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Guest editorial:

INTEGRATED SPATIOTEMPORAL-METABOLIC MODELLING BRIDGES THE GAP BETWEEN METABOLISM ON THE CELLULAR LEVEL AND ORGAN FUNCTION

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Recently, Schliess et al. (2014) have introduced a novel concept of spatiotemporal modelling. This work is of general interest, because it offers a possibility to bridge the level of metabolic functions at the subcellular level to tissue architecture and organ function. The authors used an already established spatiotemporal model of a liver lobule (Hoehme et al., 2010; 2007). This model simulates the position and coordinated movement of all hepatocytes in a representative lobule during the destruction and regeneration process after intoxication with hepatotoxic compounds. Moreover, it contains the microvessel of the liver lobule that allows simulation of perfusion and dry transport. The authors used this model to additionally integrate metabolic process into the simulated hepatocytes (Schliess et al., 2014). Metabolic pathways of ammonia metabolism, the urea cycle in periportal and glutamine synthetase in the pericentral comportment of the liver lobule, were modelled as differential equations and integrated into the hepatocytes of the spatiotemporal model. The resulting integrated model allows the simulation of ammonia and its metabolites in the liver vein (the 'liver outflow') for a given concentration in the portal vein (the 'liver inflow'). Moreover, the model predicts to which degree a certain extent or pattern of liver tissue destruction will compromise ammonia detoxification. This novel technique of integrated spatiotemporal tissue modelling may have a major impact on studies of organ toxicity in future (Wierling, 2014; Godoy et al., 2013; Drasdo et al., 2014; Hammad et al., 2014). Currently, studies on hepatotoxicity are often performed *in vivo* in rodents (Nussler et al., 2014; Zhang et al., 2013; Ghallab, 2013; Kanda et al., 2008; Monteiro et al., 2013; Köhle et al., 2008; Jaeschke et al., 2012; van Kesteren et al., 2013; Hammad et al., 2013; Hadi et al., 2013; Lo et al., 2012). On the other hand *in vitro* systems with hepatocytes represent a popular system to analyse molecular mechanisms (Messner et al., 2013; Godoy et al., 2009, 2010a, b; Hengstler et al., 2009; Klingmüller et al., 2006; Schyschka et al., 2013; Watzek et al., 2013; Muguruma et al., 2008; Grinberg et al., 2014; Schaap et al., 2012; Schug et al., 2013; Doktorova et al., 2012a, b; Ilkavets, 2013; Gagné et al., 2012; Fraczek et al., 2013; Fernandes et al., 2003). Although cultivated hepatocytes represent a valuable tool to qualitatively study molecular mechanisms it still is difficult to extrapolate their impact at the organ level. The work of Schliess et al. (2014) is a first step in establishing modelling techniques that bridge the levels of intra or even subcellular metabolic pathways to the functionality and metabolic performance of entire organs.

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