Multiscale mechanistic models in Systems Pharmacology: development of a model describing Atorvastatin PK through integration of metabolic network in PBPK models

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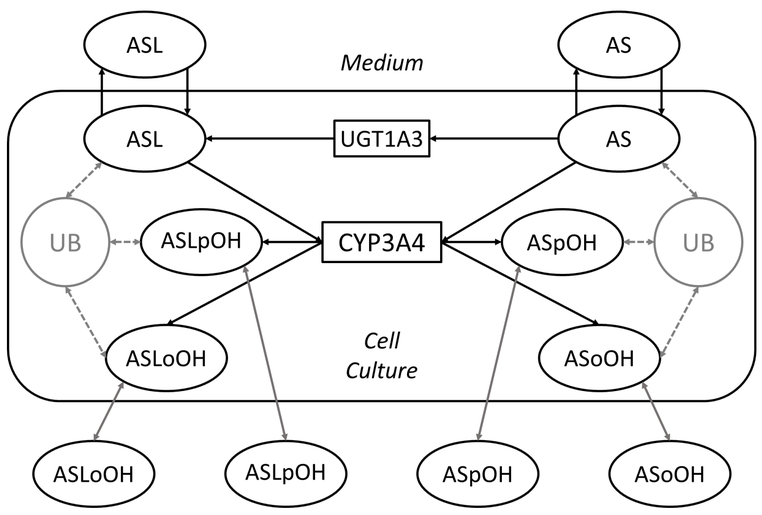
BACKGROUND.

This work aims to develop a Whole Body Physiologically Based Pharmacokinetic (WB-PBPK) model of Atorvastatin (AS), an HMG-CoA reductase inhibitor, and its metabolite AS-lactone (ASL) to predict drug plasmatic concentration in human through integration of *in vitro* experiments and prior physiological knowledge. Drug hepatic metabolism was described using a rescaled *in vitro* derived metabolic network coupled with the PBPK model. All the analysis were performed with an in-house PBPK platform written in MATLAB.

MATERIALS AND METHODS.



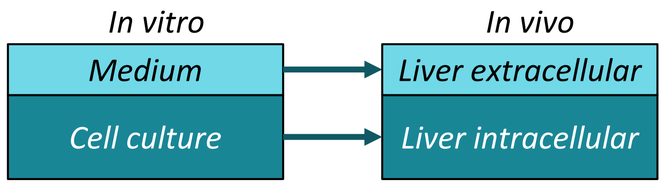
In vitro

1) *In vitro* model of AS metabolism.

A metabolic network describing the metabolism of AS parametrized through *in vitro* experiments with hepatocytes was taken from the literature [1].

2) *In vitro – In vivo* rescaling of the network.

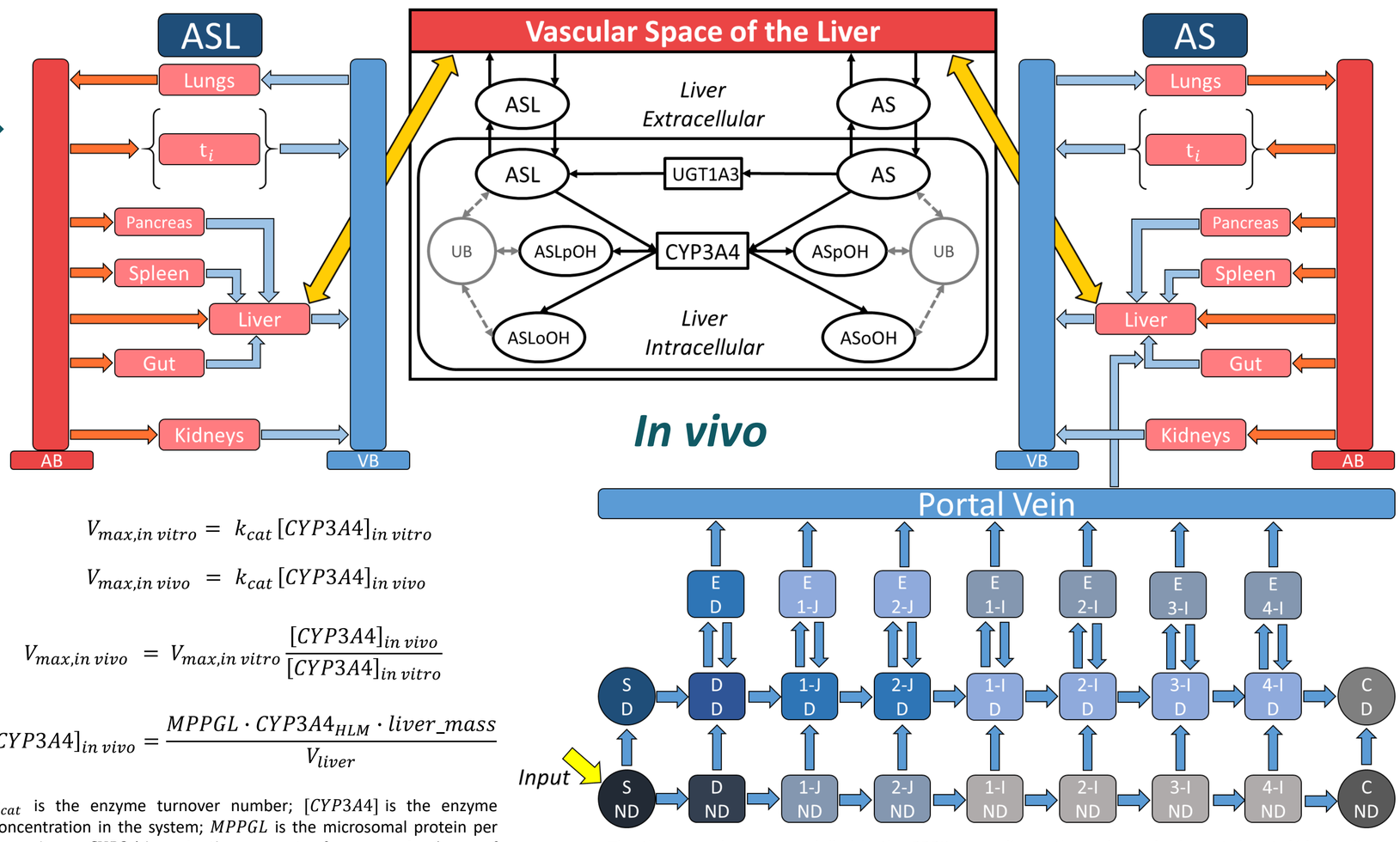
The idea was to use this *in vitro* derived metabolic network to describe the *in vivo* metabolism of AS in the liver. The network was rescaled considering the difference in terms of enzymatic amount between the culture of hepatocytes and the liver.



3) Development of the PBPK model and integration with the metabolic network.

An ACAT model was built for AS. Metabolism due to CYP3A4 activity in enterocytes was added using an intrinsic clearance derived from *in vitro* experiments [2] as in [3] and the Q_{gut} model [4] was used to model the absorption in portal vein. Two PBPK models were developed, one for AS and the other for ASL, and were coupled with the ACAT model. Each PBPK models thirteen organs and tissues, each one described as *well-stirred* compartment, except the liver that was modelled as *permeability limited* and was coupled with the rescaled metabolic network. All the parameters used come from *in vitro* experiments and prior physiological knowledge.

$$\frac{dc_{liver,extr}}{dt} = \frac{Q_{liver}}{V_{liver,extr}}\left(c_{art} - \frac{c_{liver,extr}}{P_{t:p}/P_{b:p}}\right) + \sum_{i=1}^{7} exit\_enterocytes_i + venous_{input} - k_{in,network}\ c_{liver,extr} + k_{out,network}\ c_{liver,intr}$$



$$V_{max,in\ vitro} = k_{cat}\,[CYP3A4]_{in\ vitro}$$

$$V_{max,in\ vivo} = k_{cat}\,[CYP3A4]_{in\ vivo}$$

$$V_{max,in\ vivo} = V_{max,in\ vitro}\,\frac{[CYP3A4]_{in\ vivo}}{[CYP3A4]_{in\ vitro}}$$

$$[CYP3A4]_{in\ vivo} = \frac{MPPGL \cdot CYP3A4_{HLM} \cdot liver\_mass}{V_{liver}}$$

k_{cat} is the enzyme turnover number; $[CYP3A4]$ is the enzyme concentration in the system; $MPPGL$ is the microsomal protein per gram liver; $CYP3A4_{HLM}$ is the amount of enzyme in $1mg$ of microsomal protein.

The tissues and organs modelled in the PBPK are: *adipose tissue*, *bone*, *brain*, *gut*, *heart*, *kidneys*, *liver*, *lungs*, *muscle*, *pancreas*, *skin*, *spleen*, *arterial* and *venous blood*.

RESULTS.

Predicted C_{max}, AUC and t_{max} of AS venous plasma concentration for $40mg$ oral administration are in the range of one standard deviation from the mean of clinical data collected by [5]. For the dose of $20mg$ predicted AS C_{max} and t_{max} remain in the range of one standard deviation from the mean of the data [5] but AUC is underpredicted. Concerning ASL the model under-predicts all the metrics except t_{max}. This is probably due to the conversion from AS to ASL that occurs in other sites than liver where UGT enzymes are expressed, for example gut wall and kidney. Finally a global sensitivity analysis was performed to understand how the parameters variation affects model output metrics C_{max} and AUC.

Compound	Single oral dose of AS (mg)	C_{max} (ng/ml)		t_{max} (h)		AUC ($ng \cdot h/ml$)	
		Predicted	Observed[a]	Predicted	Observed[a]	Predicted	Observed[a]
AS	40	14.81	12.7 ± 7.8	1.34	1 (0.5 – 3)	79.54	61.4 ± 36.2
ASL	40	0.18	4.2 ± 2.4	1.34	3 (1 – 8)	0.98	53 ± 27.3
AS	20	7.39	6.9 ± 3.66	1.33	1.8 ± 1.0	39.7	98.7 ± 48.4
ASL	20	0.09	3.6 ± 2.4	1.40	3.4 ± 2.5	0.49	75.1 ± 40.1

[a]*Data collected in [5], presented as Mean ± Standard deviation, or Mean (min value – max value).*

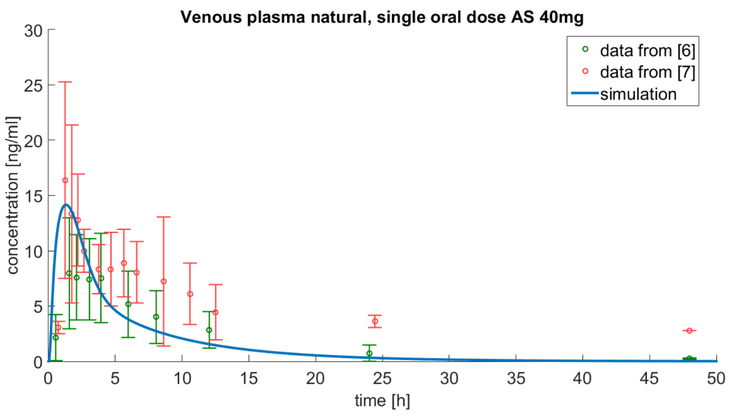


Figure I. Here the predicted venous plasmatic profile of AS following $40mg$ AS oral administration in a male subject (height $176\ cm$, weight $73\ kg$) is reported.

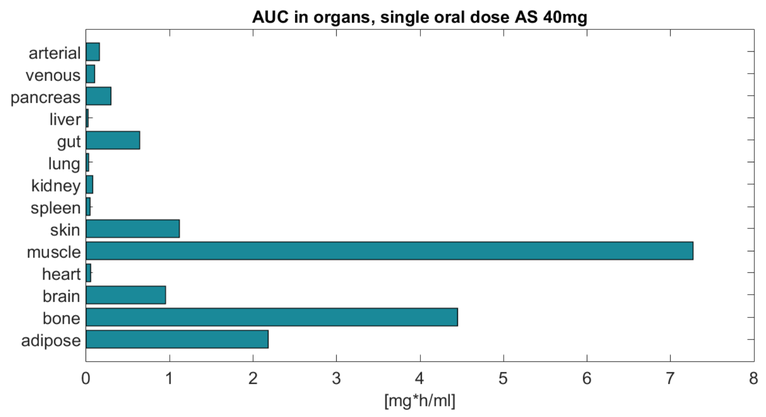
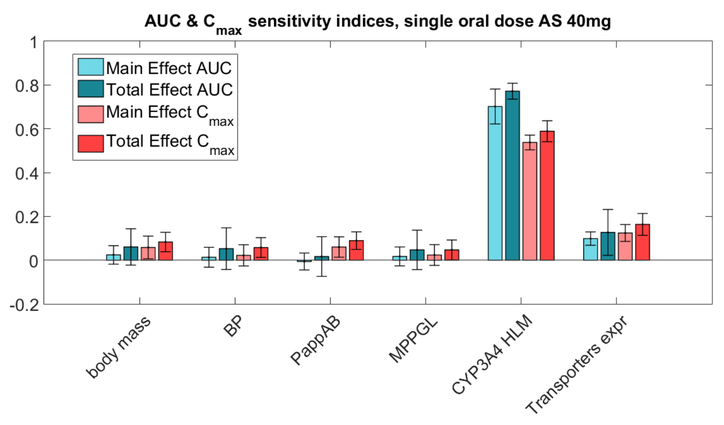


Figure II. Here AS AUC in each organ calculated from the same simulation of *Figure I* is reported. It can be seen that the drug distributes primarily in muscles, adipose tissue and bones. A so high AUC in brain could be attributed to the non-consideration of the blood-brain barrier in the model.

Figure III. Global sensitivity analysis was performed using a variance based method as described in [8]. If possible the range of variation of all the parameters was set to their physiological one, otherwise the range was set from 0.5 to 1.5 the value of the parameter. It can be seen that the variance of both the metrics is majorly explained by the variation of the CYP3A4 amount in liver microsomes $CYP3A4\ HLM$.



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