Uncertainty quantification in next generation risk assessment

John Paul Gosling

Overview

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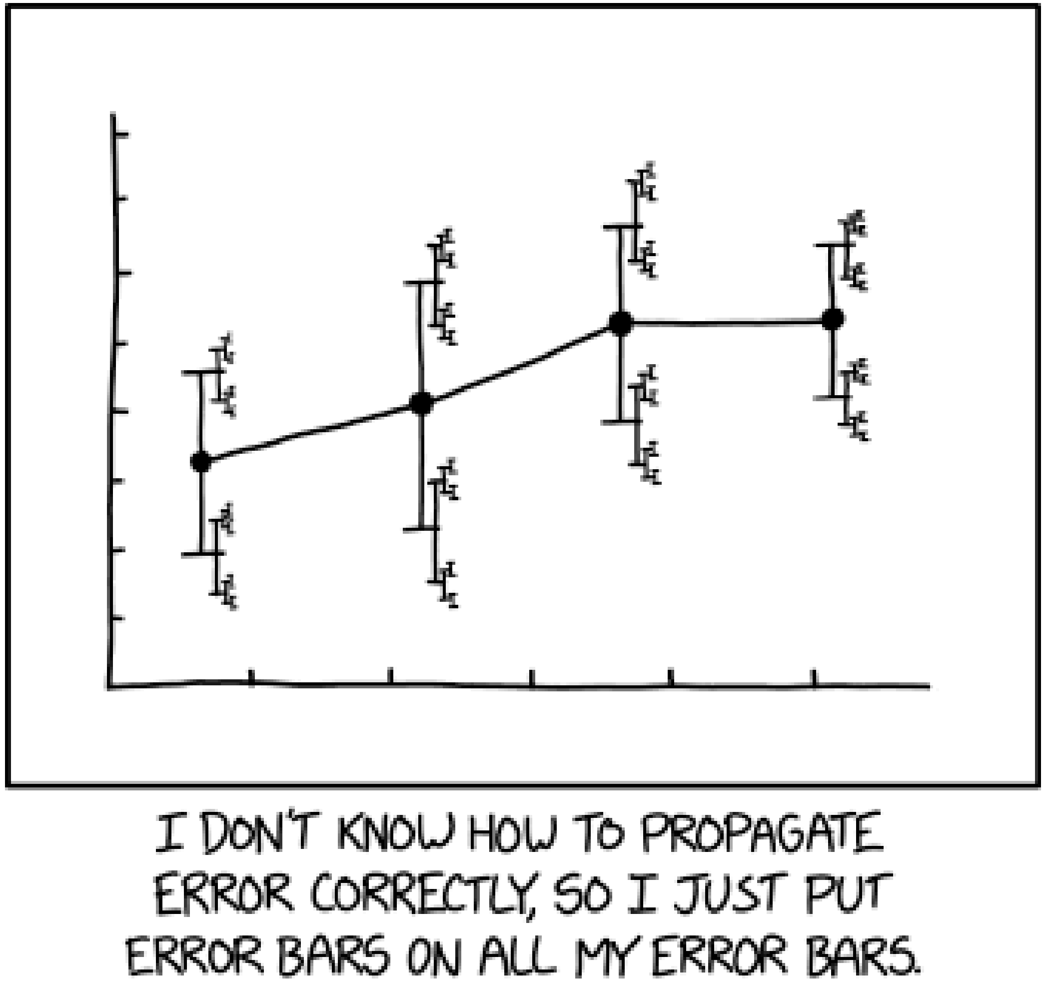
1. Subjectivity and probability
2. Next generation risk assessment

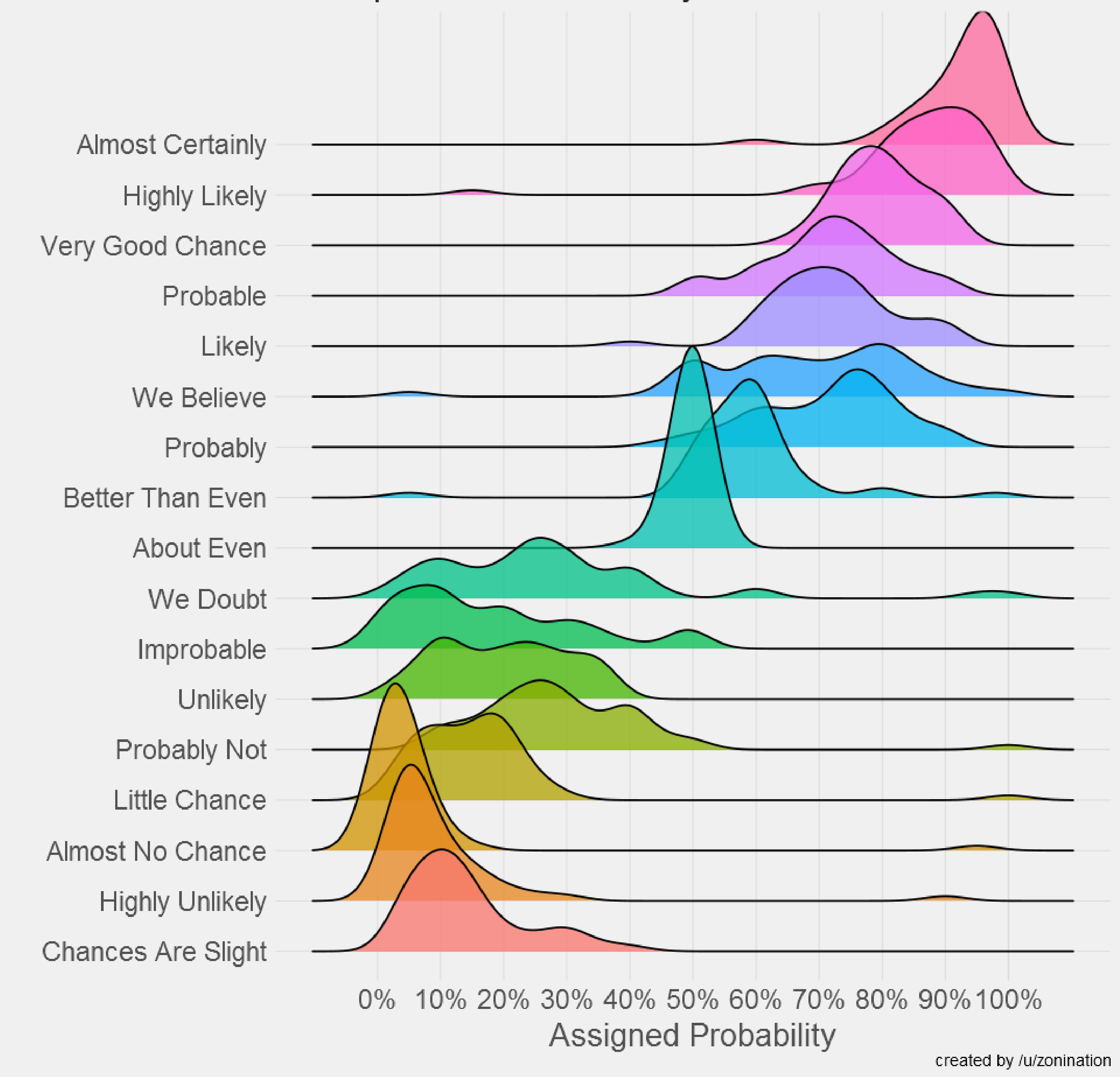
Quantitative methods will be ~~discussed~~ mentioned throughout.



Expressing uncertainty

An important component of uncertainty is due to our incomplete knowledge.

Expressing uncertainty through phrases adds an additional layer of subjective interpretation.



Probability as degree of belief

Probability is an expression of our uncertainty about events on a 0-1 scale.

We are absolutely certain it will not happen.

We are absolutely certain it will happen.

Probability as degree of belief

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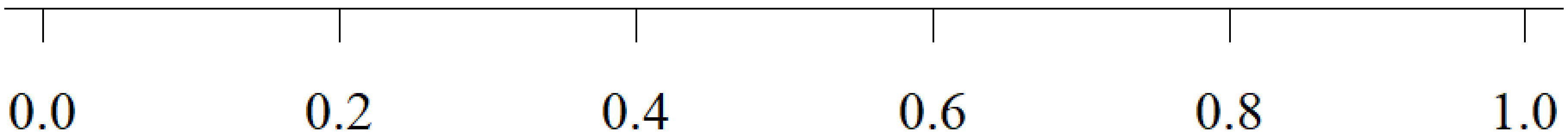

This form of probability can be operationalised and captured by considering an individual's gambling preferences.

Direct measurement of probability is possible through comparison with 'known' probabilities.

Probability as degree of belief

Consider an unknown quantity, we have many probabilities to contend with:

Probability as degree of belief

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Consider an unknown quantity, we have many probabilities to contend with:

$$\Pr(\text{Quantity} < 0),$$

Probability as degree of belief

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Consider an unknown quantity, we have many probabilities to contend with:

$$\Pr(\text{Quantity} < 0),$$

$$\Pr(\text{Quantity} > 10),$$

Probability as degree of belief

Consider an unknown quantity, we have many probabilities to contend with:

Pr(Quantity < 0),

Pr(Quantity > 10),

Pr(Quantity < X) for any **X**…

Probability as degree of belief

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We can represent infinitely many probabilities in a mathematically convenient form.

Probability as degree of belief

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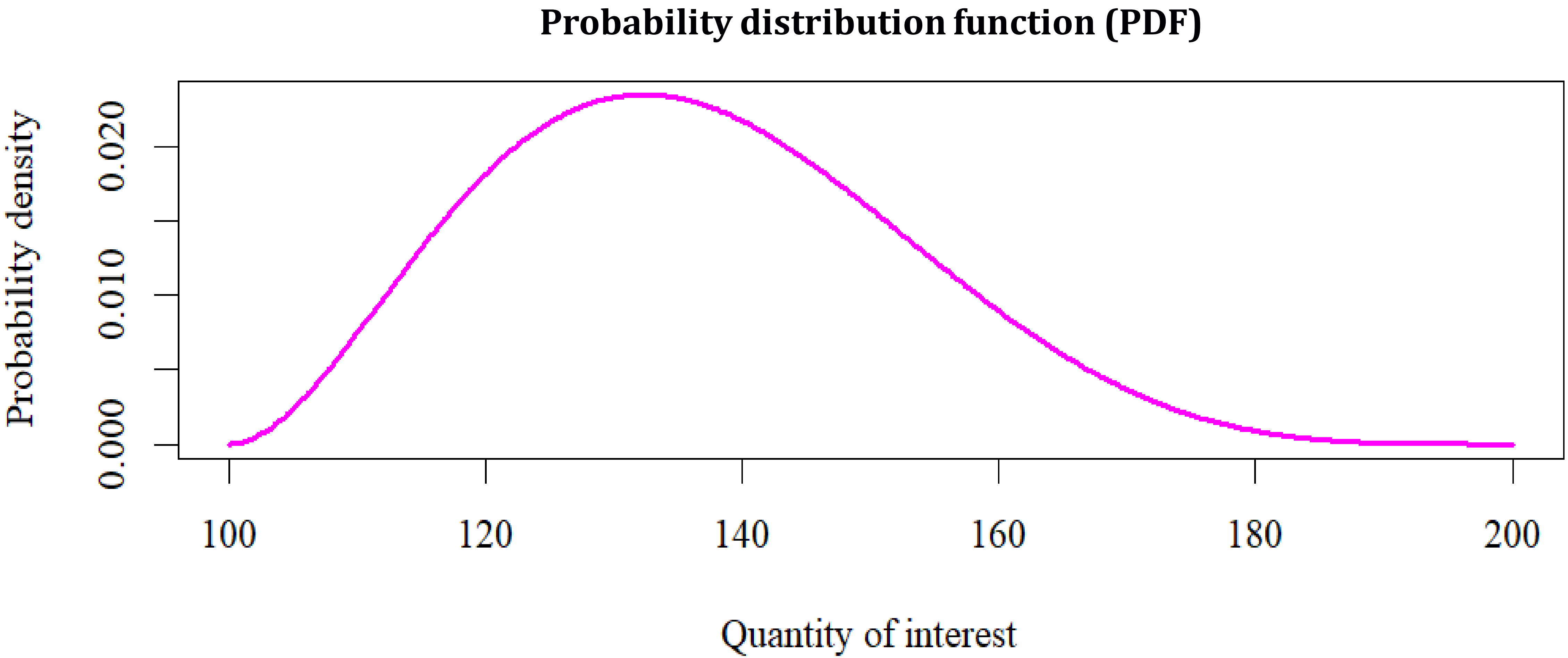

Probability as degree of belief

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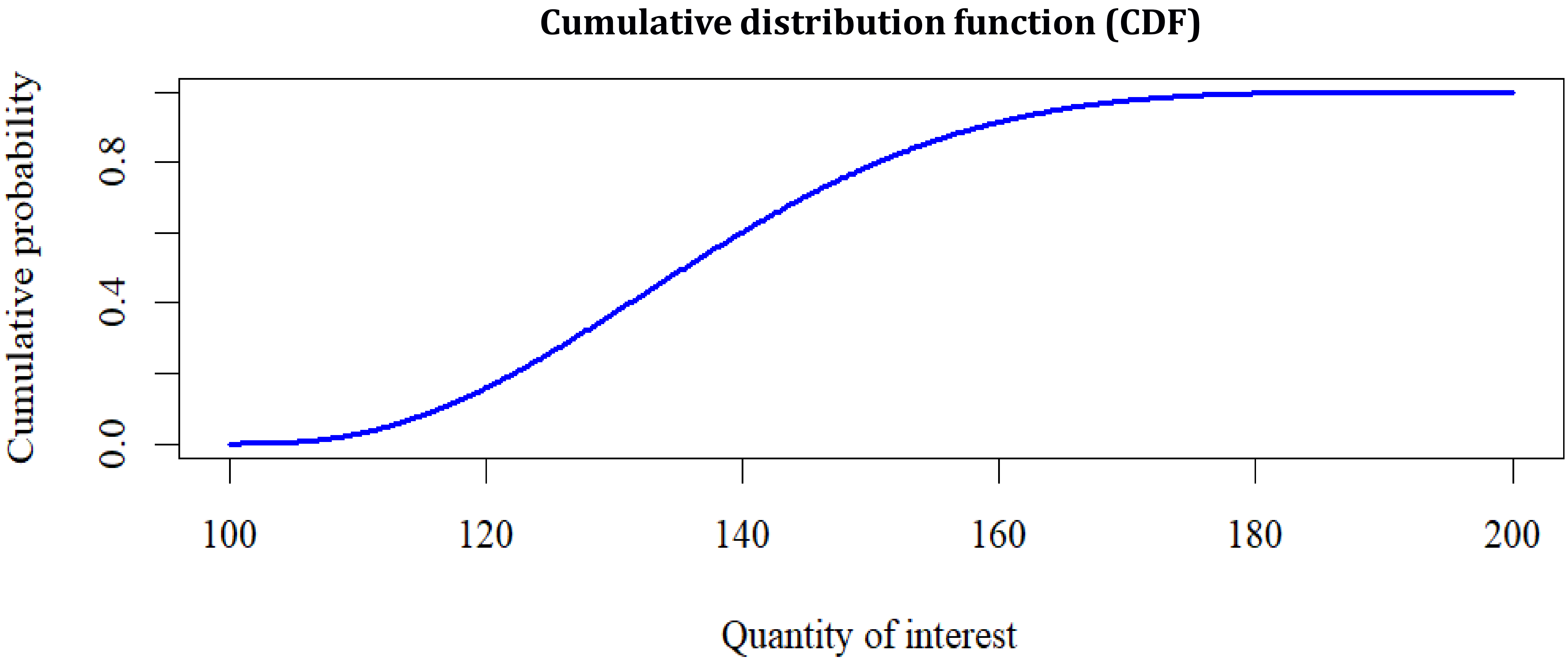

Expert knowledge elicitation

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Facilitated group information sharing

Individual judgements based on bias-reducing questioning

Facilitated discussions to reach consensus

A set of documents covering the process

Gosling (2018). SHELF: the Sheffield elicitation framework. In *Elicitation.*

Expert knowledge elicitation

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Group reviews evidence

Plausible range

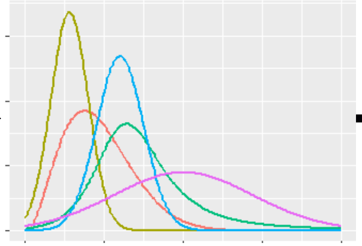
LL | | UL |

Experts estimate individual medians and quartiles

Median |

Q1 | | Q3 |

Elicitor fits a distribution for each individual



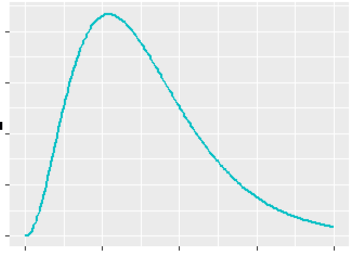
Group discuss results and agree collective judgements

Pr(X>3) |

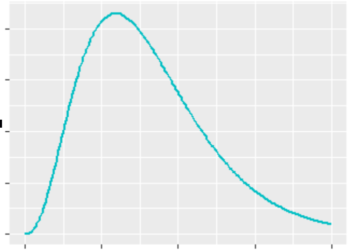
Pr(X<0) |

Pr(X<1) |

Elicitor fits a distribution for the group



Group discuss and adjust distribution

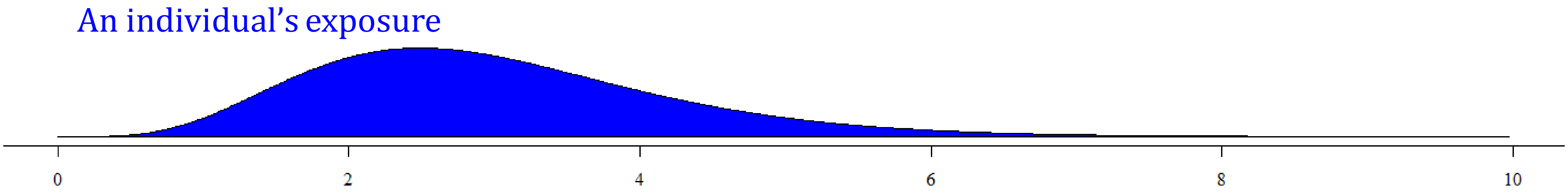


Group confirm final distribution

Quantitative decision making

We want to know what proportion of the population may be affected in a certain chemical exposure scenario.

We must consider both variability in exposures and hazards and uncertainty in their characterisation.



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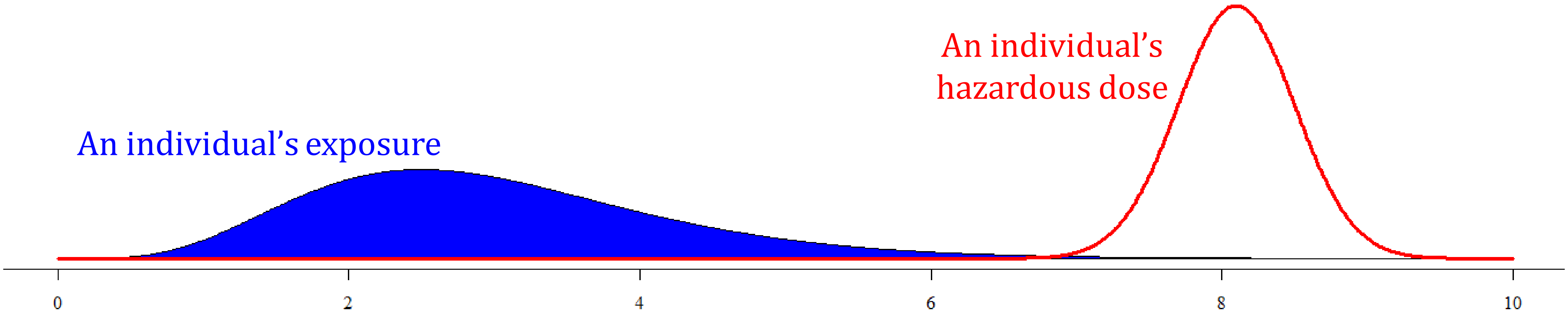

What is the probability that exposure will exceed the hazardous dose?

Next Generation Risk Assessment (NGRA)

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Traditionally, risk assessors have put their faith in animal experiments and safety assessment factors:

Dangerous exposure for

divided by **10^x** = **Safe** exposure for humans

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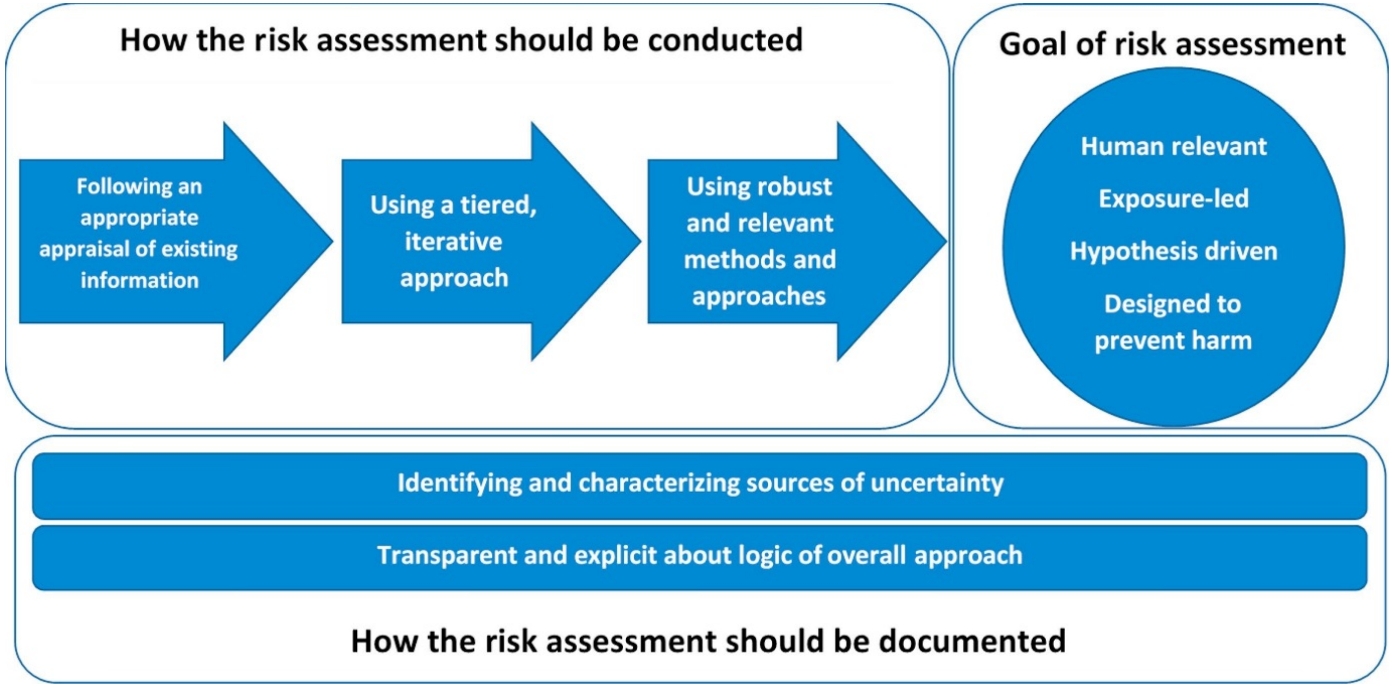
NGRA aims to incorporate modern technologies whilst accommodating uncertainty:



Dent et al. (2018). Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients, *Computational Toxicology*, **7**.

Next Generation Risk Assessment (NGRA)

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Difficulties emerge when *in vitro* or *in silico* experiments contradict each other or when unforeseen effects appear *in vivo*.

Uncertainties stem from:

- Experimental variability (lab, batch, operator ...)
- Measurement errors,
- *In-vitro*-to-*in-vivo* extrapolations:
  - Is the environment the same?
    - Physical conditions,
    - Regulatory functions present,
    - Metabolites, ...
  - Are the time scales consistent?
  - Are the test cells (or proteins or ...) human relevant?

Methods for Capturing Uncertainty

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There are many methods in common use:

Traditional statistical methods (for variabilities),

Bayesian statistical methods (modelling uncertainty & combine data),

Expert knowledge elicitation (formal capturing of knowledge),

Network modelling (capturing and visualising dependencies),

Probabilistic modelling and Monte Carlo (uncertainty propagation),

Uncertainty tables (a qualitative appreciation).

Weight-of-evidence

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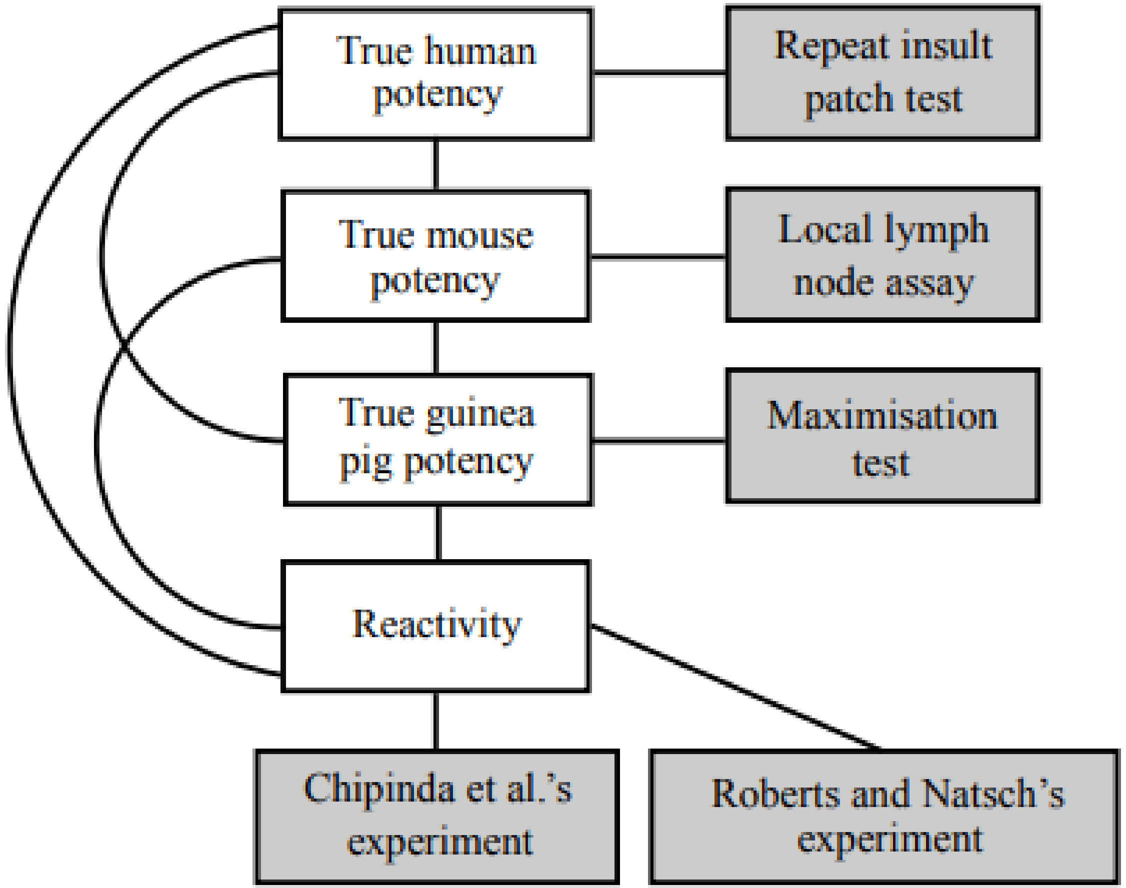
How do the sources of information link to the quantity of interest?

Here is an example of using networks to capture dependencies.

All experimental data can be used to influence our beliefs about the human end-point.



Gosling et al. (2013). A Bayes linear approach to weight-of-evidence risk assessment for skin allergy, *Bayesian Analysis*, **8**.

Weight-of-evidence

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Bayesian statistics gives us a mechanism for formally weighing data and updating our uncertainty.

$$\underbrace{\pi(\text{Human Toxicity})}$$

We have prior beliefs about human toxicity for our new chemical.

Weight-of-evidence

Bayesian statistics gives us a mechanism for formally weighing data and updating our uncertainty.

$$\underbrace{\pi(\text{Human Toxicity}|\text{Data})}_{\text{We want to know how these beliefs change in the light of data.}}$$

Weight-of-evidence

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Bayesian statistics gives us a mechanism for formally weighing data and updating our uncertainty.

$$\pi(\text{Human Toxicity}|\text{Data}) \propto \pi(\text{Human Toxicity}) \times \pi(\text{Data}|\text{Human Toxicity})$$

These are our prior beliefs.

This is our model of the data.

Weight-of-evidence

Bayesian statistics gives us a mechanism for formally weighing data and updating our uncertainty.

$$
\begin{aligned}
\pi(\text{Human Toxicity}|\text{All data}) \propto \pi(\text{Human Toxicity}) \\
\times\, \pi(\text{Dataset 1}|\text{Human Toxicity}) \\
\times\, \pi(\text{Dataset 2}|\text{Human Toxicity}) \\
\times\, \pi(\text{Dataset 3}|\text{Human Toxicity})
\end{aligned}
$$

These are models based
upon different data sources.

Weight-of-evidence

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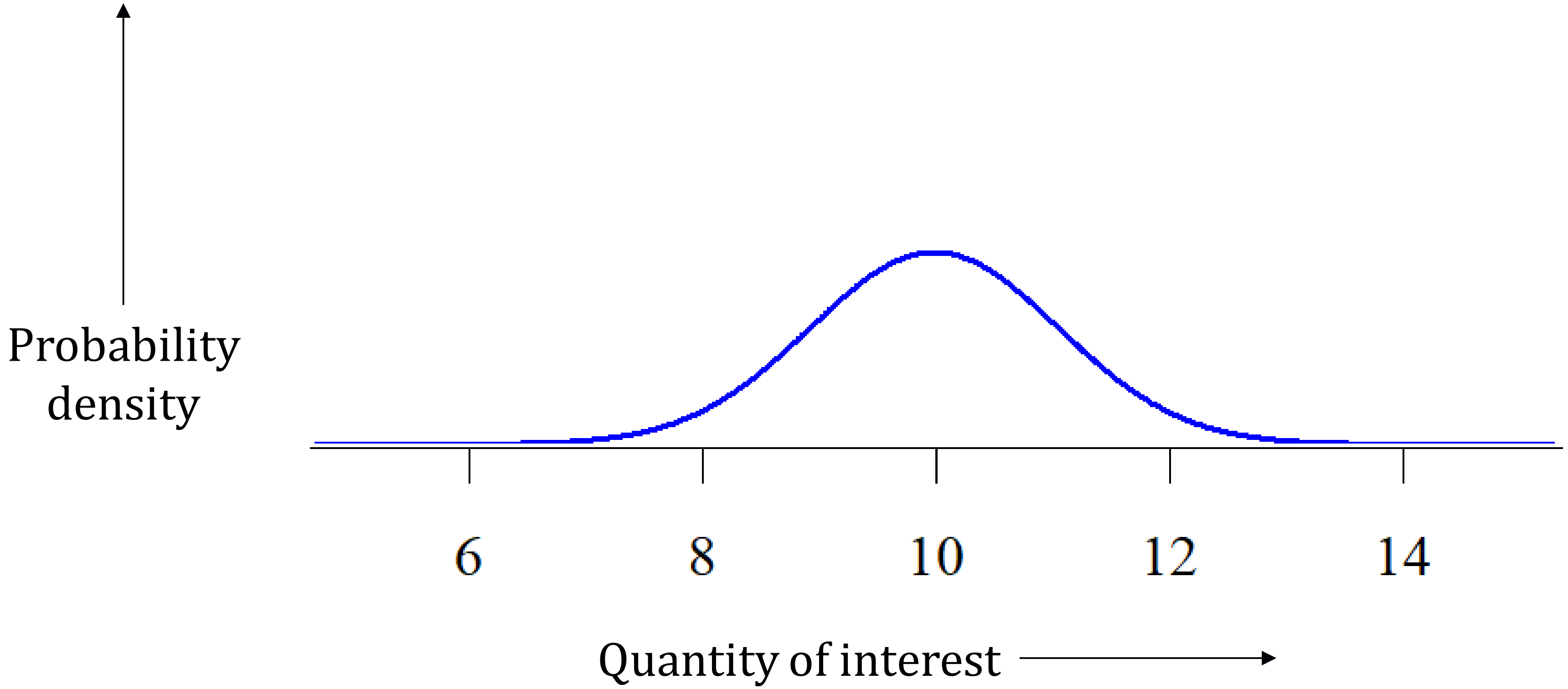

Weight-of-evidence

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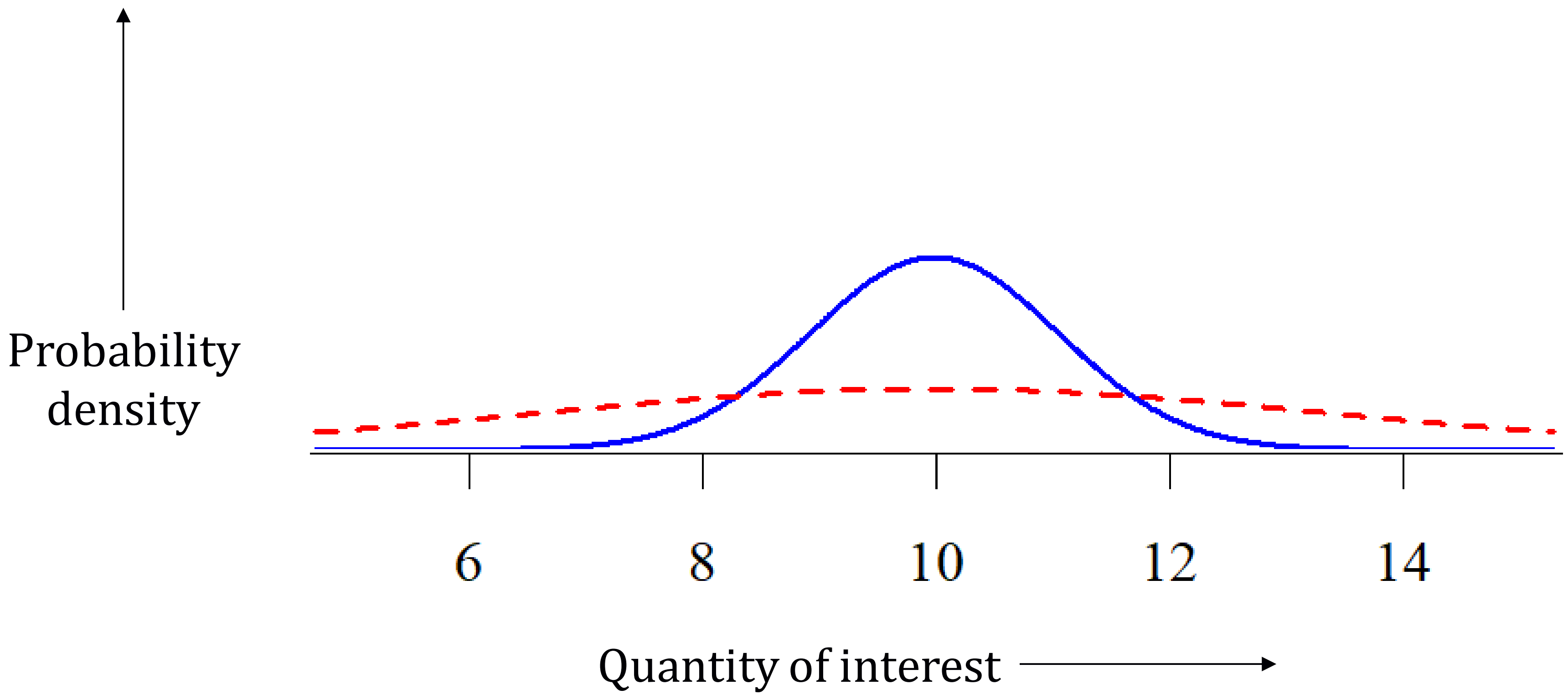

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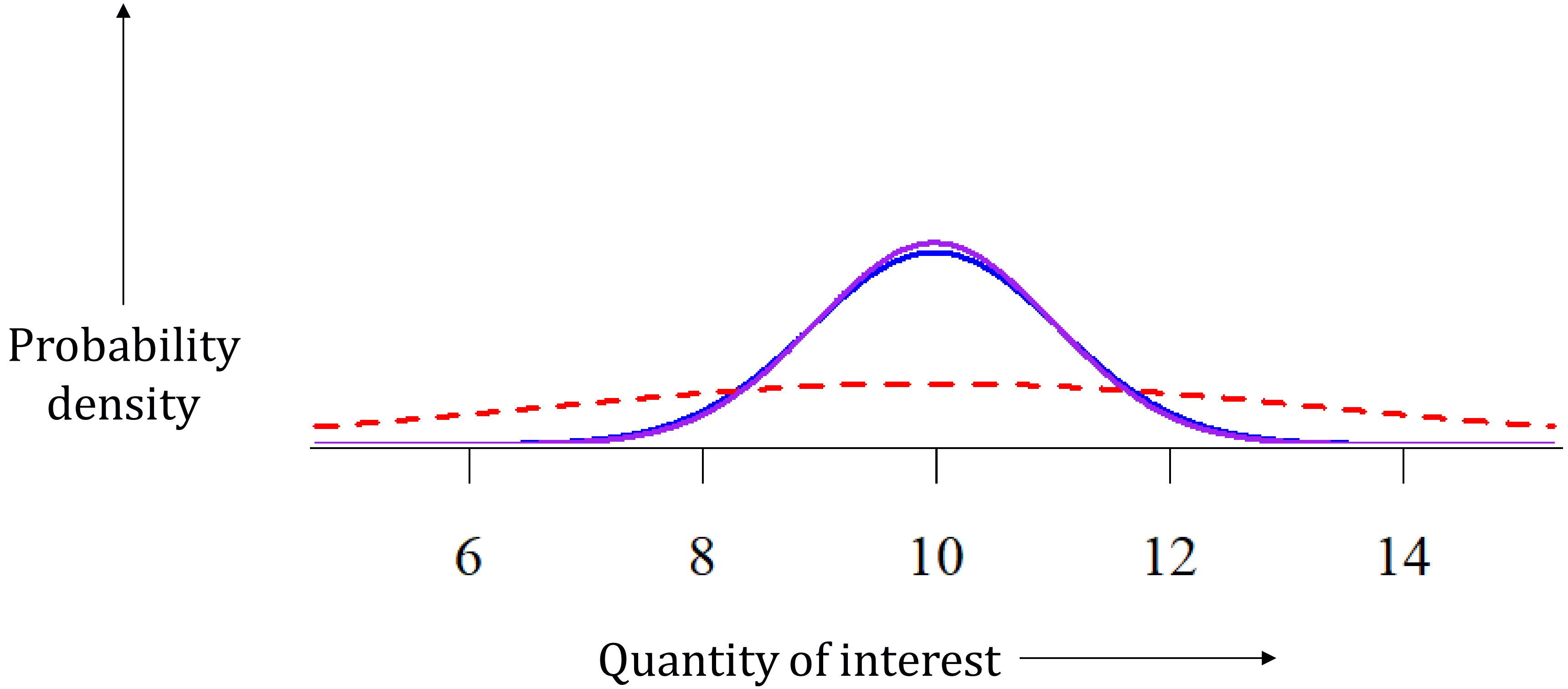

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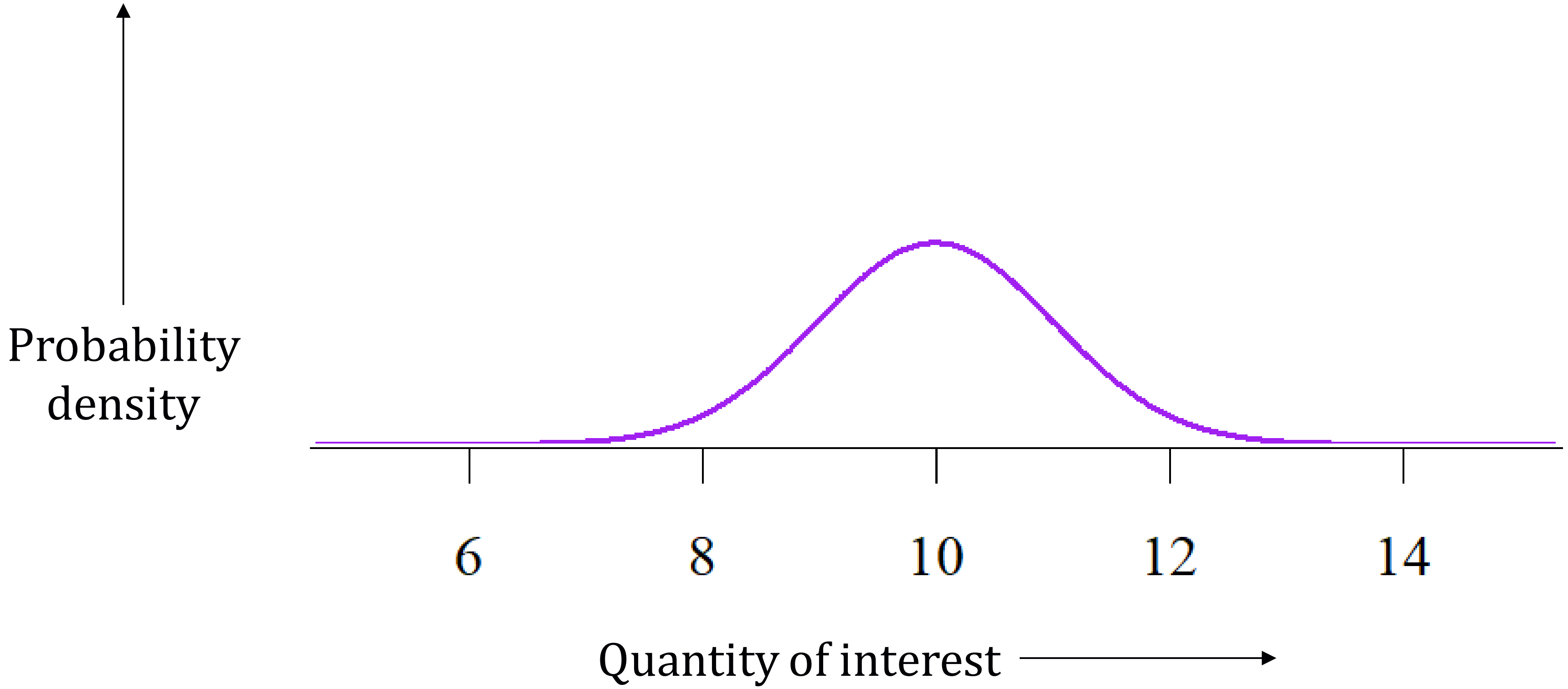

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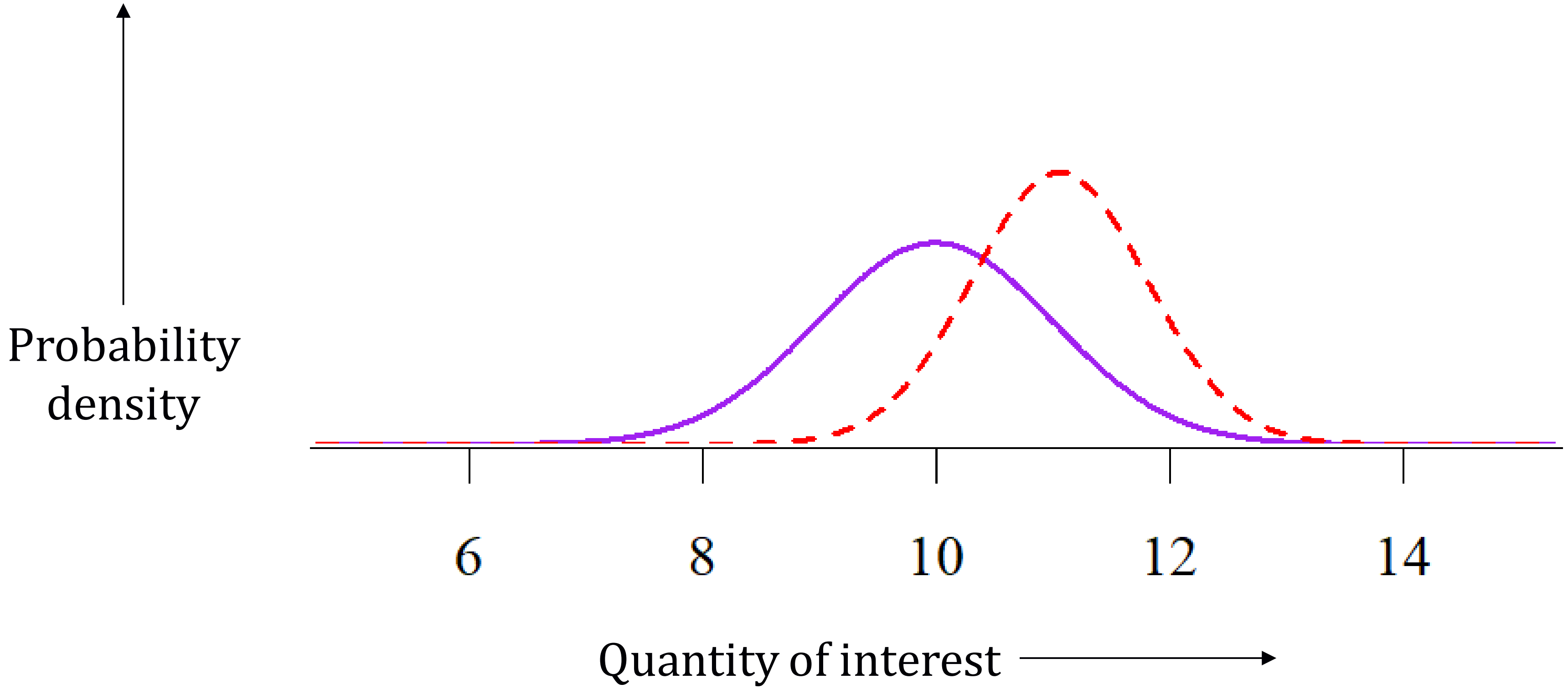

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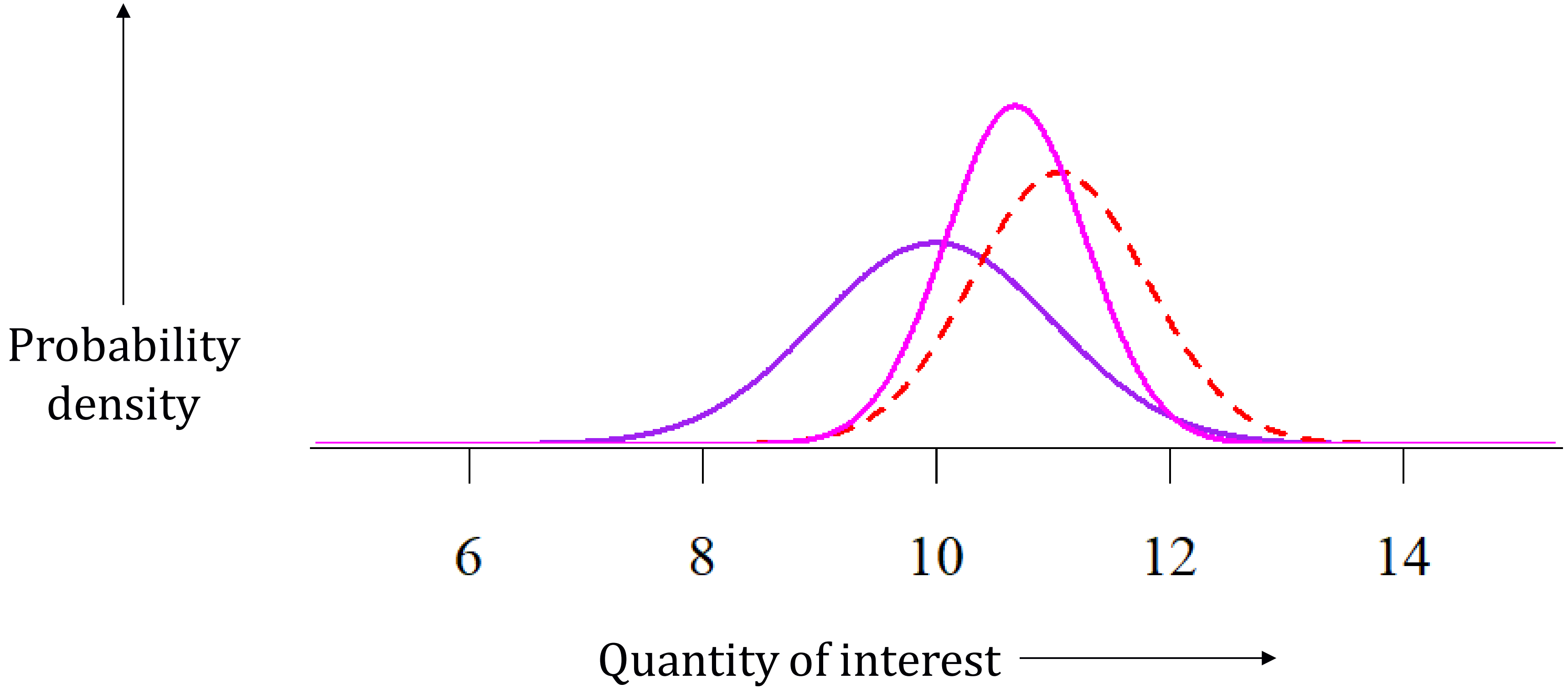

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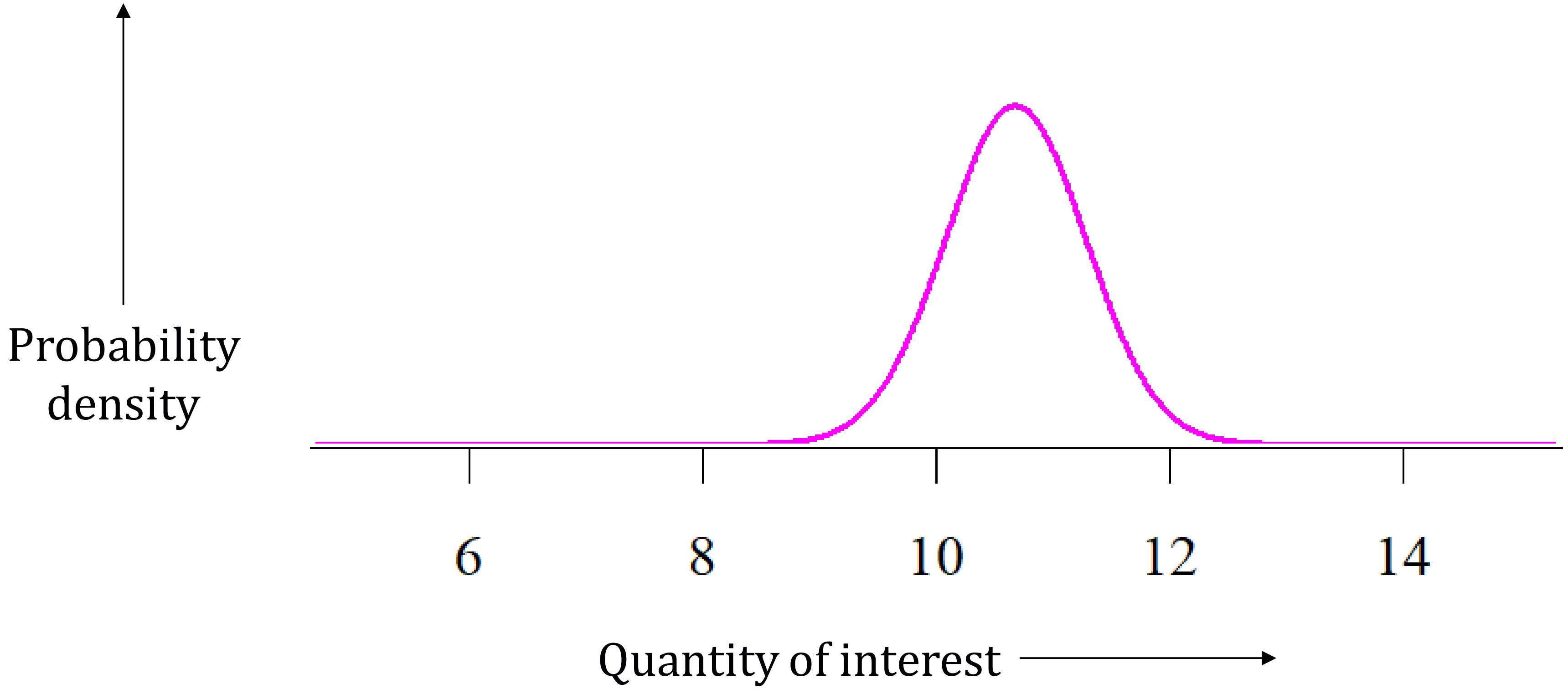

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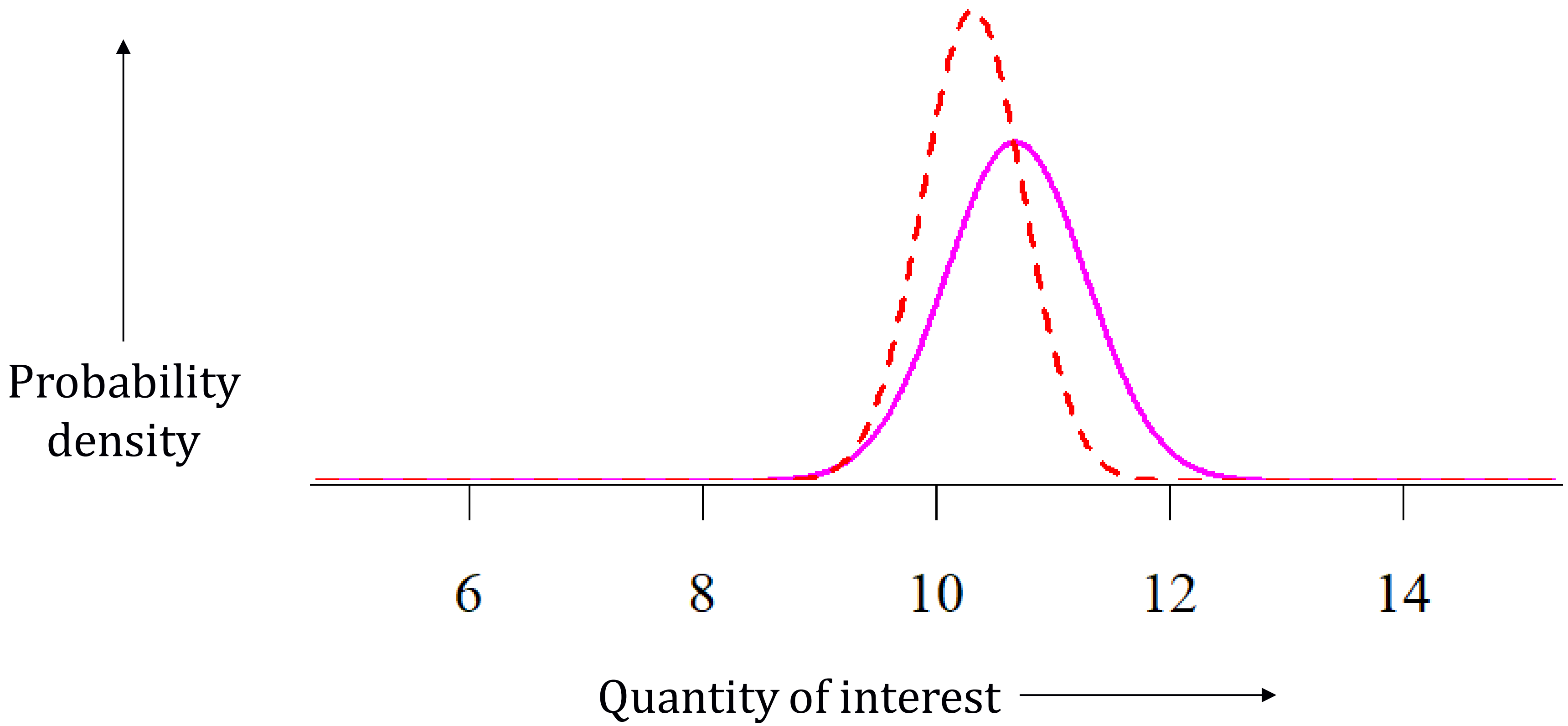

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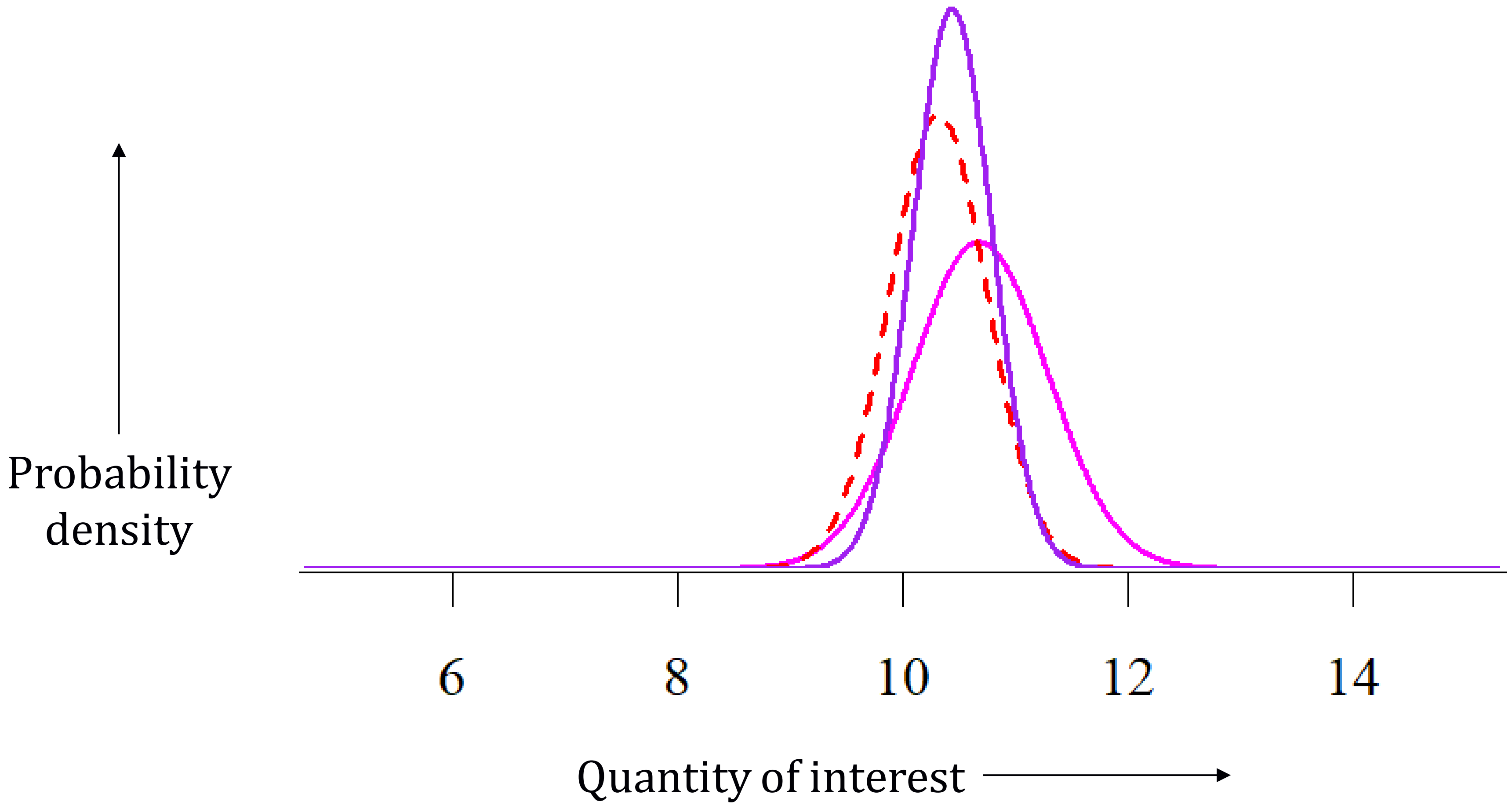

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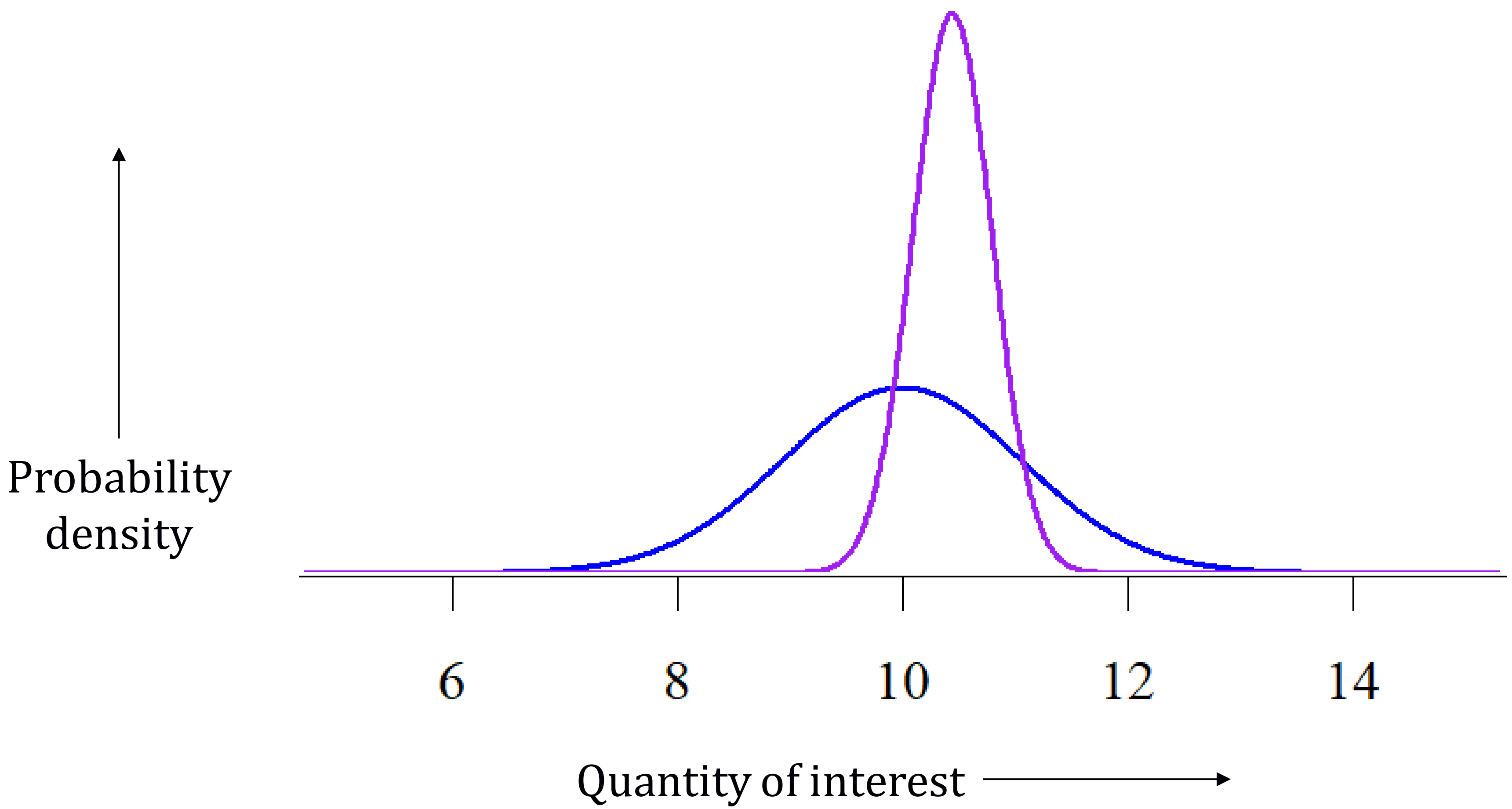

Mathematical models as alternatives

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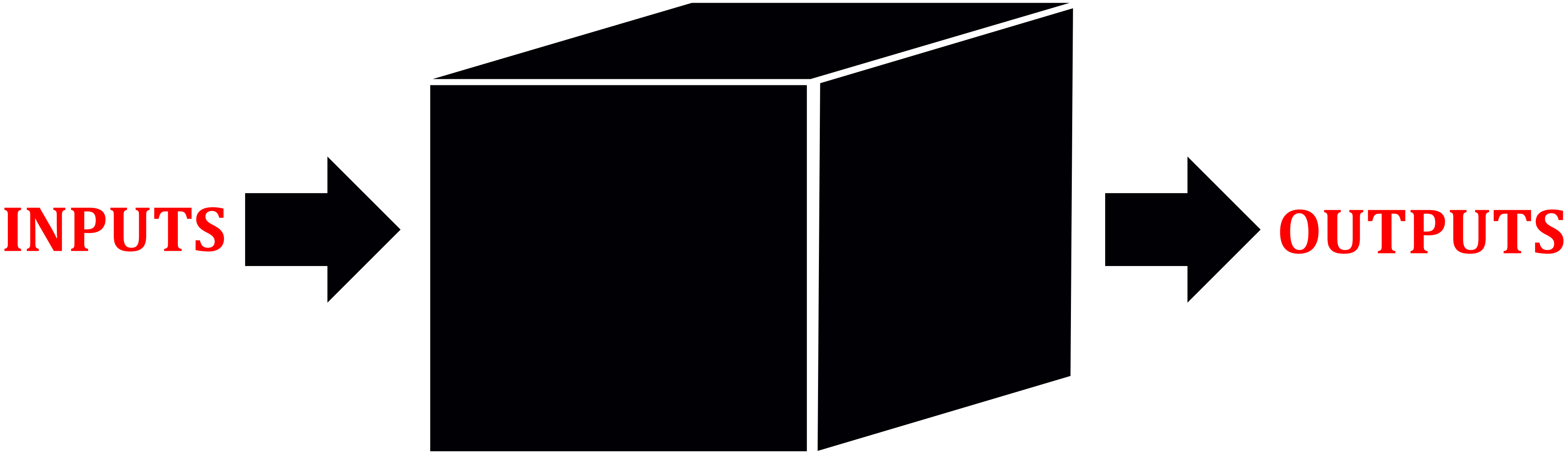
Increasing trust and improving adoption:

1) Understand the scientific principles underlying the model.
2) Understand the limitations of the model.
3) Account for the uncertainty when applying the model.



Gosling (2019). The importance of mathematical modelling in chemical risk assessment and the associated quantification of uncertainty. *Comp. Tox*, **10**.

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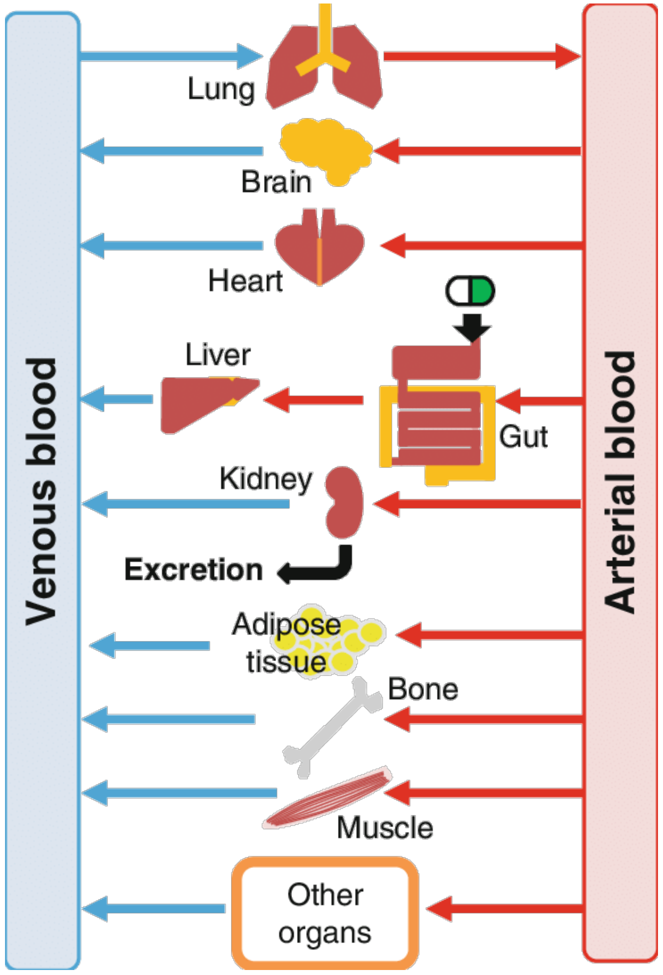

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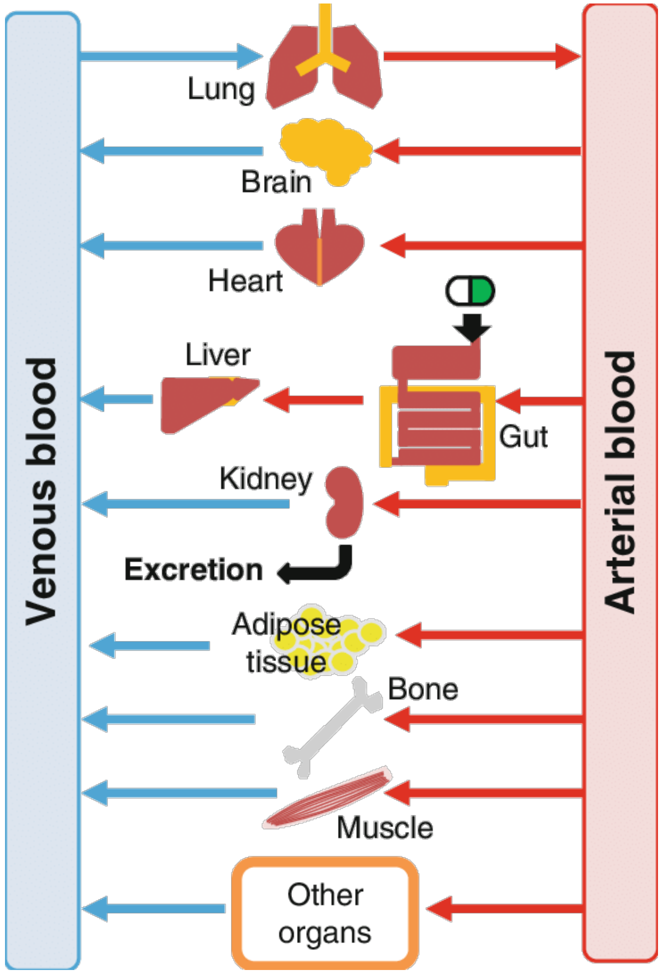

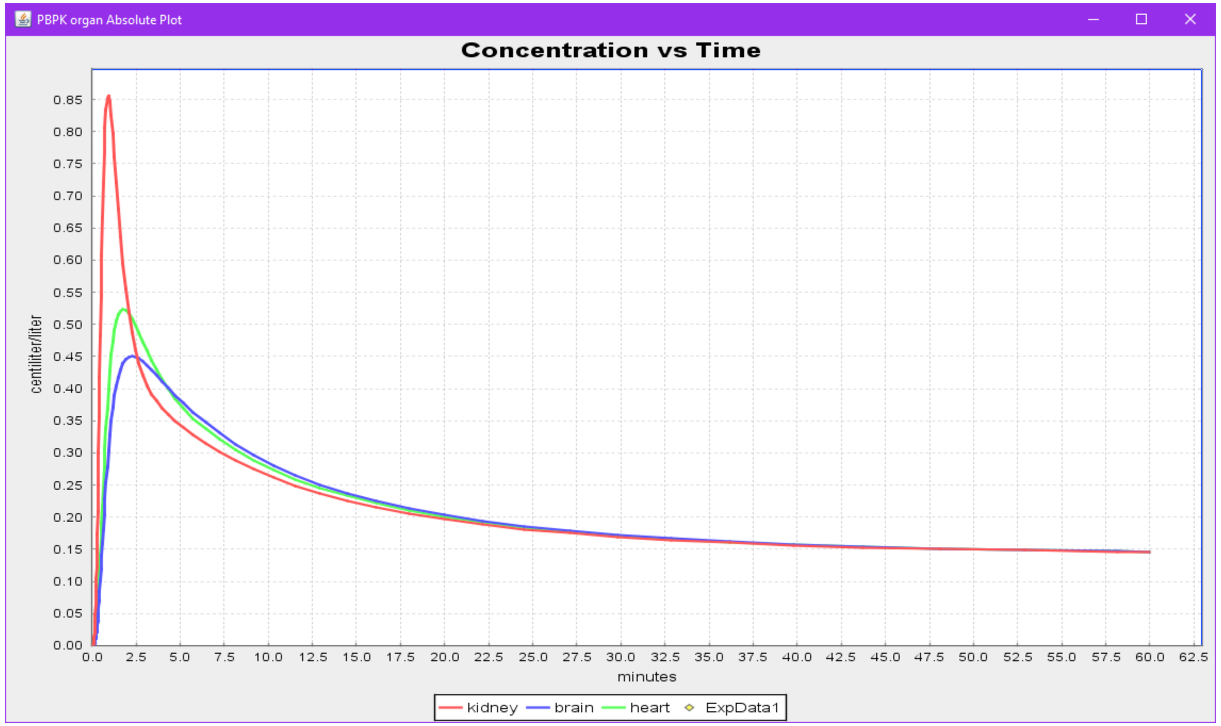

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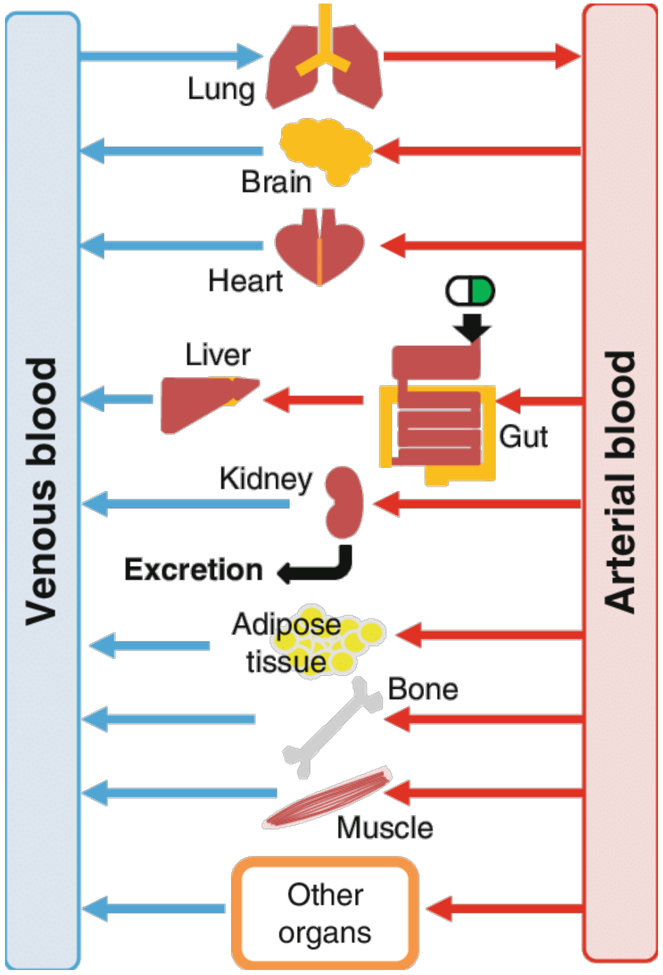

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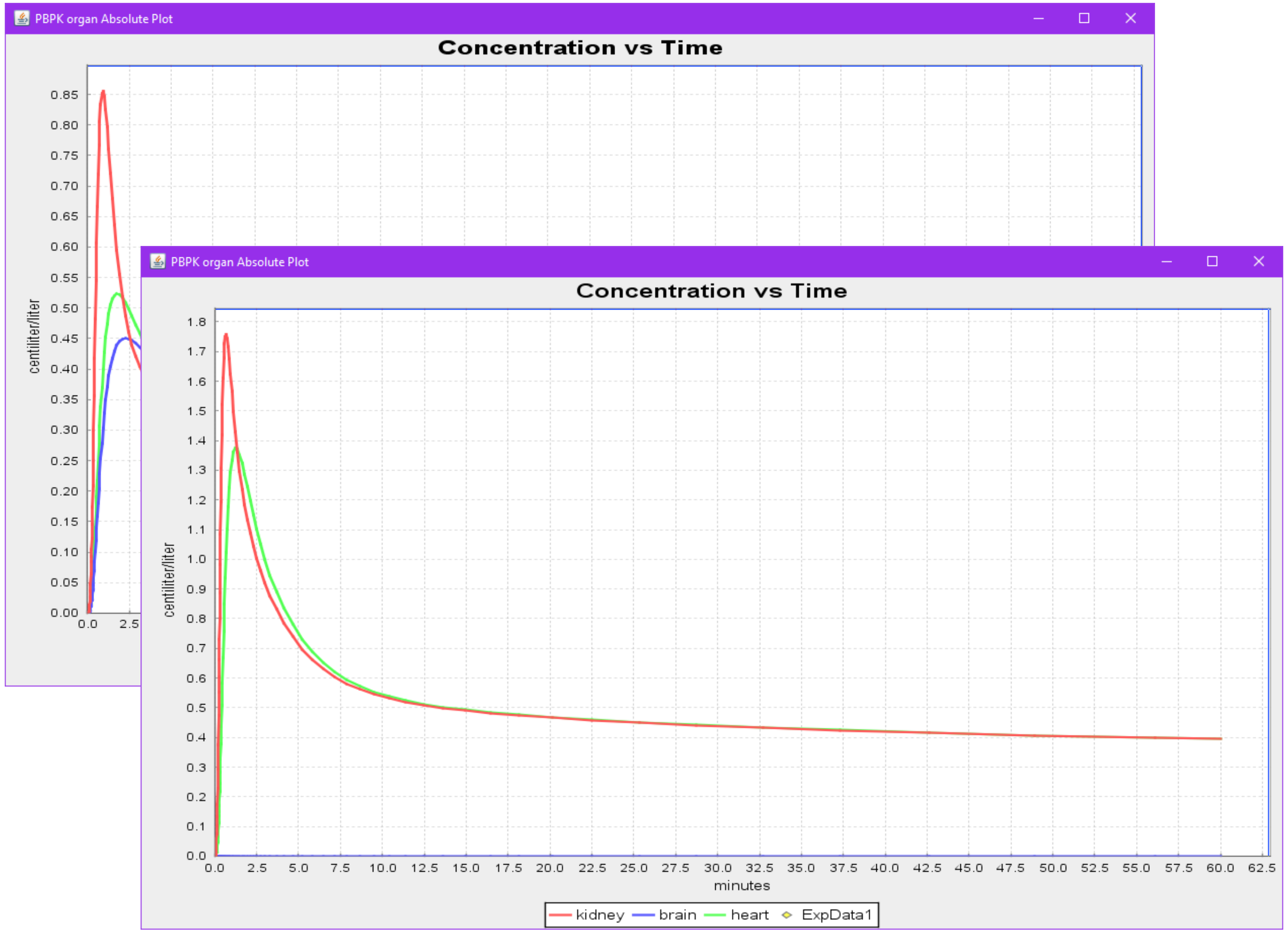

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Mathematical Models as Alternatives

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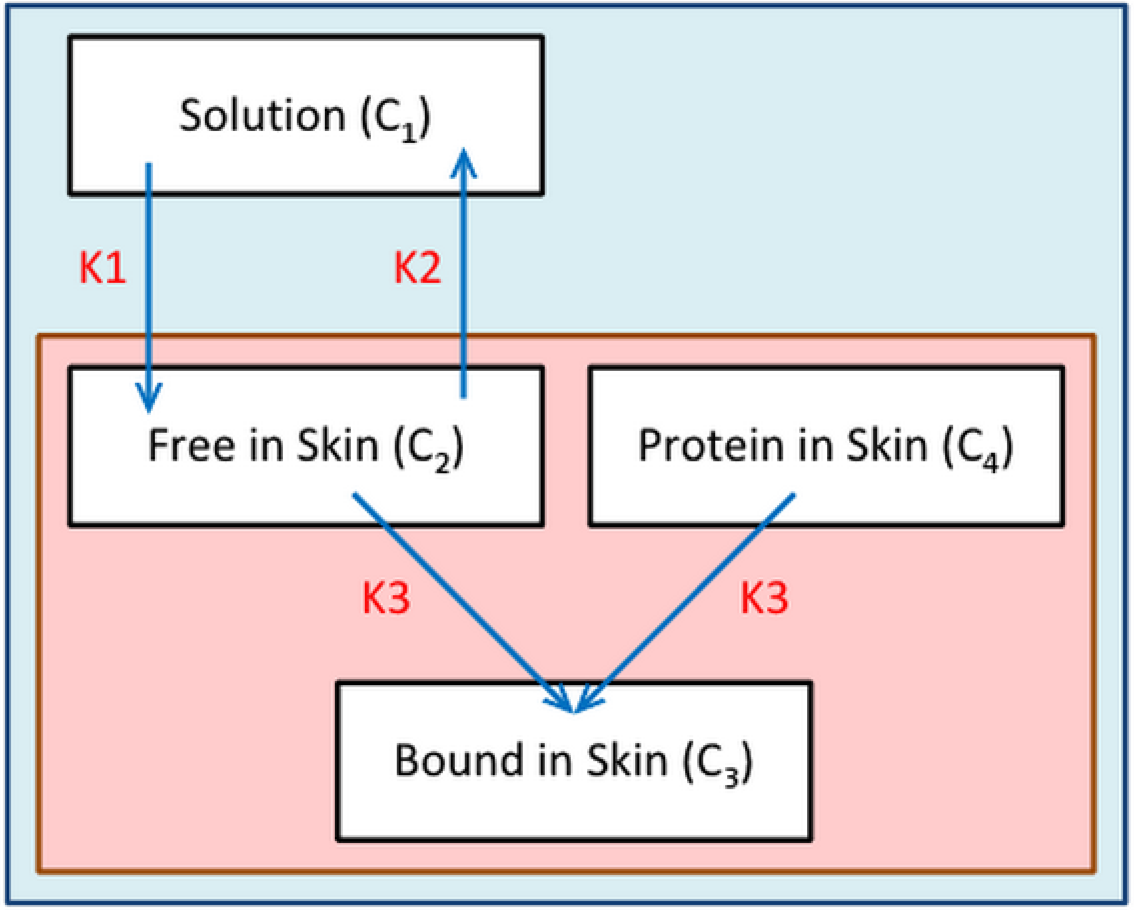

$$\frac{dC_1}{dt} = \frac{-k_1 C_1 + k_2 C_2}{V_{Solution}}$$

$$\frac{dC_2}{dt} = \frac{k_1 C_1 - k_2 C_2 - k_3 C_2 C_4}{V_{skin}}$$

$$\frac{dC_3}{dt} = \frac{k_3 C_2 C_4}{V_{skin}}$$

$$\frac{dC_4}{dt} = \frac{-k_3 C_2 C_4}{V_{skin}}$$

Davies *et al.* (2010). Determining epidermal disposition kinetics for use in an integrated non-animal approach to skin sensitization risk assessment. *Toxicological Sciences*, **119**.

Mathematical Models as Alternatives

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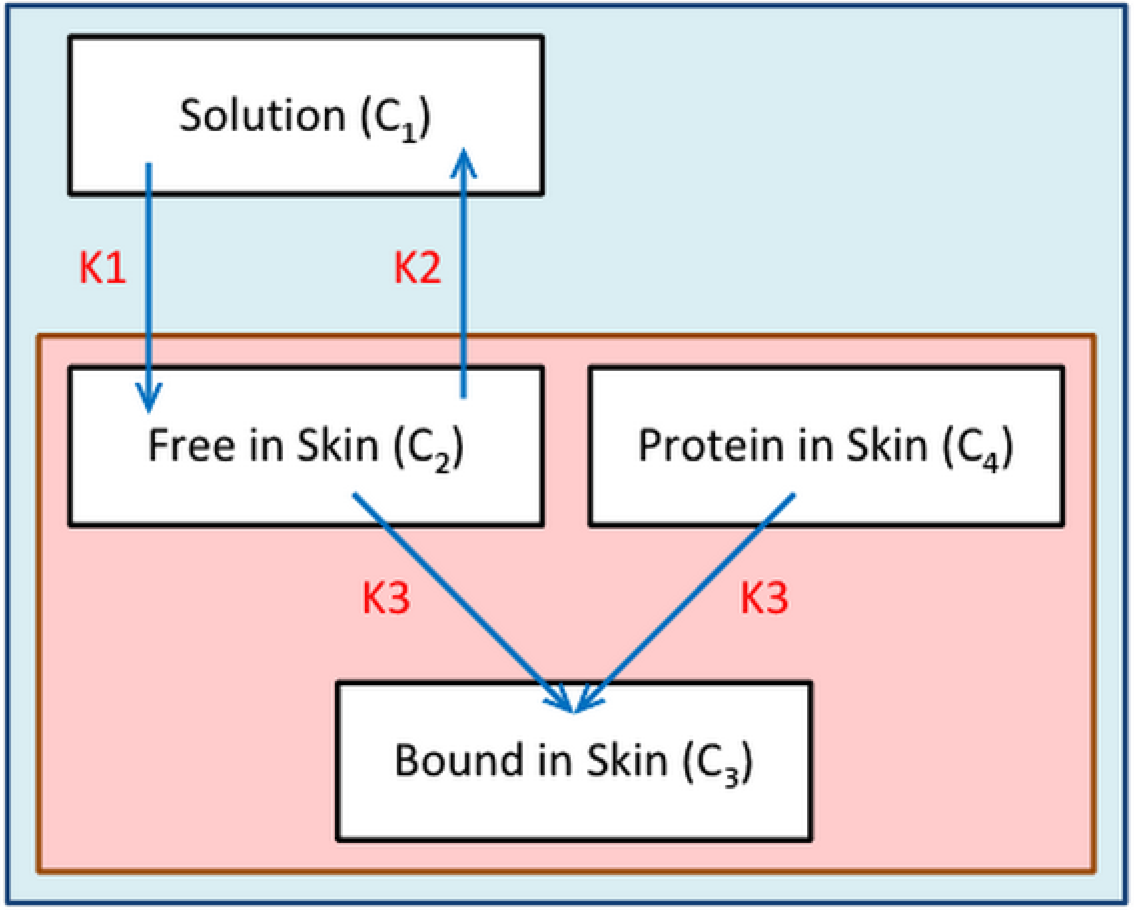

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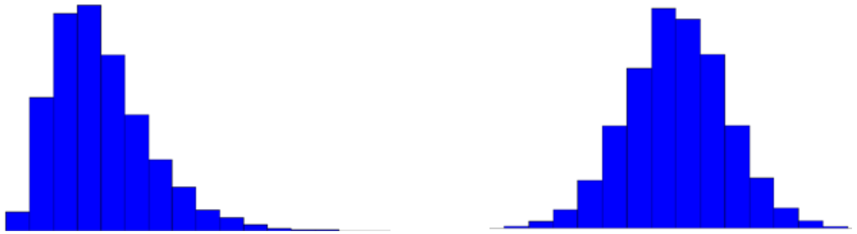
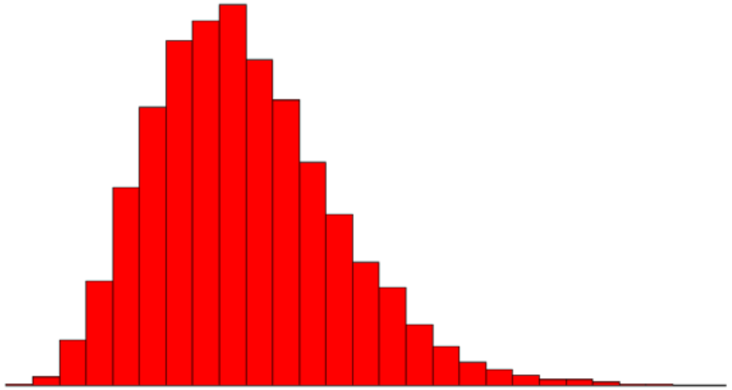
We can use Monte Carlo methods to propagate uncertainties:

INPUT UNCERTAINTY



AMOUNT BOUND IN SKIN



Model Verification

Does the model do what I think it is doing?

Model Validation

Is the model a true representation of reality?

Model Verification

Does the model do what I think it is doing?

Defining model scope,
Checking model equations,
Dual coding,
Bug checking,
Sensitivity analysis.

These are all conditioning on the model being true.

Clark et al. (2004). Framework for evaluation of PBPK models for use in safety or risk assessment, *Risk Analysis*, **24**.

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Model Validation

Is the model an adequate representation of reality for our purposes?

Sensitivity analysis,
Robustness analysis,
Assumption justification,
Model argumentation,
Structured calibration,
Predictive performance,
Proper scoring rules,
Relation to reality.

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Uncertainty in NGRA

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Understanding and quantification of uncertainty is crucial for NGRA:

- We will never be able to perform the experiments that confirm the relevance of the methods for all chemicals.
- Decisions can be more effective when we know how wrong we could be and what is more likely.
- Assessors need to know how new models compare with competing data sources.
- Discussing uncertainty and model assumptions improves scientific rigour and transparency.

References

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Excellent places to start are the EFSA journal articles entitled
Guidance on…

Expert Knowledge Elicitation in Food and Feed Safety Risk Assessment,

Uncertainty Analysis in Scientific Assessments,

Communication of Uncertainty in Scientific Assessments.

See individual slides for rest.