



1.0 Quick Start

A. Signing up, handling files and Menus

1. Registering, opening and handling files.

A. Create an account, or log in if you have not registered already, from any page of our website www.visinets.com. Registration is free and will also allow you to use Visinets public library of pathway models and tools.

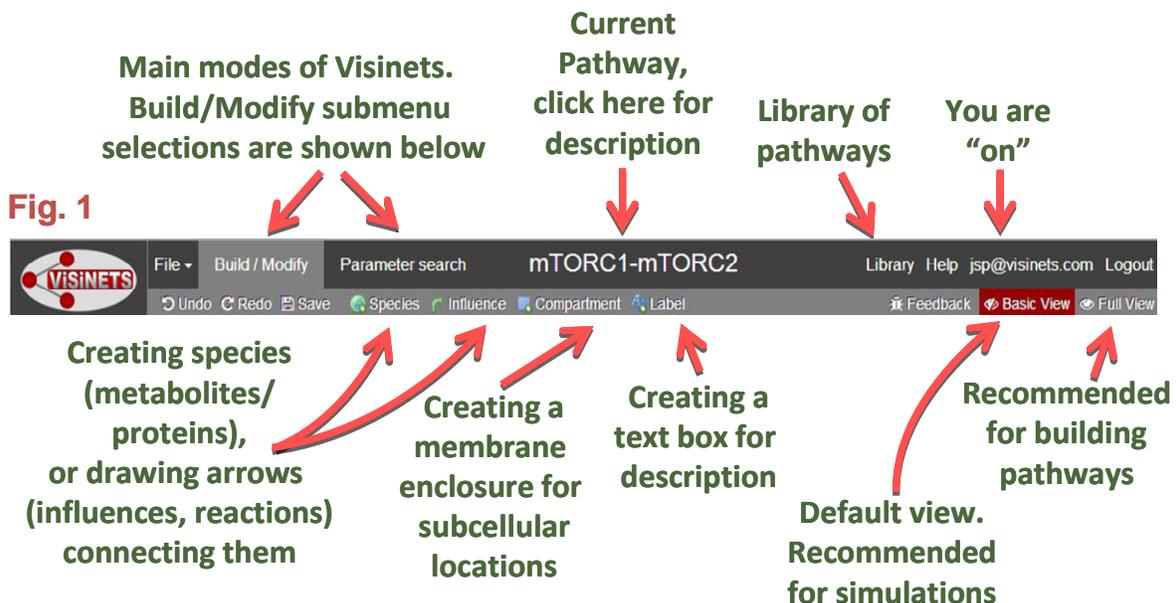
B. Open Visinets and choose an existing pathway from the Public library or click on “Create a new pathway” button. The software main window will appear.

C. Users can save public pathways under different name (save as) and use/modify them as their own. When open new or existing file the user have to remember to save it frequently on his/her own: the software doesn’t automatically save the modified file.

D. Public pathways have attached description and references that could be accessed by clicking on the pathway title (current pathway in **Fig. 1**) below, after specific pathway has been selected for viewing and use.

2. Bars and menus in a nutshell

A. Main Bar:





B. Species pop-up menu

Fig. 2. Click on any Species to bring this pop-up menu up. Species menu contains attributes related to each species (component/node). It lists Initial value (C_{ini}), maximal value (C_{max}), Alpha value, and all influences (including their mode of action and weights). Alpha parameter reflects the “responsiveness” of a species to influence. In general, larger alpha causes faster change of the concept (more in: **Simulation Engine**). Maximal C (C_{max}) value may be useful in larger networks where adherence to mass conservation of some selected species is critical.

Source	Action	Weight
SOS	inhibition	0.01
RG	activation	0.5
SOS	inhibition	0.4
RShG	activation	0.01
SOS	inhibition	0.4
ShGS	activation	0.2
Grb	inhibition	0.3
SOS	activation	0.7
GS	activation	0.7

C. Influence pop-up menu

Fig. 3. Click on any Influence (arrow) to bring this menu up. Reaction menu lists attributes related to each reaction: “weight” which reflects rate constants in chemical reactions, mode of action (activation or inhibition) and Group function. Group function allows two or more influences in a reaction module to change in unison. It also allows for chemical reactions to better follow mass action law.

RP + Shc → Rp-Shc

Weight: 0.9900

Action: activation

Group weights with

RP + Shc | RP Remove

RP + Shc | Shc Remove

Select a reaction Add

Construct Remove

3. Side bars: lists of Species, Reactions and Rules for Parameter Search Mode

On the left hand side of the working space there are two buttons representing pull out lists of all species and reactions (**Fig. 4**). Those lists are for the convenience of reviewing all reactions and comparing initial values, alpha values and weights among the number of species and reactions. These values could be changed by typing-in new numbers. In addition, they include the check box for selecting species for plotting.



Fig. 4

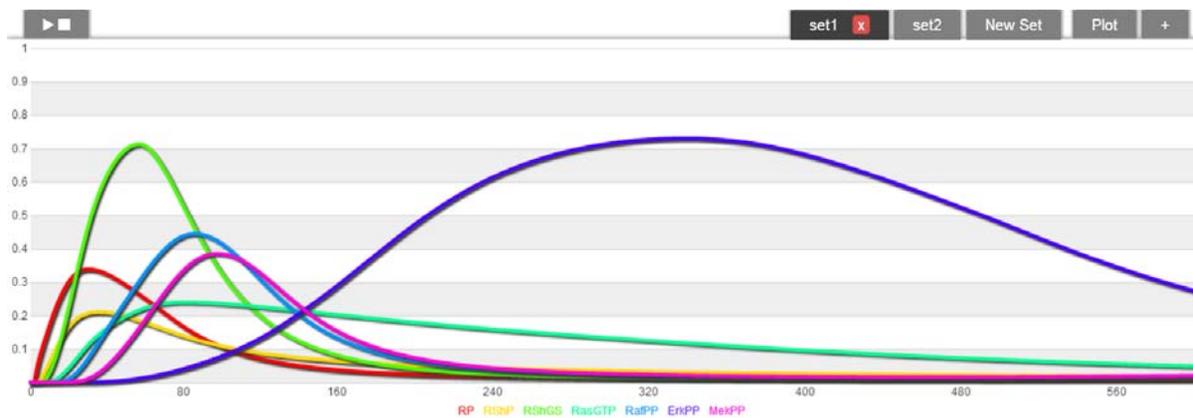
name	value	alpha	plot	
EGF	0.7	1.2	<input checked="" type="checkbox"/>	Species
GS	0.5	1.2	<input type="checkbox"/>	
R	0.7	1.2	<input checked="" type="checkbox"/>	Species
Rp-GS	0	1.2	<input type="checkbox"/>	Reactions
Rp-Shc	0	1.2	<input type="checkbox"/>	
Rp-pShc-GS	0	1.2	<input type="checkbox"/>	
Rp-pShc	0	1.2	<input type="checkbox"/>	
Rd	0	1.2	<input type="checkbox"/>	Criteria
RP	0	1.2	<input checked="" type="checkbox"/>	
pShc-GS	0	1.2	<input type="checkbox"/>	
Shc	0.5	1.2	<input checked="" type="checkbox"/>	
pShc	0	1.2	<input type="checkbox"/>	
RE	0	1.2	<input type="checkbox"/>	
Ri	0	1.2	<input type="checkbox"/>	
EGF*	0	1.2	<input checked="" type="checkbox"/>	

name	weight	action	
RE † RE	0.9	inhibition	Species
Rd † Rd	0.5	inhibition	
RP † RP	0.9	inhibition	Reactions
Ri † Ri	0.1	inhibition	
pShc → Shc	0.3	activation	
Ri → Rd	0.9	activation	
RP → Ri	0.9	activation	
Rd → RP	0.5	activation	Criteria
Rd † Rd	0.1	inhibition	
RE → Rd	0.7	activation	
Rd → RE	0.5	activation	
EGF + R → RE	0.5	activation	
RE † RE	0.05	inhibition	
EGF + R † EGF	0.5	inhibition	

4. Plot and Simulation functions

At the bottom of Visinets workspace area there two buttons: “Plot” (right hand side) for showing the activity/concentration vs “time” plot for selected species (selected as described above), and Play/Pause button (left hand side), to initiate/pause/stop the simulation. If the graph contains the large number of lines, the user can place the pointer over a selected species to “highlight” its activity plot in the plot area. If there is more than 20 species within the pathway the plot will show only first 20 graphs and user can additionally select/deselect species of his/her choice. The activity plot for specific species could be also visually singled out by clicking on the name below the plot. To initiate signal propagation throughout the network (start simulation) all the user needs to do is to click the Play button (▶) and vertical progress bar will show up for illustration of the progress. The user can quickly advance this bar by clicking anywhere in the plot

Fig. 5





area (**Fig. 5**). The plus sign in the upper right corner of the plot panel may be used to combine two or more plots of individual species as a “synthetic” single plot of them.

In addition to plot function, user can visually determine each node activity during simulation by monitoring their transparency status. Nodes with high concentration/activity will display less transparency (darker color) and the user may visually identify spots of high activity/concentration. User is encouraged to use one of our more complex network to run simulation and experience the dynamic way of pathway visualization in Visinets.

Simulation time. Simulation time setting is equivalent to the number of iterations and is accessible from the File > Options dialog box (**Fig. 6**). User can adjust the simulation time by typing-in the new number. User can also speed-up the simulation by pressing +/- buttons on the keyboard. In most cases the number of iterations may approximate the “time” (arbitrary units) of simulation with one iteration representing roughly one second in most cases.

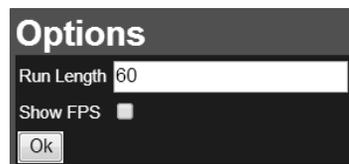


Fig. 6

Multiple parameter sets. User can save multiple parameter sets for any network (**Fig 5**). This will allow for quick comparison of different initial conditions and weights setting. Each new parameter set is derived from the current (in play) and is placed as the last one. Sets not needed anymore may be deleted using the small red button withn each parameter name.

5. Graphical style of species and dynamic graphical representation of Influences and Species during simulation.

Style menu. From the Species pop-up menu (**Fig. 2**) click “Style” button to activate the “graphics panel” and chose the graphical appearance of the selected species (**Fig. 7**).

Within this menu user can select colors for species background (Fill Color), font or for species line (Stroke Color) and can apply shape and shading style from the pull down menus. To select the color just click anywhere within the color scheme panel. To automate the selection of style, and make it uniform to any area or branch of the pathway, user can also set certain style as default style (Set as Style) and apply it to any other species (Apply Style). Those functions are also available from the main menu when in Build/Modify mode, so the user doesn't have to go to a Species pop-up box:



just select species (click on), and the “Apply Style” “Set as Style” will show up above the Visinets workspace.

Fig. 7



Dynamic graphical representation of Influences and Species during simulation. During simulations both influences and species are represented differently. In their basic depiction when building a model, arrow (influences) thickness represents the relative value of weights, i.e. arrows are thin where weights have small values and their thickness increases proportionally with increasing weights values. Thus, the user can visually assess all relative weights (reaction rates) assigned to influences within the network. In this basic mode the graphical representation of species is shown with the colors (Style) selected by the user and with no transparency applied. During simulation both arrow (influence) thickness and species transparency changes according to the strength of the signal transduced: arrows are thicker where the signal is stronger and species are more transparent (color less intense) where the transduced signal is weaker. At a very low activity arrows may disappear completely. This method of graphical depiction allows for better visual determination of where the signal transduction is the weakest, or the strongest, and allows the user to easily identify potential causes for “roadblocks” or “overstimulation” within the biological network.