SPIKE: a database of highly curated human signaling pathways

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ABSTRACT

The rapid accumulation of knowledge on biological signaling pathways and their regulatory mechanisms has highlighted the need for specific repositories that can store, organize and allow retrieval of pathway information in a way that will be useful for the research community. SPIKE (Signaling Pathways Integrated Knowledge Engine; http://www.cs.tau.ac.il/~spike/) is a database for achieving this goal, containing highly curated interactions for particular human pathways, along with literature-referenced information on the nature of each interaction. To make database population and pathway comprehension straightforward, a simple yet informative data model is used, and pathways are laid out as maps that reflect the curator’s understanding and make the utilization of the pathways easy. The database currently focuses primarily on pathways describing DNA damage response, cell cycle, programmed cell death and hearing related pathways. Pathways are regularly updated, and additional pathways are gradually added. The complete database and the individual maps are freely exportable in several formats. The database is accompanied by a stand-alone software tool for analysis and dynamic visualization of pathways.

INTRODUCTION

The dynamic behavior of biological systems and their response to various stimuli and physiological changes are driven by signaling networks mobilized primarily by alterations in gene and protein activity. Identifying the signaling pathways and specific regulation mechanisms is a major effort in biomedical research. Many of these regulations have been identified individually using ad hoc techniques. More recently, high-throughput techniques are rapidly adding new information by generating data on a larger scale albeit at lower fidelity (1–5). The volume of this information is such that even for a single pathway, it is difficult to recall all the interactions involved and the experimental source of each piece of information. SPIKE (Signaling Pathways Integrated Knowledge Engine; http://www.cs.tau.ac.il/~spike/) aims to construct, archive and actively maintain a database of highly curated interactions for particular human pathways, along with information on the nature of each interaction and its reference in the literature. High curation quality is obtained by supervision of map creation by leading domain experts. The pathways are laid out as maps that reflect the curator’s understanding and intuition and make pathway utilization straightforward. The current focus of the database is primarily on pathways describing DNA damage response, cell cycle, programmed cell death and hearing related pathways, and additional pathways are being added continuously. The database is accompanied by a stand-alone software tool for analysis and dynamic visualization of pathways (6). Here we focus on the structure and contents of the database.

There are several important databases that collect and curate protein interactions and pathways. Among those are KEGG Pathways (7), Reactome (8), ConsensusPathDB (9), IntAct (10) and NetPath (11). SPIKE differs from some of these in the choice of data model, emphasizing a simple model using a single entity per gene/protein in the underlying database, in its focus on signaling regulations (and excluding others, e.g. metabolic reactions), and in the continuous update of focus maps.

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It is unique in the focus on specific pathways of expertise, for which highly curated information is provided and regularly updated by domain experts. In fact, due to the differences in data model and curation policy, maps of the same process in SPIKE and other databases may manifest marked dissimilarities, with consequences for downstream analysis (see Supplementary Table S1 for comparison between few SPIKE and KEGG maps which cover the same pathway/process). The simple model and intuitive maps allow new maps to be readily constructed by experts in a distributed community effort. Like many other databases, it imports data from other databases and also allows freely export of the data in commonly used formats, such as BioPax (12).

One of the main utilities of pathway databases is in analyses pipelines of ‘omics’ data sets. Such data sets provide genome/transcriptome/proteome-wide snapshots of cellular processes and mining meaningful biological insights out of them poses a major challenge. To cope with this task we have integrated SPIKE maps in the EXPANDER package which is developed in our lab (13). The availability of SPIKE maps in standard formats readily allows their integration in other ‘omics’-analysis tools.

While SPIKE imports data and pathways en masse from other databases, it emphasizes completeness of its core pathways, performing continuous updates based on recent reports in the literature. All interactions are stored in the database with reference information, and pathways are graphically laid out by experts for best comprehension by users. Those interested in modifying layouts and exploring the pathway ‘boundaries’ using additional data stored in the database can download the software tool and then manipulate and explore the subnetworks in many ways.

DATA MODEL

The need to represent biological knowledge in a formal language within electronic knowledge-bases is well recognized and several ontologies have been defined [e.g. (14)]. We envisioned and implemented the SPIKE database as a community tool whose ‘upper tier’ contains highly-curated data, contributed by experts in various domains in the biomedical research (see Supplementary Data for a description of our curation policy). To allow swift and easy database population in a distributed fashion and to keep SPIKE maps easy to comprehend, we adopted model simplicity as a major design principle. Accordingly, the data model focuses on fundamental features that characterize regulatory events that build signaling networks while deliberately ignoring, for the sake of simplicity, other aspects of such events, which we deem less crucial. The data model includes five types of biological entities (nodes in SPIKE maps) and the members they contain. (i) Genes encode transcripts/proteins share most of their biological activities. (ii) Families are groups of isoform genes (encoded by distinct genomic loci) with high sequence homology and whose encoded transcripts/proteins share most of their biological activities. (iii) Complexes groups of proteins that carry out a specific function only when associated with their complex mates. The complex entity supports a layered structure, namely, a complex may contain sub-complexes.

The types of relationships between SPIKE entities are: (i) containment defines relationships between families/complexes and the members they contain. (ii) Regulation defines a directed and signed regulatory link between its source and target entities. Each regulation is defined by a source, a target and effect. It is also associated with several additional attributes: the biochemical mechanism by which it is driven (e.g. phosphorylation, transcriptional regulation), one or more supporting references, quality level for quality control (see the Supplementary Data), and the submitter/data source. (iii) Interaction defines an undirected and unsigned physical link between two protein nodes. Each interaction is defined by its two participating proteins, and also has an attribute that indicates the experimental method used to identify it (e.g. Y2H, co-immunoprecipitation) in addition to attributes indicating supporting reference(s), quality and the data source.

DATA SOURCES AND EXCHANGE WITH OTHER DATABASES

SPIKE database imports data from multiple sources (Figure 1B). Genes in SPIKE database are imported from Entrez Gene (15) (we include in SPIKE only genes with ‘Reviewed’ RefSeq status) and chemical molecules are imported from ChEBI (16). SPIKE’s data on relationships between entities come from three sources: (i) Highly curated data submitted directly to SPIKE database by SPIKE curators and experts in various biomedical domains. (ii) Data imported from external signaling pathway databases. At present, SPIKE database imports such data from Reactome (8), KEGG (7), NetPath (11) and The Transcription Factor Encyclopedia (http://www.cisreg.ca/cgi-bin/tfe/home.pl). (iii) Data on protein–protein interactions (PPIs) imported either directly from wide-scale studies that recorded such interactions [to date,
Figure 1. SPIKE’s data model and links with other databases. (A) The data model. SPIKE’s data model includes five types of biological entities (nodes in SPIKE maps) and three types of relationships between entities (edges in the maps). The types of entities are: (i) Genes/Proteins. Protein-coding genes are displayed in the maps as violet (e.g. ATM in the figure); non-coding genes are light-blue nodes (e.g. MIR34C). (ii) Families (yellow nodes, e.g. MIR-34), (iii) Complexes (green nodes, MRN), (iv) Chemical molecules (orange nodes, wortmannin) and (v) General entities (dark-pink nodes; e.g. ‘cell-cycle progression’ in this map). The types of relationships are: (i) Containment links between families or complexes and their members, shown as green edges (e.g. miR34B is contained in the MIR-34 family). (ii) Regulations, displayed as directed blue edges; arrows represent positive regulation (e.g. ATM activates TP53) and T-shape edges indicate negative regulation (e.g. wortmannin inhibits ATM). (iii) Interactions shown as undirected blue edges (not included in this figure). Red/green dots within a node indicate that the node has additional regulations/containments in the SPIKE database that are not included in the map. The dots on the edges can be used in the SPIKE stand-alone version to identify the literature reference to the relationship and as a
PPI data were imported from Stelzl et al. (17), Rual et al. (3) and Lim et al. (18) or from external PPI databases [IntAct (10) and MINT (19)]. Relationship data coming from these different sources vary greatly in their quality and this is reflected by a quality level attribute, which is attached to each relationship in SPIKE database (Supplementary Data). Each relationship in SPIKE is linked to at least one PubMed reference that supports it.

In addition to the individual maps, the complete database is freely available for download in several exchange formats. See under ‘Data availability’ below.

**BROWSING THE DATABASE**

SPIKE website offers basic searching utilities over the SPIKE database. Users can search the databases for each of the basic building blocks of SPIKE data model (namely, the five types of biological entities and the three types of relationships). For each entity, pertinent information is displayed (e.g. full name, description and external-ID for genes; data source, supporting PubMed references and quality level for regulations) and a list of the maps that contain the inquired entity is shown (Figure 2). The same interface serves SPIKE curators and registered users for uploading data to the database.

**DATABASE CONTENTS**

SPIKE-database was greatly expanded since our previous publication (6). The number of highly curated regulations has increased 8-fold, and the number of maps has increased from less than 10 to 23. In addition, database web-browsing capabilities were added. As of August 2010, the SPIKE database contains 20412 genes/proteins, 542...
Table 1. SPIKE maps

| Map                                      | Nodes (genes, complexes, families) | Links (regulations, interactions) | Unique references used | Creation date | Last update |
|------------------------------------------|------------------------------------|-----------------------------------|------------------------|---------------|-------------|
| Cell cycle progress and check points     |                                    |                                   |                        |               |             |
| G1-S Phase                               | 55                                 | 70                                | 28                     | August 2006   | January 2007|
| G2-M Phase                               | 78                                 | 122                               | 90                     | August 2006   | January 2010|
| DNA damage response                      |                                    |                                   |                        |               |             |
| Response to double strand breaks         | 144                                | 232                               | 144                    | January 2009  | December 2009|
| Nucleotide excision repair               | 94                                 | 136                               | 88                     | October 2009  | August 2010 |
| ATM signaling network                    | 118                                | 152                               | 120                    | January 2009  | August 2010 |
| Repair of Interstrand Crosslinks         | 86                                 | 139                               | 99                     | January 2010  | August 2010 |
| Base Excision Repair (BER)               | 82                                 | 120                               | 79                     | March 2010    | August 2010 |
| Mismatch repair (MMR)                    | 50                                 | 72                                | 48                     | March 2010    | August 2010 |
| Programmed cell death related processes  |                                    |                                   |                        |               |             |
| Apoptosis                                | 94                                 | 217                               | 168                    | January 2009  | April 2010  |
| Caspases Cascade                         | 113                                | 216                               | 151                    | October 2009  | August 2009 |
| DAPK family                              | 69                                 | 93                                | 77                     | October 2009  | August 2009 |
| Apoptosis Anti-Apoptosis Network         | 120                                | 232                               | 165                    | January 2009  | August 2009 |
| Autophagy                                | 57                                 | 93                                | 93                     | July 2009     | August 2009 |
| Stress-activated transcription factors   |                                    |                                   |                        |               |             |
| p53 Signaling Network                    | 91                                 | 111                               | 88                     | August 2006   | August 2009 |
| NFkB Signaling Network                   | 89                                 | 123                               | 137                    | August 2006   | August 2009 |
| Mitogen-activated protein kinase pathways |                                    |                                   |                        |               |             |
| MAPK signaling                           | 76                                 | 89                                | 49                     | September 2006| August 2009 |
| Immune response signaling                |                                    |                                   |                        |               |             |
| TLR Signaling                            | 134                                | 187                               | 110                    | January 2007  | March 2010  |
| HEarSpike: hearing related pathways      |                                    |                                   |                        |               |             |
| Hearing related SIX1 Interaction         | 103                                | 131                               | 79                     | June 2009     |             |
| MYO7A Interactions In The Ear            | 62                                 | 76                                | 38                     | June 2009     |             |
| NOTCH1 Signaling In The Ear              | 76                                 | 93                                | 53                     | June 2009     |             |
| Apoptosis in the ear                     | 178                                | 279                               | 195                    | March 2010    |             |
| Hearing and vision                       | 258                                | 457                               | 320                    | March 2010    |             |
| NYO3A                                    | 98                                 | 128                               | 99                     | August 2010   |             |

complexes (327 of high quality), 320 protein families (167 of high quality) and 39 small molecules. These entities are linked by 34,338 interactions (of which 2400 are of high quality) and 6074 regulations (4420 of high quality). These are associated with 5873 journal references in total. There are 23 different maps covering the areas of DNA damage responses, programmed cell death, hearing-related pathways, cell cycle regulation and more (Table 1). The database is undergoing rapid growth, and within the last 2 years the number of high quality regulations and the number of maps more than doubled. A brief description of the main domains of focus, and the maps created for each one is provided in the Supplementary Data. An example of the autophagy map is shown in Figure 3.

USER INTERFACE

In addition to the directly downloadable database, SPIKE provides a stand-alone software package for visualization and analysis of the database and maps. The software is available for download from SPIKE site (http://www.cs.tau.ac.il/~spike/download.html). The installation package contains the complete database with fully updated data. The visualization package allows interactive graphic representations of regulatory interactions stored in the database and superposition of functional genomic and proteomic data on the maps. The software also includes an algorithmic inference engine that analyzes the networks for novel functional interplays between network components. Interconnection with analysis and visualization tools is under development (Supplementary Data).

Accessing public maps with SPIKE software enables viewing the maps with the same layout and visual properties as they were constructed and allows the user to edit them. Furthermore once a map is opened using the tool, every object in the map is scanned for updates in the SPIKE database. All new regulations and interactions that were updated in the database since the map was created are conveniently arranged to be added or ignored. The software can save or convert the edited maps to SIF or BioPax formats.

DATA AVAILABILITY

An up-to-date snapshot of the SPIKE database is freely available for download from the SPIKE site (http://www.cs.tau.ac.il/~spike/download/LatestSpikeDB.xml.zip). Currently downloads can be made in three formats: BioPax, SPIKE’s unique XML format, and SIF. SPIKE’s specific XML format provides a copy all the information contained in the database (nodes, regulations and interactions, with associated links and literature reference information on each entity) in a format readable by the SPIKE software. The Supplementary Data describes the format and shows an example of the result of exporting a small map to XML and presenting it with Cytoscape (20). The SIF snapshot contained limited information on
interactions since this format is not rich enough include all the information. It is useful primarily for constructing graph views of the map using other software tools. Individual SPIKE curated maps are downloadable from the website as well. The maps are provided in the same formats as the database snapshot. Maps in SPIKE’s XML format are editable using the SPIKE software tool. Maps in SIF and BioPax format can be viewed using network visualization tools such as Cytoscape. The visualization of the maps in these formats will look different than it appears on the SPIKE site since graph layout information is not supported by SIF and BioPax.

SUPPLEMENTARY DATA
Supplementary Data are available at NAR Online.

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