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EDITORIAL

Systems biology meets toxicology

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In this issue of the Archives of Toxicology, Hans Westerhoff and colleagues present a comprehensive review on how systems biology tools can be applied to toxicology (Geenen et al. 2012; this issue). For decades, scientists in the field of toxicology have taken advantage of available mathematical models. Typical examples include physiologically based pharmacokinetic (PBPK) models used to predict in vivo concentrations of xenobiotics and to identify the concentration ranges for in vitro testing that are relevant to the in vivo situation (Jonsson et al. 2001; Mielke et al. 2011; Heise et al. 2012). Moreover, quantitative structure-activity relationship (QSAR) modelling has been successfully applied to predict, for example, mutagenic or irritating compounds (Lilienblum et al. 2008; Rupp et al. 2010; Dorn et al. 2008; Hengstler et al. 2006). Combinations of classical biostatistics, classification algorithms and modelling have also been applied to predict toxic pathways and patient prognosis from complex OMICS data (Ellinger-Ziegelbauer et al. 2008; Zellmer et al. 2010; Kammers et al. 2011; Hellwig et al. 2010). More recently, spatial-temporal modelling has been introduced to predict how tissues respond to toxic damage and how the damage and repair processes compromise the tissue function (Höhme et al. 2007, 2010).

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However, with the advent of systems biology, a multitude of novel technologies also became available, and although many are quite promising, none have been sufficiently integrated into toxicological research. Therefore, the editors are happy that Hans Westerhoff and colleagues have contributed a review that can easily be described as a "Manual of systems biology for Toxicologists" (Geenen et al. 2012; this issue). For their focus, they have chosen a topic that is familiar to every toxicologist: glutathione metabolism.

When toxic metabolites exceed a threshold where glutathione synthesis cannot compensate, toxicity is a likely end point.. Hans Westerhoff and colleagues use this example to illustrate the currently available systems biology tools and how they can be used to predict critical disruption of the glutathione network. Examples are.

- The use of *equations* that altogether result in ordinary differential equations (ODEs) to translate the biochemistry of reactions into mathematics
- The simulation of a oxoprolinuria patient by perturbation of the Vmax of glutathione synthetase based on *steady state analysis*
- Exploration of the impact of individual reactions on flux through the glutathione pathways by *metabolic control analysis*
- Prediction of the expected levels of change in response to toxic effects by *robustness analysis*.

The review article of Westerhoff and colleagues illustrates that the ability to quantitatively simulate the occurrence of toxicity as a result of disturbed cellular defence systems remains no longer the elusive pot of gold at the end of the rainbow! The article comes highly recommended to everyone interested in systems biology tools for toxicological research.

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