

## TIMES について (ホームページ掲載資料)



The screenshot shows the OASIS website interface. At the top, there is a navigation menu with links for HOME, ABOUT, NEWS, RESEARCH, PRODUCTS, TOOLBOX, SUPPORT, and DOWNLOADS. The main content area features a blue header with the word "SOFTWARE" and a search bar. Below this, there is a section for "TIMES" with a thumbnail image of the software box. The text describes the software's function in predicting toxicity based on metabolic activation. To the right, there is a "MODELS" section with a list of models included in the software.

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# SOFTWARE

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## TIMES

**Predicting toxicity of chemicals resulting from their metabolic activation**

TIMES (tissue metabolism simulator) is a heuristic algorithm used to generate plausible metabolic maps from a comprehensive library of biotransformations and abiotic reactions. It allows prioritization of chemicals according to the toxicity of their metabolites. The list of transformations is prioritized on the basis of estimated system-specific probabilities of occurrence of these transformations. Additionally, the reliability of generated pathways, metabolites and maps was assessed according to the extent they had been supported by observed metabolism data. Hence, besides metabolites, one could also prioritize competing metabolic pathways according to their probability of occurrence and reliability. The reliability estimates could facilitate the strategic selection of chemicals for testing in order to expand the domain of the simulator most effectively. The ability of TIMES to predict in the same interface the metabolism of chemicals and toxicity resulting from their metabolic activation is an important advantage of the method. Presently, the TIMES platform is used to predict skin sensitization, mutagenicity, chromosomal aberrations and micronucleus formation taking into account the metabolic activation of chemicals. Apart from genotoxicity the systems allows prediction of hormonal toxicity. Presently it includes models for predicting ER/AR and AhR binding affinities.

### MODELS

**MODELS INCLUDED IN TIMES**

- Human Health Endpoints
- Metabolic simulators

<http://oasis-lmc.org/products/software/times.aspx>

# MATABOLISM

## In vitro Rat S9 Metabolism

### Endpoint

The *in vitro* rodent microsomal/S9 metabolic simulator (transformation table) reproduces and predicts the metabolic pathways of xenobiotic chemicals for *in vitro* experimental systems such as rodent (mostly rat) liver microsomes and S9 fraction.

### Data

The metabolism training set contains experimentally observed (documented) *in vitro* metabolic pathways for 261 parent chemicals of a wide structural diversity, and 1070 observed metabolites compiled into a searchable electronic database. Published data on the metabolism of these chemicals in rodent (mostly rat) liver microsomes and S9 fraction, collected mainly from research publications in scientific journals and, also, from some websites were extracted and introduced into an electronic database [1].

### Model

The simulation of metabolism is focused on the correct reproduction of experimentally observed metabolites [2, 3]. The current *in vitro* rat liver metabolic simulator represents electronically designed set of 509 structurally generalized, hierarchically arranged biotransformation reactions. These molecular transformations are characteristic for the metabolism in the presence of *in vitro* experimental systems such as rodent (mostly rat) liver microsomes and S9 fraction. Each transformation in the simulator consists of source and product structural fragments, and inhibiting "masks". A probability of occurrence is ascribed to each transformation, which determines its hierarchy in the transformation list. Thus the modeling is based on the set of principal molecular transformations, and the *in vitro* "logic" of the commonly observed metabolism with the corresponding experimental systems.

The following types of molecular transformations are included into *in vitro* simulator:

- ▶ 25 - 30 abiotic (non-enzymatic) and, also, a few enzyme-controlled reactions believed to occur at a very high rate as compared to the duration of the tests. The highest priority (probability of occurrence) is assigned to these reactions. This subset of reactions includes also transformations of highly-reactive functional groups and intermediates, such as tautomerizations, arene epoxide rearrangements to phenols, etc. which occur spontaneously.
- ▶ 450 - 470 enzymatic phase I (mostly CYP450-catalyzed) transformations such as aliphatic C-oxidation, aromatic C-hydroxylation, oxidative N- and O-dealkylation, epoxidation, ester and amide hydrolysis, carbonyl group reduction, nitro and azo group reduction, N-hydroxylation, etc.
- ▶ 15 - 20 enzymatic phase II transformations, such as glucuronidation, sulfation, glutathione conjugation, N-acetylation, etc. Significantly lower priorities are assigned to these transformations as compared to phase I ones in accordance with the observed *in vitro* metabolism pattern.

### Domain

The derivation of the structural domain of simulator is based on atom-centered fragments.

### Statistics

Average sensitivity (probability that the metabolite is predicted, given that the metabolite is truly observed) is 80 %.

Average predictability (probability that the metabolite is truly observed, given that the metabolite is predicted) is 36 %.

# TIMESの操作画面

The screenshot displays the TIMES software interface with several key components:

- Parent chemical and list of generated metabolites:** A list of chemical structures and their corresponding metabolites is shown in the top-left pane.
- Hierarchically ordered list of transformations:** A list of transformations is displayed in the middle-left pane, ordered hierarchically.
- Preview of the generated metabolic tree:** A metabolic tree diagram is shown in the bottom-left pane, illustrating the relationships between the parent chemical and its metabolites.
- Metabolites Filter Options:** A dialog box titled "Metabolites Filter Options" is open in the bottom-right, allowing users to filter metabolites based on various criteria such as Quantity, Probability, LogP, and Water/Lipidity Ratio.

Chemical structure shown: CC(=O)C1OC1

Metabolites Filter Options dialog details:

- Quantity: 4 from 5 unique, 4 from 9
- Probability: [checkbox]
- LogP: [checkbox]
- Water/Lipidity Ratio: [checkbox]
- Filter by type of transformation: [checkbox]

CLOSE X