-left (the direction of

the reaction). Elements such as proteins and bounds may be re-rendered back to their default layout. Any highlighted elements will not be moved when re-rendering occurs, thus you can select sections of the process/element to remain static.



NOTE: When you select a protein or bound, the “Edit Selected” menu will contain the options for editing both the protein/bound and any of its associated processes.



Editing the visualization details of an element will allow you to change the templates used for elements and edges. Different templates can be selected by entering text and searching or using the arrow keys to scroll through the choices. Some choices

are colored to indicate the color of the visualization. You can also change the z-index (i.e. layer) of the visualization.

A NOTE ABOUT THE SIDEBAR: Changes made on the sidebar will appear automatically. As this may slow performance on larger pathways, automatic updating can be turned off using the "Update visualization automatically" checkbox on the top of the sidebar. When off, an "Update" button will appear on the sidebar to allow you to update your visualization manually.

f. Other Options (Canvas Size, Importing, etc.)

From the "Other" menu link various options can be accessed.

Turn On/Off Autosave: Click to turn autosave on and off. If autosave is on, it will be indicated in the top right corner. When autosave is off the indicator will be replaced with a "Save Pathway" button, which is used to manually save your pathway.

A NOTE ABOUT AUTOSAVE: By default, PathWhiz will save your diagram each time you move an element. With larger pathways, this may cause a decrease in performance; if this is the case you may wish to turn off autosave. Note that autosave only applies to the pathway layout: element movement, rotation, and re-sizing. Regardless of whether you have autosave turned on or off, edits to element visualization details, element/process additions and removal, and changes to canvas size will still be saved (i.e. any action where you leave the main drawing canvas). With autosave turned off you can save updates to the pathway layout using the "Save Pathway" button in the top right corner, or reset the pathway to the last save using the "Reset Pathway" option in the "Other" menu.

Turn On/Off Grid: Click to turn the drawing grid on and off.

Change Canvas Size: Allows the canvas size to be increased and decreased. The anchor point can be specified when altering the canvas size; this indicates the direction in which the size should be increased/decreased.

Fit Canvas to Pathway: Will resize the canvas to fit around your pathway with an even margin around the edges. Not necessary, but should be used when you are done drawing to produce centered images.

Import Pathway: This allows an existing pathway visualization to be copied into the current visualization. You can select an existing pathway and an E-value (for BLAST). If the species selected is different from the species the original pathway was drawn for, PathWhiz will use BLAST to try and replace the original proteins with the appropriate protein homologs. If no suitable homologs can be found for a

protein, an “Unknown” protein will be put in its place. Note that BLAST can take up to several minutes to run, depending on the number of proteins.

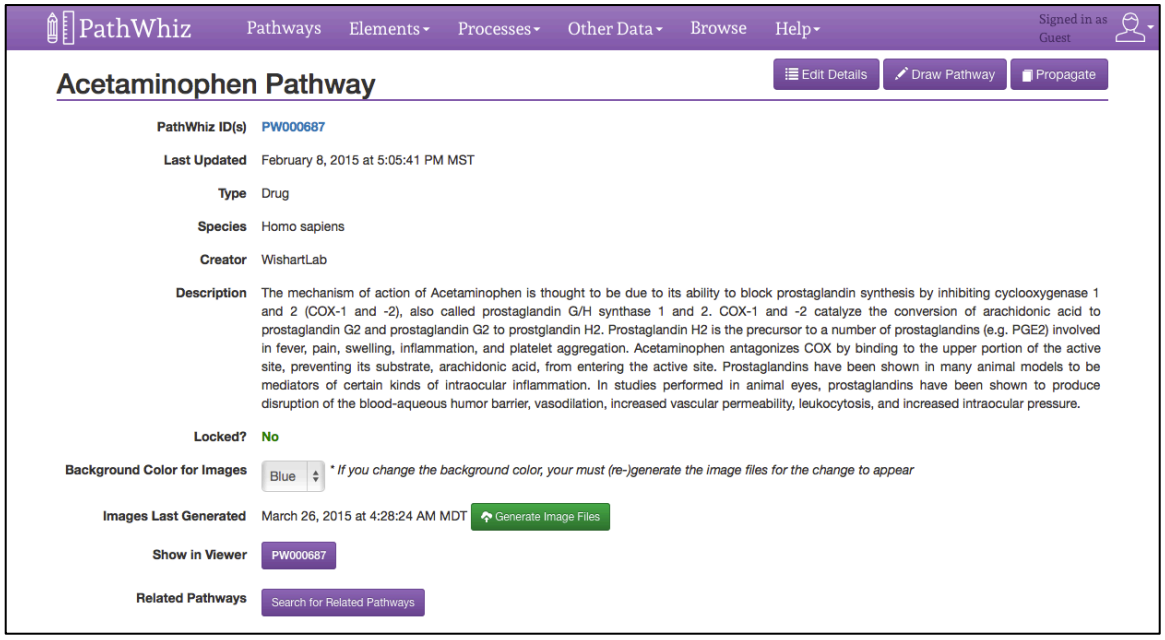
Clear All Elements: This removes all elements from the visualization.

V. Viewing a Pathway

From the "Pathway" menu link of the drawing system you can edit your pathway details, or view and export the pathway visualization.

a. Exporting

When you are ready to export your pathway, select "Export and View" from the "Pathway" menu link. This will take you to a page showing the pathway details.



Click on the green "Generate Image Files" button to export the pathway. You may first choose to generate the images with a blue or white background.

In addition to generating PNG and SVG image files, BioPAX, SBGN, SBML, and PWML files will also be generated. These are textual data exchange formats that you can read more about here:

BioPAX: http://biopax.org

SBGN: http://www.sbgn.org

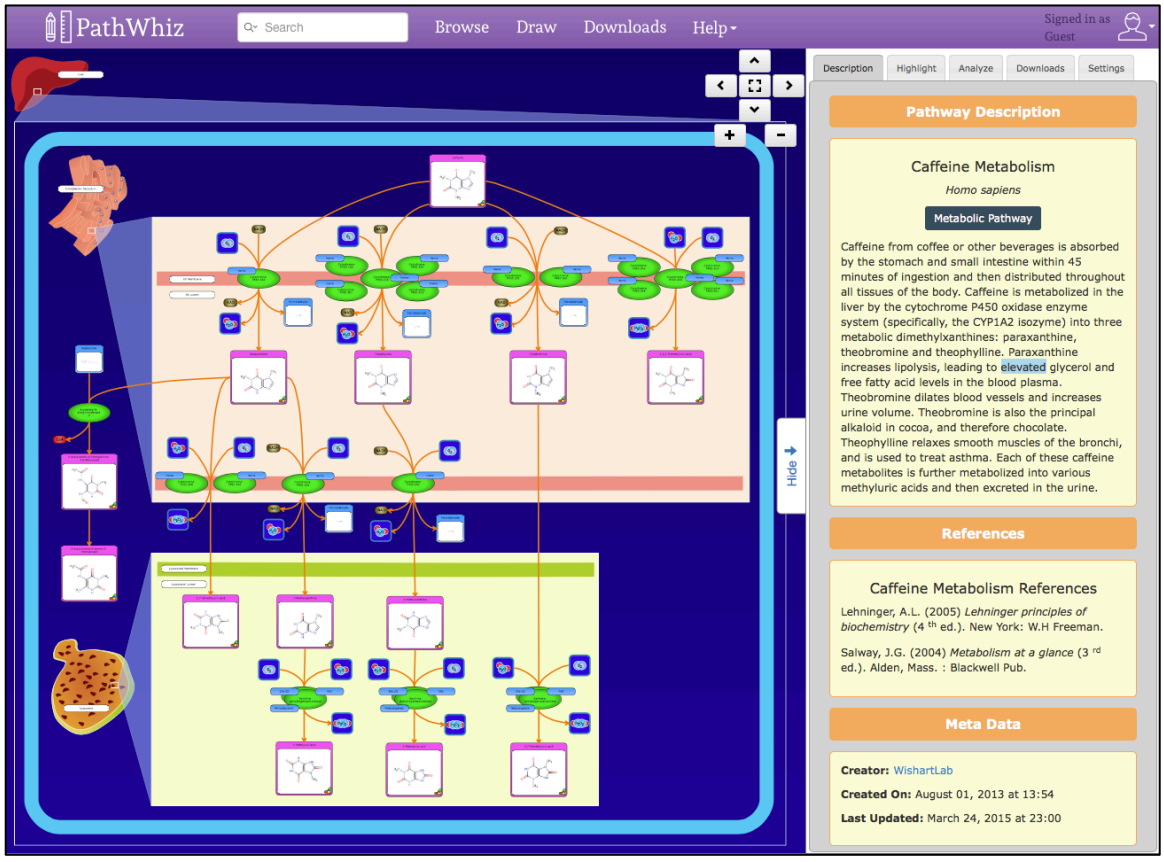
SBML: http://sbml.org

PWML: Documentation in progress

Pathways must be exported before they can be viewed in the pathway viewer. This process can take several minutes. Once complete, the time of export will be recorded and a link to your pathway (a purple button with its PathWhiz ID) will

appear under “Show In Viewer”. Click this button to view your pathway and download its associated files in the interactive PathWhiz Viewer, described below.

b. Using the Pathway Viewer



Using the Pathway Viewer, a pathway diagram can be zoomed in and out and navigated in a similar fashion to Google Maps, using standard navigation buttons in addition to conventional mouse-activated click, drag, and scroll operations.

If the appropriate metadata is available, pathway elements in the Pathway Viewer are hyperlinked and when clicked, will show a pop-up window that gives a synoptic view of the selected element, including its participating processes, biological state information, and external database links.

The side bar of the Pathway Viewer has a “Highlight” tab; selecting pathway components using the checkboxes on this tab will highlight them in red in the pathway diagram and move the viewport to the last selected item.

On the “Analysis” tab, relative concentration values can be added and mapped to a colour gradient that is applied to the annotated elements. On both the “Highlight” and “Analysis” tabs the pathway can be toggled between color and black and white modes for easier viewing.

The “Downloads” tab contains links the SVG, PNG, BioPAX, SBGN, SBML, and PWML files.

On the “Settings” tab the displayed background color can be toggled from blue to white. This does NOT affect the color in the downloadable images. On this tab complex membrane visualization can also be toggled. NOTE: Complex membranes are depicted as a detailed phospholipid bilayer, and may slow viewer performance due to the high number of components.