

Simulating kinetics of metabolism. QSAR application

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INTRODUCTION

Toxicodynamics (i.e., hazard) and toxicokinetics (i.e., absorption, distribution, metabolism, elimination; ADME) are the foundational elements of predictive toxicology. Over the past 50 years, toxicodynamics has been the main focus of predictive toxicology. More recently, toxicokinetic factors have been shown to be essential for providing a transparent and comprehensible scientific basis for many toxicological predictions.

The chemical reactions involved in simulating metabolism can be organized into metabolic pathways. Each step along a pathway represents a molecular transformation that converts the source molecule into one or more products. The rate at which each transformation occurs determines how much of the source molecule will be depleted over a given period, making reaction rates an essential focus of toxicokinetics.

For predicting the rates of metabolic reactions we rely on both global and local molecular descriptors. In this proof-of-concept, hydrolysis, hydroxylation and dealkylation transformations are covered. To achieve our goal, we first developed a formalism to represent metabolite quantities as functions of time, and then estimated the parameter values used in the model equations in a way that maximizes the performance over external chemicals.

EVOLUTION OF SIMULATING METABOLISM

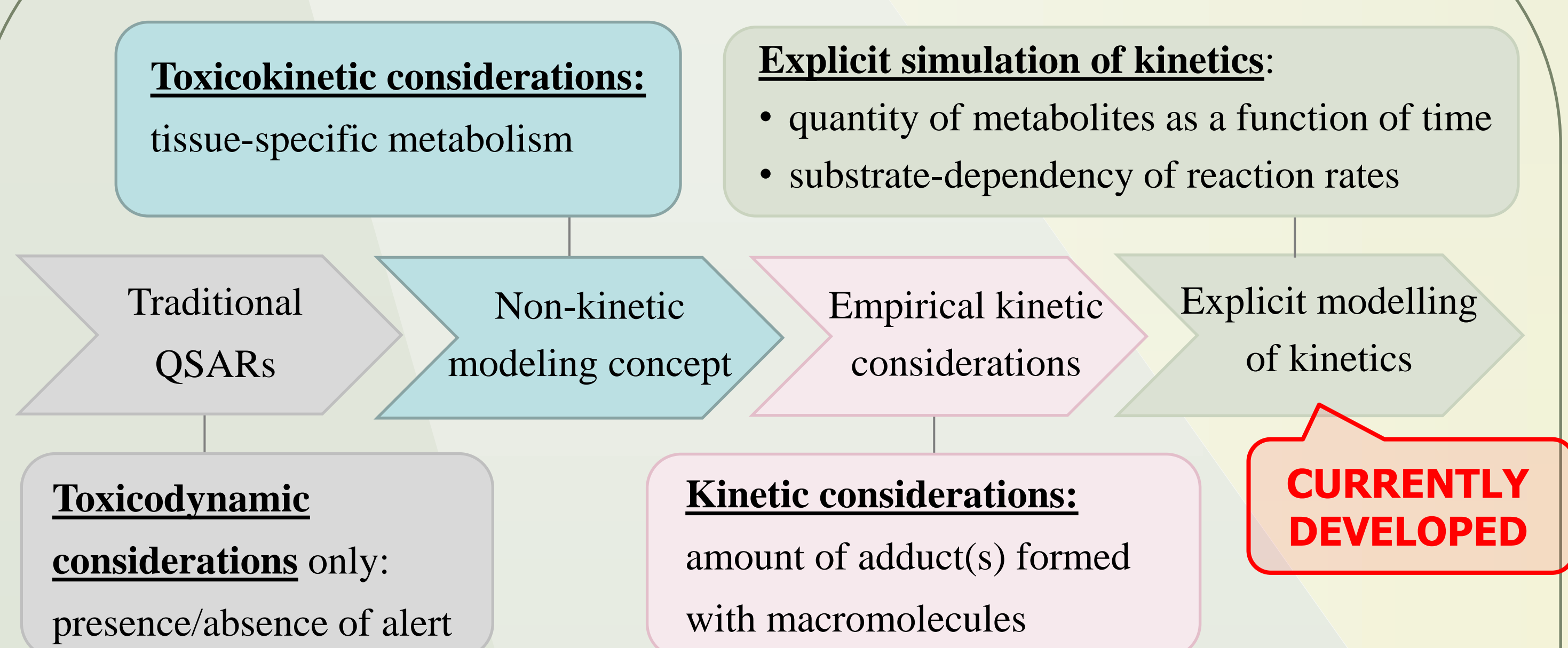


Fig. 1. History of LMC efforts in simulating metabolism

- 1) Traditional mechanistic (Q)SAR models – provide predictions based on toxicodynamic factors justified by the presence of alert in the parent molecule
- 2) Non-kinetic modelling concept – relies on simulating tissue-specific metabolism and searching for alerts within the parent and all generated metabolite(s)
- 3) Empirical kinetic considerations – relate the effect to the extent of damage that could be caused to macromolecules:
 - ✓ The presence of alerts is necessary, but not sufficient for eliciting effect
 - ✓ The amount of formed adducts is time-dependent
 - ✓ Empirical thresholds of the formed protein adducts are defined for each potency level
- 4) Explicit simulation of kinetics – quantity of metabolites are calculated through elaborated formalism and predicted rates of reactions

EXPLICIT SIMULATION OF KINETICS - ASSUMPTIONS AND FORMALISM

The current work is founded on the following assumptions [1]:

- Quantities of metabolites follow the kinetics of first order,
- Parallel transformations contribute simultaneously and independently to the overall rate of the reaction, and
- Depletion rates of reactions depend on the type of transformation AND the properties of the chemical undergoing the transformation.

First-order kinetics

$$\frac{dQ_L(t)}{dt} = -k_L Q_L(t) + g_L Q_{L-1}(t)$$

L – level of metabolism
 $Q_L(t)$ – quantity at level L as function of time
 k_L – rate of depletion for Q_L
 g_L – rate of generation for Q_L

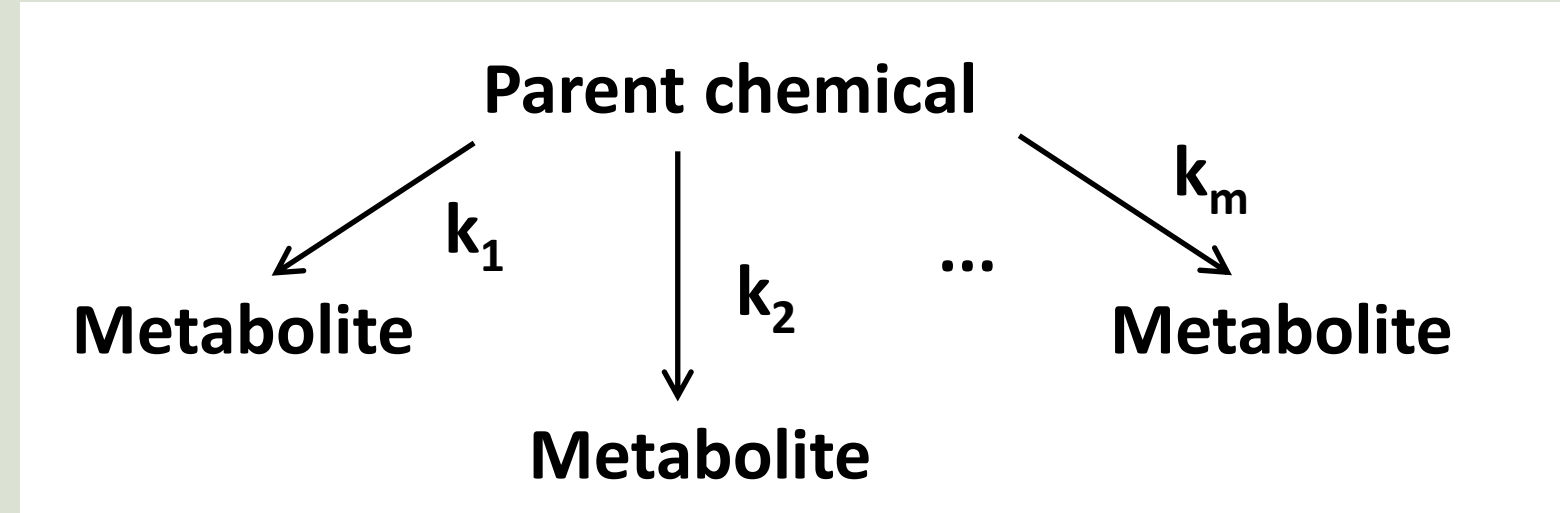
$$Q_0(t) = Q_0(0) e^{-k_0 t}$$

$$Q_1(t) = Q_1(0) e^{-k_1 t} - Q_0(0) g_1 \left[\frac{e^{-k_0 t}}{k_0 - k_1} + \frac{e^{-k_1 t}}{k_1 - k_0} \right]$$

...

Parallel transformations

$$k_{total} = k_1 + k_2 + \dots + k_m$$



- The number of combinations transformation + chemical is infinitely large
- A model for predicting depletion rates is required

References:

- [1] Chapkanov et al., *Comput. Toxicol.*, 37(2026), 100394. doi:10.1016/j.comtox.2025.100394
- [2] Ramanujulu et al., *Eur. J. Med. Chem.*, 63(2013), 378-386. doi:10.1016/j.ejmech.2013.02.007

BUILDING OF THE MODEL

Available experimental data

Experimental values for half-life (HL) were collected due to lack of depletion rates:

- 2302 HL for 1497 chemicals remained after pre-processing,
- Inter-test variability is approx. $0.25 \log_{10}$ based on 23 HL values,
- Now, we focus on Phase I reactions, resulting in more electrophilic metabolites,
- Current model was built over 113 HL values for rat, for 113 chemicals undergoing only hydrolysis, hydroxylation or dealkylation reactions.

Generalization of transformations and selection of parameters

The transformations were generalized via “elementary” transformations:

- 1) Attaching a heavy atom, and
- 2) Cutting a bond between heavy atoms.

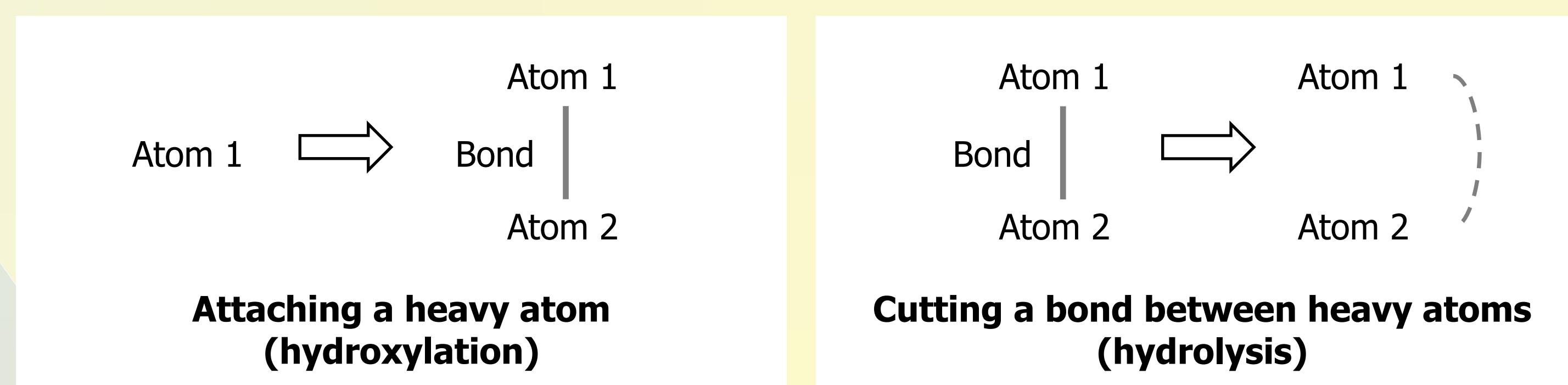


Fig. 2. Outline of elementary transformations

A separate equation was introduced for each elementary transformation.

Various kinds of parameters were employed in order to account for different aspects of the depleted chemical:

- Global parameters (2D and 3D), and
- Local (atomic and bond) parameters.

Accuracy of predictions

- The best model's RMSE is $0.31 \log_{10}$ for training chemicals and $0.38 \log_{10}$ for validation chemicals (selected via bootstrapping),
- The decomposition of the RMSE yields $0.25 \log_{10}$ experimental and $0.19/0.28 \log_{10}$ modelling error.

Examples

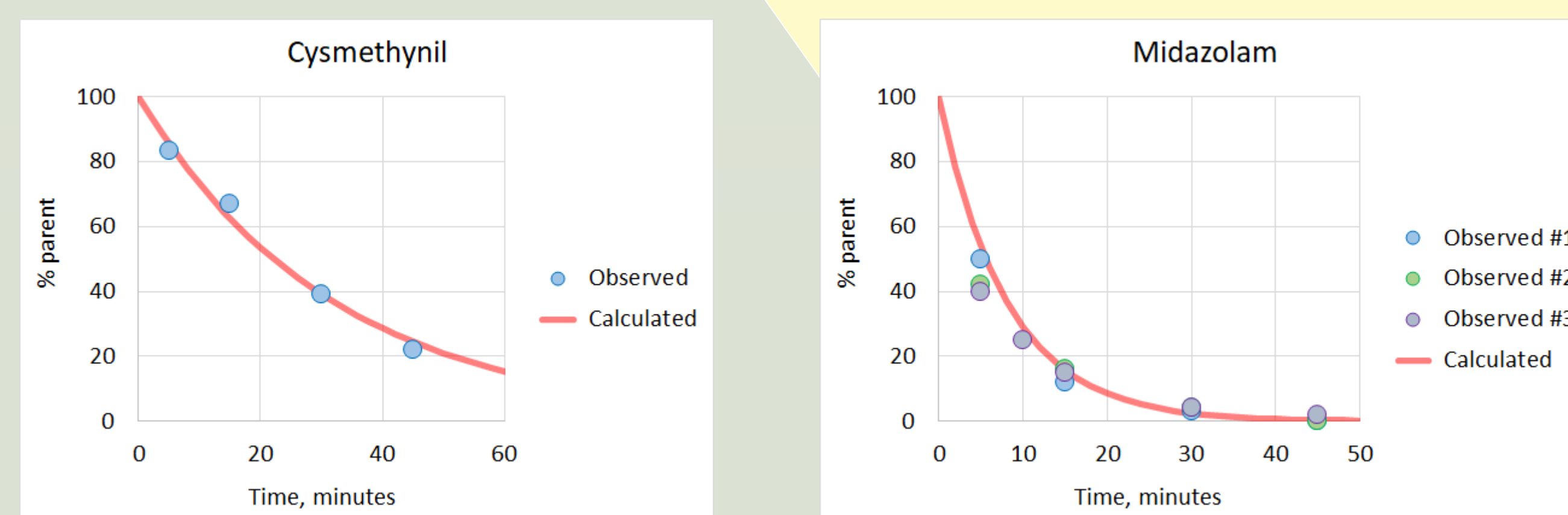


Fig. 3. Observed versus calculated quantities for cysmethynil (test compound, left) and midazolam (positive control, right) relative to initial amounts in rat liver microsomes [2]; both are external chemicals belonging to the parametric domain of the model

CONCLUSIONS

1. The accurate simulation of metabolism requires knowing of reaction rates and quantities of metabolites formed with time.
2. The current work demonstrates that using modelling descriptors related to the entire molecule, alongside local parameters for the fragments depicting the transformations a chemical undergoes, produces stable models with reliable predictions.
3. The described results should be viewed as preliminary, nevertheless they are promising as the modelling error is comparable with the experimental uncertainty.