Machine-Learning Aided Multi-Scale Modelling Framework for Toxicological Endpoint Predictions in the Dog

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Introduction

Preclinical studies on two species, i.e. a rodent and a non-rodent (e.g. dog) are routinely conducted to provide safety evidence according to current regulatory guidelines for new chemical entities (NCEs), resulting in large numbers of animals used in research and development (R&D). At the same time, a large amount of data and knowledge about animal physiology and biology have been generated and gained, calling for refinement or reconsideration of the two-species paradigm. Hence an integrative in-silico approach is proposed to assess NCEs by conveying available info into a virtual species to avoid or reduce the extensive testing on animals.

Objectives

Our work aims to develop a suite of virtual dogs to refine, reduce and potentially replace dog testing, especially in chronic toxicity studies. We develop a machine-learning aided multi-scale modelling framework (MLMMF) to integrate kinetic, molecular, and physiological knowledge. The MLMMF combines advanced modelling and computational technologies including ordinary differential equation (ODE) modelling and ML-aided automatic computational workflow to visualize, curate, and integrate various data and knowledge maps (e.g. adverse outcome pathways), illustrated in Figure 1.

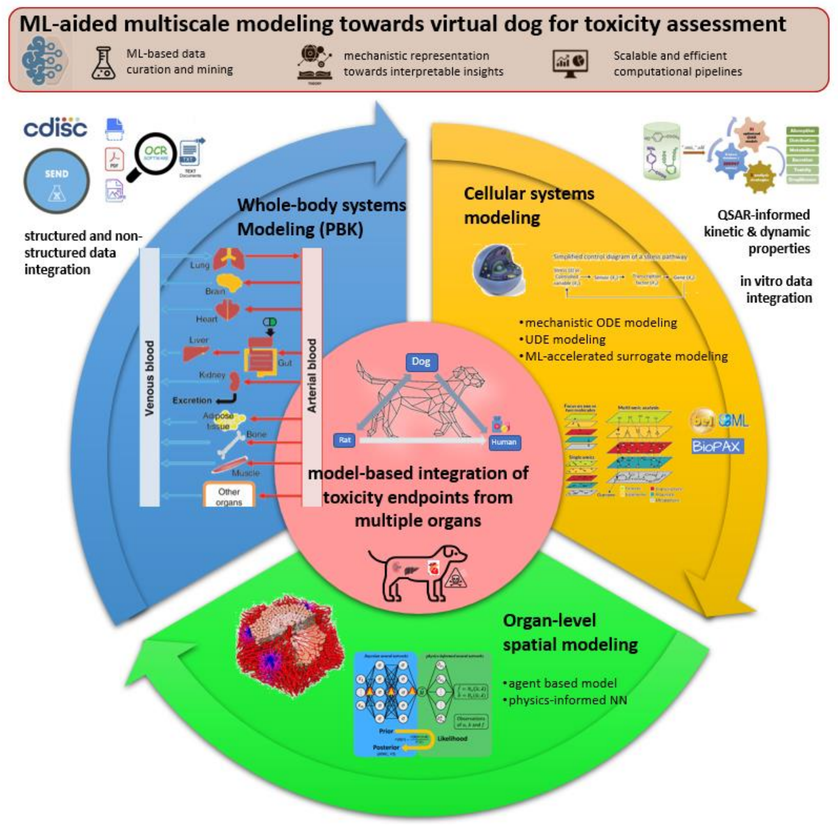

Figure1:Machine-learning aided multi-scale modelling framework(MLMMF) for the integration and translation of molecule and systems knowledge to predict (systemic) exposure and toxic effects in dogs. The MLMMF will combines several computational, modelling &simulation technologies, integrated with existing and to be curated data(-bases) and knowledge maps, to develop a library of mechanistic PBK and toxicodynamic models.

Proof of concept study

As a prove-of-concept (PoC) study to test the MLMMF as illustrated in Figure 2, our presented study focuses on hepatotoxicity (e.g. steatosis), as one of the most frequent types of toxicity observed [1]. The toxic effect is modelled in a knowledge-based but key-event centric fashion, offering insights into different levels of biology.

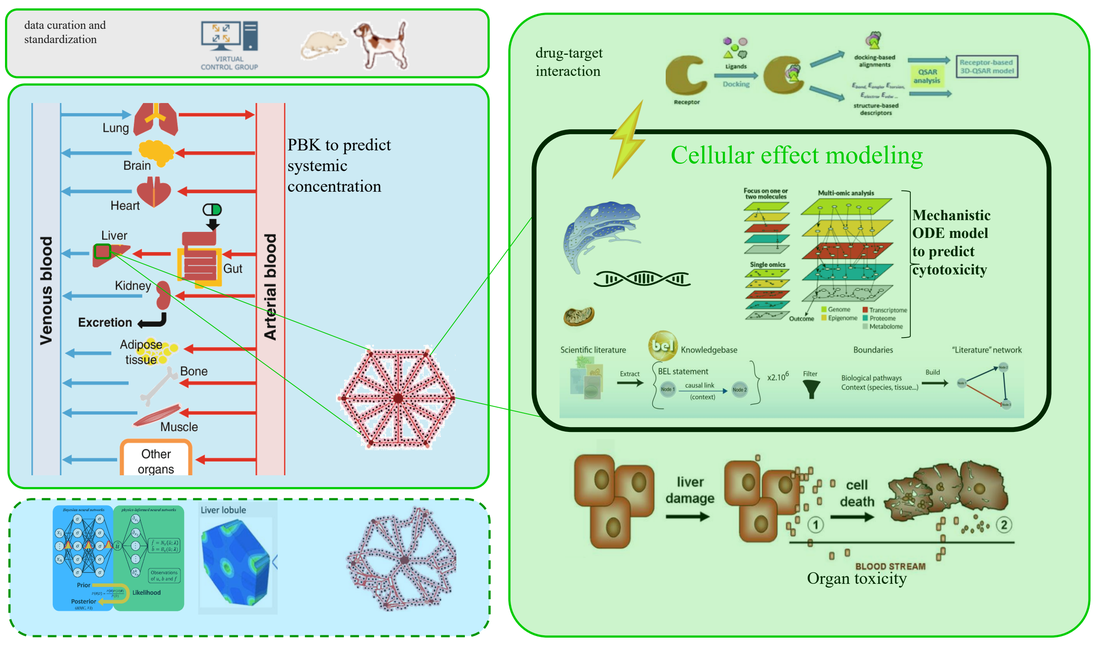

Figure 2: For the PoC study we standardise and analyse in-vivo data from dog control groups donated from project partner, eTRANSAFE. A single toxicological endpoint and corresponding use-cases was selected based on data richness and prior computational modelling knowledge, focusing on adverse outcomes with well-established AOPs in the liver. The cellular effect model will be integrated with the dog WB-PBK compound models.

These models first incorporate cellular apical key processes related to hepatoxicity [2]. Second, we incorporate liver metabolism and cellular signalling like cellular stress, nuclear receptor, and cytotoxicity pathways [3]. Such integration is empowered by both manual and automatic curation of dog-specific knowledge and data from various resources. Third, we extend cell turnover or cytotoxicity models to mimic organ effects, resulting in multiscale models. Established multiscale models enable further integration with ODE-based whole-body physiologically based kinetic (WB-PBK) models for dogs in the Open Systems Pharmacology Suite [4], see PBK template of beagle and associated physiological parameters in Figure 3 and Table 1, respectively.

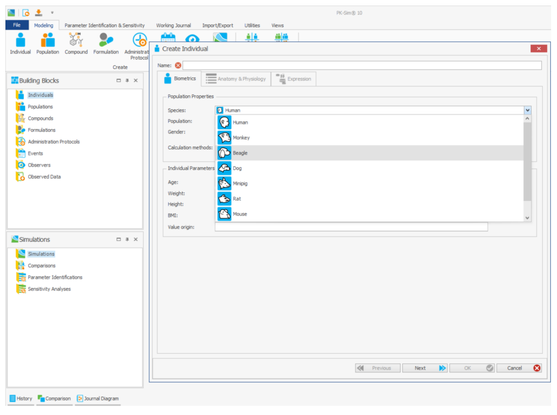

Figure 3: PK-Sim snapshot of the various species, laboratory animals, rodents and dogs, farm animals, birds and humans that the PBK model can run for. Beagle as well rat are also part of the list. Physiological parameters of a beagle is incorporated in PK-Sim beagle template, see Table 1.

Table 1. Physiological parameter of the beagle (BW 10.5kg) relevant for PBK modeling as reported from (Willmann et al., 2010 and in PK-SimV10)

Tissue	Organ Volume (ml)	Organ blood volume flow (ml/min)
Bone	880	172
Brain	73	51
Adipose (fat)	2101	65
Gonads (Testes)	10	2
Heart	81	103
Kidneys	50	346
Stomach	85	53
Small intestine	266	232
Large intestine	61	69
Liver	373	102
Lung	68	1915
Muscle	5387	457
Pancreas	22	39
Skin	500	154
Spleen	27	72
Portal vein	150	464

We adapt a (sub)model of liver lipid metabolism from [5] and generate simulations of steatosis associated molecules like triglycerides (tag) when the level of cholesterol is perturbed, see simulations in Figure 4.

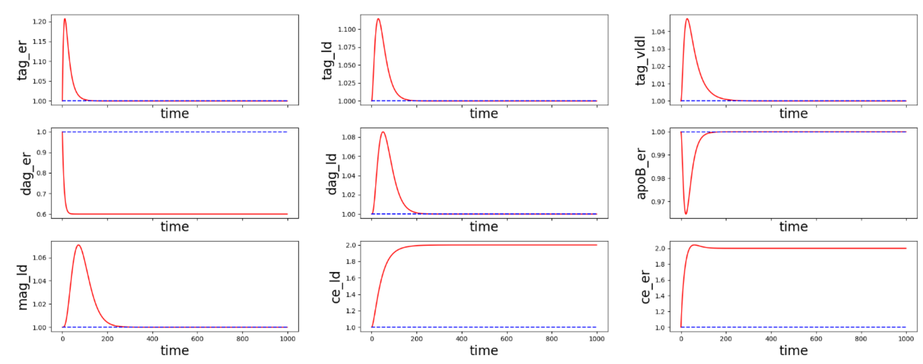

Figure 4 Simulations of molecules under steady state and perturbed conditions. Simulations account for normalized dynamics of triglycerides and related molecules including diglycerides (dag), monoglycerides (mag), Apolipoprotein B (apoB), cholesteryl esters (ce) in multiple cellular compartments like very-low-density lipoprotein (vldl), lipid drop (ld).

Virtual control group of dog studies and modeling integration

To facilitate uptake in pharmaceutical research and development, our MLMMF is tailored to “the standard for the exchange of non-clinical data” (SEND). Our framework is further equipped with a user-friendly interface to visualize and analyse virtual control groups (VCG) for dogs implemented in both R and Jupyter notebook. We showed a sample of laboratory test results from SEND datasets donated from eTRANSAFE consortium [7], see Figure 5. We plan to incorporate the distributions into our MLMMF simulations to predict effects in dogs under exposure of compounds with steatosis liabilities.

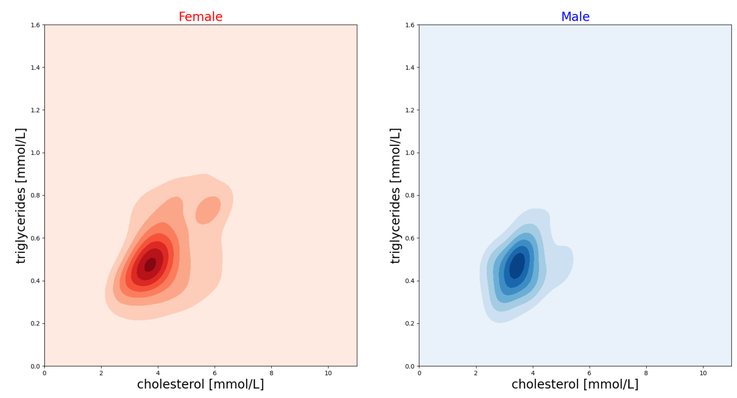

Figure 5: Distributions of cholesterol and triglycerides measured from plasma samples from dogs in control groups (original subject-level data are not presented). left for female, right for male. This info will be integrated into further development of MLMMF.

Perspectives

We plan to integrate a few identified databases with dog-specific information or knowledge into our MLMMF workflow. We envision that the MLMMF can provide significant 3Rs benefits by offering (i) insightful extraction and explanation of factors on adversity for VCGs [6], (ii) mechanistic understanding of adversity progression for treatment groups, and (iii) reliable prediction of chronic toxicity using short-term data.

References

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