Signaling Pathway Visualization with Flash and BioPAX 3.0 Pathway Exchange Format

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Desired Features for a Powerful Pathways Visualization Tool

A pathway consists of a cascade of biochemical reactions which include:

(1) Production and release of a signaling molecules,
(2) Diffusion of signaling molecules,
(3) Recognition of extracellular signals by receptor proteins,
(4) Change in the confirmation of the receptor protein yields a cascade,
(5) Desensitization of the signal to ceases additional cellular response.

To properly convey these steps in a clear and concise way an innovative visualization system should implement the following features:

Node Manipulation

Nodes should be motile. Hovering over specific nodes should highlight related nodes, such as first neighbors, and anchoring of nodes should keep them static.

Search Function

When dealing with the visualization of large networks, a search function is necessary.

Compatibility

Input compatibility maximization across databases is important for data integration. The viewer should accept input files in SBML, BioPAX, SIF, PSI-MI, and other related formats.

Layout Schemes

The pathway should have the capability of switching between layouts, such as hierarchal, force-directed, spring-embedded, organic, circular, and other such layouts.

Fig. 1 An abstracted interaction. *A* represents the source molecule which interacts by *i* with the target molecule, *B*.

Acetylation, Assembly, Binding, Dissociation, Condensation, Conjugation, Cleavage, Degradation, Dephosphorylation, Exchange, Expression, Farnesylation, Glycosylation, Hydrolysis, Hydroxylation, Indirect, Inhibition, Methylation, Oligomerization, Phosphorylation, Processing, Transactivation, Translocation, Transcription, Translation, Transregulation, Ubiquitination

Fig. 2 Types of Interactions

Ambiguous Data Handling

When pathways steps are unknown, the viewer should not only translate this appropriately, but also emphasize the incompleteness of the pathway data, such that areas for further experimentation are immediately recognized.

Interaction Representation

Accommodation for varying strengths and types of interactions is necessary (Fig. 2).

Component Localization

Designation of the subcellular compartment of individual pathway components is integral to data comprehension.

Nested subgraphs

Data that is not immediately necessary to the comprehension of the pathway should be "nested" (Fig. 3). Families, as well as complex relationships and interactions, should be folded into subgraphs, so that detailed information is accessible by expansion, but does not obscure the main cascade.

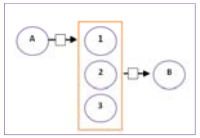

Fig. 3 A family is represented in a nested subgraph.

Abstract

Cell signaling pathways transduce a stimulus from the extracellular environment through cascades of biochemical reactions to induce biological responses. Details about components and interactions making up pathways are emerging at a fast pace, and therefore, systematic approaches to representing such information are required. Dynamic and automated presentation of signaling pathways on the web is of necessity to the scientific community. While there are several web-based pathways viewers, there is still room for improvement. To this end, we have developed a Flash-based cell signaling pathway viewer. The viewer accepts XML input files to display pathways on any web-page. To demonstrate the usability of this viewer we have implemented it for the representation of the "Neuro2A Differentiation by G alpha i/o Pathway" [Ma'ayan et al., Sci. Signal 2:54 (2009)]. Furthermore, we converted this pathway into the BioPAX (Biological Pathway Exchange) level 3.0, a newly developed exchange format created by the BioPAX community.

Conversion of the Neuro2A Differentiation $G\alpha_{i/o}$ Pathway To BioPAX 3.0

Biological pathway data is stored in different databases where each database uses different storage schemas and accession codes, rendering data integration a herculean task. The BioPAX data format was created for the purpose of standardization such data. Its newest release, BioPAX 3.0, now has extensive support for signaling pathways representation.

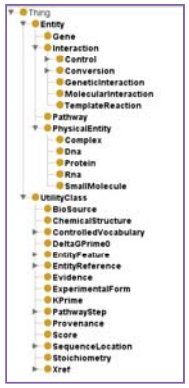

Fig. 5 The BioPAX 3 Class Structure

The BioPAX ontology is written in OWL, the Web Ontology Language. It is a system of terms which define biological components and their relationships (Fig. 4). Mapping pathways to this format can be done through the creation of instances for the distinct classes (Fig. 5).

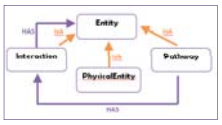

Fig. 4 The BioPAX ontology is composed of a root level *Entity* class, and child classes.

For example, a pathway instance would contain various pathway steps, which would each contain one or more interactions taking place between physical entity participants, such as a complex or a protein, each of which is an entity.

Perhaps the most notable feature of the BioPAX ontology is the Xref subclasses, which allow for cross-referencing of publications and entities in external databases such as the PubMed, and Gene Ontology databases.

Fig. 6 Part of the Neuro2A Differentiation by G alpha i/o Pathway transcribed to the BioPAX 3.0 format.

GraphView: Flash/AS3.0 Web-Based Pathway Visualization

GraphView allows for the dynamic representation of pathway data on the web, addressing issues with other more static online viewers. Written in ActionScript 3.0, the viewer is delivered as a Flash .swf output file that reads in an XML file (Fig. 4). Layouts can be predefined through pixel mapping, or can be achieved using a variety of layout algorithms. Node colors and shapes designate component localization and entity information. Edges can be directed or undirected and defined as activatory, inhibitory, or neutral. Most importantly, molecule and interaction details can be accessed by simply hovering over nodes and edges (Fig. 8).

Fig. 7 GraphView accepts XML input files

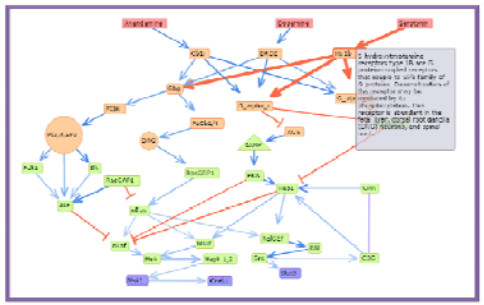

Fig. 8 Neuro2A Differentiation by G alpha i/o Pathway Visualized using GraphView.

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Acknowledgments

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