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Michigan Molecular Interactions (MiMI): putting the jigsaw puzzle together

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ABSTRACT

Protein interaction data exists in a number of repositories. Each repository has its own data format, molecule identifier and supplementary information. Michigan Molecular Interactions (MiMI) assists scientists searching through this overwhelming amount of protein interaction data. MiMI gathers data from well-known protein interaction databases and deep-merges the information. Utilizing an identity function, molecules that may have different identifiers but represent the same real-world object are merged. Thus, MiMI allows the users to retrieve information from many different databases at once, highlighting complementary and contradictory information. To help scientists judge the usefulness of a piece of data, MiMI tracks the provenance of all data. Finally, a simple yet powerful user interface aids users in their queries, and frees them from the onerous task of knowing the data format or learning a query language. MiMI allows scientists to query all data, whether corroborative or contradictory, and specify which sources to utilize. MiMI is part of the National Center for Integrative Biomedical Informatics (NCIBI) and is publicly available at: http://mimi.ncibi.org.

1 INTRODUCTION

Both the volume and number of data sources in molecular biology are increasing rapidly. Often multiple resources provide overlapping, partial and polymorphic views of the same data. These data are stored and published in a diverse set of data sources. Each source is distinct with respect to its biological focus (e.g. SNPs, gene promoters, etc.), organism (e.g. fly) and format (e.g. tab delimited file, relational database, etc.). Even after narrowing the problem down to a subset of biological information, such as protein interaction information, there is a deluge of information. With such a rich variety of sources to choose from, a scientist who wishes to visualize the full picture concerning a particular protein must visit a myriad of sites, learn a plethora of names, aliases and identifiers, compile information from journal papers, and then piece the resulting jigsaw puzzle together. This task becomes even more onerous due to several complicating factors. First, no naming or identification scheme has been agreed upon. Thus, the scientist must painstakingly map her protein of interest to a series of different names and identifiers. Second, many interaction databases, or even lab web pages, place an interaction in the public domain even if it is supported by only one experiment. This forces scientists to search through multiple databases for conflicting or corroborating evidence. Third, heterogeneous sources storing information in their own unique formats force scientists to become programmers in order to trawl through large volumes of data and reorganize it into an understandable format. Finally, once a researcher has gathered data from several sources, sifted through it and amalgamated it, there is usually no trail left linking the data to their original sources. At this stage, if the scientist discovers mutually exclusive pieces of information existing in her amalgamated view, she has no way of making an informed decision about how to correct the data.

The work of (1,2) minimizes the burden on the user by integrating a large number of disparate sources containing information over a range of attributes, such as expression, structure and family. However, while the integration is from a large number of heterogeneous sources, it is a shallow integration. Michigan Molecular Interactions (MiMI) helps scientists search through large quantities of information by integrating all information from participating data sources through the process of deep-merging. As a result, redundant data are removed and related data are combined. Moreover,

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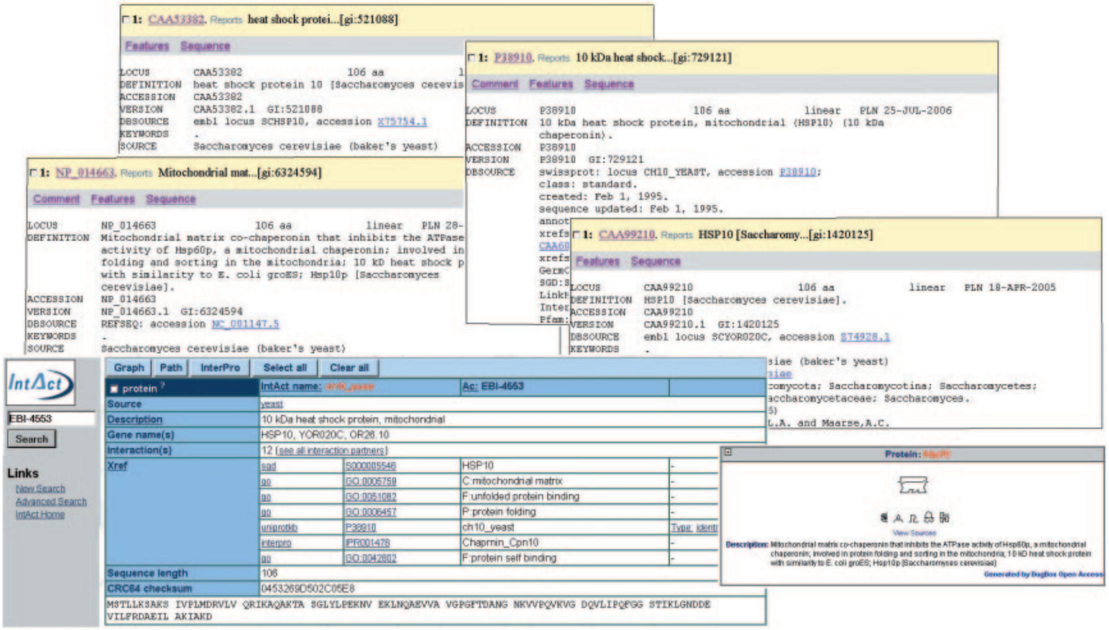
The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors.



```
□ 1: CAA53382. Reports heat shock protei...[gi:521088]
Features  Sequence

LOCUS       CAA53382                106 aa              1
DEFINITION  heat shock protein 10 [Saccharomyces cerevis
ACCESSION   CAA53382
VERSION     CAA53382.1  GI:521088
DBSOURCE    embl locus SCHSP10, accession X75754.1
KEYWORDS    .
SOURCE      Saccharomyces cerevisiae (baker's yeast)
```

```
□ 1: P38910. Reports 10 kDa heat shock...[gi:729121]
Comment  Features  Sequence

LOCUS       P38910                  106 aa            linear   PLN 25-JUL-2006
DEFINITION  10 kDa heat shock protein, mitochondrial (HSP10) (10 kDa
            chaperonin).
ACCESSION   P38910
VERSION     P38910  GI:729121
DBSOURCE    swissprot: locus CH10_YEAST, accession P38910;
            class: standard.
            created: Feb 1, 1995.
            sequence updated: Feb 1, 1995.
            annot
            xrefs
            CAA60
            xrefs
            GermC
            SGD:S
            LinkH
            Inter
            Pfam:
```

```
□ 1: NP_014663. Reports Mitochondrial mat...[gi:6324594]
Comment  Features  Sequence

LOCUS       NP_014663               106 aa            linear   PLN 28-
DEFINITION  Mitochondrial matrix co-chaperonin that inhibits the ATPase
            activity of Hsp60p, a mitochondrial chaperonin; involved in
            folding and sorting in the mitochondria; 10 kD heat shock p
            with similarity to E. coli groES; Hsp10p [Saccharomyces
            cerevisiae].
ACCESSION   NP_014663
VERSION     NP_014663.1  GI:6324594
DBSOURCE    REFSEQ: accession NC_001147.5
KEYWORDS    .
SOURCE      Saccharomyces cerevisiae (baker's yeast)
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```
□ 1: CAA99210. Reports HSP10 [Saccharomy...[gi:1420125]
Features  Sequence

LOCUS       CAA99210                106 aa            linear   PLN 18-APR-2005
DEFINITION  HSP10 [Saccharomyces cerevisiae].
ACCESSION   CAA99210
VERSION     CAA99210.1  GI:1420125
DBSOURCE    embl locus SCYOR020C, accession Z74928.1
KEYWORDS    .
            siae (baker's yeast)
            siae
            comycota; Saccharomycotina; Saccharomycetes;
            accharomycetaceae; Saccharomyces.
            5)
            L.A. and Maarse,A.C.
```

■ protein ?	IntAct name: ch10_yeast		Ac: EBI-4653	
Source	yeast			
Description	10 kDa heat shock protein, mitochondrial			
Gene name(s)	HSP10, YOR020C, OR26.10			
Interaction(s)	12 (see all interaction partners)			
Xref	sgd	S000005546	HSP10	-
	go	GO:0005759	C:mitochondrial matrix	-
	go	GO:0051082	F:unfolded protein binding	-
	go	GO:0006457	P:protein folding	-
	uniprotkb	P38910	ch10_yeast	Type: identi
	interpro	IPR001478	Chaprnin_Cpn10	-
	go	GO:0042802	F:protein self binding	-
Sequence length	106			
CRC64 checksum	0453269D502C05E8			

```
MSTLLKSAKS IVPLMDRVLV QRIKAQAKTA SGLYLPEKNV EKLNQAEVVA VGPGFTDANG NKVVPQVKVG DQVLIPQFGG STIKLGNDDE
VILFRDAEIL AKIAKD
```

Protein: Hsp10

Description: Mitochondrial matrix co-chaperonin that inhibits the ATPase activity of Hsp60p, a mitochondrial chaperonin; involved in protein folding and sorting in the mitochondria; 10 kD heat shock protein with similarity to E. coli groES; Hsp10p [Saccharomyces cerevisiae]

Figure 1. Sample protein data for Hsp10 from IntAct, NCBI and BIND.

the provenance of each piece of information is tracked throughout the system, allowing scientists to choose which data to trust (3). MiMI allows users to ask more advanced questions than each of its component databases can answer independently. MiMI attempts to relieve scientists of the burden of tracking down multiple sources, mapping multiple identifiers and merging redundancies. By integrating well-known datasets, such as HPRD (4) and BIND (5), MiMI creates a deep-merged repository that is a synergy of all the merged datasets. By such integration, MiMI shows scientists when facts are corroborated by different datasets, and when facts are contradicted among datasets. Moreover, the provenance of each data item is annotated, allowing scientists to view information from only the sources they trust, and facilitating understanding of contradictory information. MiMI's integration is distinctly different from the approach used by the International Molecular Exchange Consortium (IMEx). While several of the integral components of MiMI also belong to IMEx, the tasks are very different. IMEx is attempting to increase the rate of data curation by separating curation tasks among different groups. Once curation is done, the information is shared among all. However, regardless of any cooperation between data curation sites, or partitioning of resources, there will always be some data overlap or redundancy among them. MiMI does not attempt to find new data to curate, but to augment known information by highlighting redundancy and contradictions. Additionally IMEx itself is in the very infancy of data exchange, and there is as yet no cohesive, united and deeply merged dataset produced by it.

MiMI provides a simple interface that allows new users to pose complex queries. Utilizing a simple point and click method, our user interface allows scientist to formulate advanced queries without specialized programming skills. Additionally, MiMI output complies with the PSI-MI format and Cytoscape (6), allowing users to take advantage of industry tools for viewing interactions. The following is a brief description of the underlying concepts of MiMI, as well as a detailed list of datasets employed by MiMI.

2 DATABASE CONSTRUCTION

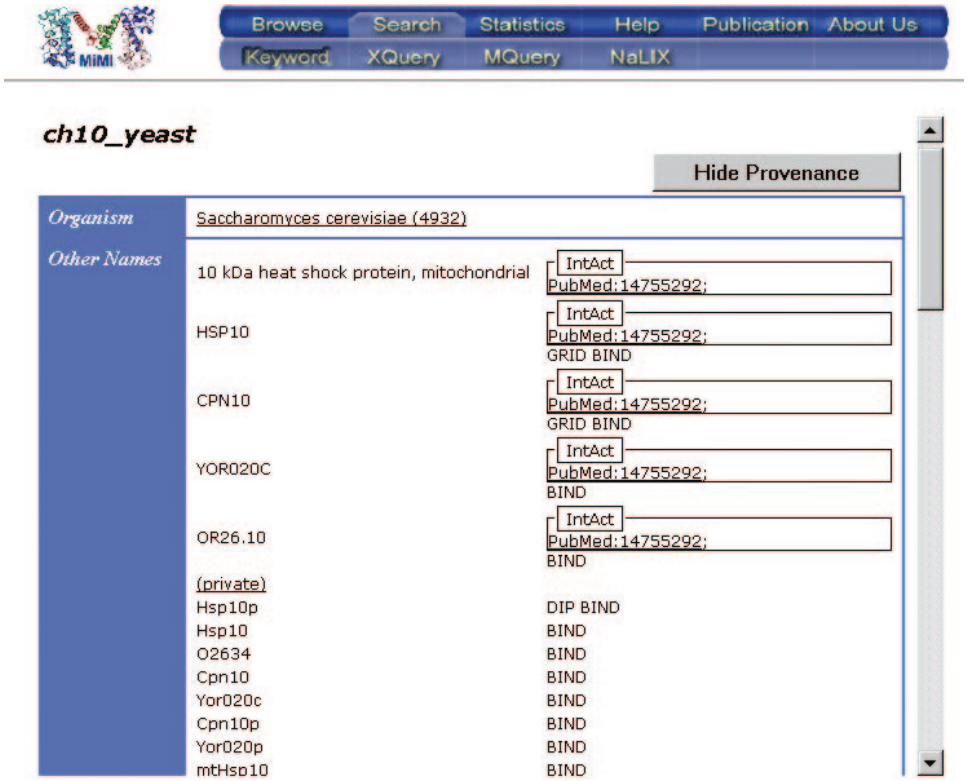
MiMI uses XML as its data model. XML is the current lingua franca of biological data exchange, and gives the MiMI data model the flexibility to change as biological understanding increases. The physical storage of MiMI is built upon Timber (7), a native XML database. MiMI is a component of the National Center for Integrative Biomedical Informatics (http://www.ncibi.org), and is publicly available at: http://mimi.ncibi.org.

Datasets

MiMI currently has 117 549 molecules and 256 757 interactions, and is the result of integrating BIND (5), DIP (8), BioGRID (9), HPRD (4) and IntAct (10) as well as datasets from Center for Cancer Systems Biology at Harvard (11) and the Max Delbrueck Center (12). Additionally, supplementary protein information was integrated from: GO (13), InterPro (14), IPI (15), miBLAST (16), OrganelleDB (17), OrthoMCL (18) PFam (19) and ProtoNet (20).

Identity

The issue of identity is determining when two database entries refer to the same real-world object. For instance, to a human, it is obvious that an Hsp10p molecule found in yeast and listed in DIP is the same as the Hsp10p molecule found in yeast and listed in BIND. In the simplest case, identity is defined by the uniqueness of a key attribute (set); in this case, the name. However, in protein identification, no



ch10_yeast

Organism	Saccharomyces cerevisiae (4932)	
Other Names	10 kDa heat shock protein, mitochondrial	IntAct PubMed:14755292;
	HSP10	IntAct PubMed:14755292; GRID BIND
	CPN10	IntAct PubMed:14755292; GRID BIND
	YOR020C	IntAct PubMed:14755292; BIND
	OR26.10	IntAct PubMed:14755292; BIND
	(private)	
	Hsp10p	DIP BIND
	Hsp10	BIND
	O2634	BIND
	Cpn10	BIND
	Yor020c	BIND
	Cpn10p	BIND
	Yor020p	BIND
	mtHsp10	BIND

Figure 2. The Hsp10 information from Figure 1 after a Deep Merge.

Table 1. Number of molecules and interactions for each source as well as total deep-merged molecules and interactions in MiMI v.2.6

Source	# Molecules	# Interactions
BIND	111 394	175 678
IntAct	62 667	67 955
HPRD	18 839	66 723
BioGRID	15 687	53 378
DIP	19 050	54 511
Center for Cancer Systems Biology dataset	3134	6726
Max delbrueck center dataset	1909	3269
MiMI	117 549	256 757

key exists across all datasets, necessitating keyless identity functions.

For example, in BioGRID, there is an entry for HSP10, and an external reference to NCBI's RefSeq NP_014663. In BIND, there is an entry for Hsp10, with an external reference to NCBI's GI 6324594. From a human perspective, it is obvious these are the same proteins with different capitalizations. However, there is no linking identifier in either BioGRID or BIND. Further searching reveals that NCBI's records hold a link between this GI and RefSeq. Given less obviously matching names for this protein, such as CPN10 (BioGRID) and Yor020p (BIND) and different external identifiers, matching identical records is not a trivial task for an individual. Combine this with the thirteen known names for this object in BIND, DIP, BioGRID and IntAct, and the human user is bound to miss incorporating some relevant data. MiMI utilizes keyless identity functions to determine which proteins represent the same real-world object. Once this identity has been determined, the entries are deep-merged.

Deep-merge

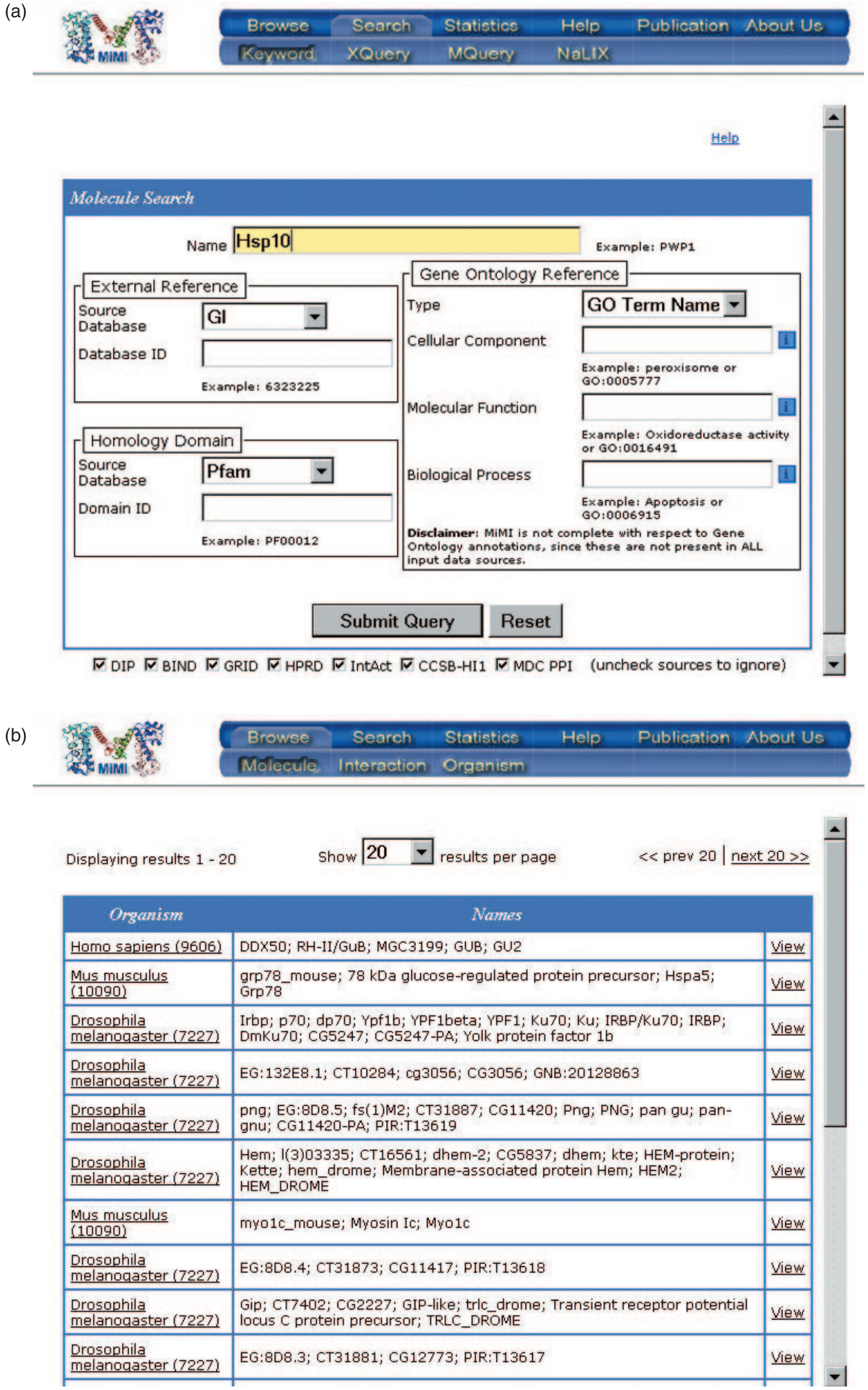
Datasets frequently have overlapping, and sometimes even contradictory information content. Our goal is to fuse information from multiple sources, even when these sources have overlapping or contradictory information, and present a cohesive result to the user. We call this process deep-merging or deep integration. (In contrast, shallow integration performs just the schema translations and groups the datasets together). To appreciate the issues involved, let us consider an example.

Example 1. Figure 1 shows a brief look at some of the entries for Hsp10. Each database has different identifiers and names for the molecule. Bind in 1 calls the protein Hsp10, while IntAct in 1 calls it ch10_yeast. NCBI itself has at least four versions of this protein with the exact same sequence, and different supportive information. Assuming that an appropriate identity function is found that integrates all six molecules, shallow integration would result in 15 listed interactions. However, there are only 13 non-redundant interactions reported in the datasets. A similar problem occurs for other information on the molecule, such as PTMs. Figure 2 shows a view of the resulting deep-merging process.

There is significant redundancy across data sources. Table 1 shows the number of molecules and interactions provided by each source. It also shows the resulting number of molecules and interactions after a deep-merge. For molecules there is a whopping 49% redundancy rate, while 40% of the interactions are redundant across sources.

Provenance

Using the identity functions discussed above, datasets can be deep-merged into MiMI. However, not all datasets are created equal. Some are the result of careful curation and fact checking, while others can be from a single lab after one round of experiments. Knowing where the data came from augments its reliability. MiMI tracks the provenance of each data item, allowing the user to determine which sources to use or ignore. Moreover, database queries can use sources as a search criterion, returning only trusted information to the user.



(a)

Molecule Search

Name: Hsp10 Example: PWP1

External Reference
Source Database: GI
Database ID:
Example: 6323225

Homology Domain
Source Database: Pfam
Domain ID:
Example: PF00012

Gene Ontology Reference
Type: GO Term Name
Cellular Component:
Example: peroxisome or GO:0005777
Molecular Function:
Example: Oxidoreductase activity or GO:0016491
Biological Process:
Example: Apoptosis or GO:0006915

Disclaimer: MiMI is not complete with respect to Gene Ontology annotations, since these are not present in ALL input data sources.

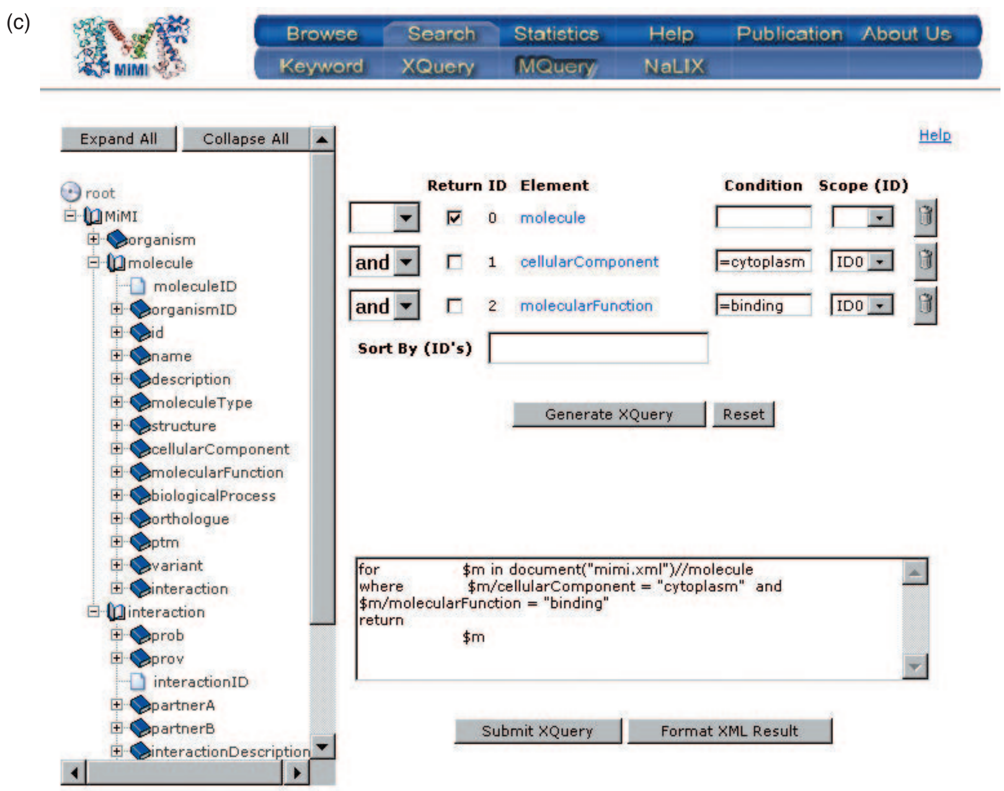
Submit Query | Reset

☑ DIP ☑ BIND ☑ GRID ☑ HPRD ☑ IntAct ☑ CCSB-HI1 ☑ MDC PPI (uncheck sources to ignore)

(b)

Displaying results 1 - 20   Show 20 results per page   << prev 20 | next 20 >>

Organism	*Names*	
Homo sapiens (9606)	DDX50; RH-II/GuB; MGC3199; GUB; GU2	View
Mus musculus (10090)	grp78_mouse; 78 kDa glucose-regulated protein precursor; Hspa5; Grp78	View
Drosophila melanogaster (7227)	Irbp; p70; dp70; Ypf1b; YPF1beta; YPF1; Ku70; Ku; IRBP/Ku70; IRBP; DmKu70; CG5247; CG5247-PA; Yolk protein factor 1b	View
Drosophila melanogaster (7227)	EG:132E8.1; CT10284; cg3056; CG3056; GNB:20128863	View
Drosophila melanogaster (7227)	png; EG:8D8.5; fs(1)M2; CT31887; CG11420; Png; PNG; pan gu; pan-gnu; CG11420-PA; PIR:T13619	View
Drosophila melanogaster (7227)	Hem; l(3)03335; CT16561; dhem-2; CG5837; dhem; kte; HEM-protein; Kette; hem_drome; Membrane-associated protein Hem; HEM2; HEM_DROME	View
Mus musculus (10090)	myo1c_mouse; Myosin Ic; Myo1c	View
Drosophila melanogaster (7227)	EG:8D8.4; CT31873; CG11417; PIR:T13618	View
Drosophila melanogaster (7227)	Gip; CT7402; CG2227; GIP-like; trlc_drome; Transient receptor potential locus C protein precursor; TRLC_DROME	View
Drosophila melanogaster (7227)	EG:8D8.3; CT31881; CG12773; PIR:T13617	View



	Return	ID	Element	Condition	Scope (ID)
	☑	0	molecule		
and	□	1	cellularComponent	=cytoplasm	ID0
and	□	2	molecularFunction	=binding	ID0

Sort By (ID's)

```
for          $m in document("mimi.xml")//molecule
where         $m/cellularComponent = "cytoplasm"  and
$m/molecularFunction = "binding"
return
              $m
```

Figure 3. Database access options: (**a**) Keyword query (**b**) browse (**c**) MQuery.

3 DATABASE ACCESS

MiMI is stored in the Timber native XML database (7). This means that the data format follows a specific schema, and can be queried using XQuery. However, learning somebody else's internal schema is an onerous task. Additionally, writing declarative queries in a database query language, such as XQuery, has a steep learning curve. Our goal is to make MiMI easily accessible in an intuitive manner that does not rely on specialized skills.

Traditional search options

MiMI provides the user with several traditional search options, such as browse and keyword search. From the browse interface, a user may view the list of molecules, interactions or organisms included in MiMI. However, while browsing gives a general overview of the data, it is a slow way to find a particular protein. To this end, we have included a keyword query facility to allow the user quick and easy access to specific information. Figure 3a and b depict these traditional options in MiMI. This is a standard form-based search option that is similar to forms found in many online biological databases.

MQuery

Traditional approaches, such as keyword forms can be stifling and restrictive to the scientist. However, the alternative—writing a query in a declarative database query language—is prohibitive. Writing efficient XQuery is an acquired skill; browsing and keyword-based searching restricts the user's ability to pose non-trivial queries. MQuery addresses this dilemma. It combines the ease of form-based queries with the power of custom query writing (21). Additionally, the XQuery produced by MQuery is tuned to the underlying database technology and will produce an efficient XQuery.

One of the major obstacles to writing declarative queries is the need to understand the underlying document structure. MQuery allows the user to point and click on various schema elements, place conditions on them and combine these conditions conjunctively or disjunctively. Figure 3c depicts a query a beginner user could easily build by browsing through the schema on the left, clicking on fields of interest, and filling in search words. In this case, the user chose 'cellularComponent' and 'moleculeFunction', and specified that she was only interested in proteins in the cytoplasm that are involved in binding. Once the user has created a customized form according to her specifications, she presses 'Generate XQuery', and the appropriate XQuery statement is generated and displayed to the user. This allows the user to learn the general form of an XQuery statement, and revise the current MQuery if needed before submitting it to the database to obtain the results of the query.

Viewing information

Information from MiMI can be viewed in a variety of formats. The simplest way is to view all information via the web browser. Each page succinctly shows all recorded information for each protein as well as the provenance associated with each piece of data. A second option is to view all interactions via Cytoscape. We package all information such that it can be easily loaded and viewed in a Cytoscape browser. Finally, all information is downloadable in three different formats: XML using MiMI's internal schema, PSI-MI format (version 2.5) and plain text. Information can be downloaded from several different places: the individual molecule display page, the interaction display page and the MQuery result page.

4 FUTURE DEVELOPMENTS

MiMI is continuously changing. We are constantly looking for public datasets that would either complement the existing data or expand it. We actively encourage biologists and other users to inform us of deficiencies in either the data, or the usability of the website. Our aim is to create an essential, comprehensive and biologist-friendly database of protein interactions.

Pathway information, from sites, such as Reactome (22) will be included in the next release of MiMI. In addition to molecules and interactions, complexes, polymers, biochemical reactions and pathways will also be merged. Thus, a user viewing a complex found in both Reactome and BIND will be able to see the deep-merged record with data from both sources.

ACKNOWLEDGEMENTS

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Conflict of interest statement. None declared.

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