Bridging statistical and mathematical modelling

or

The most important things I could think to teach you about data, maths/stats, and infections in 90 minutes given your other lectures

Chris Wymant

These materials + more: `github.com/ChrisHIV/teaching`

e.g. maths refresher, statistical modelling refresher, Stan, how to write a paper

Terminology apology

By statistical modelling I actually only mean likelihood-based statistical modelling, using my own experience. Comments may generalise to other types of statistics, machine learning etc. YMMV

Lecture structure

1. Revisiting probability
2. Statistical and/or mathematical modelling
3. Counterfactuals
4. Case study with random effects / multilevel models: HIV immune system decline

Part 1: Revisiting probability:
Feeling at home with the basic laws

Analogy, motivation

Job	Legislator	Scientific data* analyst
Task	Write laws (in England)	Determine compatibility between data and hypotheses
Language for that task	English	Probability
Would they benefit greatly from a high level of fluency in that language	Yes	Yes
How should their core statements be written to be defensive against misinterpretation	Legalese	Equations for conditional probabilities
Example	"(3) A person who is guilty of fraud is liable— (a) on summary conviction, to imprisonment for a term not exceeding [F1 the general limit in a magistrates' court] or to a fine not exceeding the statutory maximum (or to both);" (Actual text of the Fraud Act 2006)	"$P(y_i \mid x_i, m, c, \sigma) = N(y_i \mid mx_i + c, \sigma^2)$" (Supplementary Information or Methods section of your article.)
Is it helpful to provide a simpler explanation in addition to the technical core statements	Yes	Yes
Example	"A person convicted 'summarily' (not so serious as to warrant a trial in court) can get jail sentence and/or fine up to some maximum amount." (Public-facing resource to clarify laws.)	"We used a simple linear regression model to predict y given x." (Main text of your article.)

* reminder that qualitative data is still data, just outside my expertise

Probability fundamentals: your lectures so far

Probability refresher - Some terminology

- Sample point:
  - A possible outcome of a random experiment
- Sample space:
  - The collection of all sample points
  - i.e. all possible outcomes of a random experiment
  - often called Ω

Probability refresher - Some terminology

- Event:
  - Collection of possible outcomes
- Distribution:
  - Assignment of values to events satisfying the probability axioms

Probability refresher – The three axioms of probability

1. The probability of an event A is a value P(A) between 0 and 1
2. P(Ω)=1
3. If A1,A2,... are mutually exclusive events, then

   P(A1UA2U...)=P(A1)+P(A2)+....

Probability refresher – Random variables

- Variables whose possible values are numerical outcomes of a random phenomenon
- Subject to variation due to chance
- A probability is associated to each of the possible values the variable can take
- There are two types of random variables:
  - Discrete
  - Continuous

Probability refresher – Discrete random variables

- Can take only a number of distinct values
- In general (but not always), they are counts
  - e.g. number of defective bulb lights in a box
- Have a probability mass function
  - Assigns probabilities to the possible values of the random variable P(X=x), where X is the random variable and x the possible value

The probabilities must follow some requirements:

$p_i \geq 0 \; \forall i$ Probabilities must be positive numbers $\sum_{i=1}^{n} p_i = 1$ The sum of the probabilities must be 1

Probability refresher – Discrete random variables

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Values	P(X=x)
1	0.20
3	0.50
7	0.30

The probability of the random variable being exactly 1 is 0.2

Probability refresher – Continuous random variables

- Can take an infinite number of possible values
- In general, they are measurements
  - e.g. the time required to run a mile
- Have a probability density function
  - specifies the probability that the value of the random variable falls within a specific range
  - it is represented by the area under the density function (integral)

The PDF needs to satisfy the following requirements:

Probabilities must be positive numbers $f(x) \geq 0 \; \forall \; x$ $\int_{-\infty}^{+\infty} f(x)dx = 1$ The area under the entire density curve must be 1

Probability refresher – Continuous random variables

The PDF needs to satisfy the following requirements:

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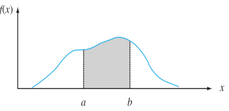
- For example, considering a random variable X measuring the depth of a lake in various spots
- The probability that X takes on a value in the interval P(a ≤ X ≤ b) is the area under the density function curve
- The probability that X takes an exact value of x is 0



Definition of probability, 0 ≤ P(A) ≤ 1, sum to 1

Probability definitions

P(A) = probability of A.

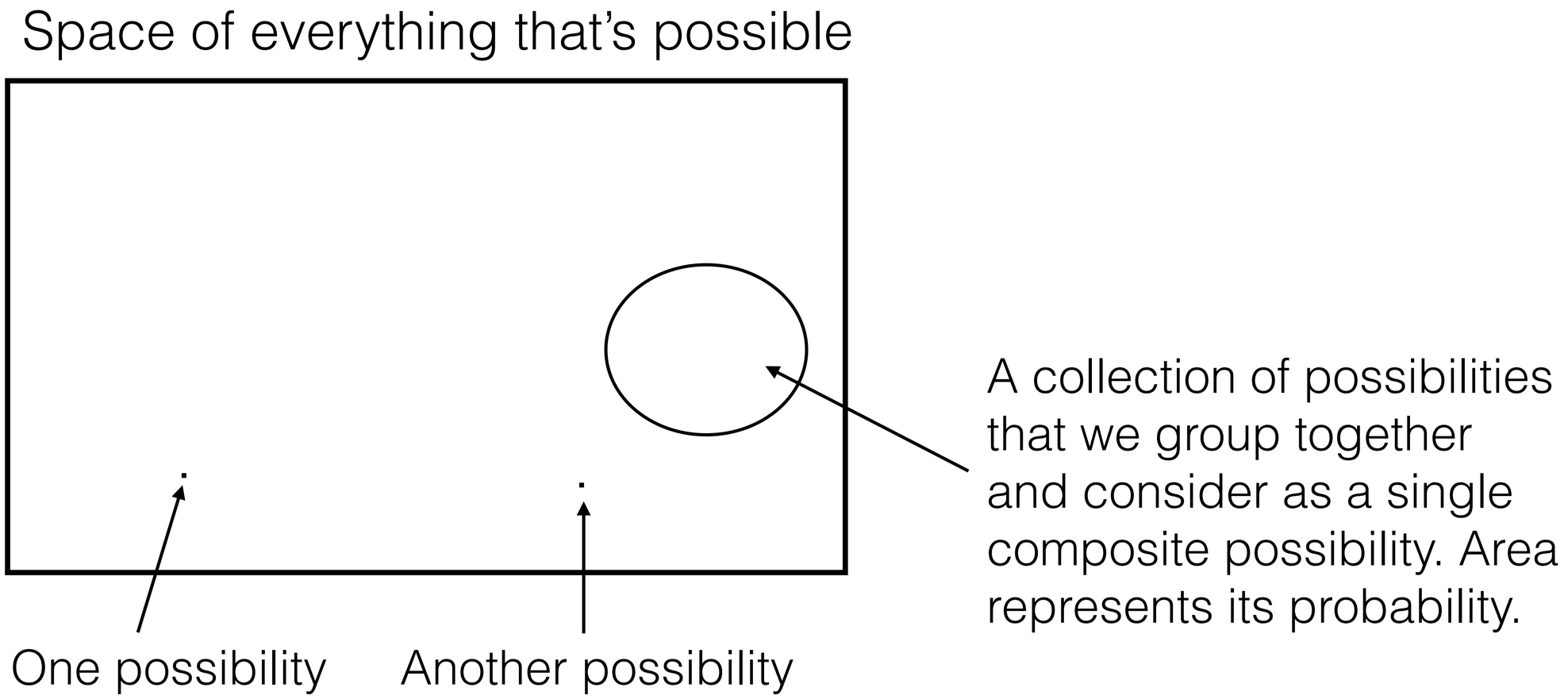
$0 \leq P(A) \leq 1$

Frequentist probability: defined only for random variables, i.e. outcomes of stochastic experiments that can be repeated.

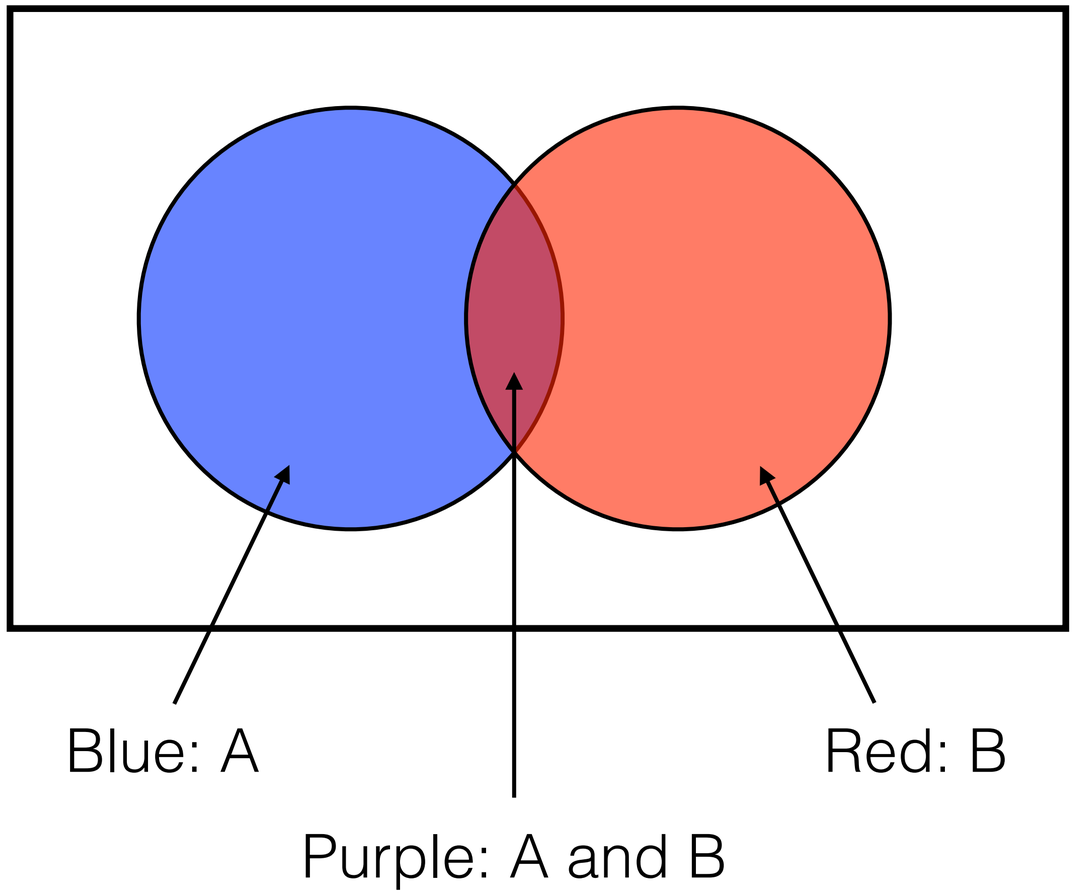
$$P(A) = \lim_{N \to \infty} \left(\frac{\text{number of } A \text{ outcomes}}{N} \right)$$

Bayesian probability: as above but *also* used to quantify uncertainty, i.e. degree of belief.

Venn diagrams



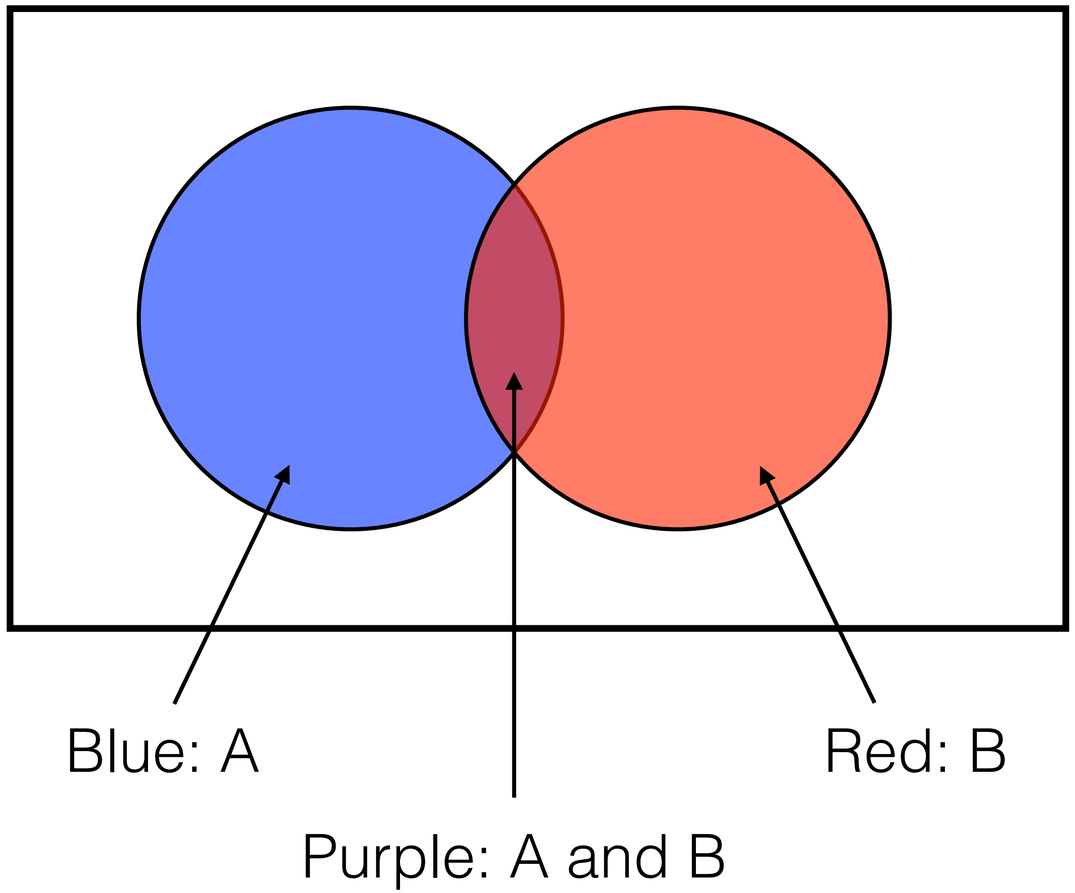
“and”, “or”



$$P(A) = P(A \text{ and } B) + P(A \text{ and not-}B)$$
$$P(B) = P(B \text{ and } A) + P(B \text{ and not-}A)$$

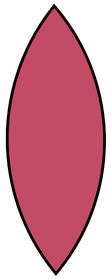
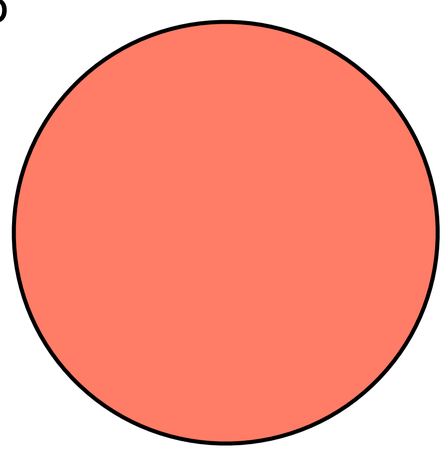
$$\therefore P(A \text{ or } B) = P(A) + P(B) - P(A \text{ and } B)$$

Conditional probability

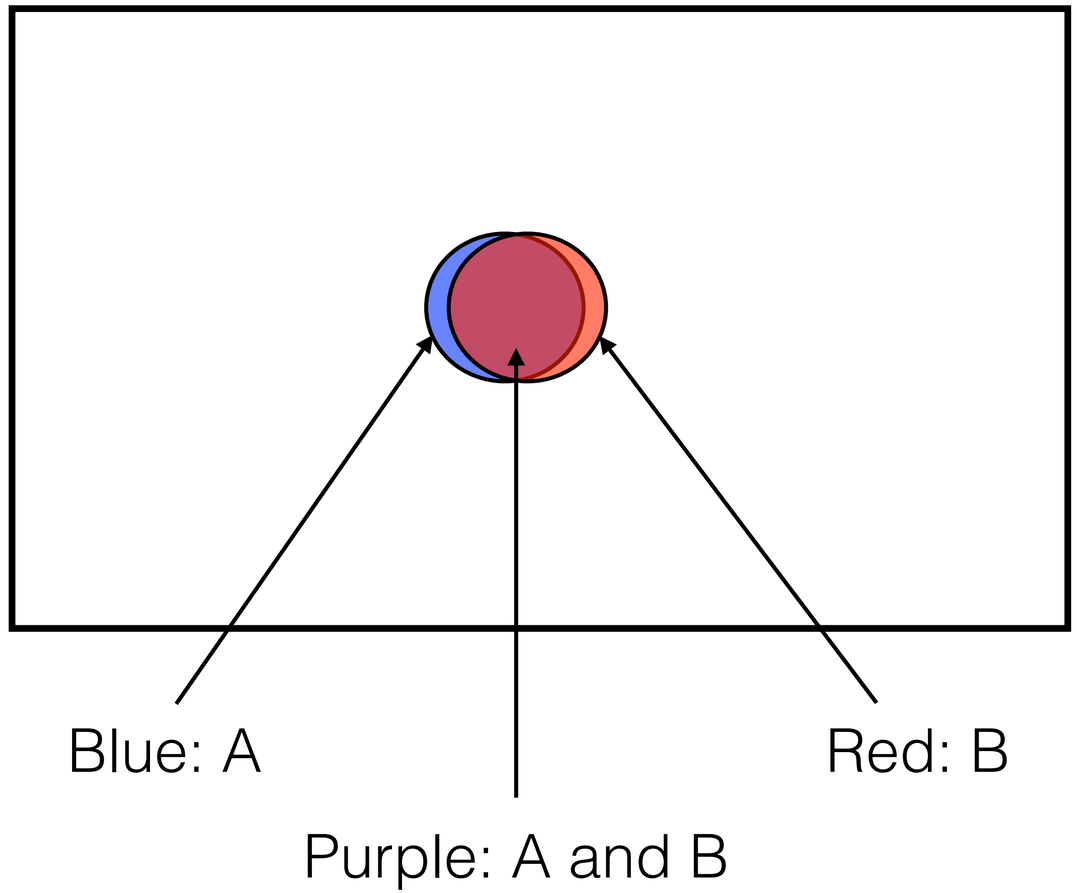


| means “given (that)” or “conditional upon”

Definition: P(A|B) = P(A and B) / P(B)
= fraction of outcome space that’s A within the space that’s B

= area of  / area of 

Conditional probability: given what?



"Lies, damn lies, and statistics"
or, "the | operator changes everything"

P(A) and P(A|B) can be very different!

Ask (them/yourself) *given what* every time you encounter a probability.

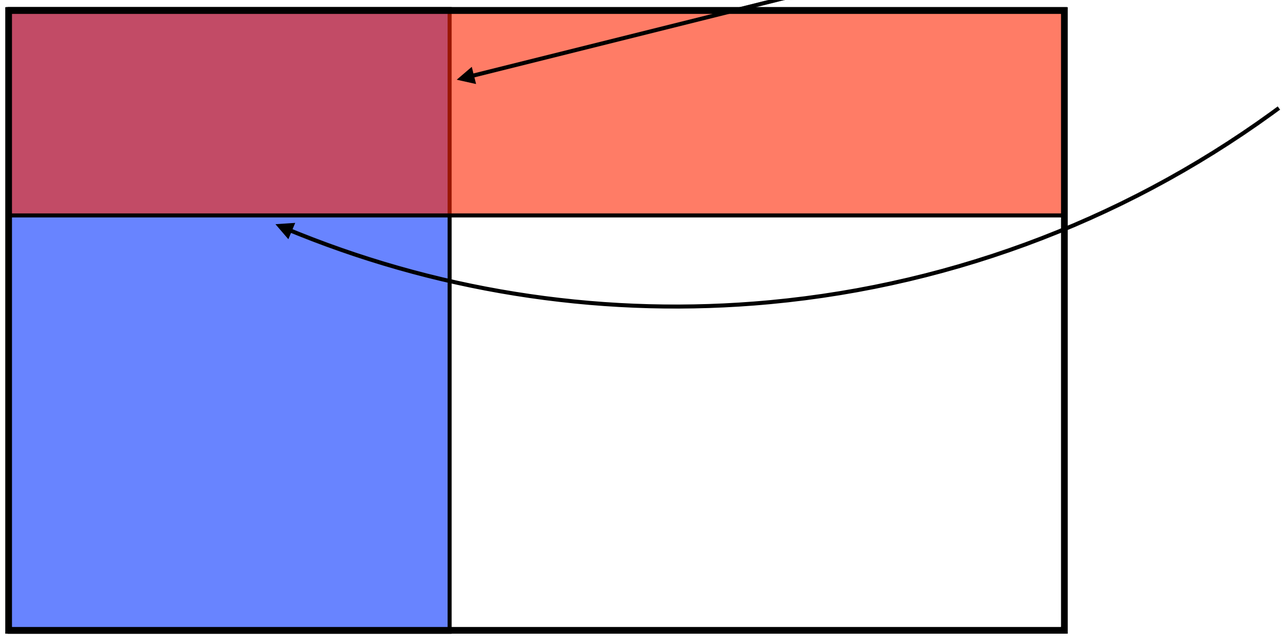
Independence

A and B are outcomes of independent events

⇔ knowing B is wholly uninformative regarding A and vice versa

⇔ P(A | B) = P(A) and P(B | A) = P(B)

⇔ P(A and B) = P(A)P(B)



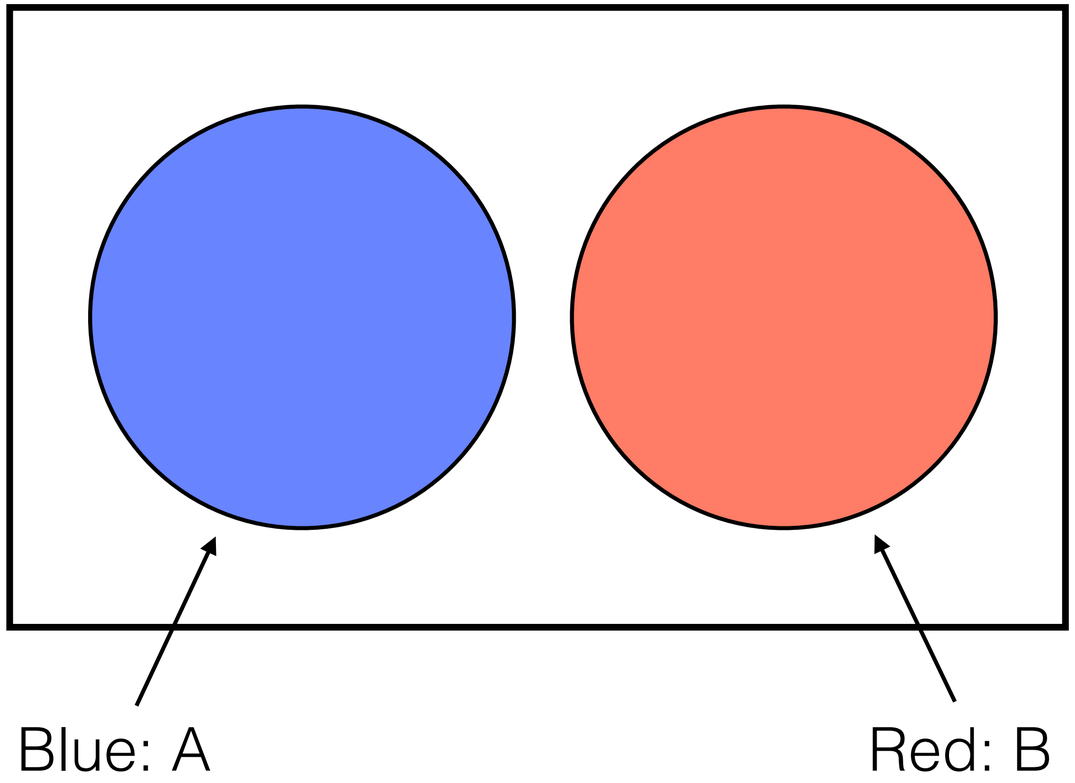
Fraction of *red* that's (also) blue
= fraction of *everything* that's blue

Fraction of *blue* that's (also) red
= fraction of *everything* that's red

Very common for likelihoods to be built using an assumption of *conditional independence*:

P(all data | params) =
P(datum 1 | params) ×
P(datum 2 | params) × …

Mutual exclusivity



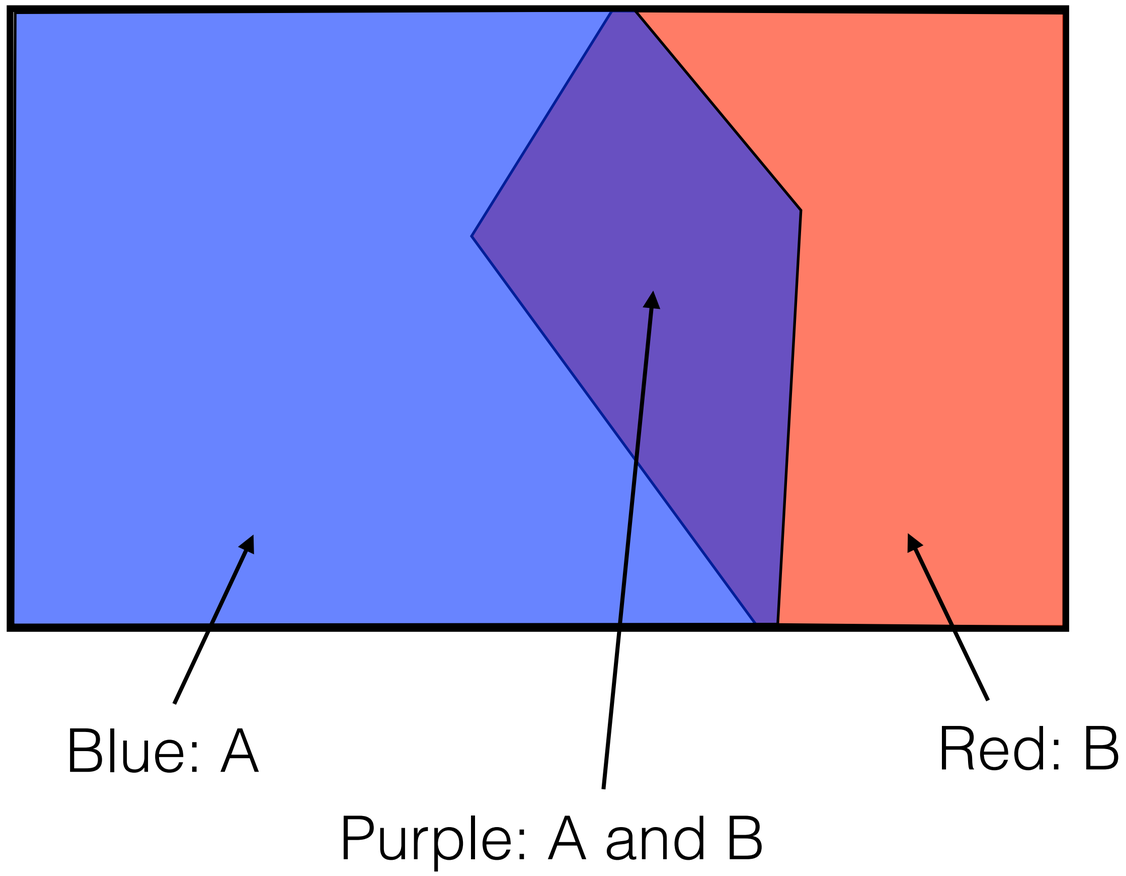
A and B are “mutually exclusive”

⇔ at most one of them is true

⇔ P(A and B) = 0

⇔ P(A or B) = P(A) + P(B)

Collective exhaustion



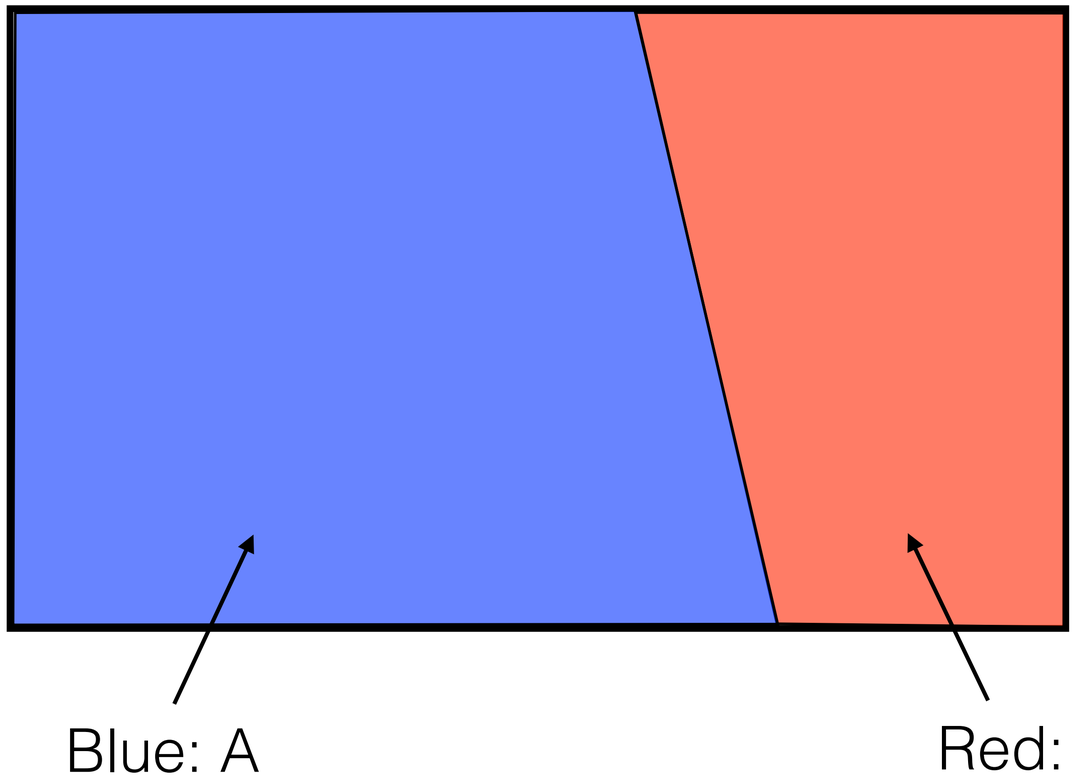
A and B are “collectively exhaustive”

⇔ at least one of them is true

⇔ P(A or B) = 1

⇔ P(not-A and not-B) = 0

Mutually exclusive and collectively exhaustive



A and B are mutually exclusive and collectively exhaustive (ME&CE)

⇔ at most one of them is true AND

at least one of them true

⇔ exactly one of them is true

⇒ P(A) + P(B) = 1

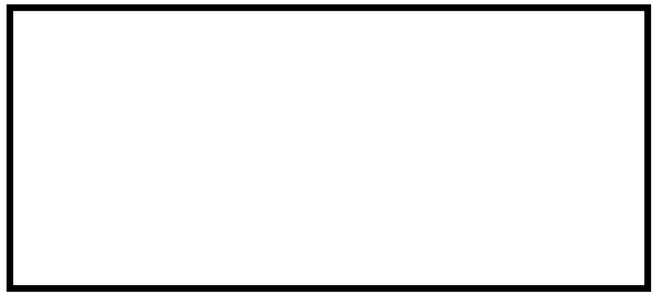
Example sets of possibilities for the result of rolling a die once:

	Mutually exclusive	Not mutually exclusive
Collectively exhaustive	●Result is 1-3 ●Result is 4-6	●Result is 1-4 ●Result is 4-6
Not collectively exhaustive	●Result is 1 ●Result is 2	●Result is 1-2 ●Result is 2-3

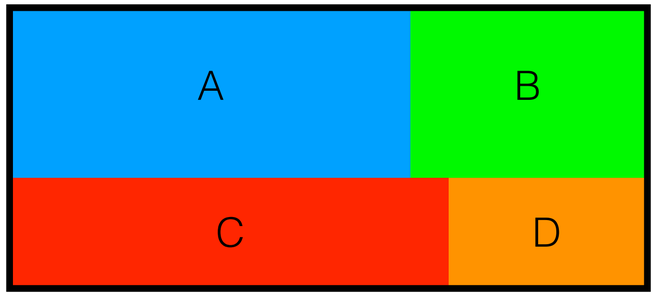
You can take the collection of all things that are possible and split it into ME&CE groups in different ways.

e.g. the day of the week today = Mon, Tue, … Sun, and
The mean temperature here today is <10°C, or ≥10°C

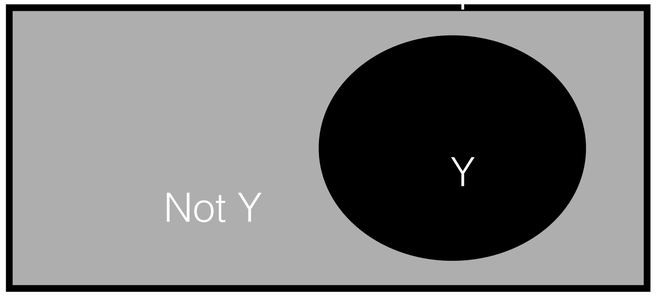
Space of everything that's possible



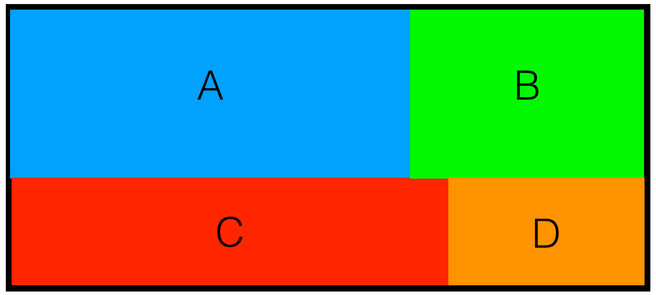
One way of splitting into ME&CE groups: A, B, C or D



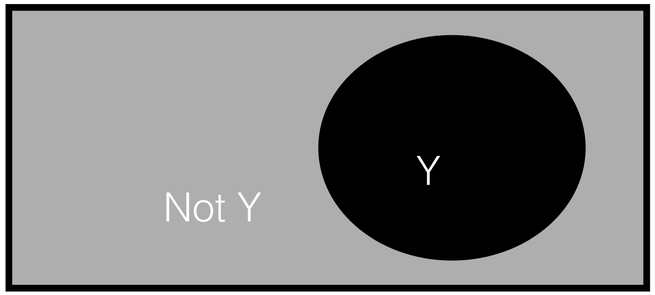
Another way of splitting into ME&CE groups: Y or not Y



One way of splitting into ME&CE groups: A, B, C or D

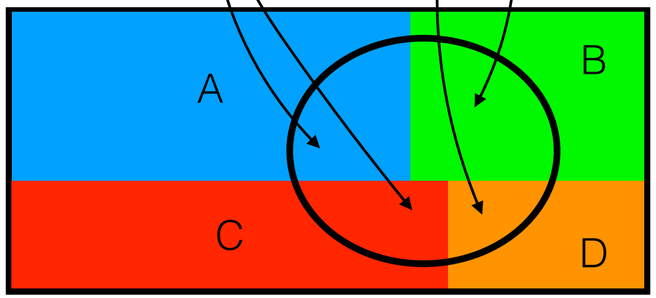


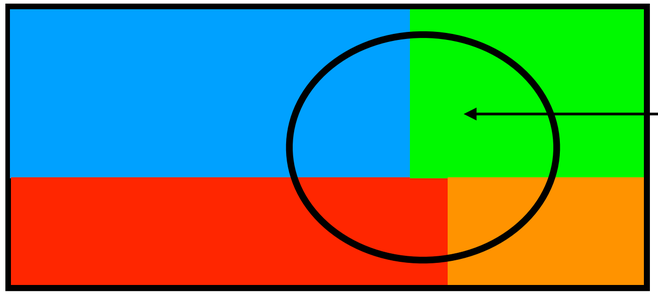
Another way of splitting into ME&CE groups: Y or not Y



Because exactly one of A, B, C or D is true, we can say

P(Y) = P(Y and A)
+P(Y and B)
+P(Y and C)
+P(Y and D)





P(Y and B)
= fraction of whole space that's Y × fraction of Y that's B
= P(Y) P(B | Y)
= P(B | Y) P(Y)

So in the end,

$$P(Y) = P(Y \mid A)\,P(A) + P(Y \mid B)\,P(B) + P(Y \mid C)\,P(C) + P(Y \mid D)\,P(D)$$

Using the *law of total probability*:

- Decide on your possibility of interest, Y,
- Decide on some way of splitting up the space of everything that's possible into a set of ME&CE possibilities A_1, A_2, … A_N (any way you like except "Y or not Y" which would result in something true but unhelpful)
- then you have

$$P(Y) = \sum_i P(Y|A_i)P(A_i)$$

Academics' favourite answer to anything: "it depends". Conditional probabilities are easier to calculate.

Decision makers need to make a decision, so "it depends on something we don't know for sure" is not helpful. Remove the dependence on A_i (sometimes called a nuisance parameter.)

and its integral equivalent for continuous A rather than discrete A_i.

Summing/integrating over A_i in proportion to $P(A_i)$ is called *marginalising* over A_i.

Sensitivity to unknowns

$$P(Y) = \sum_i P(Y|A_i)P(A_i)$$

	P(Y I A_i) is sensitive to A_i	**P(Y I A_i) is *in*sensitive to A_i**
P(A_i) is broad	P(Y) is very broad	P(Y) is moderately broad
P(A_i) is narrow	P(Y) is moderately broad	P(Y) is narrow

Frequentist and/or Bayesian

$$P(H \mid E) = \frac{P(E \mid H)P(H)}{P(E)}$$

↑ Bayes' Theorem or Bayes' Rule. *Always true*.

Using this or not is a separate issue from whether you're "a Frequentist" or "a Bayesian".

Frequentism permits use of Bayes' Theorem, but only when both H and E are random variables. Bayesianism permits H to be a hypothesis (and E to be evidence): powerful for inference.

Frequentist and/or Bayesian

Let D denote the hypothesis of having a disease, let $\bar{D}$ denote "not D" i.e. not having the disease, and let "+" denote the observation of a positive test result.

$$P(D \mid +) = \frac{P(+ \mid D)\, P(D)}{P(+)}$$

$$= \frac{P(+ \mid D)\, P(D)}{P(+ \mid D)\, P(D) \;+\; P(+ \mid \bar{D})\, P(\bar{D})}$$

(Having marginalised P(+) over the ME&CE possibilities D and $\bar{D}$)

$P(+ \mid D)$ and $P(+ \mid \bar{D})$ are just the test sensitivity and 1-specificity.

Bayesian doctor:

- $P(D)$ is the prior probability of their current patient having the disease. Use the fraction of people in the general population.
- $P(D \mid +)$ is the posterior probability of this patient having the disease. This object *is* the inference drawn.

Frequentist doctor:

- $P(D)$ is the fraction of people in the general population having the disease.
- $P(D \mid +)$ is the fraction of positive patients that have the disease. *Use* this object to draw an inference.

Part 1 summary:

- understand laws of (conditional) probability
- ask *given what* for each probability statement you encounter
- Use statements of conditional probability to build connections between data and hypotheses, and to communicate your method & results

Part 2: Statistical and/or mathematical modelling

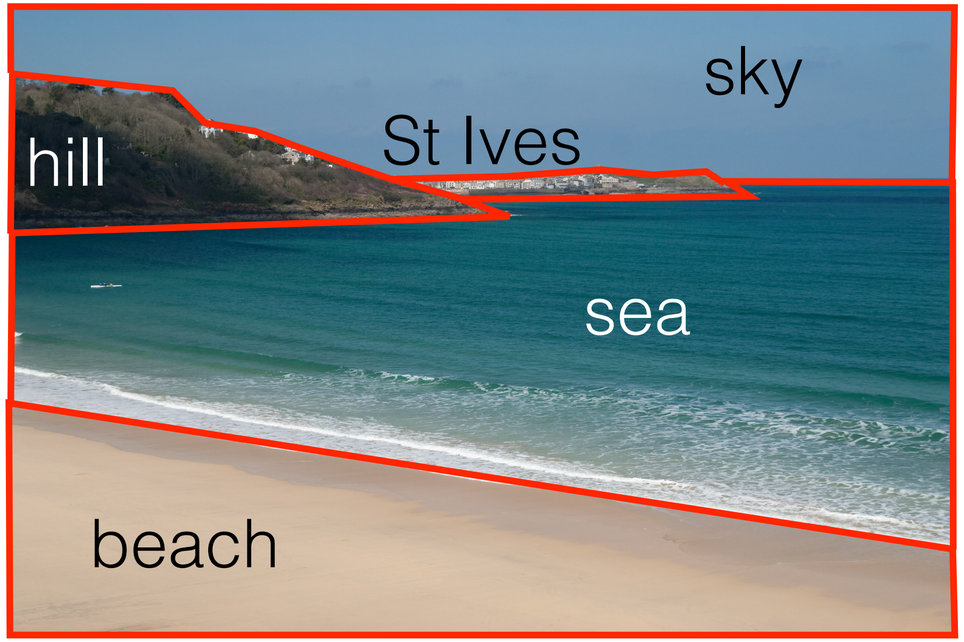
Models

A model: a simplified picture of complex reality.

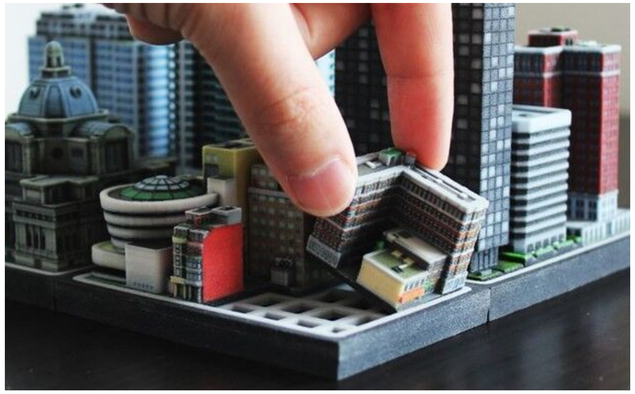
Creating and using models is essentially the only way we understand the world: we must choose which factors are relevant to our question and which are not.

e.g. “Where there’s smoke there’s fire”

e.g. “Border closures only delay a pathogen’s public health impact, they do not reduce it”



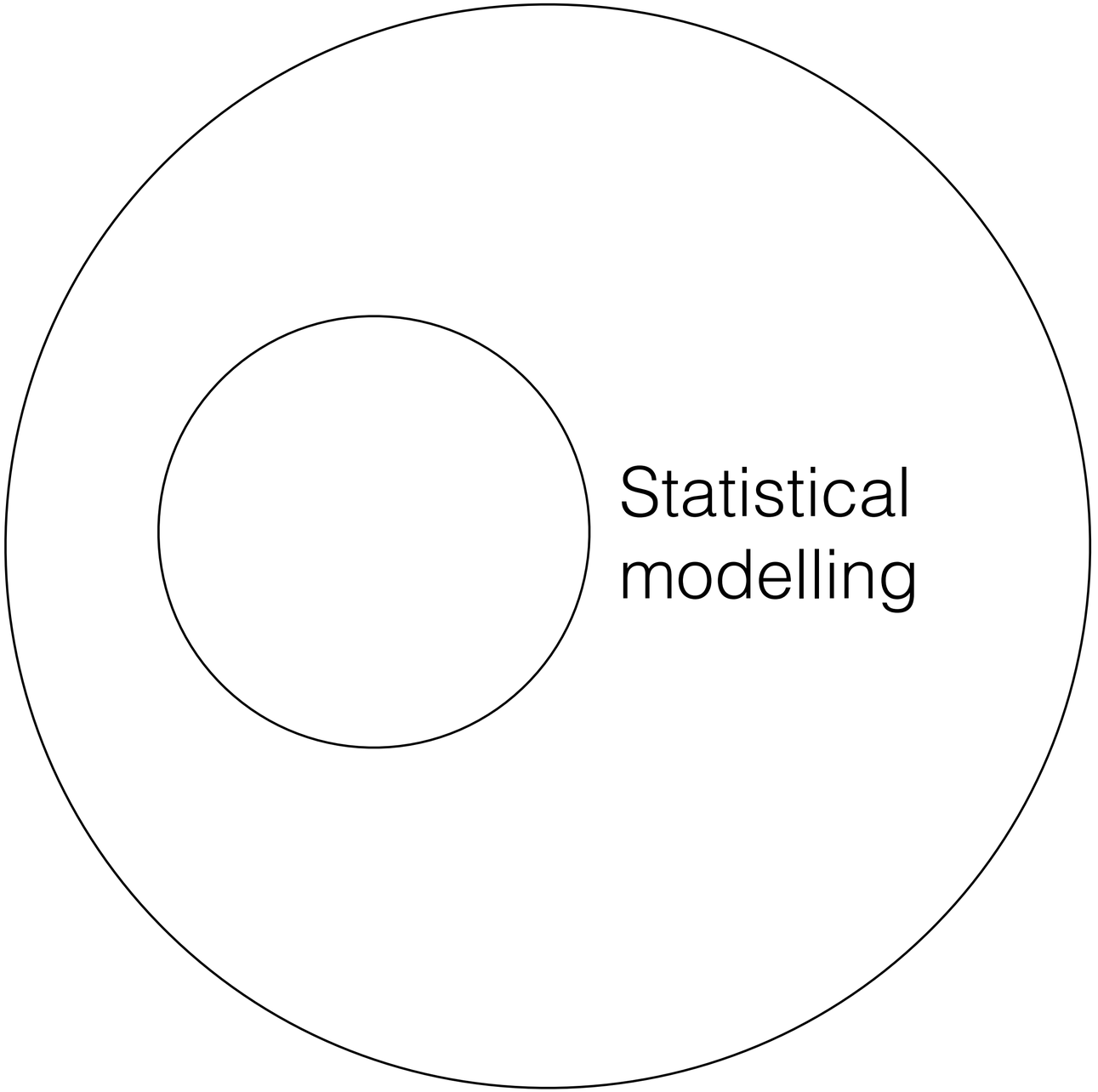
A model of what’s in this photo



model city

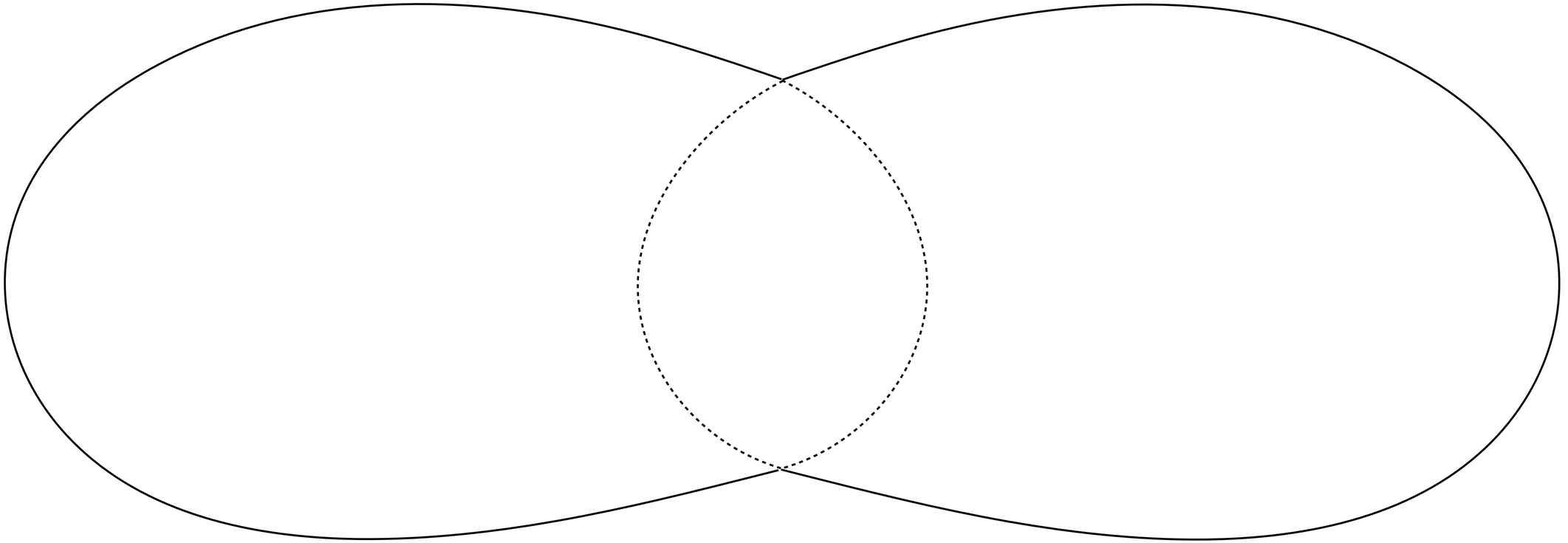
Image: Ittyblox

In theory,



because statistics
uses maths.

In practice,

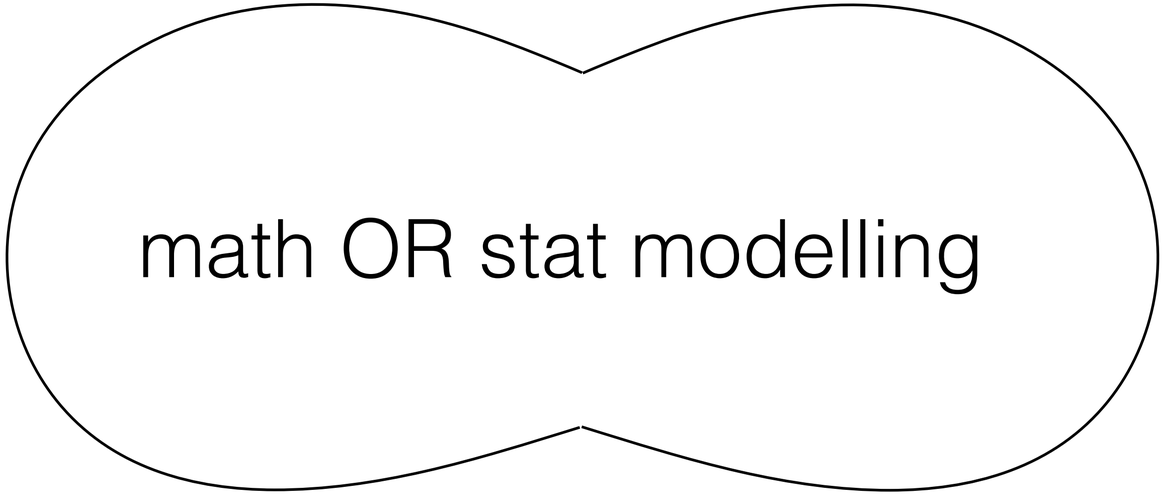


“Mathematical modelling” “Statistical modelling”

Math and stat modelling: similarities

both involve

- making a model that involves maths,
- *parameterising* the model: coming up with a possible way of expressing the parameters that control the model
- often thinking about what the parameters should be in light of current knowledge
- learning from what the model tells you.



Math modelling: *if this then what*

- *if this*: pick the structure of the model, pick values for the parameters controlling the model.
- *then what*: what does the model imply given those assumptions? Often: what dynamic behaviour results.
- Model may or involve probability (‘stochastic’) or not (‘deterministic’)

Stat modelling: which *if?*

- Model the data-generating process
- Learn about the parameters of that process, using the data it has generated
- Model requires probability

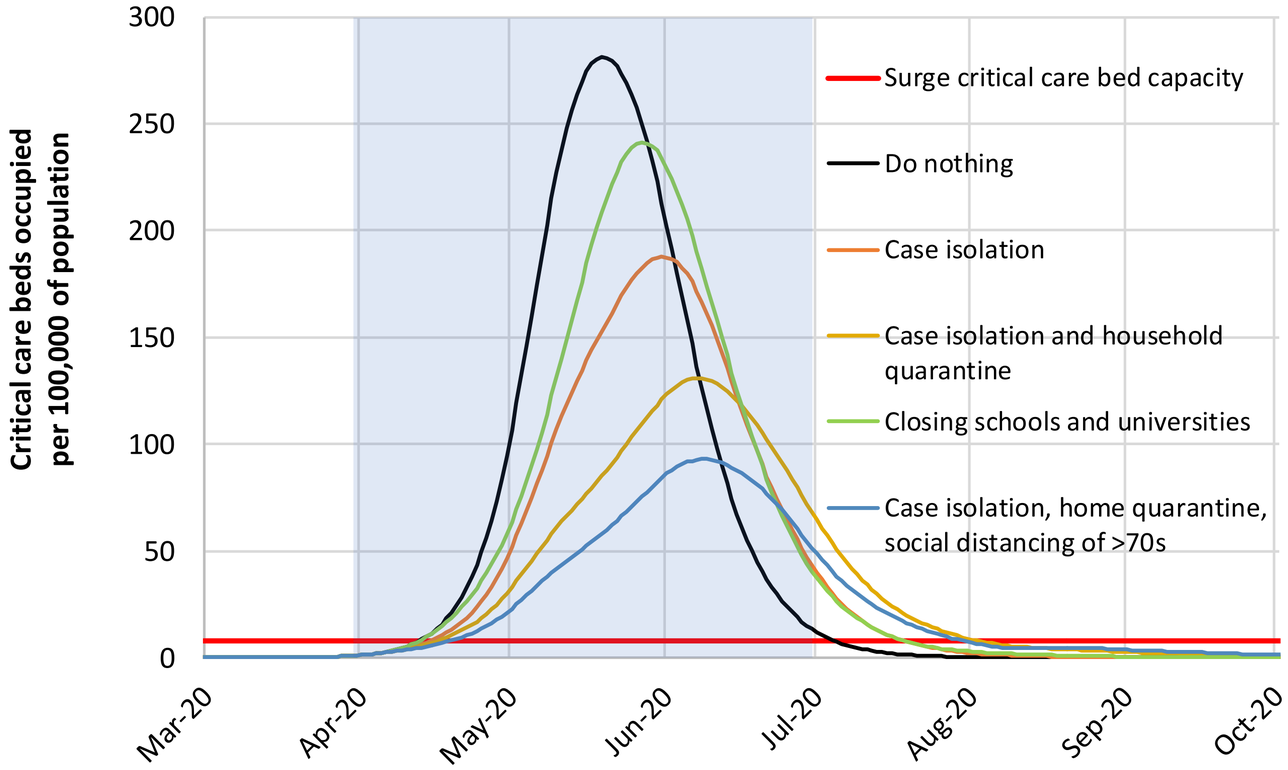
$$P(y_i \mid \hat{y}_i, \sigma^2) = N(y_i \mid \hat{y}_i, \sigma^2)$$

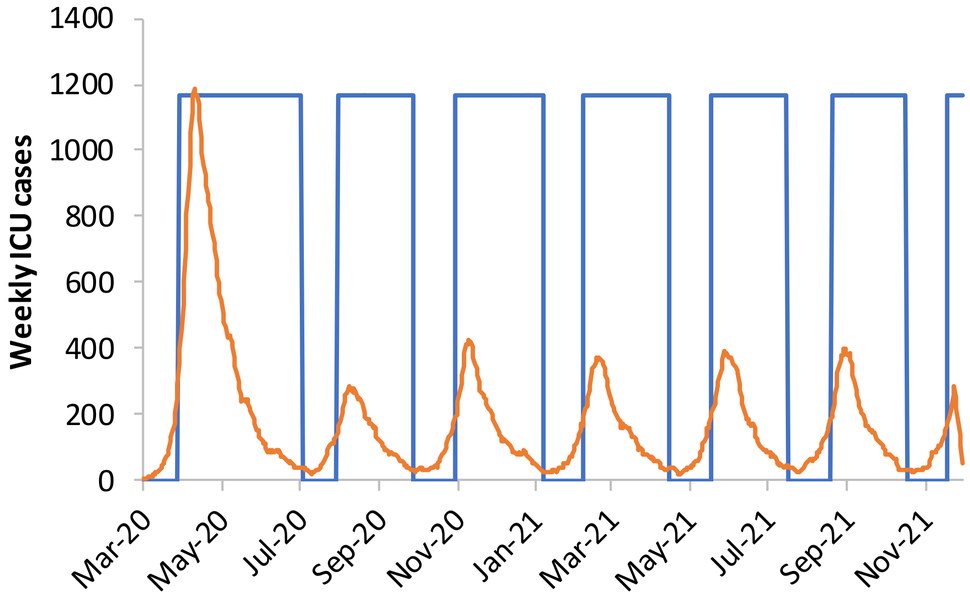
$$\hat{y}_i = mx_i + c$$

Explore the relationship between y, m, x and c

Fit to data, learn values of m, c and σ

Exploring y = mx + c… sounds a bit easy and useless no?

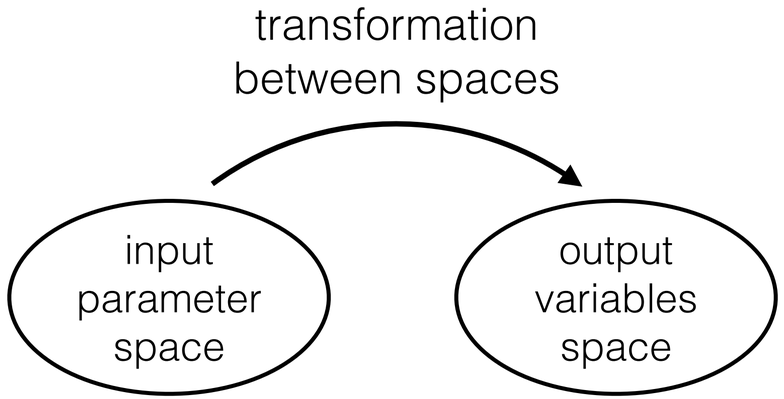




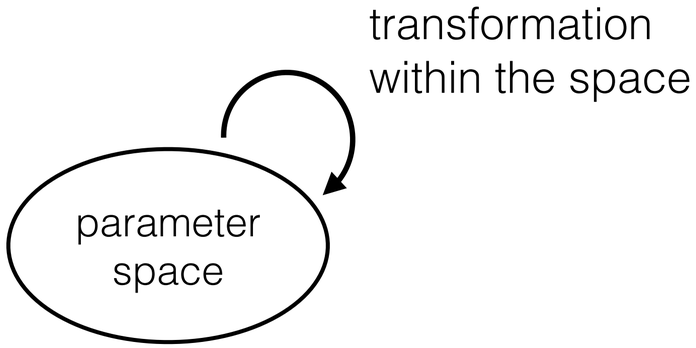
Ferguson et al 2020, “Imperial Report 9”

Math vs stat modelling: Bayesian view

A mathematical model is a transformation from the input parameter space to some other space of output variables, by modelling the relation between spaces



A statistical model is a transformation between two distributions defined on the same parameter space (from the prior to posterior) by modelling P(data | parameters)

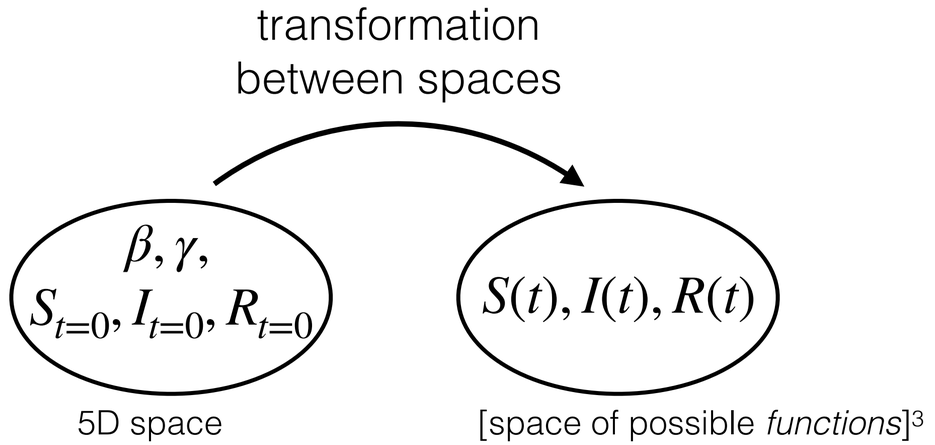


(Only for Bayesians because Frequentists can never talk about the probability of a parameter.)

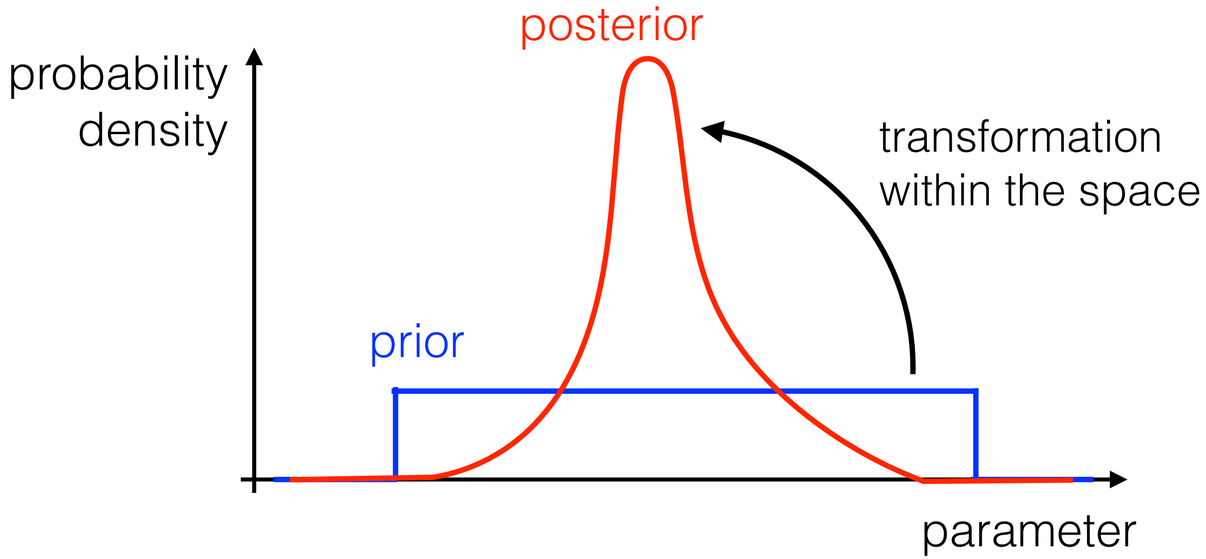
Math vs stat modelling: Bayesian view examples

SIR math model:

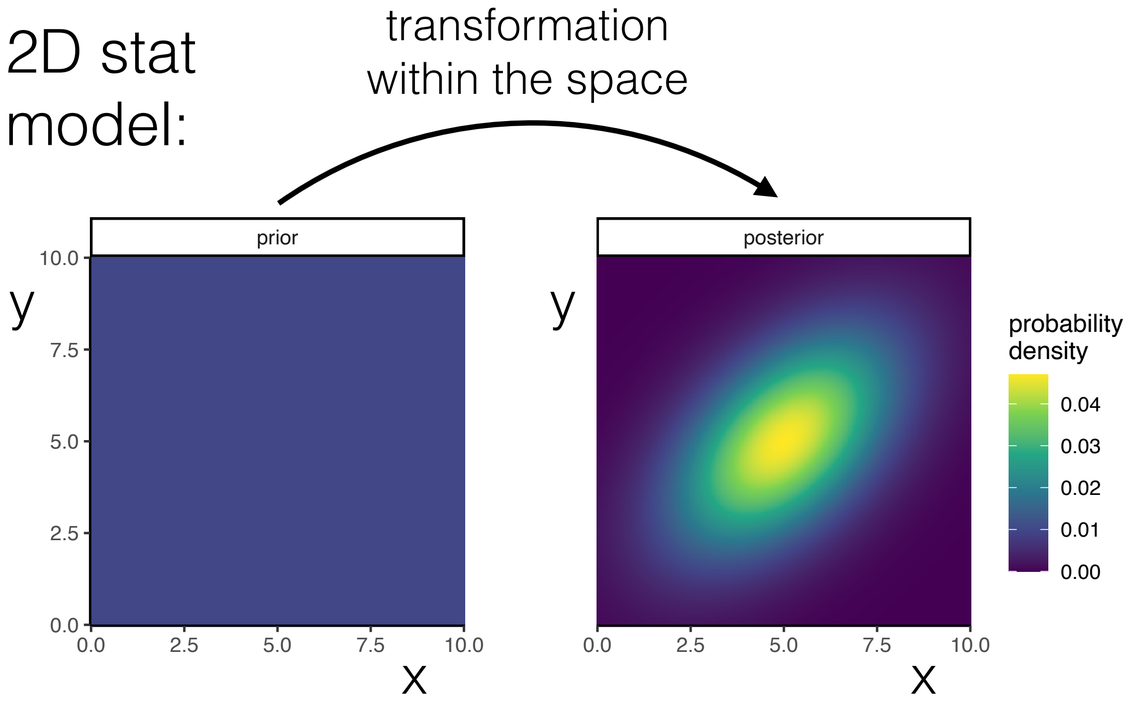
$$\frac{dS}{dt} = -\frac{\beta IS}{N}$$
$$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$



1D stat model:



2D stat model:



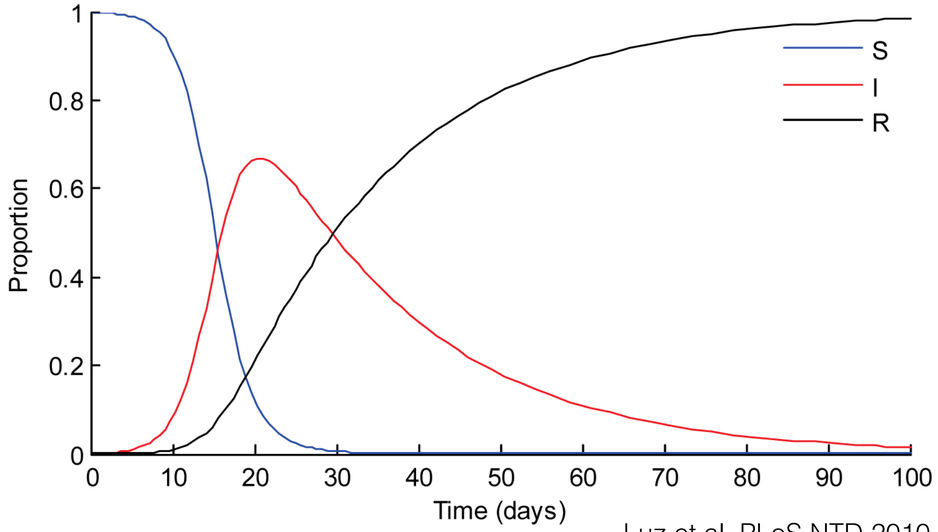
Deterministic vs stochastic math models

Deterministic SIR:

$$\frac{dS}{dt} = -\frac{\beta IS}{N}$$

$$\frac{dI}{dt} = \frac{\beta IS}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$



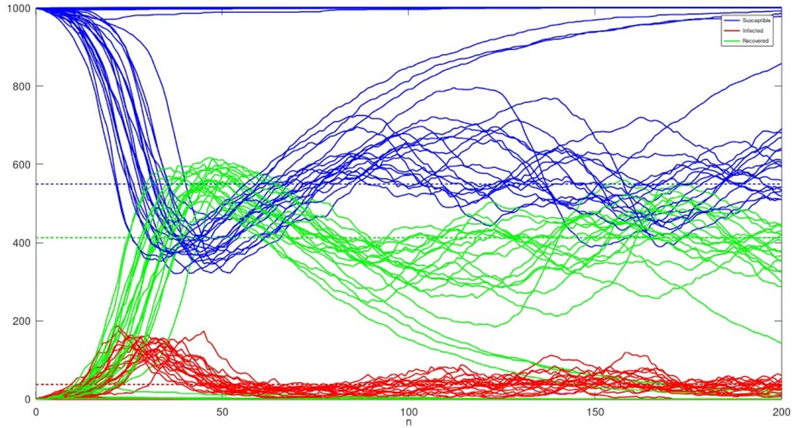
Luz et al, PLoS NTD 2010

Stochastic models:
Instead of specifying derivatives, specify a probability distribution for the finite change in each variable at each finite time step.

$$P(\delta S) = \ldots$$

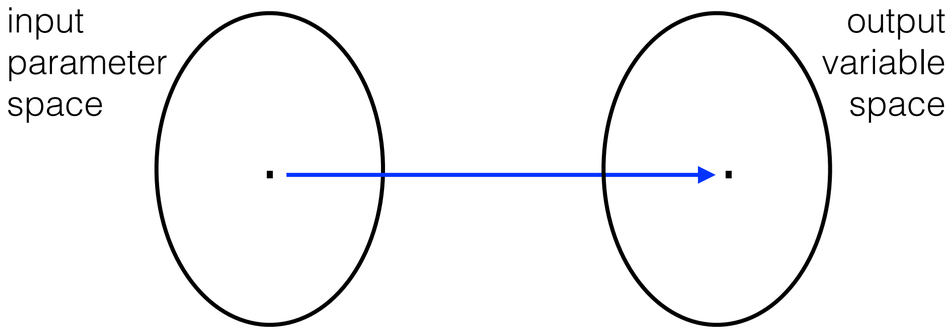
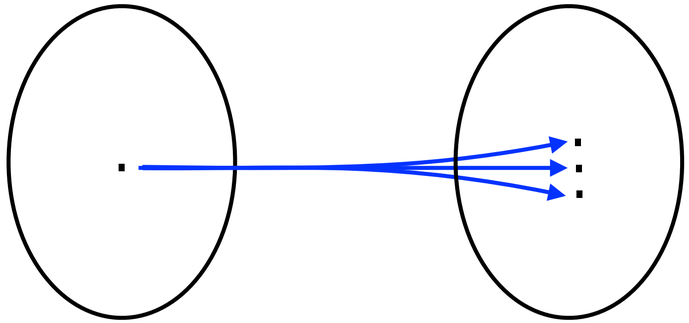
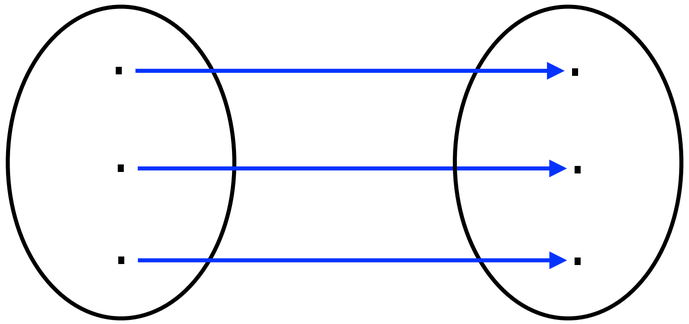
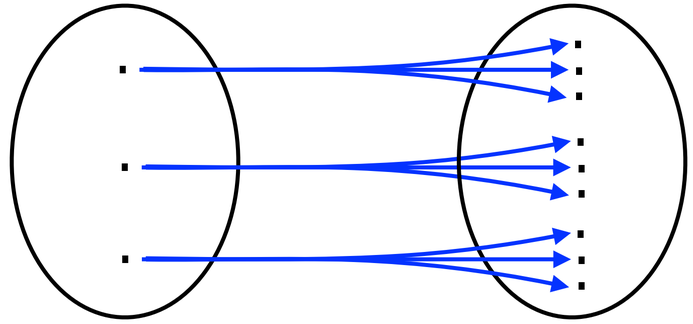
$$P(\delta I) = \ldots$$

$$P(\delta R) = \ldots$$



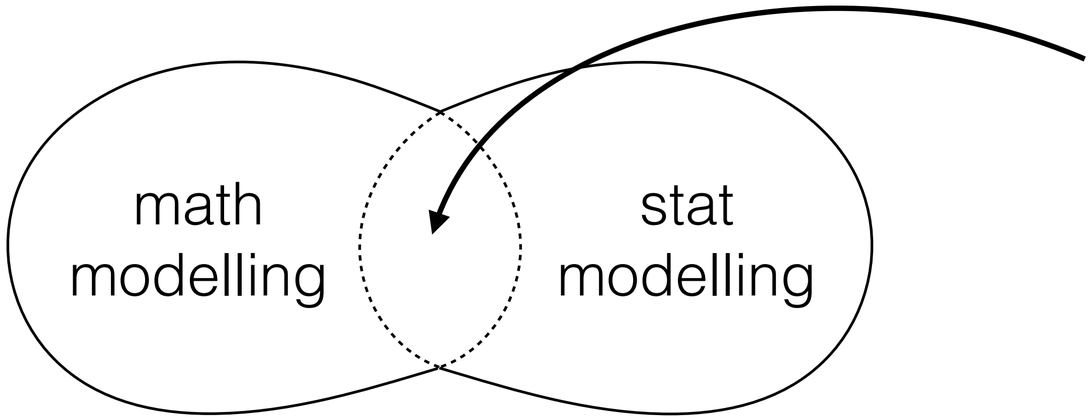
Mark Panaggio video

Math model mappings & uncertainty

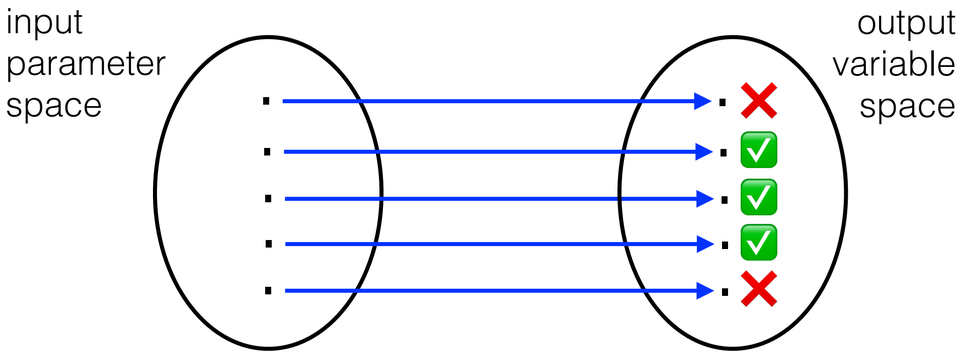
	Deterministic model	**Stochastic model**
Input = 1 parameter point	 Output = 1 point, capturing no uncertainty	 Output = distribution, capturing inherent/ stochastic/ontological uncertainty in the process
Input = distribution over parameters	 Output = distribution, capturing epistemological uncertainty in the parameters	 Output = distribution, capturing both inherent/ stochastic/ontological uncertainty in the process and epistemological uncertainty in the parameters

Generally best not to say ‘confidence intervals’ for this uncertainty. Instead e.g. “the central 95% of uncertainty capturing…”

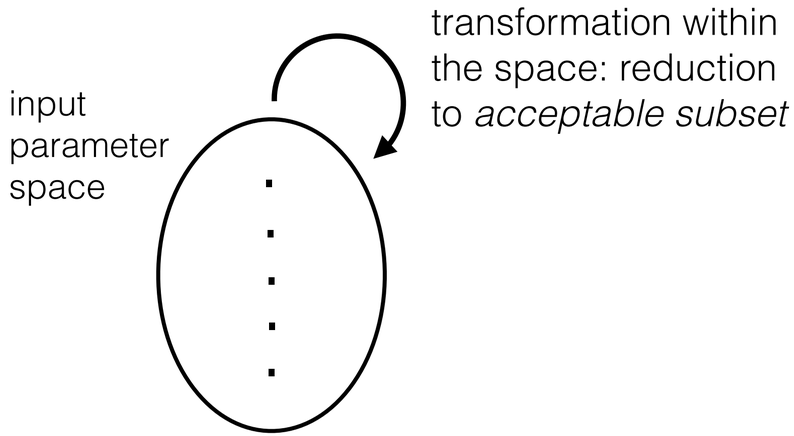
The grey area



Calibration of a math model is the process of choosing one or more points in the input parameter space, based on whether their transformation to the output variable space matches data.



is equivalent to



Calibration is usually done as a preliminary step to counterfactual modelling: first asking “which if” for some parameters, then asking “if this then what” for other parameters. e.g. first “what parameters describe pathogen transmission so far”, and then “if we intervene, how much will we reduce transmission”.

Part 3: Revisiting counterfactuals:
a cross-cutting concept in saying anything

Three tasks in data science:

1. Description (e.g. summaries, clustering)
2. Prediction (inputs → outputs)
3. Counterfactual prediction / causal inference (what if)

Hernán, Hsu & Healy 2019

Think in terms of counterfactuals

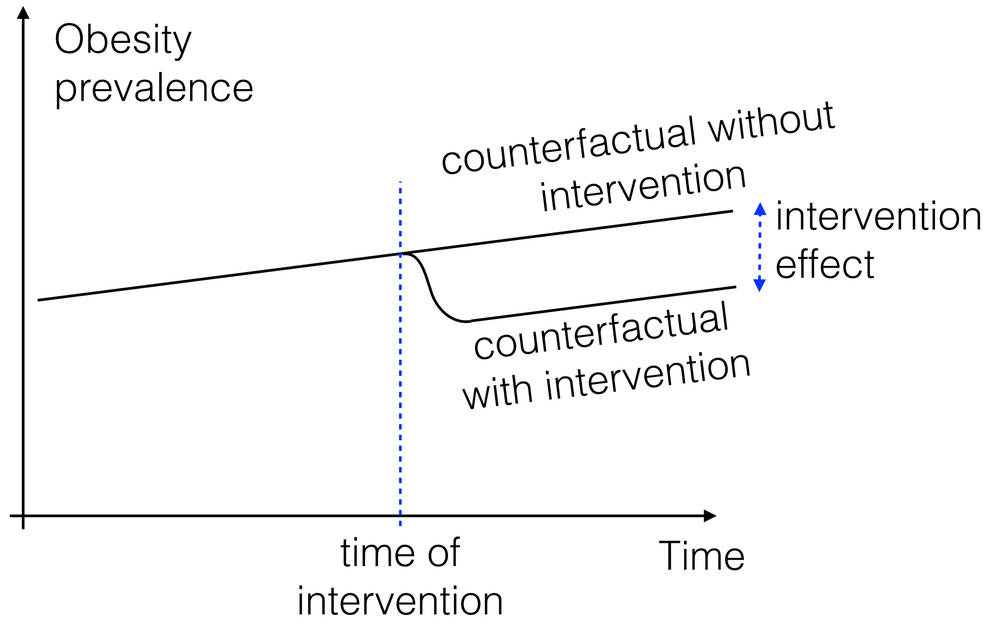
Counterfactuals / scenarios / potential outcomes: things that could have happened (past) or could happen (future).

An intervention: an action that causes two counterfactuals to begin diverging from that point in time.

A comparison of precisely defined counterfactuals is necessary to:

- define causality and related words like “affects”, “because of” (i.e. attribution). e.g. “obesity causes poor health” is an ill-defined statement because the intervention is not specified. Reducing obesity by chopping off arms would not improve health.

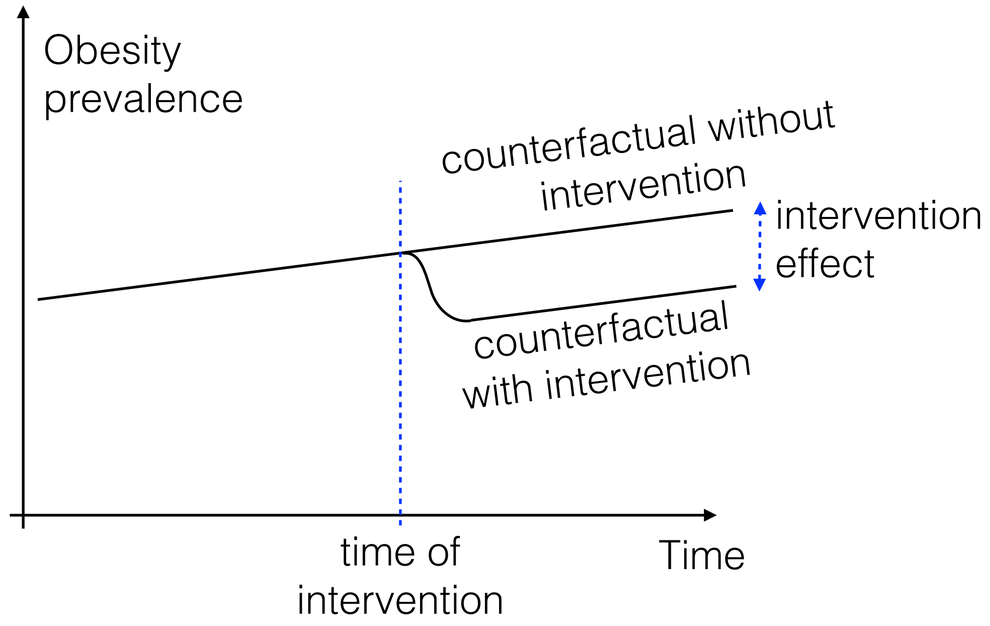
- define the meaning of some common but loaded words like *should*: “we should do X” rests upon defining some measure of value and finding this is higher when doing X than when doing some precisely defined alternative to X.



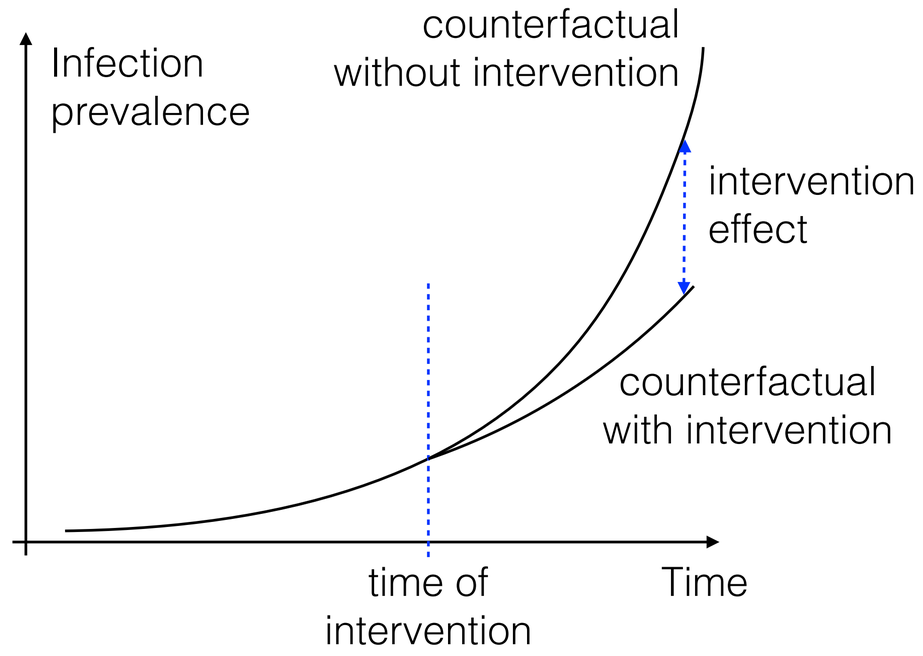
Obesity example credit: Christophe Fraser, I think

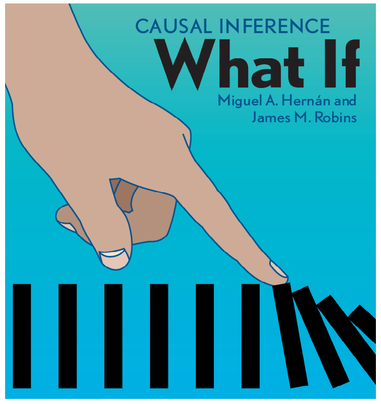
Interacting systems

Non-communicable diseases:



Communicable (infectious) diseases:





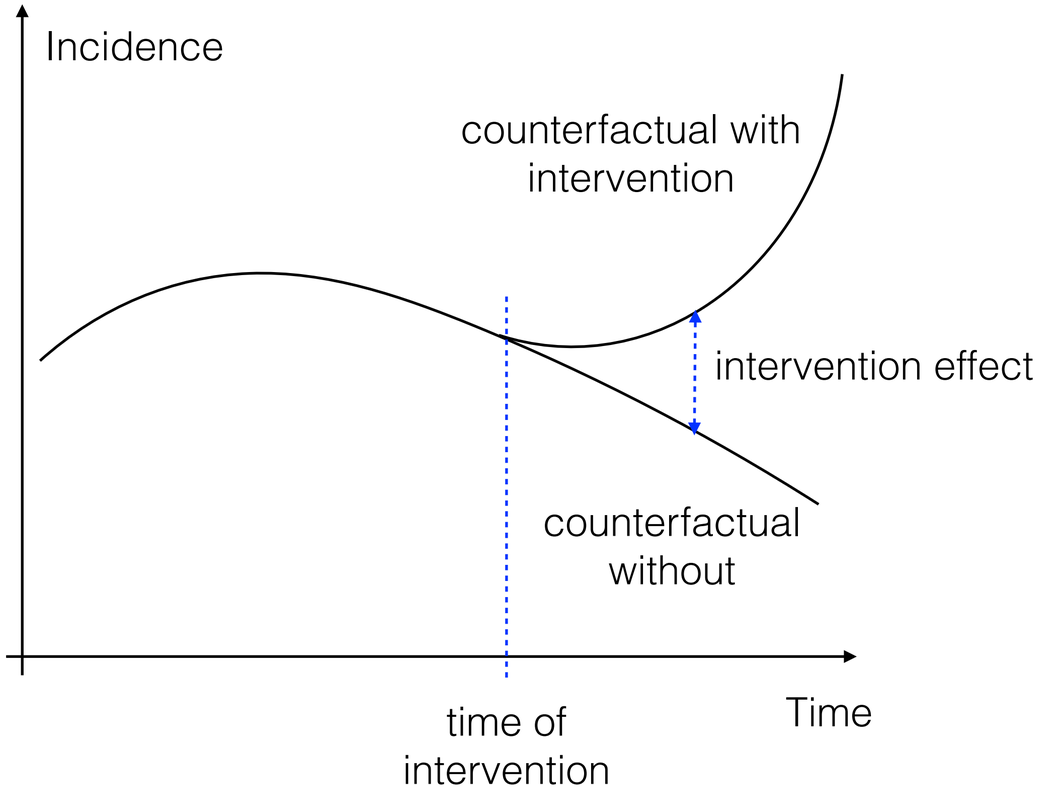
Interventions in interacting systems can put you on a diverging path, taking you far away from the ← unseen counterfactual

"The intervention failed to control spread" ✅ but 🙄

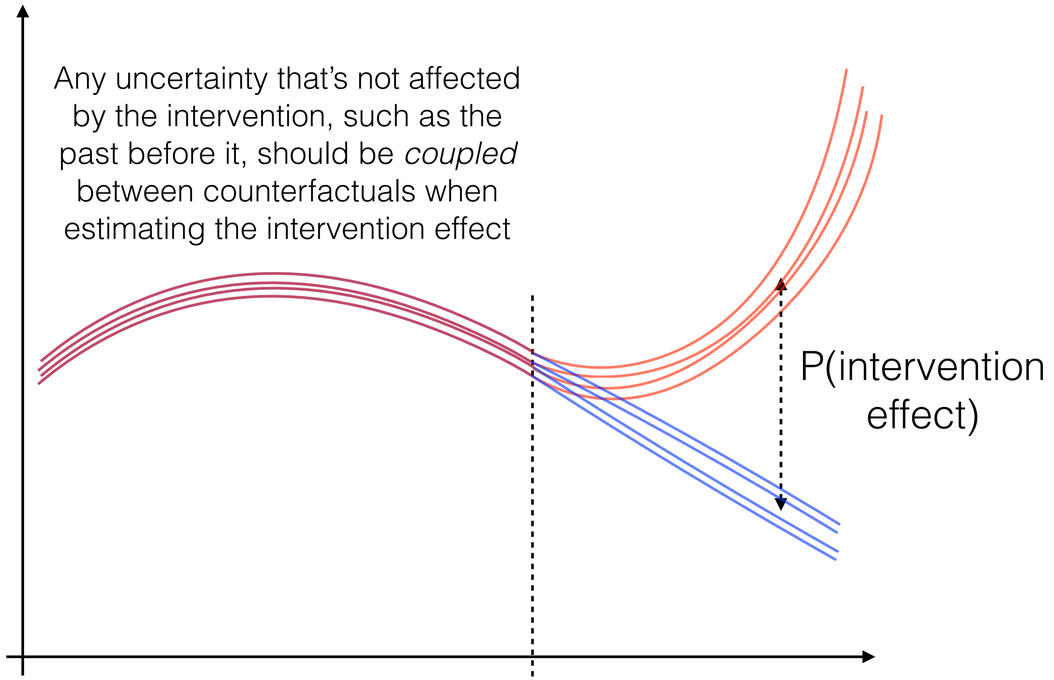
"Things got worse after the intervention" ✅ but 🙄

"Things got worse because of the intervention" ❌❌❌

Certain dynamics (precisely known and deterministic)



Uncertain dynamics (imprecisely known and/or stochastic)

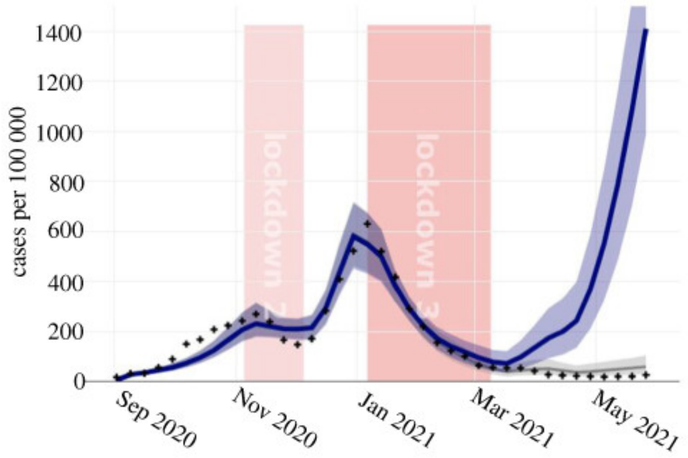


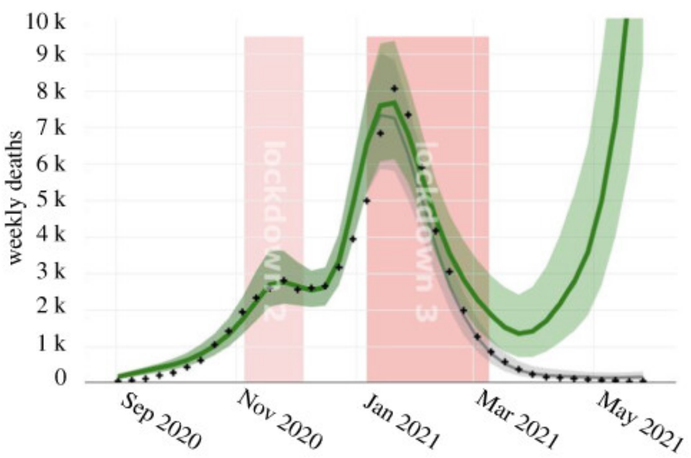
$$\text{Cumulative intervention effect on X} = \int (\text{effect of intervention on } dX/dt)\, dt$$

$$\text{e.g. cumulative cases averted} = \int (\text{incidence in factual - incidence in counterfactual})\, dt$$

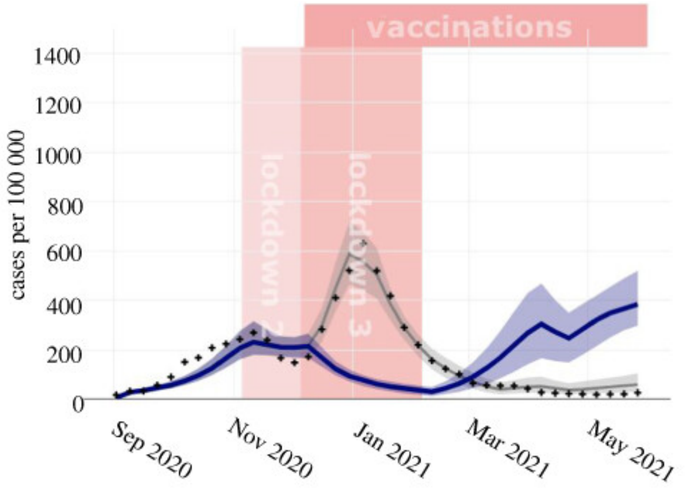
cases

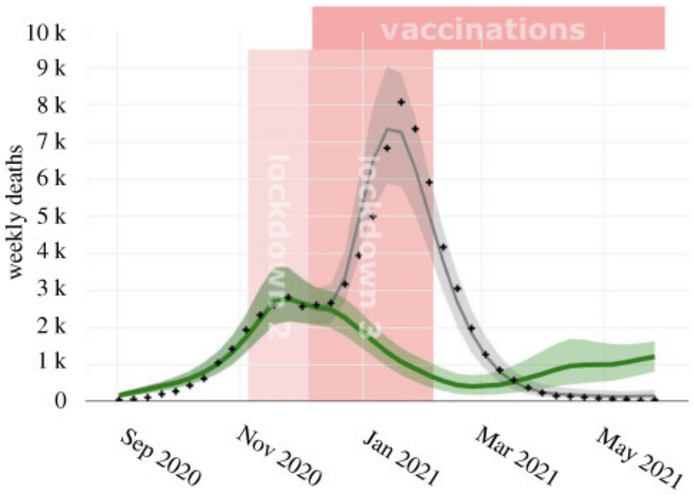
deaths





Factual vs counterfactual comparison 1:
what if we'd had no vaccines?





Factual vs counterfactual comparison 2:
what if we'd done lockdown 3 earlier?

"total deaths would have been approximately 30 k (24 k–38 k) lower between January and May 2021"

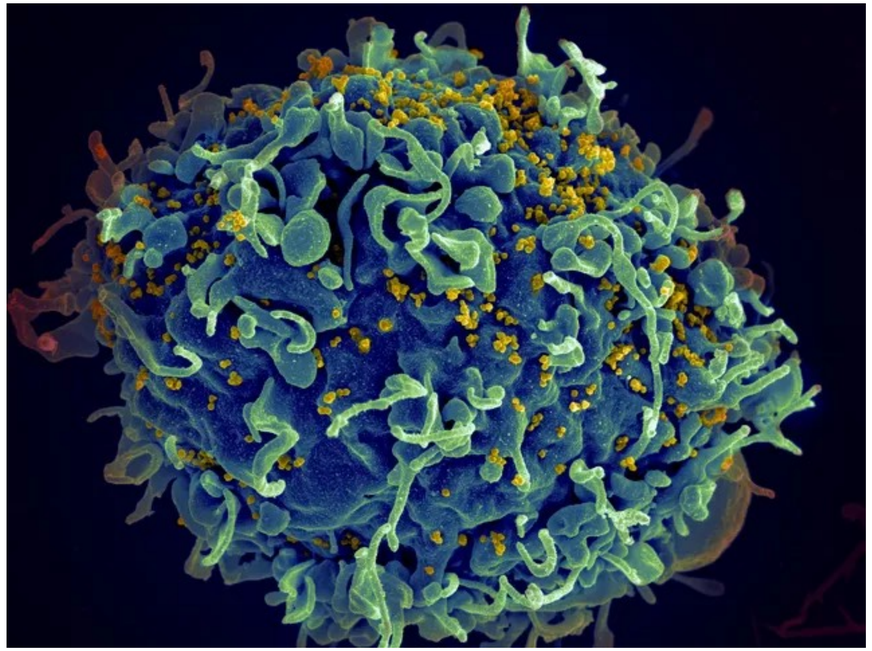
Points = data
Grey = model fit to data (the factual)
Blue = counterfactual model, cases
Green = counterfactual model, deaths

R Hinch et al, PLoS CB 2021
R Hinch et al, PTRSA 2022

Part 4: Case study with random effects / multilevel models: HIV immune system decline

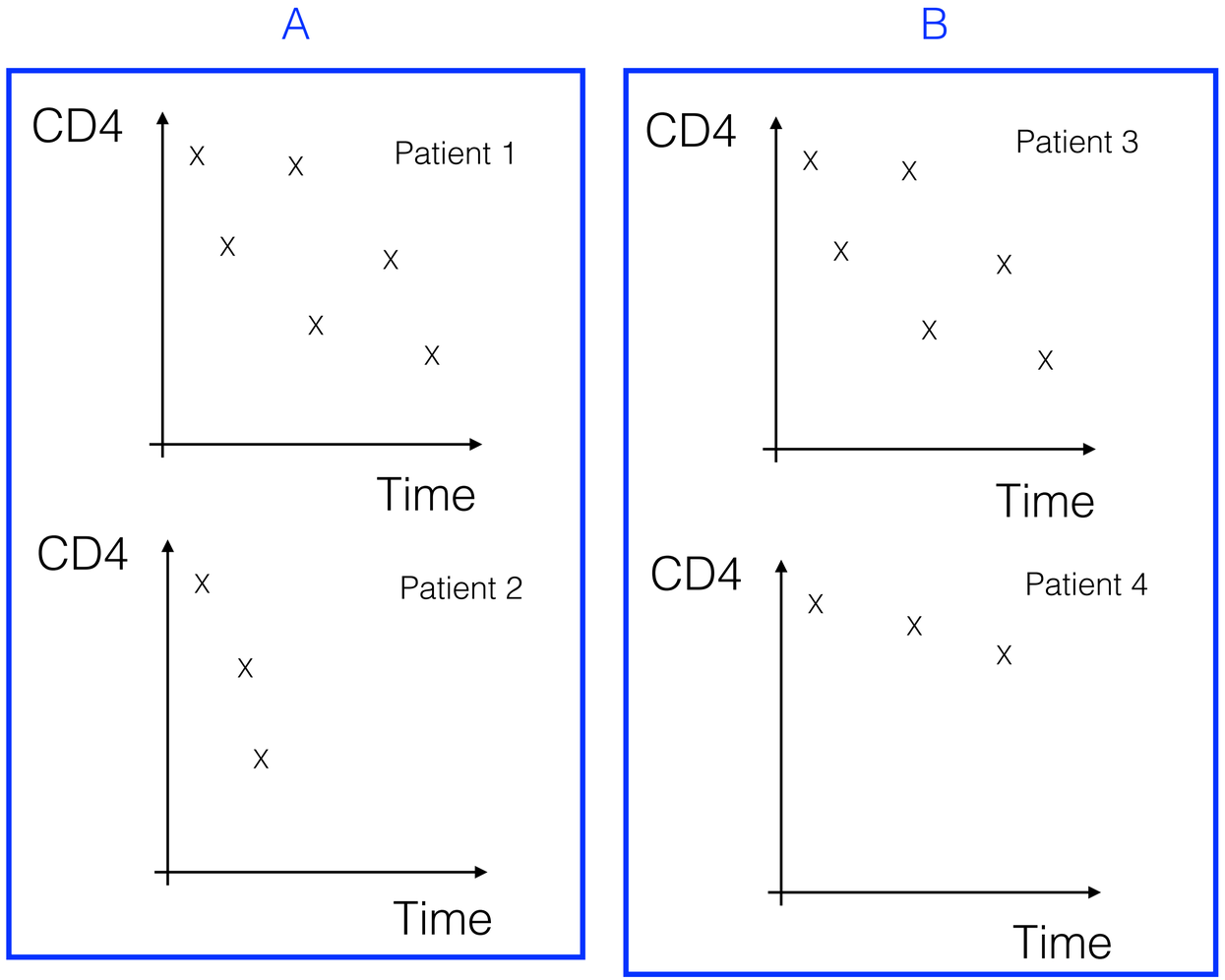
CD4+ T cell decline

HIV virions kill CD4+ T cells, causing their number to decline until a person living with HIV starts antiretroviral treatment.



Yellow = HIV virions
Image: US NIH

Imagine we want to compare CD4 decline between two groups of patients, A and B.

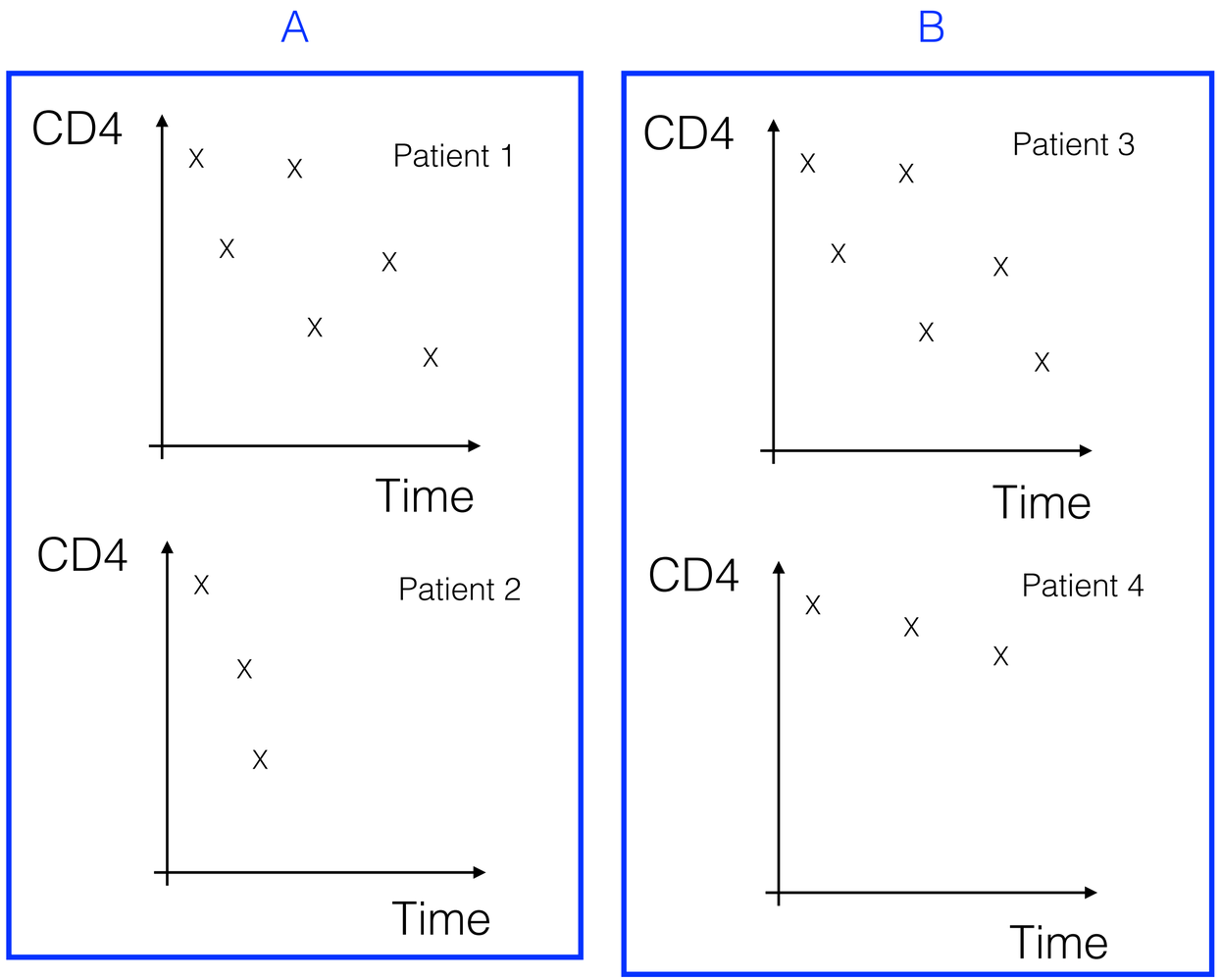


Full pooling of data?

Full pooling = treating all data from within the same group as coming from the same distribution.

Bad idea: there are systematic differences between patients in the same group. Ignoring these is under-fitting the data.

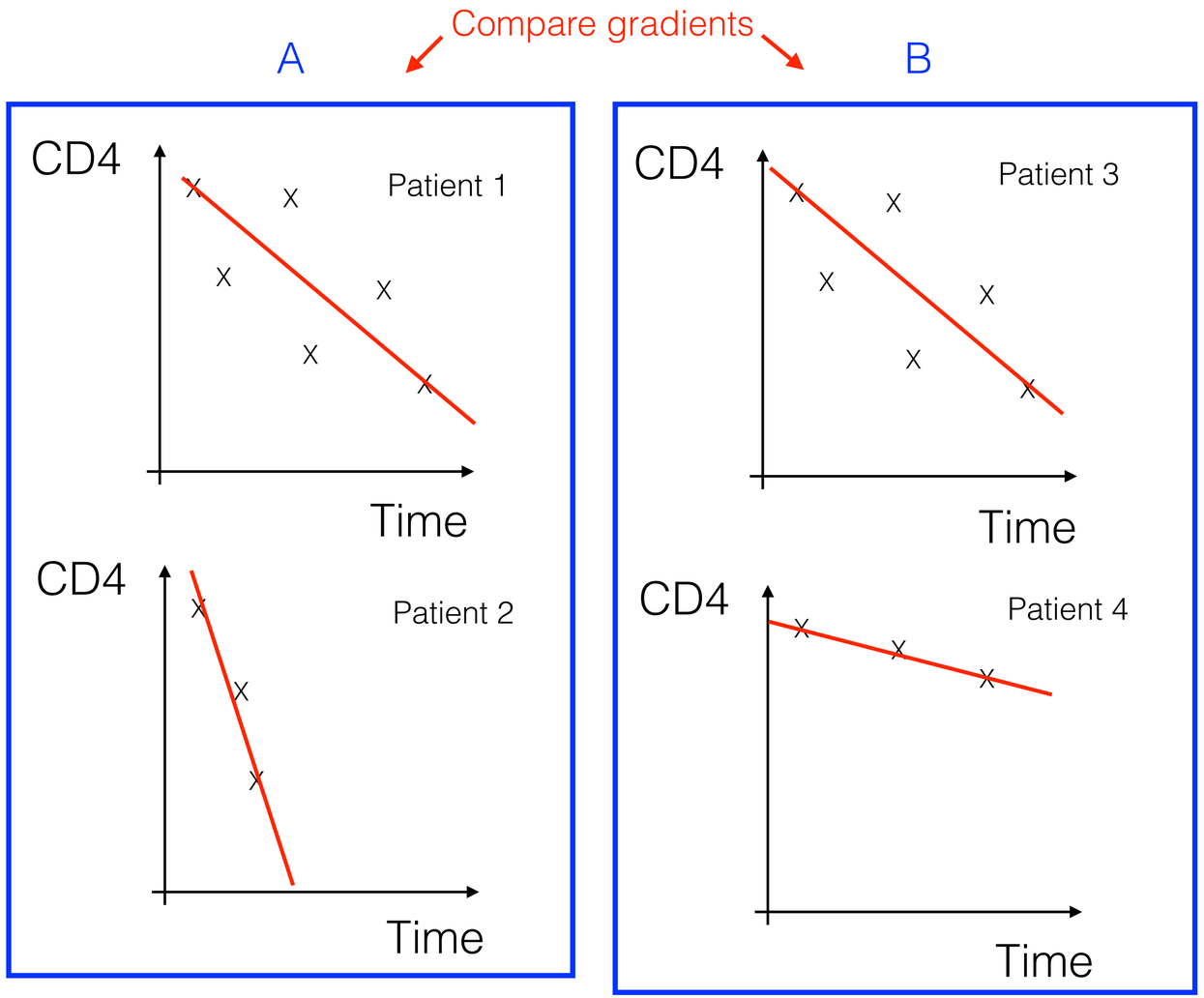
If we want to predict a new observation at the same point for two different individuals in the same group, we should not make the same prediction for both.



No pooling of data?

We could estimate the **per-patient decline** for patients 1-4 separately. However,

i. these aren't directly of interest: we'd need a second step comparing these estimates for A vs B;
ii. silly to do estimation for different patients completely independently, i.e. saying that what we learn from all *other* patients is wholly uninformative for *this* patient.

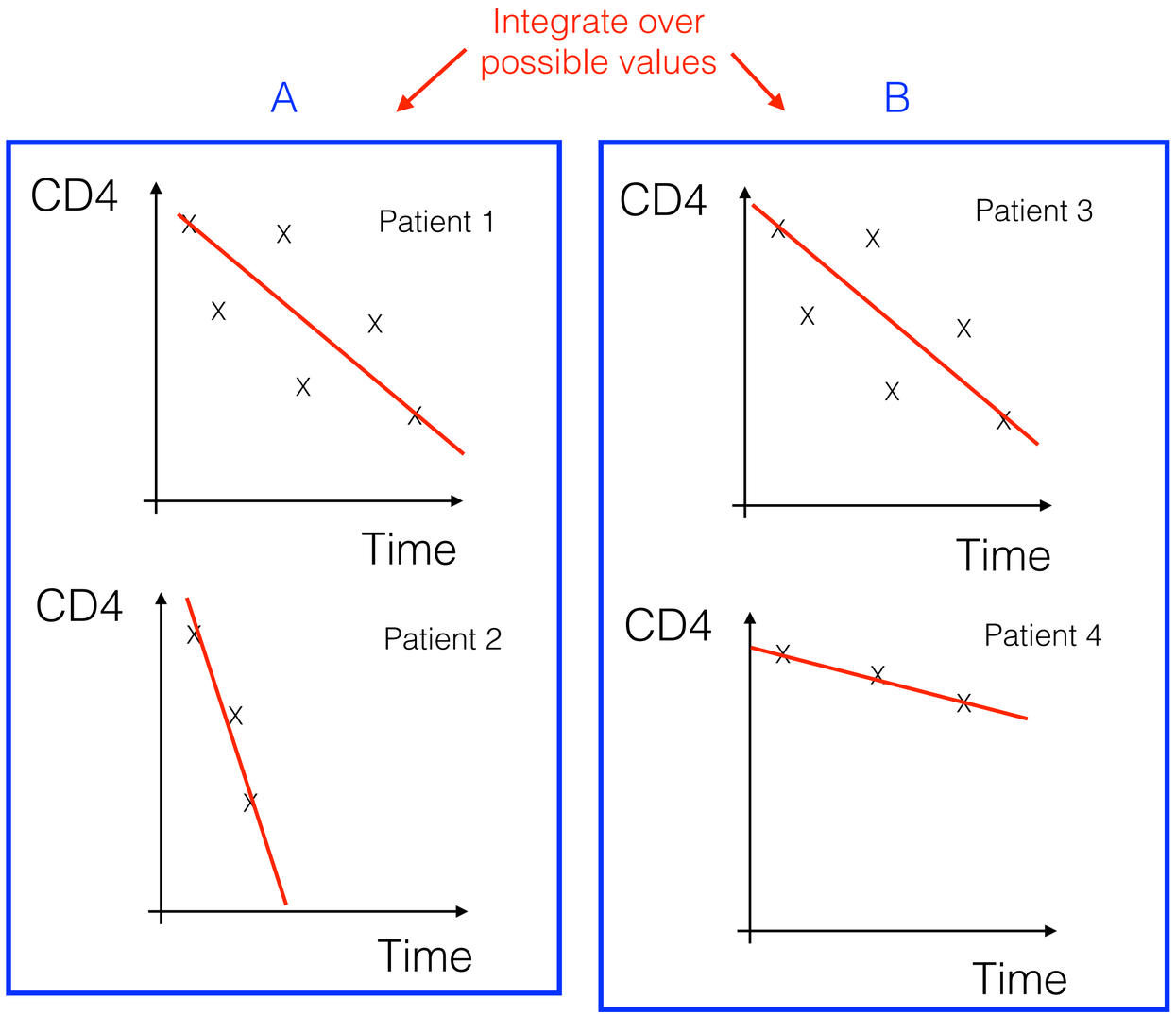


Group-level parameters as *nuisance parameters*

Group-level parameter values are effectively *nuisance parameters*. Per the law of total probability, they should be integrated over weighted by how likely they are. But how likely are they? We need to specify a model.

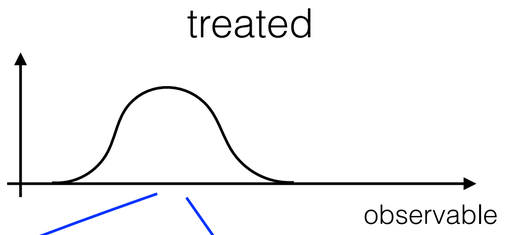
Generally, assume the value for each group has the same distribution of others: assume exchangeability of patients. This shares information between patients - “partial pooling” - instead of examining each one independently of the others. We then estimate the parameters of this distribution.

Random effects for a Bayesian: any parameters whose prior distribution is controlled by parameters that are also estimated.

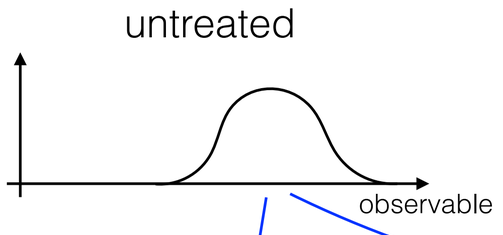


The hierarchy

Terminology change:
A, B → treated, untreated
Patient → unit

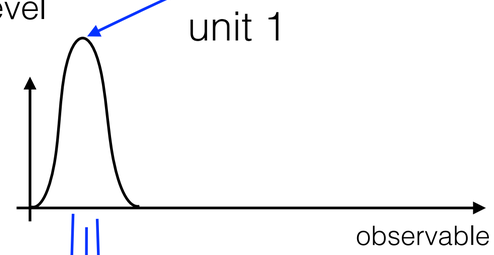


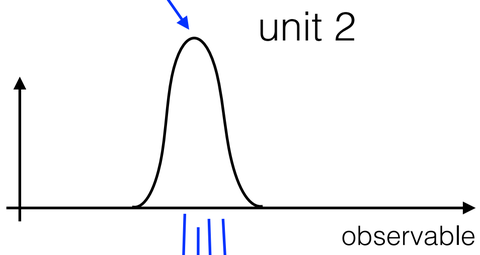
difference = treatment effect

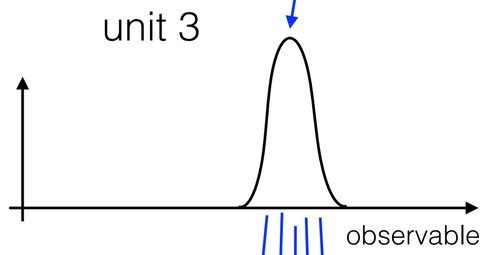


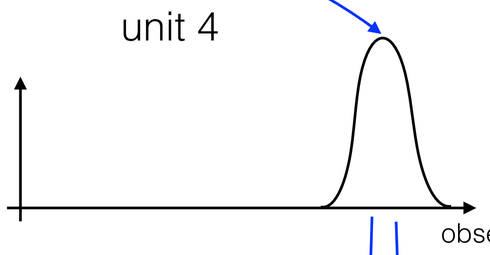
The treatment level: the effect of the thing of interest on the observable. This specifies P(unit-level parameters | treated or untreated)

The unit level: comes from the treatment level. Specifies P(within-unit data | unit-level parameter)

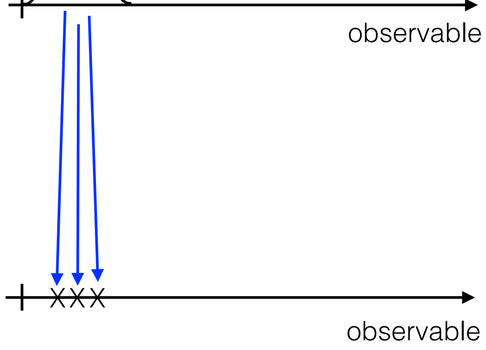


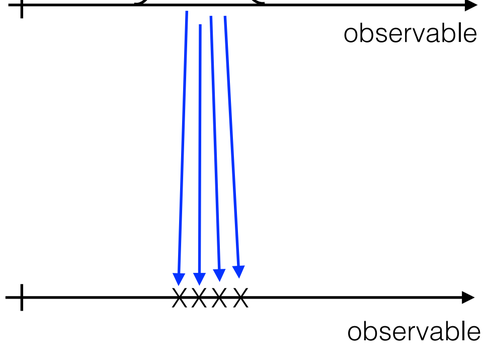


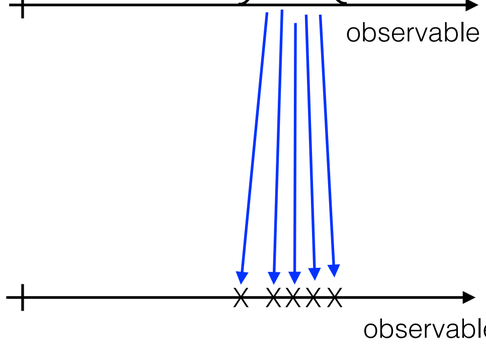


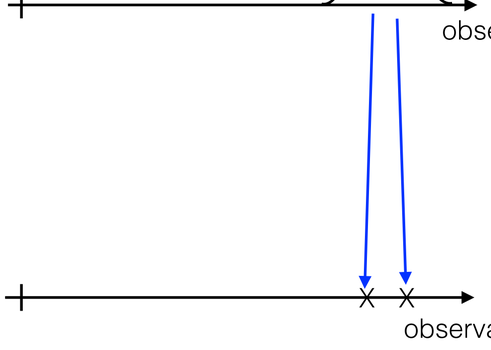


Data within each unit is drawn from its own distribution









The unit-level parameters (ULPs, defining a distribution for each unit) are an intermediate between the data and the object of interest: the distribution for treated vs untreated.

$$P(\text{data} \mid \text{treatment effect}) = \int P(\text{data} \mid \text{ULPs})\, P(\text{ULPs} \mid \text{treatment effect})\ \ d\,ULPs$$

Wymant et al, Science 2022

beehive.ox.ac.uk/hiv-lineage

FINANCIAL TIMES

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Medical science + Add to myFT

New HIV variant discovered in the Netherlands

deVerdieping Trouw

TROUW VRIJDAG 4 FEBRUARI 2022

Wat ik niet weet, weet ik niet

bisschop Gerard de Korte, de Verdieping 8|9

WWW.TROUW.NL | 80STE JAARGANG NR 23700 | E-MAIL VIA WWW.TROUW.NL/SERVICE | POSTBUS 859 1000 AW AMSTERDAM | REDACTIE 020-562 9444 | KLANTENSERVICE 088-056 1588 | BEZORGING 088-056 1599

Hiv-variant biedt les voor corona-aanpak

npr

Discovery of HIV variant shows virus can evolve to be more severe — and contagious

EL PAÍS

LA PANDEMIA DE VIH/SIDA >

Descubierta una nueva variante del VIH más contagiosa y virulenta

El hallazgo, en un centenar de personas en Países Bajos, es una constatación de que los virus pueden evolucionar hacia formas más agresivas

NBC NEWS

A 'highly virulent' HIV strain is 'no cause for alarm,' scientists say

The newly identified, more infectious strain of HIV likely began circulating in the Netherlands in the 1990s and responds well to treatment, according to researchers.

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Identifying a more infectious HIV variant

A new but treatable variant of HIV has been uncovered in the Netherlands. A reminder that as viruses evolve, even after 40 years they can become more virulent and infectious.

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30 minutes

SPIEGEL Wissenschaft

Zufallsfund bei Studie

Aggressivere Variante von HIV in den Niederlanden entdeckt

Bei einer Langzeitstudie sind Wissenschaftler einer bisher unbekannten Variante des HI-Virus auf die Spur gekommen. Sie ist wohl leichter übertragbar. Dennoch geben Experten Entwarnung.

NIEDERLANDE

Aggressivere HIV-Variante entdeckt

Im Rahmen einer Langzeitstudie ist ein Forschungsteam in den Niederlanden auf eine bisher unbekannte Variante des HI-Virus gestoßen, die unter anderem leichter übertragbar ist. Ein Grund zur Sorge soll diese aber nicht sein.

ALJAZEERA News Ukraine war Features Economy Opinion Video

Is there a 'new' HIV variant?

The Human Immunodeficiency Virus (HIV) is one of the fastest mutating viruses ever studied. Now a team of scientists, led by Oxford University, with key contributions from the Dutch HIV Monitoring Foundation, have identified a strain of HIV, being called the "VB" variant, which has been found to be highly virulent.

Forbes

Newly Discovered HIV Variant Can Cause Patients To Develop AIDS Twice As Fast, Researchers Say

UNAIDS

PRESS STATEMENT

Identification of fast-spreading HIV variant provides evidence of urgency to halt the pandemic and reach all with testing and treatment

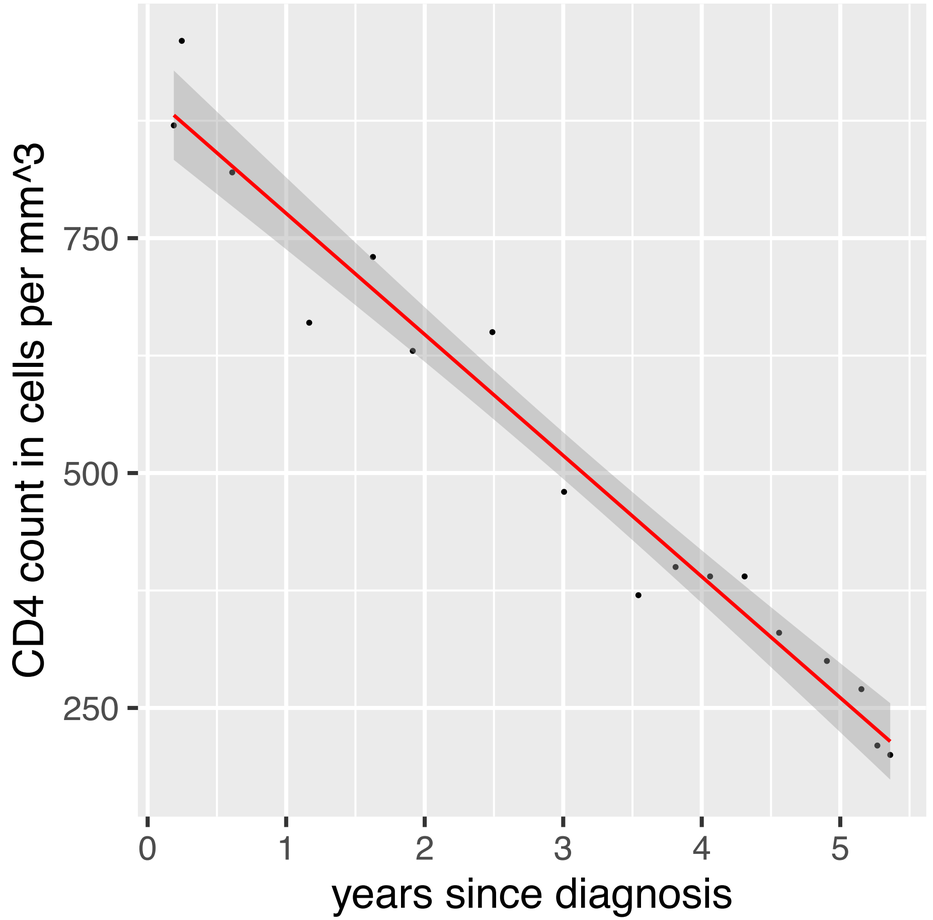
TF1

Un nouveau variant du VIH plus virulent identifié aux Pays-Bas, mais "pas de raison de s'alarmer"

Effect of VB variant on CD4 before ART: model

$$y = mx + c$$

y



x

Let *m* and *c* be different for:

- VB and not-VB (fixed effect)
- males and females (fixed effect)
- each age category (fixed effect, *c* only)
- different viral loads (optional, fixed effect, assumed linearly dependent on log(VL))
- every individual (random effect: variation constrained to be normally distributed)

Terminology apology: “the lineage” = the VB variant

```
lmm <- lmer(data = df_cd4_decline,
            # Model CD4 counts as...
            cd4_count ~
              # a linear function of time,
              years_since_diagnosis +
              # with a fixed effect of age on the intercept,
              age_diagnosed +
              # a fixed effect of sex on both intercept and slope,
              years_since_diagnosis * sex +
              # a fixed effect of the lineage on both intercept and slope,
              years_since_diagnosis * in_lineage +
              # and a random effect of the individual on both intercept and slope
              (years_since_diagnosis | id_paper))
```

github.com/ChrisHIV/hiv_vb_variant

```
lmer(cd4_count ~ years_since_diagnosis +
                 age_diagnosed +
                 years_since_diagnosis * sex +
                 years_since_diagnosis * in_lineage +
                (years_since_diagnosis | id))
```

Revisit this slide for practical exercise 3b

*n*th CD4 count for individual *i* is normally distributed around some expected value with a variance parameter common to all observations

$$P(y_{i,n} \mid y_{i,n}, \epsilon^2) = N(y_{i,n} \mid \bar{y}_{i,n}, \epsilon^2)$$

For individual *i*, the expected CD4 count changes linearly with time ($x_{i,n}$ = time of *i*'s *n*th CD4 count)

$$\bar{y}_{i,n} = m_i x_{i,n} + c_i$$

The slope for *i*
G_i = sex of *i* (0 or 1), γ = effect of sex on slope
L_i = lineage of *i* (0 or 1), λ = effect of lineage on slope
s_i = random effect of "being i" on slope

$$m_i = m + \gamma G_i + \lambda L_i + s_i$$

The intercept for *i*
Γ = effect of sex on intercept
Λ = effect of lineage on intercept
$A_{i,age}$ = 0-or-1 coding of *i*'s age group
α_{age} = effect of age group on intercept
r_i = random effect of "being i" on intercept

$$c_i = c + \Gamma G_i + \Lambda L_i + \sum_{\text{ages}} \alpha_{\text{age}} A_{i,\text{age}} + r_i$$

$$P\left(\begin{pmatrix} r_i \\ s_i \end{pmatrix} \mid \sigma_r, \sigma_s, \rho\right) = N\left(\begin{pmatrix} r_i \\ s_i \end{pmatrix} \mid \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_r^2 & \rho\sigma_r\sigma_s \\ \rho\sigma_r\sigma_s & \sigma_s^2 \end{pmatrix}\right)$$

The random effects are normally distributed around zero. Correlation ρ ∈ [-1, 1] between the effects on slope and intercept for same individual i; no correlation between random effects for different individuals *i* and *j*.

Bayesian implementation of the same model with Stan

```
data {
  ...
}

parameters {
  ...
  real slope_pat_scale;
  real inter_pat_scale;
  real rho;
  vector[2] inter_and_slope_per_pat_unscaled[num_pats];
}

transformed parameters {
  ...
  vector[num_data] cd4_expected;
  cd4_expected = inter_ref + slope_ref * time +
    design_matrix_for_inter * beta_inter +
    design_matrix_for_slope * beta_slope .* time;
  for (i in 1:num_data) {
    cd4_expected[i] = cd4_expected[i] +
      inter_and_slope_per_pat_unscaled[pat[i], 1] * inter_pat_scale +
      time[i] * inter_and_slope_per_pat_unscaled[pat[i], 2] * slope_pat_scale;
  }
}

model {
  inter_and_slope_per_pat_unscaled ~ multi_normal(zeros, Rho);
  cd4 ~ normal(cd4_expected, sd_error);
}
```

σ_r

σ_s

$$\left(\begin{pmatrix} r_1/\sigma_r \\ s_1/\sigma_s \end{pmatrix}, \begin{pmatrix} r_2/\sigma_r \\ s_2/\sigma_s \end{pmatrix}, \dots \right)$$

$$\bar{y}_{i,n} = m_i x_n + c_i$$

$$m_i = m + \gamma G_i + \lambda L_i + s_i$$

$$c_i = c + \Gamma G_i + \Lambda L_i + \sum_{\text{ages}} \alpha_{\text{age}} A_{i,\text{age}} + r_i$$

$$\frac{s_i}{\sigma_s} \times \sigma_s$$

$$x \times \frac{r_i}{\sigma_r} \times \sigma_r$$

$$\begin{pmatrix} r_i/\sigma_r \\ s_i/\sigma_s \end{pmatrix} \sim N\left(\mathbf{0}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right)$$

$$y_{i,n} \sim N(\bar{y}_{i,n}, \epsilon^2)$$

Closing thought: your question

"An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem"

John Tukey (regarded by some as the parent of Data Science, apparently.)

❌ Data → do things to it → get result → speculate what it means

✅ What questions *could* you ask → which question *should* you ask → what are the possible answers → to what extent do the data discriminate between them

Reposted by Peter Tennant, PhD

Sean Mackinnon @seanpmackinnon.bsky.social · 17h

Stats consulting is constantly like:

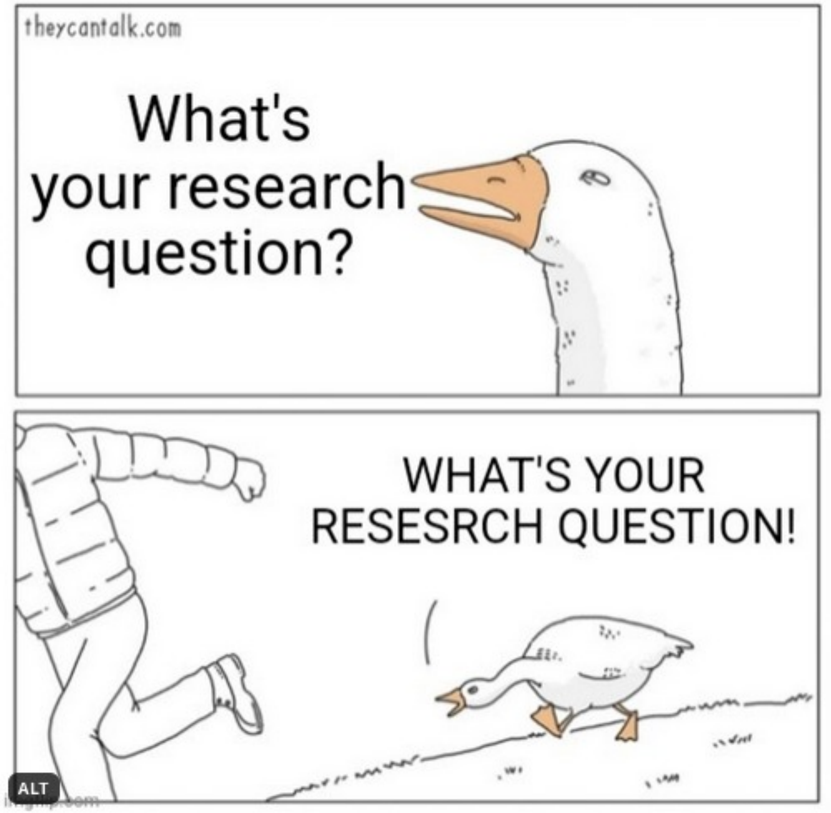
Them: I want you to run (complex stats)

Me: OK, what's your research question though?

Them: ...A (complex stat)?

Me: Research question?

Them: You know, like the stats in this journal article. Something reviewers will like.



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