Predicting metabolic pathways by logic programming

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This paper discusses logic programming and its application for the expert system I use to simulate the metabolic fate of substances. An expert system called Metabolexpert accepts the formula of the compound to be metabolized and produces a treelike picture of the metabolites generated together with the formula of the compounds. On request, three-dimensional (3D) pictures of the metabolites are also displayed and hydrophobicity (logP) values of the compounds calculated. A retrospective investigation of Metabolexpert's achievement showed that the expert system can reproduce almost all primary, secondary and tertiary metabolites of amphetamine. A compound series has been suggested for benchmark testing of metabolic transformation knowledge bases.

Keywords: logic programming, expert system, Metabolexpert

Kowlaski[1] introduced the concept of using mathematical logic directly as a programming tool ("logic programming," or LPG). LPG has been gaining more and more popularity in the scientific world during the last decade and a half, especially through the spread of the programming language Prolog,[2] which essentially realizes the idea of LPG. In the field of drug design, an LPG-based approach for predicting interactions of new drugs was published in 1976.[3]

Since then, researchers have developed expert systems for calculating logP values,[4] predicting carcinogenic activity,[5] automatically calculating and interpreting QSAR equations,[6] assisting in conformation analysis[7,8] and predicting 3D structures of proteins.[9]

This work reviews LPG and its application for predicting metabolic pathways. After presenting a survey of the metabolism prediction problem, I will deal with a logic-based model for problem solving. After providing an overview of the expert systems which implement the model, I will report on my experiences with the program and draw conclusions.

PREDICTING METABOLIC PATHWAYS

Predicting metabolites of a substance absorbed by an organism (human, animal or even a microorganism) is a common interest of many fields. It is important in the preclinical and clinical phases of drug development and relevant when environment or health hazards of organic materials are estimated. In all of the listed cases, even a partial prediction of the expected metabolites might spare considerable time, energy and money.

Foreseeing the metabolic fate of drug candidates is significant for nonclassical drug design, where diminution of unwanted side effects or toxic symptoms at the clinical level is required rather than enhancement of the activity on in vitro or low-level in vivo tests. The importance of knowledge of the expected metabolites has been stressed in fields such as the design of chemical delivery systems[10] or prodrugs.[11]

In a simplified form, the metabolism-prediction problem resembles the problem of finding retrosynthetic pathways in the synthetic design of organic chemicals. In a recent paper[12] a synthetic pathway discovery program, Synchem2, was used for this problem, and two earlier approaches[13,14] were also based on this idea. Synthesis design, however, deals with reactions of small organic molecules in a vessel with controlled conditions; in the case of metabolic prediction, at least one reaction component is a protein, and the conditions are not controllable. In addition, transformations proceed in a living system, where the next "reaction" follows only if the metabolite reaches the site of metabolism. The transport conditions, however, depend on physico-chemical properties of the metabolites. Thus, metabolism prediction is similar to a synthesis design task, where one of the reactants and the reaction conditions are not fully known and a conditional series of reactions is involved with a partially known set of conditions.

The inherently more complicated nature of metabolic prediction requires knowledge-based domain-specific problem solving. This type of artificial-intelligence-based approach has been applied by Tinker and Gelerter[12] and by Seressiotis and Bailey.[15] The Seressiotis-Bailey system aims to find pathways that transform a compound into a target metabolite. The users are assumed to be genetic engineers capable of manipulating enzyme activity by using recombinant DNA techniques.

LPG provides an excellent possibility for domain-specific problem solving and has proved to be a suitable tool for building up a family of expert systems related to metabolic pathway prediction: Metabolexpert,[16] a system for predicting metabolic pathways for a drug; Hazardexpert, a system for predicting systemic toxicity for a substance and its metabolites; and Prosoftdrug,[17] a system for predicting soft analogues of an active substance.

USING LOGIC PROGRAMMING FOR METABOLIC PREDICTIONS

Appendix I summarizes the mathematics underlying LPG. As can be seen, the most expressive elements of the predicate calculus logic are the Horn clauses (HCs). They can also be used as a kind of metalanguage for formulating the most important facts and relationships ("general axioms") of an investigated problem. As Appendix I suggests, a straightforward relationship exists between a conditional or a simple affirmative sentence and its representation in HC. For example,

A compound will possibly be metabolized as hippurate if it contains an aromatic carboxyl group. [1]

```
POSSIBLE__METABOLITE (*ANY COMPOUND,
                      HIPPURATE):
                      CONTAINS (*ANY__COMPOUND,
                      AROMATIC__CARBOXYL__
                      GROUP).                    [2]
```

I have used the following conventions to assign [2] to [1]:

- Some words are merged by forming composite expressions; possible__metabolites.
- n-ary function(s) are formed. For that, the most essential element of the sentence (perhaps a composite expression) is picked up as name of the function, while other words or composite expressions of the sentence are used as arguments of the function (they are put between brackets). Unbound (free) variables are represented with an asterisk as the first character.
- "if" of the conditional sentence is substituted by a special character series, i.e., by:-

In order to describe simultaneously the metabolic and transportation fate of a compound, the following simple model was introduced.[16]

If we hypothesize that after administration a substance ($c1$) undergoes a series of transport processes ($t1$,$t2$) and metabolic transformations ($m1$,$m2$) at different organs (organ1. .organ3), then compounds $c1$. .$c3$ are present at concentrations ($cc1$. .$cc6$) at different time units ($t1$. .$t6$) in the organs, as summarized in Figure 1 by graph G, a biotransformation graph.

A vertex of G corresponds to an HC [3]:

```
STATE(*STRUCTURE__OF__A__
COMPOUND,
*ORGAN,*TIME,*
CONCENTRATION).                              [3]
```

An edge of G might be represented by the HC [4]:

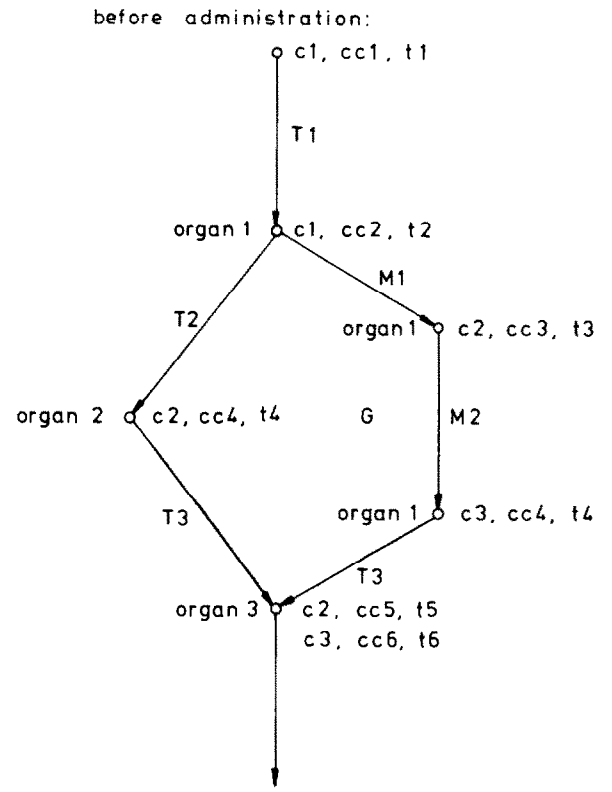

Figure 1. Biotransform graph: a graph representing transport and metabolic pathways of a compound

```
TRANSFORMATION(*TYPE,*PRECONDITIONS).        [4]
```

The transformation might be either a transport process or a metabolic reaction.

The biotransformation graph can be defined as a set of vertices and edges:

```
GRAPH__ELEMENT(*TRANSFORMATION,
*STATE,*TRANSFORMATION) G                    [5]
```

If we are interested in the question of whether a biotransformation will be accomplished or not, then we should reformulate [5] in order to get a production rule:

"If a starting product cX undergoes process P in organ N at time T and in concentration Q, then the end product cY will be formed in organ M at time U in concentration Q." In HC form:

```
END__PRODUCT(*COMPOUND1,*ORGAN1,
    *TIME1,*CONCENTRATION1):                 [6]
    START__PRODUCT(*COMPOUND2,
  *ORGAN2,*TIME2,*CONCENTRATION2),
    PROCESS(*PROCESS__NAME,
    *PREREQUISITES)
```

Formula [6] is an example for one of the general axioms (see Appendix I) of Metabolexpert. These axioms, which form the skeleton, so to speak, of the system, can be classified into four groups:

(1) description of the living system
(2) description of the chemical structure of compounds
(3) description of metabolic reactions

(4) description of transport processes

Appendix II presents a more detailed list of general axioms.

THE METABOLEXPERT FAMILY

In logic programming, a strong connection exists between the model represented by HCs and the programs, or the knowledge bases assigned to the program. Essentially, you can use a good part of the HCs formed during the problem definition and analysis directly or indirectly to write the pilot version of the program, since Prolog accepts the HCs without modifications and the built-in theorem-prover of the language lets you answer questions by reasoning directly on the HCs. Similarly, the HCs provide a way of formalizing the knowledge bases in the design phase.

At the same time pilot versions help to give some idea of what the existing hardware possibilities allow in problem solving if your goal is a realistic running time limit. The expert system for predicting metabolic pathways by building up a biotransformation graph was produced in five different, evolving versions. The most sophisticated one, Metabolexpert 4.1,[19] provides a complete build-up of the biotransformation graph with 20 organs (or compartments).

Besides generating metabolism pathways, the system can simulate pharmacokinetic behavior of the compounds by built-in calculation modules for first- and second-order kinetics. Structural dependencies of transport phenomena have been considered by calculating the logP of the compounds with PRO-LOGP, an LPG-based expert system.[17] PRO-LOGP uses Rekker's approach[18] to estimate logarithmic 1-octanol/water partition coefficients of the compounds. A rule-based module limited transport of the compounds between organs and compartments depending on their logP value. Albumin binding was estimated by calculating QSAR equations (if they related to the compound). Unfortunately, Metabolexpert 4.1, working on an IBM AT, was not very effective, since running times were long and memory space limited the storage of knowledge bases.

In addition, the present practice of considering metabolic and pharmacokinetic investigations as separate disciplines that are normally performed at different company departments limited the real need for such a complex system. Metabolexpert 5.40[20] is tailored to the needs of organic chemists and researchers involved in investigations of drug metabolisms. The knowledge base of the system is composed of rules of possible metabolic transformations, extracted from Testa-Jenner's textbook.[21] The standard knowledge base has 112 rules. A flexible module enables the user to modify or delete existing rules or input new ones. Every rule is composed of four series of definitions:

- substructures to be changed during the metabolic transformation
- new substructures formed
- a list of substructures that should be present in the molecule for the transformation
- a list of substructures whose presence excludes the metabolic transformation

Metabolic pathways are generated automatically or under manual control of the run. In metabolite generation, a breadth-first strategy has been used: Transformation possibilities are searched in the order in which they appear in the knowledge base. After finishing the formation of the first-order metabolites, second- and higher-order products are formed. It is possible to limit the maximum number of metabolites. By searching manually, you can exclude formation of a metabolite (and, consequently, its higher-order metabolites, too).

Chemical structures of the metabolites are displayed on the screen just after the system has suggested their formation. Metabolexpert 5.40 uses a Smile-like linear notation for representing chemical structures.[21] An attachment to a molecular graphics program (Molidea[22]) forming and displaying 3D structure of the parent compound and its metabolites is also provided.

The connection between the parent compound and its metabolites might be quite complicated — some metabolites are formed from different intermediates, others by different metabolic routes. A treelike picture representing the metabolic fate of the substance helps to orient the researcher performing the run. On request, the system also calculates logP values for the parent compound and its metabolites by using PRO-LOGP. Calculation time is under one minute per compound.

Metabolexpert 5.40 runs on an IBM AT (with 640K-byte core memory, CGA or EGA color monitor); a VAX version is under preparation.

PROGRAM RESULTS WITH METABOLEXPERT

Metabolexpert allows users to modify and complete the metabolism transformation knowledge base by drawing from their own experiences. This feature might be used to improve the prediction ability of the system in a specific case. Such a change always risks the possibility that the modification diminishes the predictive precision of the system for other compounds. A benchmark series of compounds is needed that lets users check the overall effect of the knowledge base modifications.

A benchmark series for metabolism investigations should be composed of compounds that represent the structural variation within the field of interest — in our case, common compounds synthesized during medicinal chemistry research. In addition, only those substances that have carefully measured and well-known metabolic pathways should be included. The pathways should also represent the typical and important metabolic transformations within the targeted field, medicinal chemistry. For the composition of the series, personal decisions whether to include or exclude some controversial metabolites are also indispensable. Taking all of these in mind, we decided to include Testa-Jenner's selected metabolic scheme[21] in the Metabolexpert compound

Table 1. Benchmark compounds for Metabolexpert

Name	No. of identified metabolites
Amphetamine	11
Caffeine	7
Diazepam	6
Diphenidol	6
Hexobarbital	8
Imipramine	13
Lidocaine	9
Medazepam	8
Methadone	10
Nicotine	17
Oxazepam	8
Perazine	5
Propranolol	9
Thebaine	9
Trimetoprim	6

database as a standard benchmark series. As Table 1 shows, there is a wide variety of structural and pharmacological activity.

In the case of the benzodiazepines, the metabolisms of the three listed compounds are not independent of each other, since oxazepam and diazepam might be formed in vivo from medazepam. As a consequence, they have common metabolites. The metabolites listed by Testa and Jenner are detected in humans or in common laboratory animals.

Figure 2 depicts the metabolic fate of amphetamine and its reproduction by Metabolexpert 5.40. It is well known[23] that phenylethylamines are hydroxylated on the methylene group adjacent to the aromatic ring. The reaction is probably catalyzed by dopamine-β-hydroxylase, which normally transforms dopamine to epinephrine. Metabolexpert reproduced the reaction well. p-Hydroxylation of amphetamine resulting in III was found in many species,[24] while p-hydroxylation of norperinephrine (leading to IV) is the main metabolic pathway in man and rat.[23] Both derivatives were generated by the system, too. Metabolexpert failed to suggest, however, the formation of the N-hydroxy metabolite (XII), which is formed in rabbits. Consequently, formation of phenylacetone oxime (XIII) was also not predicted.

Deamination of amphetamine leading to phenylacetone (VII) is believed to be performed by microsomal amine oxides[24] in man and rat. Formation of VII was correctly predicted by Metabolexpert. Unfortunately, the system failed to predict further transformations starting from VII: its reduction to phenylisopropylalcohol (VIII) and the oxidation and sulfonylation producing IX and X. It is worth mentioning, however, that the ratio of phenylacetone VII and phenylisopropanol VIII varies widely among species.[24] Thus, this metabolic transformation is a somewhat typical case in which the knowledge acquisitor took a different position than the experts preparing the metabolic chart. Finally, Metabolexpert correctly suggested glucuronide conjugations of the hydroxylated products (III, IV).

Run time for generating a total of six metabolites of amphetamine was less than 4 minutes on an IBM AT with a clock speed of 6 MHz.

CONCLUSIONS

LPG offered a lot of advantages when building up Metabolexpert. It provided a metalanguage for formalizing the mathematical model, for collecting the knowledge base and putting together the first pilot version of the program. A collection of the metabolic transformations in HCs seems to be a good compromise between human and machine, since this form of knowledge representation is both human and machine readable. Human control assures the correct semantic meaning of the rules, while machine intelligibility allows them to be interpreted in a manner that is relatively free of subjective errors. In fact, from the standpoint of LPG, Metabolexpert may be considered a formal tool that interprets a compound's metabolic possibilities over the knowledge base.

The example in the last section shows, on the other hand, that the predictive achievement of Metabolexpert is not negligible. In fact, all the primary metabolites were correctly predicted except one, and the same holds for the secondary metabolites. As for the tertiary metabolites (in this case, phase II transformations), glucuronidation of the generated second-order metabolites was also correctly predicted. No extra metabolites were predicted in this case, although this is not typical: Metabolexpert routinely predicts substantially more metabolites than published in the literature. Some of these compounds, however, are derivatives, which, according to our present knowledge, might be formed within the body, and, theoretically, they can sometimes still be detected.

Metabolexpert is currently used in universities and pharmaceutical companies. Routine use of the system revealed three theoretical and practical problems, as follows:

(1) Current formulation of the rules treats compounds as independent sets of substructures. This approach makes it difficult to draw conclusions when a property assigned to the whole compound controls the metabolic transformation. A good example is the p-hydroxylation of aromatic rings in non-condensed polyaromatic compounds, where normally only one or a few benzene rings will be hydroxylated.

(2) Stereoselectivity is still not handled by the system, while a number of metabolic reactions cannot be treated without considering stereoselectivity.

(3) Controversial difficulties arise on attempting to formalize rules when selectivity within and between species, or dependency on experimental conditions, may seriously influence metabolite formation.

As to problem 1, efforts are underway to incorporate quantum chemical calculations into the system at a later

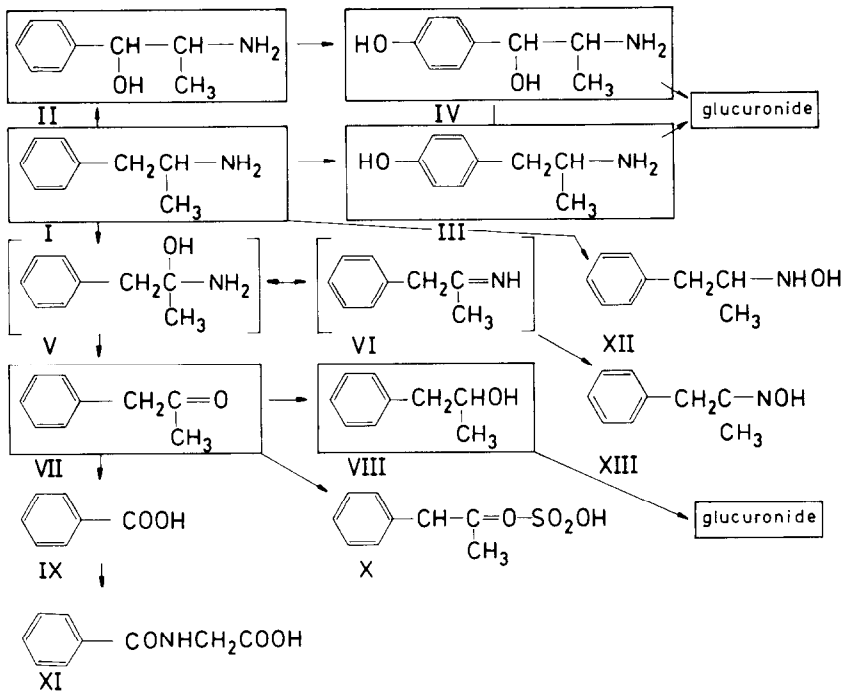

Figure 2. Metabolic chart of amphetamine according to Testa and Jenner[21]

development stage. Metabolexpert is a host-type system that accepts calculation programs. On the other hand, consideration of stereoselectivity (as required by problem 2) calls for a complete revision of the present system. Problems in rule formation (like problem 3) can be circumvented partially by asking experts in particular areas of metabolic transformation to contribute their knowledge to the system. The first step has just been taken in that direction.[25] A second possibility is to obtain more feedback by publicizing the system more widely. To encourage this, the latest version of Metabolexpert comprises a full list of metabolic rules. An electronic bulletin-board system to collect responses is also being organized.

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APPENDIX I

First-order predicate calculus (FOPC) can be considered a specific branch of formal logic, which is derived from Aristotelian logic.[26] If we use FOPC to describe a particular domain of the world, we should express hypotheses and facts as axioms. You can express FOPC in an especially machine-readable form by converting it to Horn clauses (HC). Prolog and its many dialects (such as MPROLOG, TPROLOG, Quintus Prolog, Turbo Prolog, Arity Prolog[27]) are computer languages that can accept, interpret and handle HCs more or less directly. In fact, their elementary operation is a kind of machine reasoning (or, more precisely, the pattern-matching operation necessary to perform *modus ponens* reasoning of FOPC). In addition, every PROLOG dialect should include nonlogical elements like input/output operations and string manipulation on HCs or lists.

FOPC is a formal system[26] that has an object language, a set of axioms and an inference rule.

Object language of FOPC is constructed of the first-order logic. First-order logic can be constructed from a set of primitive symbols and a set of elements. Primitive symbols of FOPC are (a) parentheses, (b) variables, constants, mathematical functions and letters denoting predicate names, (c) logical connectors like and (&), or (V), not(−), implication (−>), or equivalence (<−>); logical quantifiers: "for all," and "there exists." Elements of the language are composed of the primitive symbols. A term is defined recursively as a constant or variable, or if f is an n-ary function, and $t1, t2, \ldots tn$ are terms, then $f(t1, t2, \ldots tn)$ is a term. Thus, "AMPHETAMINE" or "*ANY__COMPOUND" is a term. Another method you can use to denote an object is to use a predicate symbol for that purpose. Predicate symbols can have variables: POSSIBLE__METABOLITE(*X,*Y).

Suppose we have P as an n-ary predicate symbol and $t1, t2, \ldots tn$ as terms. Then, $P(t1, t2, \ldots tn)$ is called an atomic formula. An atomic formula used in assertive or in negative sense is a literal. Thus, -POSSIBLE__METABOLITE(*X,*Y) is a literal. A clause is a set of literals in which all of the variables are implicitly universally quantified and correspond to this formula:

$$L1 \,\&\, L2 \,\&\, \ldots \,\&\, LM -> M1 \; V \; M2 \; V \ldots . \; V \; MN \qquad [7]$$

where L and M are literals. Clauses where n is 1 or 0 are called Horn clauses (HCs).

Axioms of the FOPC are HCs that describe the domain modeled. Axioms representing the most important features of the models (normally, types of facts) are the general axioms (GAs), like [6]. Axioms describing particular features of the model are particular axioms (PAs), like [2].

As an inference rule, the classical *modus ponens* has been used in FOPC.

APPENDIX II

Below is a summary of the most important general axioms (GAs) of Metabolexpert. Readers interested in more details are advised to consult Reference 28.

(a) GAs for describing the living system. The human body is described as being assembled from organs, some of which are connected to each other, each containing one or more enzymes, which may cause metabolic reactions.

LIVING__SYSTEM(*NAME,*LIST__OF__ORGANS). [8]
CONNECTED(*ORGAN1,*LIST__OF__ORGANS). [9]
CONTAINS(*ORGAN,*LIST__OF__ENZYMES). [10]

(b) Description of the chemical structure of a compound is provided by GAs defining an element of a connection table:

CONNECTED(*ATOM1,*BOND,*ATOM2) [11]

Chemical and physico-chemical properties are assigned

to atoms, substructures or whole compounds. The chemical knowledge representation used[29] stores knowledge in a tree structure; branches of the tree correspond to the most important properties that determine reactivity toward biological material (e.g., hydrophobic, electronic and steric properties).

(c) An example of a GA representing a metabolic transformation is given by [2].

(d) Structural conditions of transport processes are represented by GAs like [12]:

TRANSPORT(*COMPOUND,*BLOOD, *BRAIN): VALUE(*COMPOUND, LOGP,1.80 < > 2.20) [12]

General axiom [12] shows that a compound might be transported from the blood to the brain if its logP value is higher than 1.80 and lower than 2.20.