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RESEARCH ARTICLE

Sample-based robust model reduction for non-linear systems biology models

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Abstract

Complex non-linear systems biology models comprise relevant knowledge on processes of pharmacological interest. They are, however, too complex to be used in inferential settings, for example, to allow for the estimation of patient-specific parameters for individual dose optimisation. Thus, there is a need for simple models with interpretable components to infer the drug effect in a clinical setting. In particular, it is essential to accurately quantify and simulate the interindividual variability in the drug response in order to account for covariates like body weight, age and genetic disposition. To this end, non-linear model order reduction and simplification methods can be used if they maintain model interpretability during reduction and consider an entire population rather than just a single reference individual. We present a sample-based approach for robust model order reduction and propose two improvements for efficiency. In particular, we introduce a new sampling method to generate the virtual population based on transformed latin hypercube sampling. Thereby, the sample is stratified in the relevant parameter-space directions, which are identified using empirical observability Gramians. We illustrate our approach in application to a blood coagulation pathway model, where we reduce the complexity from a 62-dimensional highly non-linear to a six-dimensional and a nine-dimensional system of ordinary differential equations for two scenarios, respectively.

1 | INTRODUCTION

An increasing understanding of biological processes has led to large-scale systems biology models that can be used to simulate varying scenarios relevant to pharmacology. On the other hand, in clinical settings, individual drug dosing relies on small empirical drug-effect models that allow for parameter inference for individual patients. It would be desirable to exploit the knowledge comprised in systems biology models using model reduction to build more mechanism-based drug effect models. An essential requirement for these types of models in order to be used in the clinical setting is the interpretability of the model components with respect to clinical biomarkers. Moreover, the transient dynamic during a finite time frame is often of particular interest in the clinical setting. Considering these requirements, typical model

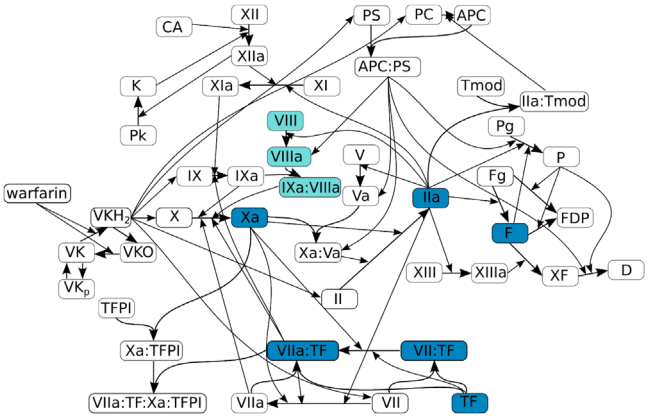

FIGURE 1 Sketch of the blood coagulation model (modified from Knöchel et al. [2]). In the reduced model for the PT test scenario, the states coloured dark blue remain dynamic. In the reduced model for the modified PT test scenario, additionally the light blue states remain dynamic.

order reduction techniques that are used to capture the steady state of a system or that rely on state space transformations like balanced truncation or proper orthogonal decomposition [1] cannot be used. Thus, we build upon a first approach to derive simple mechanism-based drug effect models from systems biology models by state elimination introduced in Knöchel et al. [2].

While systems biology models are often parametrised for a reference patient, drug effect models need to be able to represent a diverse patient population in order to be useful in a clinical setting. Only then can interindividual differences in the drug response be explained by covariates like body weight, age and genetic disposition. If only the reference parameter set is taken into account during the model reduction, the reduced model might neglect components that are not influential for the reference patient but are important for a certain subpopulation. Several methods exist that consider model reduction with random parameters. For linear time-invariant systems, robust model reduction approaches exist that limit the maximal possible error [3], but this is not conferrable to non-linear models. A related concept concerns model reduction under uncertainty [4], where the population variability is preserved, but a good approximation of single individuals is not ensured. In systems biology, sample-based methods (considering a virtual population of individual parameter vectors) have been proposed that guarantee a bound of the sample mean of individual approximation errors [5]. While this still does not ensure a good approximation for single individuals in the population, we use a similar approach but guarantee a bound on the 95%-quantile of individual approximation errors to ensure a good approximation for the majority of the virtual individuals. We have designed a robust model reduction process that considers all parameter sets in a diverse virtual population such that the reduced model is likely suitable for a realistic population [6].

The need to repeatedly solve the model for all individuals during the model reduction process makes the process computationally expensive with increasing population size. In this article, we introduce a backtracking strategy to accelerate the robust model reduction and propose a new, improved sampling method based on empirical observability Gramians that allows using a smaller sample size.

2 | BLOOD COAGULATION MODEL

One systems biology model of interest is the blood coagulation model, illustrated in Figure 1, which is able to simulate different pharmacologically relevant scenarios, for example, the treatment with the anticoagulant warfarin, envenomation with different snake venoms or the *prothrombin time* (PT) test, a measure for treatment effect [7, 8]. As the model includes these very different scenarios, it is obvious that not every component is needed for any single scenario. Model reduction proves useful to extract simpler models for single scenarios, while the full systems biology model is a comprehensive, biologically accurate model of human blood coagulation, including many scenarios.

The blood coagulation model is defined by a system of nonlinear *ordinary differential equations* (ODEs)

$$\dot{x}(t) = f(x(t), \theta), \quad x(0) = x_0 + u \tag{1}$$

$$y(t) = h(x(\cdot), t) \tag{2}$$

with $x \in \mathbb{R}^{62}$ the state vector, $\theta \in \mathbb{R}^{149}$ the parameter vector and y the output. The initial value consists of the pre-stimulus state vector x_0 and the input/stimulus u. The model is defined for a reference individual with extended parameter vector $q_{\text{ref}} = (x_{0,\text{ref}}, \theta_{\text{ref}})$ [7].

We want to focus on two versions of the PT test for the numerical simulations. The standard PT test is a typical way to measure an anticoagulant effect, in which the clotting time is measured after coagulation is induced artificially in a blood sample. The output function for the PT test is

$$h(x) = \min\left\{ \tau \geq 0 \middle| \int_0^\tau x_F(s)\mathrm{d}s \geq \delta \right\}, \tag{3}$$

where x_F is the component of x corresponding to the concentration of the important coagulation factor Fibrin and δ is a fixed threshold.

The input is given by a perturbation in the component corresponding to tissue factor ($u_{\text{TF}} = 100$) and no change ($u_i = 0$) elsewhere. In a modified version, the amount of tissue factor is drastically reduced ($u_{\text{TF}} = 5 \cdot 10^{-5}$), which results in slower coagulation and more coagulation factors taking part in the process. For further details on the coagulation model and PT test, see Wajima et al. [7].

3 | ROBUST MODEL REDUCTION PROCEDURE

In this section, we summarise the (robust) model reduction procedure introduced in Refs. [2, 6]. We aim for a reduced model that can robustly approximate the full model also for individuals differing from the reference individual. Therefore, we generate a virtual population $\mathcal{P}$ of parameters q, which is considered during the model reduction. The population needs to be diverse enough to cover the realistic range. On the other hand, if the population is too broad and its parameters arbitrarily extreme, no significant reduction will be possible.

So, to balance robustness and reducibility, the population must not be too wide or too narrow. To obtain a population $\mathcal{P}$ of parameter vectors with random interindividual variability, we draw the parameters and initial values independently from a log-normal distribution around the reference values

$$q_j \sim \ln \mathcal{N}([q_{\text{ref}}]_j, 0.4^2), \tag{4}$$

for the extended parameter vector $q = (x_0, \theta)$.

The goal of the model reduction is to yield a model that is as simple as possible while approximating the full model well enough in the given virtual population. To this end, we require, given a population $\mathcal{P}$, that the reduced model $\mathcal{M}_{\text{red}}$ approximates the full model to within 10% at any time for at least 95% of the population:

$$\varepsilon_{\mathcal{P}}^{\mathcal{M}_{\text{red}}} := Q_{0.95}\left(\left(\varepsilon_i^{\mathcal{M}_{\text{red}}} \right)_{i \in \mathcal{P}} \right) \overset{!}{\leq} 0.1, \tag{5}$$

$$\text{where } \varepsilon_i^{\mathcal{M}_{\text{red}}} := \max_{t \in [0, t_{\text{end}}]} \frac{\left| y^{(i)}(t) - y^{(i)}_{\mathcal{M}_{\text{red}}}(t) \right|}{|y^{(i)}(t)|}, \tag{6}$$

where $y^{(i)}$ and $y^{(i)}_{\mathcal{M}_{\text{red}}}$ are the outputs of the full and the reduced model for parameter vector $q^{(i)}$.

The 95% quantile $Q_{0.95}$ instead of the maximum over a population was chosen to be more robust regarding random realisations of the virtual population.

We use an iterative reduction, where each state is either kept *dynamic* (modelled by an ODE) or eliminated by setting to zero (*negligible*) or fixed to its initial state (*environmental*). The procedure starts with a model where all states are classified as dynamic. The states are then considered for re-classification in order of increasing importance, measured by the *input-response indices* [2]. For each considered state, the model is simulated with all three possible classifications, while other states are kept as previously classified. If setting negligible or environmental meets the error criterion Equation (5), then the one with smaller error is chosen. As more states are eliminated, the reduced model gets increasingly smaller. Once all states are considered, a similar procedure is performed for the parameters. Parameters are set to zero if this meets the

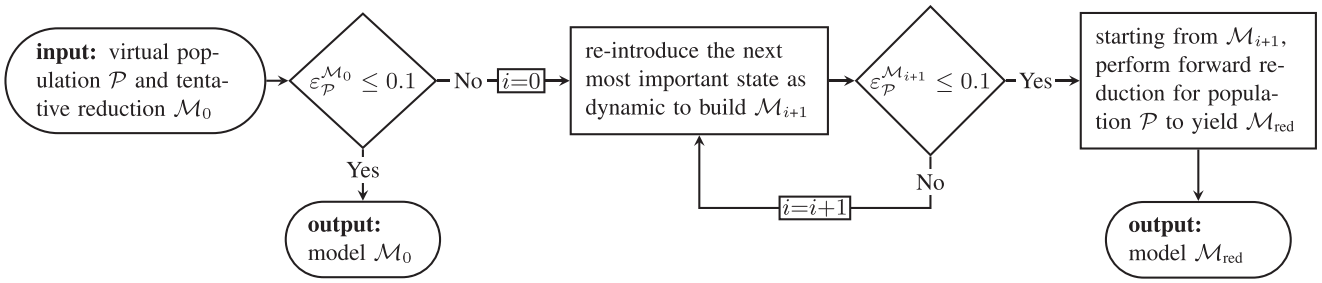

FIGURE 2 Flowchart for the backtracking algorithm, that efficiently performs robust reduction for a (new) virtual population when a tentative reduction is given.

error bound; otherwise, they are set to infinity if this meets the error bound and otherwise kept at the original value. For further details on the robust model reduction, see Falkenhagen et al. [6].

This combined state and parameter reduction yields reduced models (illustrated in Figure 1) with six and nine ODEs and 13 and 21 parameters for the PT test scenario and the modified PT test scenario, respectively.

The robust model reduction method still has some disadvantages that we tackle in the following. First, the need to simulate the model repeatedly for every individual and every state variable leads to a considerable computation time. Moreover, once a new population (or even just a slightly expanded population) is considered, the process needs to be started from scratch to account for the whole population in the model reduction.

4 | BACKTRACKING FOR EFFICIENCY

Suppose a reduced model has been obtained by considering only the reference individual and afterwards, a robust reduction for a virtual population is desired. Instead of starting from scratch, the previously obtained reduced model can be used as a starting point. We use backtracking as a strategy to efficiently deal with a new population, after an initial reduced model was obtained. While in the model reduction, we start from the full model and neglect states in the order of input-response indices, here, we start from a reduced model and iteratively add states in the reverse order. We go backwards through the states until the error threshold is attained. The process is stopped at the latest once the full model is reached. Then, we go forward once again to exclude states that were included unnecessarily, for example, some could be set environmental. The strategy is illustrated in Figure 2.

Often, this reduces the number of simulations to solve, as many states that have no influence at all in a given scenario, do not have to be considered again. By this, we could reduce the time needed to perform model reduction on the blood coagulation model for the PT test scenario to one fourth for a population of size $n = 1000$.

5 | A NEW STRATEGY FOR IMPROVED SAMPLING BASED ON EMPIRICAL OBSERVABILITY GRAMIANS

When robust model reduction given a defined parameter distribution is desired, technically, the model reduction would have to be performed for a very large population $\mathcal{P}_0$ that is representative of the theoretical parameter distribution. As model reduction for this full representative population would be very computationally expensive, we attempt to find a reduced representative population $\mathcal{P}_1$. The reduced model $\mathcal{M}_{\text{red},\mathcal{P}_1}$ obtained for the reduced population $\mathcal{P}_1$ evaluated for the full representative population $\mathcal{P}_0$ is *acceptable* if $\varepsilon_{\mathcal{P}_0}^{\mathcal{M}_{\text{red},\mathcal{P}_1}} \leq 0.1$. In order to accelerate the model reduction, we want to find the minimal sample size that is needed for the reduced population to yield an acceptable model with a high probability. A strategy for improved sampling is helpful if the required sample size is smaller when using the new sampling strategy than when using simple random sampling.

Theoretically, $\varepsilon_{\mathcal{P}_0}^{\mathcal{M}_{\text{red},\mathcal{P}_1}} \leq 0.1$ could be achieved if the population $\mathcal{P}_1$ would consist of only very extreme parameter vectors, as then only little or no reduction might be possible, thus approximating the full model very well in any population. As this is not in line with the goal of the model reduction, we prevent this by requiring the population to still be distributed as defined in Equation (4), which we chose to balance robustness and reducibility.

So we need to ensure that the sample size is large enough for the empirical distribution function to approximate well the distribution function in Equation (4). To cover the parameter space well is particularly difficult in a high-dimensional setting. But we can take measures to faster converge to the desired distribution even in a high-dimensional parameter space.

Latin hypercube sampling (LHS)

LHS is a method to generate stratified random samples from a hypercube [9]. For a specified sample size n, this is done by dividing all sides of the hypercube into n sections of equal size. Then the points are drawn iteratively by drawing each coordinate uniformly at random from the still vacant sections in each dimension. Thus, a good coverage of the marginal parameter space in each dimension is guaranteed. The method can be used to draw from a given probability distribution by drawing a sample in the unit-hypercube and transforming it with the inverse distribution function. The empirical distribution function resulting from LHS has been shown to converge faster to the generating distribution function than with simple random sampling [9, 10]. The advantages of LHS are most profound when the output is influenced by only few of the marginal dimensions [9]. While the standard LHS approach covers the single parameter directions well, the influence of parameters on the model output is often highly correlated. It would be desirable to instead ensure a good coverage of the dominant directions in the parameter space that are not necessarily parallel to the canonical coordinates. To find a basis for the relevant directions, we use empirical observability Gramians [11]. We will introduce the analytical observability Gramians for linear systems [1, Ch. 4.3] and base our arguments on a simplified linear setting, but will later apply the strategy to our non-linear system Equation (1).

Observability Gramians

Consider a linear time-invariant ODE system

$$\dot{x}(t) = Ax(t) + Bu(t), x(0) = x_0, \tag{7}$$

$$y(t) = Cx(t), \tag{8}$$

where A, B and C are matrices, u is an input and y is the output. The time-limited observability Gramian is defined as

$$W_O := \int_0^T e^{A^\intercal \tau} C^\intercal C e^{A\tau} \mathrm{d}\tau \tag{9}$$

and measures how much a change in the state variables is reflected in the output [1, Ch. 4.2.2]. This operator can be used to assess if the system is observable or which (linear combinations of) states are observable (the unobservable states are in the kernel of W_O). More specifically, the quadratic form defined by the observability Gramian is equal to the norm of the output $y_{x_0=x}$ given initial state x:

$$x^\intercal W_O x = \int_0^T x^\intercal e^{A^\intercal \tau} C^\intercal C e^{A\tau} x \mathrm{d}\tau = \int_0^T \|Ce^{A\tau}x\|_2^2 \mathrm{d}\tau = \|y_{x_0=x}\|^2_{L^2([0,T])}. \tag{10}$$

The quadratic form and thus y changes most in the directions of the eigenvectors corresponding to the largest eigenvalues of W_O. Therefore, we can use the singular value decomposition (SVD), which is equivalent to eigendecomposition for Gramians, to transform the state space into a coordinate system of dominant eigendirections of the observability Gramian. Thus, drawing a sample using LHS in the transformed space, we can transform back to get a sample in the original state space that is stratified in the dominant directions.

Specifically, performing SVD on the observability Gramian $W_O = UDU^\intercal$, we can transform a sample point $x \in \mathbb{R}^n$ to yield a new sample point $\tilde{x} = Ux$. For the norm of the output, we get

$$\|y_{x_0=\tilde{x}}\|^2_{L^2([0,T])} = \tilde{x}^\intercal W_O \tilde{x} = (Ux)^\intercal UDU^\intercal Ux = x^\intercal Dx. \tag{11}$$

Here, y changes most in x in directions parallel to the axes, as the matrix D is diagonal. Thus, if x is drawn using LHS, the sample points are stratified in the dominant directions and so are the transformed sample points $\tilde{x}$ in the original parameter space.

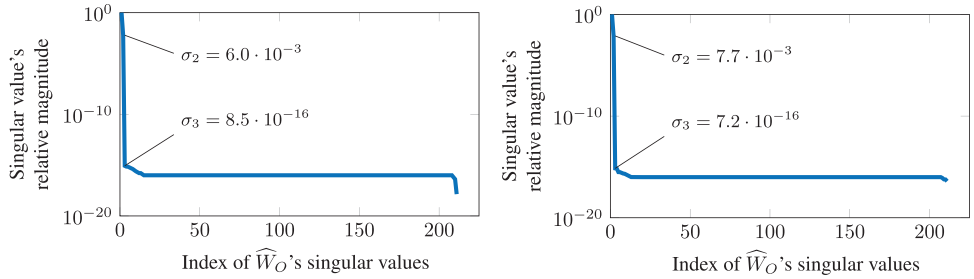

FIGURE 3 Singular values of augmented empirical observability Gramian $\widehat{W}_O$ for PT test scenario (left) and modified PT test scenario (right).

Empirical observability Gramians

For a non-linear ODE system

$$\dot{x}(t) = f(x(t), \theta), \tag{12}$$

$$y(t) = h(x(t)) \tag{13}$$

the time-limited empirical observability Gramian is defined as in Knöchel [12, Sec. 4.1] with notation from Himpe [13, Sec. 3.1.2]:

$$\widehat{W}_O := \frac{1}{|S_x|} \sum_{d_l \in S_x} \frac{1}{d_l^2} \int_0^T \Psi^l(t) \mathrm{d}t, \tag{14}$$

$$\Psi^l_{ij}(t) := (y^{li}(t) - \bar{y}(t))^\intercal (y^{lj}(t) - \bar{y}(t)) \in \mathbb{R}, \tag{15}$$

with perturbation set $S_x = \{d_l \in \mathbb{R} | l = 1, \dots L\}$, output trajectories $y^{li}(t)$ for the initial state configurations $x_0^{li} = \bar{x} + d_l \bar{x}_i \epsilon_i$ (perturbing in direction of standard unit vector ϵ_i by $d_l \bar{x}_i$) and the offsets $\bar{x}$, $\bar{y}$. For our setting, we used $S_x = \{-\frac{1}{2}, 1\}$ and offsets $\bar{x} = x_{0,\mathrm{ref}}$ and $\bar{y} = y_{\mathrm{ref}}$ as in Knöchel [12, Sec. 4.1]. We consider finite-time Gramians, as we are interested in a transient behaviour during a specific time-frame only, not the asymptotic behaviour of a system. For linear systems and under certain conditions, the time-limited empirical observability Gramian and the time-limited analytical observability Gramian coincide [12], up to numerical quadrature error.

Particularly, we compute the augmented empirical observability Gramian, for which the parameters of the underlying system are included into the system as additional (but constant) states as in Refs. [14, 15]:

$$\dot{\tilde{x}}(t) = \begin{pmatrix} \dot{x} \\ \dot{\theta} \end{pmatrix} = \begin{pmatrix} f(x(t), \theta) \\ 0 \end{pmatrix} \tag{16}$$

$$y(t) = h(x(t)). \tag{17}$$

Then the augmented empirical observability Gramian has the following block structure:

$$\widehat{W}_O = \begin{pmatrix} W_X & W_M \\ W_M^\intercal & W_P \end{pmatrix}, \tag{18}$$

where W_X is the state-space observability Gramian, W_P the parameter-space observability Gramian and $W_M = W_M^\intercal$ the mixed block.

In contrast to the observability Gramian, the empirical observability Gramian can be efficiently computed for non-linear systems (with the above-mentioned adaptations), based on simulating trajectories for perturbed initial states. We computed the empirical observability Gramians for the two scenarios of the blood coagulation system using the Empirical Gramian Framework [13].

The singular values are plotted in Figure 3 and indicate that only two directions in the parameter space (given by the eigenvectors of the first two eigenvalues) are relevant, for each of the two scenarios. All other parameter space directions

TABLE 1 Share of accepted reduced models based on virtual populations obtained via different sampling methods for different sample sizes for PT test scenario (left) and modified PT test scenario (right).

Sample size	Simple	LHS	Trans-LHS
20	67%	74%	84%
50	96%	99%	98%
100	100%	100%	100%
200	100%	100%	100%

Sample size	Simple	LHS	Trans-LHS
20	54%	60%	71%
50	84%	91%	96%
100	92%	97%	97%
200	99%	100%	98%

have negligible impact on the Gramian. This small number of relevant parameter space directions might surprise given the large system including many non-linear reactions. However, it is not implausible that a mechanistic model of physiological processes that can describe very different scenarios can be significantly simplified when considering only a single scenario. Also, the empirical observability Gramian is only an average of linear approximations which might not capture the whole complexity of the model. Still, we suspect that the information gained from the empirical observability Gramian helps in the generation of the improved virtual population, as it at least captures the linear components of the system. The parameters that mainly contribute to the vectors corresponding to the two largest singular values agree with the parameters that we would expect to be important, from previous experience and previous model reduction results. While more than 20 single parameters influence the output considerably, they can be compiled into only two directions in the parameter space, which makes the transformed LHS look promising as the advantages of LHS can then be fully exploited. The high-dimensionality is, thus, rendered manageable. Of note, while for generation of a virtual population, it is acceptable to use transformation based on insights about the model, the model reduction itself, in order to maintain interpretability, should not use transformation.

While the quadratic form defined by the analytic observability Gramians in the linear case equals the norm of the output, the empirical observability Gramians in the nonlinear case is an averaged linear approximation [11] to the actual nonlinear observability Gramian (computation of which is currently unfeasible). We use the strategy motivated by the arguments in the linear case and define the transformed sample

$$\tilde{x} = Ux, \tag{19}$$

where U is obtained via SVD of the empirical observability Gramian: $\widehat{W}_O = UDU^\intercal$.

6 | IMPROVED SAMPLING APPLIED TO MODEL REDUCTION FOR BLOOD COAGULATION MODEL

We performed a numerical experiment to assess the usefulness of the improved sampling approach in reducing the required sample size of the reduced population for model reduction in the blood coagulation model. We compare simple random sampling, LHS and transformed LHS using the empirical observability Gramian. First, we drew the full representative population $\mathcal{P}_0$ for which a reduced model is desired, with a size $n = 10\,000$, using LHS. Then, for the exemplary sample sizes {20, 50, 100, 200} and each sampling method, 100 independent reduced populations $\mathcal{P}_{\text{red}}$ were drawn and the model reduction was performed to yield 100 reduced models $\mathcal{M}_{\text{red}}$ each. These reduced models were then used to simulate the full representative population $\mathcal{P}_0$ and calculate the error $\varepsilon_{\mathcal{P}_0}^{\mathcal{M}_{\text{red}}}$. The share of acceptable models for the exemplary sample sizes for each sampling method can be seen in Table 1 for both the PT test scenario and the modified PT test scenario. As expected, the share increases with increasing sample size. Also, it increases from simple random sampling to LHS to transformed LHS, which validates the improvement. If setting 95% to be the threshold to be sure enough to yield an acceptable model, then the sample size required for a reduced representative population is considerably smaller when using improved sampling than when using simple random sampling in the modified PT test. The required sample size differs between the two very similar scenarios and is expected to differ even more when looking at further scenarios, other models or different error thresholds.

7 | CONCLUSION

We found that the previously introduced sample-based robust model reduction can be accelerated by using a backtracking approach that was presented in this article.

Further acceleration is possible by using a smaller sample size of the virtual population, which we have shown to yield good results if improved sampling methods are used to build the virtual population. LHS allows to use a smaller virtual population in comparison to simple random sampling and transformed LHS based on empirical observability Gramians was shown to decrease the required sample size further. We plan to investigate the promising results for further scenarios and models.

As the required sample size differs even for the very similar scenarios considered in this analysis, we plan to investigate an adaptive sample size choice, which is made possible by the backtracking algorithm.

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