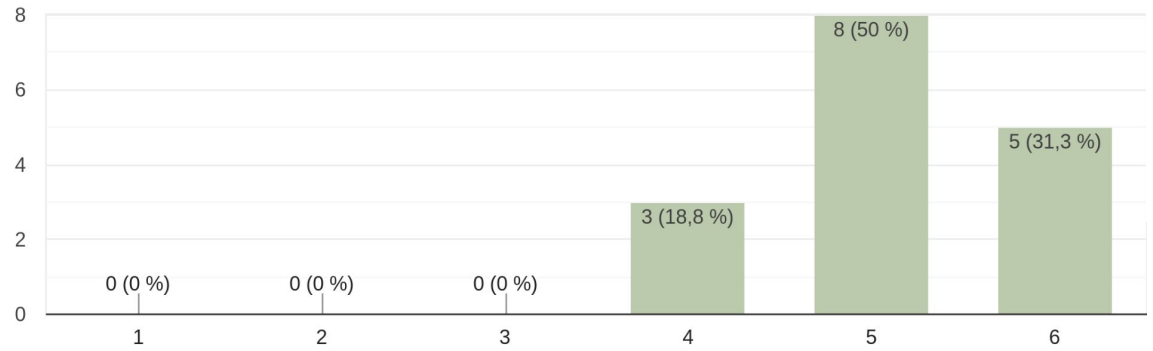
# Feedback of Lecture 5

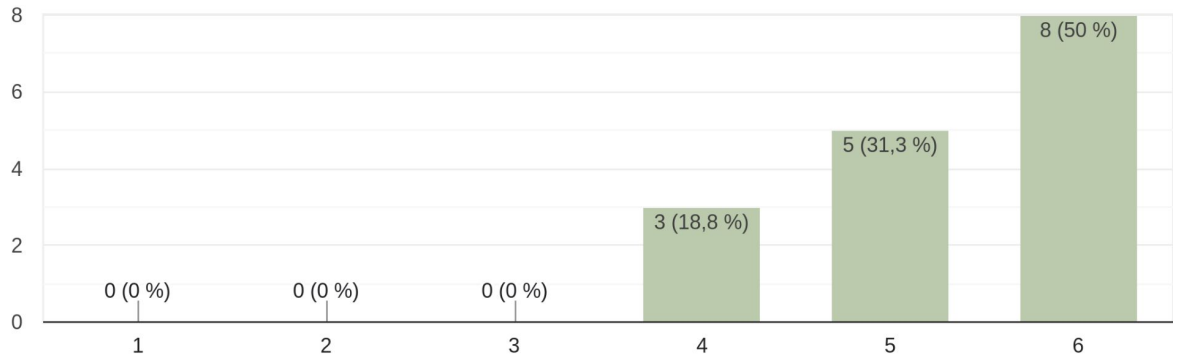
How was your overall impression of the fifth lecture?

16 Antworten



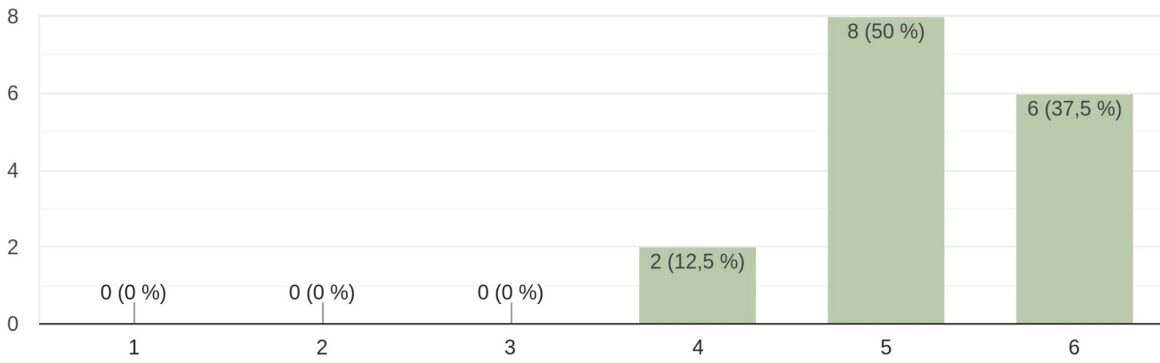

How well could you understand and follow David (the lecturer)?

16 Antworten



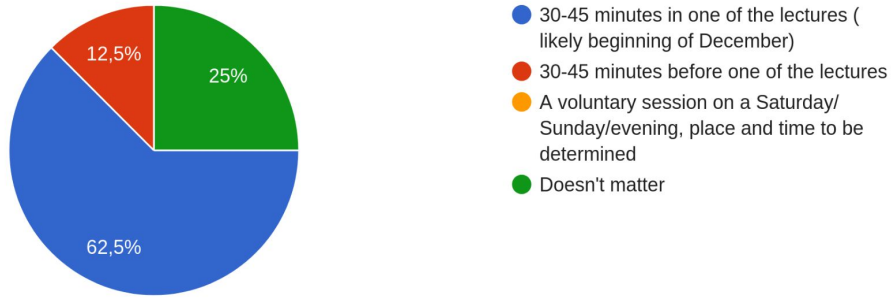

How did you experience the interactions between your peers and David, and among the peers?

16 Antworten



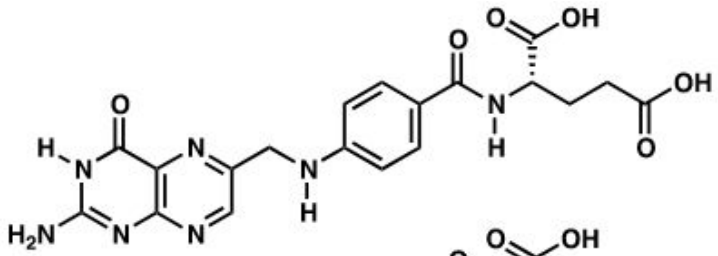

About the possible Ask Me Anything session, what's your most preferred option

16 Antworten

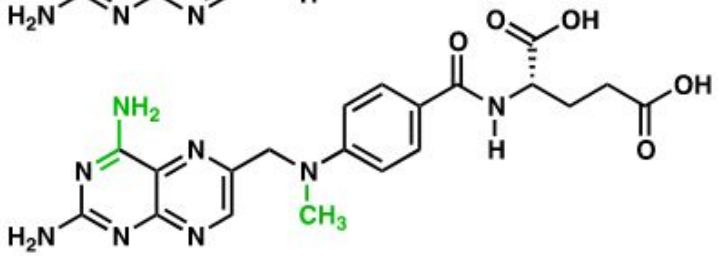



- More time for slides and questions
- Teach math slowly with chalk and board
- How attendance is graded?

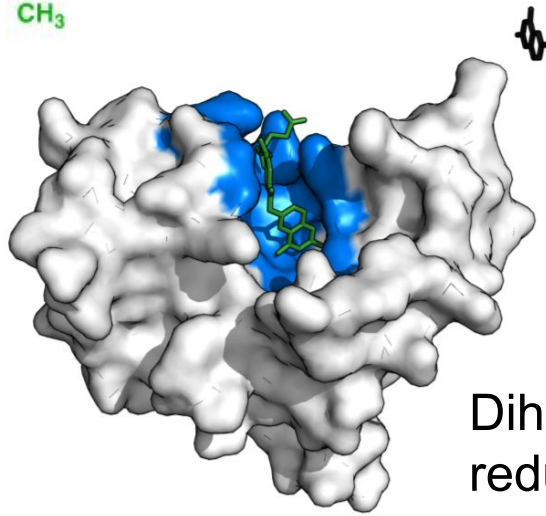
# AMIDD Lecture 6: Statistical models and causal inference



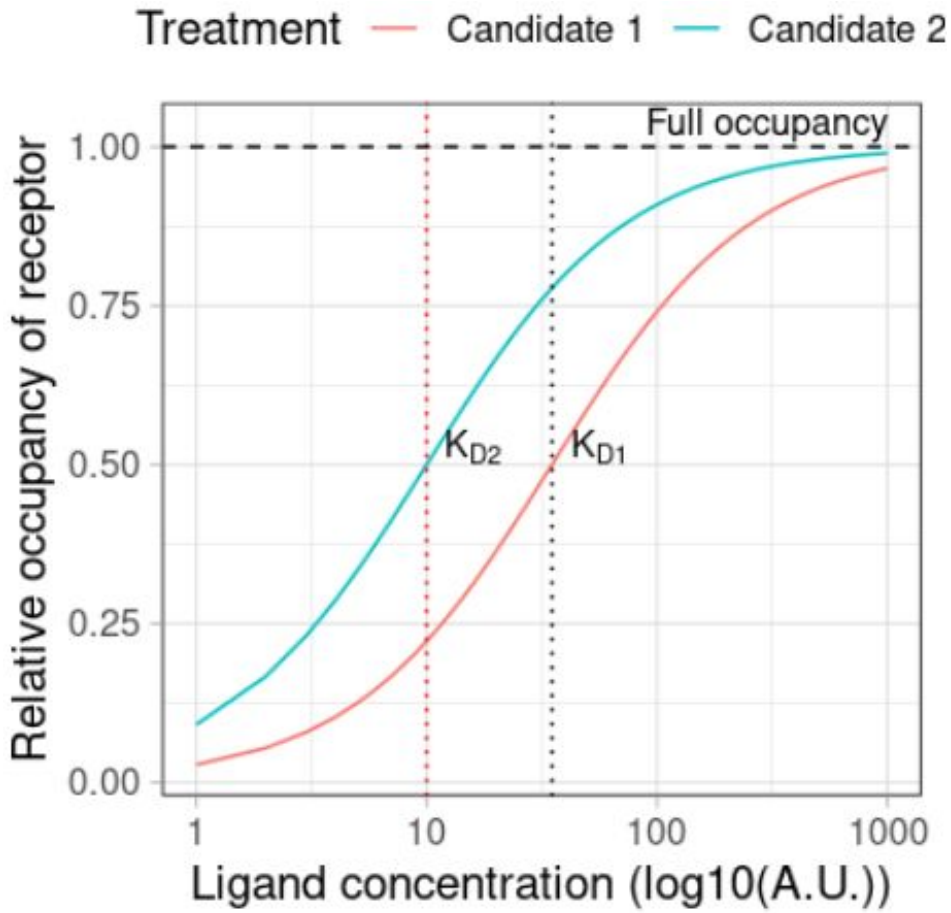
Dihydrofolic acid



MTX



Dihydrofolate reductase (DHFR)





*Dr. Jitao David Zhang, Computational Biologist*

*[1] Pharmaceutical Sciences, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche*

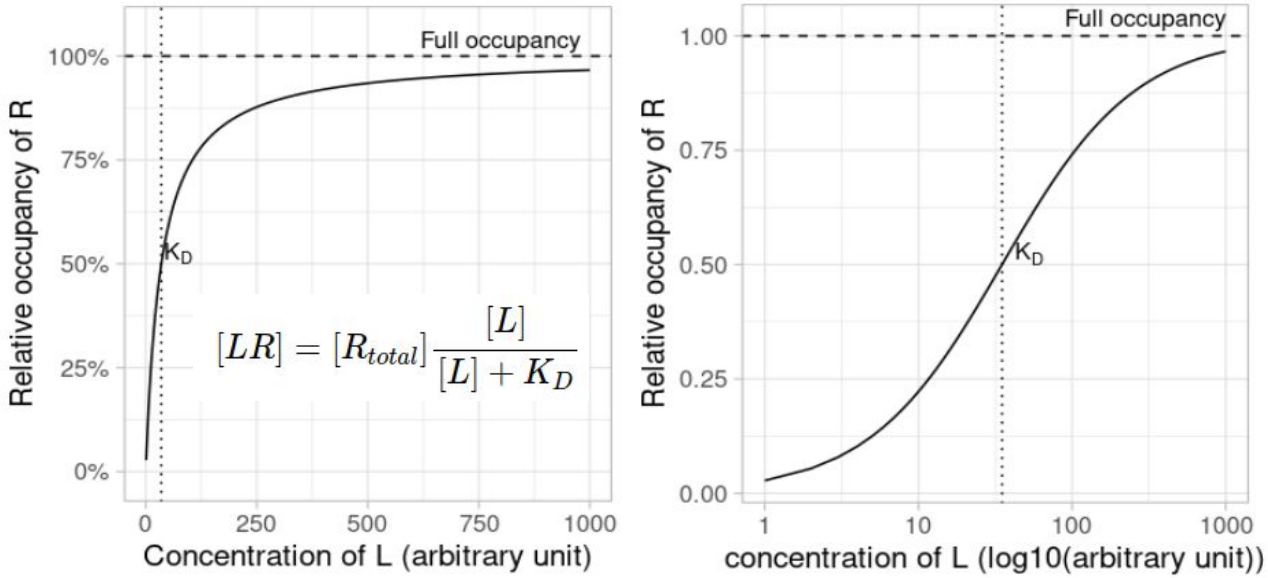
*[2] Department of Mathematics and Informatics, University of Basel*

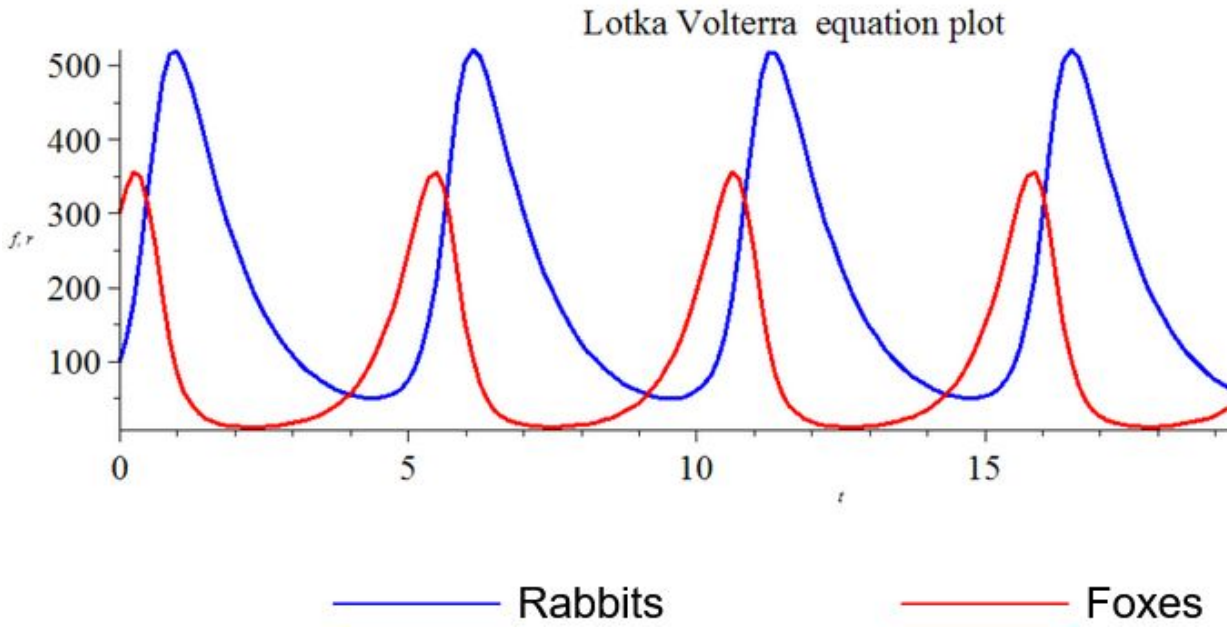
# Recap of mechanistic modeling with compartment models

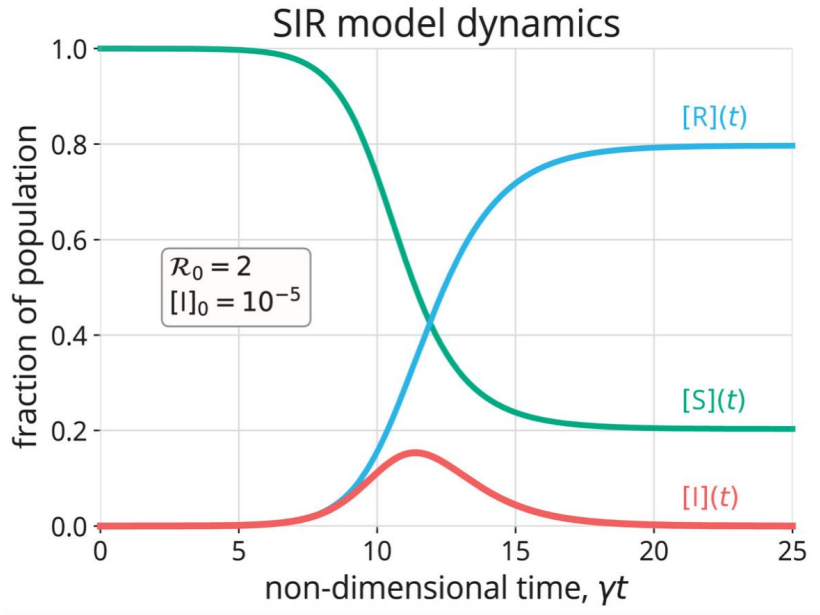
Top right: **Hill-Langmuir function** of target occupancy at equilibrium.

Bottom left: **Lotka-Volterra model** of bait-prey relationships.

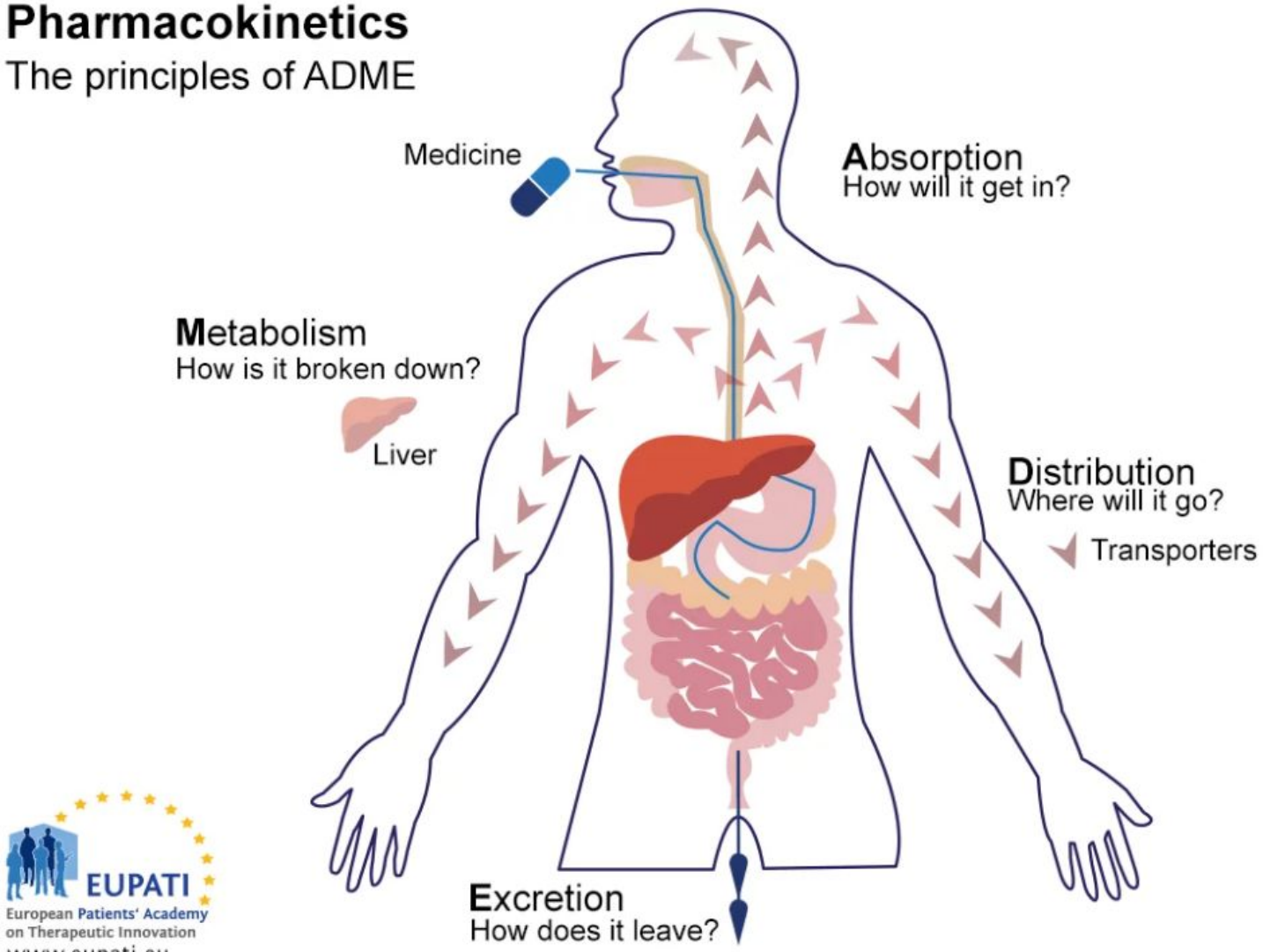
Bottom right: **Susceptible-Infectious-Removed (SIR) model** of transmissible diseases in a defined population.



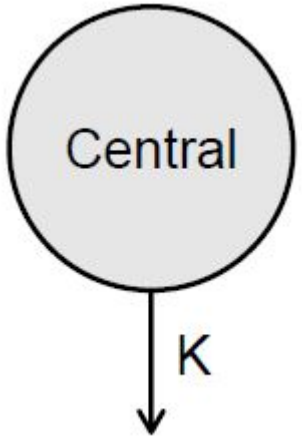



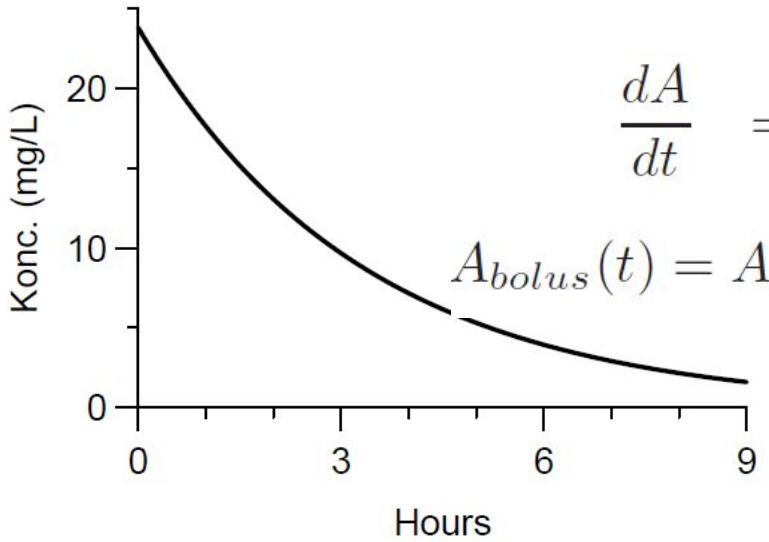
# ODE-based models are powerful tools to model ADME/PK profiles of drugs



# ODE-based mechanistic models are often used in pharmacokinetic modelling

- Pharmacokinetics (PK) describes how the drug is absorbed, distributed, metabolised, and excreted by the body.

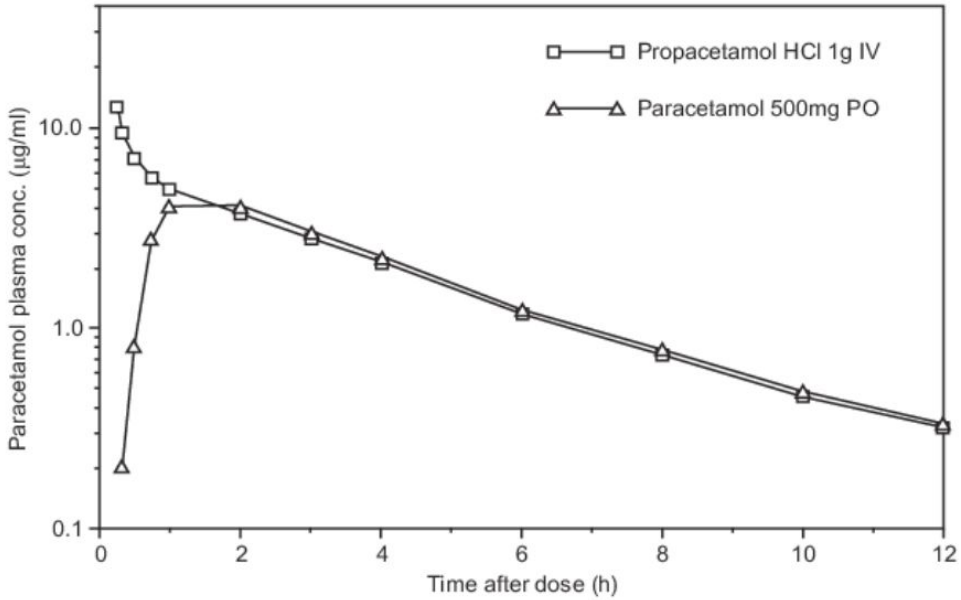



$$\frac{dA}{dt} = -K \cdot A$$

$$A_{bolus}(t) = A_0 \exp(-K \cdot t)$$

- A basic mathematical model of PK is a compartment model, i.e. one or more ordinary differential equations that describe the relationship between drug concentration and time. The simplest model is the decay model of bolus (injection).
  - $A_0$: initial concentration
  - A(t): drug concentration at time *t*
  - K: rate of clearance
- A real-world example: PK of propacetamol, a pro-drug of paracetamol, delivered via IV.



# Quantitative Structure-Activity Relationships (QSARs) as an example of statistical modelling

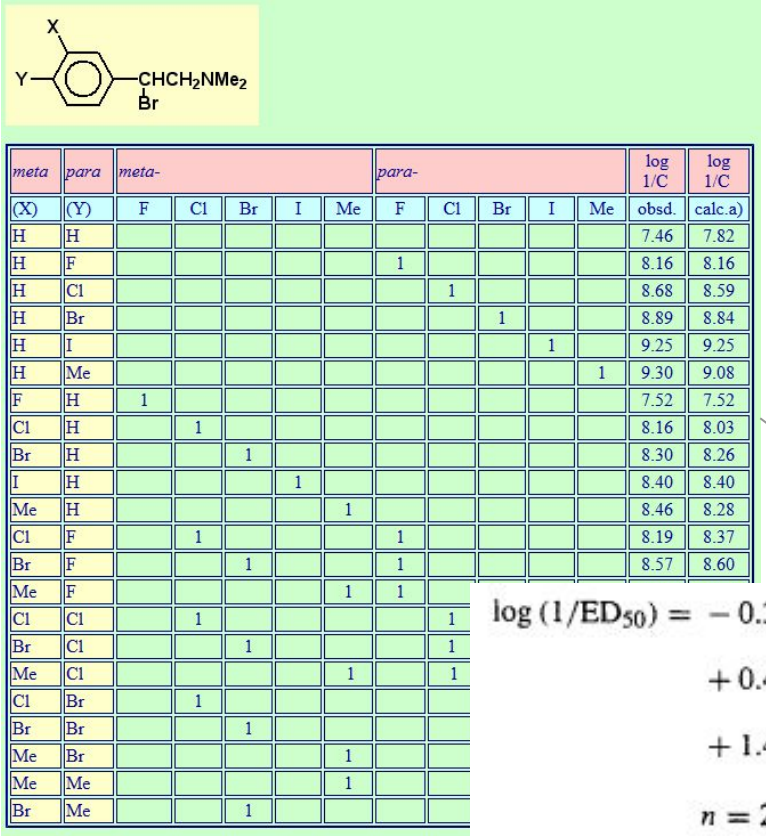
QSAR is a statistical modelling of correlation between biological activity and physicochemical properties, or $\Delta\phi = f(\Delta S)$, where $\phi$ indicates a biological activity and S indicates a chemical structure (1868-1869).

**Molecular Descriptors (MD)**

| | Target property | $MD_1$ | $MD_2$ | ... | $MD_M$ |
|---|---|---|---|---|---|
| **Compounds (C)** | | | | | |
| $C_1$ | $y_1$ | $x_{1,1}$ | $x_{1,2}$ | ... | $x_{1,M}$ |
| $C_2$ | $y_2$ | $x_{2,1}$ | ... | ... | ... |
| $C_3$ | $y_3$ | ... | ... | ... | ... |
| $C_4$ | $y_4$ | ... | ... | ... | ... |
| ... | ... | ... | ... | ... | ... |
| ... | ... | ... | ... | ... | ... |
| $C_N$ | $y_N$ | $x_{N,1}$ | $x_{N,2}$ | ... | $x_{N,M}$ |

The basic form of a QSAR model: find a function *f* that predicts *y* from *x*, y~f(x)

An example: **The Free-Wilson analysis.** The assumption: the biological activity for a set of analogues could be described by the contributions that substituents or structural elements make to the activity of a parent structure.



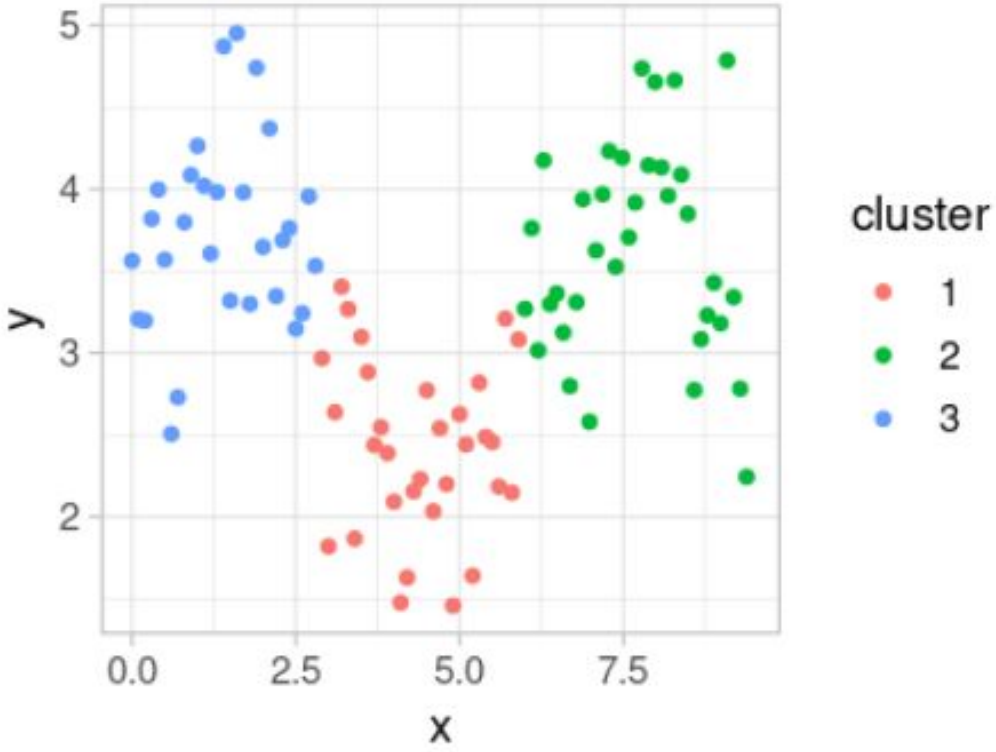

| meta | para | meta- | | | | | para- | | | | | log 1/C | log 1/C |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (X) | (Y) | F | Cl | Br | I | Me | F | Cl | Br | I | Me | obsd. | calc.a) |
| H | H | | | | | | | | | | | 7.46 | 7.82 |
| H | F | | | | | | 1 | | | | | 8.16 | 8.16 |
| H | Cl | | | | | | | 1 | | | | 8.68 | 8.59 |
| H | Br | | | | | | | | 1 | | | 8.89 | 8.84 |
| H | I | | | | | | | | | 1 | | 9.25 | 9.25 |
| H | Me | | | | | | | | | | 1 | 9.30 | 9.08 |
| F | H | 1 | | | | | | | | | | 7.52 | 7.52 |
| Cl | H | | 1 | | | | | | | | | 8.16 | 8.03 |
| Br | H | | | 1 | | | | | | | | 8.30 | 8.26 |
| I | H | | | | 1 | | | | | | | 8.40 | 8.40 |
| Me | H | | | | | 1 | | | | | | 8.46 | 8.28 |
| Cl | F | | 1 | | | | 1 | | | | | 8.19 | 8.37 |
| Br | F | | | 1 | | | 1 | | | | | 8.57 | 8.60 |
| Me | F | | | | | 1 | 1 | | | | | | |
| Cl | Cl | | 1 | | | | | 1 | | | | | |
| Br | Cl | | | 1 | | | | 1 | | | | | |
| Me | Cl | | | | | 1 | | 1 | | | | | |
| Cl | Br | | 1 | | | | | | | | | | |
| Br | Br | | | 1 | | | | | | | | | |
| Me | Br | | | | | 1 | | | | | | | |
| Me | Me | | | | | 1 | | | | | | | |
| Br | Me | | | 1 | | | | | | | | | |

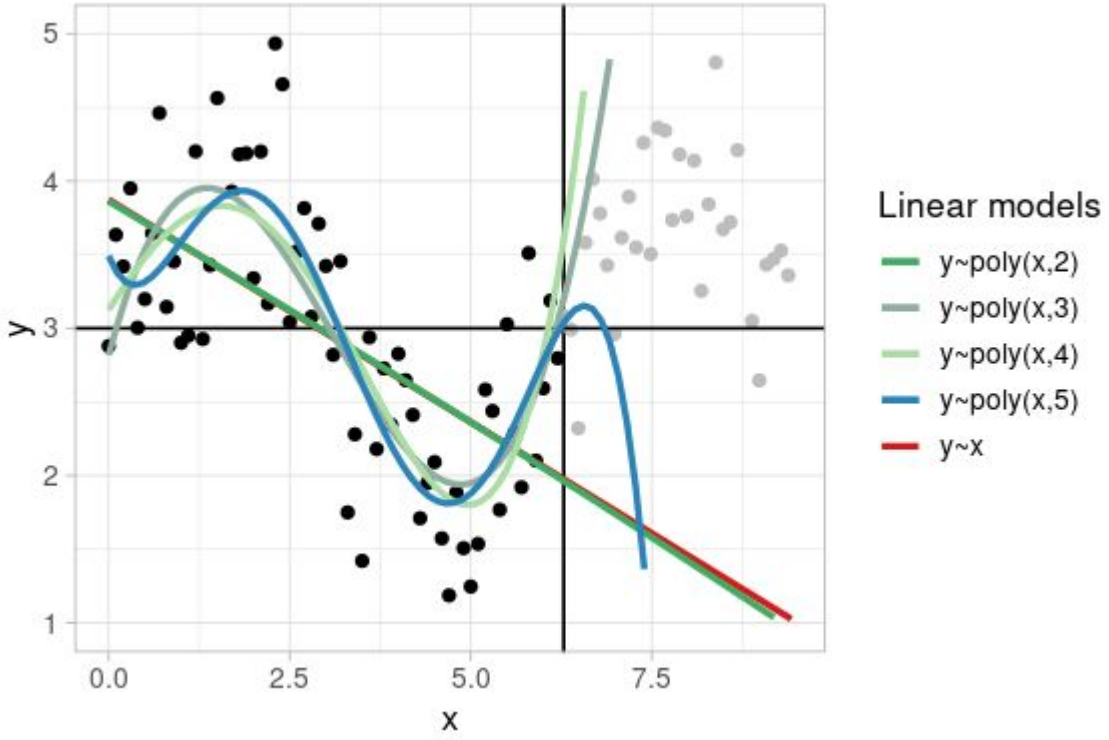
Multivariate regression analysis

$$\log(1/ED_{50}) = -0.301[m\text{–F}] + 0.27[m\text{–Cl}] + 0.434[m\text{–Br}] + 0.579[m\text{–I}] + 0.454[m\text{–Me}] + 0.340[p\text{–F}] + 0.768[p\text{–Cl}] + 1.020[p\text{–Br}] + 1.429[p\text{–I}] + 1.256[p\text{–Me}] + 7.821$$

$$n = 22,\ r^2 = 0.94,\ s = 0.194,\ F = 17.0$$

# Unsupervised versus supervised models



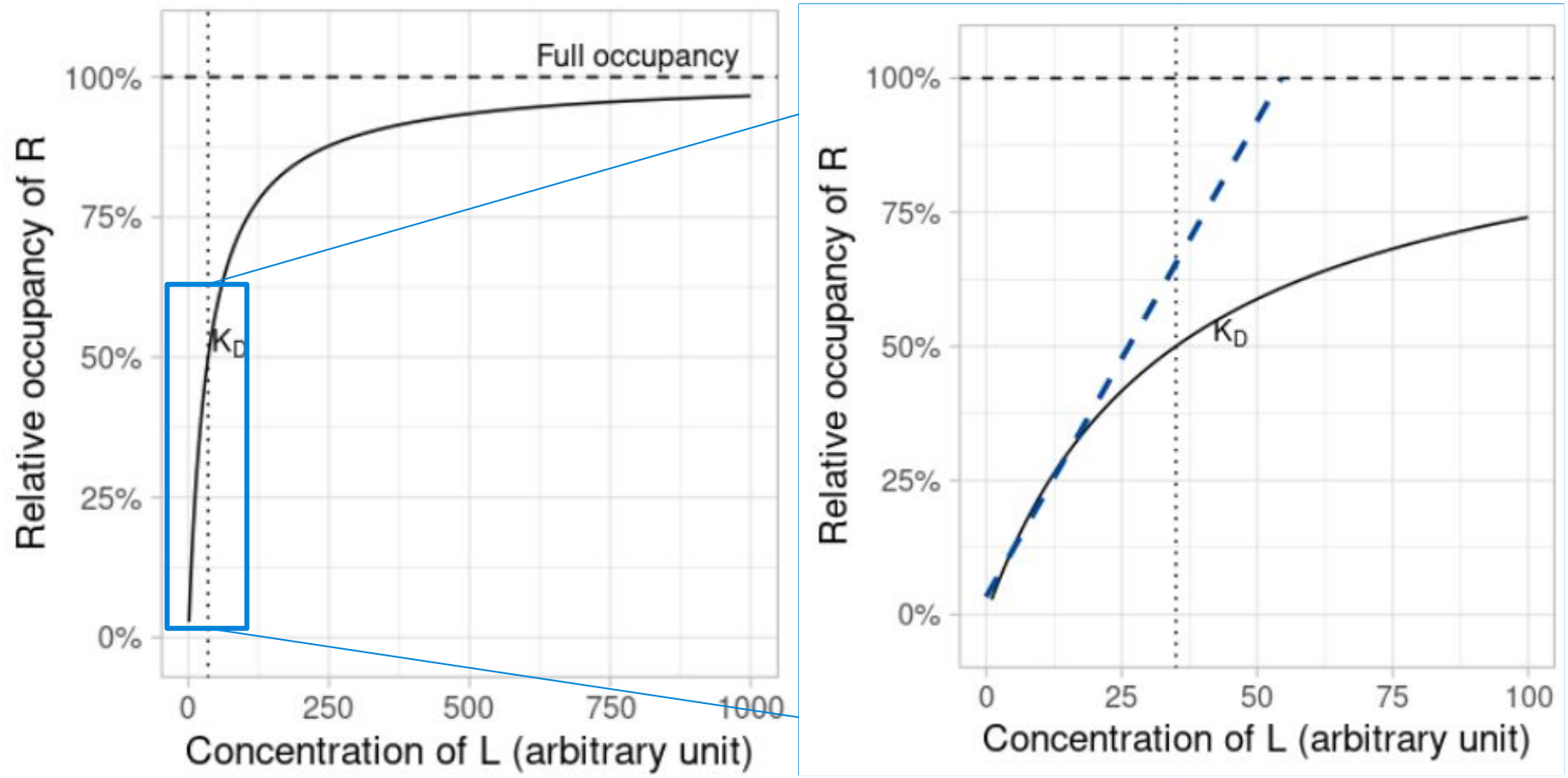



# Linear model can be used to model local effects of non-linear models

$$\mathrm{L} + \mathrm{R} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{LR}$$

$$K_D \equiv k_2/k_1$$

$$[LR] = [R_{total}]\frac{[L]}{[L] + K_D}$$

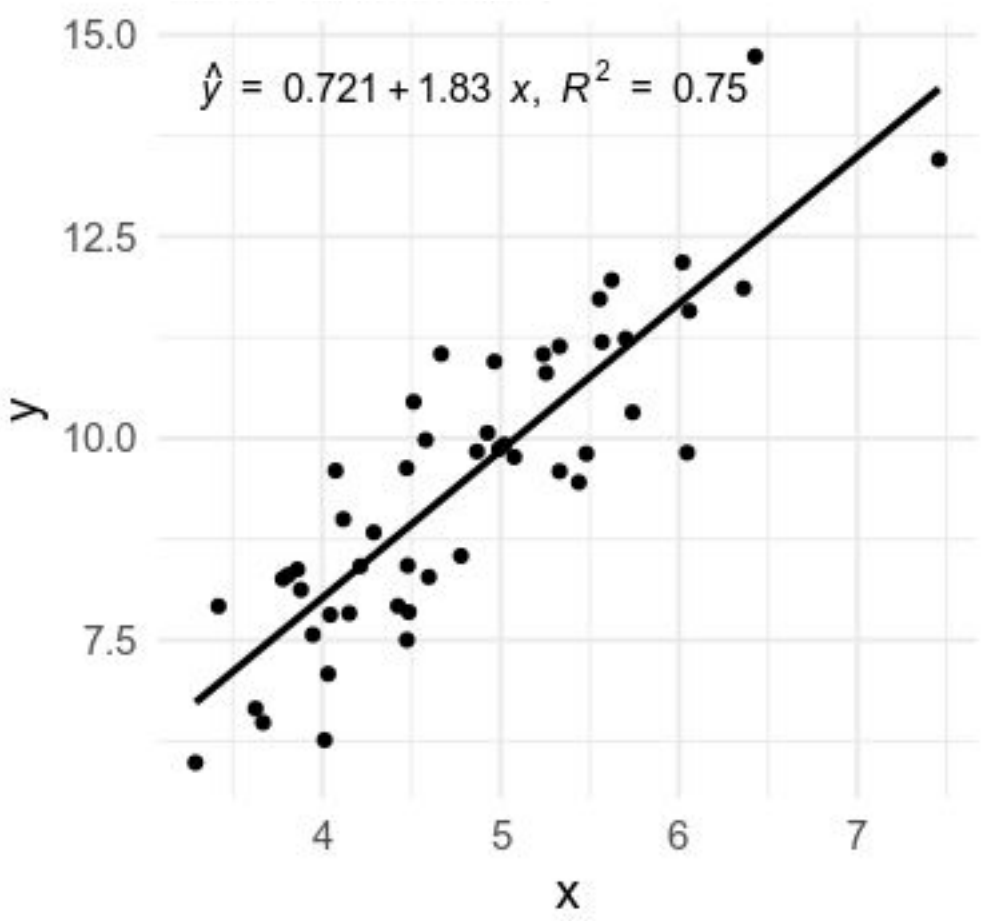


# The simplest linear model has three components: the intercept, the slope, and a measure of fit

In this example, the coefficient of determination ($R^2$) is used as the measure.

$R^2$ measures the relative fit of the linear model with regard to a baseline model, where the mean value of *y* is used as a fit.

| | x | y |
|---|---|---|
| 1 | 4.926791 | 10.067779 |
| 2 | 4.479734 | 8.424283 |
| 3 | 4.289686 | 8.835629 |
| 4 | 4.474023 | 9.630499 |
| 5 | 4.214551 | 8.416680 |
| 6 | 6.057431 | 11.578080 |
| 7 | 4.597903 | 8.283025 |
| 8 | 5.021571 | 9.922731 |
| 9 | 3.627323 | 6.651222 |
| 10 | 5.622794 | 11.959972 |
| 11 | 5.555025 | 11.727815 |
| 12 | 4.966007 | 10.951562 |
| 13 | 5.076791 | 9.768299 |



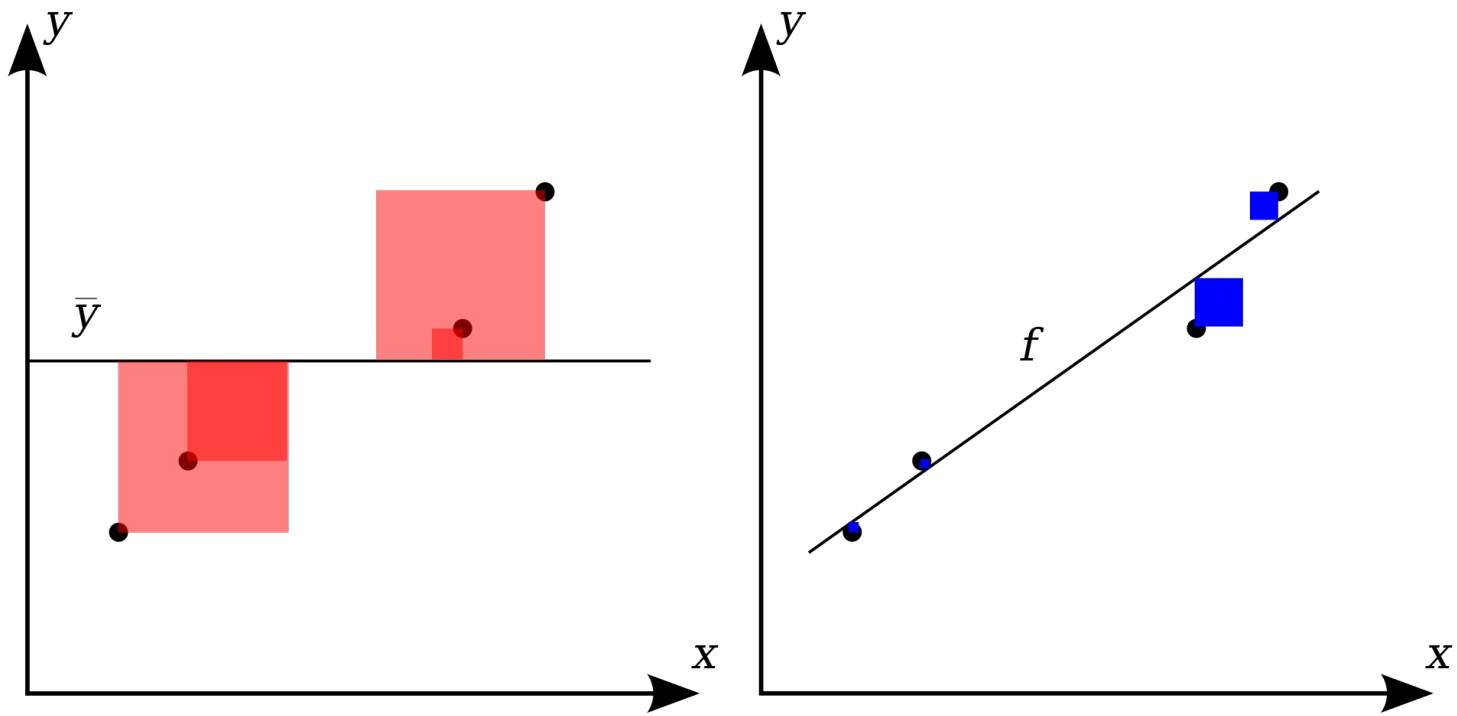
# A visual explanation of $R^2$

The better the linear regression (right) fits the data in comparison to the average (left), the closer the value of $R^2$ is to 1.

The areas of the blue squares represent the squared residuals with respect to the linear regression. The areas of the red squares represent the squared residuals with respect to the average.

$R^2$ is defined as 1-(blue area)/(red area).

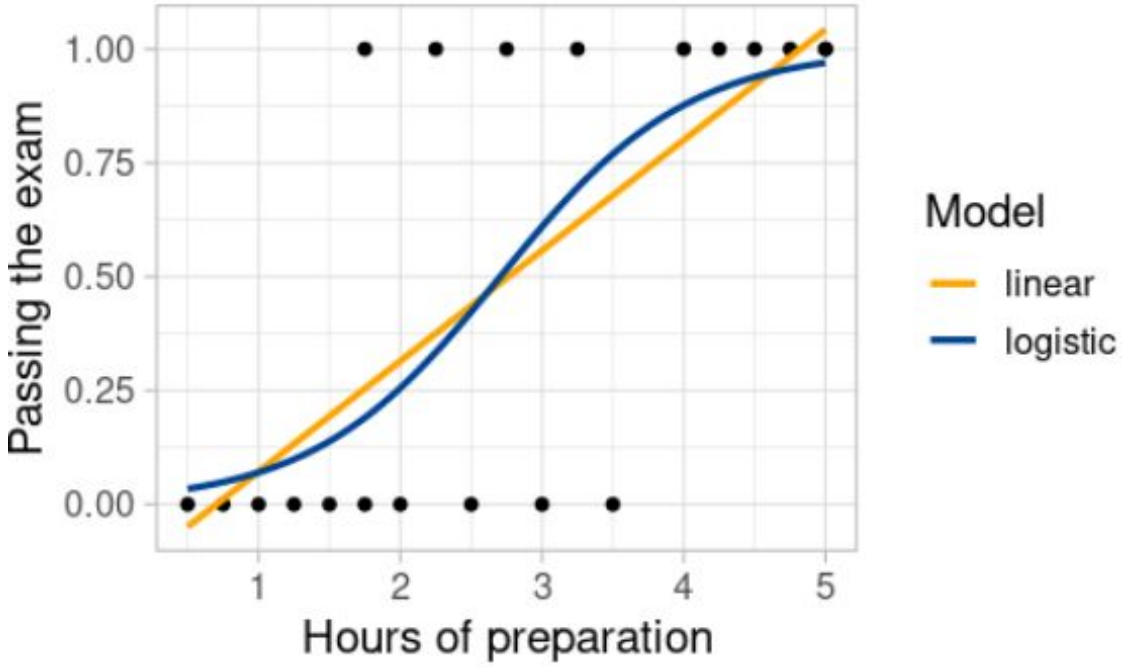
**Question**: can $R^2$ be negative?




Work by Orzetto, CC-SA 3.0, from Wikimedia

# Logistic regression is a example of *generalized* linear model, which allows dependent variable defined other than real numbers

- Dependent variable of a linear regression model is defined on $\mathbb{R}$.
- *Generalized* linear models allow the dependent variable to be defined on other domains than real numbers, for instance binary (0/1), counts (non-negative integers), etc.
- Logistic regression maps input real numbers to the range between 0 and 1 in two steps: (1) building a simple linear regression, (2) applying the *logistic function* to map the intermediate dependent variable to the desired domain (0,1).



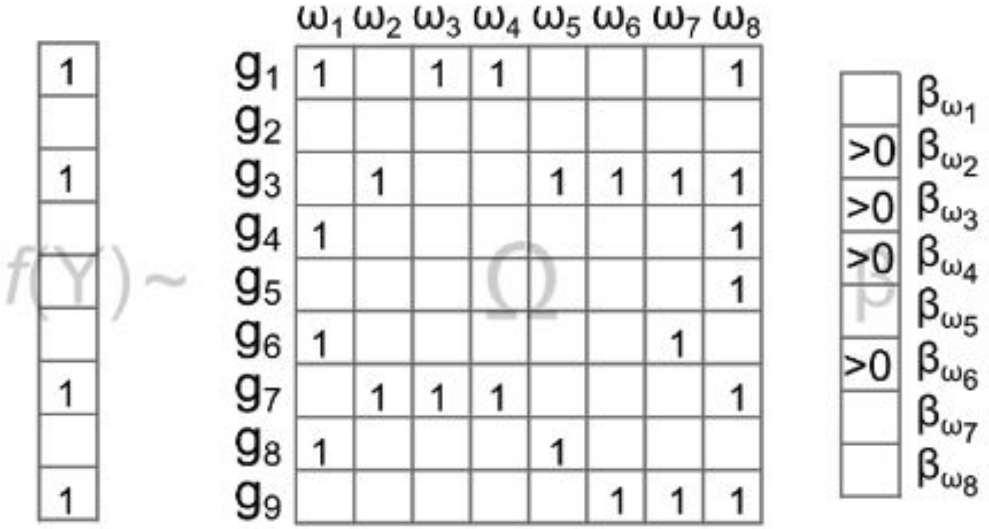

Data come from Wikipedia's item on logistic regression

$$t = \alpha + \beta x \qquad y = \frac{1}{1 + e^{-t}}$$

# Multiple regression with regularization

- We may have multiple independent variables. For instance, in the example on the right side, we want to predict *which topics contribute to passing the exam.* In such cases, we apply *multiple regression*.
- In multiple regressions, we often wish for a sparse solution: i.e. we wish to know the few most important features that contribute to the prediction. A technique to achieve this is *regularization.*
- Regularization penalizes large coefficients. It effectively push coefficients towards zero. For instance, the equation below shows the *error function* of *ridge regression*.

$$\widetilde{E}(\mathbf{w}) = \frac{1}{2}\sum_{n=1}^{N}\{y(x_n, \mathbf{w}) - t_n\}^2 + \frac{\lambda}{2}\|\mathbf{w}\|^2$$




**f(Y)**: a binary label to indicate whether someone pass an exam

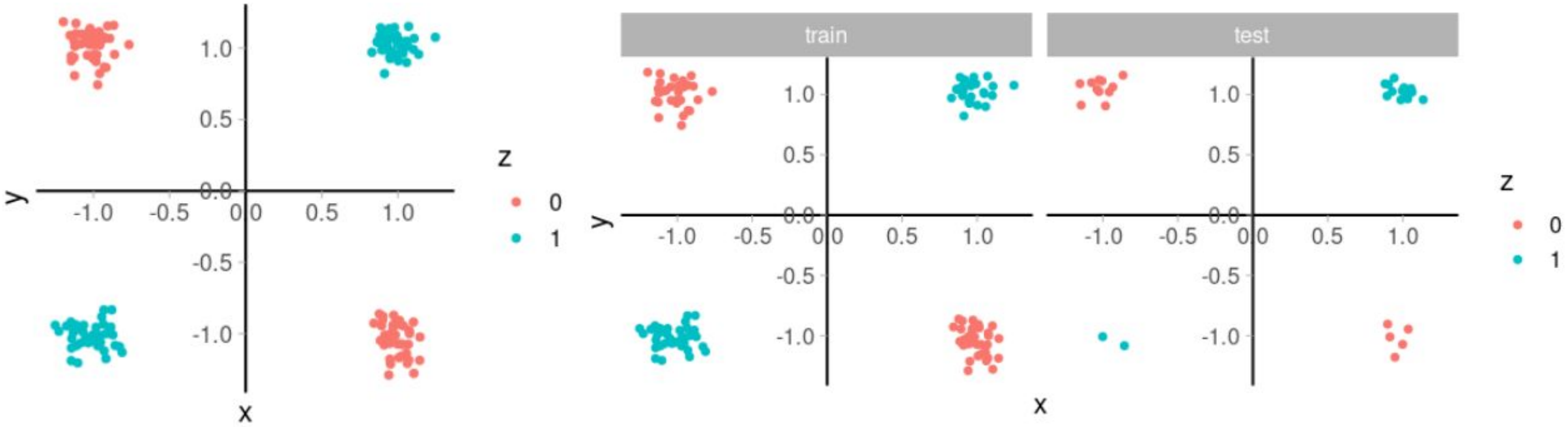
**$g_1$-$g_9$**: students

**□$_1$-□$_8$**: topics

**$\beta_{□1}$-$\beta_{□8}$**: coefficients of topics

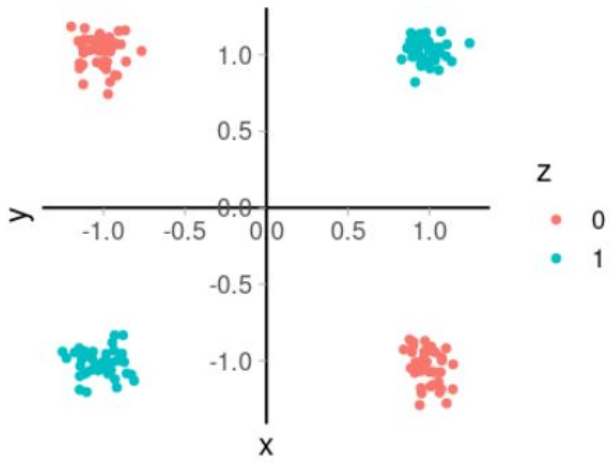
Equation: Bishop, Christopher M. Pattern Recognition and Machine Learning, page 10

# We next address two problems: (1) unknown performance of model when new data are met, and (2) non-linearity

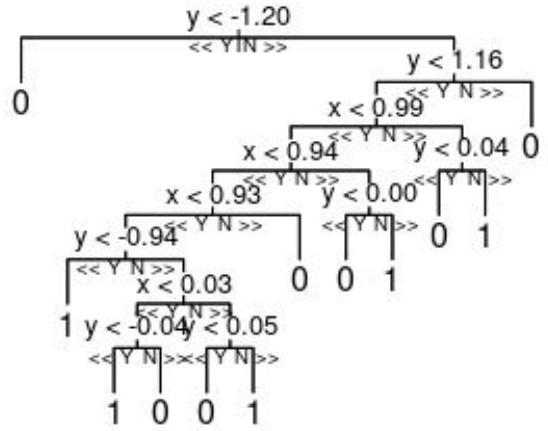



- Left: a simple example of non-linearity: linear models cannot predict *z* well based on values of *x* and *y*. We need something else.
- Right: a model is usually trained in some data, and the performance is assessed in unseen test data.

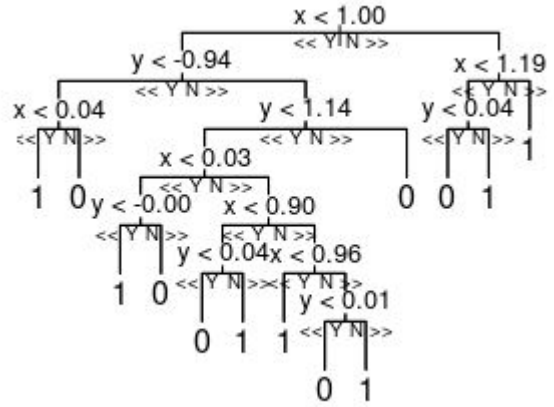
# We can use random forest to model non-linearity



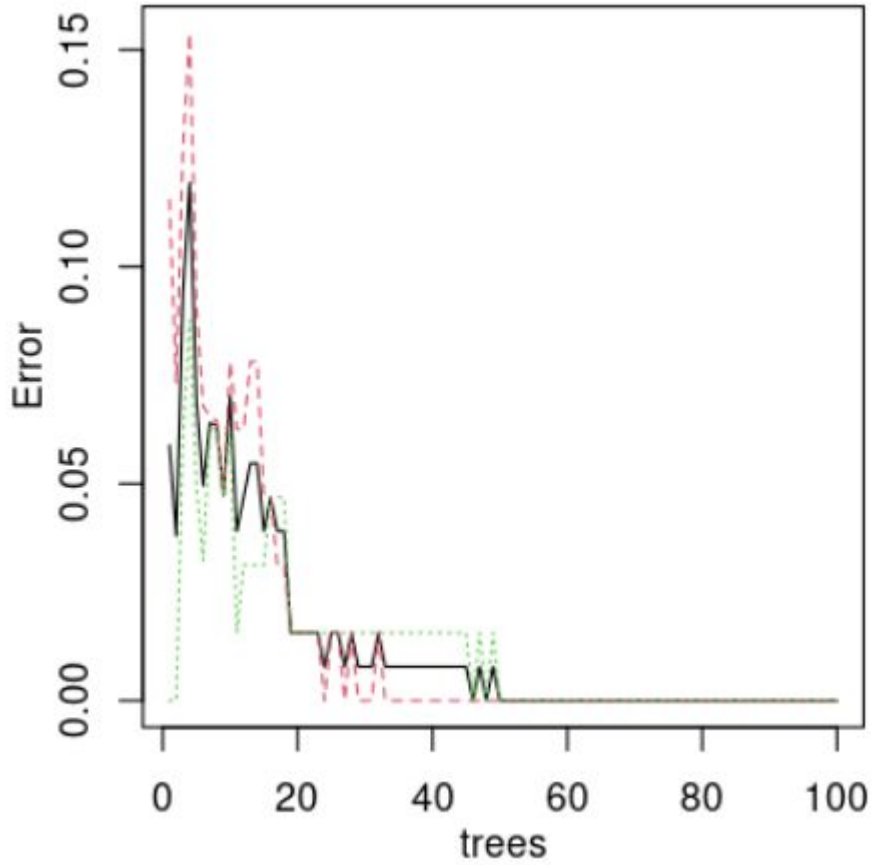

Tree #1




Tree #20



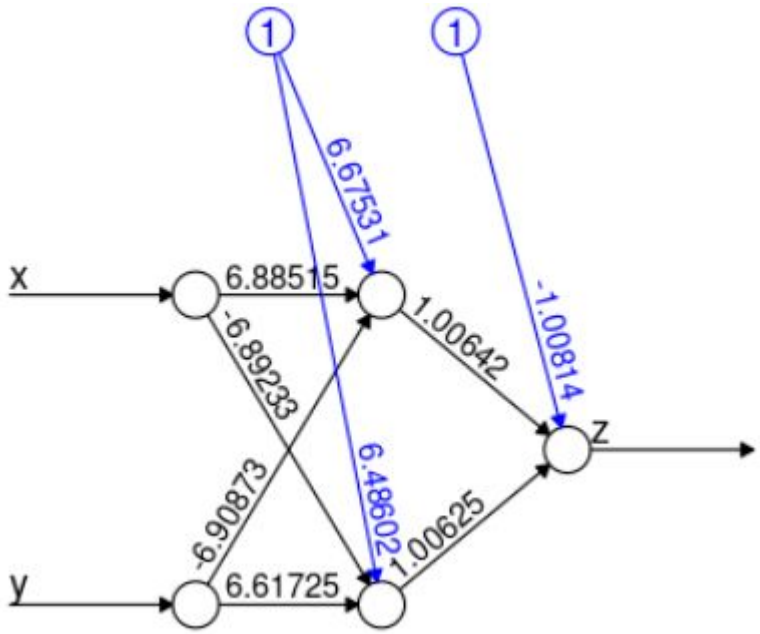

- Random forest is a collection of *decision trees*. Each tree partitions the input data to make predictions.
- Random forest is an example of *ensemble methods*: each tree has weak performance, however the consensus can perform surprisingly well.



# Neural network can be used to model non-linearity, too

- Neural network models non-linearity by applying multiple linear combinations subsequently in the forward propagation.
- Once the architecture (# hidden layers, # nodes, etc.) is fixed, weights of edges neural network are initialized with random numbers, and then optimized by iterative forward and reverse propagation to minimize the error.
- Right figure: the trained neural network with the example data. Blue nodes indicate intercepts.

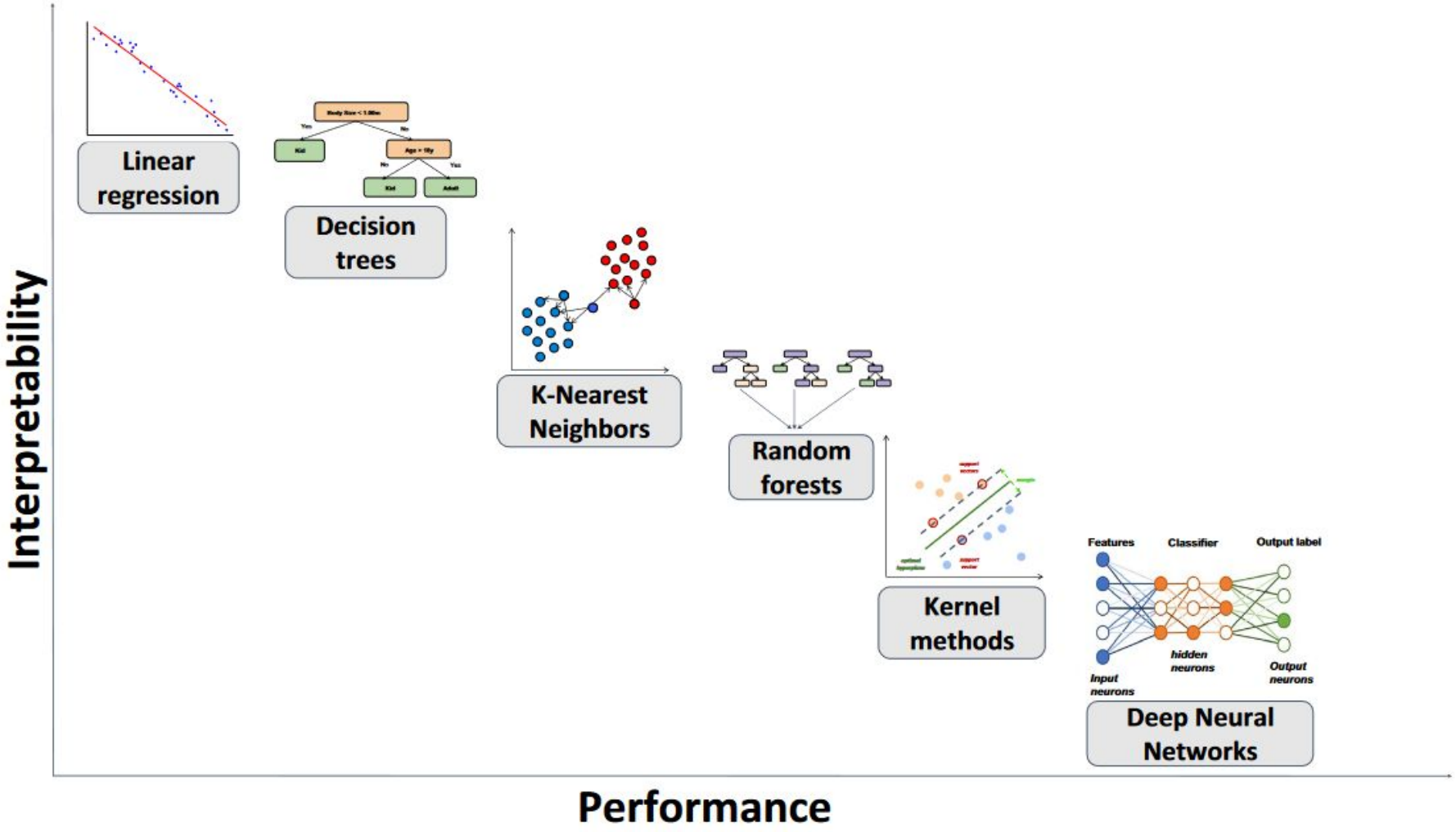
| | Reference | |
|---|---|---|
| Prediction | 0 | 1 |
| 0 | 16 | 0 |
| 1 | 0 | 16 |




Hidden layer

Error: 0.000172 Steps: 1085

# Generally, well-performing models tend to be less interpretable

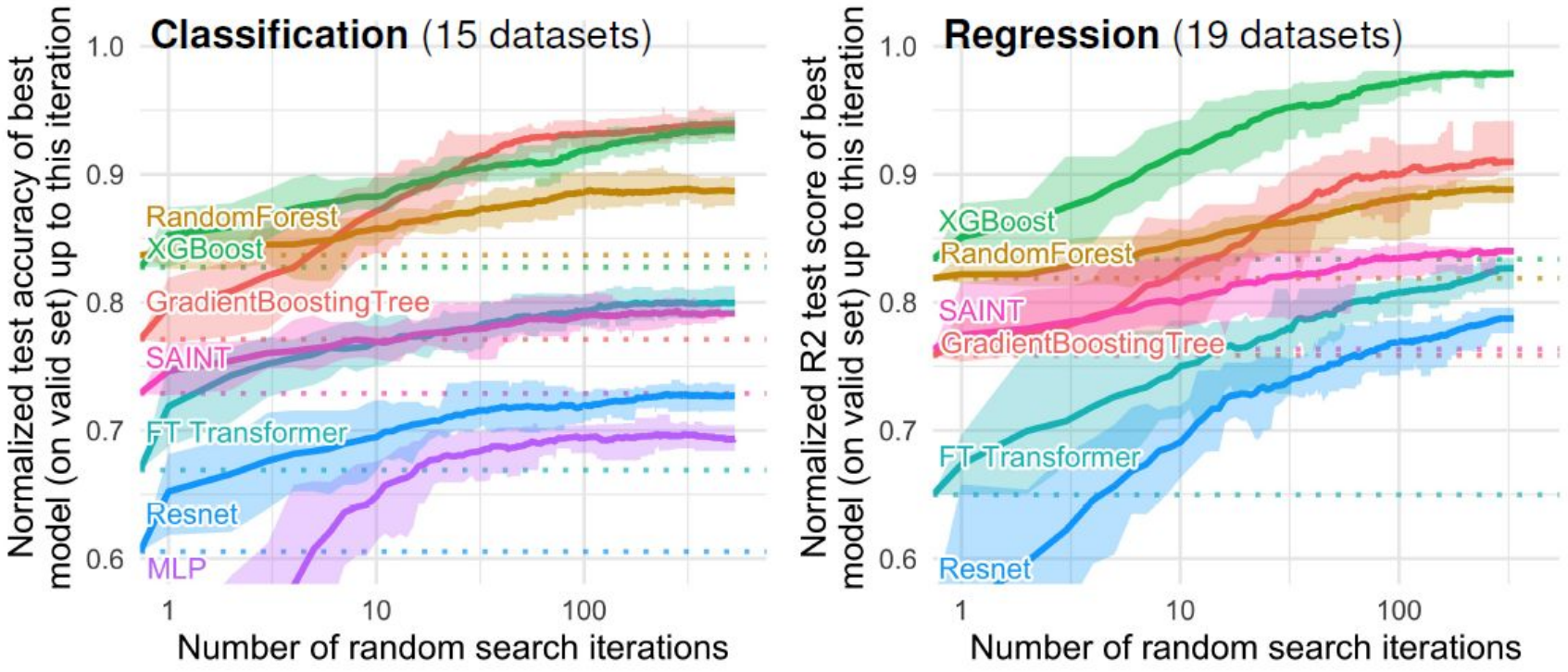


# For tabular data: tree-based methods are well interpretable and generally outperform deep learning… until *TabPFN* (2022-25)

The authors collected 45 tabular datasets from varied domains.

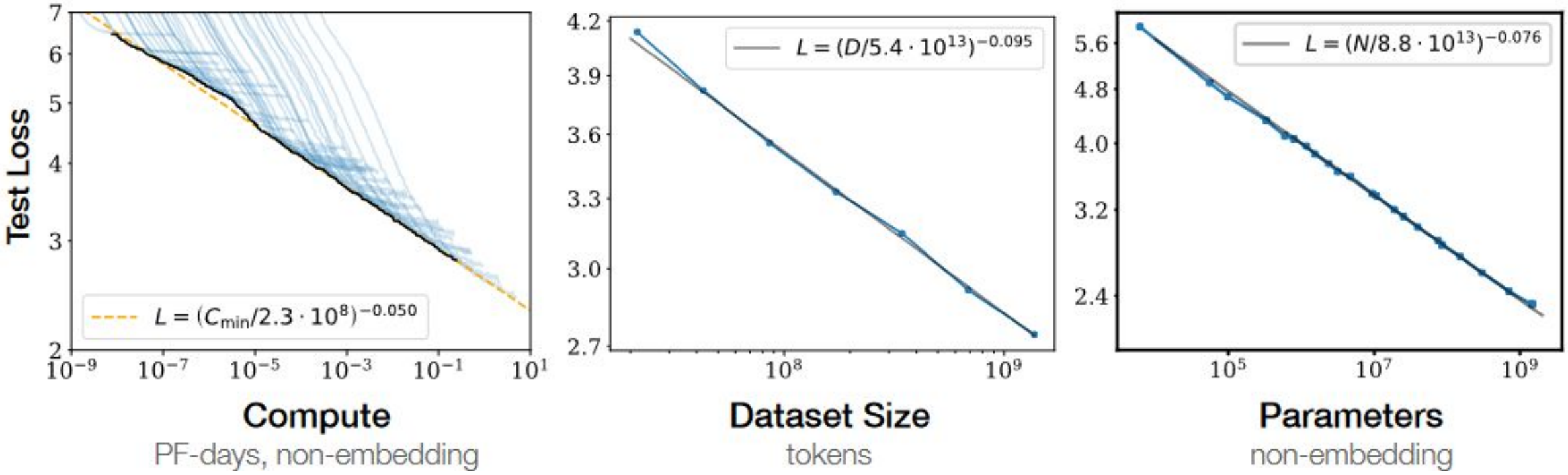
They found that tree-based models remain state-of-the-art on medium-sized data (~10k samples), even without considering the speed.

**Conclusion**: when working with tabular data, consider tree-based methods, … or TabPFN (next lecture)



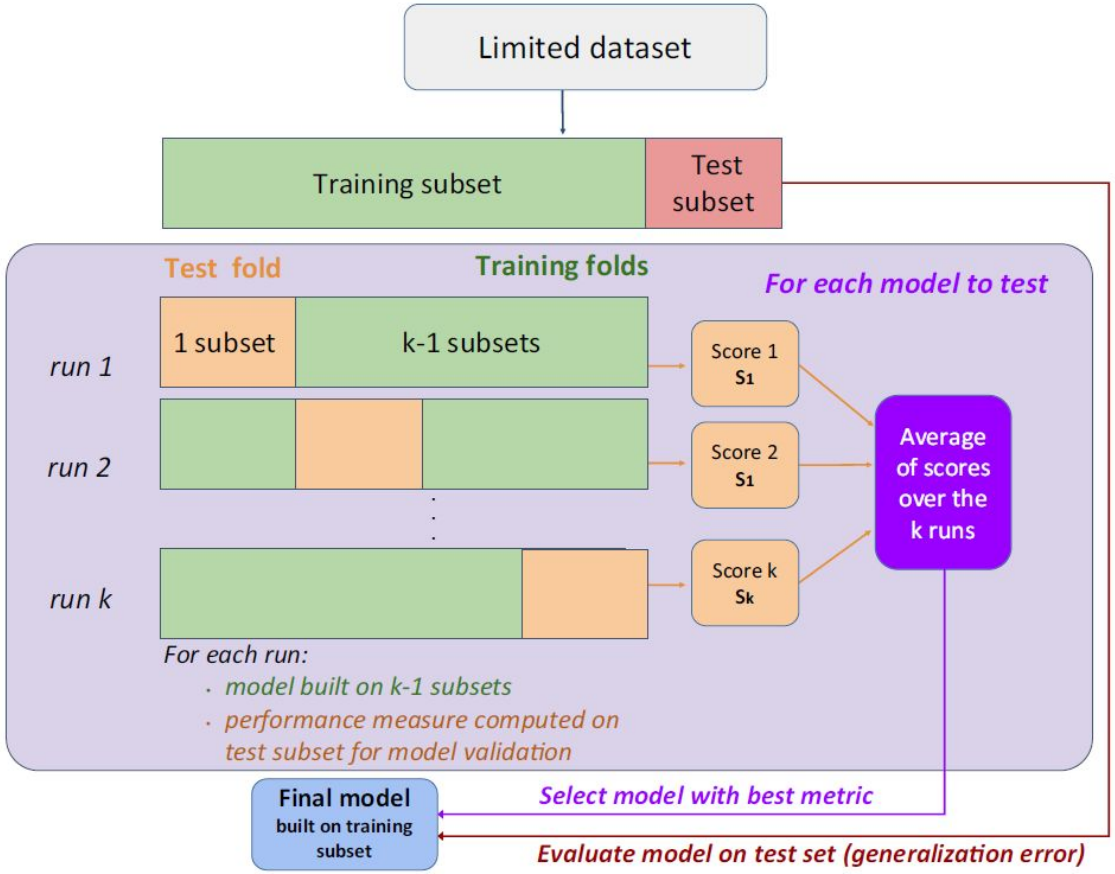

Grinsztajn, Léo, Edouard Oyallon, and Gaël Varoquaux. "Why Do Tree-Based Models Still Outperform Deep Learning on Tabular Data?" arXiv, July 18, 2022. https://doi.org/10.48550/arXiv.2207.08815.
GitHub repository: https://github.com/LeoGrin/tabular-benchmark

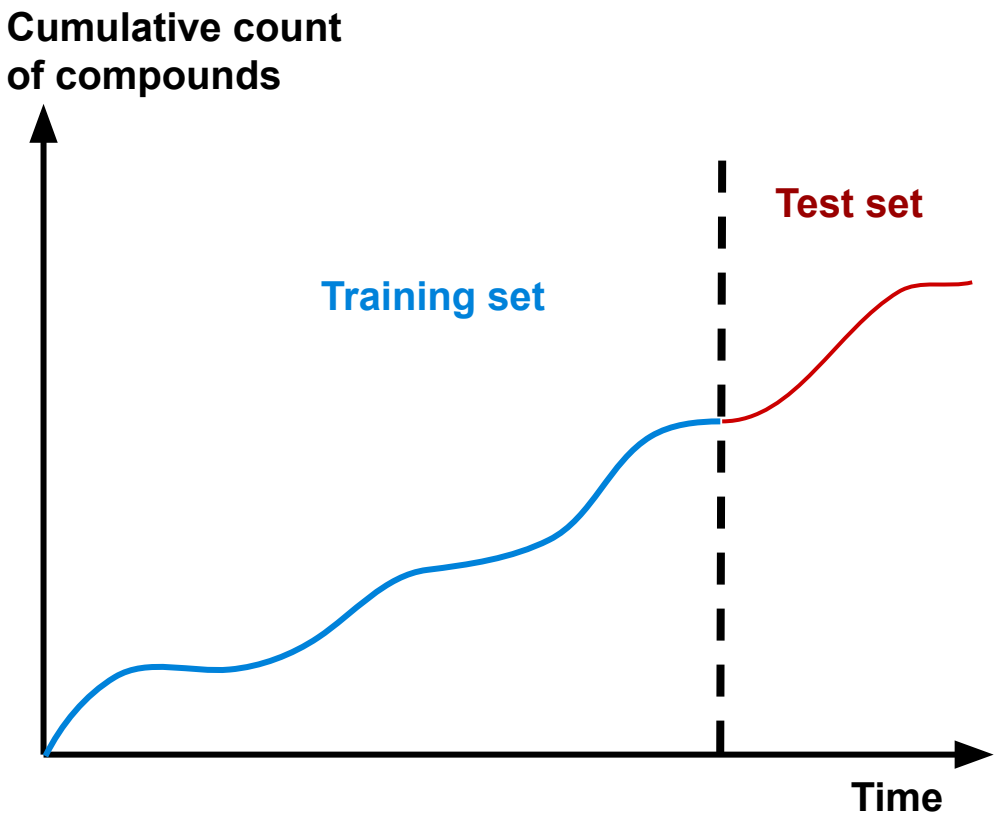
# Performance neural networks improve as data amount, computational power, and model size increases




Language modeling performance improves smoothly as we increase the model size, dataset size, and amount of compute used for training. PF-days: Peta-FLOPs. From: Kaplan, J. et al. Scaling Laws for Neural Language Models (2020).

# Watchout 1: Temporal validation is essential for drug discovery

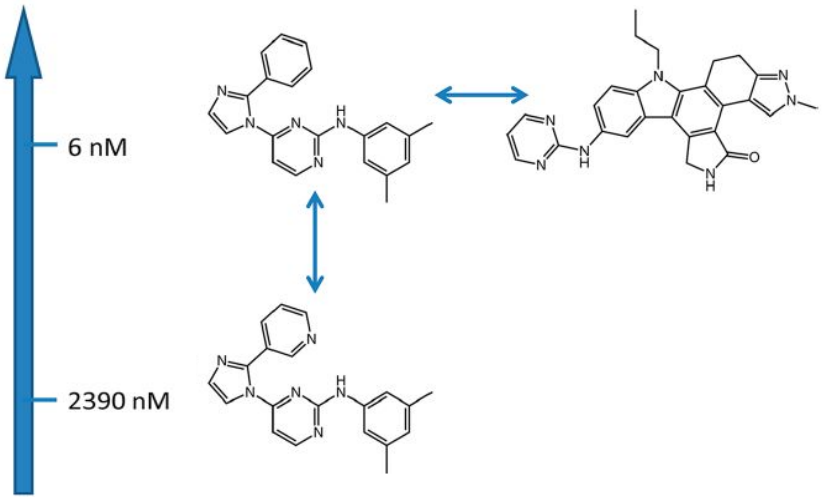


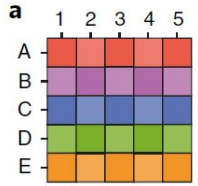




(Left) To assess the generalization ability of a supervised learning algorithm, data are separated into a training subset used for building the model and a test subset used to assess the generalization error.

(Right) Temporal validation is especially important for drug discovery, because chemical structures used in the training set may differ substantially from those that will be tested.

# Watchout 2: Molecular similarity does not equal biological similarity

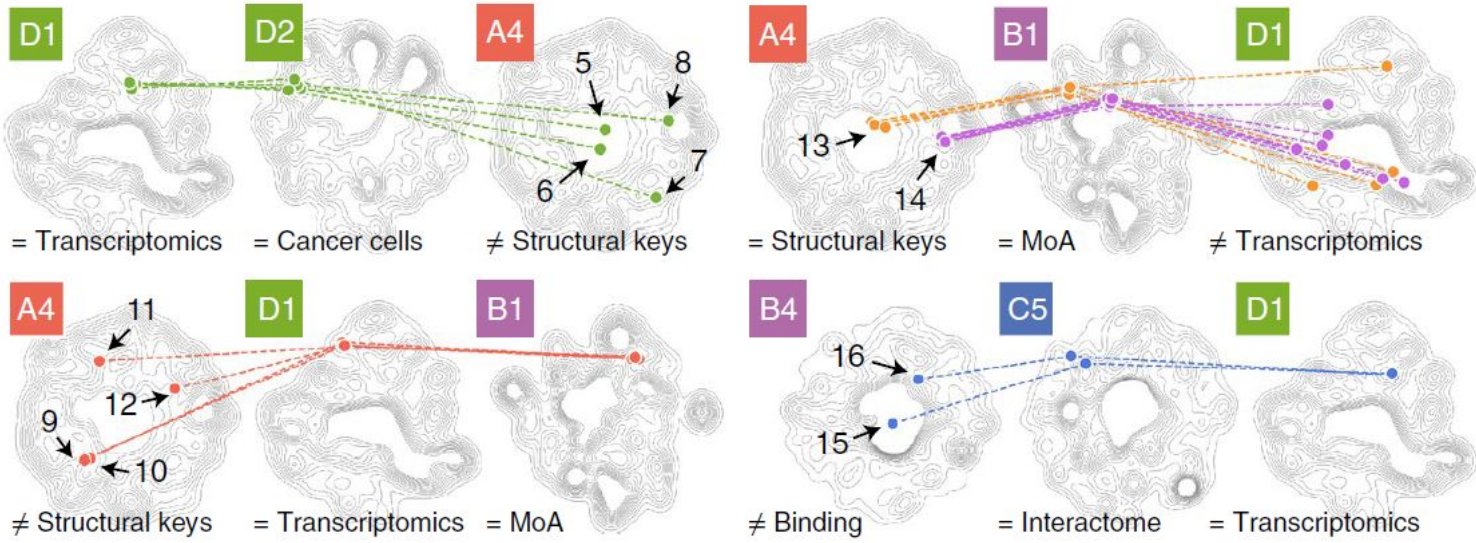



| | | | | |
|---|---|---|---|---|
| A1: 2D fingerprints | A2: 3D fingerprints | A3: Scaffolds | A4: Structural keys | A5: Physicochemistry |
| B1: Mechanisms of action | B2: Metabolic genes | B3: Crystals | B4: Binding | B5: HTS bioassays |
| C1: Small molecule roles | C2: Small molecule pathways | C3: Signaling pathways | C4: Biological proceses | C5: Interactome |
| D1: Transcription | D2: Cancer cell lines | D3: Chemical genetics | D4: Morphology | D5: Cell bioassays |
| E1: Therapeutic areas | E2: Indications | E3: Side effects | E4: Diseases & toxicology | E5: Drug–drug interactions |

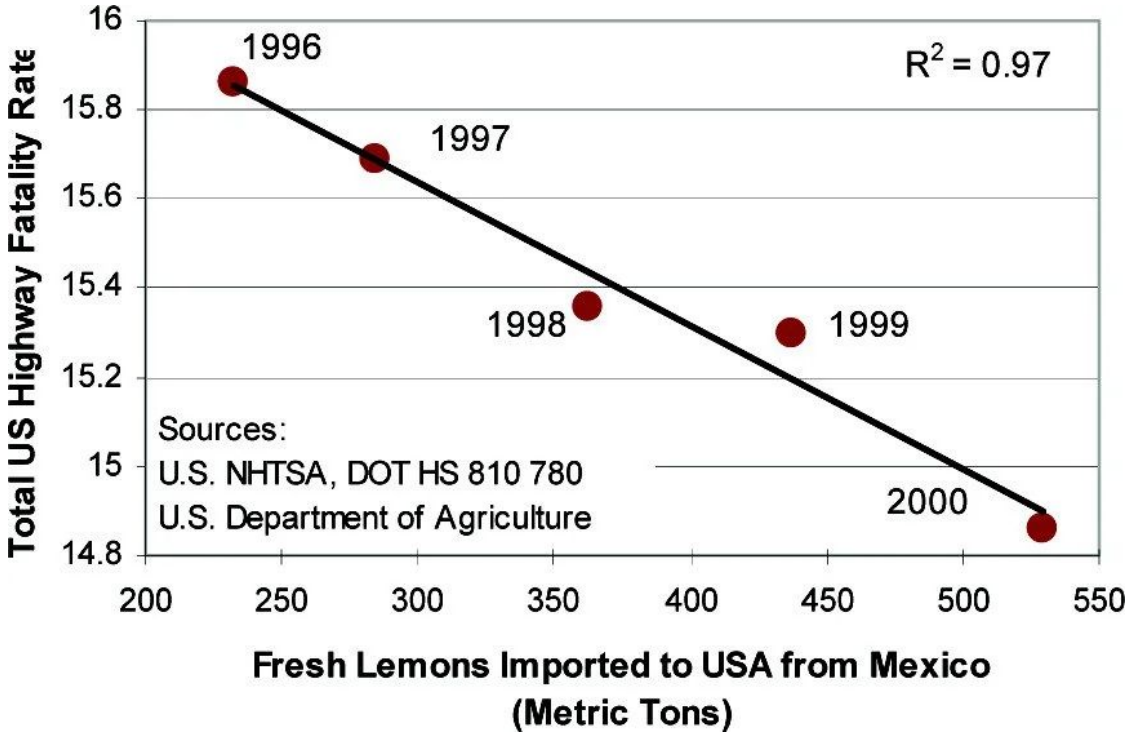
**A: Chemistry**
**B: Targets**
**C: Biological network**
**D: Cells**
**E: Clinical readout**

**Watch out biological activity cliffs:** Structural similarity does not imply similar activity. Top: three vascular endothelial growth factor receptor 2 (VEGFR2) ligands that represent different similarity−activity relationships.



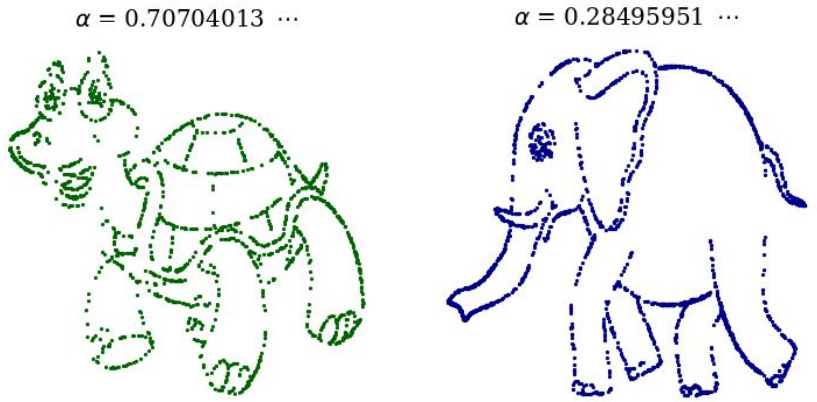

Duran-Frigola, Miquel, Eduardo Pauls, Oriol Guitart-Pla, Martino Bertoni, Víctor Alcalde, David Amat, Teresa Juan-Blanco, and Patrick Aloy. 2020. "Extending the Small-Molecule Similarity Principle to All Levels of Biology with the Chemical Checker." Nature Biotechnology, May, 1–10.

# Watchout 3: Do we need correlation or causation?




Johnson, Stephen R. "The Trouble with QSAR (or How I Learned To Stop Worrying and Embrace Fallacy)." Journal of Chemical Information and Modeling 48, no. 1 (January 1, 2008): 25–26. https://doi.org/10.1021/ci700332k

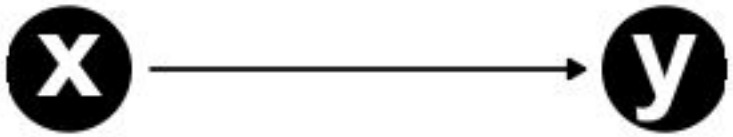
$$f_\alpha(x) = \sin^2\left(2^{x\tau} \arcsin\sqrt{\alpha}\right)$$



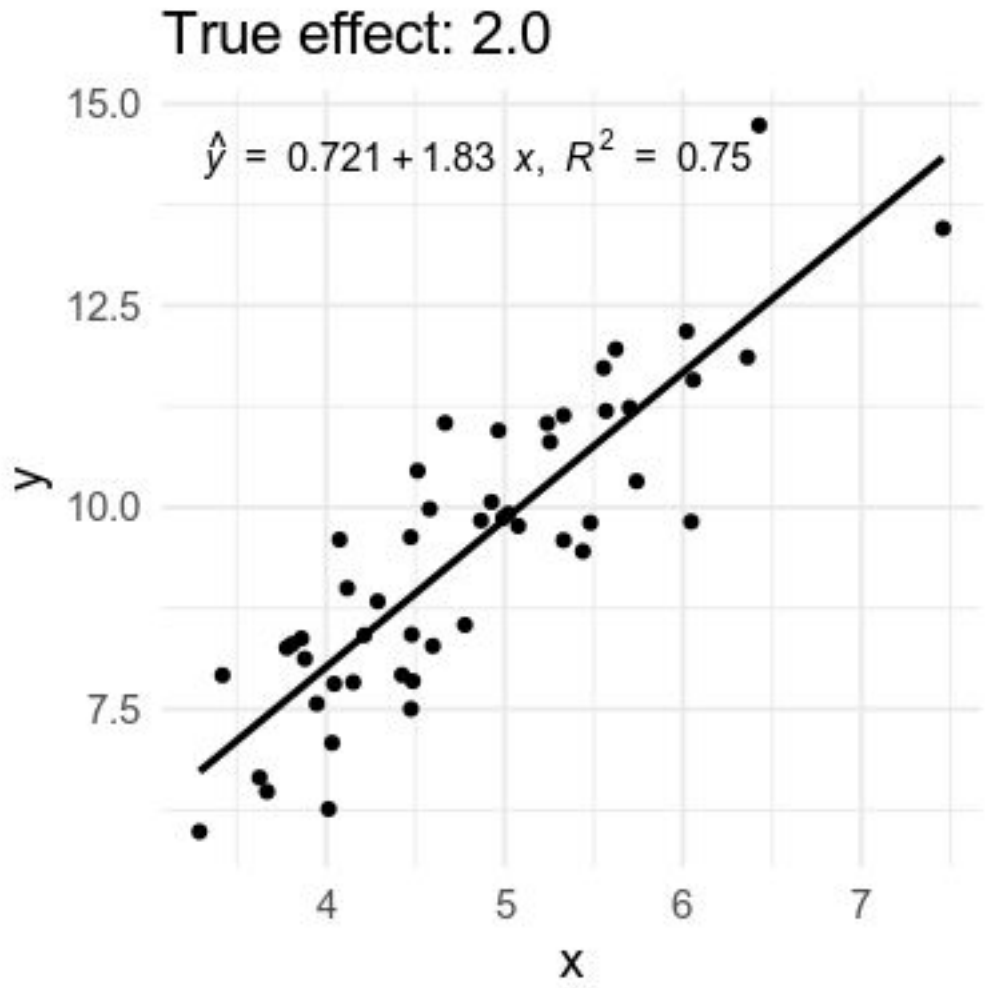

Boué, Laurent. "Real Numbers, Data Science and Chaos: How to Fit Any Dataset with a Single Parameter." ArXiv:1904.12320 [Cs, Stat], April 28, 2019. http://arxiv.org/abs/1904.12320.GitHub Repo. Also see: Drawing an elephant with four complex parameters

***End of lecture on 24.10.2025***

# *Generative models* shed light on correlation and causality



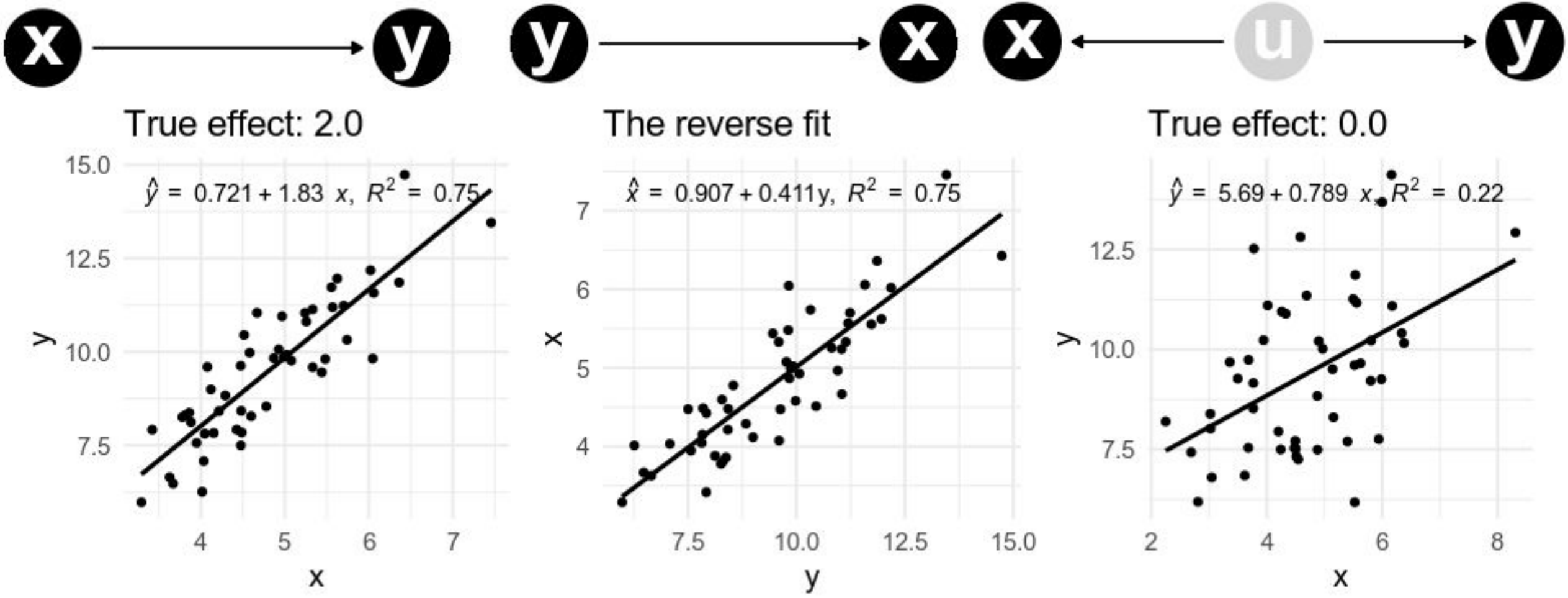

| | x | y |
|---|---|---|
| 1 | 4.926791 | 10.067779 |
| 2 | 4.479734 | 8.424283 |
| 3 | 4.289686 | 8.835629 |
| 4 | 4.474023 | 9.630499 |
| 5 | 4.214551 | 8.416680 |
| 6 | 6.057431 | 11.578080 |
| 7 | 4.597903 | 8.283025 |
| 8 | 5.021571 | 9.922731 |
| 9 | 3.627323 | 6.651222 |
| 10 | 5.622794 | 11.959972 |
| 11 | 5.555025 | 11.727815 |
| 12 | 4.966007 | 10.951562 |
| 13 | 5.076791 | 9.768299 |




Assumptions of the **generative model**:

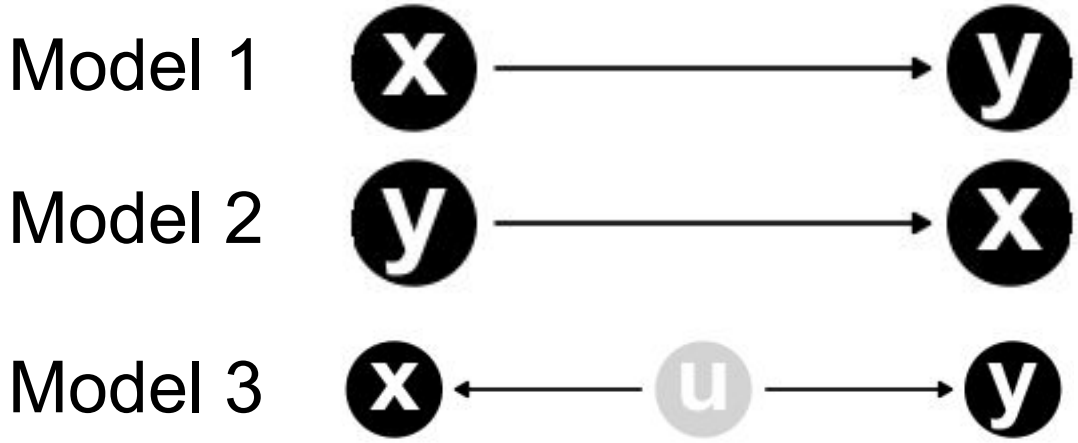
1. X is a random variable;
2. Every unit change of X induces a change of 2 units in Y.

# Correlation is caused by causation or confounding



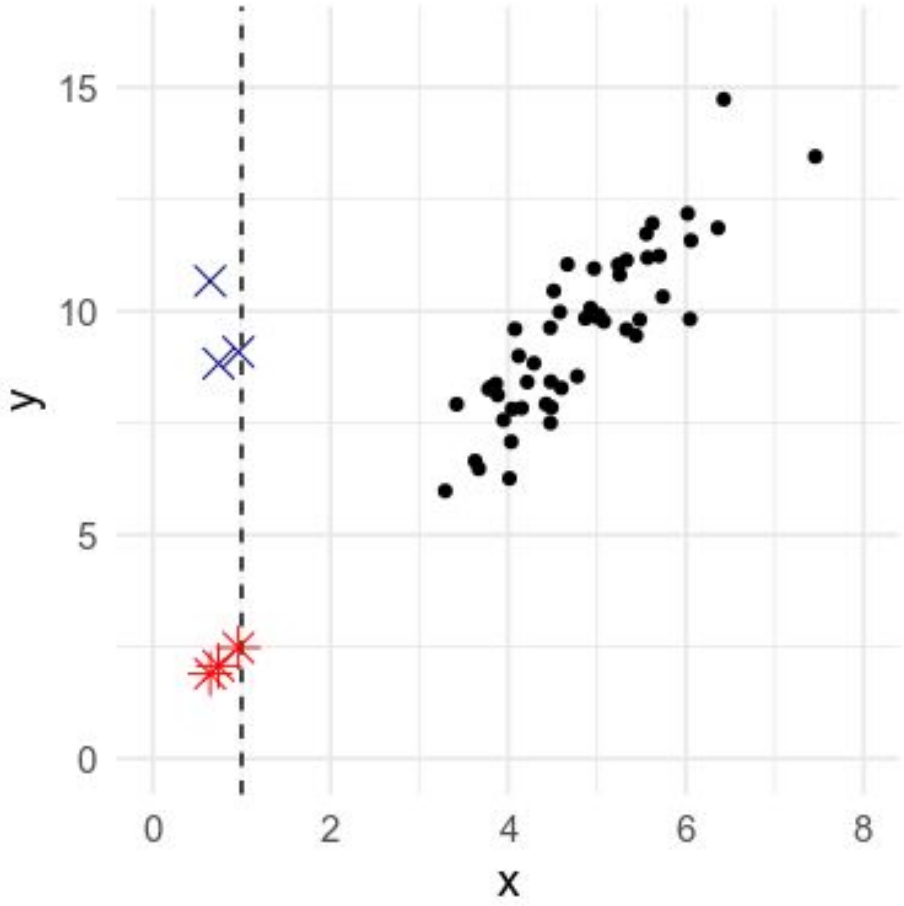

**Statistical models alone cannot derive causality from correlation**

# We learn causality by (1) listing models explicitly and (2) manipulating a variable and observe the outcomes




Assume that the data is generated by either Model 1, or Model 2, or Model 3. And assume that we can manipulate the value of X by setting it to 1.0 (the dash line).

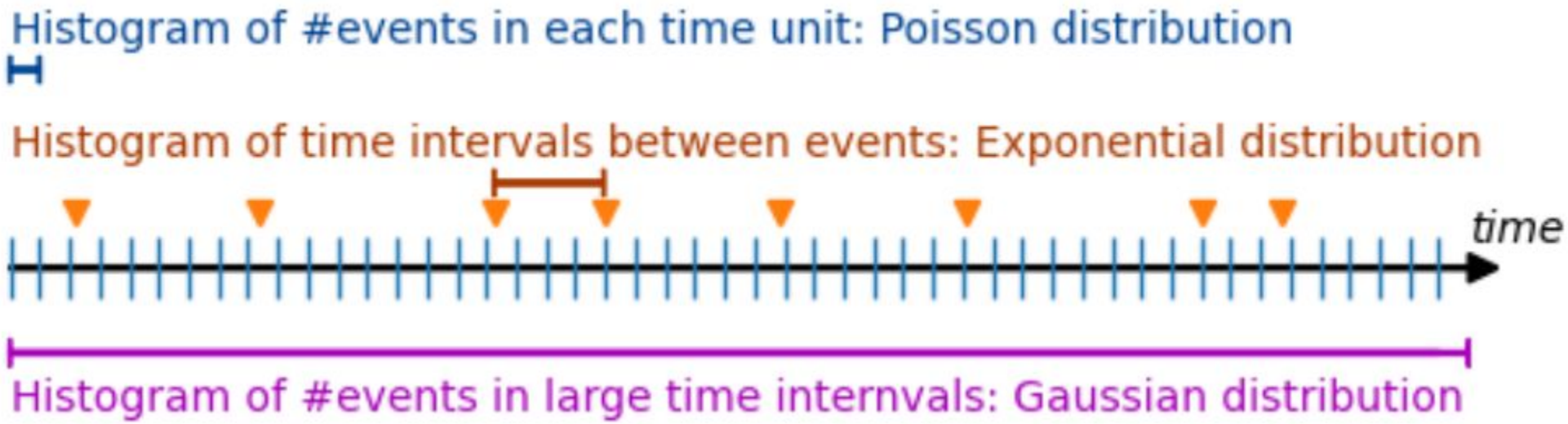
**Question: which outcomes (red stars or blue crosses) would support which models? Why?**



# Conclusions

1. Statistical and machine learning (ML) models can model linear and nonlinear relationships between variables.
2. Applying statistical and ML models in drug discovery needs to consider the facts that we always work on something new, structure similarity does not warrant activity similarity, and correlation is not causation.
3. Correlation can be caused by (1) causation, (2) confounding, (3) coincidence, (4) conspiracy, (5) collider, and (6) chronology.

# Relationship between Gaussian, Poisson, and exponential distributions




Each triangle indicates an event that happens continuously and independently from each other at a constant average rate $\lambda$. A process in which events occur so is known as a *Poisson point process*. *Histogram* in this plot means the probability histogram: the *x* axis contains count of the observed events, and the *y* axis contains count of the observed events divided by the total events.

Importantly, exponential distribution displays the property of *memoryless*. In the context of bolus PK, the *proportion* of drug degraded per time unit *k* is independent of previous degradation processes.