Development of population based approaches to describe the complex pharmacokinetics of simvastatin in different individuals.

"Bridging the gap between population and PBPK modelling"

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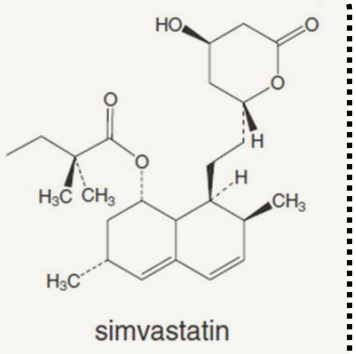
Manchester Pharmacy School

Motivation



simvastatin

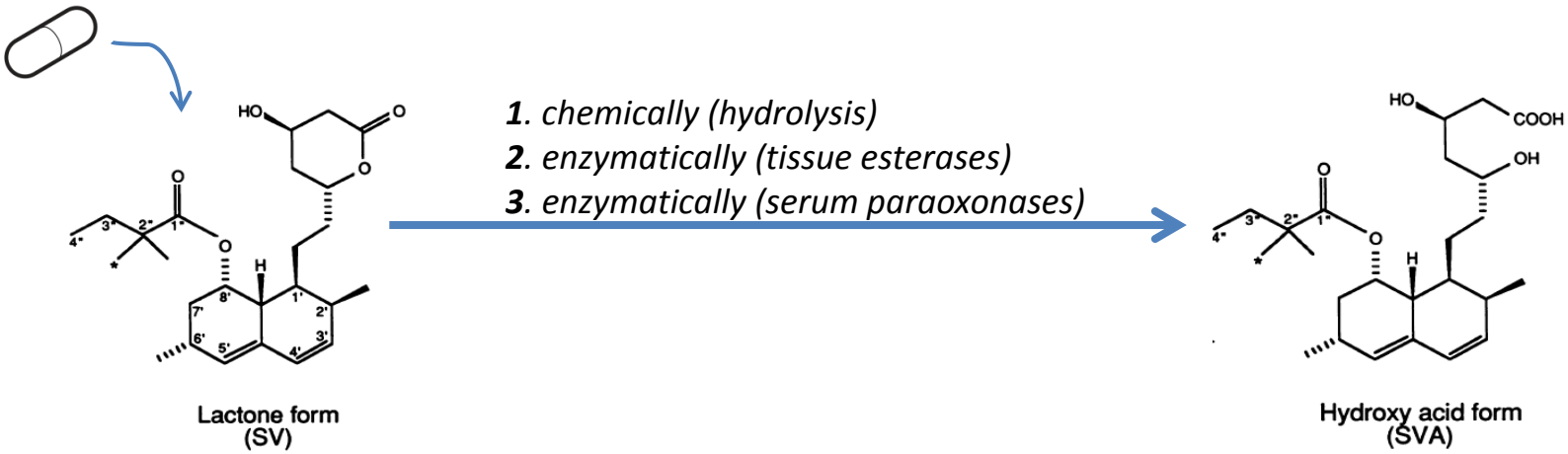
- Simvastatin (SV) is an HMG-CoA reductase inhibitor, used to treat lipid disorders.
- SV was the most commonly prescribed medication in England with 39.9 million items dispensed in 2013.[1]

- Why do we care about the PK of SV?
  - The risk for **myopathy** (the main adverse effect) is at least partly of a PK origin
  - SV is involved in clinically significant **DDIs** that arise at the PK level (e.g. CYP inhibition)
  - Several **SNPs** in enzyme/transporter genes have been clinically identified to affect its PK and subsequently PD (efficacy or safety)
  - **Inter-conversion** between SV and its main active metabolite simvastatin acid (SVA)

- However, population PK model-based approaches that can indicate individuals susceptible to DDIs and myopathy have not been widely developed.

[1] Health & Social Care Information Centre, Prescribing and Primary Care, Prescription Cost Analysis, England–2013, [http://www.hscic.gov.uk/catalogue/PUB13887]

Simvastatin: A prodrug with complex pharmacokinetics



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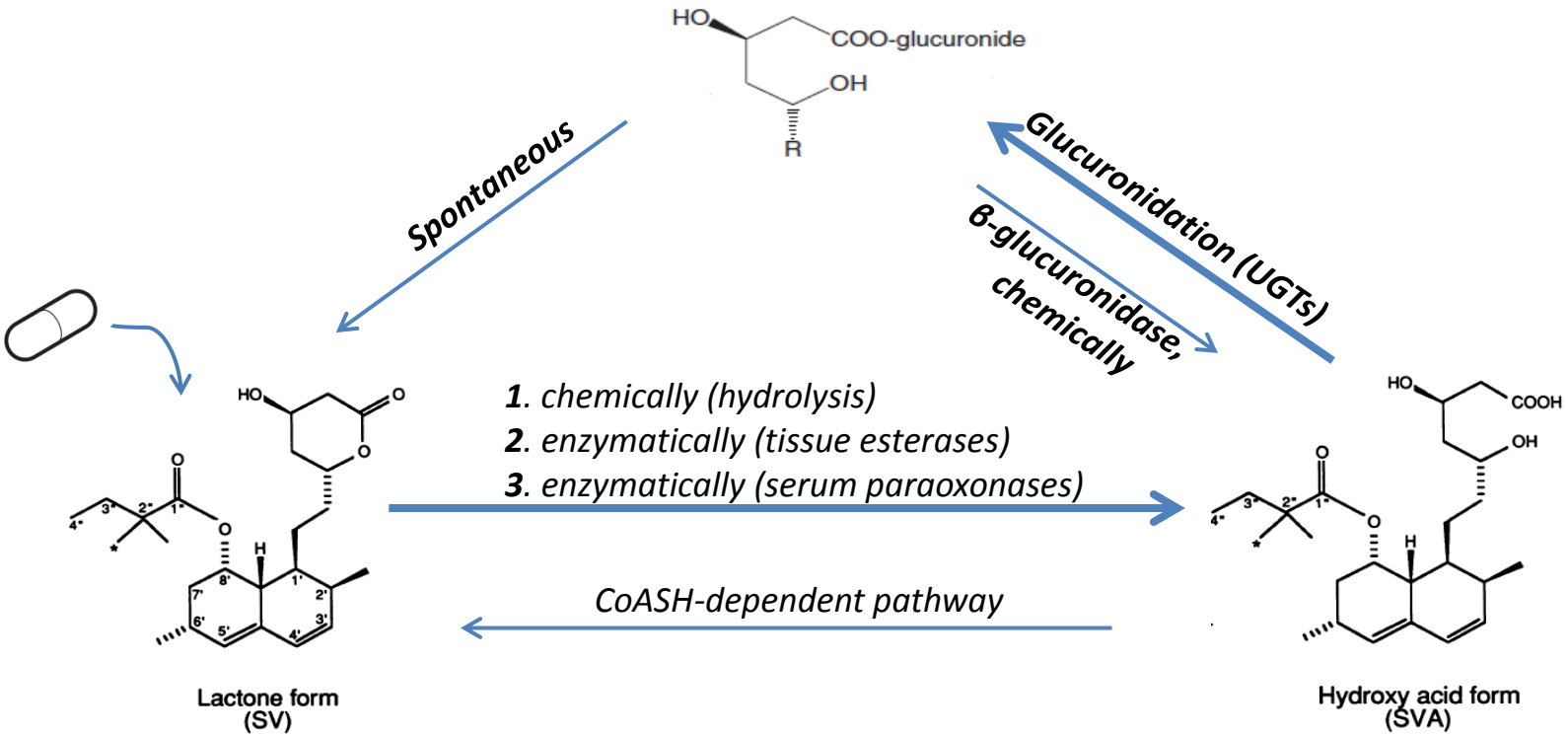

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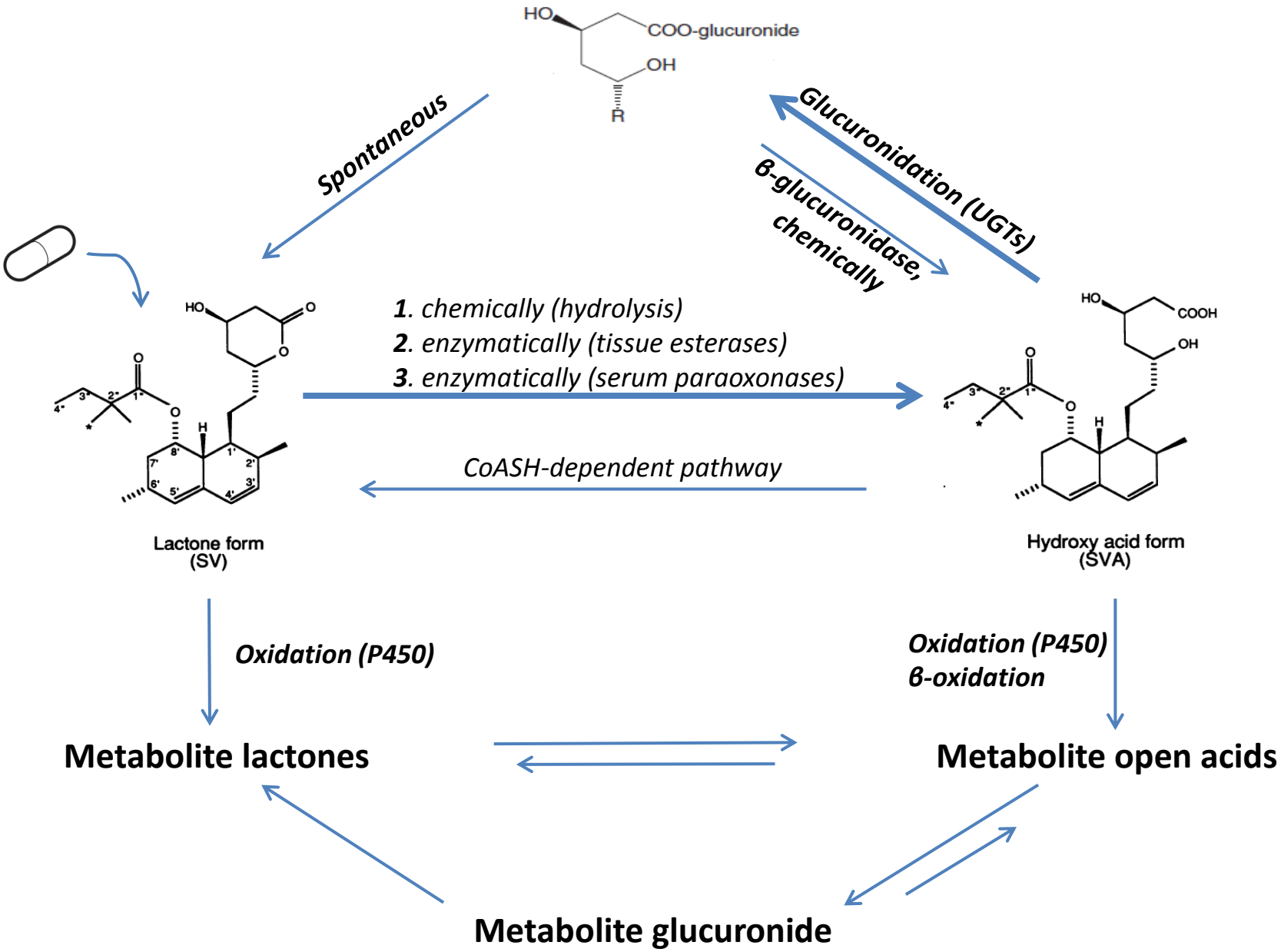

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SV pharmacogenetics

- Several factors reported to increase myopathy risk: **clinical** (e.g. DDIs), **demographic** characteristics (e.g. age and ancestry) and **genetic predisposition**
- The c.521 T>C (**rs4149056**) SNP in *SLCO1B1* is strongly associated with elevated SVA plasma levels[1] and increased risk of myopathy[2]
- Recent guidelines[3] recommend PG testing of this SNP to aid dose adjustment
- Additional SNPs in disposition related-genes have been clinically identified to affect SV/SVA PK/PD (e.g. *CYP3A4*, *CYP3A5*, *ABCG2*, *ABCB1*)
- PK studies test single gene variant effects analysed with NCA

[1]. Pasanen, *et al*, Pharmacogenet Genomics, 2006. 16(12): p. 873-9.
[2]. Link, *et al*, N Engl J Med, 2008. 359(8): p. 789-99.
[3]. Wilke, *et al*, Clin Pharmacol Ther, 2012. 92(1): p. 112-117.

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Objective

Develop a joint population SV/SVA PK model that incorporates the effects of multiple polymorphisms and clinical/demographic characteristics

Clinical data

Study 1: 16 healthy volunteers, two 40mg doses with 24h interval, rich sampling

Study 2: 18 healthy volunteers, a single 20mg dose, rich sampling

Study 3: 40 patients, 40mg daily, sparse sampling (peak and trough)

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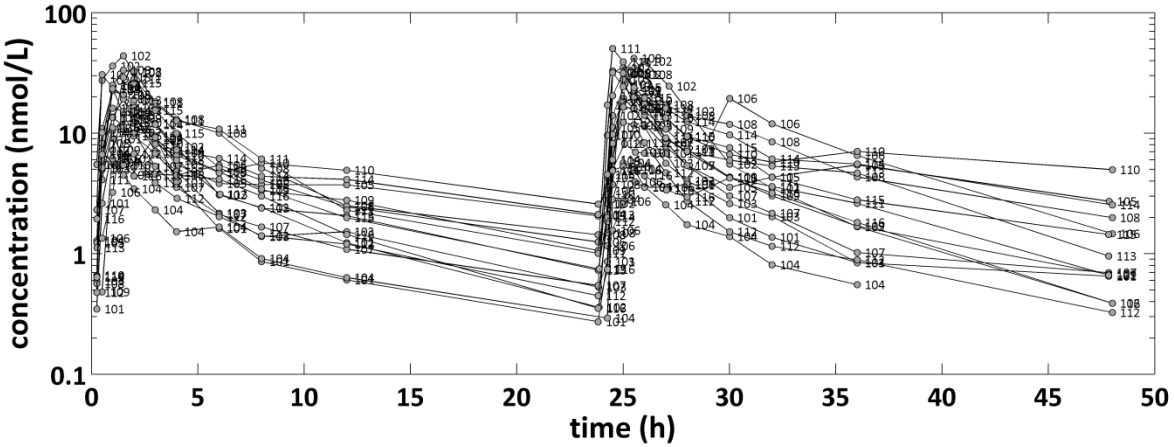
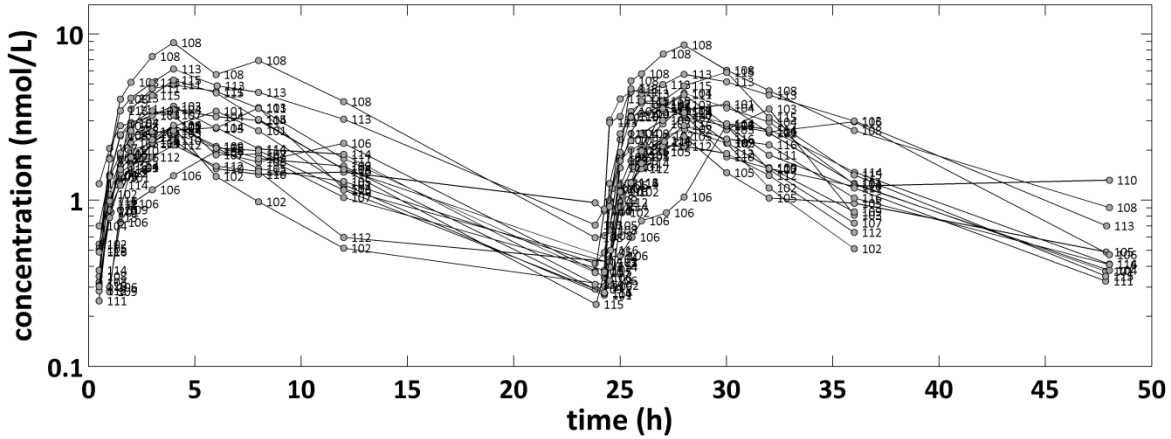


SVA



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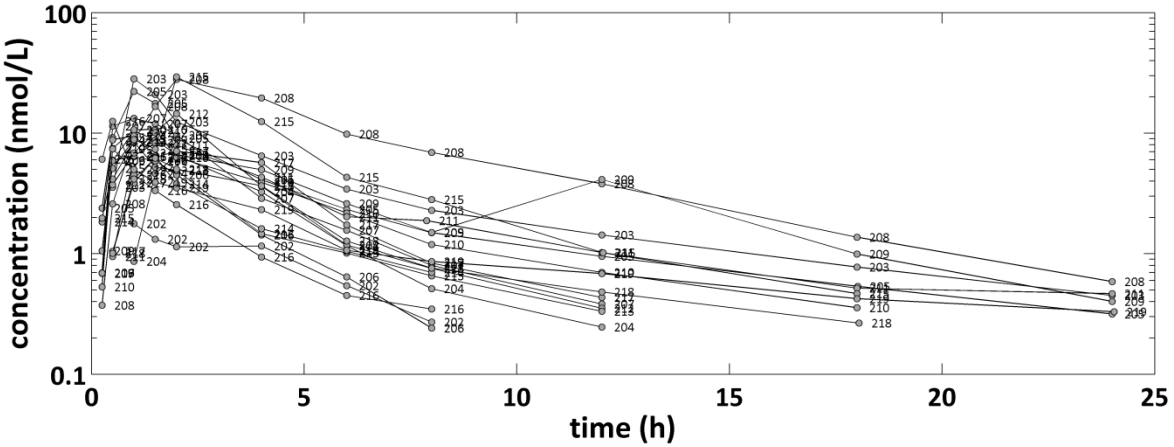

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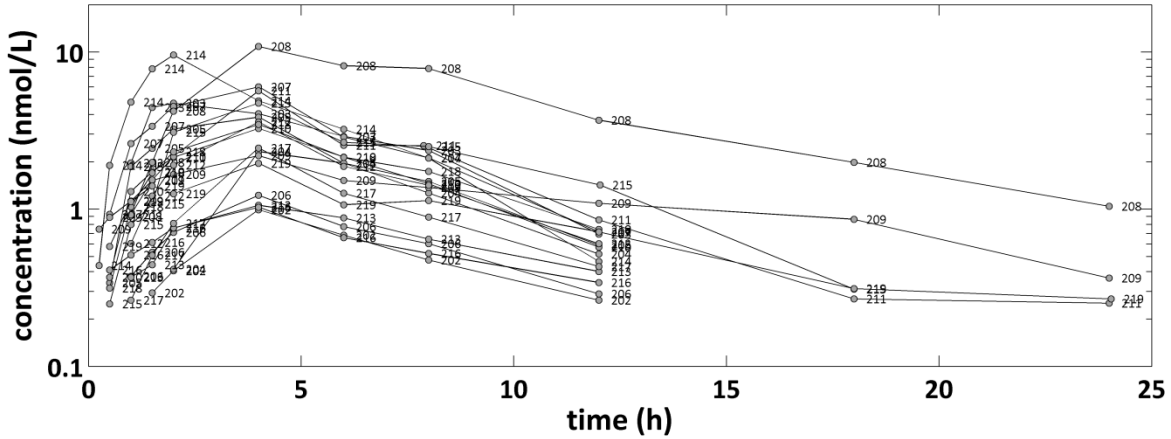

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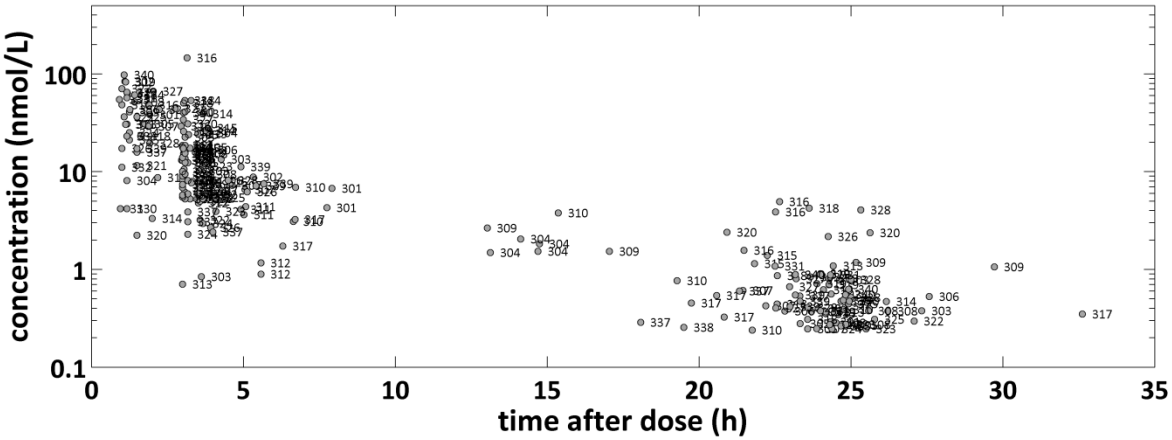

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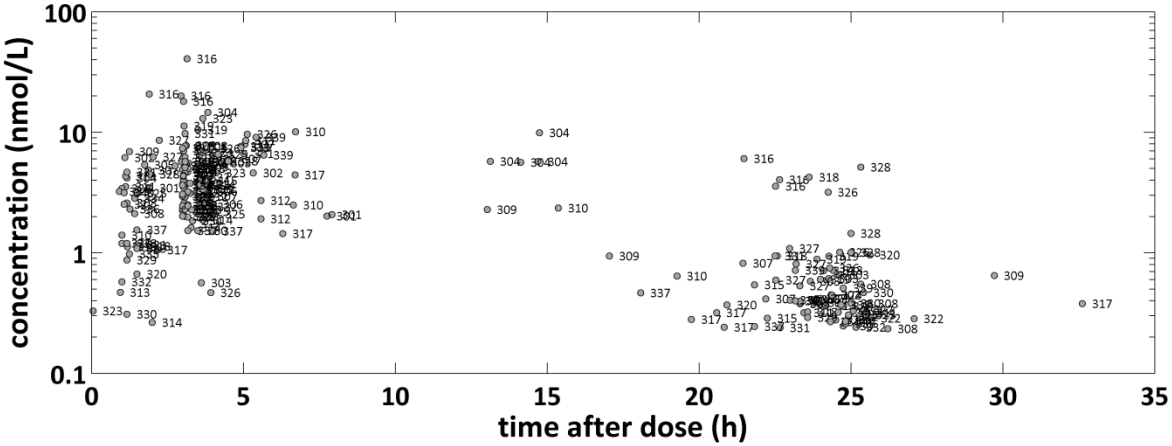
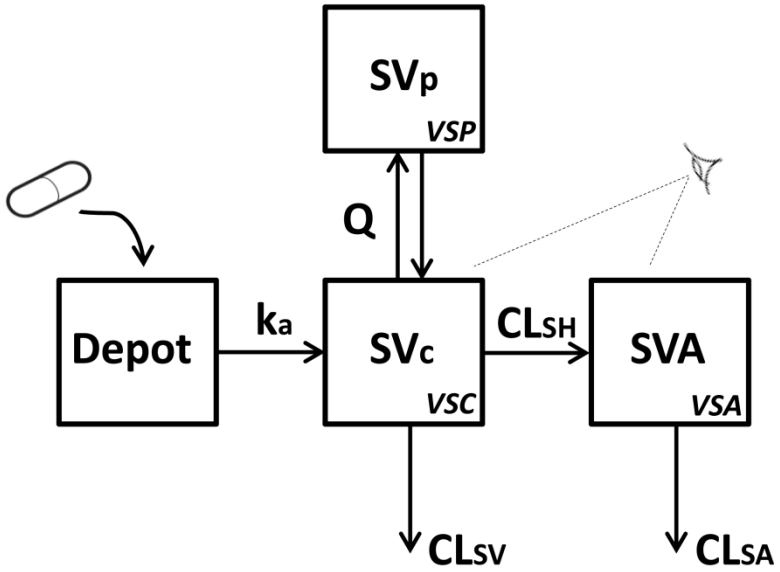


Model development

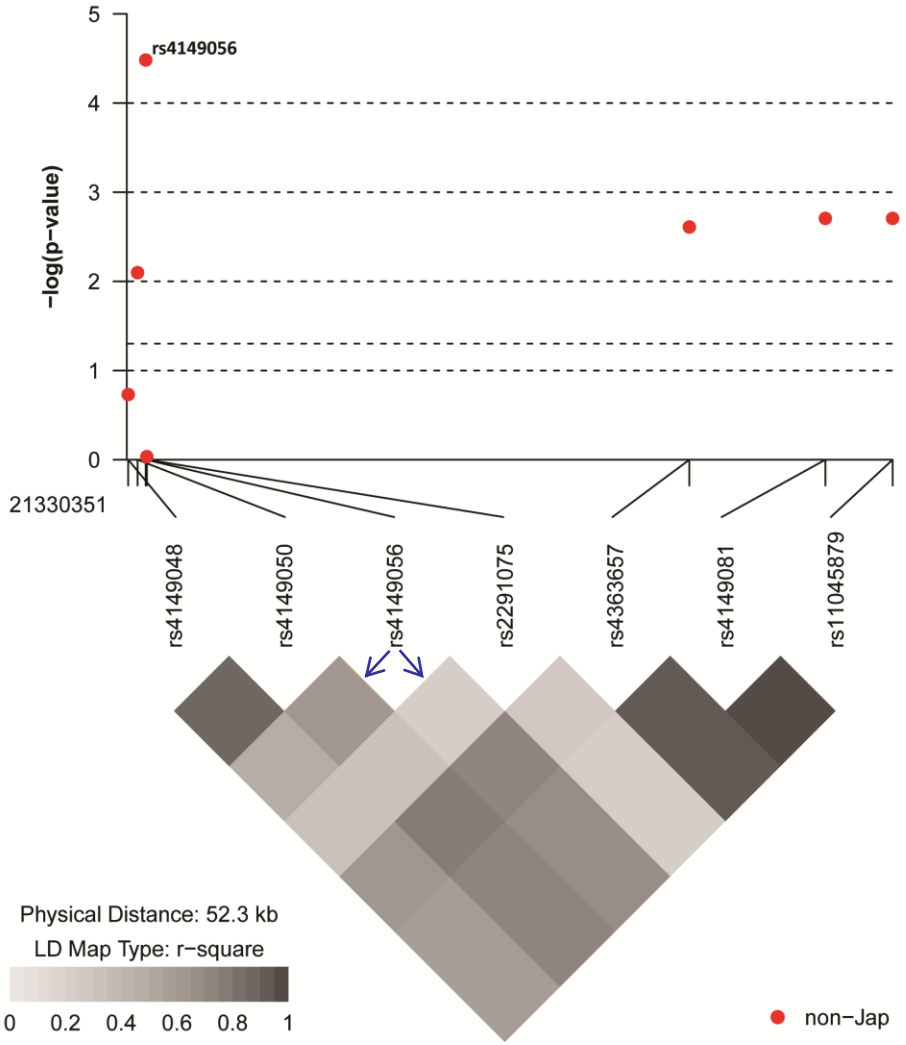
- SV/SVA plasma concentrations from 74 individuals were analysed (NONMEM 7.2)
- Ethnicity: Caucasian (n=47), Japanese (n=19), African (n=5), other (n=3)
- **18 SNPs** were genotyped in all participants: *ABCB1* (3), *ABCG2* (3), *CYP3A4* (1), *CYP3A5* (1), *SLCO1B1* (7), *SLCO2B1* (2), *PPARA* (1)
- Base model that best fits the data:



- Covariate selection with a forward inclusion - backward elimination process, the degree of correlation between SNPs was also assessed.

Linkage disequilibrium

- **Linkage disequilibrium (LD)** is the non-random association in a population of alleles at closely linked loci.



LD plot for OATP1B1 SNPs

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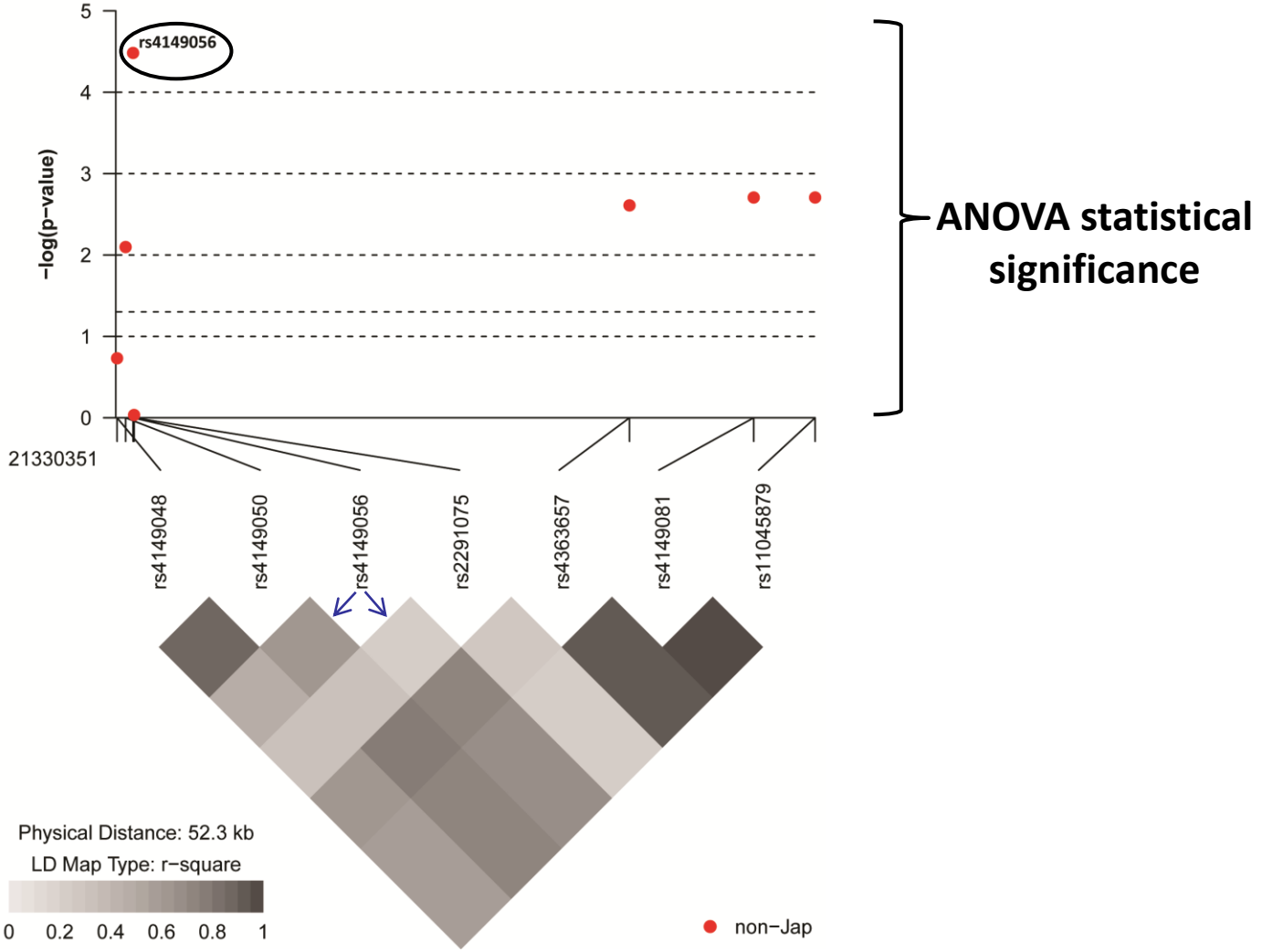

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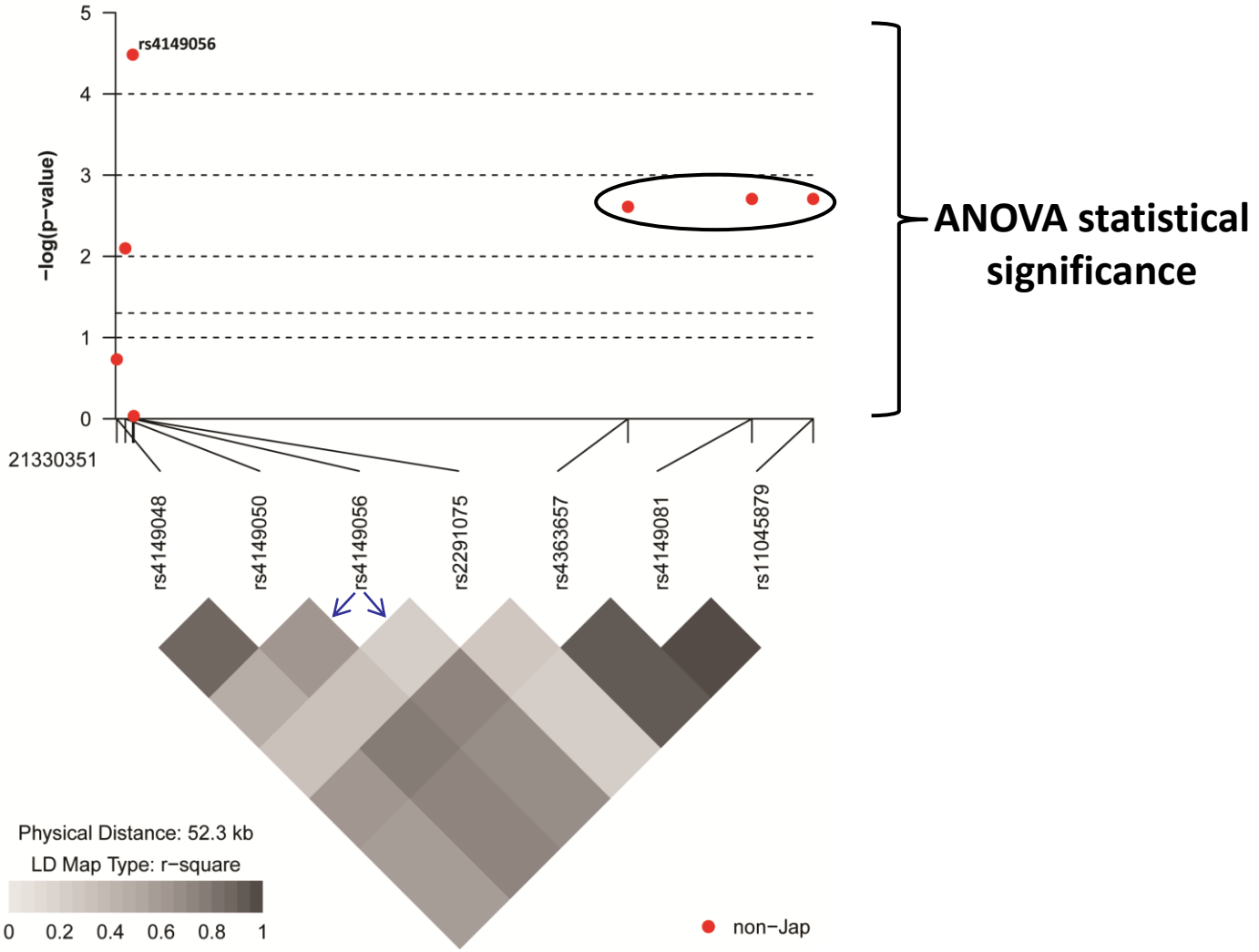

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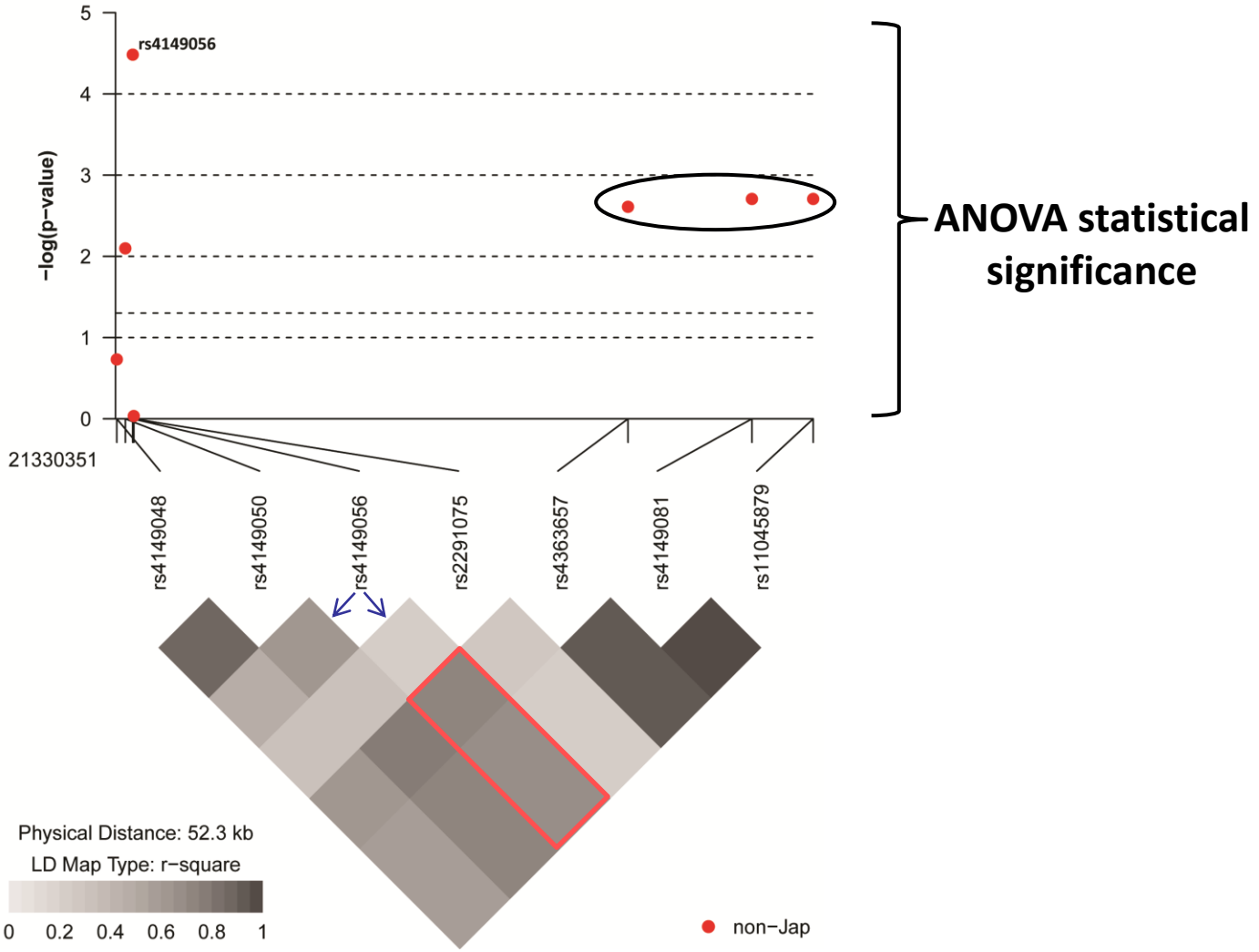
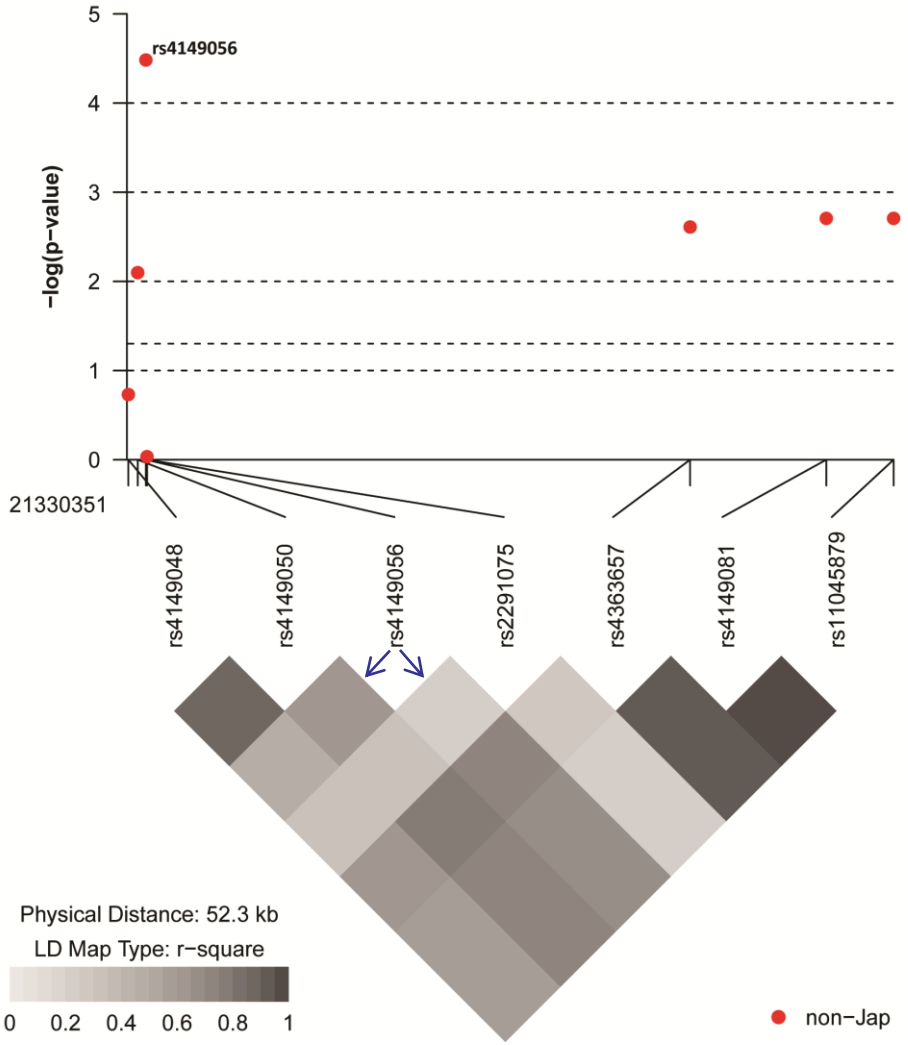


Non-Japanese subpopulation



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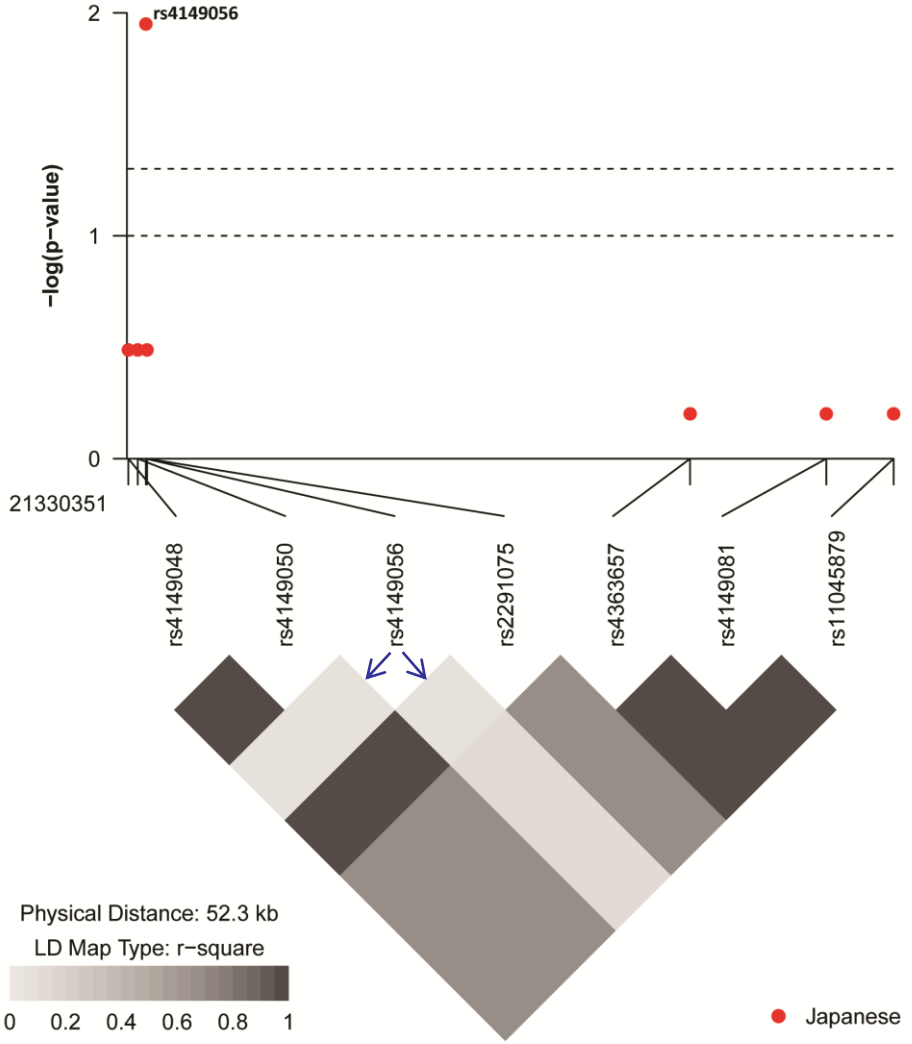

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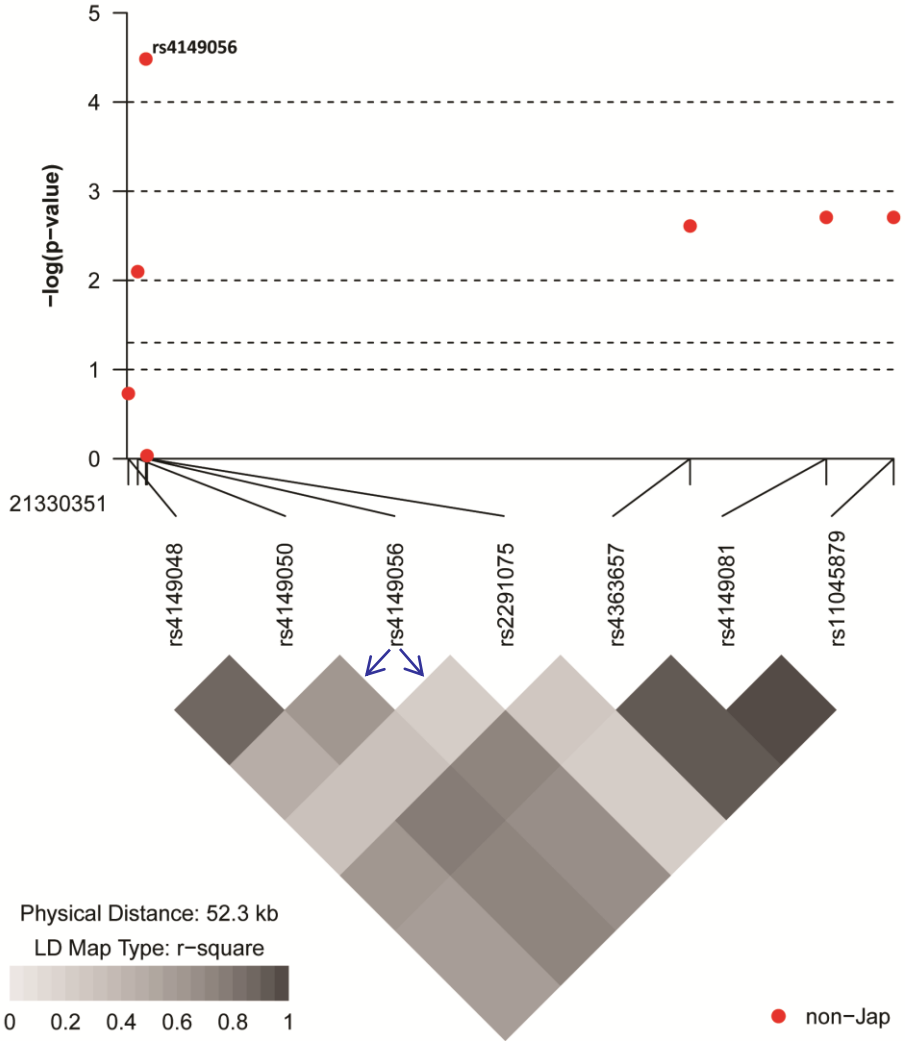

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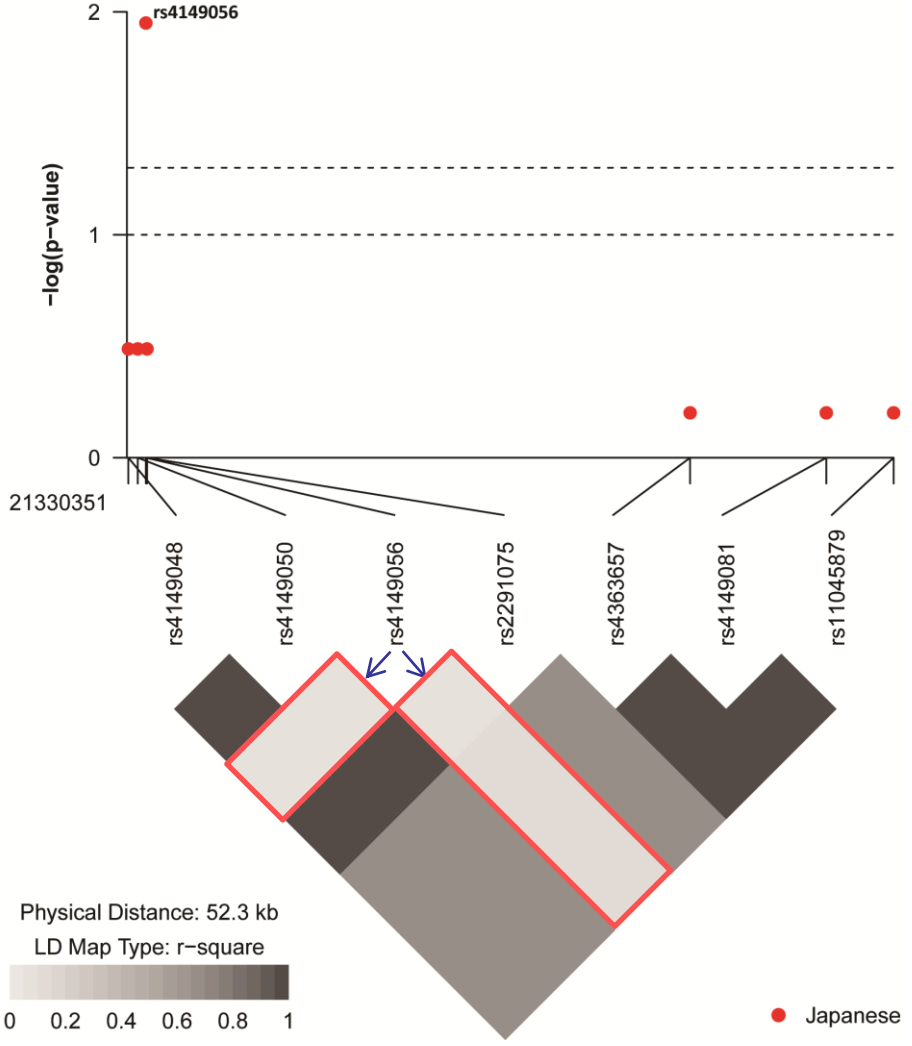


SV/SVA population model

- The final model included the effect of:

Genetic polymorphisms:

- **rs4149056 (*SLCO1B1*)**
- rs776746 (*CYP3A5*)
- rs12422149 (*SLCO2B1*)
- rs2231142 (*ABCG2*)
- rs4148162 (*ABCG2*)
- rs4253728 (*PPARA*)
- rs35599367 (*CYP3A4*)

Demographic characteristics:

- Age
- Weight
- Japanese ethnicity

Identification of the Effect of Multiple Polymorphisms on the Pharmacokinetics of Simvastatin and Simvastatin Acid Using a Population-Modeling Approach

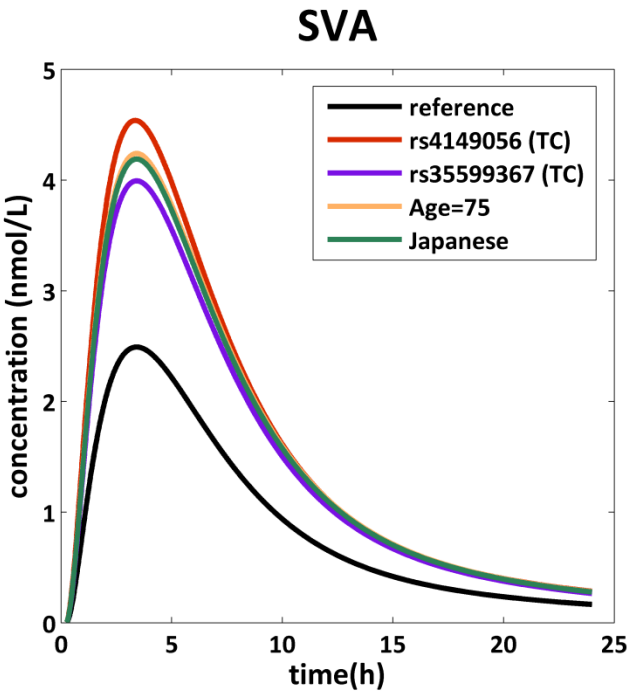
N Tsamandouras[1], G Dickinson[2], Y Guo[2], S Hall[2], A Rostami-Hodjegan[1,3], A Galetin[1] and L Aarons[1]

Clinical Pharmacology & Therapeutics, advance online publication, 2 April 2014; doi: 10.1038/clpt.2014.55

Covariate effects plasma exposure

- Using the developed model we can separately investigate the effects of different genetic and demographic characteristics

- What if these risk factors co-exist in a **high-risk individual**?

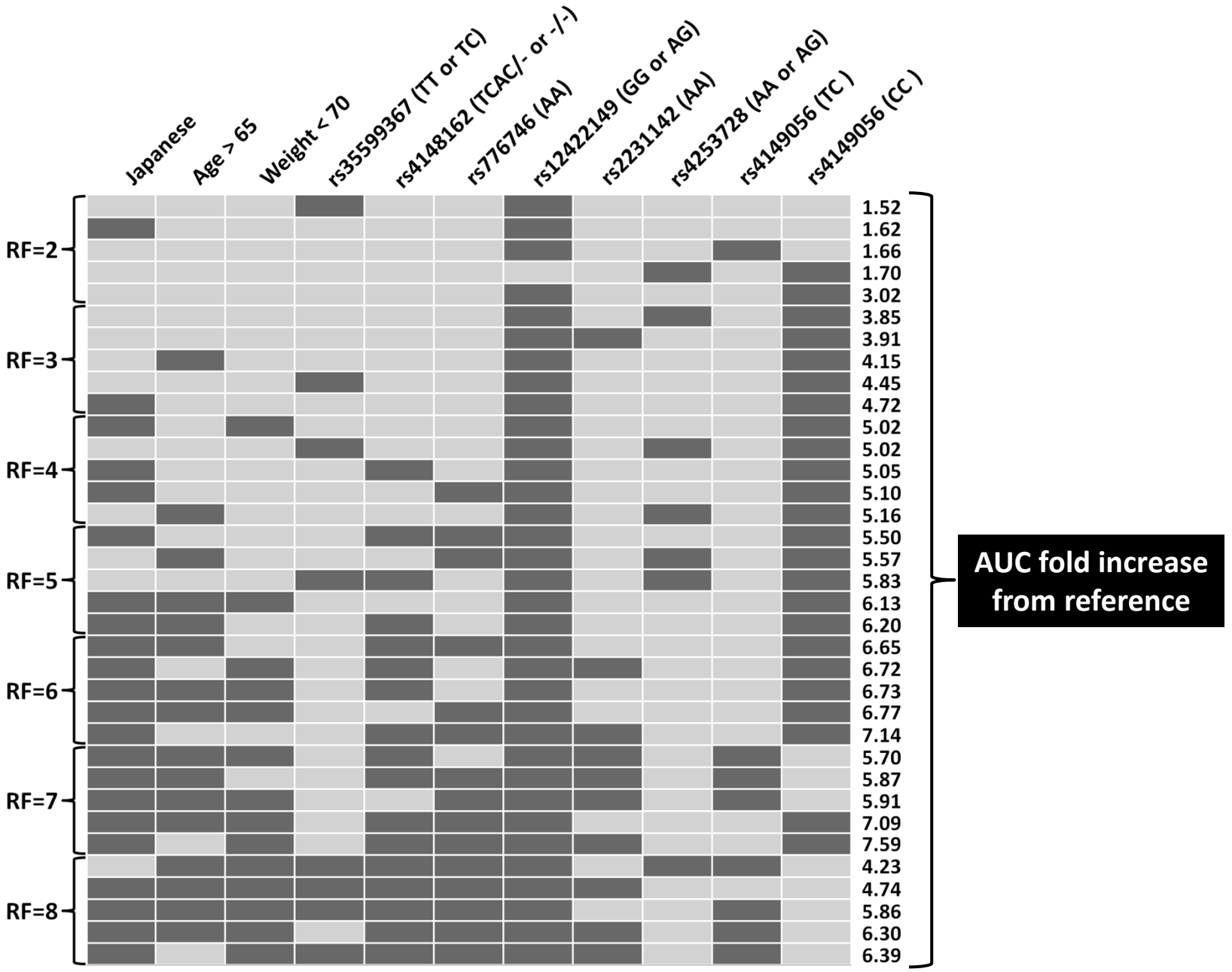


- The effects of multiple genetic and demographic risk factors co-occurrence can be assessed by analysing extensive combinations

  (-) Combinatorial explosion **(-) Some are not physiologically plausible**

- A physiologically realistic population (n=100,000) was simulated and then using a script that identifies **risk factor combination patterns** examine **their effects on SVA plasma exposure and the frequency** that these might occur.

Effect of multiple risk factors combinations



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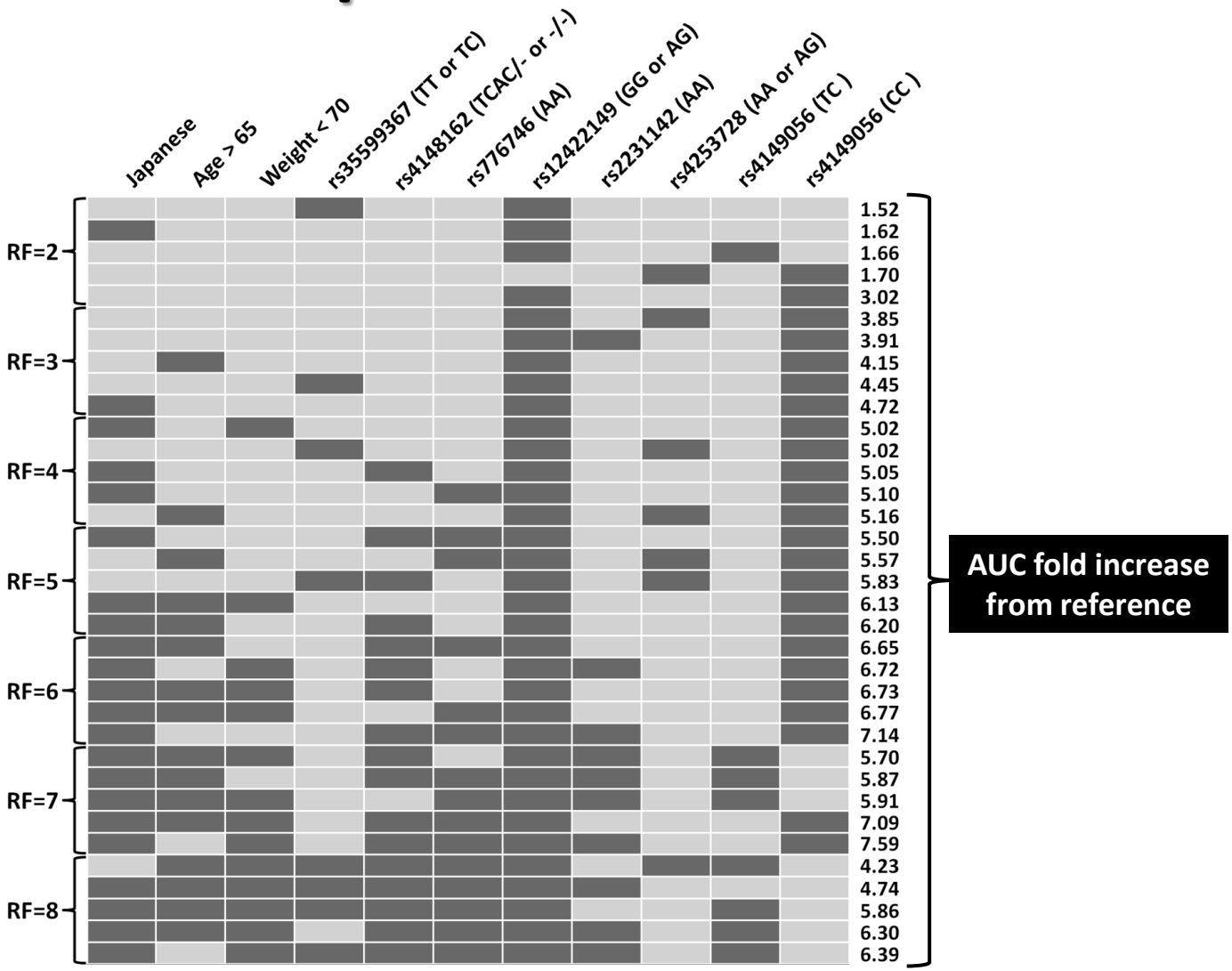
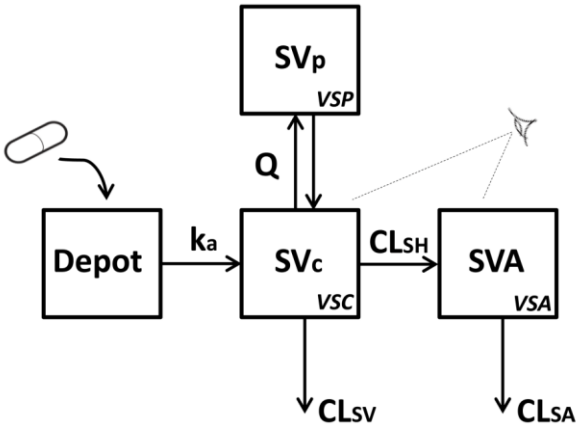


- We reported as clinically interesting only those patterns (188) that increase SVA exposure **> 3-fold** and thus have **high chance to predispose for myopathy**
- Only in **3.5%** of the simulated population, however **absolute numbers matter**

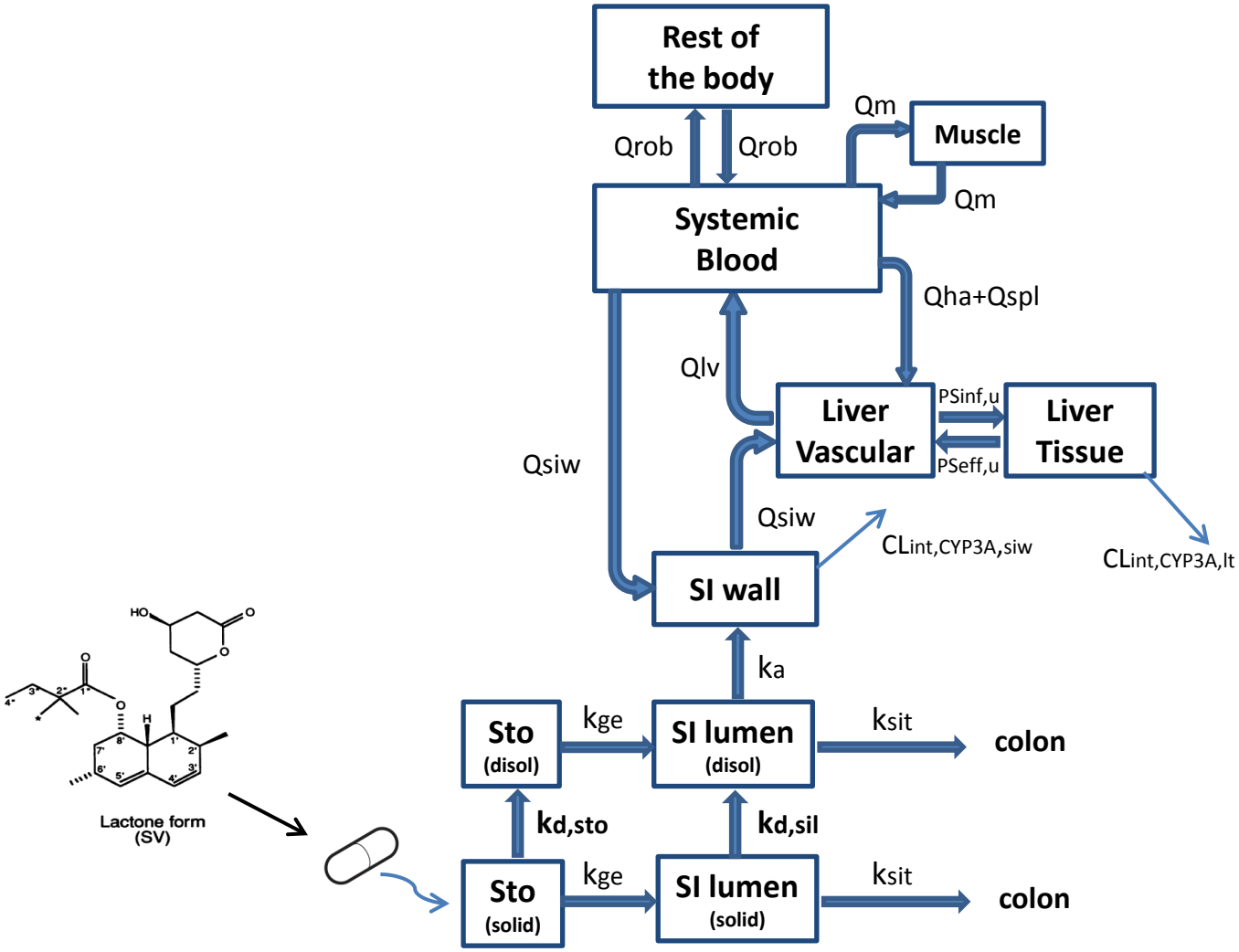
Empirical compartmental approach

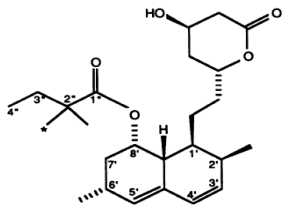
- **Advantages of this approach:**
  - **Simple** model, number of parameters is small
  - **Fast** runs, crucial if covariate model building is stepwise
  - **Mechanistic enough**, to allow genotype information to be incorporated as a covariate on a model parameter



- **Disadvantages:**
  - **Physiologically not accurate**: It does not capture the pre-systemic formation of SVA or the inter-conversion between the two forms
  - **Not assumption-free:** Despite simplicity, model is structurally unidentifiable
  - It cannot predict concentration profiles in **clinically relevant tissues** (liver, muscle)
  - Difficult to incorporate *in vitro* information and **extrapolate** outside the studied population and conditions (e.g. predict the magnitude of a DDI / polymorphism).

Development of a SV/SVA mechanistic population model

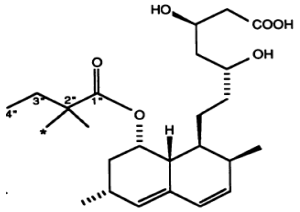




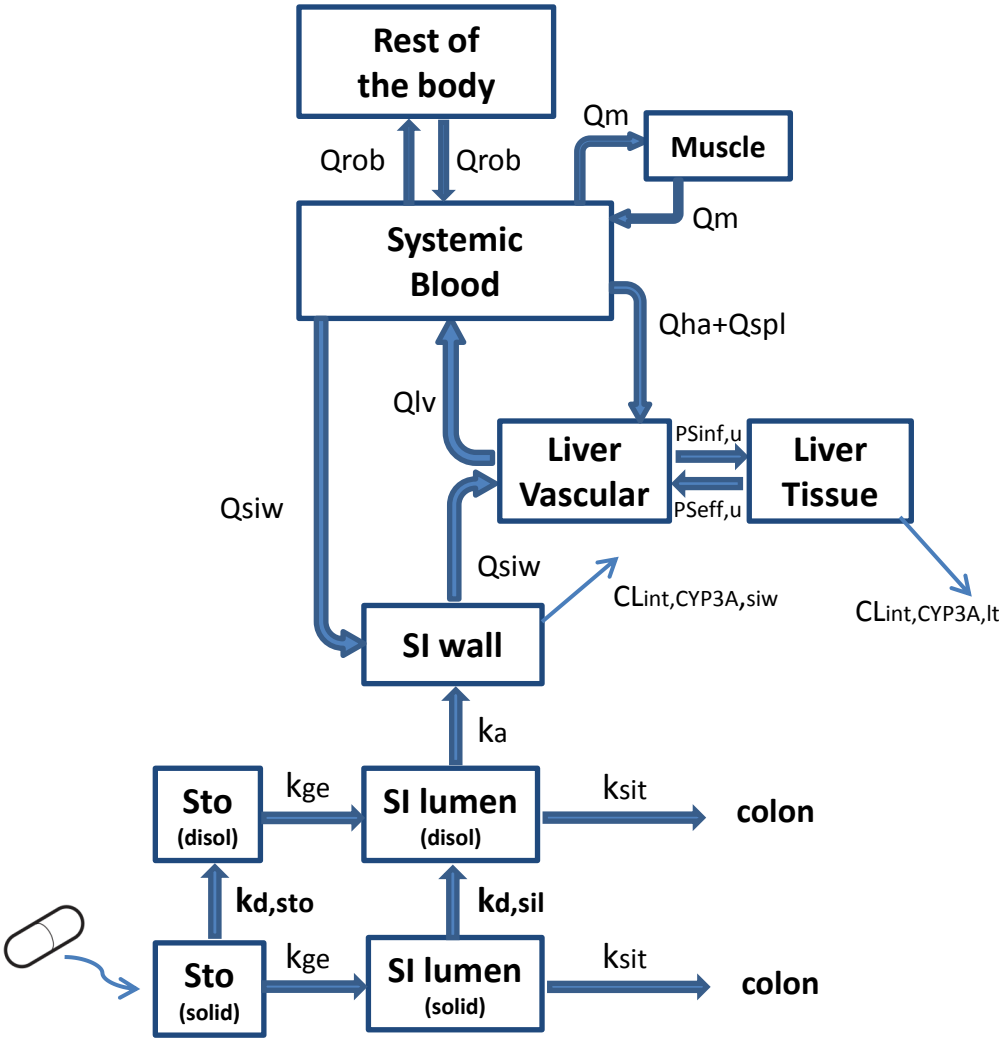
Lactone form
(SV)

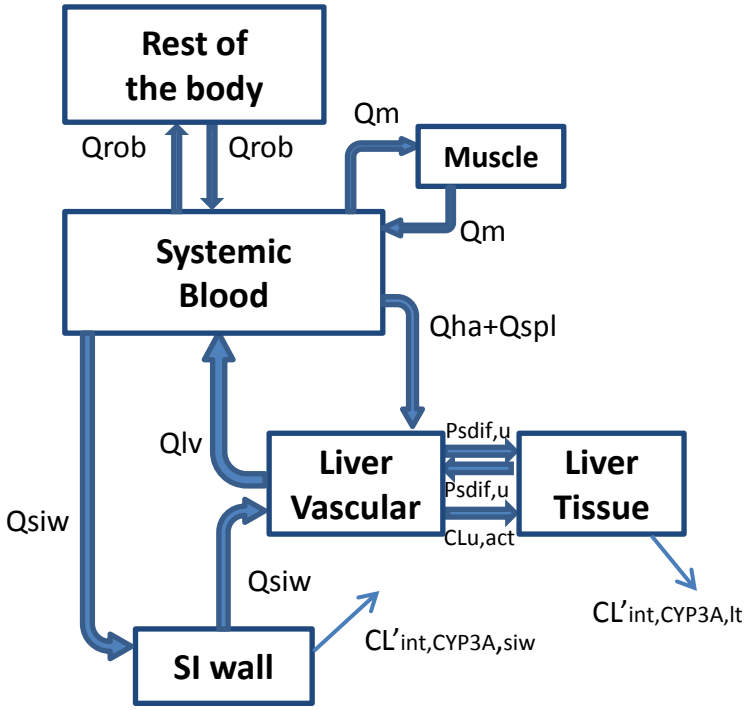
hydrolysis

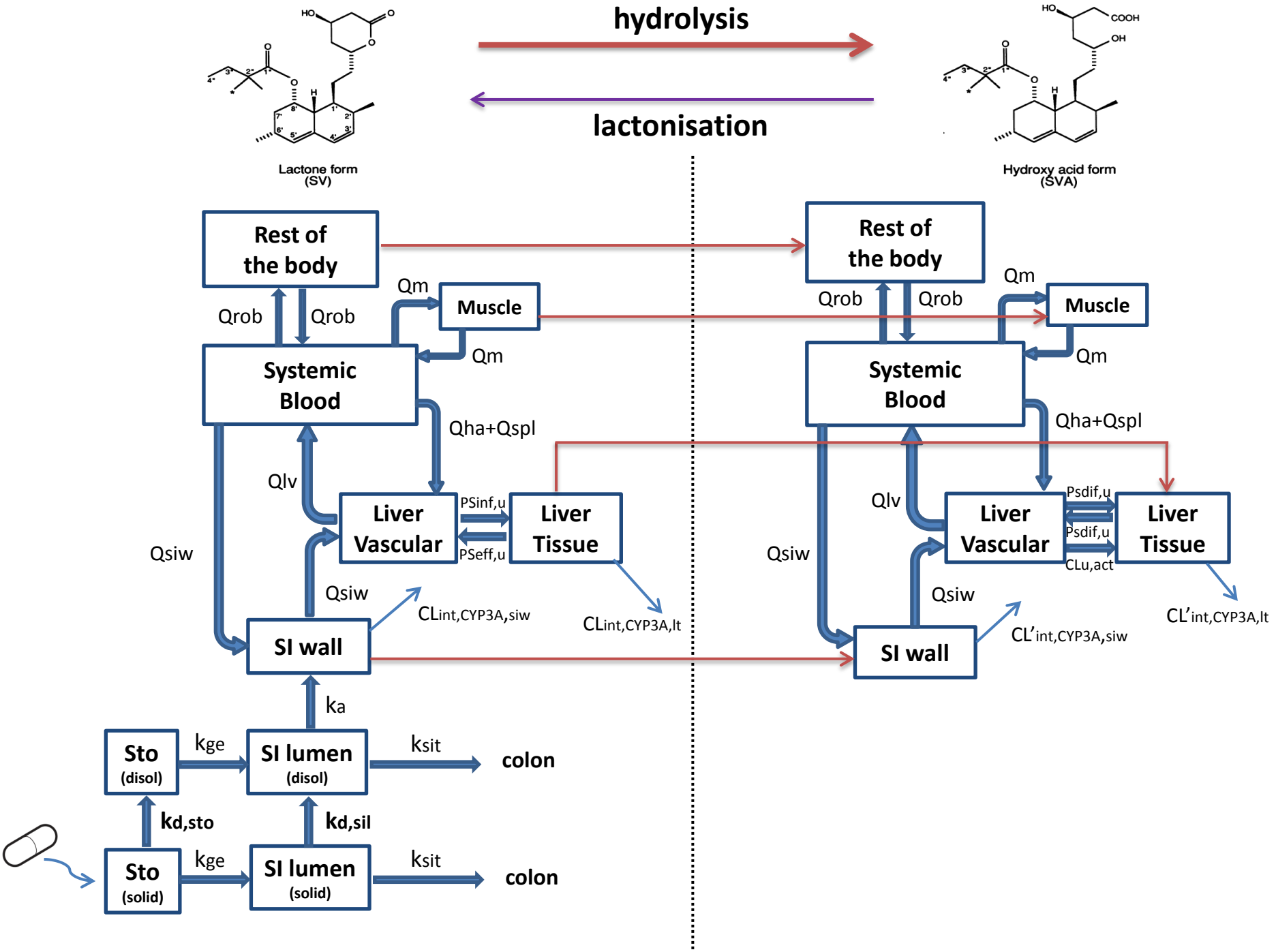
lactonisation



Hydroxy acid form
(SVA)



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Qm
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ksit
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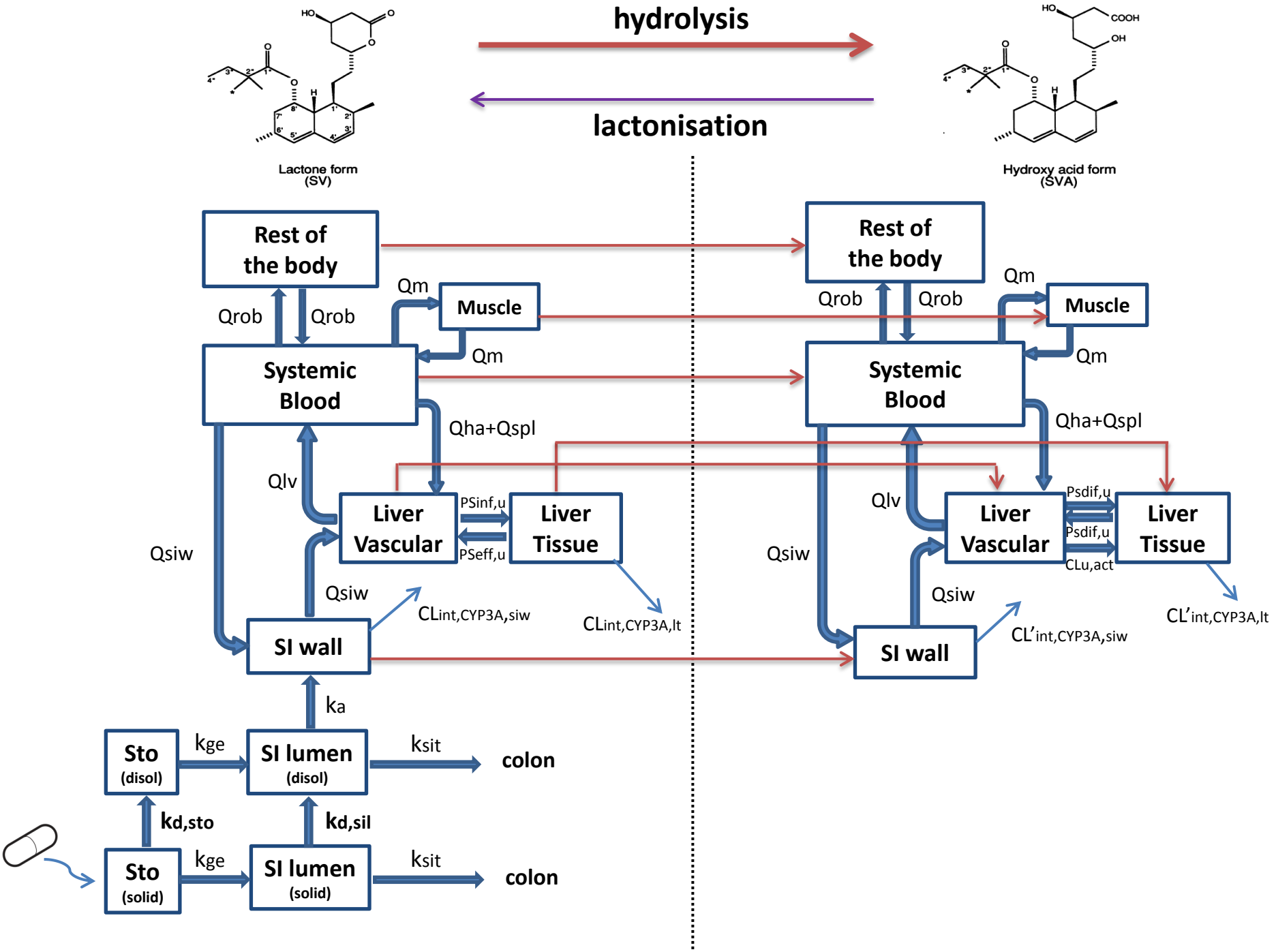
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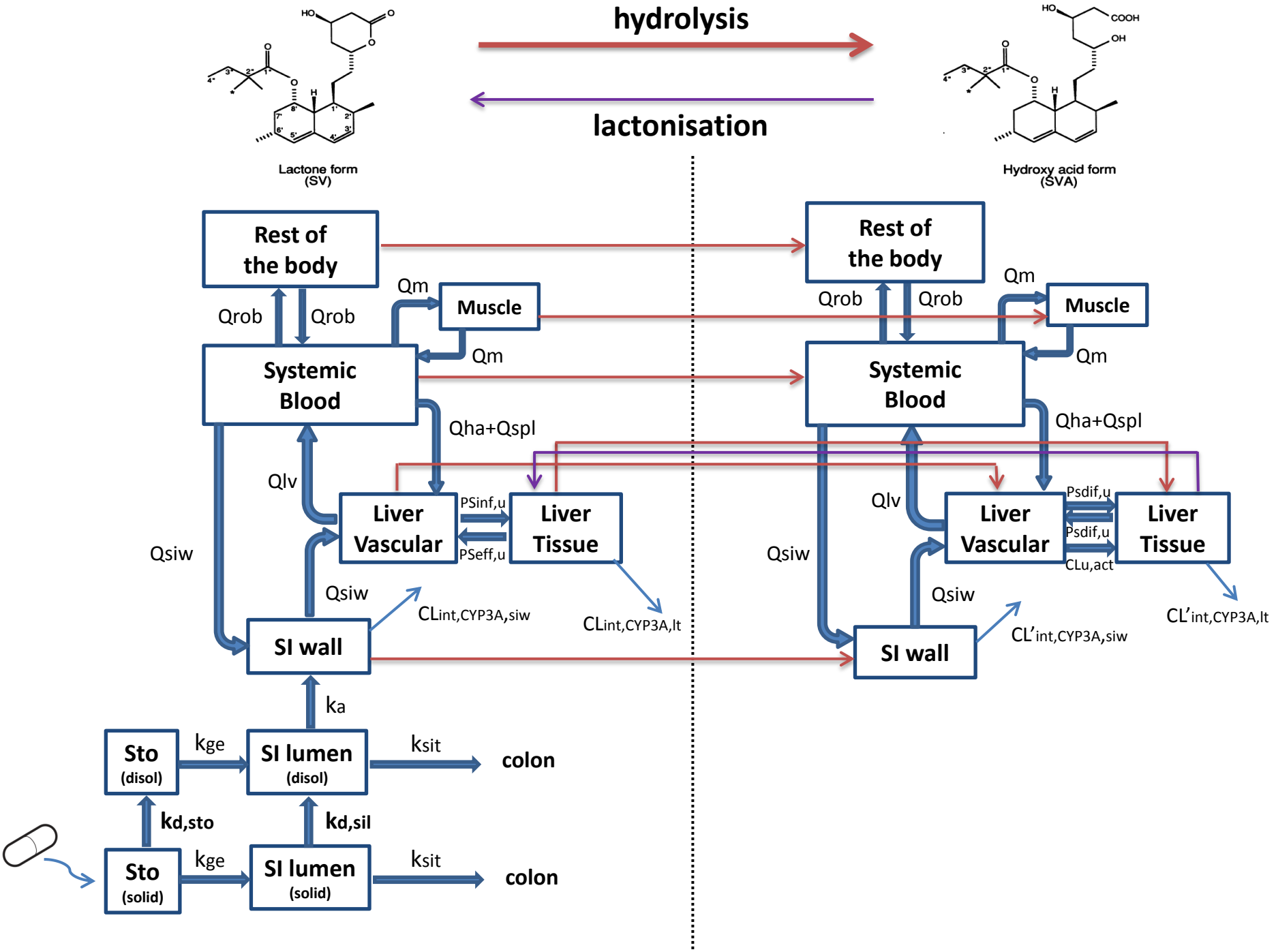
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SV/SVA mechanistic population model

- The model was implemented as a system of 16 ODEs (NONMEM 7.2, ADVAN13)

- Most of the model parameters can be *a priori* informed:
  - **Physiology/biology:** e.g. Blood flows, organ volumes
  - ***In vitro* experiments:** e.g. SV/SVA metabolism/stability assays
  - ***In silico* predictions:** e.g. SV/SVA tissue-plasma partition coefficients

- The prior functionality in NONMEM was applied to integrate prior information for model parameters and (when available) their variability with clinical data[1,2]

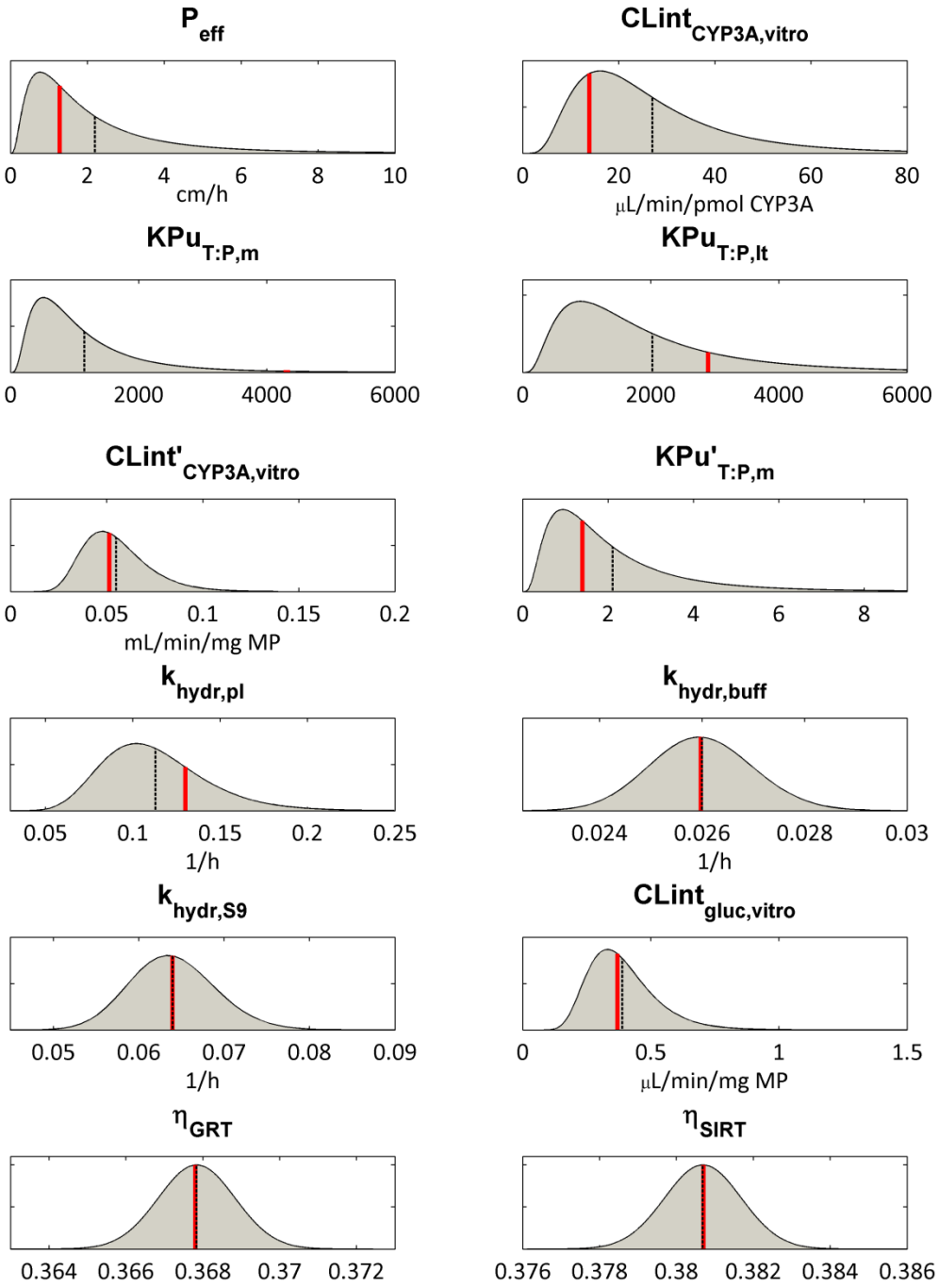
- SV/SVA plasma concentrations from Study 1 & 2 were simultaneously analysed

[1]. Gisleskog, *et al*, J. Pharmacokinet. Pharmacodyn., 2002. 29(5): p. 473-505.

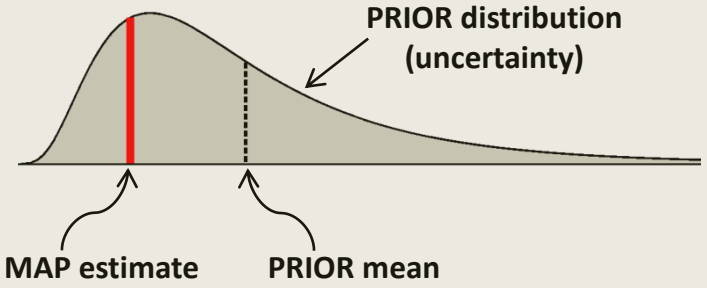
[2]. Langdon, *et al*, Eur. J. Clin. Pharmacol., 2007. 63(5): p. 485-498.

Parameter estimates

- Model parameters were precisely estimated (RSE < 25% and RSE < 50% for all fixed and random effects accordingly)



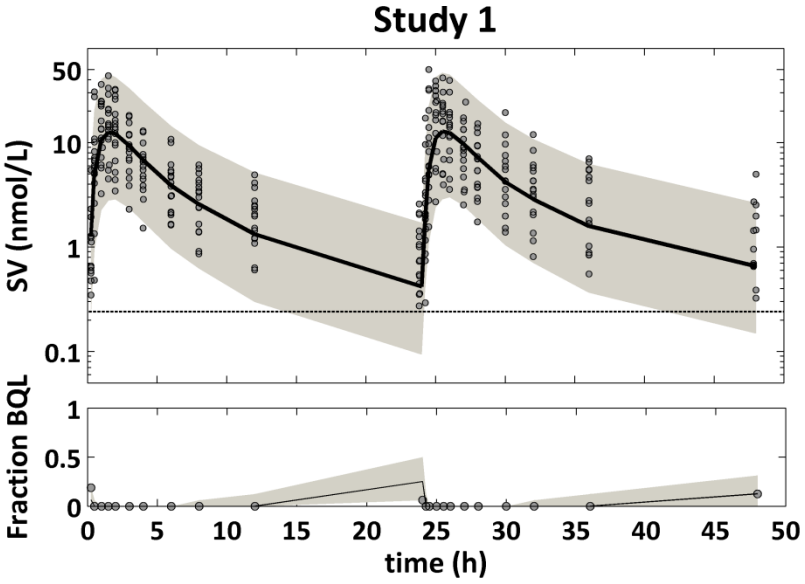
MAP estimates relatively to informative priors

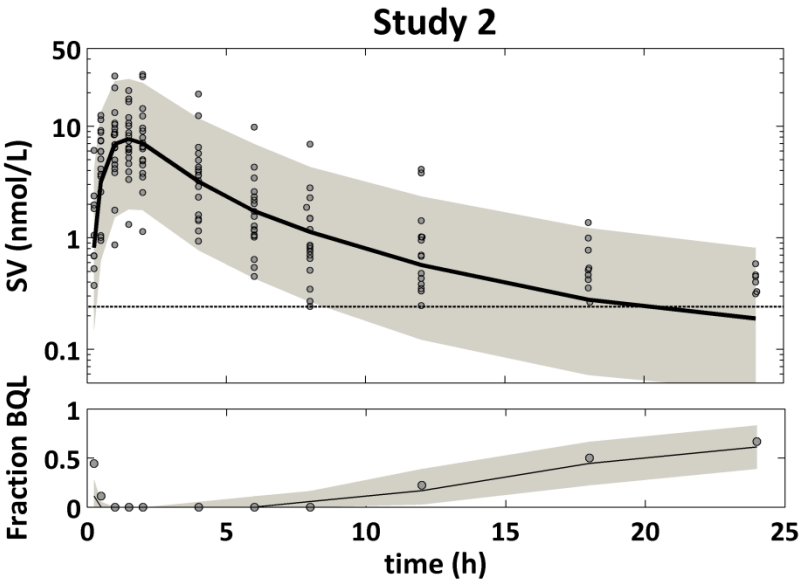


- Several model parameters were informed from the plasma data updating prior knowledge
  - e.g. SV metabolic clearance, partition coefficients
- Parameters which cannot be informed from plasma data shrink towards prior mean
  - e.g. inter-conversion inside liver, hydrolysis in muscle

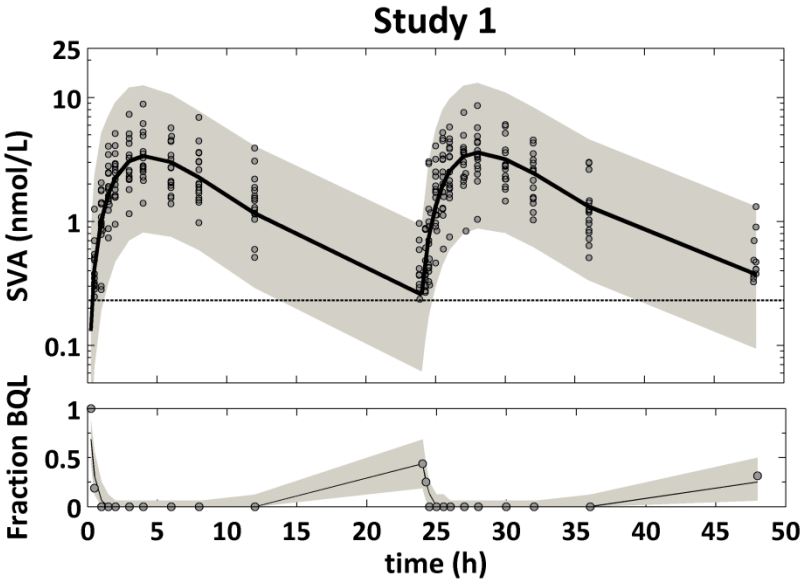
Visual Predictive Check

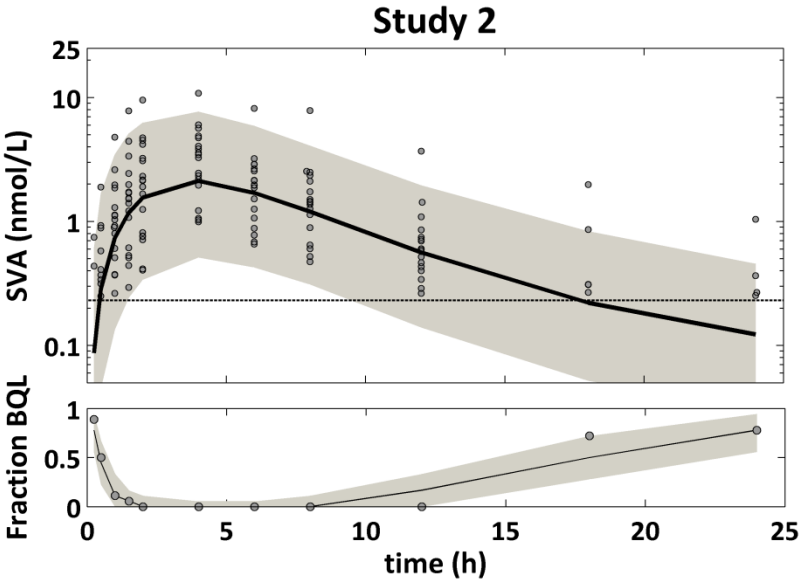
SV





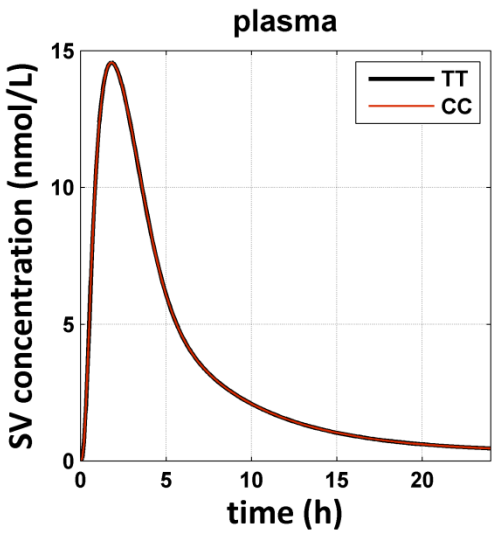
SVA

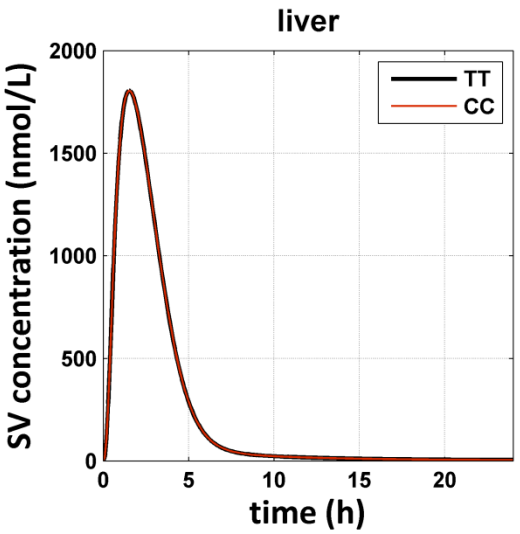


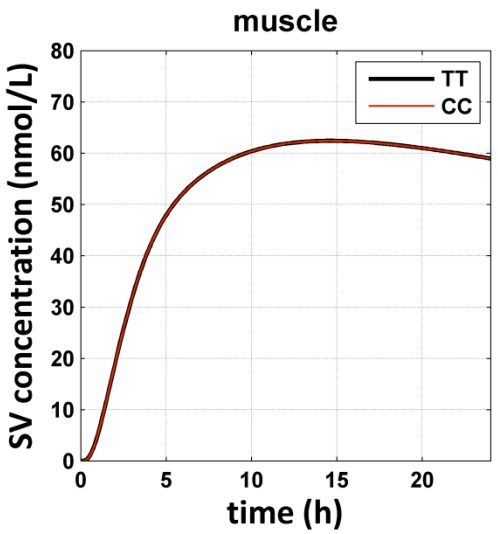


OATP1B1 rs4149056 CC effects (tissues)

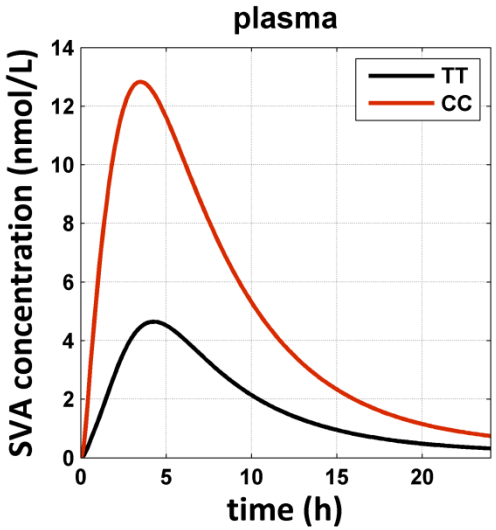
SV

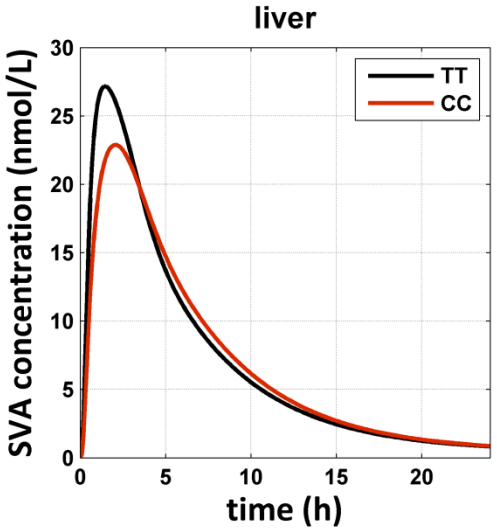


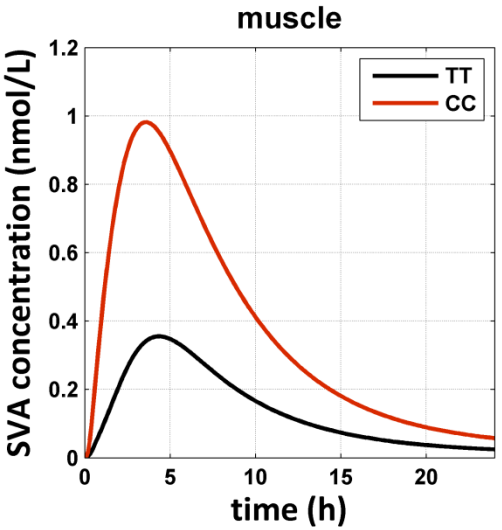




SVA

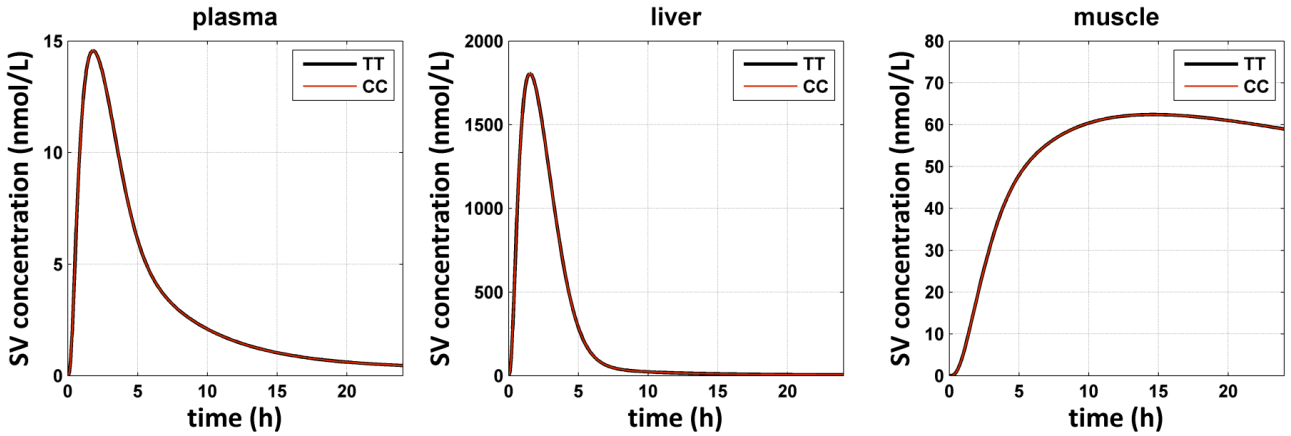




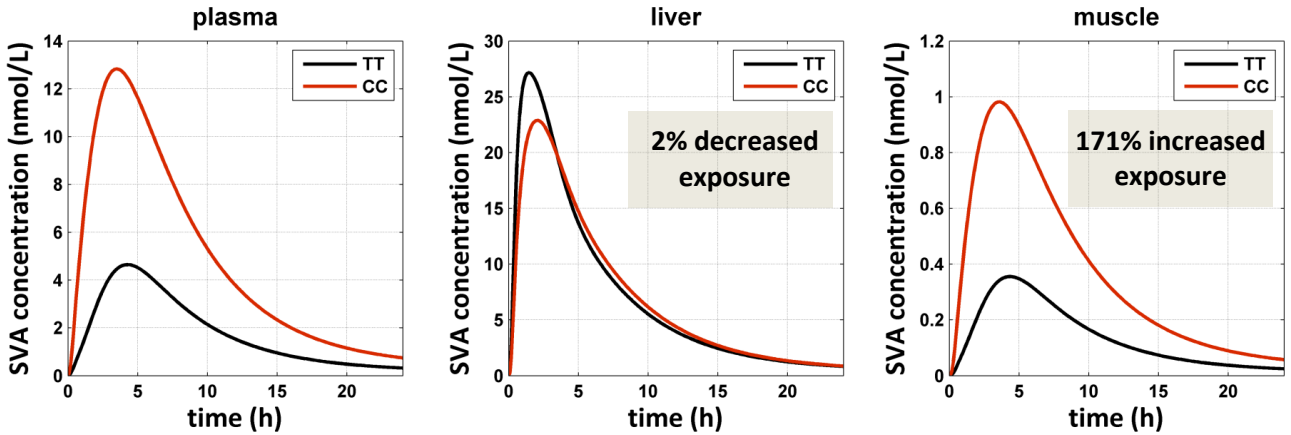


OATP1B1 rs4149056 CC effects (tissues)

SV



SVA



- Agreeing with clinically observed[1] PD effects of the *SLCO1B1* rs4149056 SNP:
  - Has been robustly and repeatedly **associated** with increased risk of **myopathy**
  - Has **not been associated** with clinically significant alterations in the **cholesterol lowering efficacy**. LDL reduction was only 2.56% smaller in CC subjects (n=16,664)

[1]. Link, et al, *N. Engl. J. Med.*, 2008. 359(8): p. 789-99.

Prediction of DDI effects

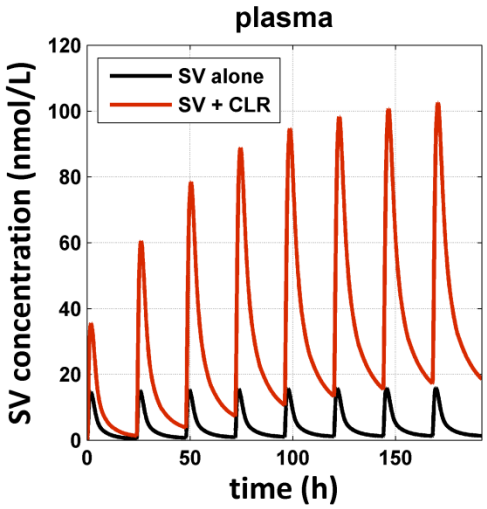
- The developed model was also able to successfully predict the effects of a range of clinically significant SV DDIs (clarithromycin, erythromycin, itraconazole, diltiazem)

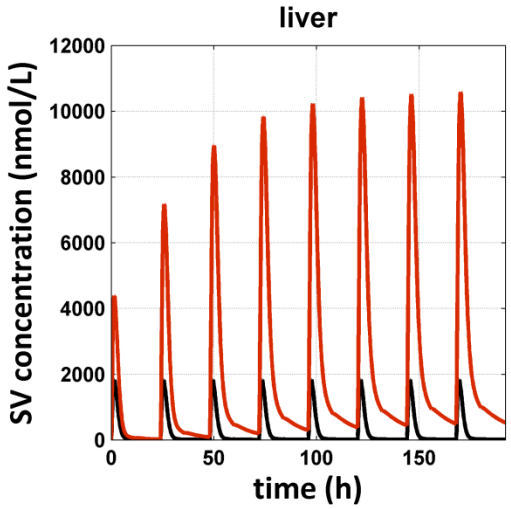
- Clarithromycin (CLR) is a mechanism-based CYP3A inhibitor. Co-adminstration with SV leads to a severe DDI that can cause lethal rhabdomyolysis [1,2].

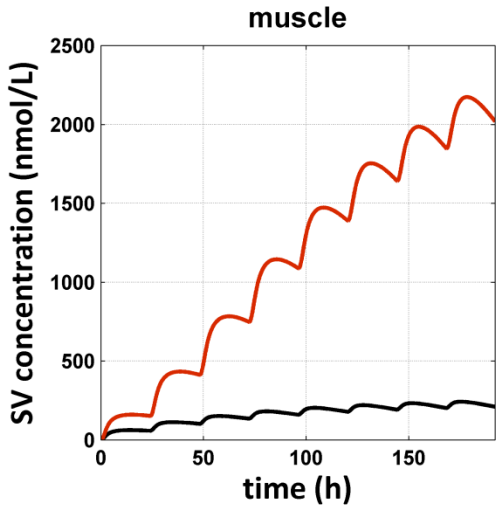
[1]. Jacobson, The American journal of cardiology, 2004. 94(9): p. 1140-6.

[2]. Lee, *et al*, The Annals of pharmacotherapy, 2001. 35(1): p. 26-31.

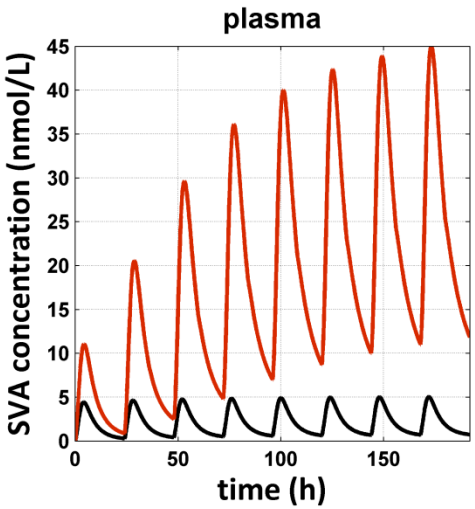
SV

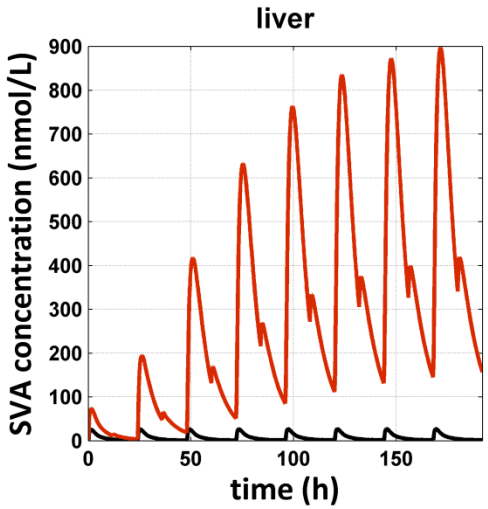


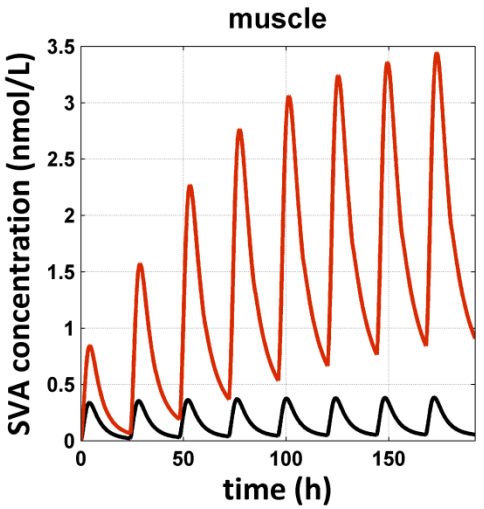




SVA







SV 40mg q.d. alone or SV 40 mg q.d. + CLR 500mg b.i.d. AUC and Cmax are reported in nmol·h/L and nmol/L respectively and they refer to plasma and the last dosing interval. Observed DDI effect data (OBS ratio) are extracted from Jacobson 2004

	SV	SV + CLR	PRED ratio	OBS ratio
SV AUC	102.54	1027.90	10.02	9.95
SV Cmax	15.81	102.54	6.49	7.14
SVA AUC	53.13	608.99	11.46	12.17
SVA Cmax	5.02	44.98	8.97	10

Conclusions

- The developed population-based approaches overall provide further insight into the PK of SV/SVA and the related population variability.
- These approaches could be of clinical application due to the widespread use of SV and the clinical burden of muscle toxicity.
- Revealed interesting PG associations. Indicated features that could explain myopathy cases which can not be solely attributed to *SLCO1B1* genotype.
- An integrated modelling approach where PBPK and population methods are combined to develop a mechanistically sound model with clinical relevance.
- Conditionally on the modelling purpose such an approach can provide advantages:
  - Extrapolation outside the studied population and experimental conditions
  - Efficacy and toxicity (PD) is not linked to the surrogate plasma concentrations
  - It can inform design of PG or DDI studies in early stages of drug development

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