FORMULATION TOXICITY

ITT5

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PROBLEM RECAP

- Agrochemical formulations are mixtures of active ingredients and various coformulants.
- Toxicity of substance is measured by animal testing.
- If we can model toxicity of formulations/ingredients, we may be able to reduce animal testing.

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- Other ingredients have toxicity in a given range, or may be discrete (e.g. “irritant”/“non-irritant”/“severely irritant”).
- Inverse toxicity of a mix is often assumed to be sum of ingredient inverse toxicities (additivity). How can we check for non-additive interactions?

PROBLEM RECAP

STEP 1: Derive Acute Toxicity Estimates (ATE) of individual ingredients

STEP 2: Calculation of ATE of a mixture and use classification criteria in the left table.

Exposure routes	Classification category or experimentally obtained acute toxicity range estimate (*see Note 1*)	Converted acute toxicity point estimate (*see Note 2*)
Oral (mg/kg bodyweight)	0 < Category 1 ≤ 5	0.5
	5 < Category 2 ≤ 50	5
	50 < Category 3 ≤ 300	100
	300 < Category 4 ≤ 2000	500
	2000 < Category 5 ≤ 5000	2500
Dermal (mg/kg bodyweight)	0 < Category 1 ≤ 50	5
	50 < Category 2 ≤ 200	50
	200 < Category 3 ≤ 1000	300
	1000 < Category 4 ≤ 2000	1100
	2000 < Category 5 ≤ 5000	2500
Gases (ppmV)	0 < Category 1 ≤ 100	10
	100 < Category 2 ≤ 500	100
	500 < Category 3 ≤ 2500	700
	2500 < Category 4 ≤ 20000	4500
	Category 5 - See footnote to 3.1.2.5.	
Vapours (mg/l)	0 < Category 1 ≤ 0.5	0.05
	0.5 < Category 2 ≤ 2.0	0.5
	2.0 < Category 3 ≤ 10.0	3
	10.0 < Category 4 ≤ 20.0	11
	Category 5 - See footnote to 3.1.2.5.	
Dust/mist (mg/l)	0 < Category 1 ≤ 0.05	0.005
	0.05 < Category 2 ≤ 0.5	0.05
	0.5 < Category 3 ≤ 1.0	0.5
	1.0 < Category 4 ≤ 5.0	1.5
	Category 5 - See footnote to 3.1.2.5.	

Ingredient(s) with unknown toxicity is <= 10 %;

$$\frac{100}{ATEmix} = \sum_{n} \frac{C_i}{ATE_i}$$

Ingredient(s) with unknown toxicity is >10 %;

$$\frac{100 - (\sum C_{unknown} \text{ if } > 10\%)}{ATE_{mix}} = \sum_{n} \frac{C_i}{ATE_i}$$

C_i = concentration of ingredient i;

n ingredients and i is running from 1 to n;

ATE_i = Acute toxicity estimate of ingredient i;

BAYESIAN LINEAR MODEL

Additivity motivates the following

$$\mathbf{y} = \mathrm{A}\mathbf{x} + \epsilon$$

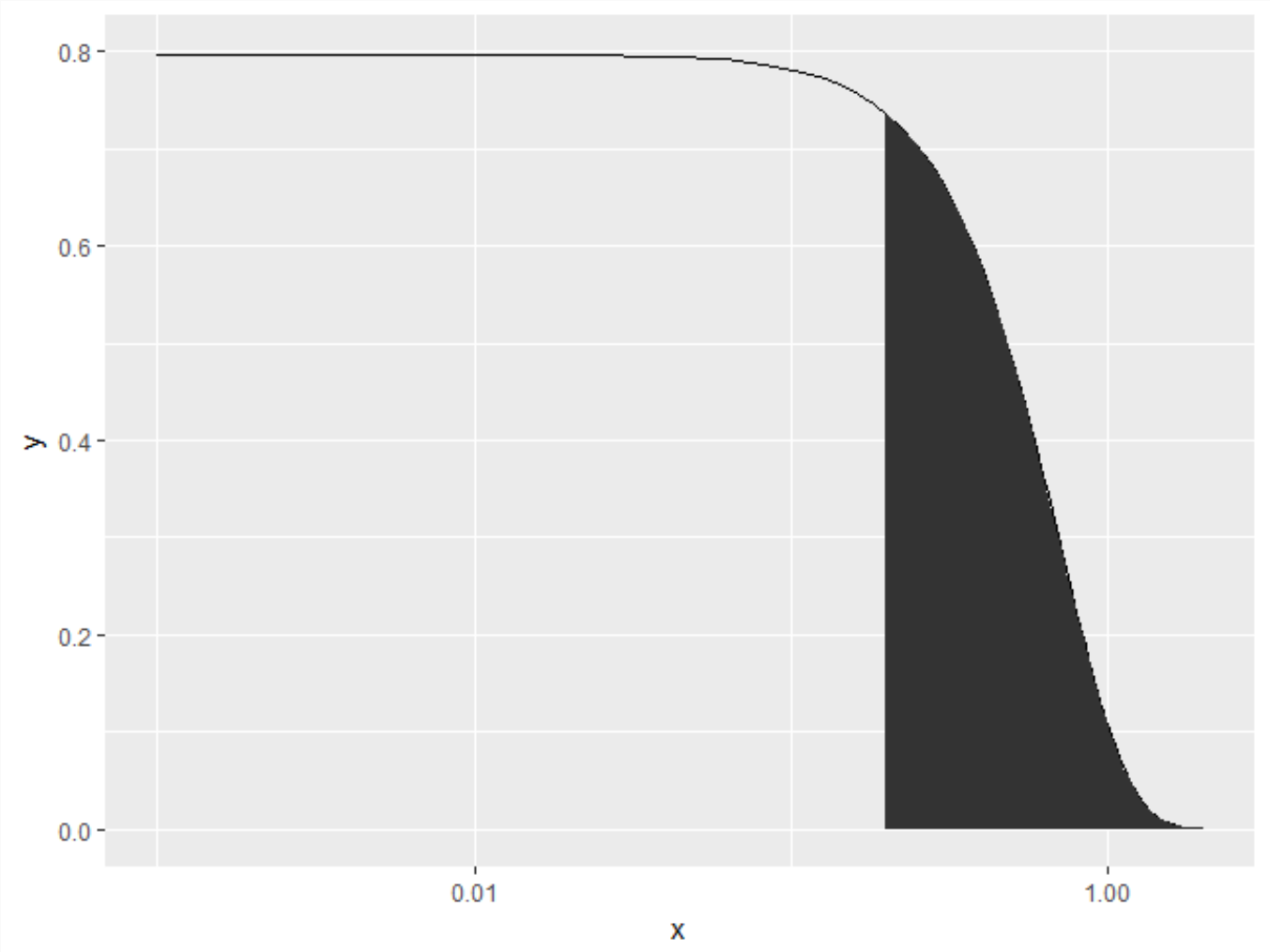
- $\mathbf{y}$ - Inverted formulation toxicities
- A - Matrix with rows containing ingredient proportions
- $\mathbf{x}$ - Inverted ingredient toxicities
- ϵ - Measurement error

Bayesian inference of $\mathbf{x}$ incorporates prior knowledge and gives confidence in the result.

PREDICTING CLASSIFICATION

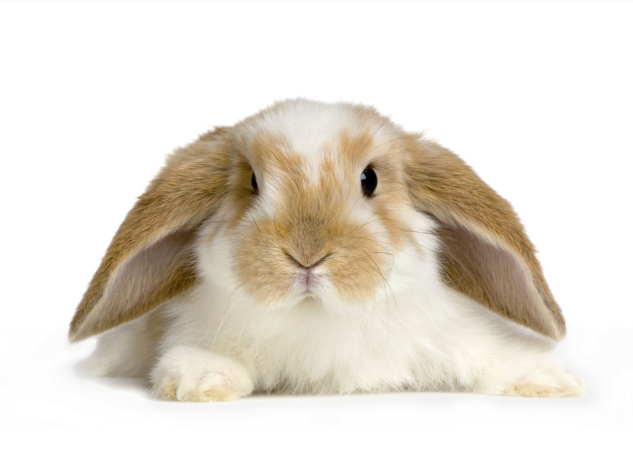
E.g. How confident can we be that an ingredient is Category 1 (< 5 mg/kg) in acute toxicity?

Simply integrate posterior over category interval:



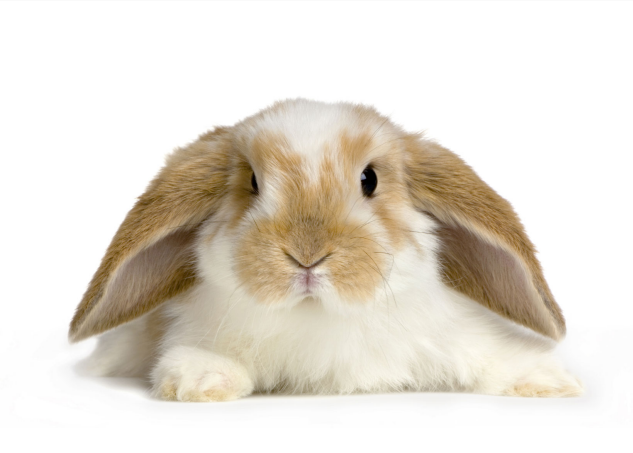
INFORMING TOXICITY TESTS

- What's the source of uncertainty in results?



INFORMING TOXICITY TESTS

- What's the source of uncertainty in results?
- If we can deduce this, could reduce animal trials by testing chemicals that are responsible for uncertainty.



WORKING WITH DISCRETE DATA

E.g. skin toxicity may simply be "Severely irritant" / "Irritant" / "Non-irritant".
How can we incorporate this discrete data into the linear model?

Class/Category	Serious Eye Damage - Category 1	Eye Irritation - Category 2A	Eye Irritation - Category 2B
Pictogram			(no pictogram)
Signal word	Danger	Warning	Warning
Hazard statement	Causes serious eye damage.	Causes serious eye irritation.	Causes eye irritation.

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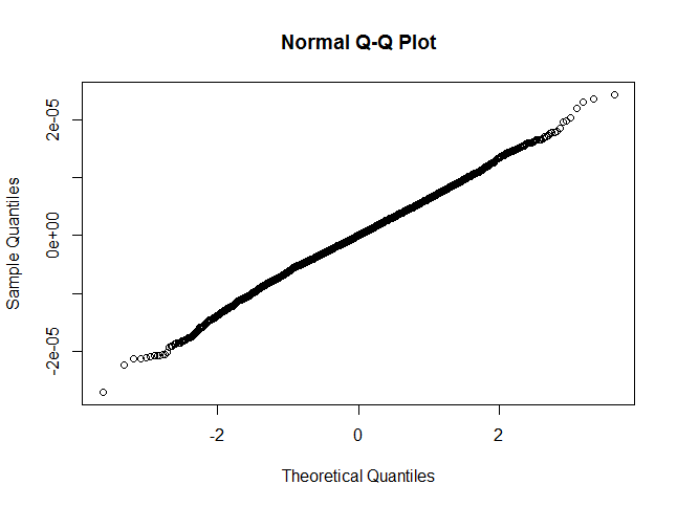
One possibility is a hidden / latent numerical toxicity in which categories are clustered.

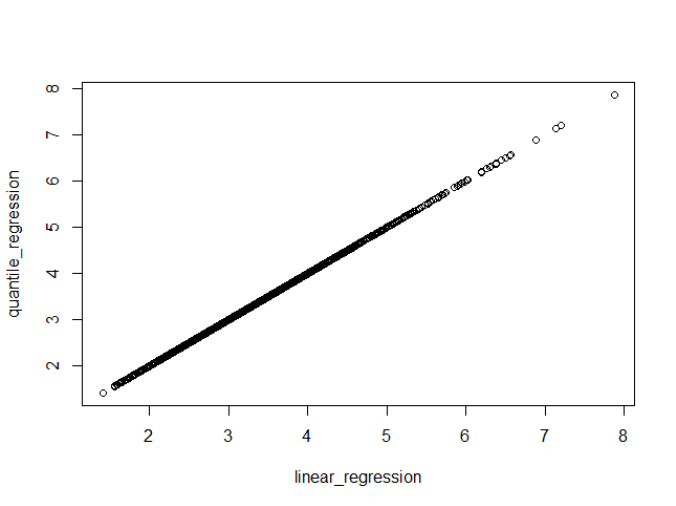
$$\mathbf{x}_i \sim \mathrm{N}(\mu_{C_i}, {\sigma_{C_i}}^2)$$

i.e. supervised learning but without direct observations of $\mathbf{x}_i$.

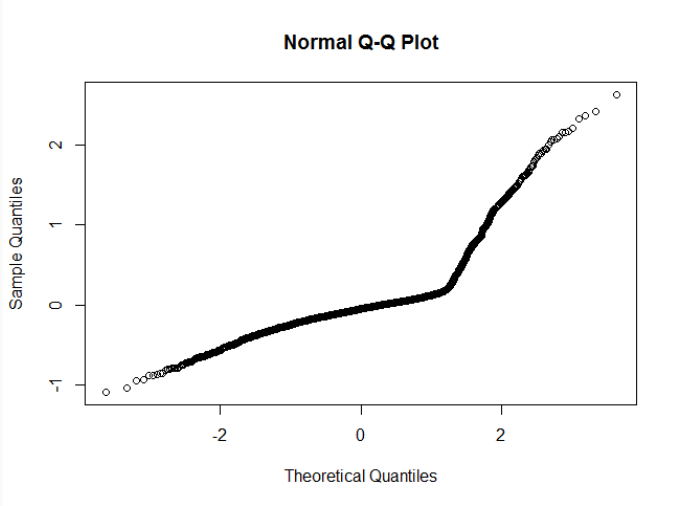
DETECTING NON-ADDITIVITY

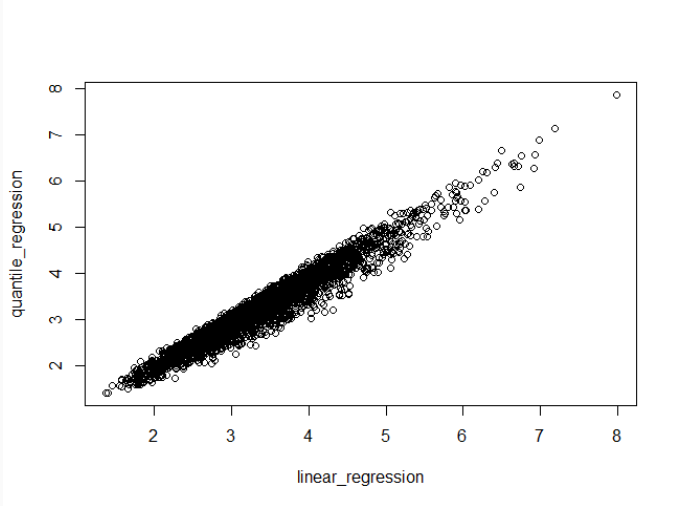
Linear Dataset





Nonlinear Dataset





SUMMARY OF PROBLEM FORMULATION

The problem requires methodology for the following:

1. A robust way to detect non-linear effects and estimate which combinations of chemicals will interact in a non-linear way.
2. Identify sources of uncertainty in results to inform what data needs to be collected.
3. Reliably predict from a mix of discrete/continuous/interval data.

Over to Tsoogii