Analytics

Qualifying dosing regimens in pediatrics using probabilistic Gaussian Processes

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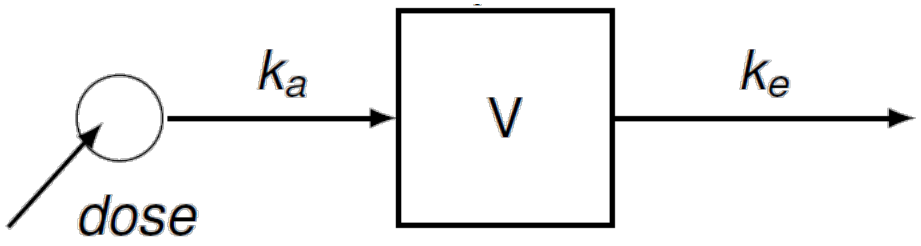
Pediatric drug development
Children are not adults…

- Pediatrics commonly developed after the adult program
  - Pharmacokinetic model is established in adults
  - Adult dosing regimen maintains exposure in therapeutic window
- Pediatric drug development
  Key development question: What dosing regimen?
  - Commonly we target the same exposure levels as in adults as the therapeutic window is assumed to be the same
  - Tested dosing regimens are **extrapolated** from adult model
    - **Allometric scaling** ("...*but maybe children are small adults*")
    - PBPK (considers in addition **maturation** of organs and much more)
  - After completion of a pediatric trial we need to address the question:
    Is the dosing regimen chosen suitable given the (sparse) data observed?
  - Framed from a modeling perspective:
    Was the model used to extrapolate the right one or do we need to adjust?

Extrapolation of PK models

Example 1-cmt model, linear absorption



- Absorption ka
- Central volume V
- Elimination ke = Cl/V
- Subject i specific parameters

Extrapolation through size dependent modeling of PK parameters

- Allometric scaling only (similar for volume)

$$\log(Cl_i) = \log(Cl_{ref}) + \alpha \log(size_i/size_{ref}) + \eta_i$$
$$\eta_i \sim N(0, \omega_{Cl}^2)$$

- Allometric scaling and age-dependent maturation

$$\log(Cl_i) = \log\left(Cl_{ref}\right) + \alpha \log\left(\frac{size_i}{size_{ref}}\right) + \log\left(M(age_i)\right) + \eta_i$$

- Maturation
  - Hill function known to work well empirically

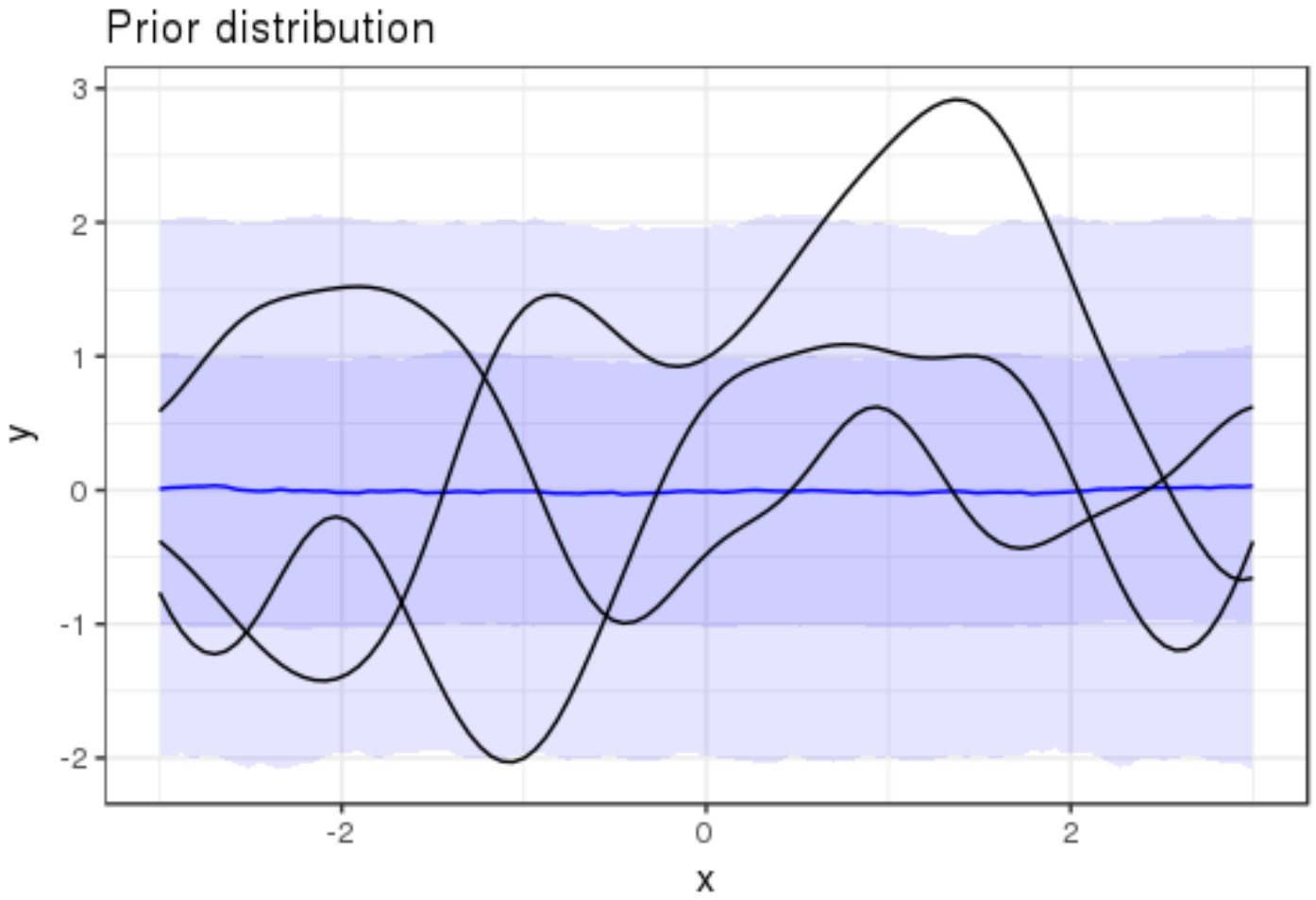
$$M(age) = \frac{age^h}{K_{age}^h + age^h} = \text{logit}^{-1}(h\,(\log(age) - \log(K_{age})))$$

  - In this work we evaluate a non-parametric approach, the Gaussian Process

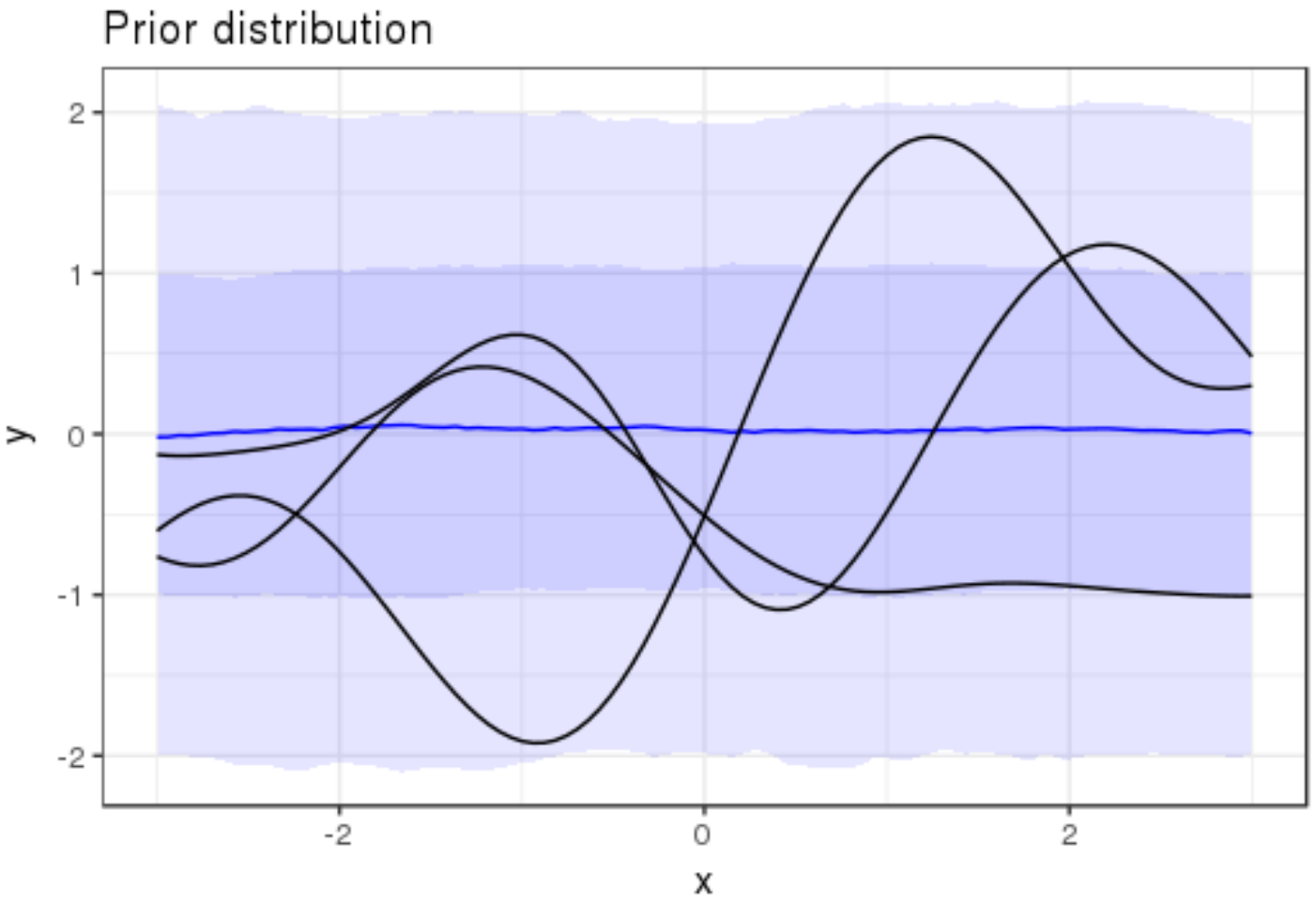
$$\log(M(age)) \sim GP(age)$$

    - Mean function (allometric scaling, linear model)
    - Covariance function (properties like smoothness & more)

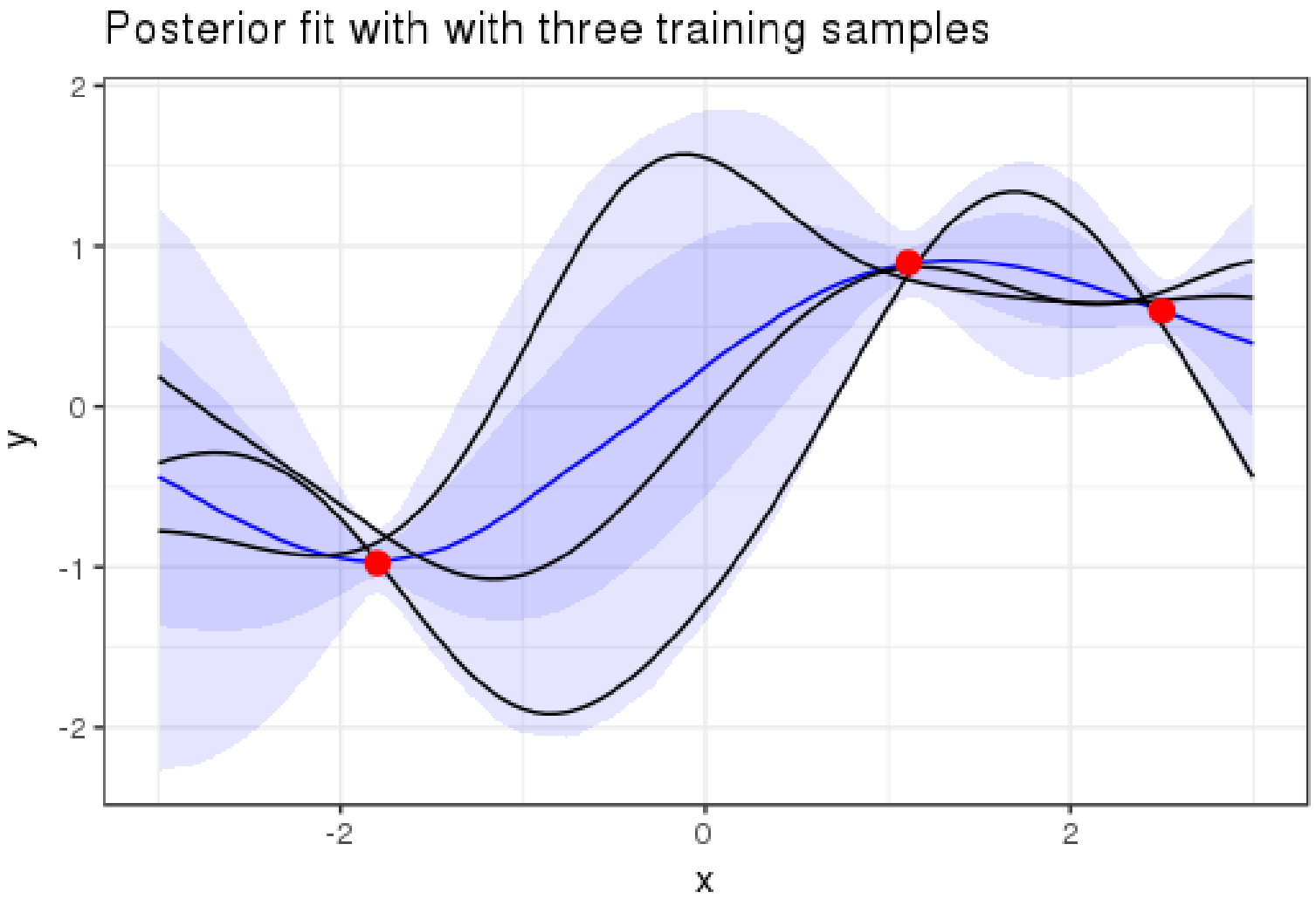
Gaussian Process (wiggly) non-parametric function prior



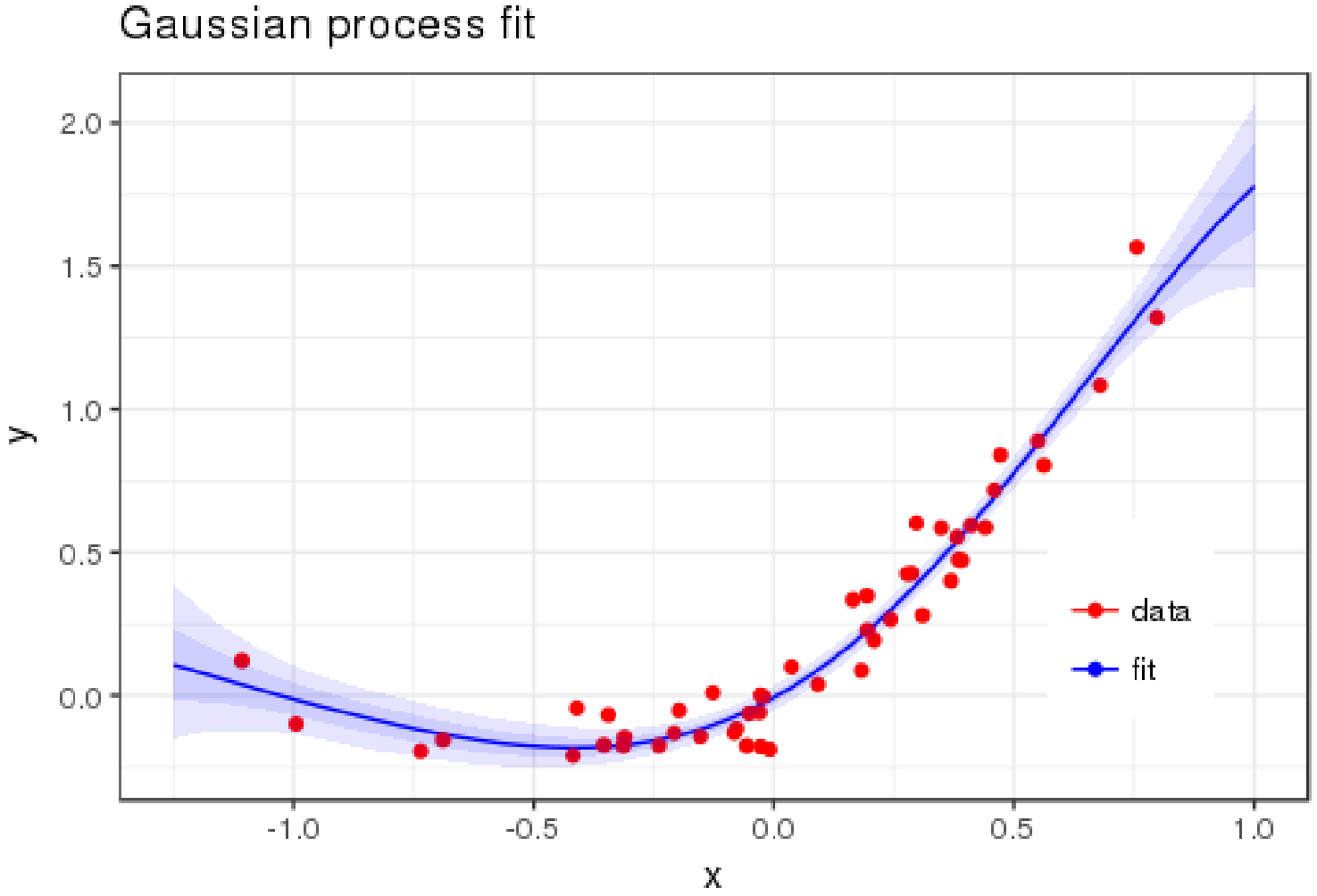
Gaussian Process (smoother) non-parametric function prior



Gaussian Process posterior



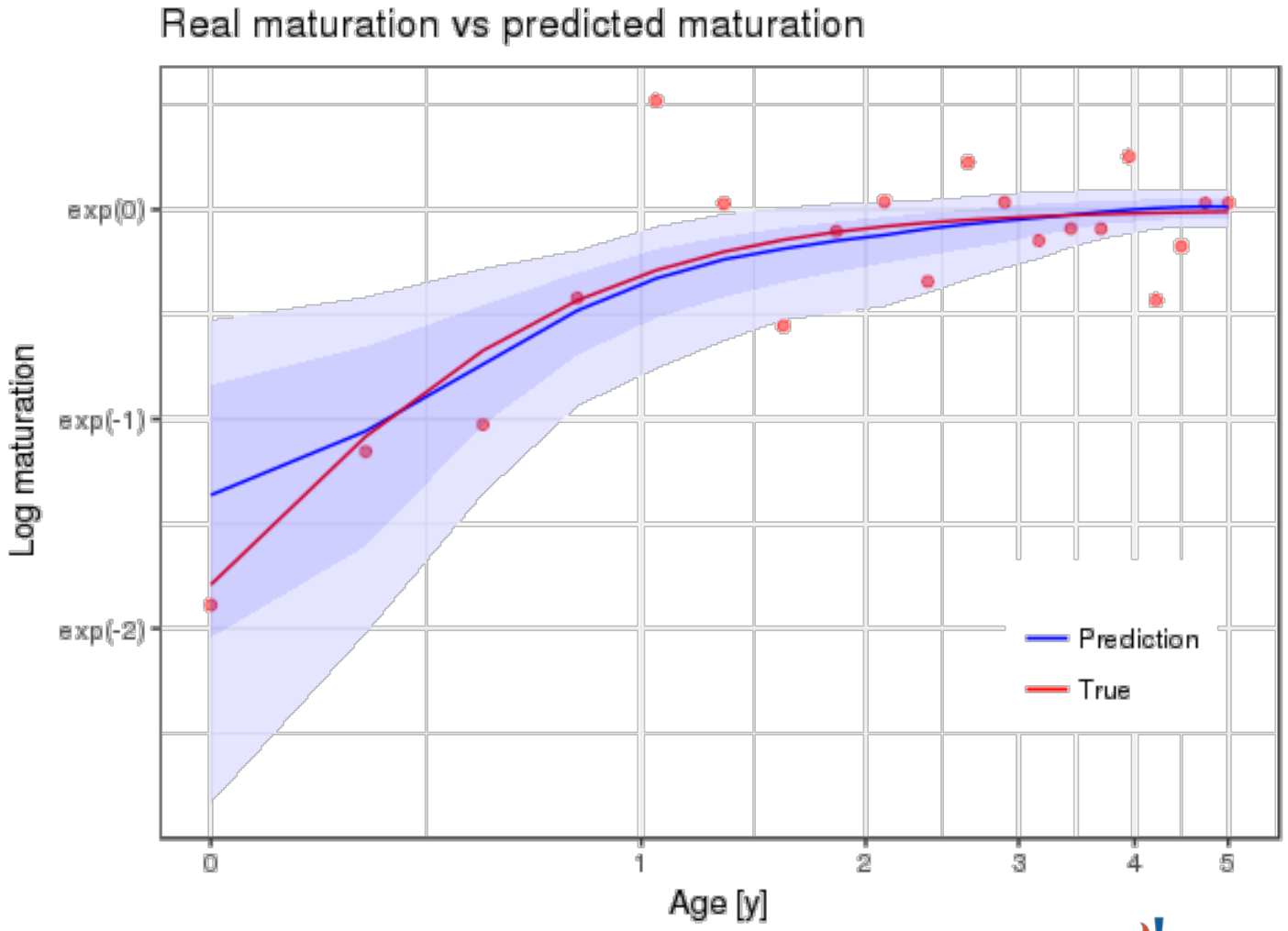
Gaussian Process posterior simulated example



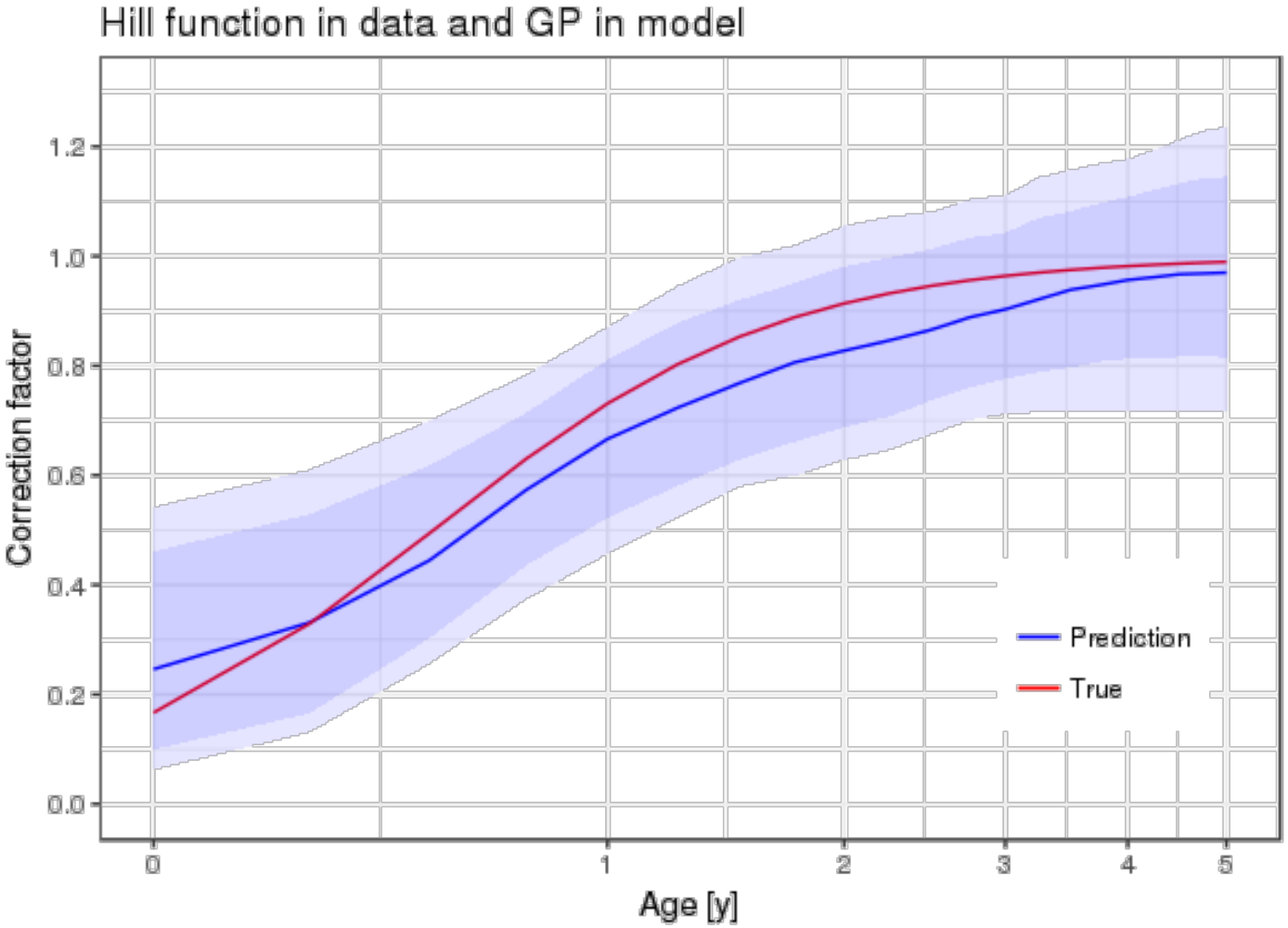
Simulated data scenarios

- No maturation case (no effect)
  Allometric scaling only for clearance and volume
  - ¾ (1) fixed power scaling for clearance (volume)
  - Adult model correct for pediatric population
- Maturation case (true effect)
  Allometric scaling and maturation (effective below 5y)
  - Allometric scaling as in no maturation case
  - Hill type maturation parametrized based on post-menstrual age (pma)
    => Adult model is incorrect for very young pediatric population
  - Age mapped to weight using standard population curves
- Children dosing adjusted assuming allometric scaling for both cases
- 20 patients in age range 0-5y
  10 trough observations per patient
- Simulation & inference performed with Stan 2.17.1

Maturation data + GP model
True clearance deviation + fitted



Maturation data + GP model
Inferred dosing correction vs age



Conclusion

- Model based pediatric drug development
  - Extrapolation from adult data and models to design trials
  - Model qualification once trial data available
  - Model refinement if trial data suggests so
- Maturation of organs may require dosing adjustments if trial was planned with allometric scaling only
  - Hill maturation function known to work empirically
  - Gaussian Process (GP) offers a data driven alternative which avoids any choice of parametric function
- GP shown to work well in realistic & sparse data scenarios through the use of prior knowledge like shape constraints
- Correcting models with a GP is a generally applicable approach known as emulator

Thank you

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Backup

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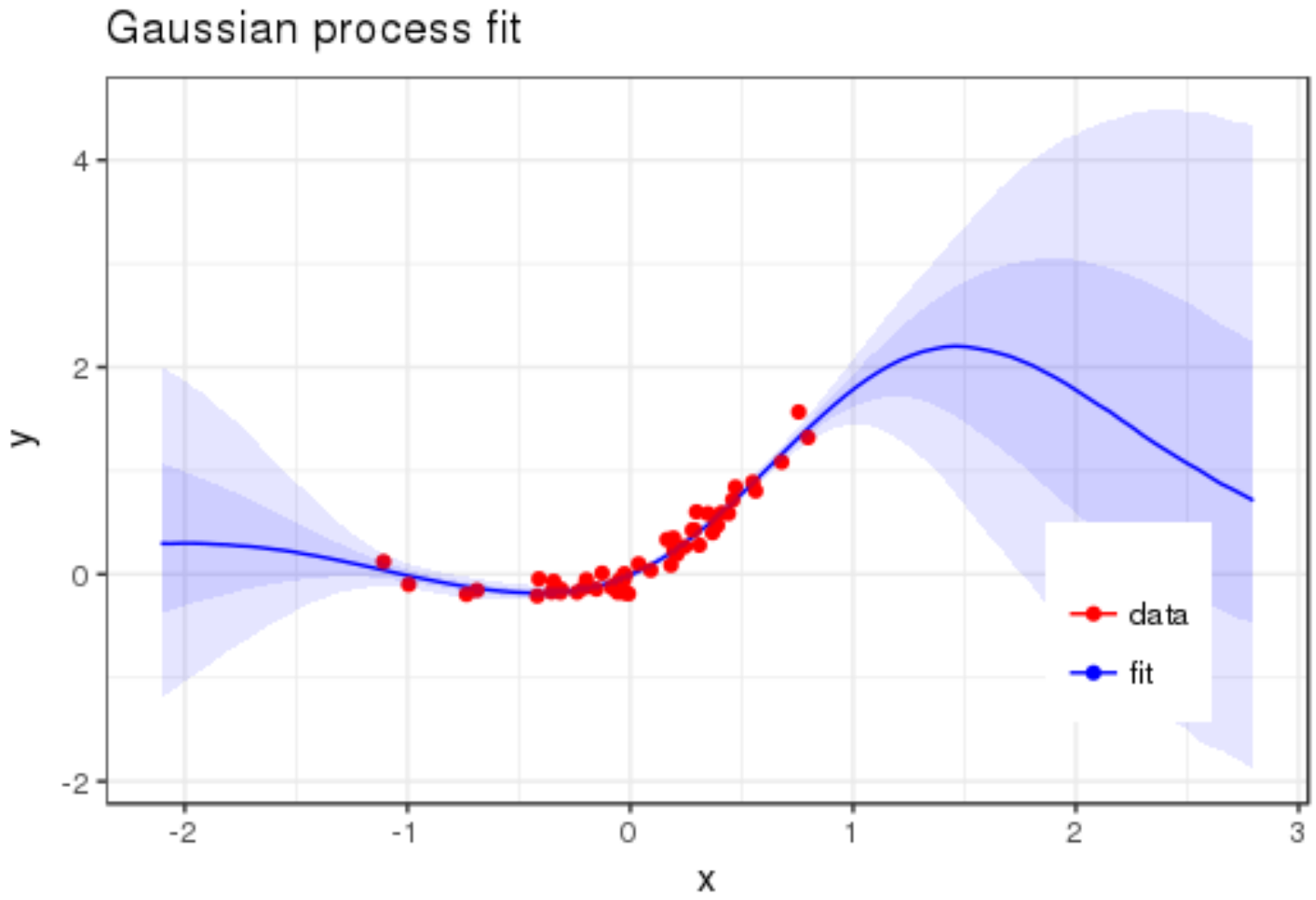
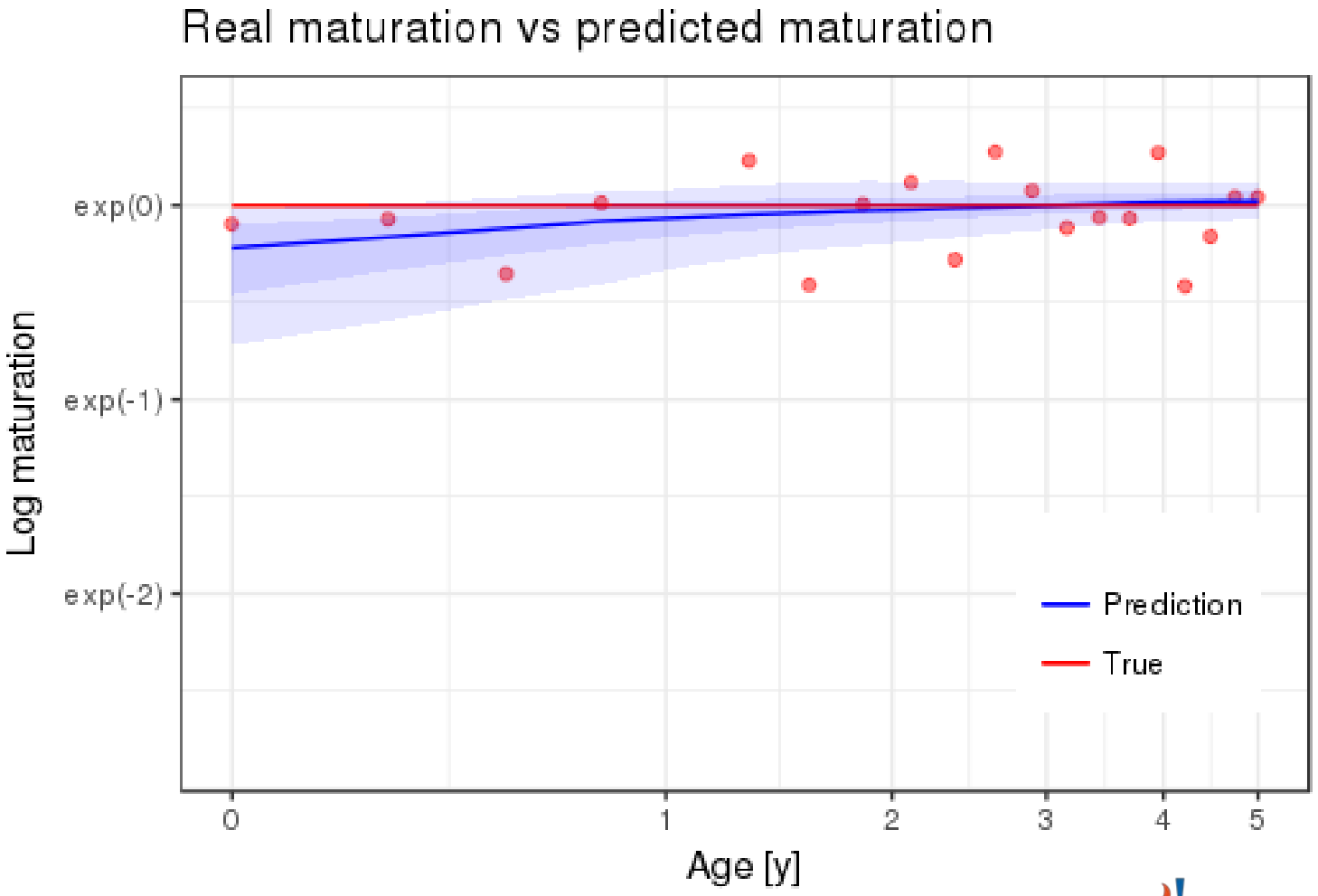
Gaussian Process posterior returns to prior outside of data



No maturation data + GP model
True clearance + fitted



No maturation data + GP model
No dosing correction inferred