

A pipeline for generating large virtual dog populations to predict preclinical drug-induced liver injury

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Introduction

Drug-Induced Liver Injury (DILI) is a major cause of drug attrition and regulatory concern. Traditional methods for assessing DILI risk include animal studies and clinical trials and face ethical, logistical, and financial limitations, particularly in identifying rare adverse events in small preclinical/clinical trial populations. Existing computational approaches ([1],[2],[3]) are empirical and mechanistic but are not open-source, lack explainability or cannot cover the often not clearly dose-dependent idiosyncratic nature of DILI [4].

Large virtual populations (10,000+ patients) enable the systematic evaluation of variability in drug response across diverse patient profiles, however, generating them efficiently is a computational challenge.

Objectives

Build a computationally efficient, scalable workflow to generate a large virtual dog population (10,000 canine virtual patients) that reproduces three major DILI phenotypes: acute liver failure, cholestasis and steatosis, including realistic incidence rates. Note: the workflow utilizes a DILI QST model developed in-house.

Methods

1. Use **Sobol Global Sensitivity Analysis** (GSA) to identify which parameters to vary.
2. Assume parameters follow a **lognormal distribution** with mean equal to the model's baseline value and use **Latin Hypercube Sampling** (LHS) to generate candidate virtual patients (VPs).
3. For each candidate VP, simulate the model to steady state without any treatment and ensure blood ALT, AST, ALP and triglycerides as well as liver fat percentage are within **biologically reasonable bounds**. A candidate VP that passes these checks is considered a plausible VP. If any of the chosen markers is outside their respective pre-defined range, reject the candidate.
4. For each plausible VP, simulate the model under three different treatment scenarios, each corresponding to a DILI phenotype, to create an **initial virtual population**. Record the number of VPs that develop acute liver failure, cholestasis and steatosis.
5. If a given phenotype is rare, in our case steatosis under chronic Amiodarone treatment, use **Bayesian optimization** (BO) to generate steatosis plausible VPs. This step includes the steady state biomarker checks from Step 3 and simulation of the treatment scenarios described in Step 4.
6. Build the final virtual population by selecting a subset of plausible VPs of size 10,000 that satisfies the incidence rate criteria for each DILI phenotype.

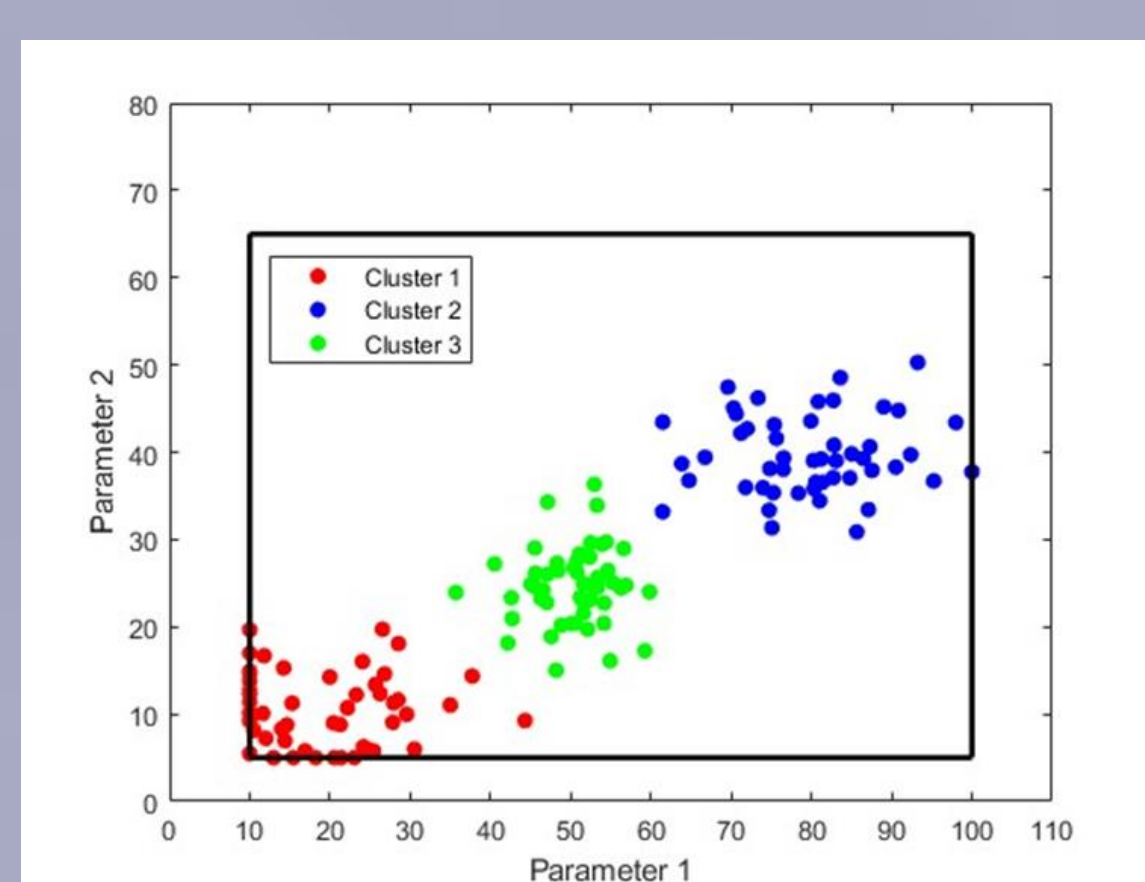
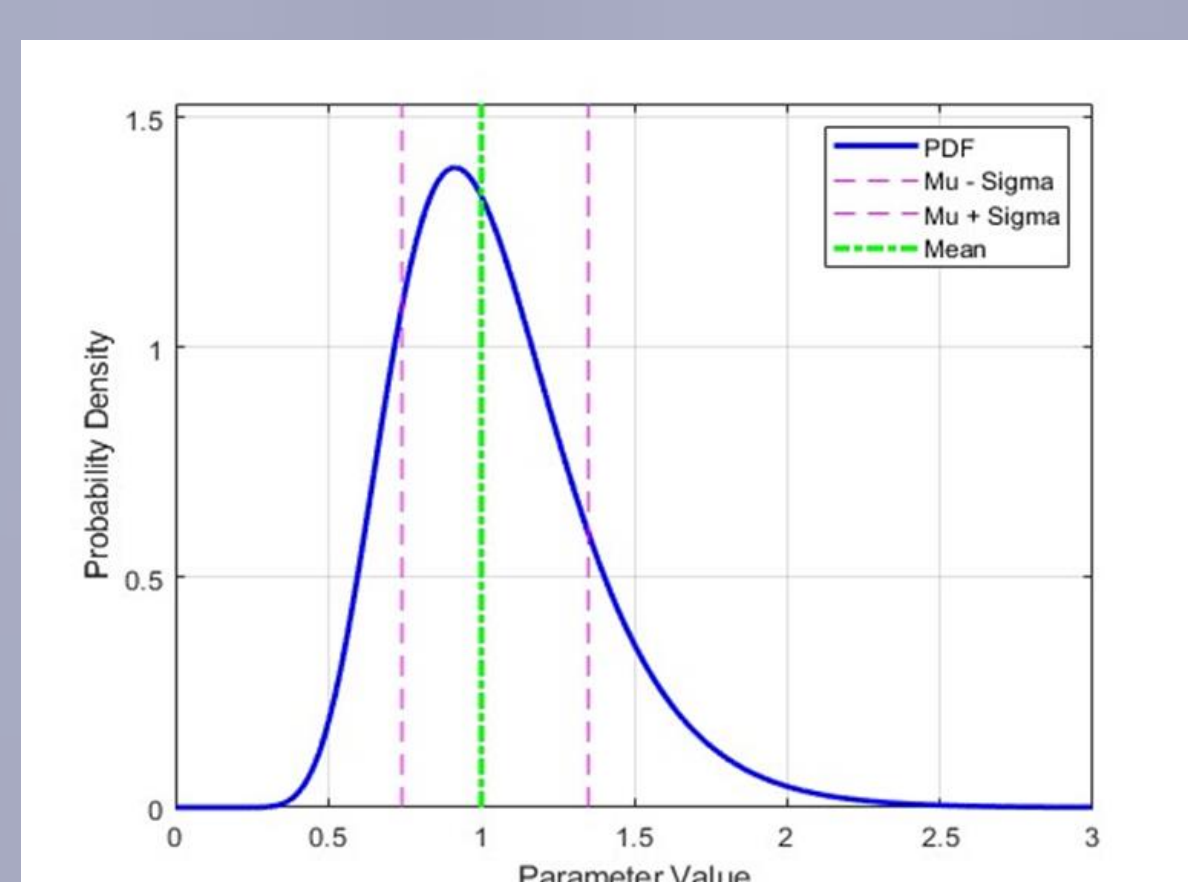
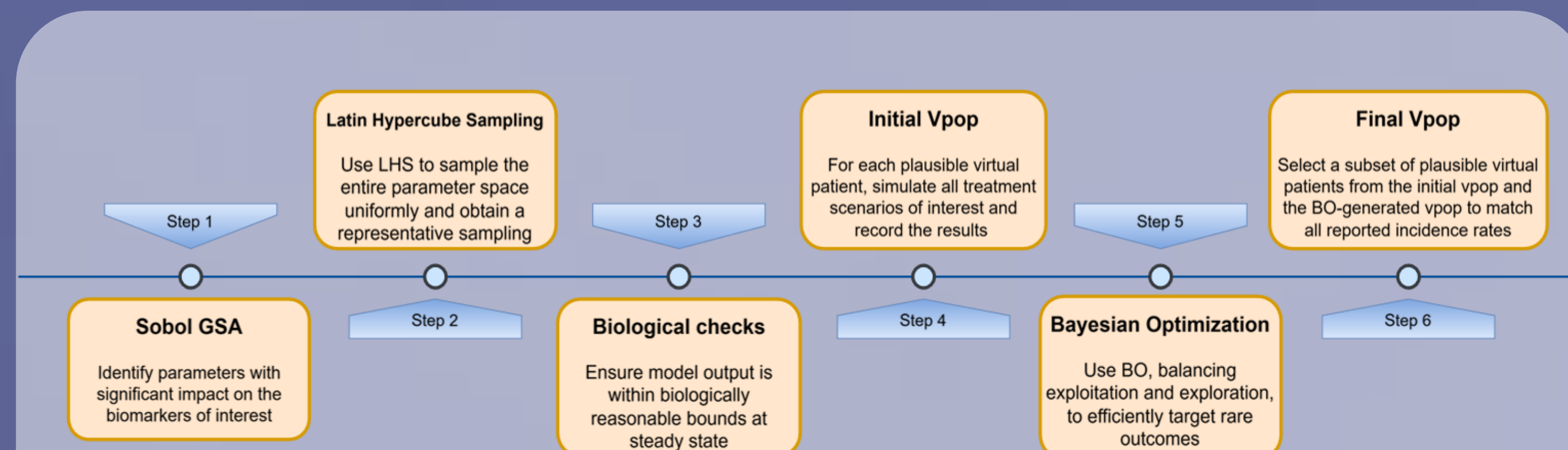


Figure 1. Visual aids for Steps 2 and 5. Left plot: Lognormal probability density function to illustrate the range over which each parameter is varied. Right plot: Two-dimensional parameter space with three arbitrarily defined clusters to illustrate potential parameter sampling limitations that LHS and BO can address.



Results

The generated virtual dog population exhibited substantial inter-individual variability in liver biomarker levels both at steady state and in treatment response, reflecting real-world diversity in DILI susceptibility.

At baseline (in IU/L):

- ALT – median: 27, IQR: 15-52, reference normal range: 12-118
- AST – median: 20, IQR: 17-33, reference normal range: 15-66
- ALP – median: 51, IQR: 18-93, reference normal range: 5-131

When simulating drug exposure, the virtual population reproduced observed inter-individual differences in DILI outcomes, with Acetaminophen overdose-induced necrosis severity, Bosentan-induced cholestasis incidence, and Amiodarone-induced steatosis rates aligning with published data.

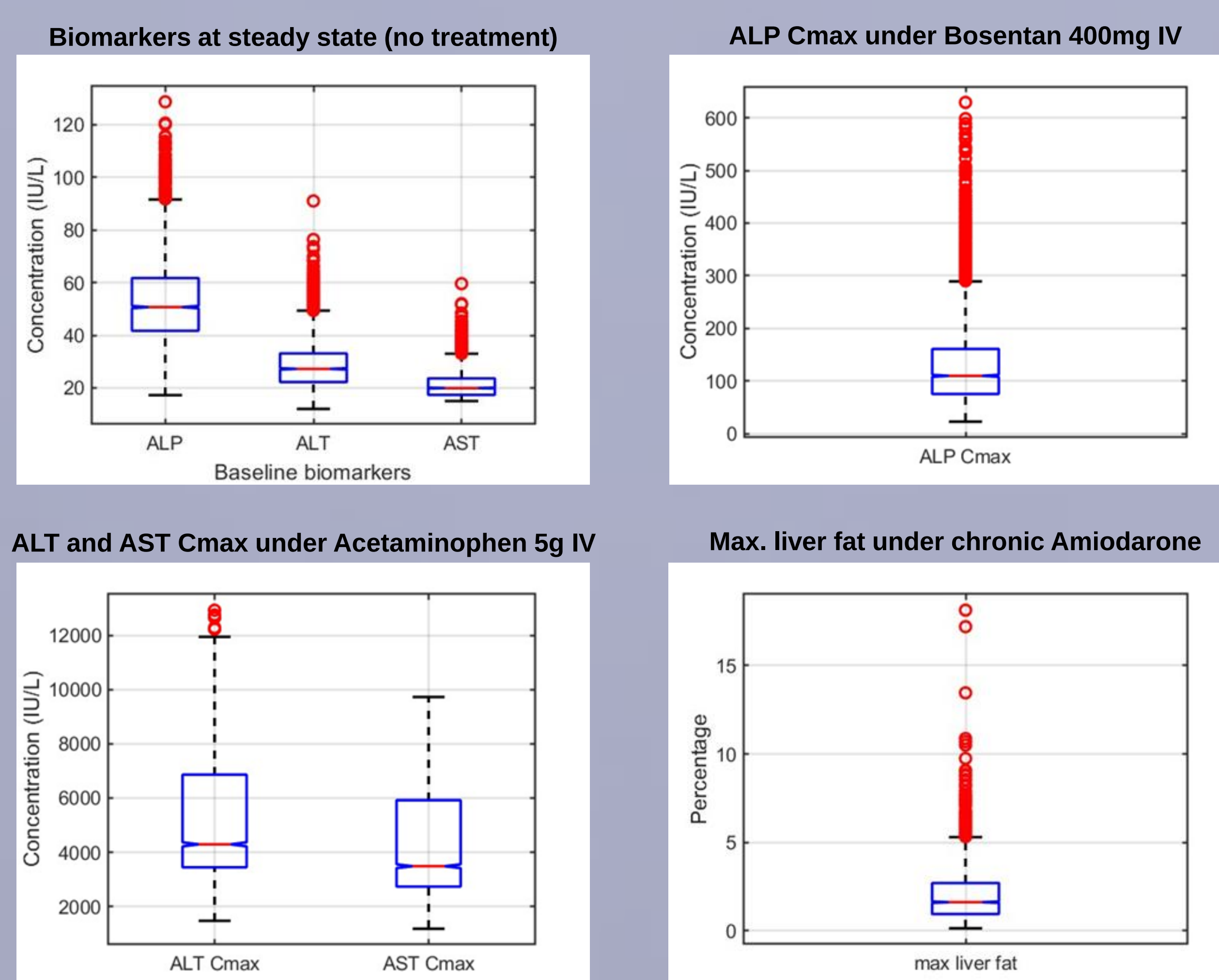


Figure 2. Boxplots showing the inter-patient variability in the final virtual population at steady-state and under treatment. Treatment scenarios: Acetaminophen 5g IV, Bosentan 400mg IV and Amiodarone 100mg q12h for 7 days, then 50mg q24h for 1 year.

Conclusion

Our DILI virtual population generation pipeline is part of an initiative that will be integrated into the CRACKIT Virtual Dog Suite, enabling efficient and robust DILI risk assessment in dog that accounts for inter-patient variability and idiosyncratic reactions along with dose-effect responses.

References

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