A Bayesian Optimization Procedure for the Automated Determination of Optimal Limited Sampling Strategies

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INTRODUCTION

Limited sampling strategies

- PK-guided dosing is a common approach for individualizing prophylactic treatment of haemophilia A patients.
- Patient blood samples are collected to individualize PK parameter estimates from prior population-PK models.
- Limited sampling strategies (LSSs) are often obtained via simulation experiments[1,2,3] where several hypotheses concerning the number and timing of samples are evaluated.

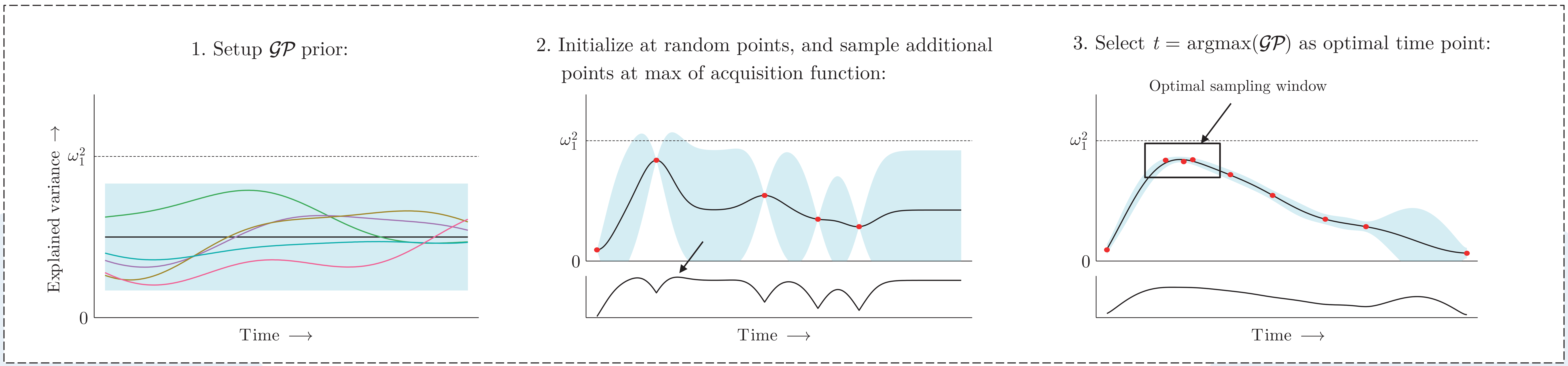
Opportunities for improvement

- Generally only convenient sampling times (e.g. in 24h intervals) are considered.
- No information on contribution of each unique sample on accuracy.
- Differences in sub-populations can only be analysed *a priori.*
- Analysis involves a lot of manual work.
- Often only the accuracy of predictions is evaluated, while its uncertainty might be more informative in practice.

Bayesian Optimization

- Bayesian optimization (BO) is a method for the efficient optimization of computationally expensive black-box functions.
- Generally a Gaussian Process ($\mathcal{GP}$) is used. A $\mathcal{GP}$ represents a distribution over functions.
- Observations are added in order to update the posterior distribution over these functions.
- An acquisition function is then used to select the most informative point to sample next.
- The resulting function $f(t)$ represents the improvement in the objective over time t.

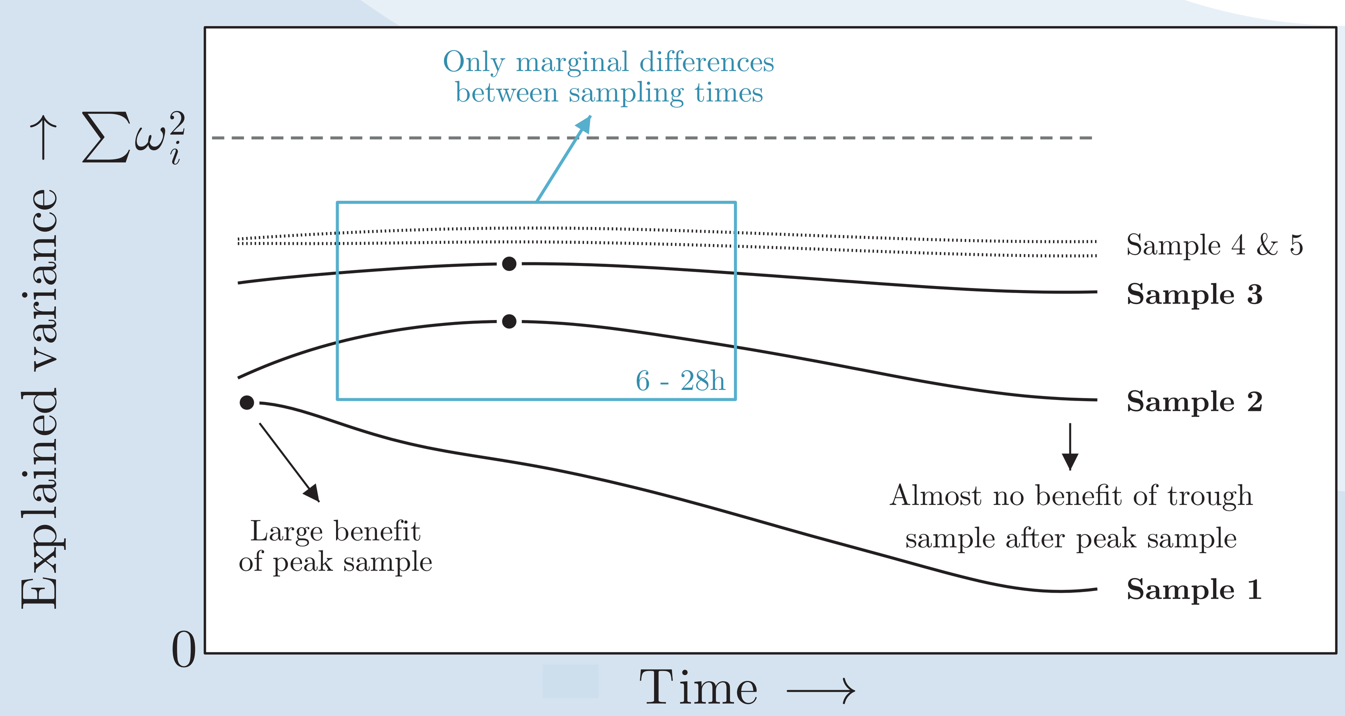
METHOD



USE-CASE: HAEMOPHILIA A

- Compare BO-LSS to prior LSSs from the literature.
- We use posterior variance of $p(\eta \mid y)$ as proxy for prediction uncertainty.

STANDARD HALF-LIFE FVIII



$$\Omega = \begin{bmatrix} 0.086 & 0.027 \\ 0.027 & 0.043 \end{bmatrix}$$

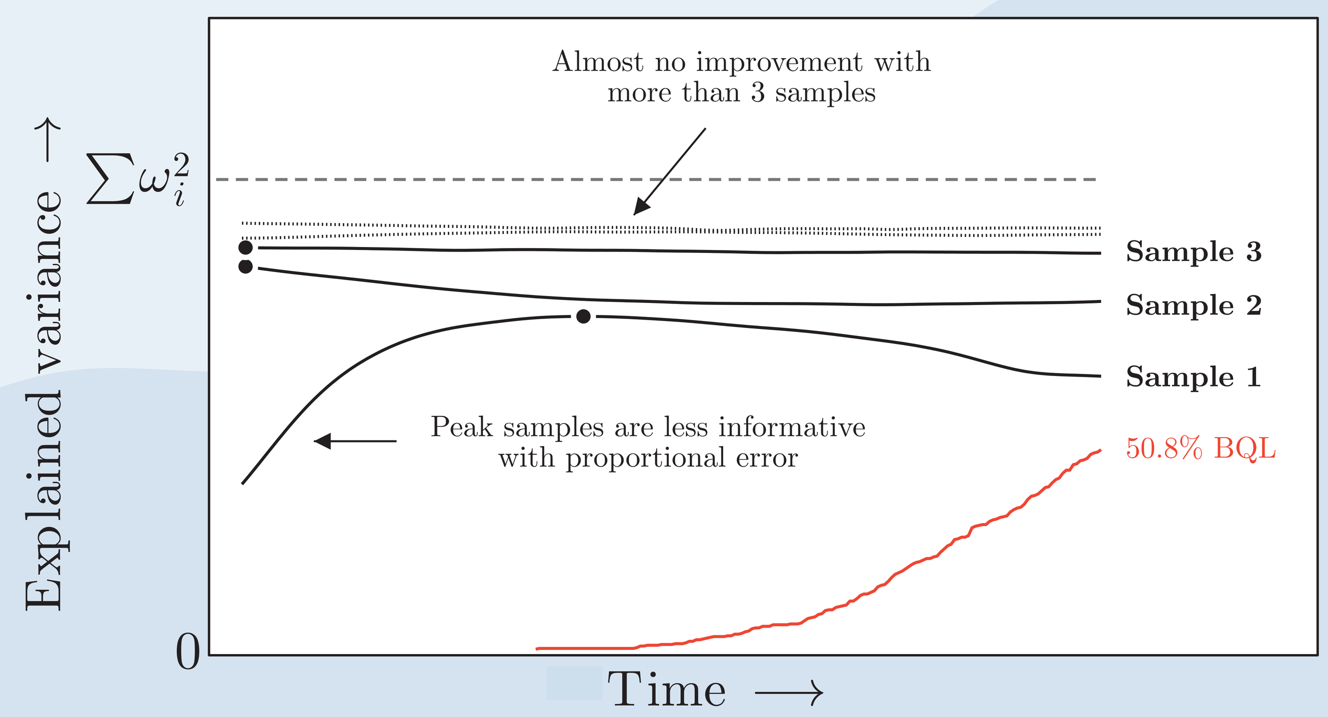
$$\sigma = [0.089]$$

- BO-LSS: samples at t = 1 and two at 16h post-infusion.
- Literature: samples at $t = 4$, 24, and 48h post-infusion[1].

APPROACH

- Simulate patients from PK model of literature study and run BO.
- For each sample, fit $\mathcal{GP}$ to $p(\eta \mid y)$ over t, take $\max(\Sigma_i\, \sigma^2[\eta_i])$, and repeat.

EXTENDED HALF-LIFE FVIII



$$\Omega = \begin{bmatrix} 0.108 & 0.029 \\ 0.029 & 0.027 \end{bmatrix}$$

$$\sigma = [0.024, 0.154]$$

- BO-LSS: two samples at $t = 1$ and one at 48h post-infusion.
- Literature: samples at $t = 1$ and two at 24, 48, or 72h post-infusion[2].

Table 1. Accuracy of BO-LSS versus literature LSS

Approach	Overall accuracy (RMSE)		Residual uncertainty (σ)				Peak interval accuracy (RMSE)		Trough interval accuracy (RMSE)	
			SHL		EHL					
	SHL	EHL	*CL*	*Vd*	*CL*	*Vd*	SHL (0 - 4h)	EHL (0 - 4h)	SHL (36 - 48h)	EHL (72 - 120h)
Literature	0.048	0.042	0.17	0.14	**0.086**	0.11	0.085	0.082	0.027	**0.014**
BO	**0.037**	**0.042**	**0.15**	**0.084**	0.10	**0.086**	**0.056**	**0.077**	**0.021**	0.014

BO: Bayesian optimization, RMSE: root mean squared error, SHL: standard half-life, EHL: extended half-life, *CL*: clearance, *Vd*: volume of distribution, σ: standard deviation

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