A query language for biological networks

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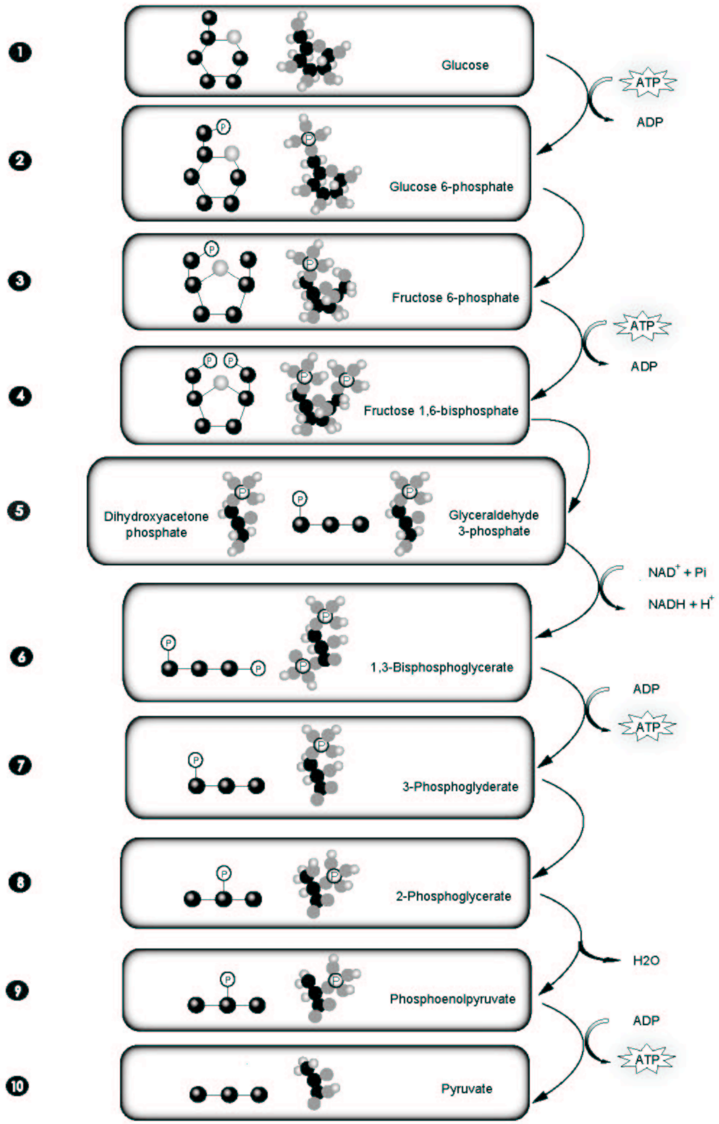
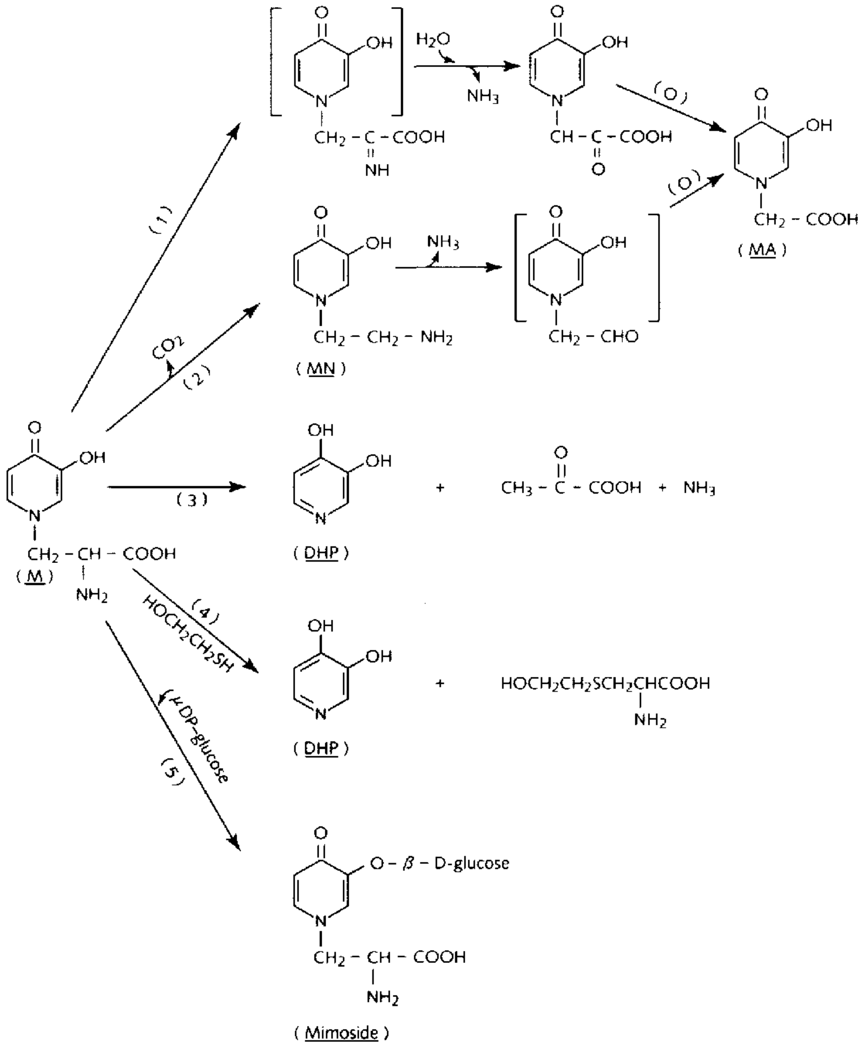
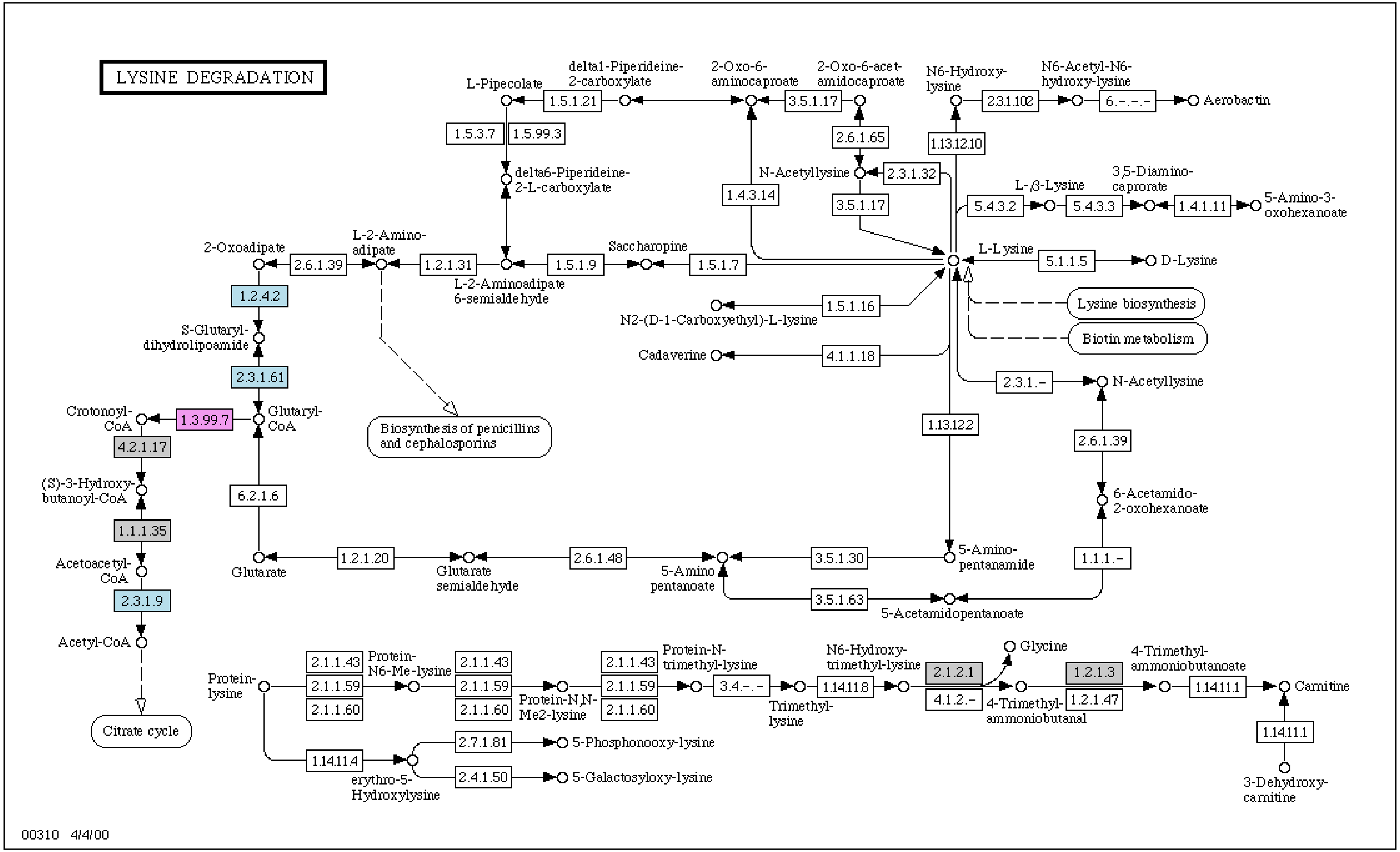




M: mimosine, DHP: 3,4-dihydroxypyridine, MN: mimosinamine, MA: mimosinic acid

Representations of Metabolic Pathways



Representations of Metabolic Pathways

Turning Pictures into Words

- Find all reactions involving a certain substance.
- Find all paths, i.e. chains of reactions, connecting two given substances.
- Find the shortest path between two substances that includes a third substance.
- Given a set of molecules, extract the subgraph which contains all these elements and has the least number of nodes.

Pathway Query Language

- Pathway Query Language (PQL) is a declarative language with syntax similar to SQL (Structured Query Language).
- A PQL query returns a graph, making nesting of queries a possible and expected usage.

Why PQL?

- Talking about a language implicitly forces one to think about the requirements that exist for querying pathways.
- A properly defined language can be used by many pathway databases, reducing the amount of duplicate work.
- A query language acts as an interface between applications and databases. (Allows abstraction.)
- Clear semantics helps to integrate data from heterogeneous repositories.

The PQL Data Model

- The basic PQL data model is a graph *G* with a set of nodes and directed edges.
- *G* represents a network of molecules and interactions.
- A node is either an interaction or a molecule.

The PQL Data Model

- The graph need not be connected.
- Data model similar to those of aMAZE, KEGG, and Reactome.
- The nodes are biological entities or interactions, including properties like *type* (“gene,” “enzyme,” “inhibition,” “catalysis,” etc.) and *function* (concepts similar to Gene Ontology).

PQL Syntax

- SELECT subgraph-specification
  FROM node-variables
  WHERE node-condition-set

- Example:

```
SELECT *
FROM A, B
WHERE A.name = ‘3-Isopropylmalate’ AND
        B.name = ‘EC1.1.1.’85
```

PQL Path Expressions

```
SELECT *
FROM B, C, D
WHERE D.name = ‘L-Lactaldehyde’ AND
B ISA ‘Enzyme’ AND B[-2]D AND
B[-*]C[-*]D AND
C.name = ‘Lactaldehyde’
```

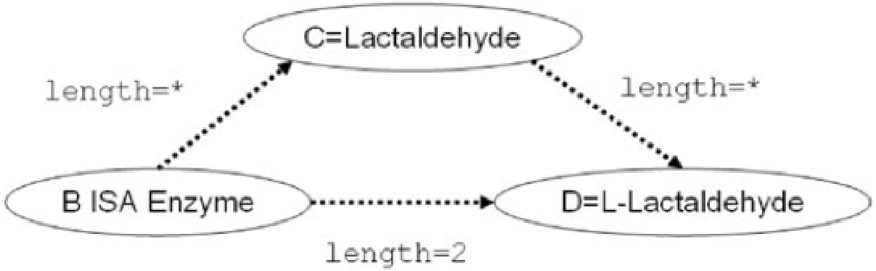
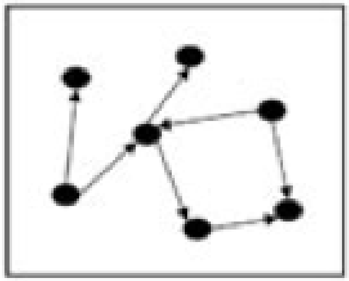
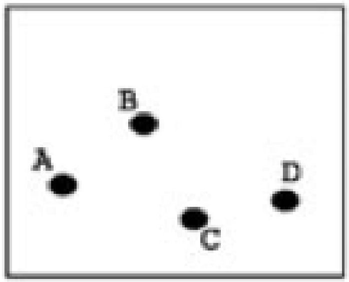


Fig. 5. Graphical representation of the query given in the text. Dashed lines represent path expressions.

Evaluation of a PQL Query

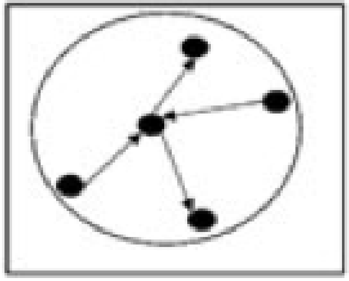


Underlying database graph



Match graph of the query. Four nodes are matched

```
SELECT B[-1]
FROM A, B, C, D
WHERE A[-1]B[-1]C[-1]D
```



Result graph of query. Nodes are added and removed, edges are added.

```
SELECT B[-1]
FROM A, B, C, D
WHERE A[-1]B[-1]C[-1]D
```

Networks with Cycles

- Biological networks contain cycles, like feedforward and feedback loops, or reversible reactions.
- PQL doesn’t handle these. PQL only evaluates on cycle-free paths.
  - In cyclical paths, the notion of “all paths” between nodes becomes undefined/infinite.
  - Cycles in larger networks would return too much of the network.
  - *Efficiency of computation.*

Examples

- *Find all genes whose expression is directly or indirectly affected by a given compound.*

-
  ```
  SELECT B
  FROM A, B
  WHERE A.name = ‘L-Glutamate’ AND
        A[-*]B AND B ISA ‘gene’
  ```

Examples

- *In the complete set of metabolic reactions, find all feedback loops including a given compound.*

-
  ```
  SELECT A[-*]B[-*]A
  FROM A, B
  WHERE A.name = ‘Methionine’ AND
        A[-*]B[-*]A
  ```

Examples

- *The user specifies a set of nodes …and prompts the system to extract the … sub-graphs that interconnect each pair of seed nodes via the smallest number of … links.*

-
  ```
  SELECT A[-s]B, A[-s]C, A[-s]D,
        B[-s]C, B[-s]D, C[-s]D
  FROM A, B, C, D
  WHERE A[-*]B[-*]C[-*]D
  ```

Examples

- *Find all processes that lead from node A to node B in less than MAX steps and more than MIN steps.*

-
  ```
  SELECT A[-*]B
  FROM A, B
  WHERE A[->M]B AND A[-<N]B
  ```

- *This query **fails** because it returns all nodes A and B for which there exists at least one path between them longer than M and at least one path shorter than N. Future PQL work?*

Examples

- *Find all enzymes for which ATP is an inhibitor.*

-
  ```
  SELECT A
  FROM A, B, C, D
  WHERE A ISA ‘enzyme’ AND
          D.name = ‘ATP’ AND
          A[-1]B AND D[-1]C[-1]B AND
          B ISA ‘reaction’ AND
          C ISA ‘inhibition’
  ```

Examples

- *Retrieval of all interactions that involve any of a set of molecular species as immediate participant.*

-
  ```
  SELECT A
  FROM A, B
  WHERE A[-2]B
  ```

Examples

- *Retrieval of a connected graph that includes a set of specified interactions.*
- NOT IN PQL

PQL Implementation

- Oracle Server v9.2
- model for data storage (**Node**, **Edge**, **Function**, **Type**)
- precomputational procedures for performance
- compiler for PQL queries
- results are returned in two tables to be interpreted by middleware
- two phases: match graph and result graph
- helper tables store all cycle-free paths
- currently 208K paths between 16K nodes and 23K edges from GO
    - these numbers will grow exponentially with larger datasets