

Modelling Chemically-Induced Cell Toxicity: an Open Source Implementation of a Virtual Cell Based Assay Model



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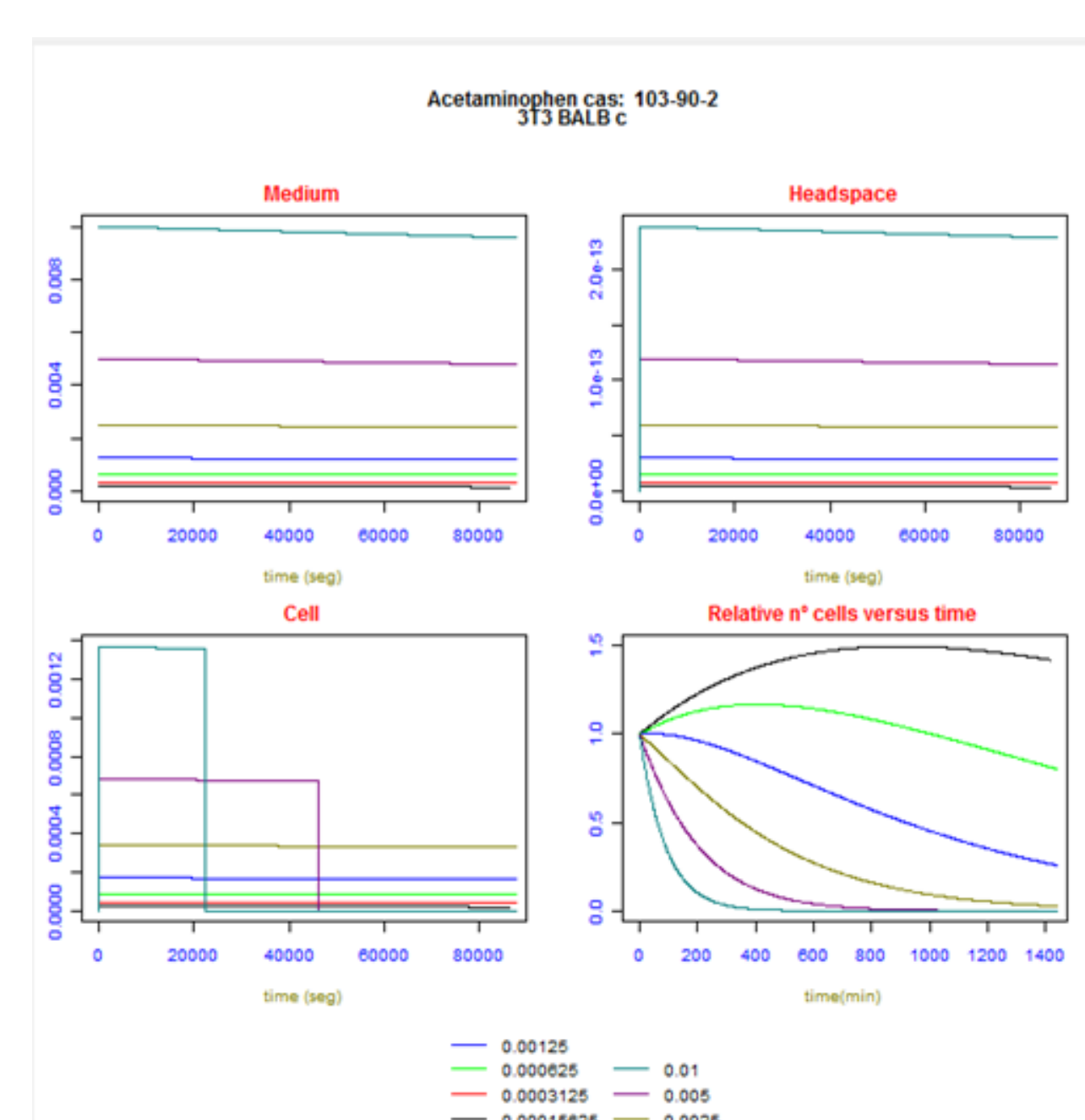
Introduction and Aims

The Virtual Cell Based Assay Model is an open source version written in KNIME, MySQL and R to analyse the chemical cell toxicity process. The Virtual Cell Based Assay Model is applied to HTS experiments and takes into account fate, cell dynamics and toxicology process. For input, a MySQL database stores the data related with cell lines, chemical compound, toxicological data, and a KNIME node created in house allows selecting specific parameters for a particular simulation. The model is written in R (KNIME) node and the output is a spread sheet and graphic (R-view KNIME node).

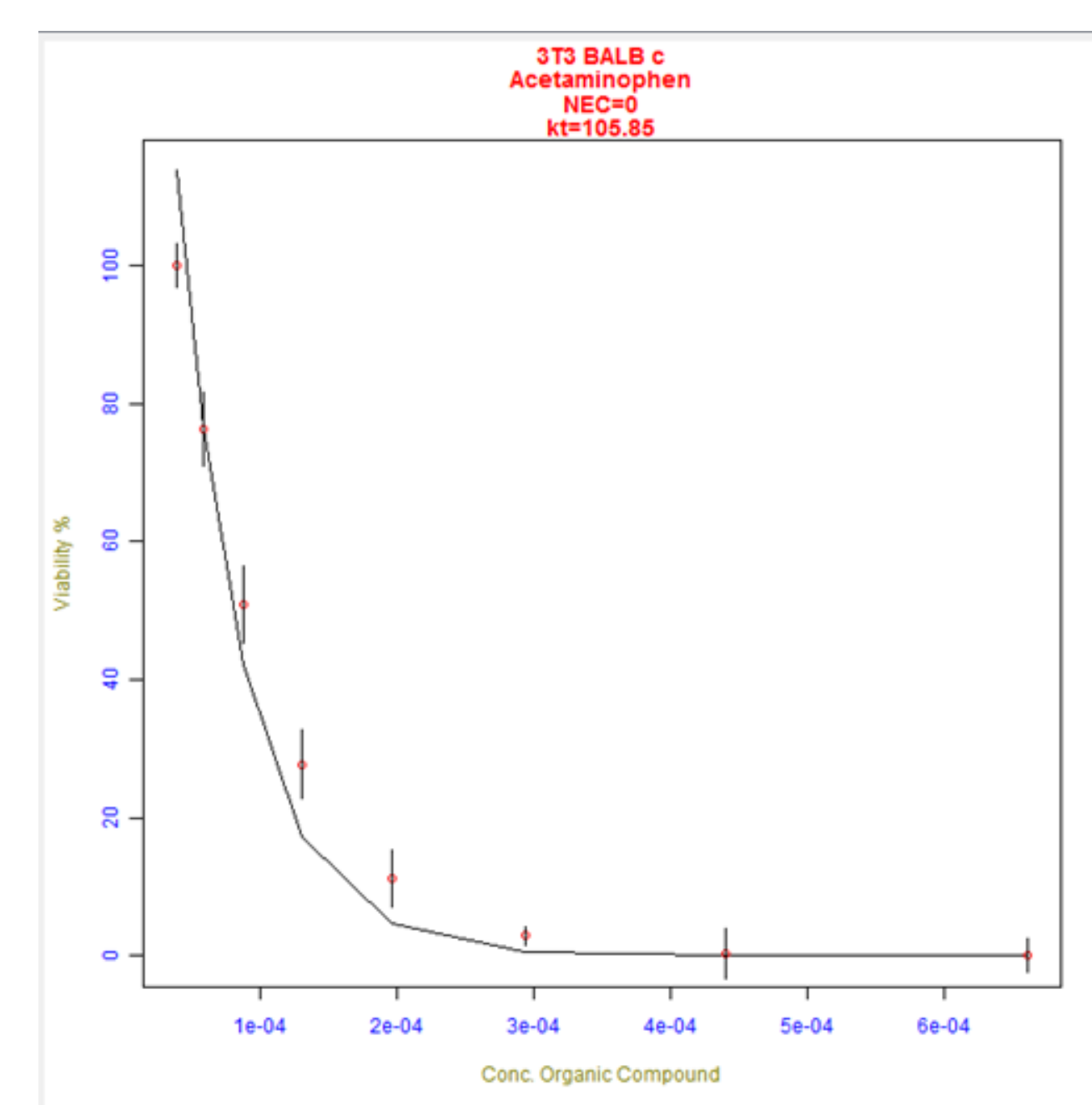
Results

Cell Based Assay Model Simulations:

- Cell Based Assay Model.
- Optimisation No Observed Effects and killing rate parameters.
- Repeat dose.



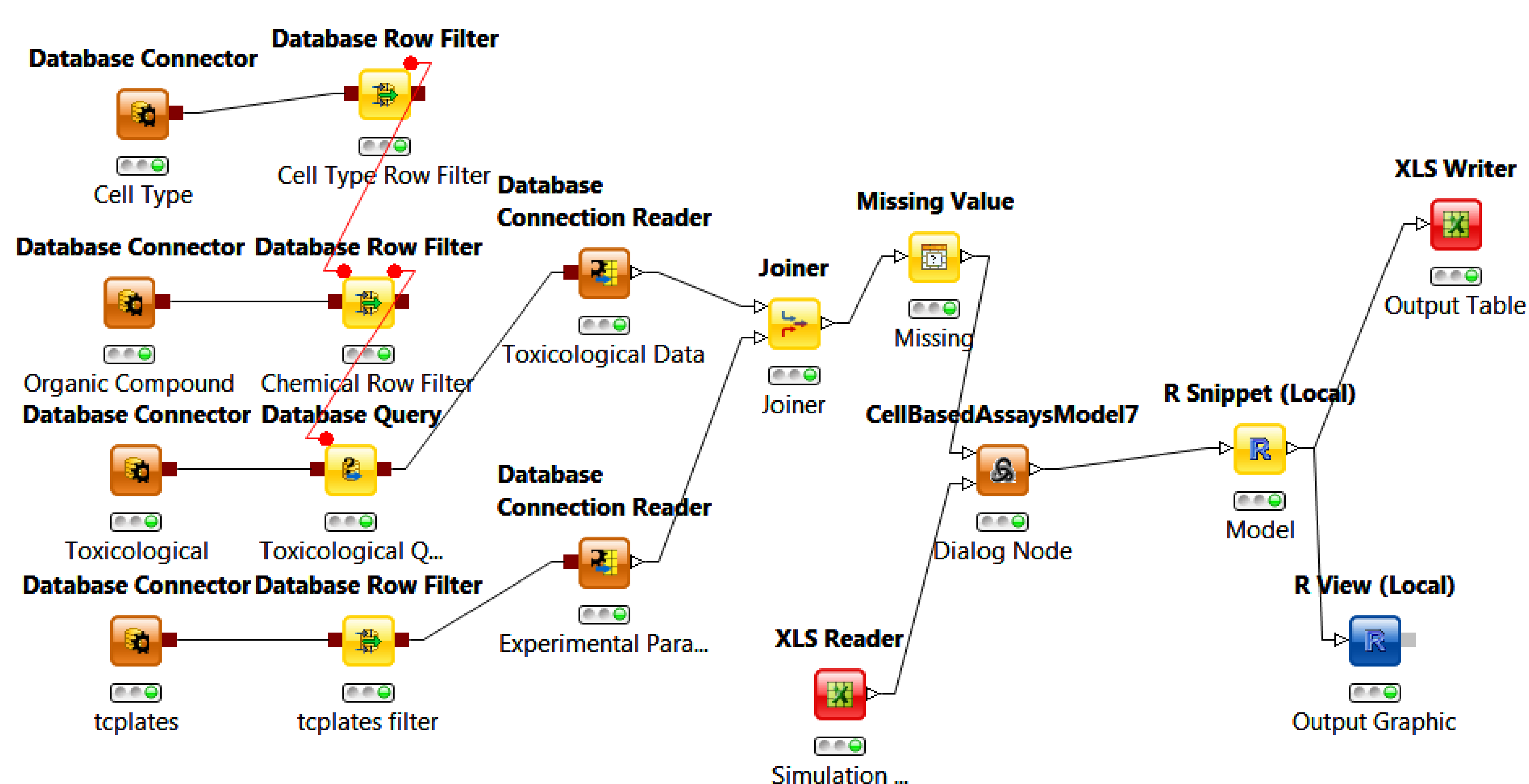
a) Cell Based Assays Model. Simulation of toxicity of Acetaminophen in 3T3 BALB cells. Conc of Aminophen in the medium, headspace, inside of the cell and cell viability versus time.



b) Parameter optimization. Values of No Effects Concentration (NEC) and killing rate are optimized by minimization of differences between experimental and simulated viability.

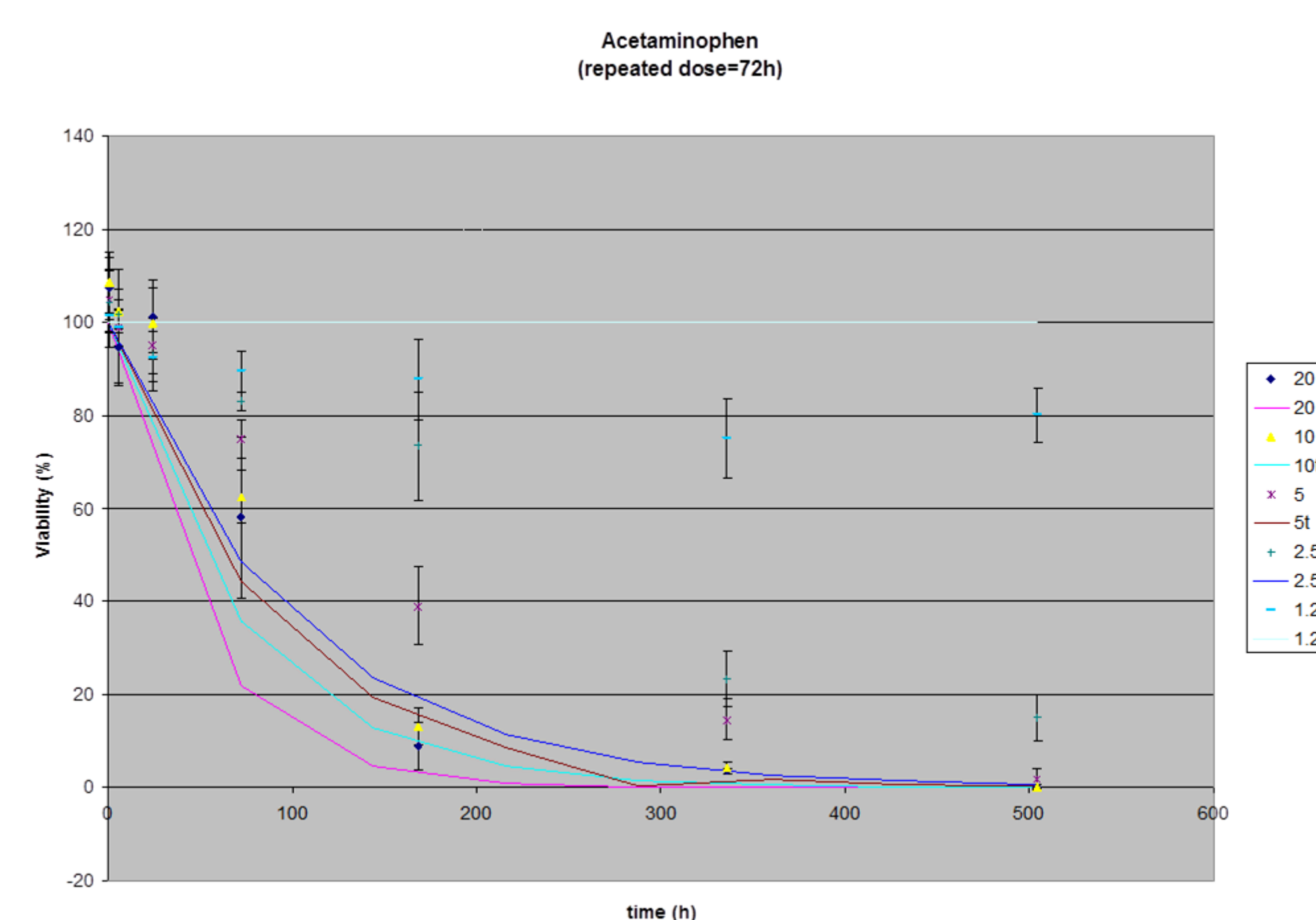
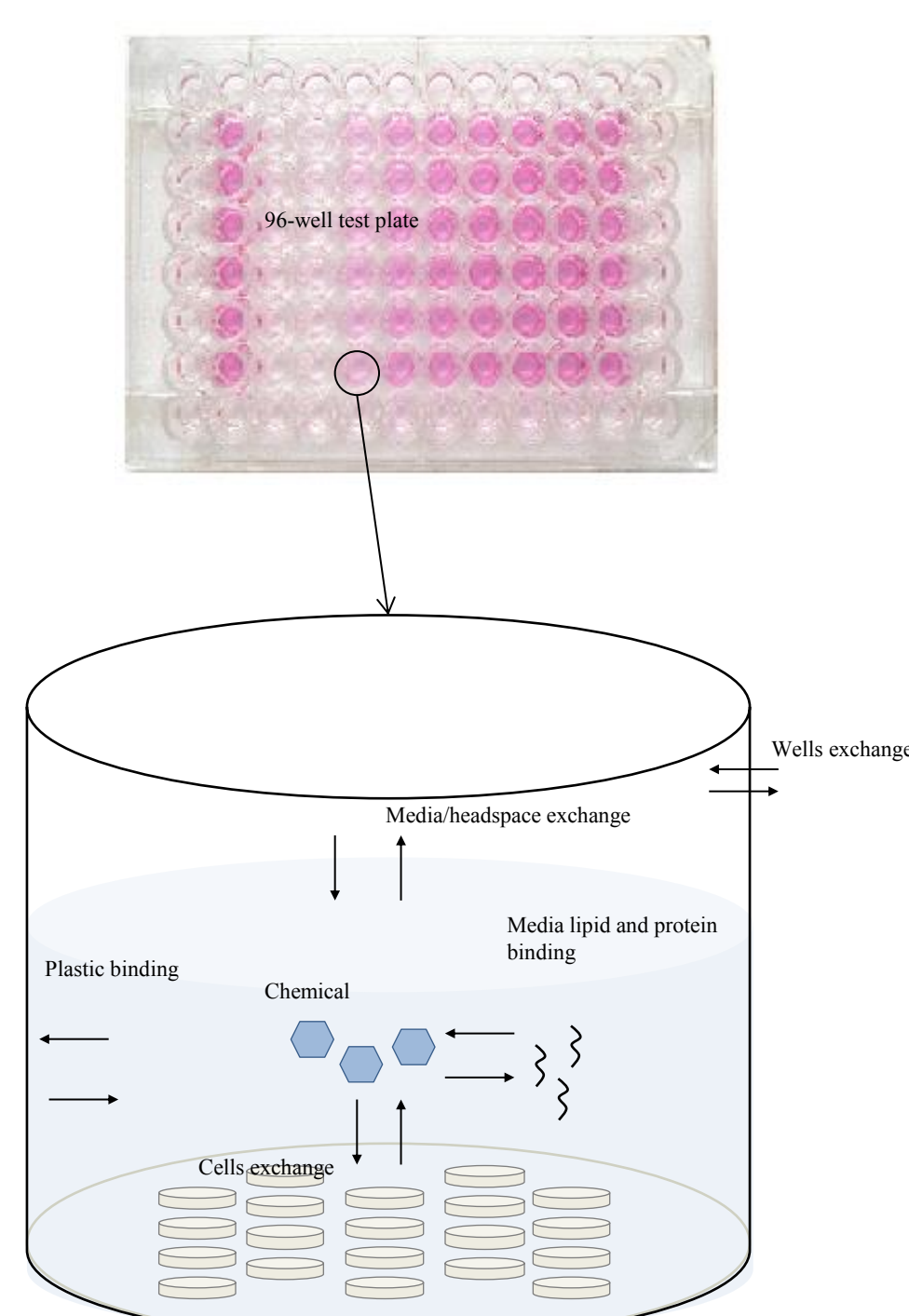
Methods

Cell Based Assay Integrated Model: KNIME Workflow details



Cell Based Assay Model characteristics:

- Several operational models:
 - Cell based Assay Model
 - Parameter Optimisation
 - Check Optimisation
 - Repeat Dose
- Clear Differentiation of Zones
 - Input
 - Modelling
 - Output



c) Repeat dose. Effect of 7 repeat doses during 72 h exp. of Aminophen in HepaRG cells. Simulated and experimental values versus time

Conclusions

Cell Based Assay model can be considered as a tool to describe the processes during an HTS lab experiment, i.e. the concentration in the medium, in the headspace, inside the cell of the chemical versus time and the viability of the cells. Knowledge of the concentration inside of the cell allows to study cell toxicity considering the concentration of the chemical that really affects the cell excluding the chemical adsorbed in the vessel, losses by evaporation and so on and thus a better tool for *in vitro in vivo* extrapolation.

Reference

Zaldívar, J. M., Mennecozzi, M., Macko, P., Rodrigues, R., Bouhifd M., and Baraibar, J. (2011) A biology-based dynamic approach for the modelling of toxicity in cell assays: Part II: Models for cell population growth and toxicity. EUR 24374 EN - 2011

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