



# ISSUES OF UNCERTAINTY AND VARIABILITY FOR PBPK MODEL APPLICATIONS

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## Summary

- Applications of PBPK models
- Uncertainty
  - Past, current, and best practices for parametric uncertainty
  - ~ for model uncertainty
  - Needs
- Variability
  - Past, current, and best practices for parametric uncertainty
  - Needs
- Quality assurance
  - Past, current, and best practices for parametric uncertainty
  - Needs
- Presentation and communication of results
- Conclusions

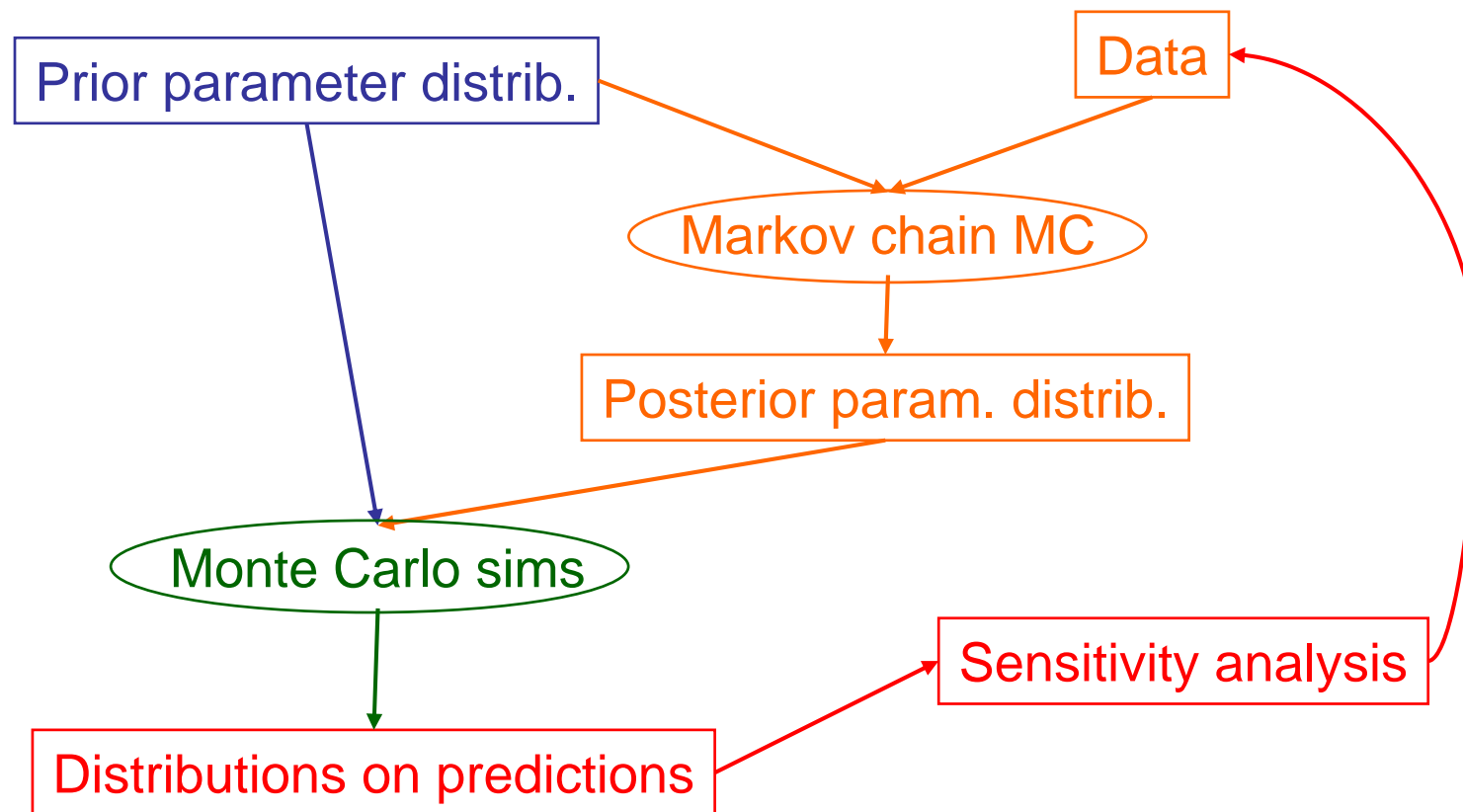


## (Known) Applications of PBPK models

- *Estimation of internal doses*
- *Extrapolations*
  - *Exposure routes and schedules*
  - *Dose levels*
  - *Time*
  - *Space...*
  - *Species*
  - *Individuals*
  - *Occasions*
- *High throughput screening*
- *Parameter identification*
- *Hypothesis Testing and Theory Checking*
- *Dose reconstruction*
- *Experimental Design*

# Uncertainty issues in regulatory applications

## Past, current, and best practices for parametric uncertainty






## Uncertainty issues in regulatory applications

### Past, current, and best practices for model uncertainty

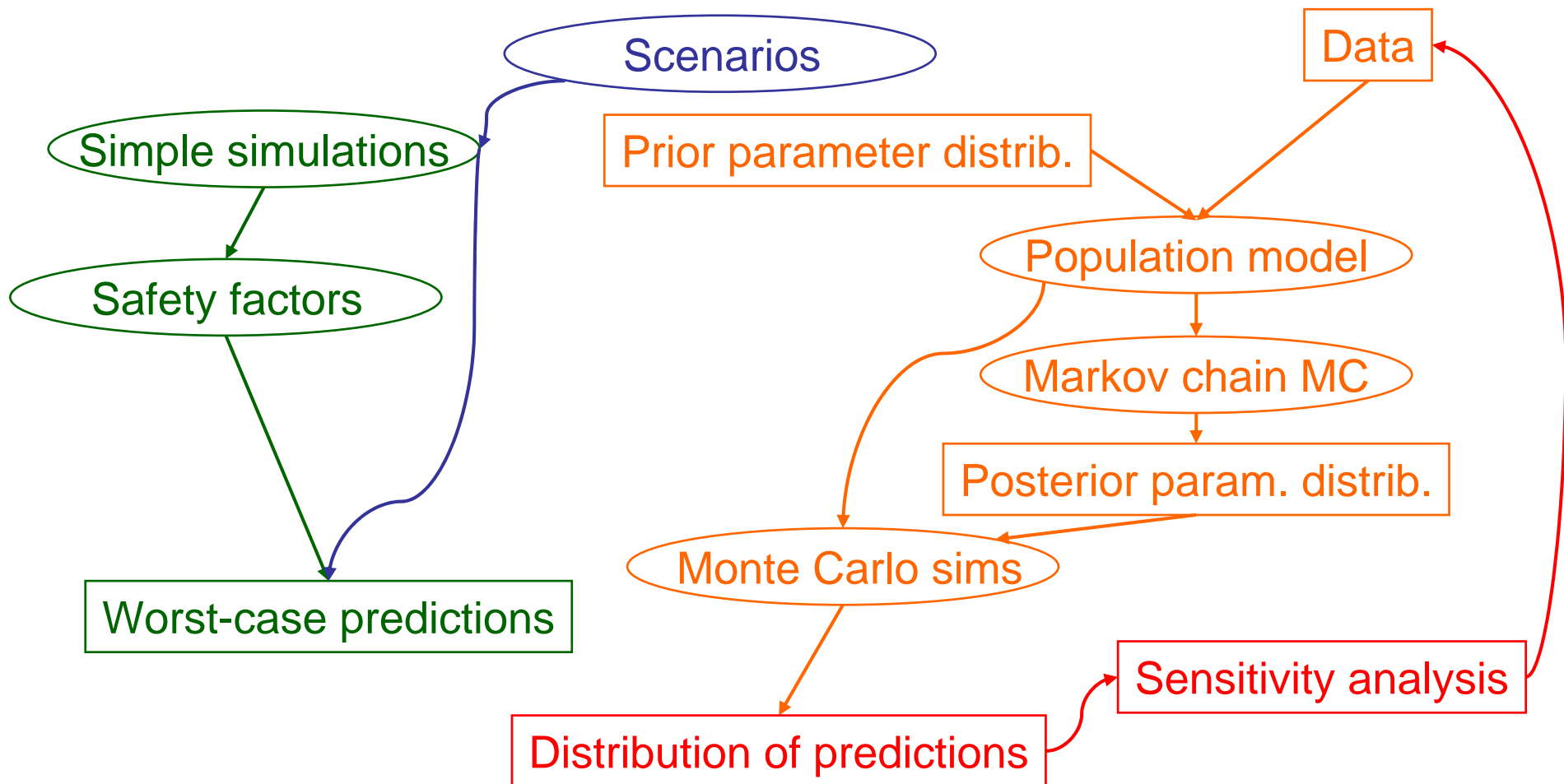
- Model choice vs. model uncertainty
  - Cross-validation, hypothesis testing
  - Model averaging
- Sensitivity to model structure
- Relaxing dubious hypotheses: nonparametric models
  - For PK structure ?
  - For statistical (e.g. population) models
- Clearly delineating a model's domain of applicability



## Uncertainty issues in regulatory applications Needs

- How to decide on the acceptable uncertainty (stick to 95%tiles?)
- Guidelines on the definition of domains of applicability
- Uncertainty about PK or metabolic network structures?
- Reference prior distributions
- Software issues

# Variability issues - Past, current, and best practices





## Variability issues

### Needs

- Inter, and intra-individual variability
- Improved deterministic modelling of variability (lifetime PBPK)
- Variability in animal populations, impact on our standard RAs
- Reference distributions
- Understanding genetic polymorphisms
- Bringing together epidemiologic and toxicologic evidence
- Impact of variability on PK model structure? (stochastic models...)
- Down to what subgroup size should RA and regulations go?



## Quality assurance - Past, current, and best practices

- Documentation of:
  - model structure
  - Parameter values or distributions
  - Procedures for model checking
- Procedures for storage of the results
- Model understanding (e.g., through sensitivity analysis)
- Discussion of alternative models



## Quality assurance Needs

- Guidelines
- Software and data repositories
- Guidance on use of historical data and past analyses
- Flexibility



## Presentation/communication of results – Past, current, best practices, and needs

- Good documentation of structure, but a trend toward model cascading...
- Partial view of model fit
- Cross validation and model checking should be developed
- Always presenting confidence intervals should be encouraged
- We need:
  - Standards, or at least good examples
  - Humility in domain of applicability claims
  - To show people how modeling works



## Conclusions

- The future of PBPK modeling is probably linked to that of system biology. Our discussion of today will probably be of value tomorrow.
- How to best regulate in front of model uncertainty? Use the "best" model (who has it?) or average models? Guidance anyone?