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ANDVisio: A new tool for graphic visualization and analysis of literature mined associative gene networks in the ANDSystem

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Abstract. The ANDVisio tool is designed to reconstruct and analyze associative gene networks in the earlier developed Associative Network Discovery System (ANDSystem) software package. The ANDSystem incorporates utilities for automated extraction of knowledge from Pubmed published scientific texts, analysis of factographic databases, also the ANDCell database containing information on molecular-genetic events retrieved from texts and databases. ANDVisio is a new user's interface to the ANDCell database stored in a remote server. ANDVisio provides graphic visualization, editing, search, also saving of associative gene networks in different formats resulting from user's request. The associative gene networks describe semantic relationships between molecular-genetic objects (proteins, genes, metabolites and others), biological processes, and diseases. ANDVisio is provided with various tools to support filtering by object types, relationships between objects and information sources; graph layout; search of the shortest pathway; cycles in graphs.

Keywords: ANDVisio, ANDSystem, ANDCell, text-mining, associative gene networks, data integration

1. Introduction

The number of publications in the areas of biology, medicine, and biotechnology increases with an alarming rate that makes imperative computer-based analysis. To date, over 20 million abstracts highly relevant to biology and medicine are stored in the PubMed database and the number keeps increasing.

To address the confounding problem of extraction of information on molecular-genetic objects from texts worldwide, approaches based on algorithms, from the simplest, such as search for co-occurrence of the biological object names in texts, to complex integrating linguistic-semantic analysis, and machine learning have been suggested and recognized.

The PubGene is an example of a co-occurrence based system for reconstruction of networks for relationships between proteins, genes, biological processes [9]. Cooper et al. [5] have developed a system for prediction of protein-protein interactions. For this purpose, they utilized a text analyzer that relied on the combination of linguistic and statistical rules. GeneScene [15] and MedScan [17] implement algorithms derived from linguistic insights: full-sentence parsing, syntactic and semantic analysis. This strategy was applied by Timur Fayruzov et al. [7] to resolve the issue of extraction of information on relationships between proteins.

There are thousands of factographic medicobiologic databases, storing compiled information on biological objects and their interactions. These databases are extremely bulky, the NCBI Gene database [16] alone contains over 7 million entries and this number keeps growing. Thousands of facts regarding biomedically and biotechnologically significant gene networks,

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metabolic and signaling pathways are deposited in the KEGG [10], EcoCyc [11], GeneNet [2] and other databases.

We benefited from previous work that made available the ANDSystem [6] designed to automatically extract information on molecular-genetic events in the cell from Pubmed texts and factographic databases. This information is continually accumulating in the knowledge base ANDCell, which is part of ANDSystem.

There are various program products to resolve the problem of visualization and analysis of biological networks. Cytoscape [20], Ondex [14], VisAnt [21], Vanted [3] are notable products. Most programs are implemented in Java. This imposes certain limitations on the size of the analyzed networks. Their other disadvantage is the lack of specialized tools for analysis of bipartite graphs.

The ANDVisio tool presented here is a new module of the ANDSystem. ANDVisio provides a graphical interface for easy access to ANDCell, and allows to reconstruct and analyze the associative gene networks comprising relationships between molecular-genetic objects (genes, proteins, metabolites), biological processes, and diseases.

The ANDvisio program is written in Pascal. The program does not require a large amount of RAM. The program allows you to work with large bipartite graphs with directed and undirected edges. A bipartite representation allows viewing of a network in which more than 2 objects are involved in one interaction. The program implements algorithms for search of the shortest pathways and cycles with network specific features taken into account.

2. Main modules of the ANDSystem

The ANDSystem incorporates tools for automated extraction of knowledge on molecular-genetic events from Pubmed texts and factographic databases that are stored in the ANDCell knowledge base [6]. The following object types are considered: proteins, genes, metabolites, microRNA, diseases, biological processes and cellular components.

The following relationships types between objects are considered.

Association type is used to define the relationships between genes and diseases. The Association is also used as a type of relationships between other objects, if a particular type of relationship has been omitted in the text.

Interactions, formation of molecular complexes (protein-protein, protein-metabolite, protein-cellular component and others).

Co-expression, simultaneous expression of several genes due to common regulator mechanisms activating gene expression under the effect of changing intracellular conditions.

Treatment, use of a molecular agent for treatment of known disease. Proteins and metabolites (drugs) can be involved in interactions of this type.

Catalytic reactions are those involving metabolites as substrates and products, also a protein as an enzyme catalyzing this reaction.

Conversion of molecules. This type is assigned a reaction in the case when a catalyst enzyme is not indicated, also when the reaction proceeds without a catalyst; metabolites are involved in the conversion. Interaction of the initial and the final products of a metabolic pathway consisting of a number of intermediate steps are referred to conversion.

Degradation of a protein (substrate) by another protein (proteolytic enzyme).

Regulation of gene expression by transcription factors, also by their ligands. This category includes both direct regulatory events, i.e. regulation of gene expression by a transcription factor that physically interacts with gene promoter, and indirect regulatory effect of their ligands, also proteins along the regulatory pathway, including receptor and proteins of the signaling pathway.

Regulation of activity or ***function*** of protein, gene cellular component or molecular-genetic process. Protein, metabolite, cellular component can serve as regulators.

Regulation of transport proteins or metabolites between cell compartments as well as the secretion of these molecules from the cell. Proteins, low-molecular substances or cellular components can serve as regulators of transport.

Regulation of stability or ***degradation*** of molecular objects. Molecular structure of protein, mRNA transcribed from genes, cellular components, and molecular-biological processes can be objects of this regulation.

Regulation of molecular-biological processes and diseases. Proteins, metabolites, cellular components, and molecular-biological processes can serve as regulators like in the above cases.

Furthermore, regulatory events are subdivided according to the effect one object has on another, i.e., activating or inhibiting of the process.

Algorithms for extraction of knowledge from text implemented in ANDSystem use dictionaries, syntactic and semantic rules (templates) [6]. Thesauri for object names were compiled using available databases. A dictionary of proteins was compiled from the Swissprot database; genes from NCBI Gene; metabolites from ChEBI; diseases from PharmGKB; microRNA from MirBase; biological processes and cellular components from Gene Ontology. About 4000 templates for extraction of knowledge on object relationships from texts were used. The ANDCell knowledge base now stores more than 5 million facts concerning relationships between molecular-genetic objects, diseases and biological processes.

The new ANDVisio module is a client's application with graphical user's interface implementing interaction with the ANDCell database. Application allows the user to perform queries to ANDCell and obtain interactive graphical networks. Networks can be analyzed by built-in tools. Networks can also be saved as a file in different formats.

3. The ANDVisio interface

The main window has the main menu, two panels with buttons for quick access to common functions, an area for display of networks as a list of all participants of the network with their properties, an area for graphic visualization of the network (Fig. 1).

The "*File*" menu contains the "*Connect*" item. The "*Connect*" item allows to recover the connection with ANDCell. In the event that it cannot be recovered, a warning message appears and all functions for further work with ANDCell are blocked.

Making queries to the associative gene networks "*Query wizard*" item opens a form for setting query parameters to ANDCell (Fig. 2). Form is comprised

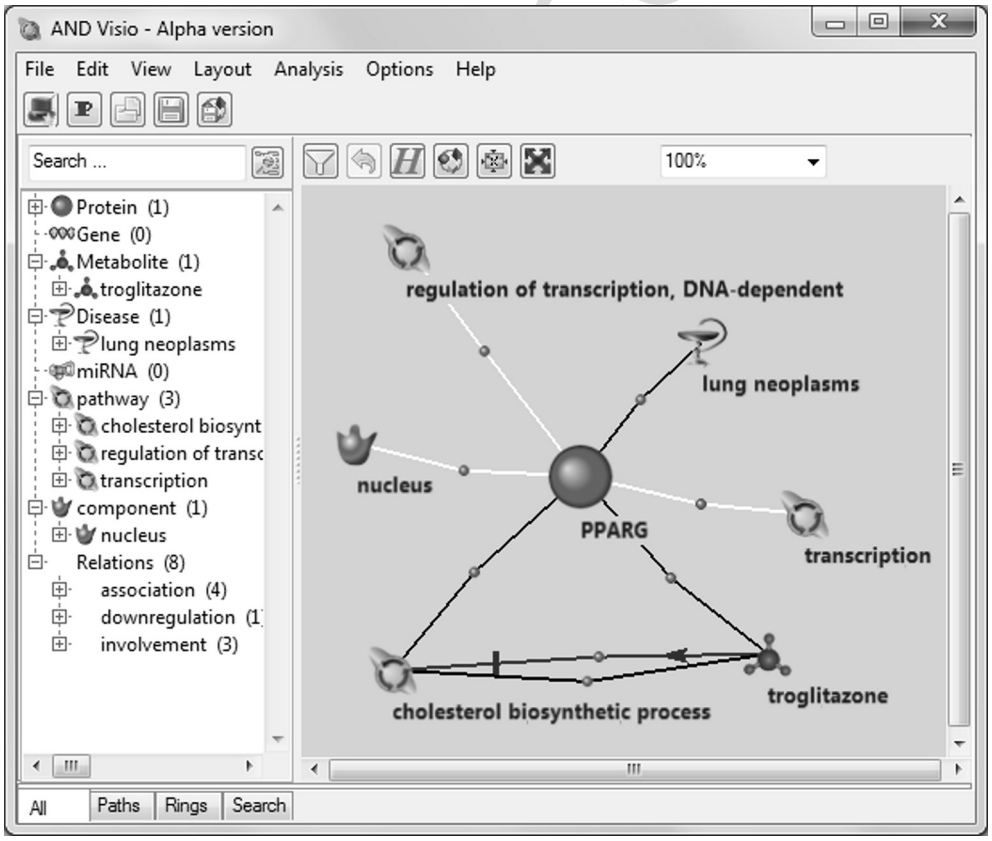

Fig. 1. ANDVisio main window. Network of the first level for protein PPARG (*Cricetulus griseus*) is given. The main window consist of three parts: main menu panel with buttons for quick access to common functions, an area for display of networks as a list of all participants of the network with their properties, an area for graphic visualization of the network.

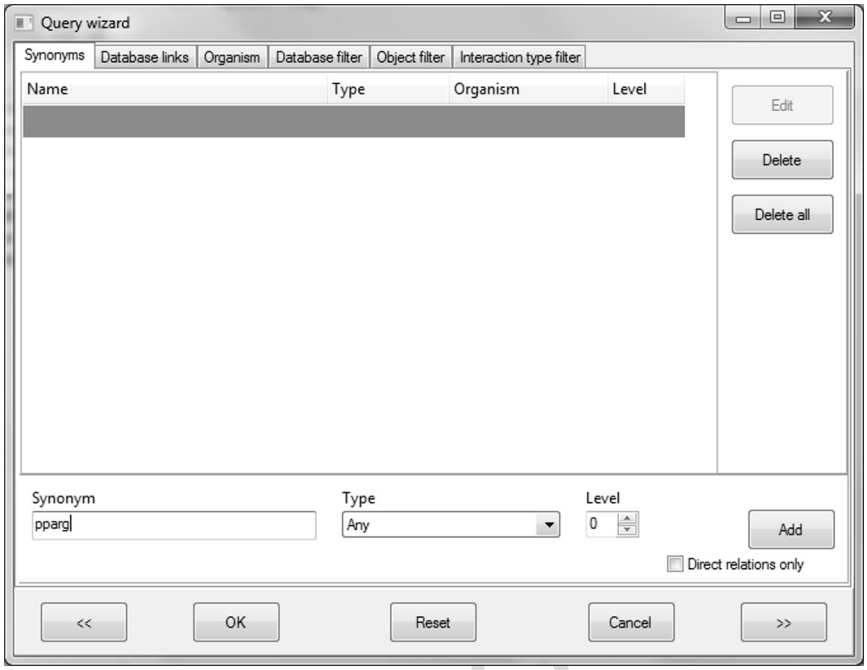

Fig. 2. "Query wizard" window. The "Synonym" tab. The name "pparg" is introduced into the "*Synonym*" field.

of a number of tabs referred to two groups. The first group contains the "*Synonyms*" and the "*Database links*" tabs. These tabs are responsible for input of objects of interest. The other tabs are of the second group and are responsible for setting of filters for the resulting network.

On the "*Synonyms*" tab, the user can input the pattern of object name and choose object type (Fig. 2). Clicking the "*Add*" button will search objects in the database that match with the name indicated by the pattern. If more than one object search conditions is found, the form for specifying objects of interest appears (Fig. 3). The form is divided into 2 parts, the accessible objects satisfying the above criterion appear on the left, the list of chosen objects appears on the right panel. For convenience of user's choice of objects of interest, all names and organism references are given for each object. There are two ways to move objects from one panel to another: either by the Drag&Drop mechanism or by clicking buttons in the middle of the form. The button functions are ">>>" and "<<<", they make possible movement of all objects from one panel to another, but ">" and "<" move all the selected objects. After confirmation of the list, the chosen objects are included in the list of "*Query wizard*".

On the "*Database links*" tab, the user can indicate objects of interest using their identifiers in external databases (Fig. 4). Identifiers can be added to the list either one at a time or several simultaneously. To add one identifier, it should be input into the "*Database ID*" field. To input several identifiers at a time, they should be saved as text file (each identifier should be written in a separate line), then the created file should be selected in the "*Filename*" field. The next step is indication of the database name whose identifiers are given. If the database name is unknown, one can try to find these identifiers across all available databases, but a lot of database identifiers intersect and correspond to completely different objects. After clicking the "*Add"* button, identifiers are added to the list of objects.

Network level means here the maximum length of the shortest pathway from the initial vertex to all other vertices. Network level can be added before the addition of new objects to the list and after it. Network level can be given individually for each object in the list.

The "*Direct relations only*" item can be checked when directly linked objects are required and the objects at level 1 do not have to be interrelated.

The "*Organism*" tab allows the user to submit the list of organisms of interest (Fig. 5). At the bottom of the "*Organism*" tab, the pattern of the organism name is entered; this is followed by clicking the "*Add*" button. If more than 1 organism meeting requirements is found, a form to specify organisms of interest will open.

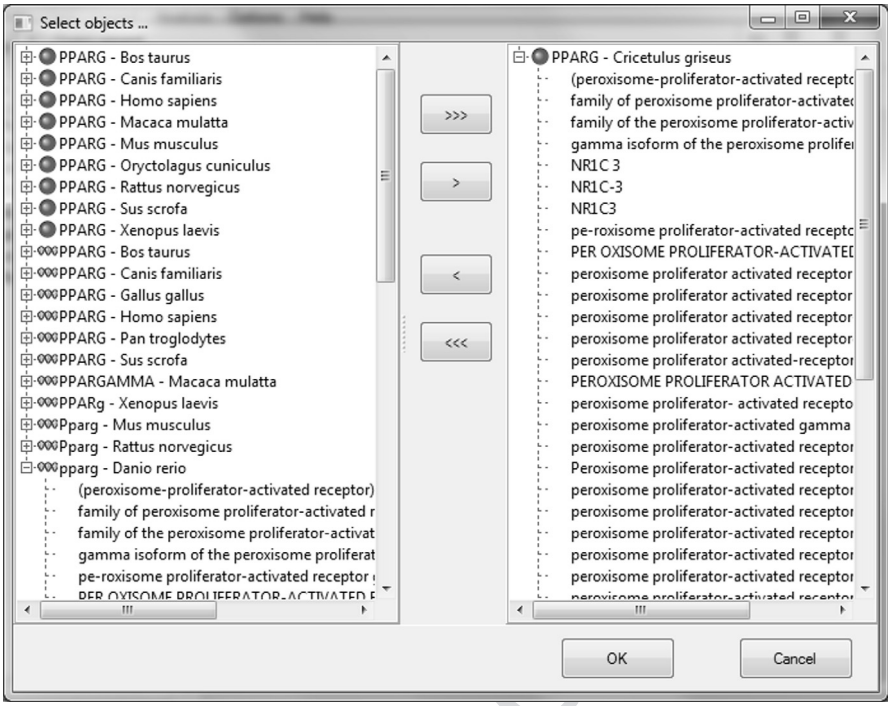

Fig. 3. Object selector window. The list of found objects is on the left. The list of chosen objects is on the right. The list of synonyms and corresponding organism name can be visualized for each object.

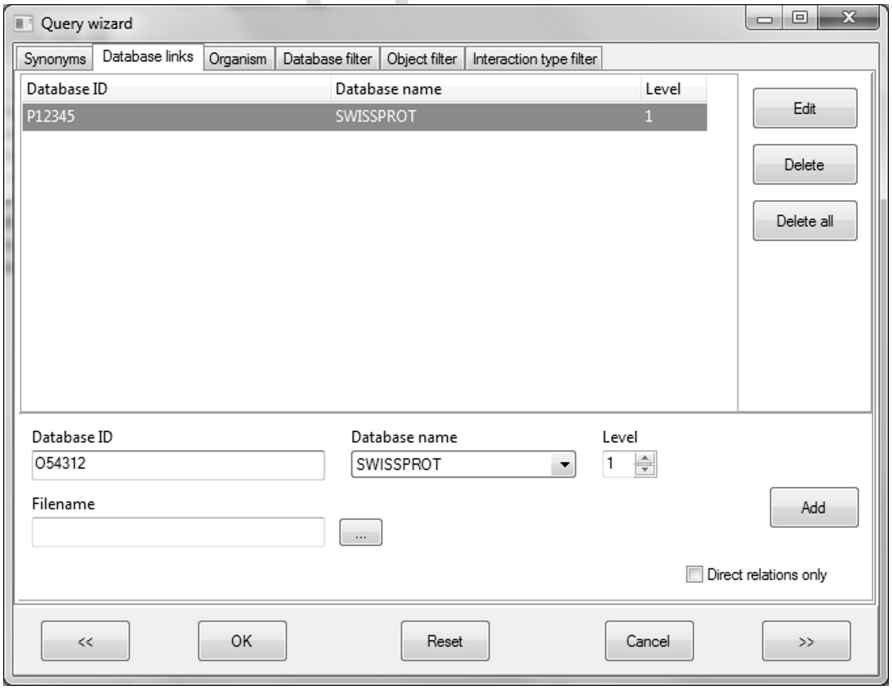

Fig. 4. "Query wizard" window. The "Database links" tab. The identifier of protein "O54312" from the Swissprot database is introduced into the "*DatabaseID*" field. Pressing the "*Add*" button will add it to the protein list with the "P12345" identifier.

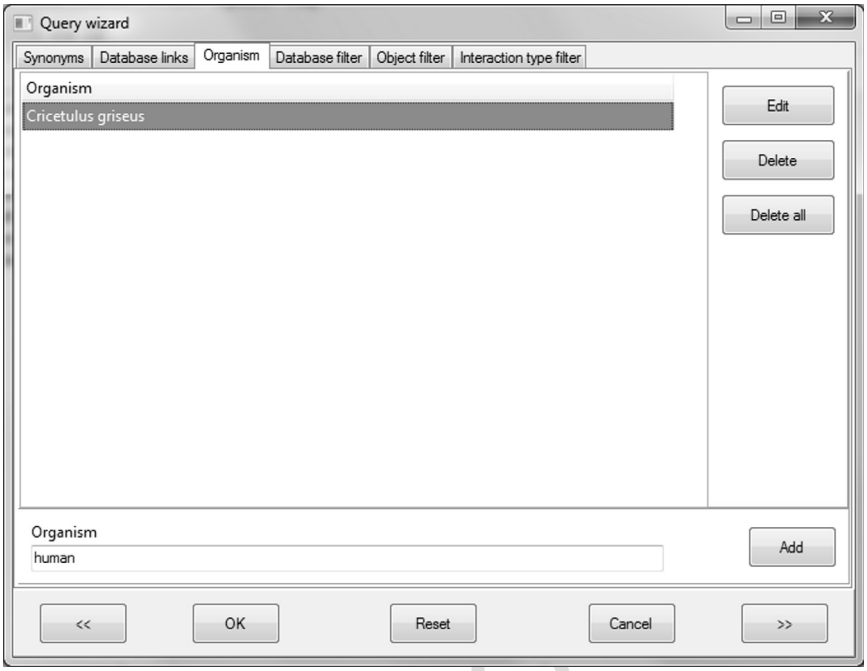

Fig. 5. "Query wizard" window. The "Organism" tab. "Human" is introduced into the "*Organism*" field. Pressing the "*Add*" button will add it to the list of "Cricetulus griseus" organism.

The "*Database filter*" tab allows to choose the databases from which relationships between objects will be selected (Fig. 6).

The "*Object filter*" tab indicates the object types necessarily presented in the reconstructed network (Fig. 7).

The "*Interaction type filter*" tab indicates the relationships necessarily presented in the reconstructed network (Fig. 8).

After filling in the "*Query wizard*" form, the "*OK*" button must be clicked; it submits the query to ANDCell. The result of the performed query is shown at the Fig. 1.

All the objects grouped by types of the associative network will appear as a tree in the left window. A list of synonyms of its names and organism is provided for each object. Double clicking the object selects it and arranges the network in a way to place the object in the center of the window. Double clicking the object in the network performs a search of the list in the left panel grouped according to types.

Relationships in the left panel are grouped according to types. All the participants and their properties are given for each relationship. Clicking mouse left button on the object selects it by highlighting in red.

Unchecking in the "*View->Show connections*" menu item will disable highlighting.

The "*View->Show names*" menu item controls display of object names.

The fit of the network to the window is achieved by clicking the "*View->Fit in screen*" menu item.

The right click of mouse button opens the context menu. To obtain more detailed information on the properties of this object, the "*Property*" item can be chosen from the context menu.

Synonyms of the object are given in the top panel of the window of the object properties, the references to its identifiers in the different databases are given in the bottom panel (Fig. 9). Clicking references provides access through the web-browser to the object's entry in the chosen database.

In the top field of the window, interaction properties, type of the interaction and its participants (name, object types, role of objects in the interaction) are indicated (Fig. 10).

In the bottom field, the interactive references to the database, the source of information on the interaction are indicated.

If the information on the interaction is retrieved from Pubmed abstracts using text-mining, the sentence from

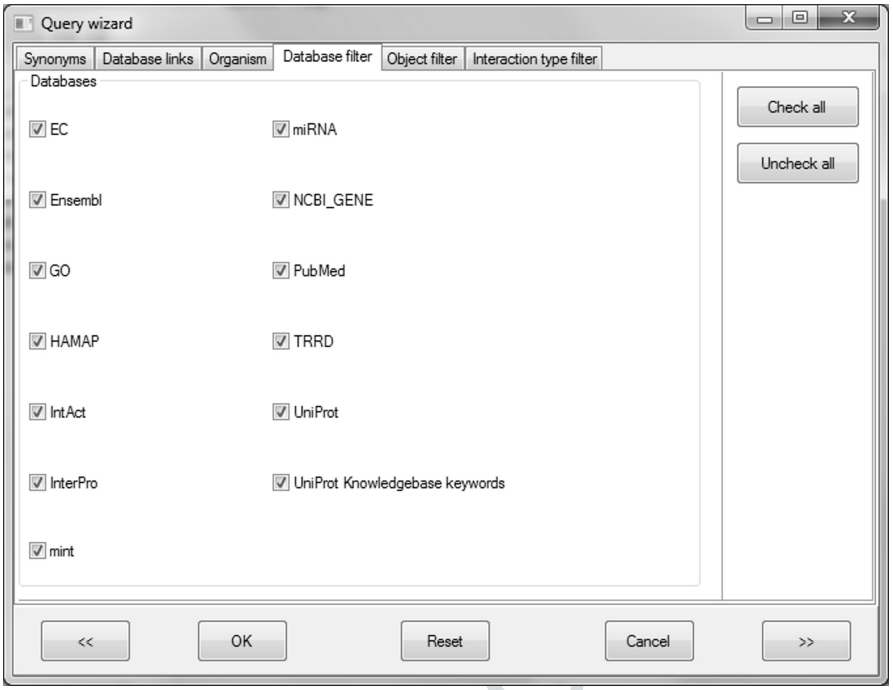

Fig. 6. "Query wizard" window. The "Database filter" tab. The user is suggested to choose the databases in which relationships will be searched.

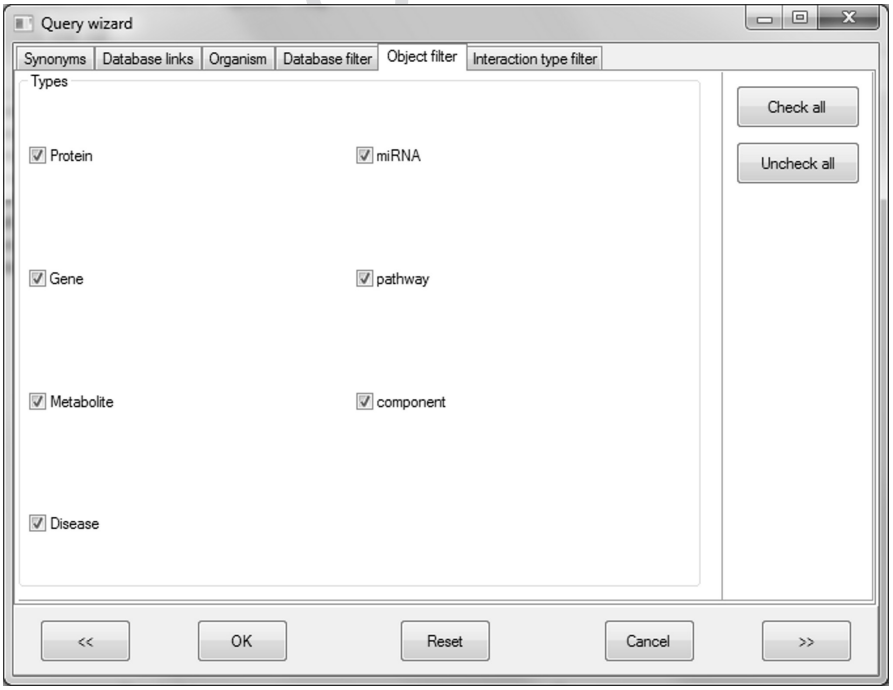

Fig. 7. "Query wizard" window. The "Object filter" tab. The user is suggested to choose the object type which will be represented in the built network.

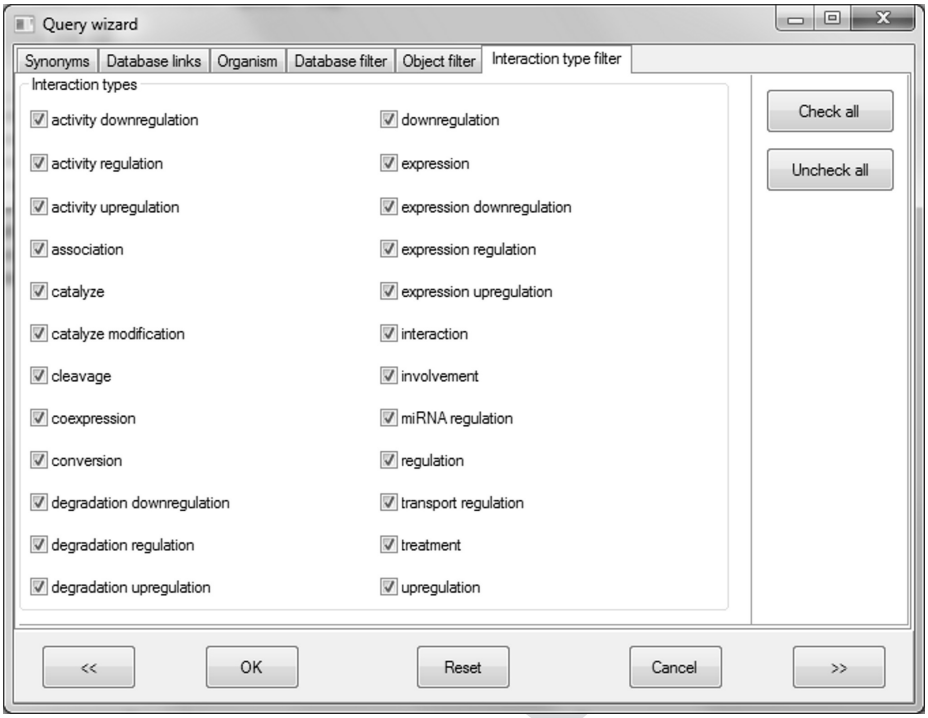

Fig. 8. "Query wizard" window. The "Interaction type filter" tab. Only the interaction types that user indicates in this tab will be searched in the ANDCell database.

which information on interaction, all the references containing it will appear.

3.1. Graph layout

A graph layout is performed automatically on a plane for the easiest visualization of networks. To re-layout after moving the objects, choose the "*Layout->Relayout graph*" menu item.

Layouts of two types are available. Fast layout "*Layout->Select layout type->Fast layout*" is designed to draft huge networks. The designation of slow layouts "*Layout->Select layout type->Slow layout*" is a more thorough layout of small networks.

The layout algorithms are based on force-directed layout algorithm [8]. In the layout algorithms, a graph is considered as a set of physically interacting objects. Graph modification precedes in the "Fast layout". All vertices with "Relationship" type are removed. As a result, the graph becomes monopartite. Virtually all of the vertices are connected to each other by springs with different stiffness. The algorithm searches the state of minimal system energy. At the end of algorithm work, the removed vertices are restored and placed in the center between interconnected vertices (the "*Straight relations"* procedure is performed). In the "Slow layout" algorithm, all the vertices of the graph are considered as charged particles with different charges. The algorithm searches the state of minimum energy system. This version of algorithm uses information on all vertices thereby allowing to improve quality of layout. However, it requires greater computational costs.

To change the layout of a network fragment, select the objects within it, then click the "*Layout->Layout selected*" menu item. Clicking the "*Layout->Straight relations*" menu item will rearrange the interactions without changing the position of the objects. As a result, the interactions will be placed between the involved objects.

3.2. Search of objects in a network

To find an object in a network by its synonym, submit it to the "*Search*" field (Fig. 1). The result is brought up as a list on the "*Search*" tab in the left

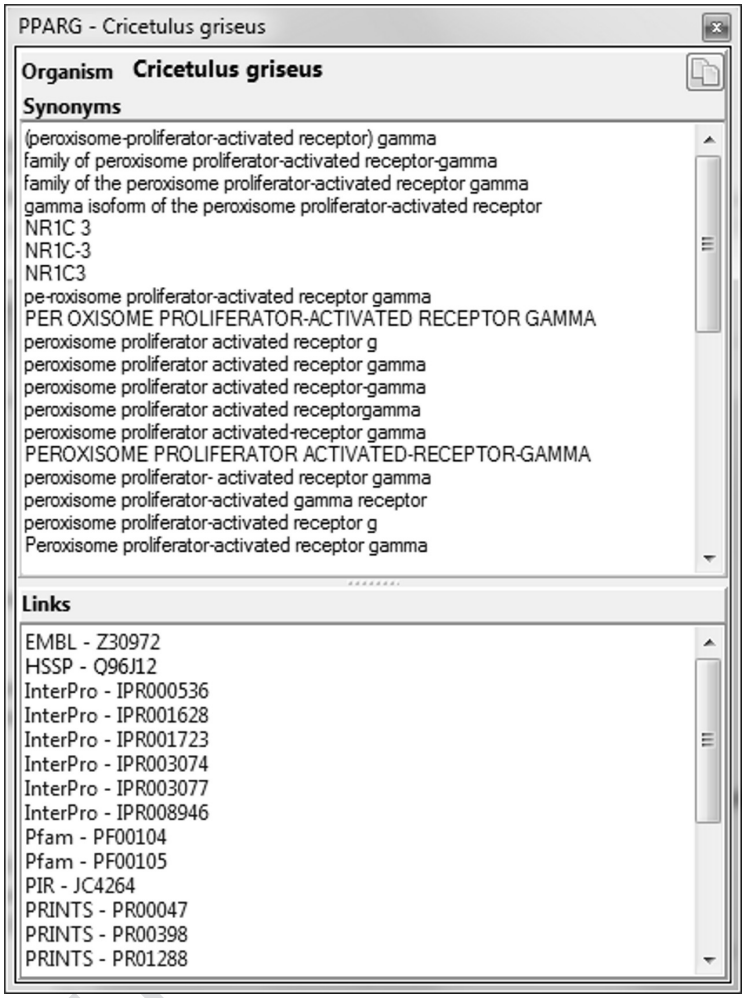

Fig. 9. Object property form. Information on organism, list of synonyms and list of object identifiers are given.

window. To return to the complete list of all participants of the network with their properties, click the "*All graph*" tab in the left window. It is admissible to enter name patterns into the search field using substitution characters * (any number of any characters) or ? (any character).

3.3. Network editing

To remove an object (a group of objects), either select it and choose the "*Edit->Hide selected*" menu item or press *Del*.

To use a filter in a reconstructed network, choose the "*Edit->Filter*" menu item. Choose filter properties as described above for "*Query wizard*".

To add an object to the reconstructed network, choose the "*Edit->Add objects*" menu item. Choose the objects and indicate filter properties, as described above for "*Query wizard*".

Check the "*Don't connect with existed objects*" item to make redundant mention of relationships between the added objects and those present earlier in the network.

To expand the network by adding new objects related to one or more objects from the reconstructed network, select these objects and choose the "*Expand*" context menu item. Indicate filter properties, as described above for "*Query wizard*". Check the "*Don't connect with existed objects*" item, so as not to show the relationships between the objects added to the network and those that have been submitted to it.

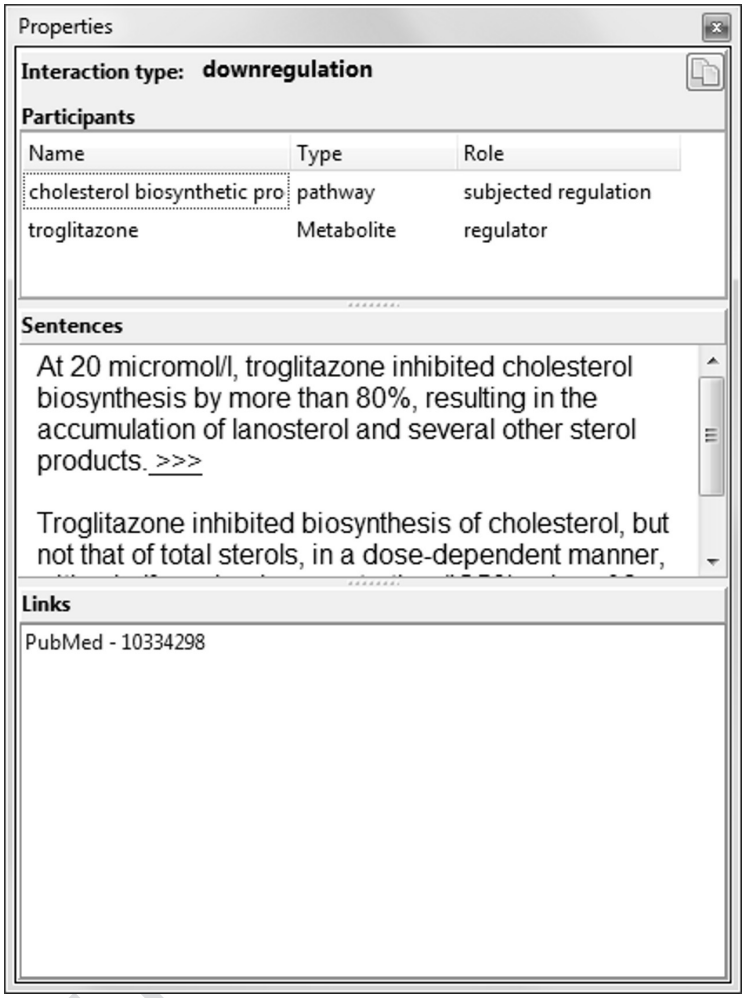

Fig. 10. Interaction property form. Information on interaction type, list of participants, proposals with indication of the relationship and identifiers of databases in which this relation is described are given.

3.4. Analysis of associative networks

ANDVisio allows to search for close cycles and the shortest pathways between two objects in an associative network. In the search of the shortest pathway, select two objects (select one object and holding down Shift, select the other). Choose the "*Analysis->Find the shortest pathways*" menu item. The list of the found pathways will appear on the "*Pathways*" tab in the left panel (Fig. 11). To view the participants of the pathway, click "+" next to the pathway name. To highlight in color or bold the pathway, click mouse right button on pathway name and choose the "*Highlight*" item from the context menu. Choose line type and color for highlighting pathway. To use this option, it is advised to disable highlighting of the selected object by unchecking the "*View->Show connections*" menu item. To search for minimum cycles comprising an object, select it and choose the "*Analysis->Find* cycles" menu item. The list of the found cycles will appear on the "*Cycles*" tab in the left panel. To view the participants of the cycle, click "+" next to the cycle name. The cycle can be highlighted in the same way as the pathway. A search of a set of fundamental cycles is feasible. The "*Analysis->Find fundamental cycles*" menu item serves for this purpose. A list of cycles will appear on the "*Cycles*" tab on the left panel. The cycles can be highlighted in the same way as the pathway.

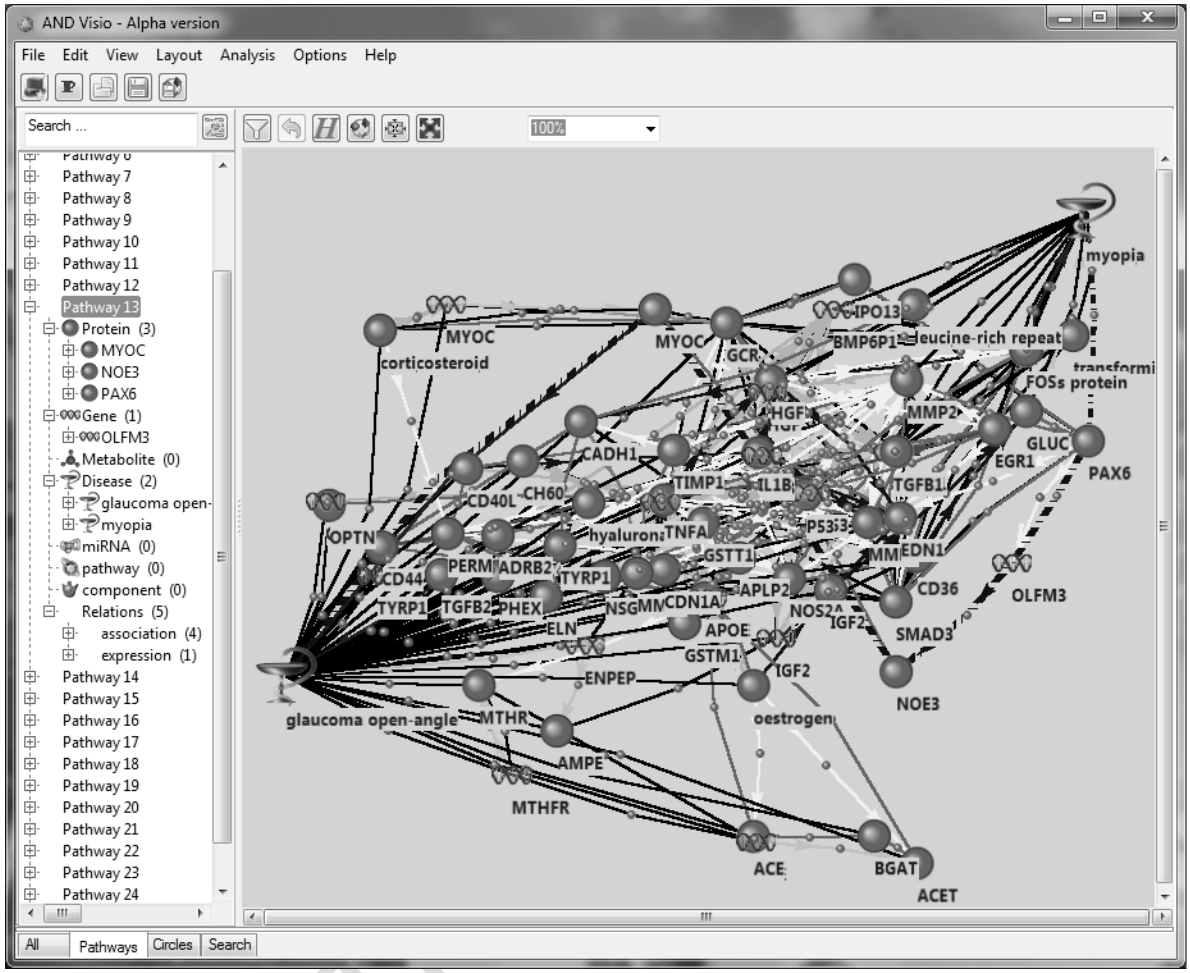

Fig. 11. Search results for shortest pathways between open angle glaucoma and myopia. In the left panel is a list of pathways. For each pathway is a list of participants. Pathway number 13 is in bold dashed line.

3.5. Saving networks

To save a built network, choose the "*File->Save as …*" menu item. Saving can be in three formats: XML (ANDVisio) (by default), AND Native, XML (GeneNet).

The XML (ANDVisio) format allows saving all the data regarding a network, the saved network can be opened. The format is insensitive to changes in the list of the vertex and edge attributes. File size can be quite large. As a consequence, RAM should be large to accommodate the file. It is safe to save up to 10000 vertices. Saving of network containing 10000 vertices can take up to 5 minutes, depending on a computer power.

An extensive network can be saved in the binary AND Native format. Files with networks saved in this format occupy much less space on a disc, as compared with the XML format. Saving and opening are fast, ever for networks containing over 200000 vertices. Runtime is somewhat more than 1 minute.

The XML (GeneNet) format is designed to export networks in the GeneNet format [2]. Some applications for graph analysis, simulation of the dynamics, among others have been developed at the Institute of Cytology and Genetics SB RAS. Their common feature is the ability to open files in the GeneNet format.

To save a reconstructed network as an image, choose the "*File->Save as image …*" menu item.

The network can be saved in the BMP, PNG or JPG formats.

To open a network, previously saved either in the AND Native or XML (ANDVisio) formats, choose the "*File -> Open …*" menu item. Files can be opened and work with the saved networks can be done regardless of whether or not there is connection with the ANDCell database.

4. Search of possible pathways for relation between myopia and open angle glaucoma

Using ANDVisio, we have previously built an associative network for relationship between human genes and proteins that are associated with open angle glaucoma on the one hand and myopia on the other [18]. The network, which we built, contains 50 proteins and 15 genes associated both open angle glaucoma and myopia as well as more than 400 relationships between them (Fig. 12). Using a tool to find the shortest pathways in the network can be identified 26 pathways between myopia and open angle glaucoma, which contains the most important objects and relationships (Fig. 11). Two of them are described in [18]. These include proteins PAX6, NOE3, MYOC, SMAD3, IPO13, GCR and the gene OLFM3. Other pathways that have been discovered, require additional analysis.

5. Conclusion

The created ANDVisio application provides graphical visualization, editing, search, saving of networks reconstructed on request to the ANDCell database. The reconstructed networks describe semantic relationships between molecular-genetic objects (protein, gene, metabolite, microRNA), biological processes, and diseases. The program provides the user with universal tools for network analysis. These include filters by types of objects and their relationships; graph layout; search for the shortest pathways; cycles in graphs. ANDVisio, which is incorporated into ANDSystem, can be helpful in resolving a number of issues in various research areas: systems biology, biomedicine, biotechnology for the reconstruction and analysis of associative gene networks. The complexity and diversity of information scattered in the different databases are ever harder to capture and stir interest in computable resources for knowledge discovery.

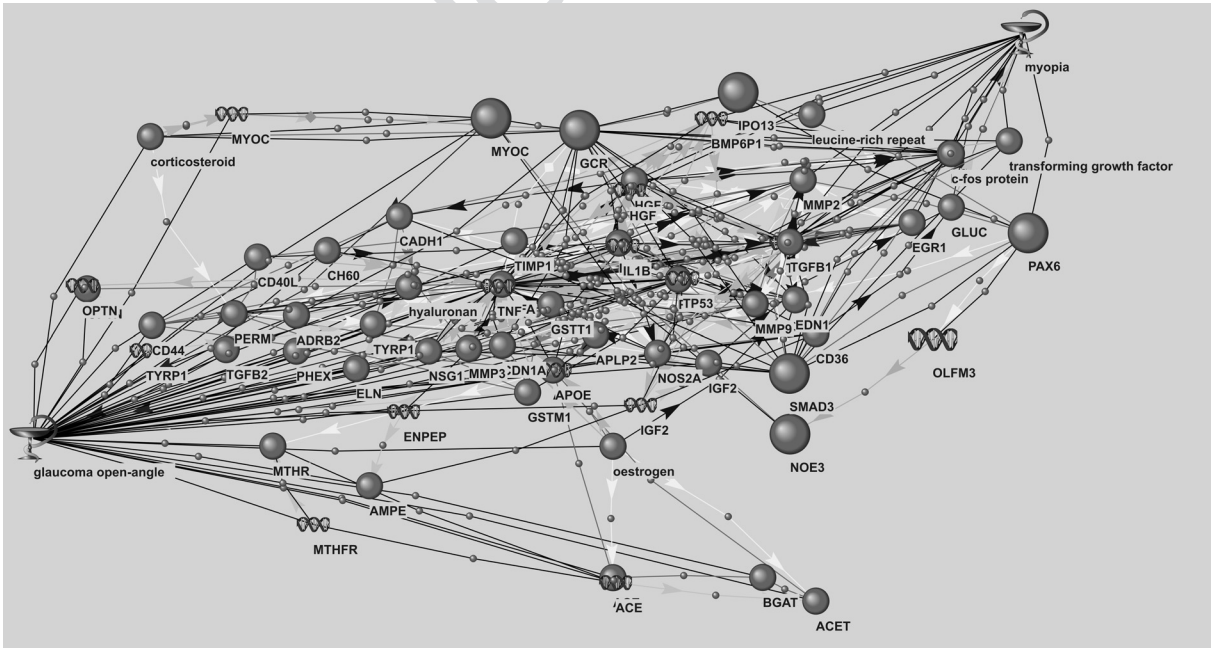

Fig. 12. The associative network for relationship between human genes and proteins that are associated with open angle glaucoma and myopia. Proteins PAX6, NOE3, MYOC, SMAD3, IPO13, GCR and the gene OLFM3 are marked by large icons.

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