School of Mathematics
FACULTY OF MATHEMATICS AND PHYSICAL SCIENCES

UNIVERSITY OF LEEDS

Dealing with uncertainty and increasing confidence when applying mathematical models in AOP-led risk assessments

John Paul Gosling

Funded by

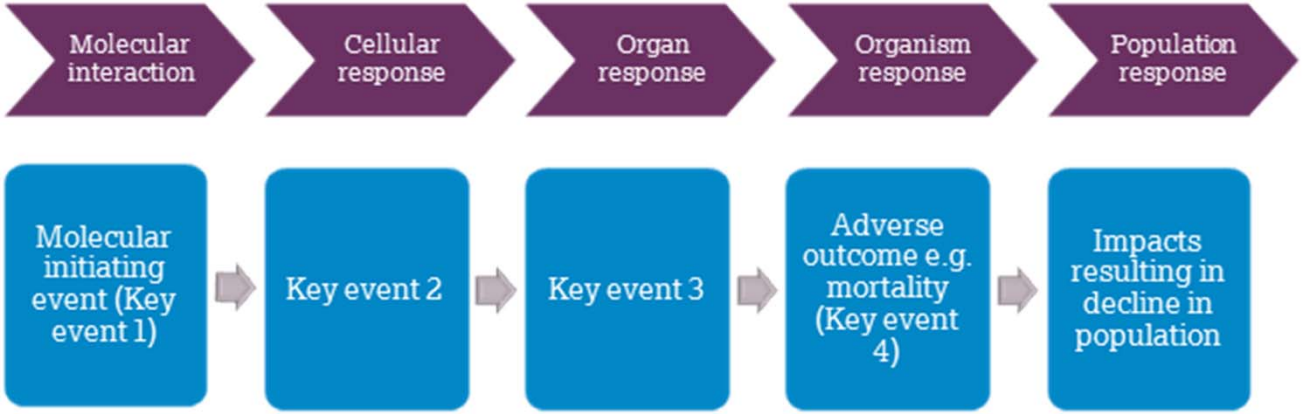
NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

EPSRC Engineering and Physical Sciences Research Council

AOP-led risk assessment

UNIVERSITY OF LEEDS

AOPs present us with a framework for making judgements about the potential adverse effect for a population.



Taken from www.nc3rs.org

These are underpinned by scientific understanding.

Computer models

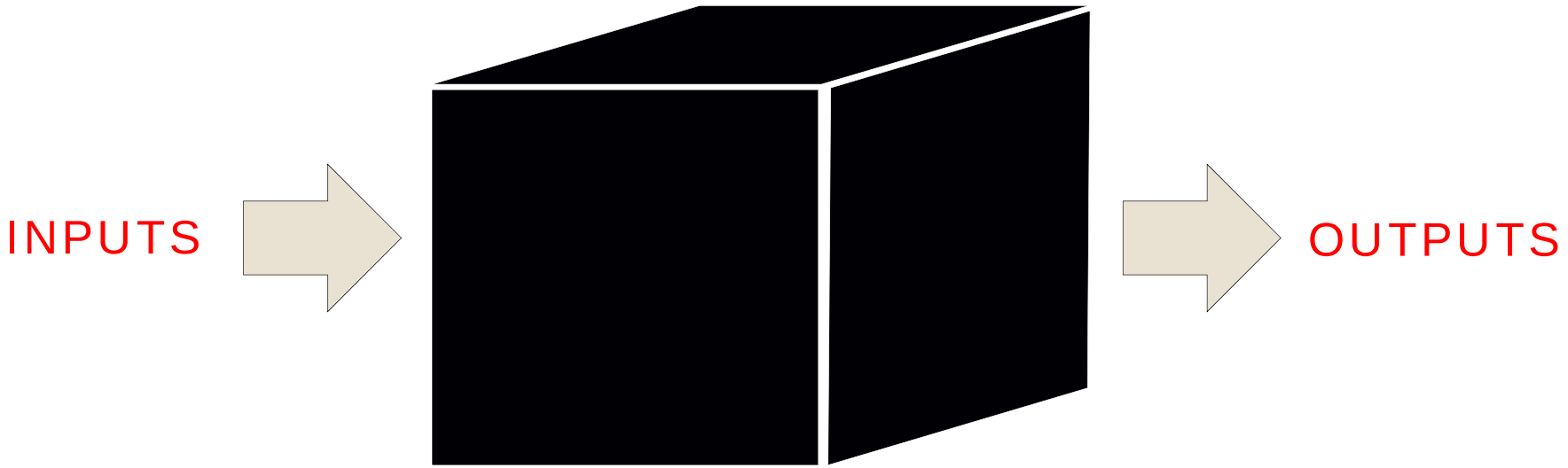
UNIVERSITY OF LEEDS

Many mathematical models are being developed across a broad spectrum of areas that could be of great use in toxicological safety assessments.

The costs of running computer-based mathematical models are far less than the costs of laboratory experimentation.

Computer models

UNIVERSITY OF LEEDS



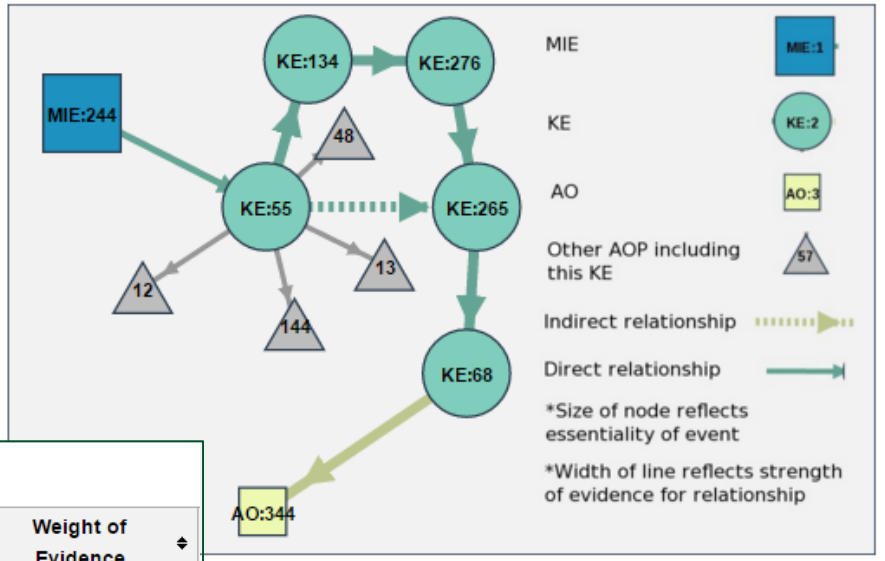
AOPs as a framework

UNIVERSITY OF LEEDS

Adverse Outcome Pathway WIKI

Protein Alkylation leading to Liver Fibrosis

Network View



Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence
Protein, Alkylation	Directly Leads to	Cell death, N/A	Moderate
Cell death, N/A	Directly Leads to	Hepatic macrophages (Kupffer Cells), Activation	Strong
Cell death, N/A	Indirectly Leads to	Stellate cells, Activation	Strong
Hepatic macrophages (Kupffer Cells), Activation	Directly Leads to	TGFbeta1 expression, Up Regulation	Strong
TGFbeta1 expression, Up Regulation	Directly Leads to	Stellate cells, Activation	Strong
Stellate cells, Activation	Directly Leads to	Collagen, Accumulation	Strong
Collagen, Accumulation	Directly Leads to	Liver fibrosis, N/A	Strong

References

1. ↑ Lee, U.E. and S.L. Friedman (2011), Mechanisms of Hepatic Fi
2. ↑ Friedman, S.L (2010), Evolving challenges in hepatic fibrosis, N
3. ↑ 3.0 3.1 Friedman, S.L. (2008), Mechanisms of Hepatic Fibrogene
4. ↑ Friedman, S.L (2000), Molecular regulation of hepatic fibrosis,
5. ↑ Bataller, R. and D.A. Brenner (2005), Liver Fibrosis, J.Clin. Inve
6. ↑ Lotersztain, S. et al. (2005), Hepatic fibrosis: molecular mechar
7. ↑ Poli, G. (2000), Pathogenesis of liver fibrosis: role of oxidative s
8. ↑ Li, Jing-Ting et al. (2008), Molecular mechanism of hepatic stel
419–428.
9. ↑ 9.0 9.1 George, J. et al. (1999), In vivo inhibition of rat stellate ce
therapy for hepatic fibrosis. Proc Natl Acad Sci, vol. 96, no. 22, p

Taken from AOP Wiki page: https://aopwiki.org/wiki/index.php/Aop:38

Uncertainty

UNIVERSITY OF LEEDS

How accurate are model predictions?

Are the predictions robust enough for high-stakes decision-making?

Uncertainty

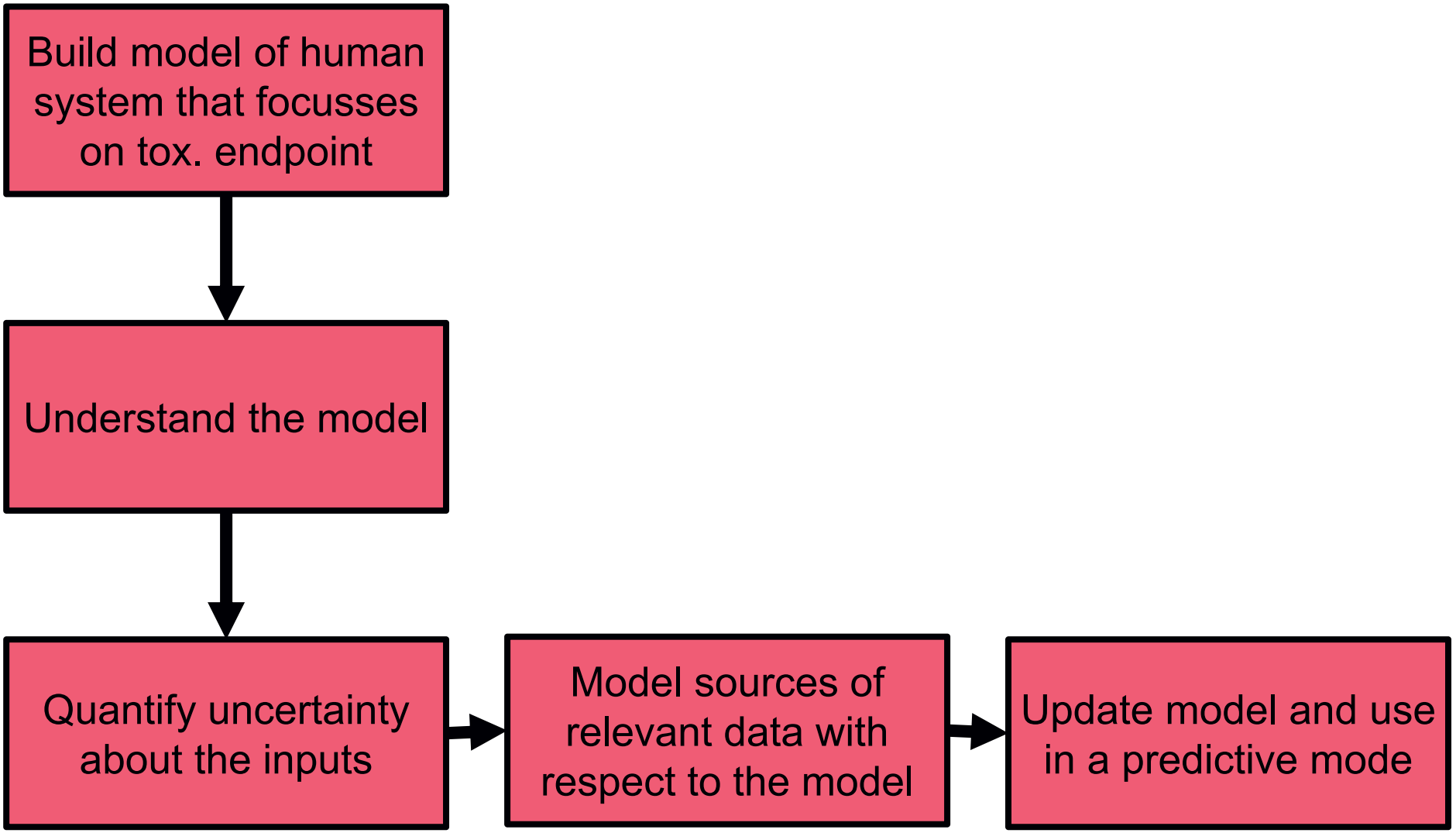
UNIVERSITY OF LEEDS

How might the simulator output differ from the real-world value?

- Error in the inputs,
- Error in model structure or solution,
- Wrong, inaccurate or incomplete science,
- Bugs and solution errors.

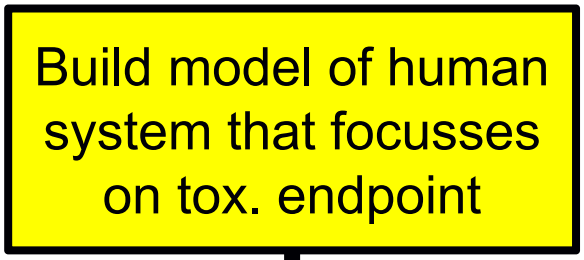
A potential work flow

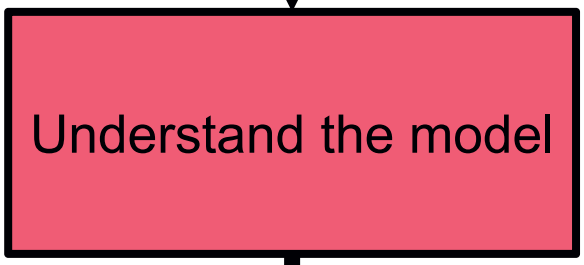
UNIVERSITY OF LEEDS

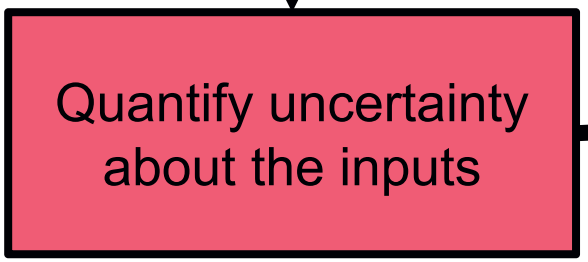


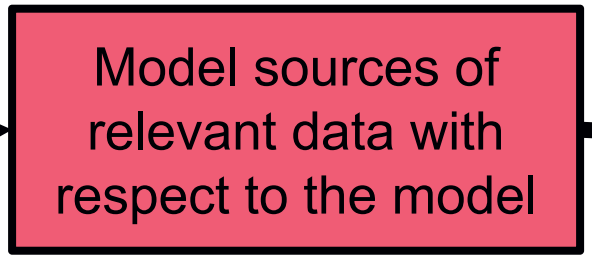
A potential work flow

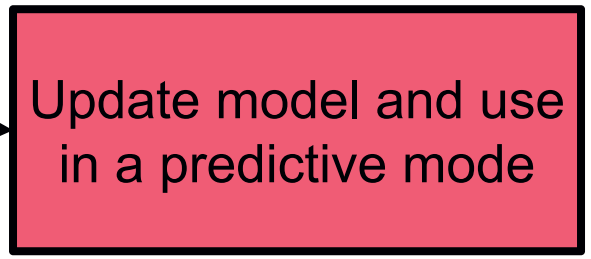
UNIVERSITY OF LEEDS







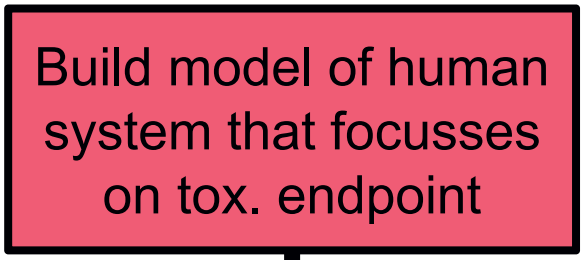


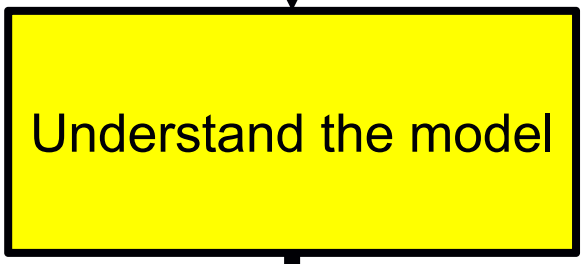


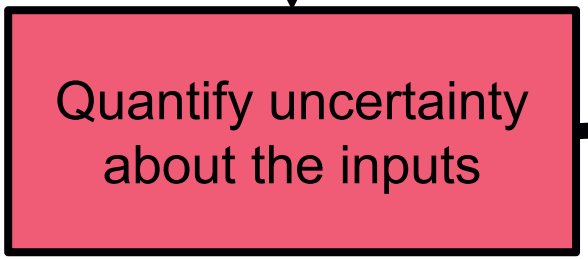
- Many, many methods for building computational models.
- If the data are few or contentious, use scientific understanding.
- Justify the assumptions and be aware of the limitations.

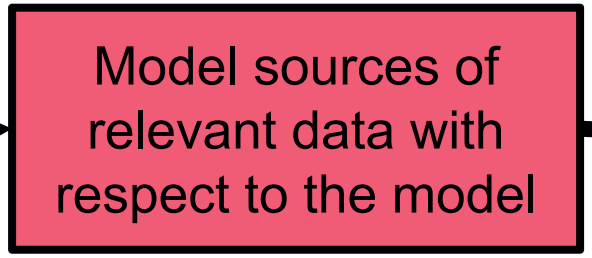
A potential work flow

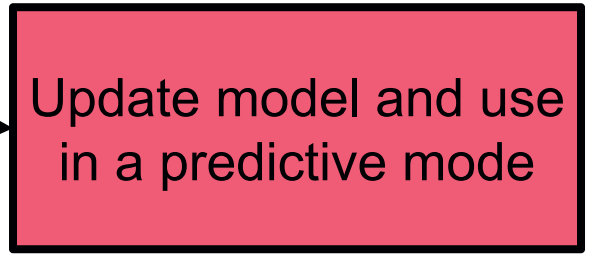
UNIVERSITY OF LEEDS











- Verify the model is behaving as expected.
- Work out which inputs are important for each output of interest:
  - *Input screening,*
  - *Sensitivity analysis,*
  - *Dimension reduction.*

A potential work flow

UNIVERSITY OF LEEDS

Build model of human system that focusses on tox. endpoint

Understand the model

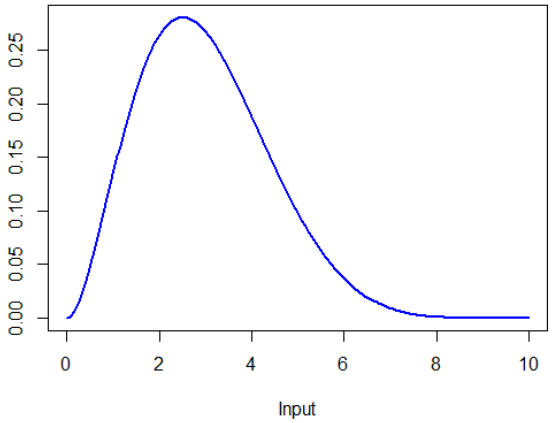
Quantify uncertainty about the inputs

Model sources of relevant data with respect to the model

Update model and use in a predictive mode

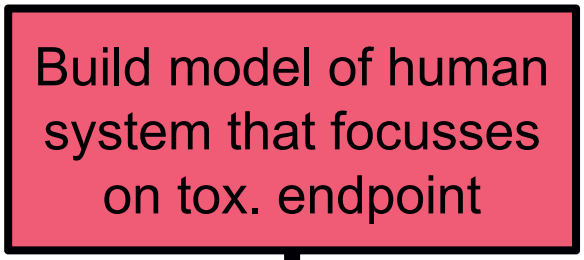
What input values are biologically plausible?

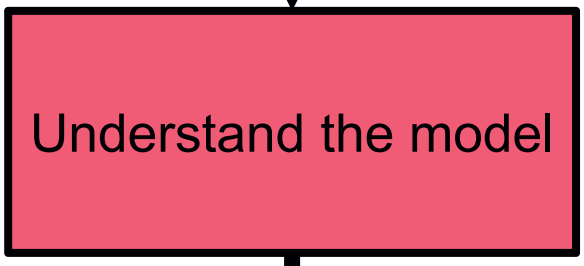
- *Literature.*
- *Expert knowledge elicitation.*

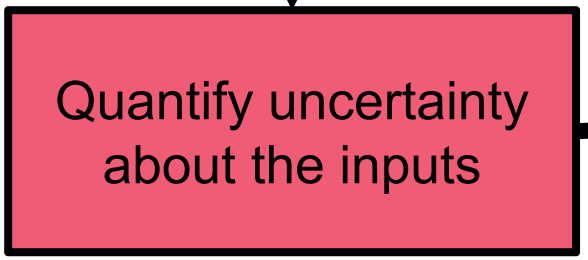


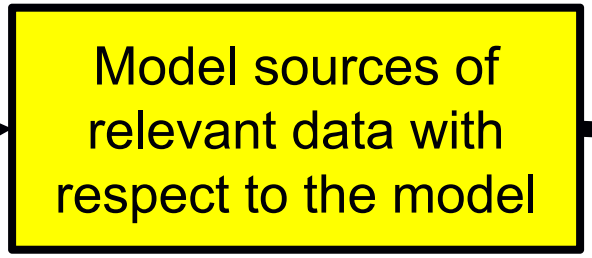
A potential work flow

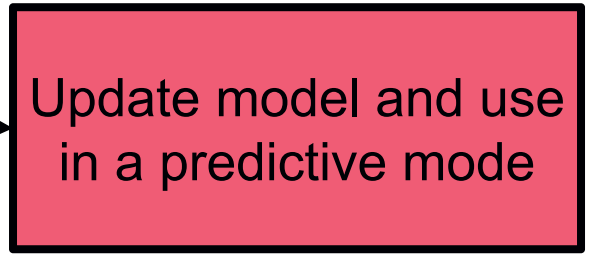
UNIVERSITY OF LEEDS











What is the likelihood of different parameter conditions given the model's limitations and the available data?

Uncertainty	Magnitude & Direction
The model for the cellular response is based upon understanding of the mouse immune system.	− − −/+
…	…

A potential work flow

UNIVERSITY OF LEEDS

Build model of human system that focusses on tox. endpoint

Understand the model

Quantify uncertainty about the inputs

Model sources of relevant data with respect to the model

Update model and use in a predictive mode

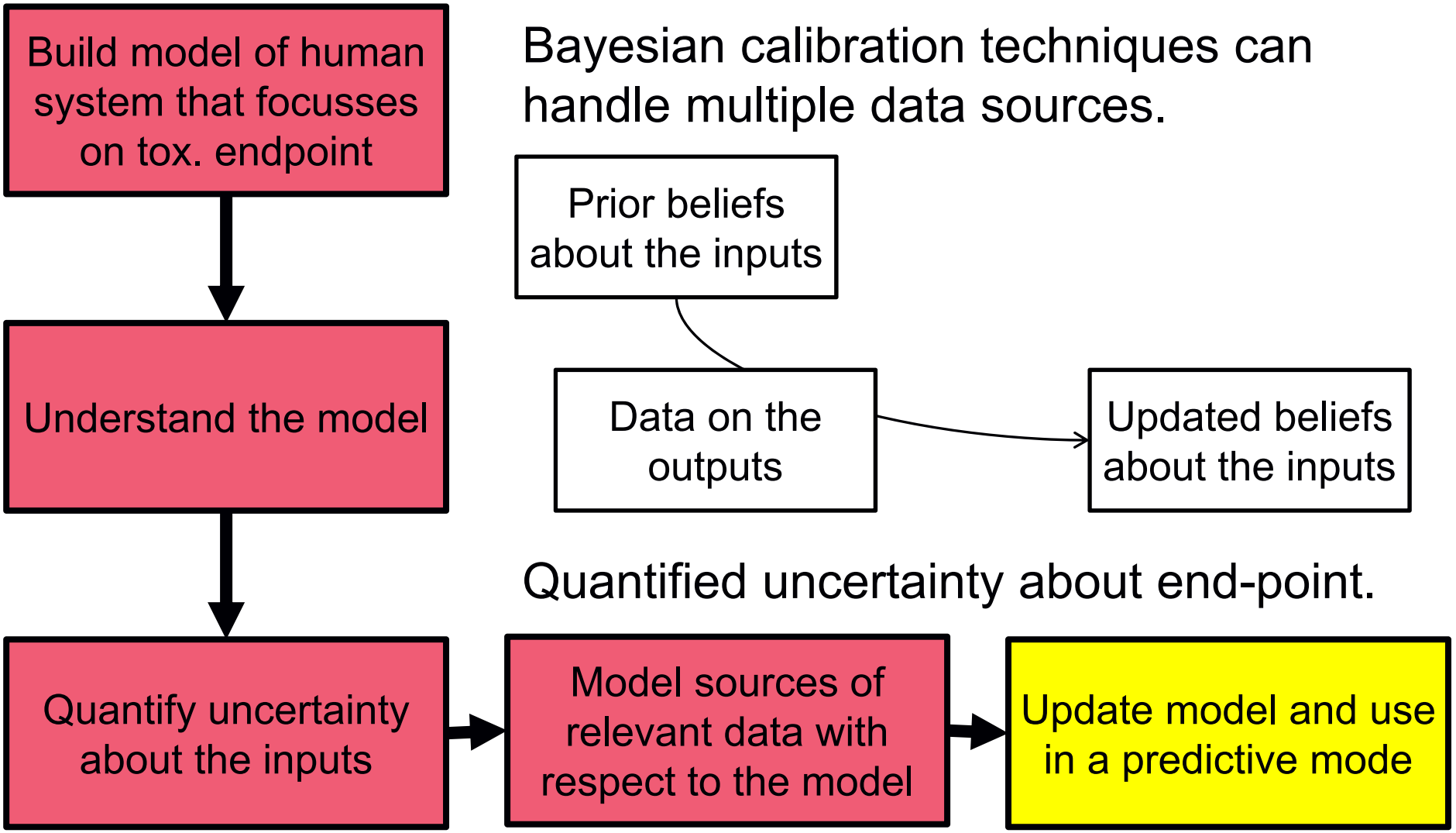
What is the likelihood of different parameter conditions given the model's limitations and the available data?

Relationships Among Key Events and the Adverse Outcome

Event	Description	Triggers	Weight of Evidence
Protein, Alkylation	Directly Leads to	Cell death, N/A	Moderate
Cell death, N/A	Directly Leads to	Hepatic macrophages (Kupffer Cells), Activation	Strong
Cell death, N/A	Indirectly Leads to	Stellate cells, Activation	Strong
Hepatic macrophages (Kupffer Cells), Activation	Directly Leads to	TGFbeta1 expression, Up Regulation	Strong
TGFbeta1 expression, Up Regulation	Directly Leads to	Stellate cells, Activation	Strong
Stellate cells, Activation	Directly Leads to	Collagen, Accumulation	Strong
Collagen, Accumulation	Directly Leads to	Liver fibrosis, N/A	Strong

A potential work flow

UNIVERSITY OF LEEDS



Difficulties

UNIVERSITY OF LEEDS

In principle, all this is straightforward.

Difficulties

UNIVERSITY OF LEEDS

In principle, all this is straightforward.

In practice, there are many technical difficulties:

- formulating uncertainty on inputs,
  - elicitation of expert judgements,
- propagating input uncertainty,
- modelling structural error,
- anything involving observational data…

Building confidence

UNIVERSITY OF LEEDS

It is okay to be uncertain.

By accounting for uncertainty, we can be more confident in our risk management decisions.

AOP's could have a key role

- justification of modelling choices,
- peer-reviewed science,
- human focus.

Engage with biologists, clinicians, experimentalists, toxicologists, etc. throughout.