A fully hierarchical Bayesian approach to sequentially update population parameter uncertainty in MIPD

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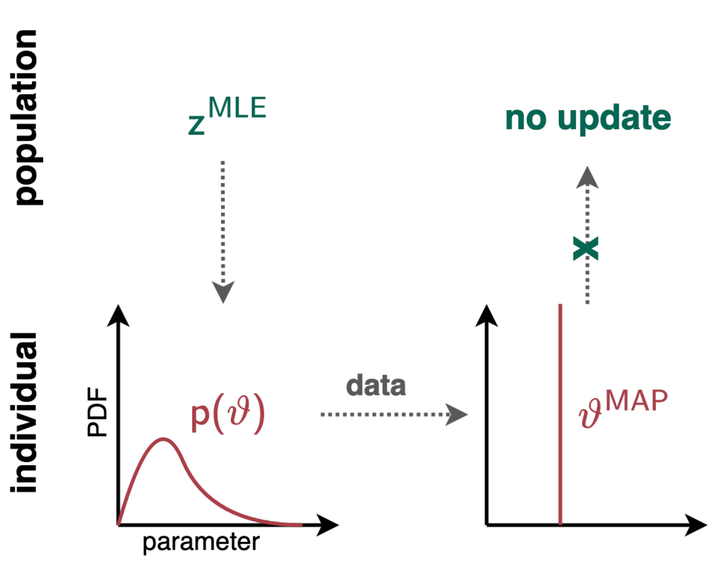
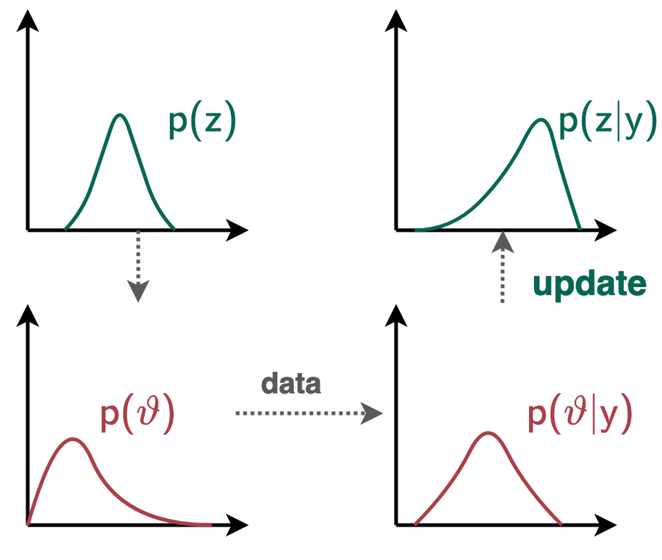
Modelling population parameter uncertainty in Model-informed precision dosing (MIPD)

Bayesian forecasting in MIPD



status quo (no update)

Full Bayesian method



with population parameter update

Background

- MIPD leverages population information from prior study data to predict individual data
- Can we introduce additional patient information from clinical practice to improve the existing model?

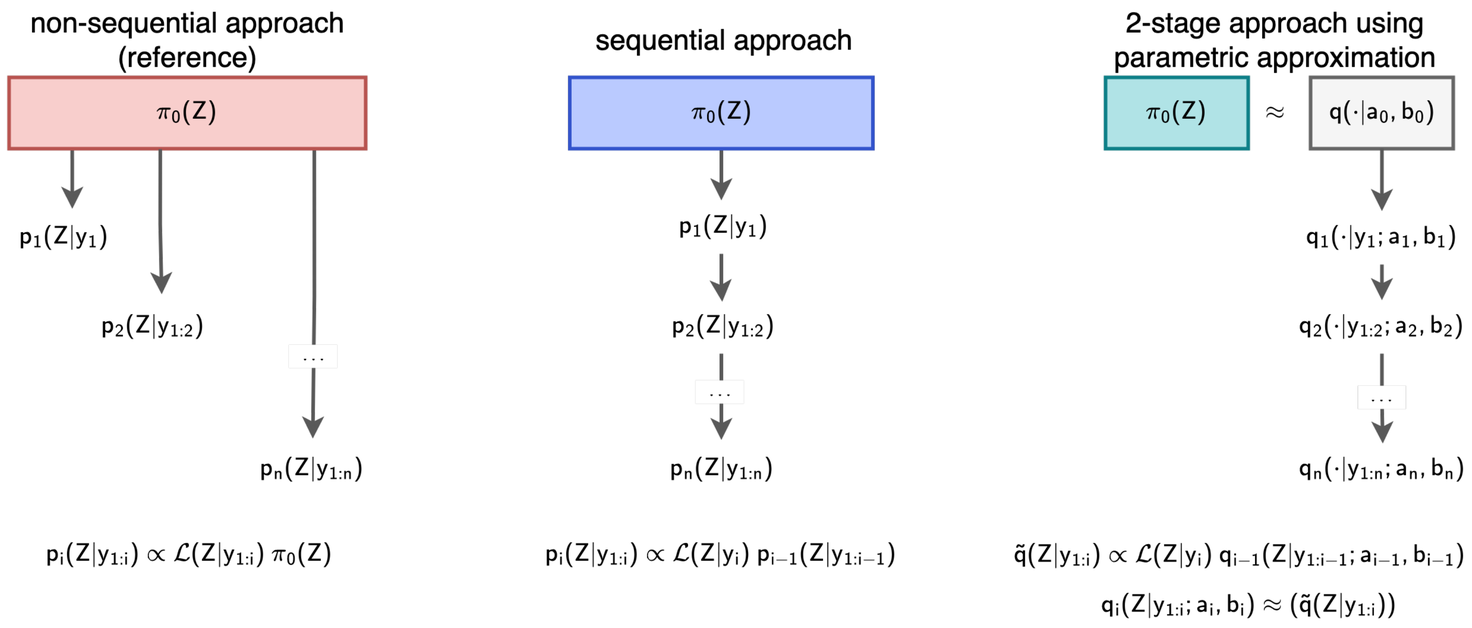
Challenge

- Update prior information as data is observed during MIPD
- Present approaches for continued learning [6,7] do not combine all given and incoming information (prior and data) to update the population prior

Idea

Use Bayesian hierarchical modelling to represent and update uncertainty in the prior parameters

Sequential and non-sequential Bayesian hierarchical methods



Non-sequential approach (reference)

- MCMC (Metropolis-Hastings)
- Data used in batch, computationally less efficient

Sequential approach

- Sequential Monte Carlo method using nested particle filters [5]
- Iterative update of posterior, data not used in batch

2-level approach [3]

- Parametric approximation of posterior, may introduce bias
- Iterative update of posterior approximation, data not used in batch

Model system hierarchy and sampling

Uncertainty

$Z = (\alpha, \beta)$ $\quad Z \sim \pi(a, b, c)$

$\downarrow$

Variability

$\Theta_i = \vartheta_i$ $\quad [\Theta|Z = (\alpha, \beta)] \sim \text{Beta}(\alpha, \beta)$

$\downarrow$

Data

$Y_i = \{y_{i,1}, \ldots, y_{i,n_i}\}$ $\quad [Y|\Theta = \vartheta] \sim \text{Bernoulli}(\vartheta)$

Simple hierarchical model system to test the approaches.
Sampling scenarios with $n = 1000$ individuals:

- dense: $n_i = 10$
- sparse: $n_i = 2$

Evaluation of Results

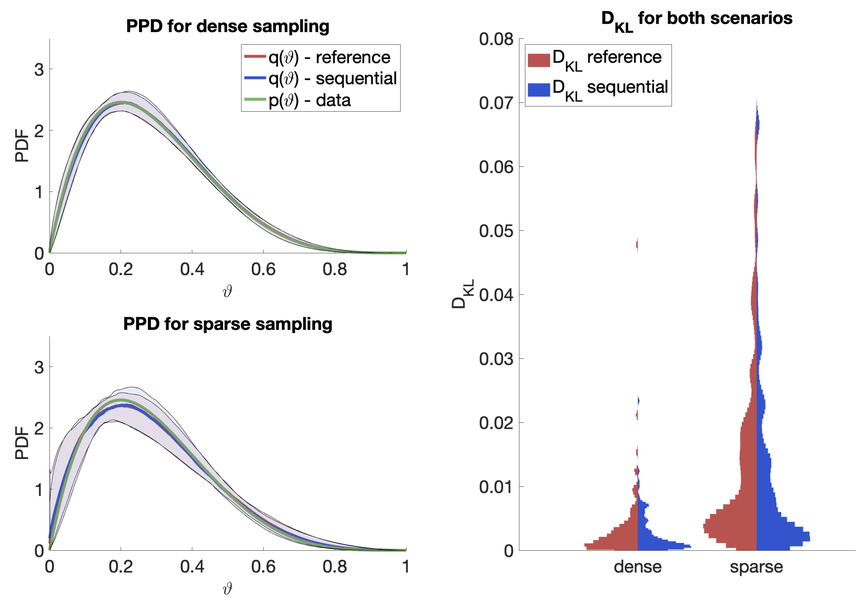
How well can we predict new individuals after observing the data?
Idea: Posterior predictive distribution (PPD)

$$p(\vartheta|y_{1:n}) = \int p(\vartheta|z)p(z|y_{1:n})dz \approx \frac{1}{R}\sum_{r=1}^{R} p(\vartheta|z_r)$$

How different are two probability distributions?
Idea: Kullback-Leibler Divergence (D_{KL})

$$D_{KL}(p||q) = \int_{-\infty}^{\infty} p(\vartheta)\log\frac{p(\vartheta)}{q(\vartheta)}d\vartheta$$

Generate posterior predictive distribution $q(\vartheta)$ of individuals and compare to data-generating distribution $p(\vartheta)$.



- Implemented sequential and non-sequential full Bayesian methods
- Sequential model is as good as non-sequential model
- Both dense and sparse sampling scenario show low divergence in the PPD

Conclusion: sequential fully Bayesian hierarchical models have potential to facilitate continued learning on real-world population without loss of information or need for storage of sensitive patient data.

References

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