Computational Biology For Novel Targets and Novel Therapeutics: A Multiscale-Modeling Approach

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Pre-read, not shown

Pre-read of the lecture

- *Multiscale modeling of drug mechanism and safety*, Drug Discovery Today (2020)
- *An introduction to machine learning*, Clinical Pharmacology & Therapeutics (2020)
- *Causal inference in drug discovery and development*, *arXiv*, 2022

Acknowledgements

- **Predictive Modeling and Data Analysis (PMDA) team members,** especially for the work introduced here performed by Fabian Birzele, Iakov Davydov, Petra Schwalie, Daniel Marbach, Guido Steiner, Roland Schmucki, Laura Badi, Klas Hatje, Martin Ebeling, Marco Berrera, Nikolaos Bertenis, Tony Kam-Thong, Alex Seitz, Sophia Maedler, Luis Wyss, Rafael Mueller, Miroslav Phan, Andrea Ciuprina, and Anthony Sonrel.
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Computational biology transforms drug discovery and development

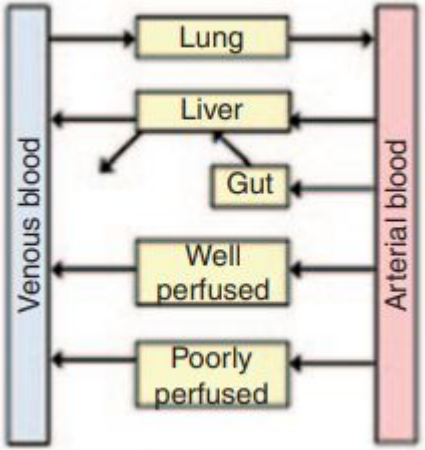
Integrating public & internal knowledge and data

Optimizing molecules by data- and model-driven approaches

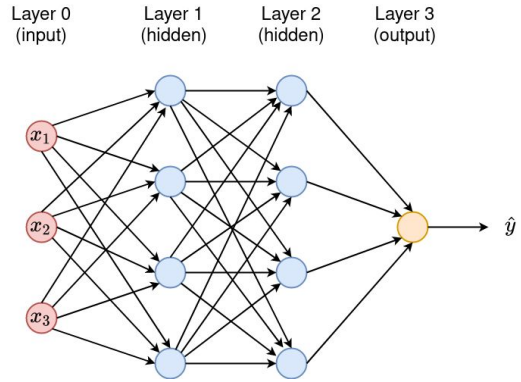
Understanding mechanism and safety profiles

Translating clinical findings to better targets, preclinical models, and molecules

Three types of computational models

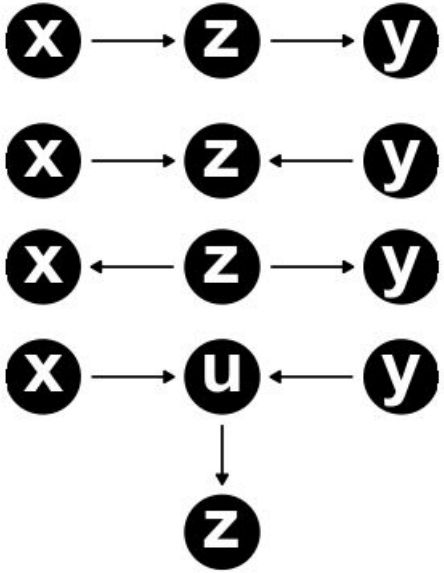


Mechanistic models



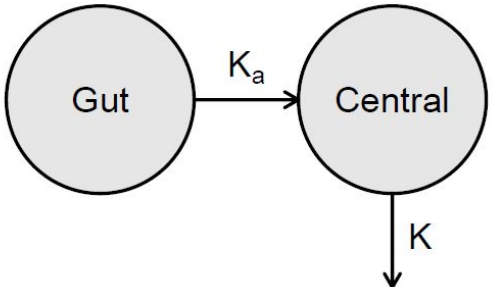
$$y \sim f(x)$$

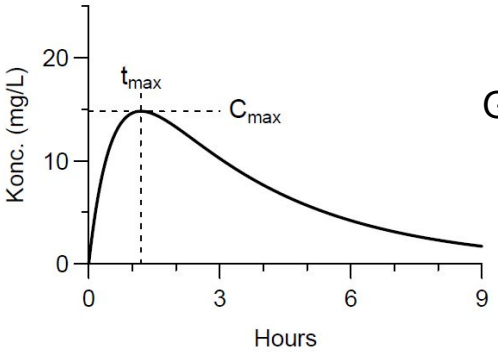
Statistical and machine-learning models



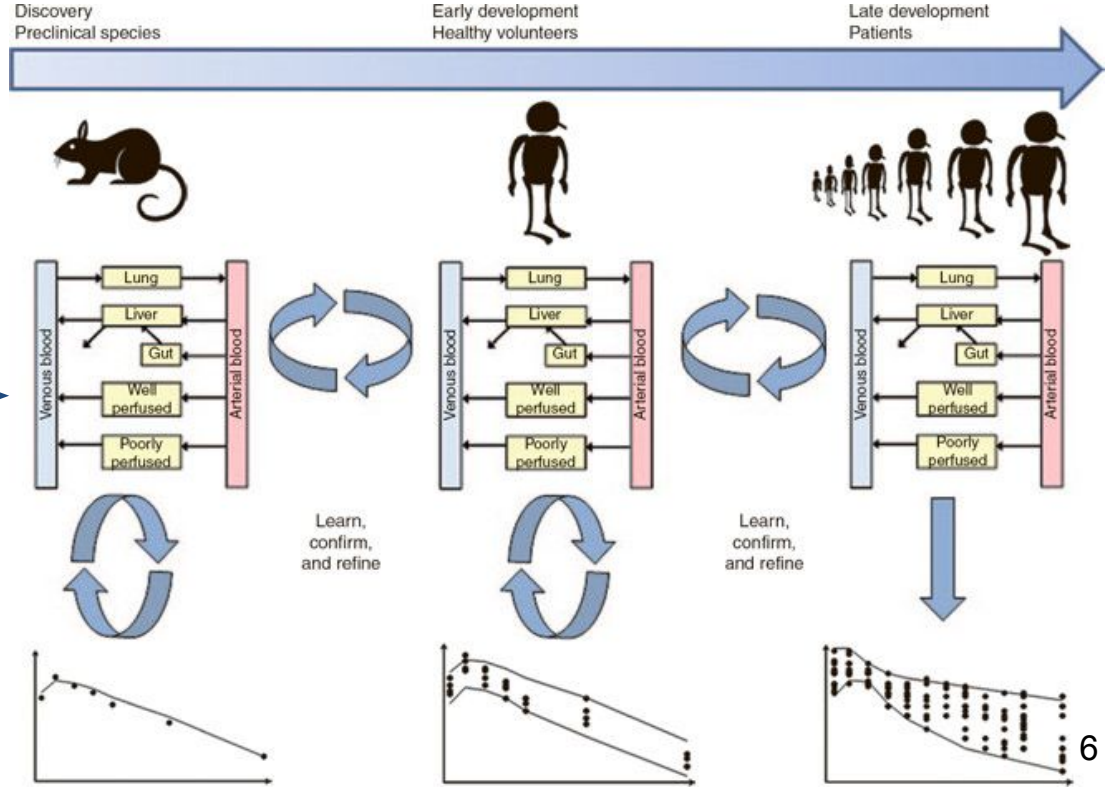
Causal models

A mechanistic model: physiologically based pharmacokinetic modeling



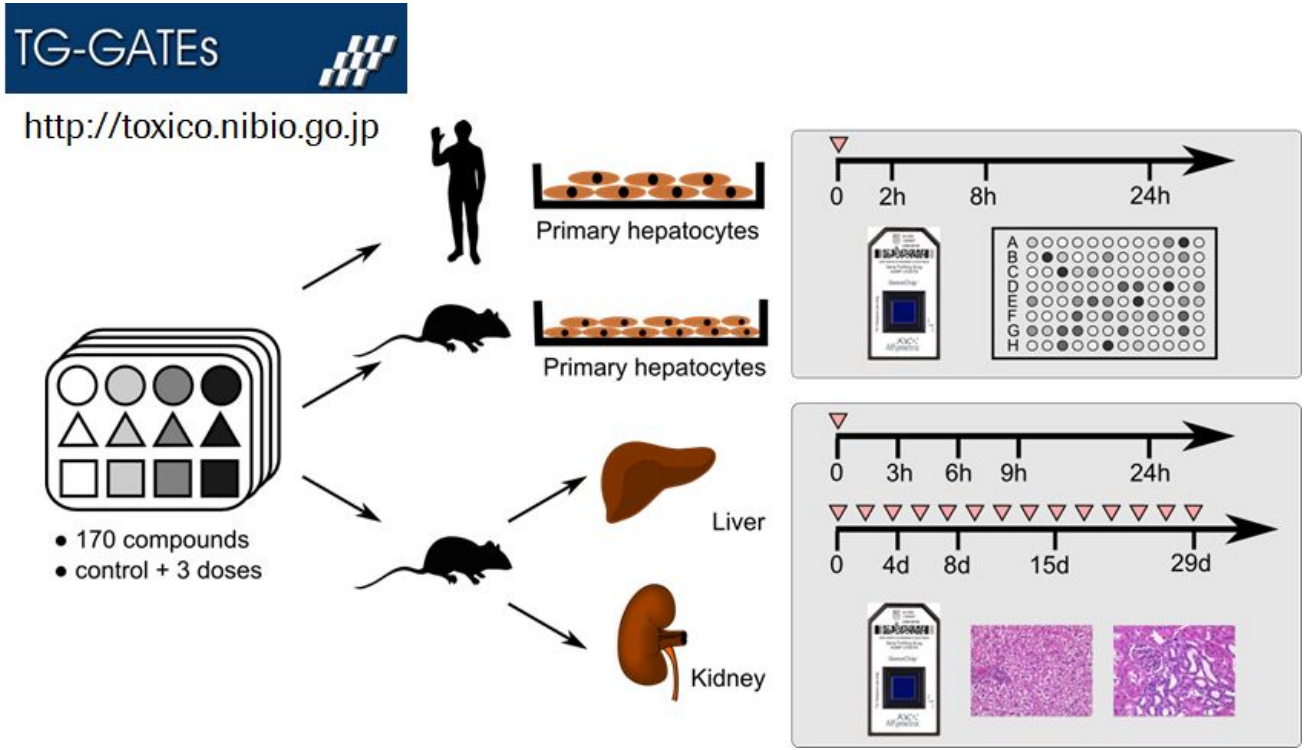


Generalization



Jones and Rowland-Yeo, 2013

No mechanistic models are available for huge amount of data



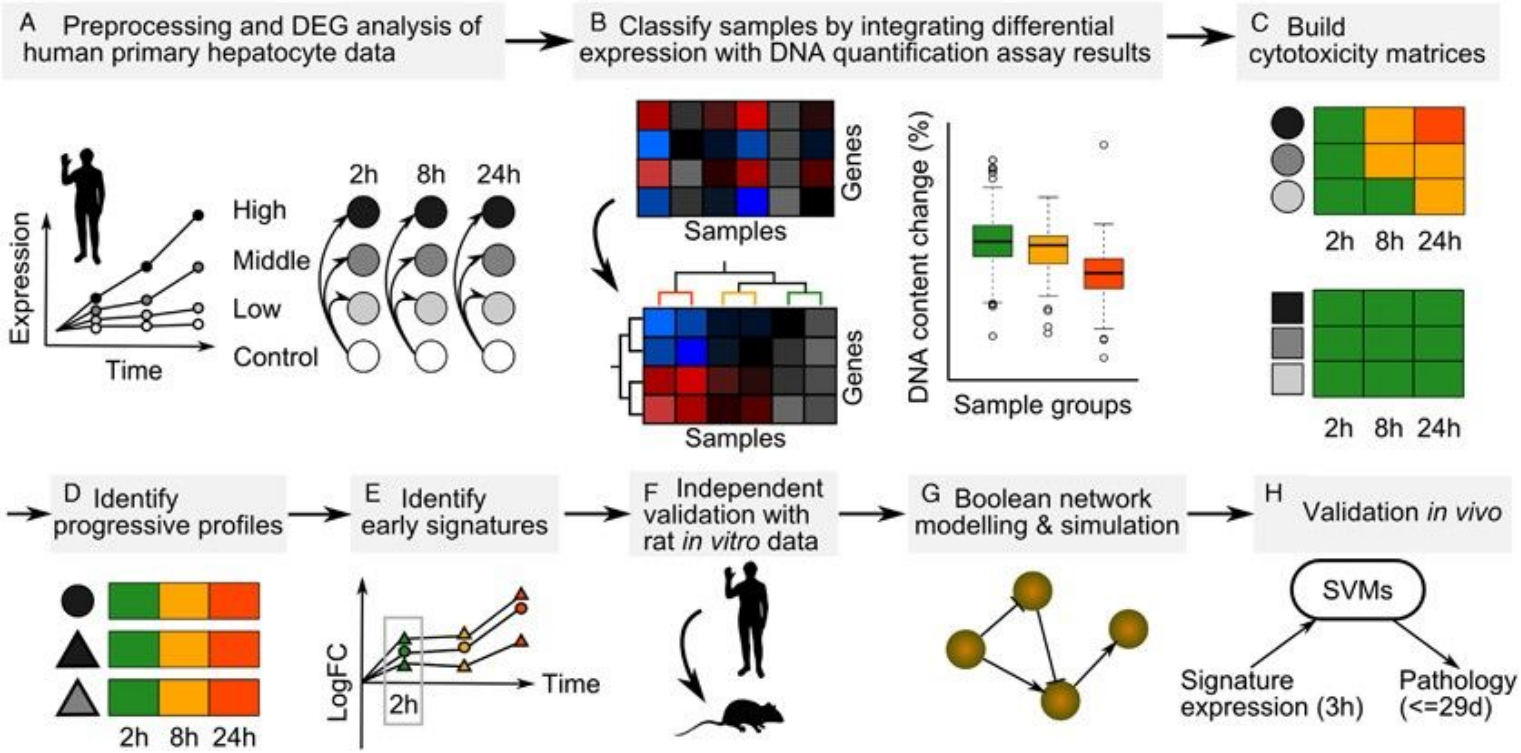
170
Compounds

>2000
Cellular assays

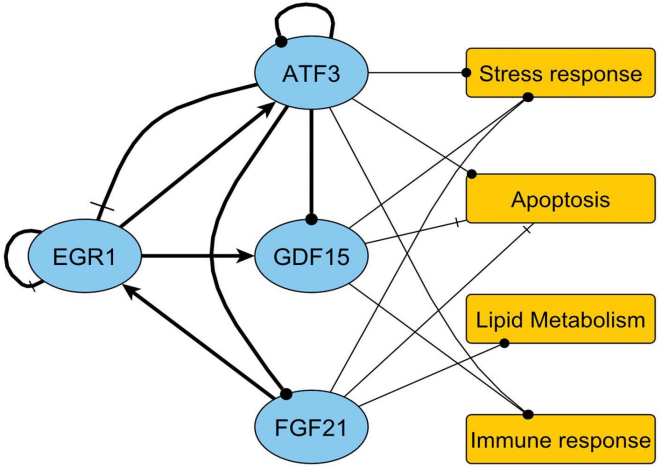
>12000
Pathology records

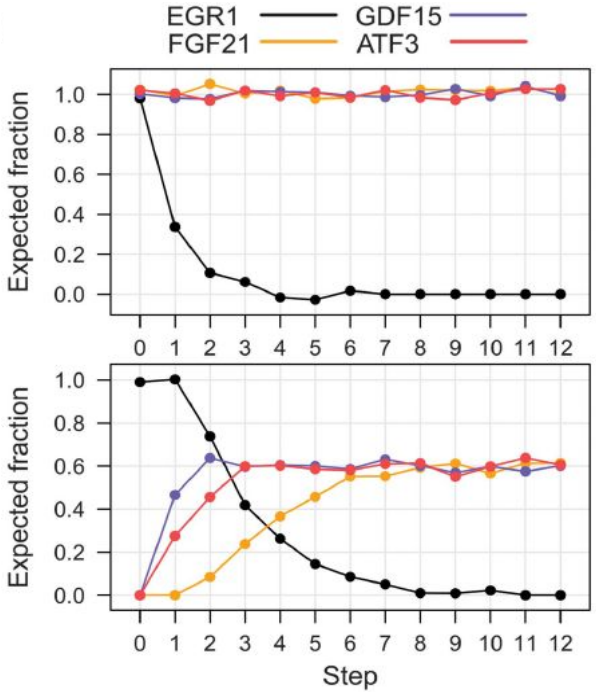
>24000
Expression profiles

Statistical models identify hidden patterns and discover correlations



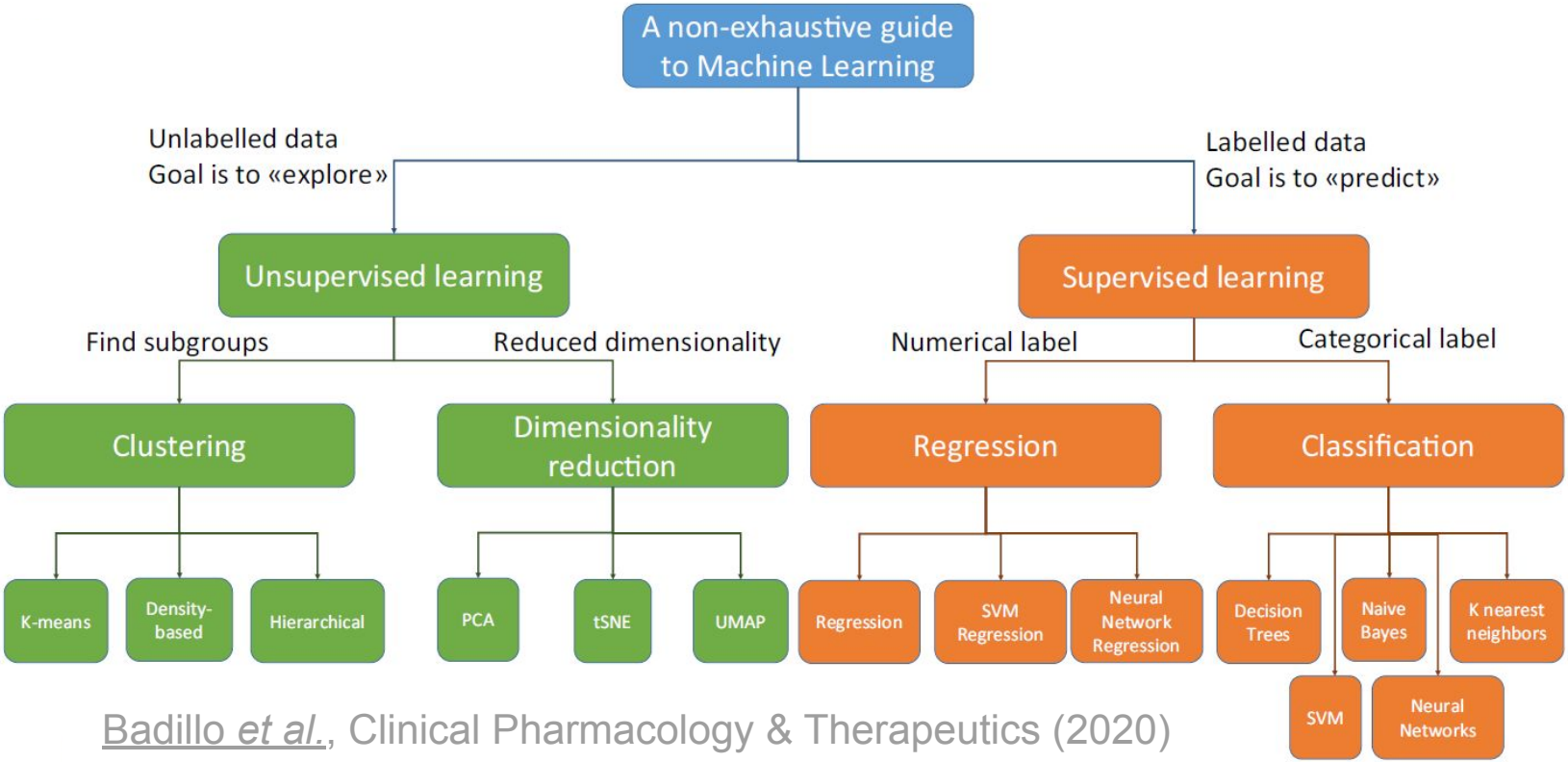
Statistical models and prior knowledge can give rise to mechanistic/causal models





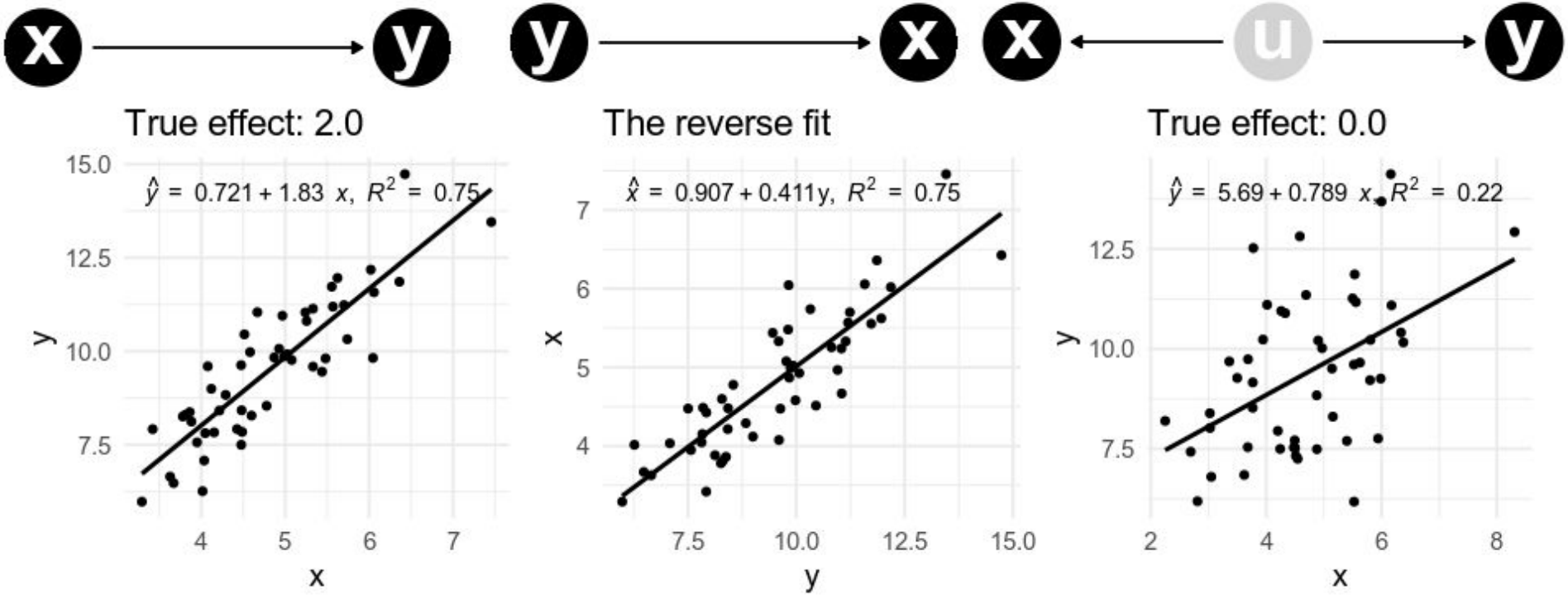
Zhang *et al.*, The Pharmacogenomics Journal (2014)

Machine learning expands and enhances statistical models



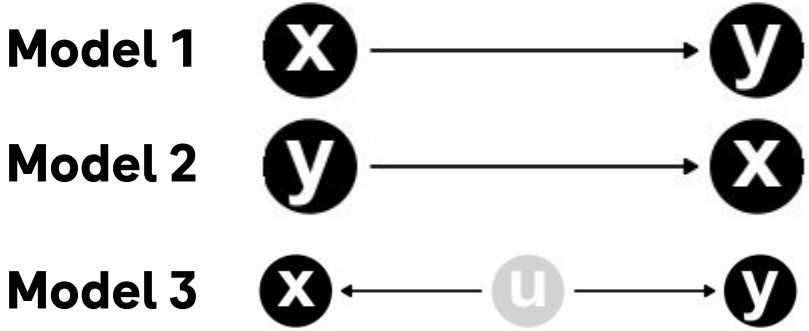
Badillo *et al.*, Clinical Pharmacology & Therapeutics (2020)

Correlation is caused by causation or confounding



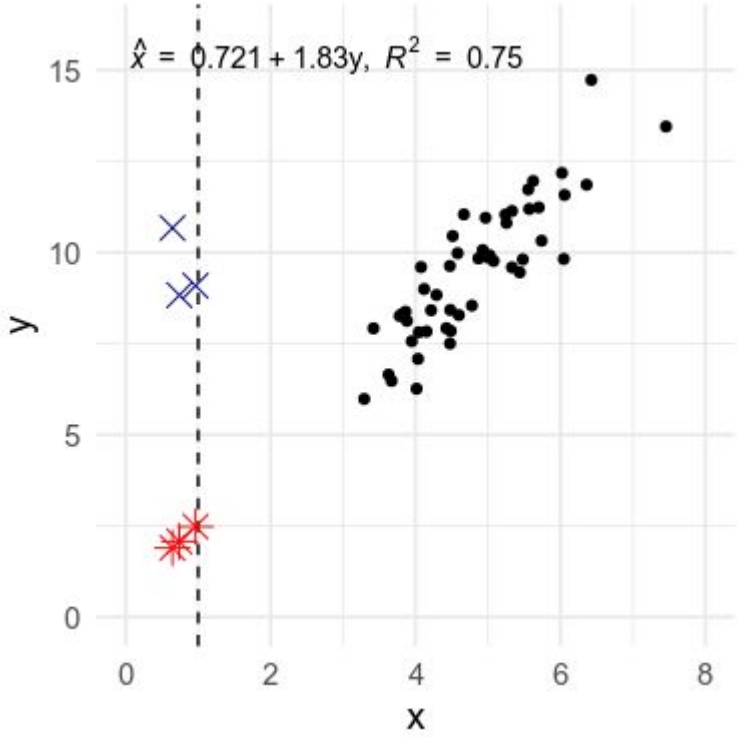
Statistical models alone cannot derive causality from correlation

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?

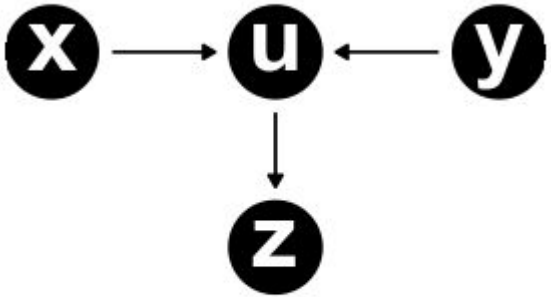


Causality is crucial for drug discovery

Biomarker, tox study, pathology, omics data, real-world data, EHR, ...

	x	z	y
1	0.835386320	1	-0.73897252
2	-0.005354014	-1	-0.82972315
3	0.058788286	1	0.76213369
4	-1.015602246	-1	-0.05951719
5	-0.339569780	-1	-0.11745910
6	-0.041077979	-1	-1.28243716
7	0.363740407	1	-0.30570762
8	0.119496314	-1	-1.19932461
9	0.257108454	-1	-1.06044066
10	0.304537158	-1	-0.43396492

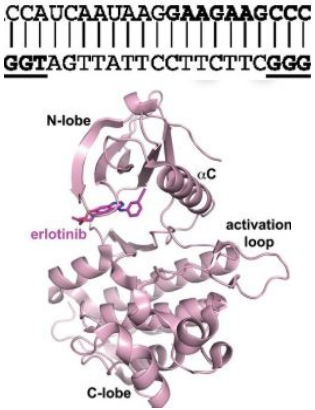
The descendant



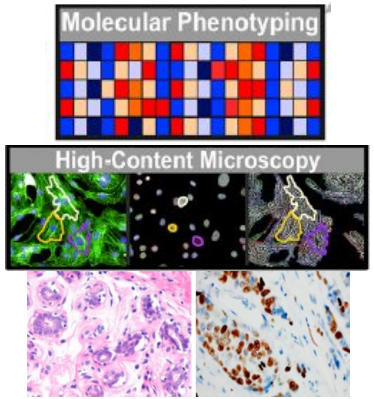
We need both models (knowledge + assumptions) and data to infer causality.

Multiscale Modelling of Drug Mechanism and Safety

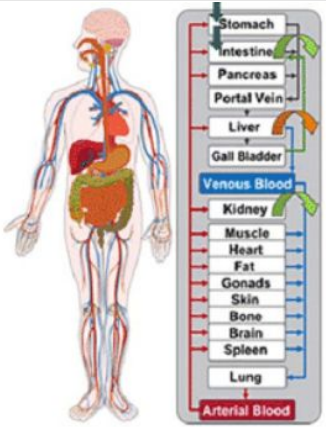
Forward translation



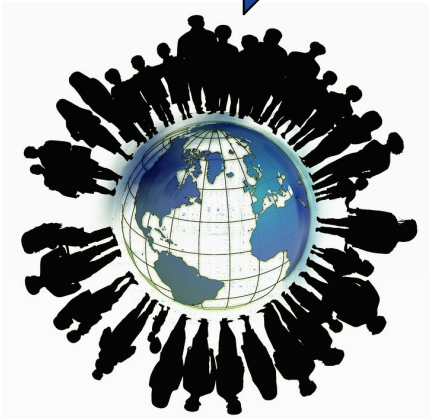
Molecular modeling



Omics & cellular modeling



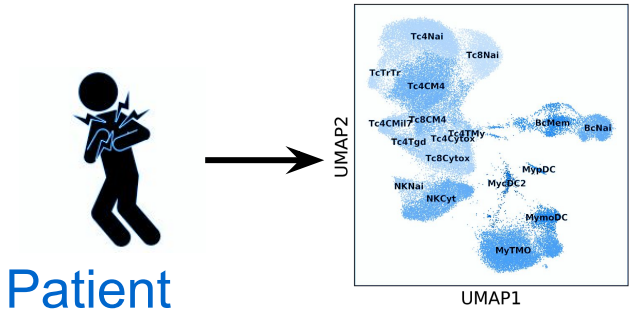
Organ & system modeling



Populational modeling

Reverse translation

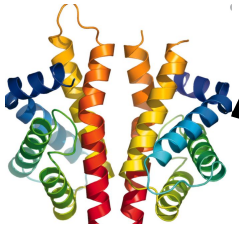
Computational biologists work with experimentalists to empower drug discovery



Single-cell biology

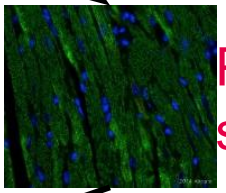
Patient

Target cell type(s)



Target-based discovery

Molecular Phenotyping



Phenotypic screening

Chemogenomic or genetic screening

Conclusions

- Computational biologists in drug discovery build and use mechanistic, causal, and statistical/machine-learning models.
- Model and data offer insights into disease biology, as well as into pharmacology and safety profiles of drug candidates.
- We experiment with a multiscale-modeling approach to drug discovery by integrating data and models at molecular, cellular, organ and system, and population levels.

Interested in learning more about quantitative aspects of drug discovery?

- Fall Semesters: *Applied Mathematics and Informatics In Drug Discovery* (AMIDD): an introductory course.
  - See more information at http://AMIDD.ch.
- Spring Semesters: *Mathematical and Computational Biology in Drug Discovery* (MCBDD), an advanced course.
  - See more information at http://MCBDD.ch.

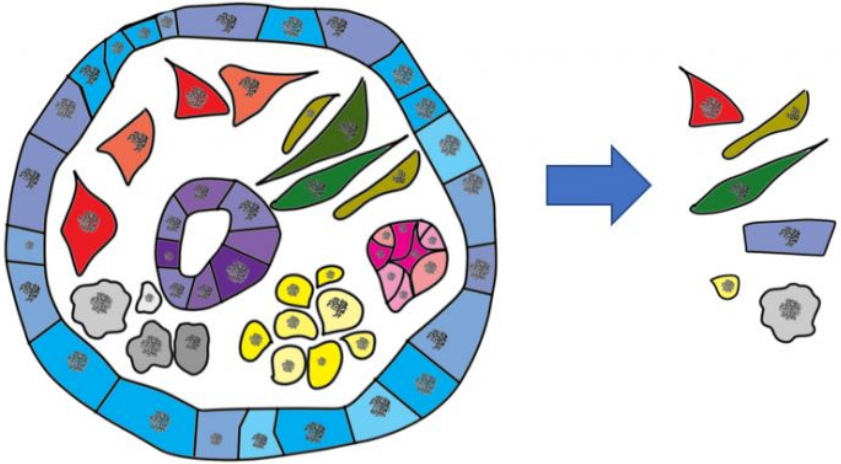
Doing now what patients need next

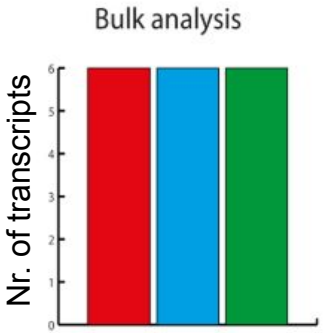
Backup material

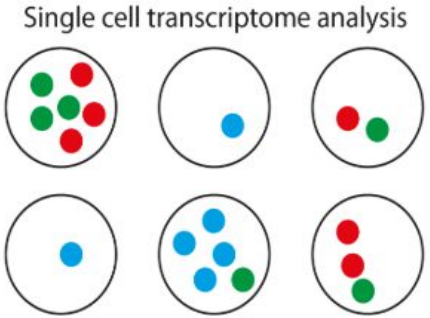
Types of computational models

	Prediction for independent and identically distributed samples	Prediction under changing distributions or intervention	Answer counterfactual questions	Obtain physical insight	Learn from data (data-driven discovery)
Mechanistic models	yes	yes	yes	yes	maybe
Causal models	yes	yes	maybe	maybe	maybe
Statistical models	yes	no	no	no	yes

Target identification and mechanism & safety understanding benefits from single-cell biology







www.evocell-itn.eu; Macaulay & Voet, PLoS Genetics 2014

Single-cell biology fuels drug discovery

Disease understanding: disease-specific cell types and states

Biomarker and patient stratification: which genes should we measure in which cell type(s)?

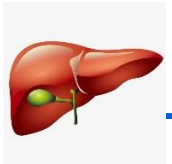
Target identification: expression pattern in health and disease across cell types

MoA and safety modeling: perturbation effect at single-cell level

Single-cell sequencing (scSeq) workflow

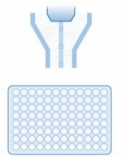
Tissue dissociation

Single cell capture and transcriptome sequencing



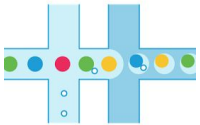
Solid tissue

Dissociated cells/nuclei



Flow cytometry 96-384 cells

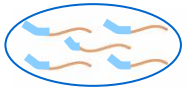
Cell/nuclei suspension



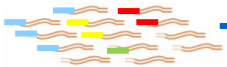
Droplet microfluidics 1000s of cells

Throughput

Single cells or nuclei



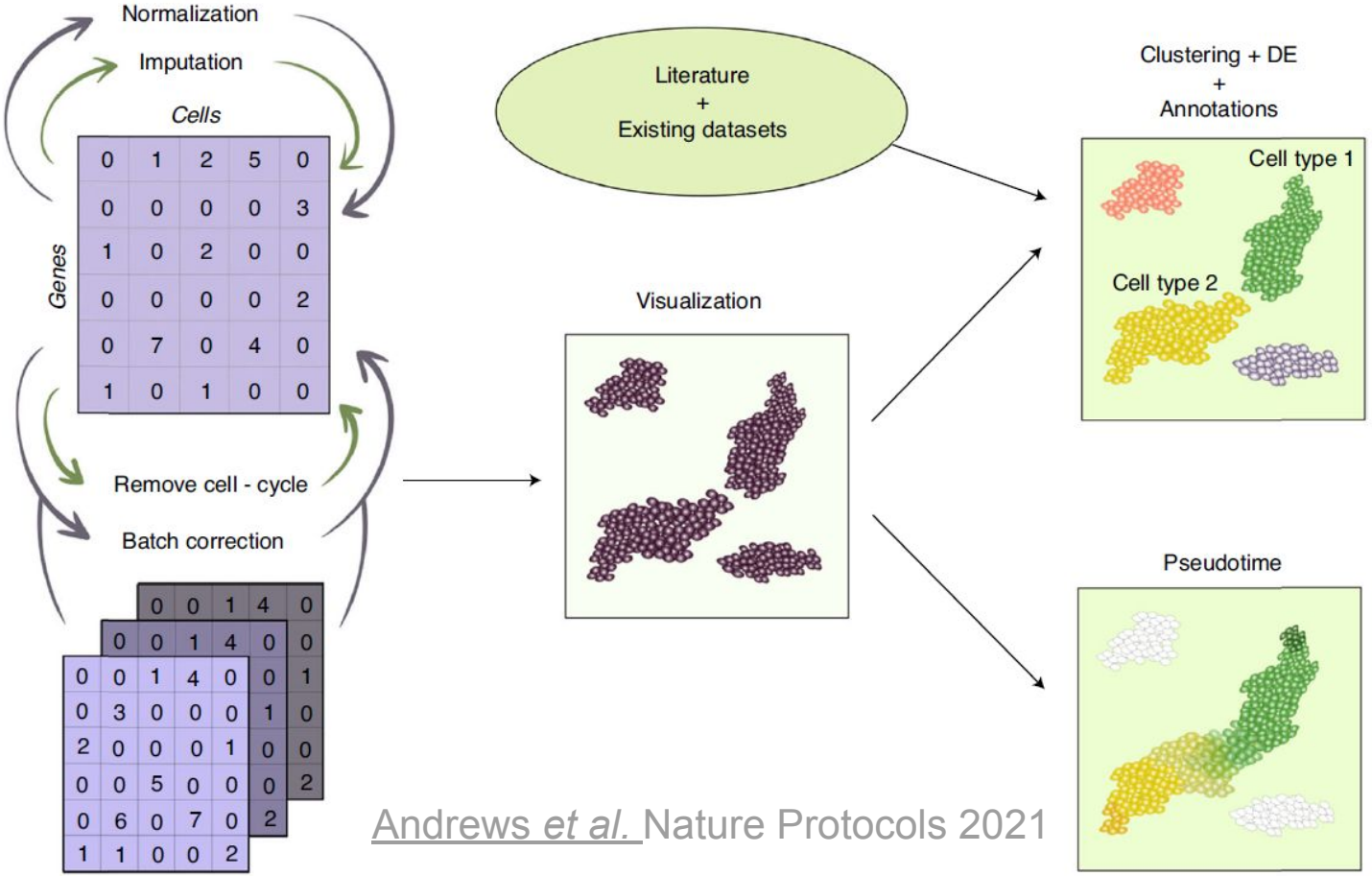
cDNA



Pooled cDNA libraries

Next-Generation Sequencing

Overview of the computational workflow



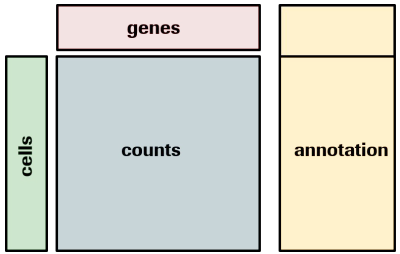
Andrews *et al.* Nature Protocols 2021

Open-source BESCA (BEDA's single cell analysis)

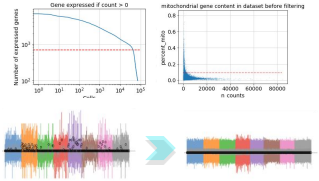
An automatized standard workflow

Data loading → Preprocessing → Clustering → Visualization → Analysis

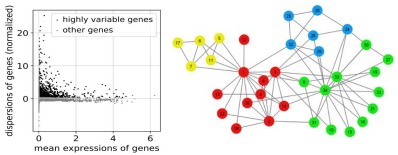
From FAIR format



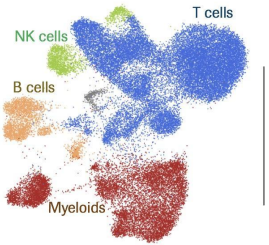
Quality Control
Filtering,
Normalization



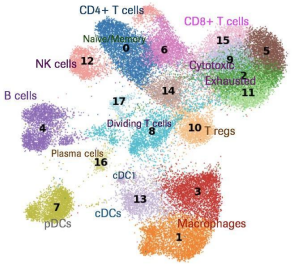
Dimensionality
reduction
Clustering



UMAP



Cell type
characterisation



Maedler et al., NAR Genomics and Bioinformatics, 2021

https://github.com/bedapub/besca

Doing now what patients need next