Mathematical and Computational Biology In Drug Discovery (2024)

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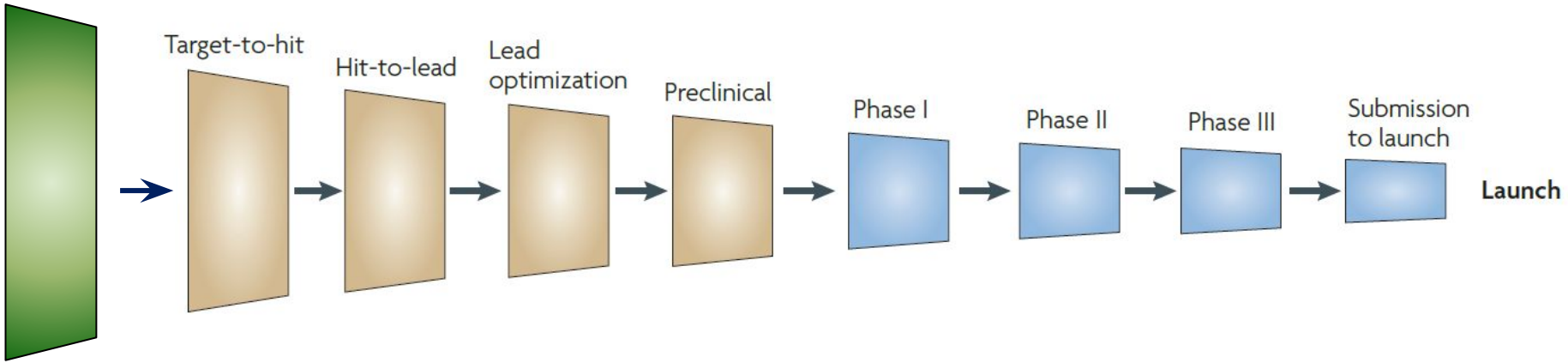
Administrivia

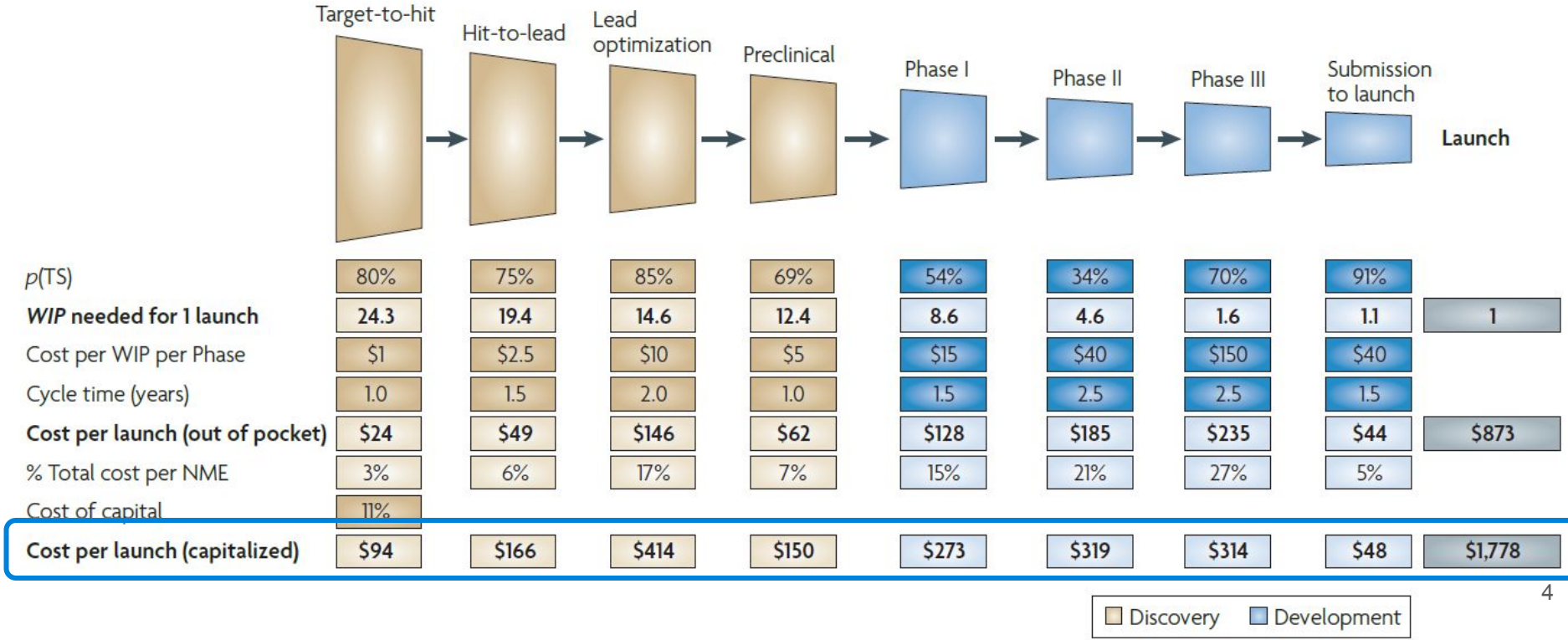
- Please fill **the pre-course survey**.
- Grades are given by participation (50%) and offline activities (50%).
- I hope the course is a seminar more than a lecture: share your question and let's discuss!
- **Any more questions?**

A linear view of drug discovery

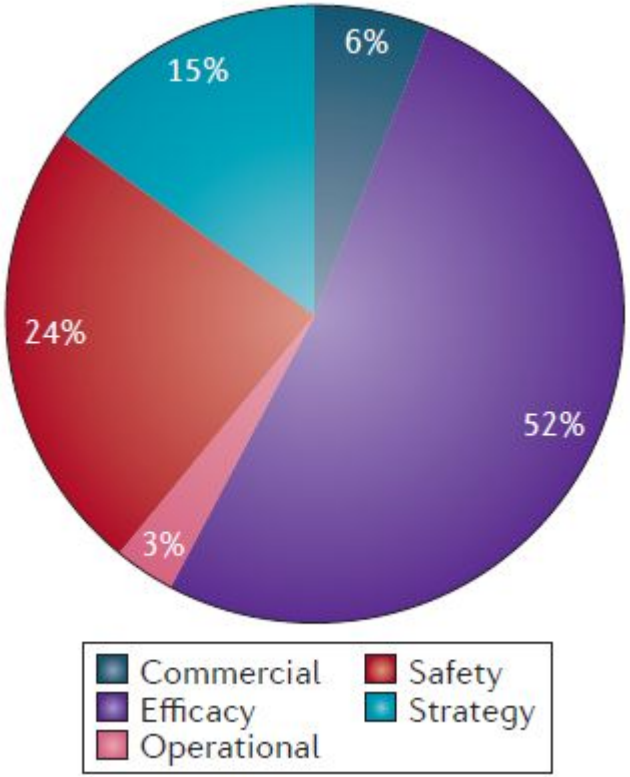
Target identification & assessment



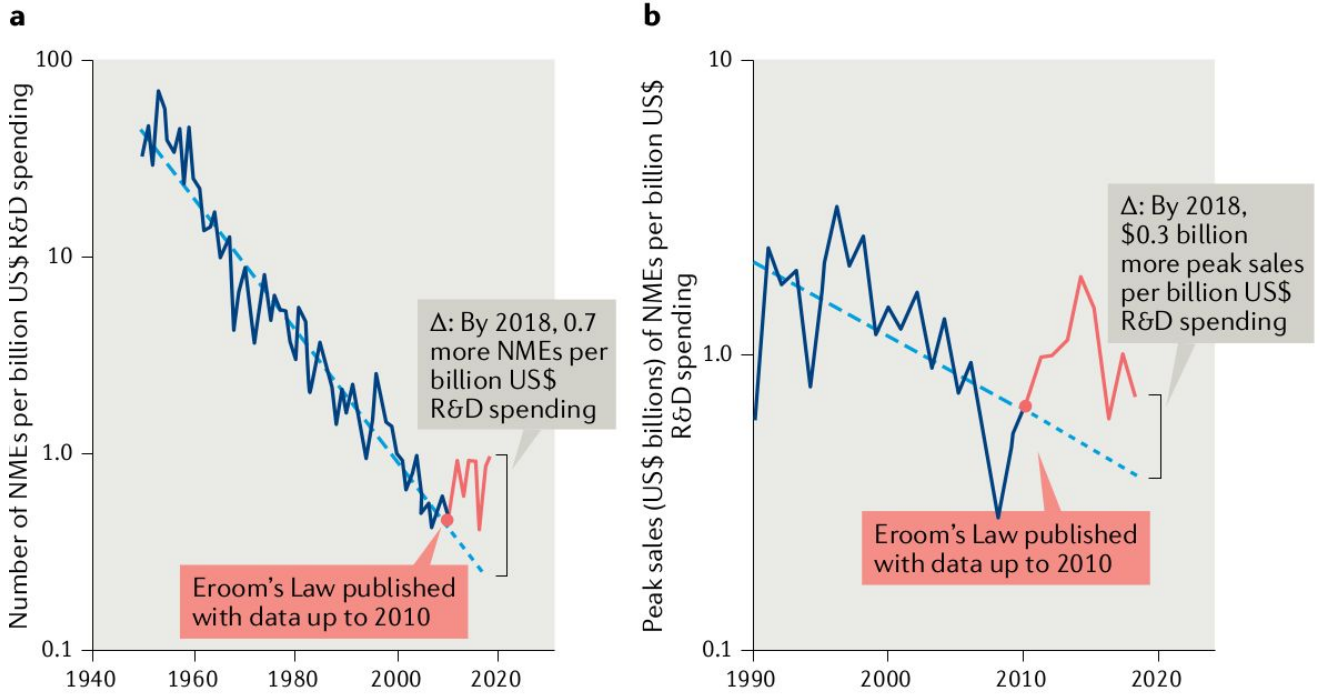
Discussion: conclusions from the figures?

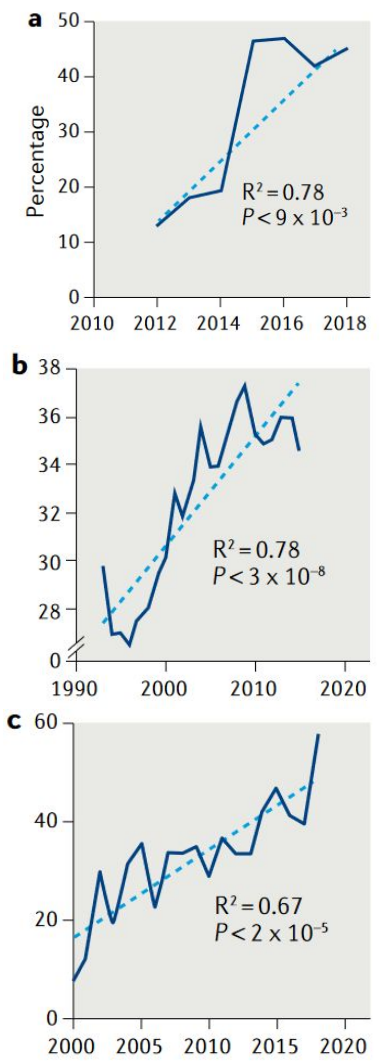


Failure analysis: 2013-2015



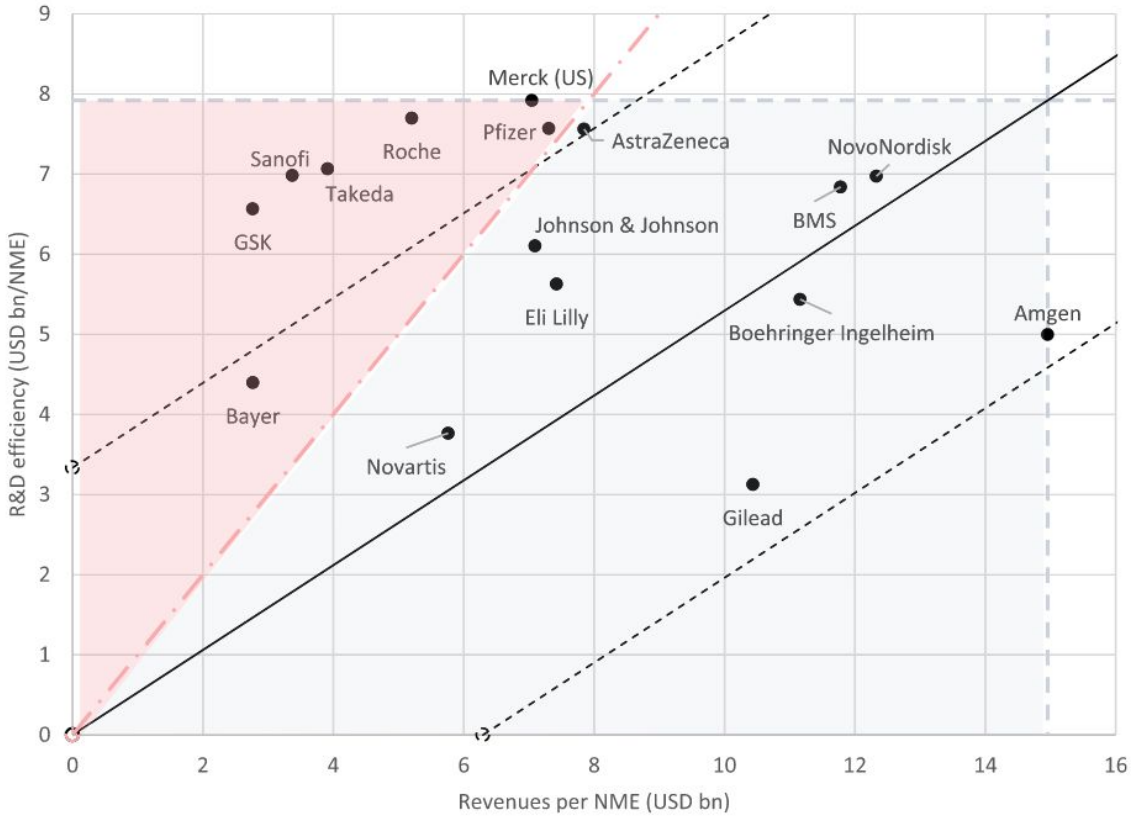
The Eroom's Law



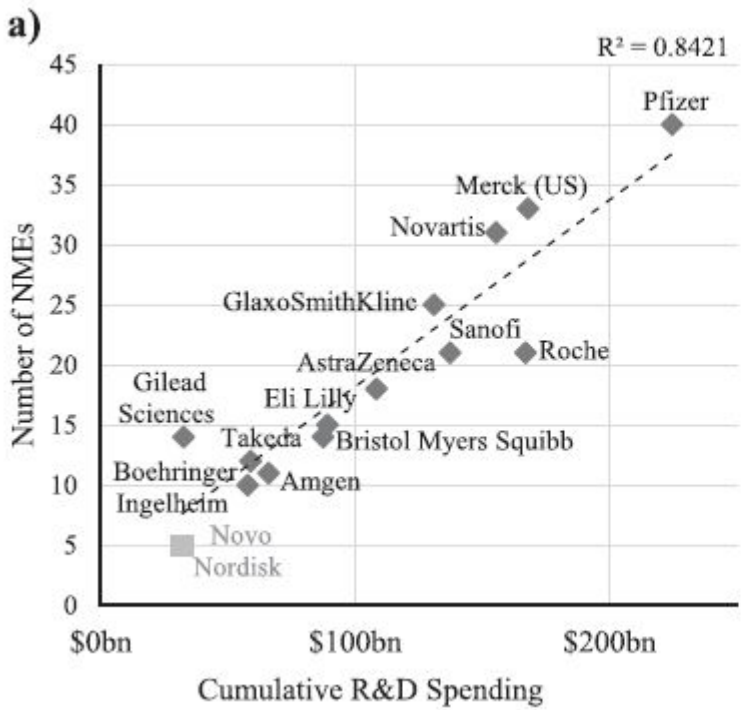


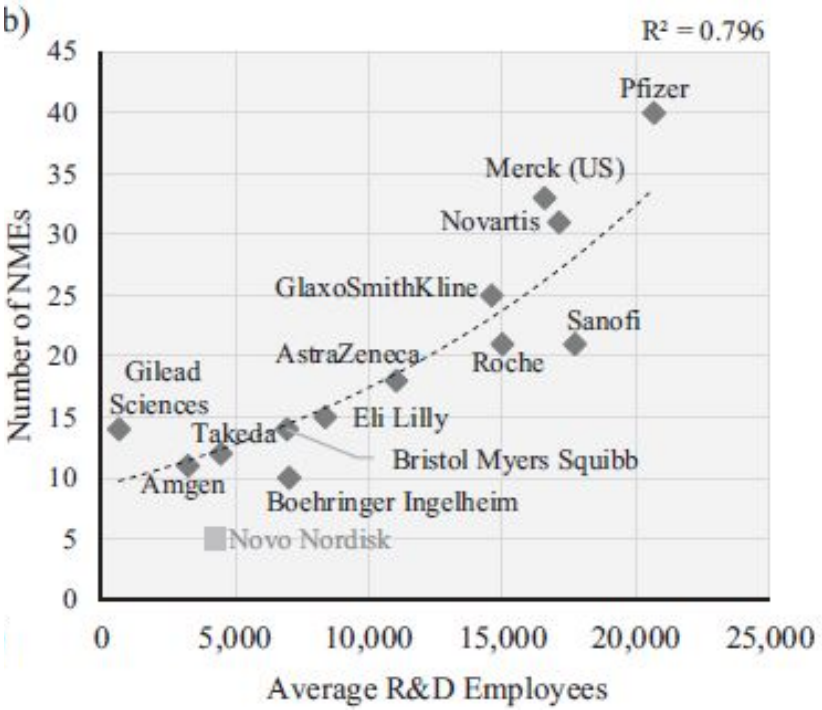
Left: R&D cost by year. Right: correlation with genetic evidence (a), focused indication (b), and rare diseases (c).

R&D productivity of leading pharma companies (2001–2020).



Investment and collaboration are necessary



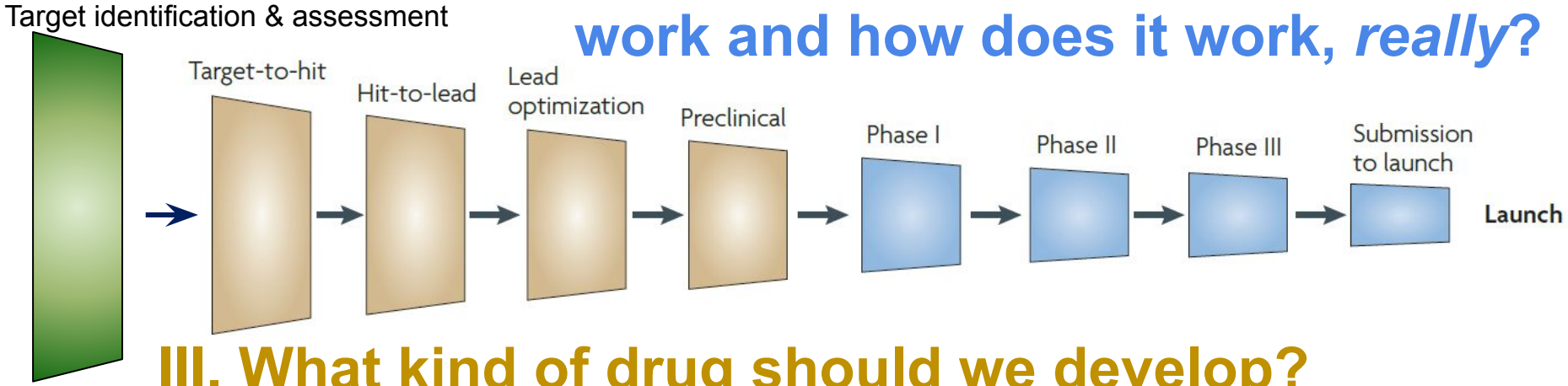


Learnings from numbers

1. Cost of target assessment and identification is not explicit.
2. Clinical studies are expensive, but picking a wrong target is twice as expensive.
3. It is probably wise to *infer* efficacy and safety profiles of drugs as accurately as possible.

Questions that we will address in this course

V: For which patients will the drug work and how does it work, *really*?



III. What kind of drug should we develop?

IV. What efficacy and safety profiles can we expect?

I. What makes a good drug target?

II. What can we do if there are no good targets?

Drug Discovery	Biology	Math./Comp.
Target identification, assessment, and phenotypic screening	• Genomics • Genetics • Gene expression • Chemical biology	• Statistical modelling • Machine learning • Mechanistic modelling
Drug modality and preclinical modelling	• RNA, antisense oligonucleotides, and antibodies • Gene expression • Network analysis	• Monte-Carlo methods • Generative models • Clustering
Biomarker, clinical modelling and reverse translation	• Population genetics • Gene expression • Pharmacokinetics and pharmacodynamics	• Causal analysis • Machine learning • Agent-based modelling

Common modelling approaches

- Statistical modelling
- Causal inference
- Mechanistic modelling
  - ODEs (compartment models)
  - Agent-based models (particle models)
  - Networks (graphical and boolean models)

Learn more about reproducible research

- The Missing Semester of Computer Science
- Software Carpentry (Unix Shell, Git, Python & R)
- Genomics Workshop of Data Carpentry
- *Clean Code* by Robert C. Martin
- Open-source tutorials of respective tools, such as sphinx, Snakemake, conda, or docker. Videos or podcasts work just as fine.

Take-home messages

- Drug discovery identifies agents modulating human disease biology as a hierarchical complex adaptive system.
- Mathematical and computational biology studies interactions within the system and help to build predictive models.
- Reproducible computational research help ourselves and others build a sustainable working environment.

Offline activities

1. Fill the pre-course survey.
2. Read ‘How a pioneering diabetes drug offers hope for preventing autoimmune disorders’ by Elie Dolgin (Nature, 2023). Think about the question: **what roles/parties of interest (pharma company, patients, etc.) are involved in the business of drug discovery and development?**

References

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10. Zeberg, Hugo, and Svante Pääbo. 2020. “The Major Genetic Risk Factor for Severe COVID-19 Is Inherited from Neanderthals.” Nature 587 (7835): 610–12. https://doi.org/10.1038/s41586-020-2818-3.
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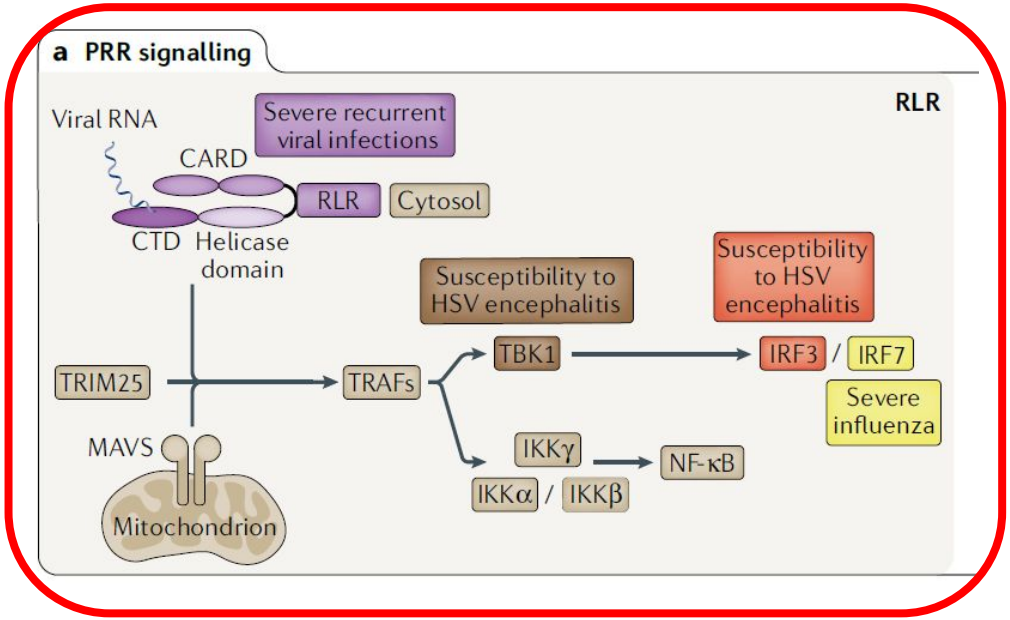
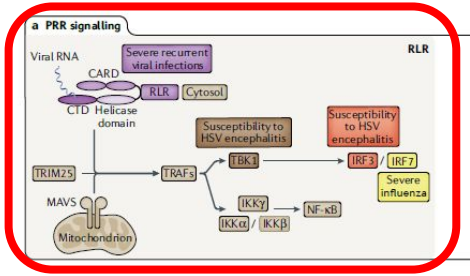
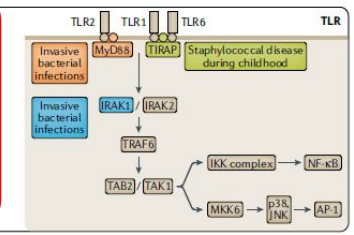
Backup and License

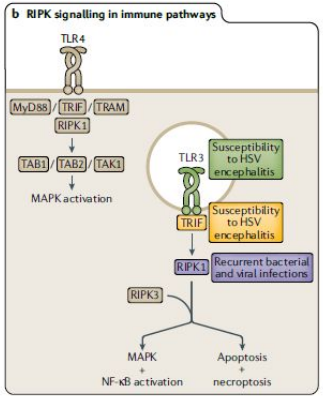
Complex Adaptive System

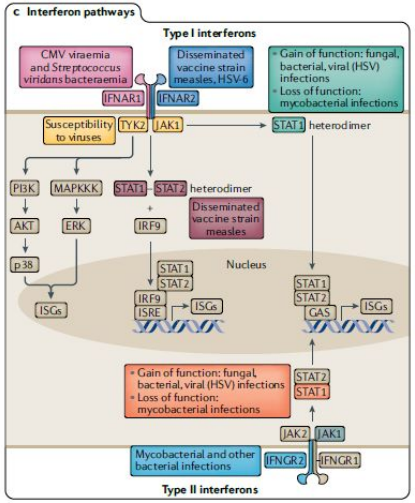
1. Parallel information channels
2. Conditional actions (if/then)
3. Modularity

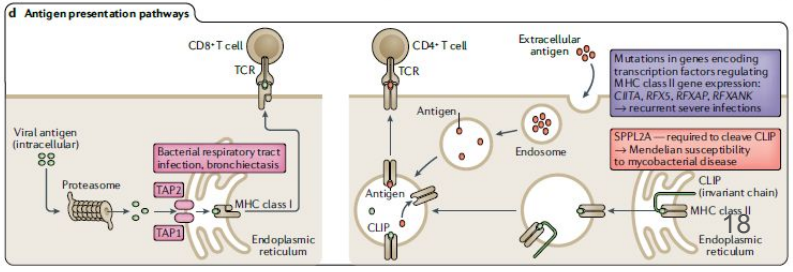












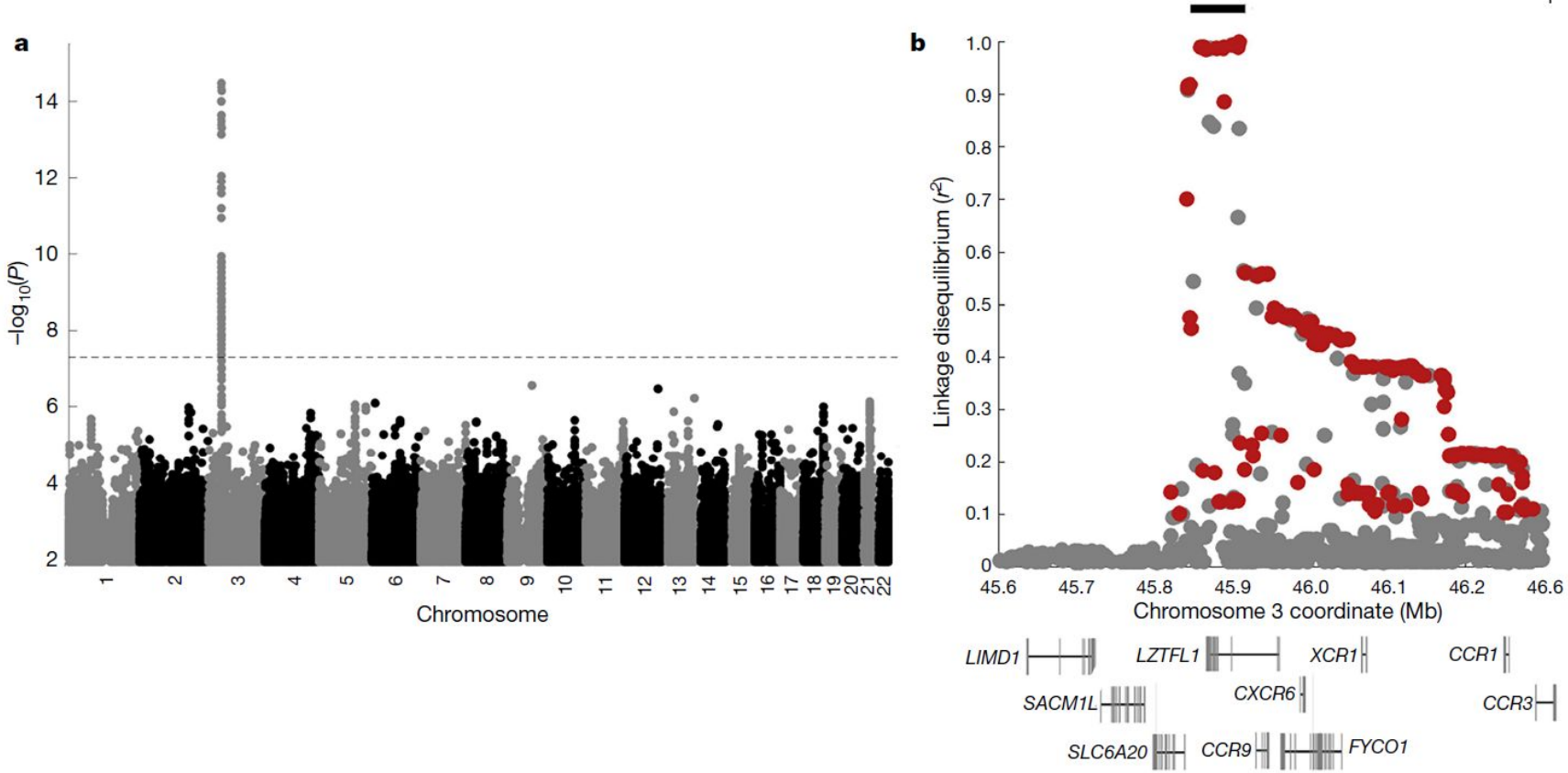
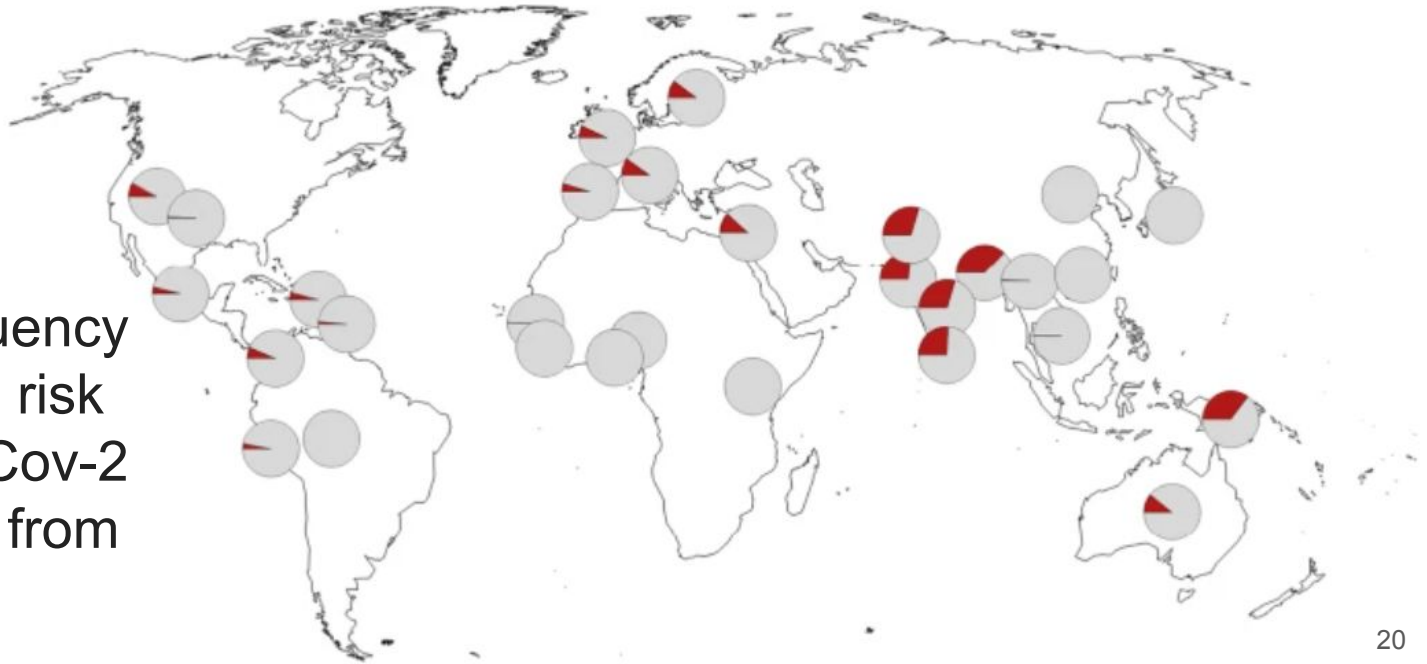


Fig. 1 | Genetic variants associated with severe COVID-19. a, Manhattan plot of a genome-wide association study of 3,199 hospitalized patients with COVID-19 and 897,488 population controls. The dashed line indicates genome-wide significance ($P = 5 \times 10^{-8}$). Data were modified from the COVID-19 Host Genetics Initiative[2] (https://www.covid19hg.org/). **b**, Linkage disequilibrium between the index risk variant (rs35044562) and genetic variants in the 1000 Genomes Project. Red circles indicate genetic variants for which the alleles are correlated to the risk variant ($r^2 > 0.1$) and the risk alleles match the Vindija 33.19 Neanderthal genome. The core Neanderthal haplotype ($r^2 > 0.98$) is indicated by a black bar. Some individuals carry longer Neanderthal-like haplotypes. The location of the genes in the region are indicated below using standard gene symbols. The *x* axis shows hg19 coordinates.

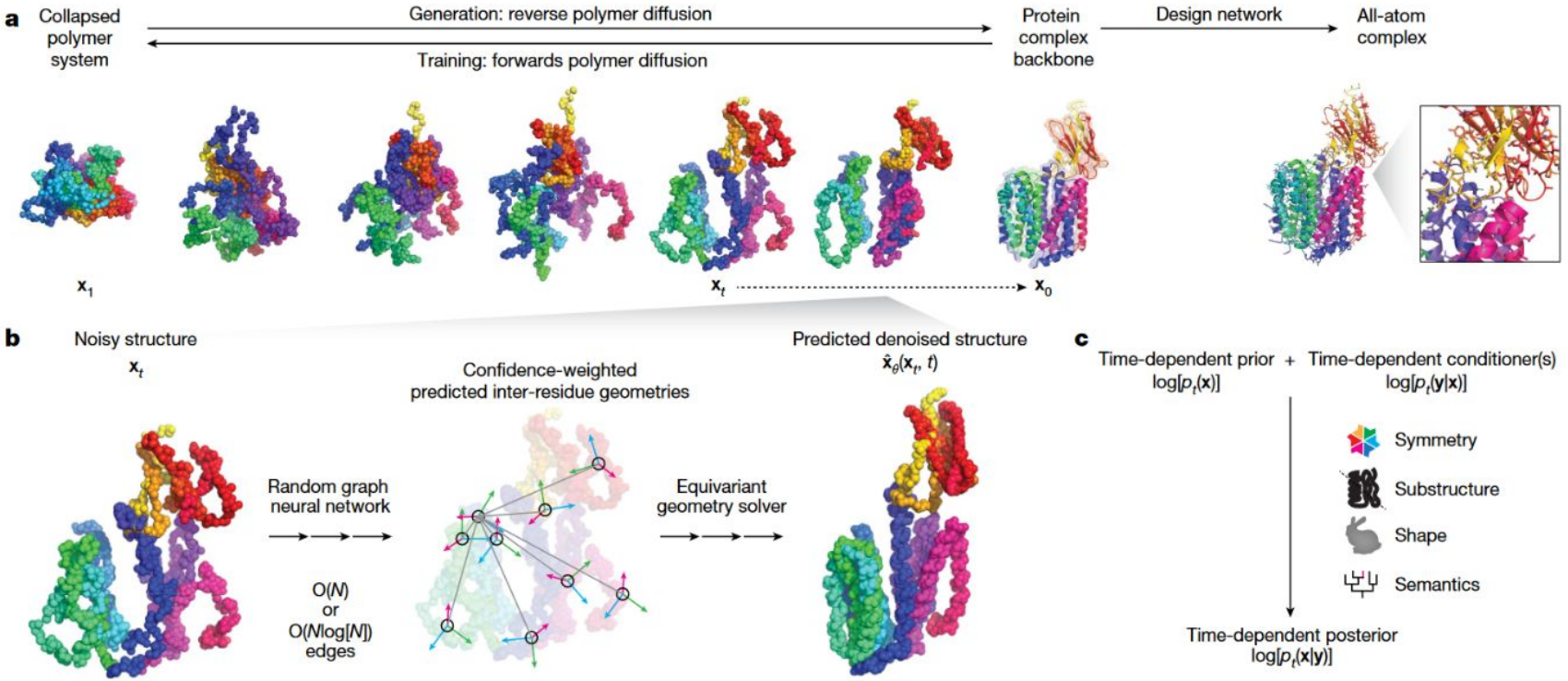
Complex Adaptive System

4. Adaptation and evolution



Minor allele frequency at rs35044562, a risk allele for SARS-Cov-2 that we inherited from Neanderthals.

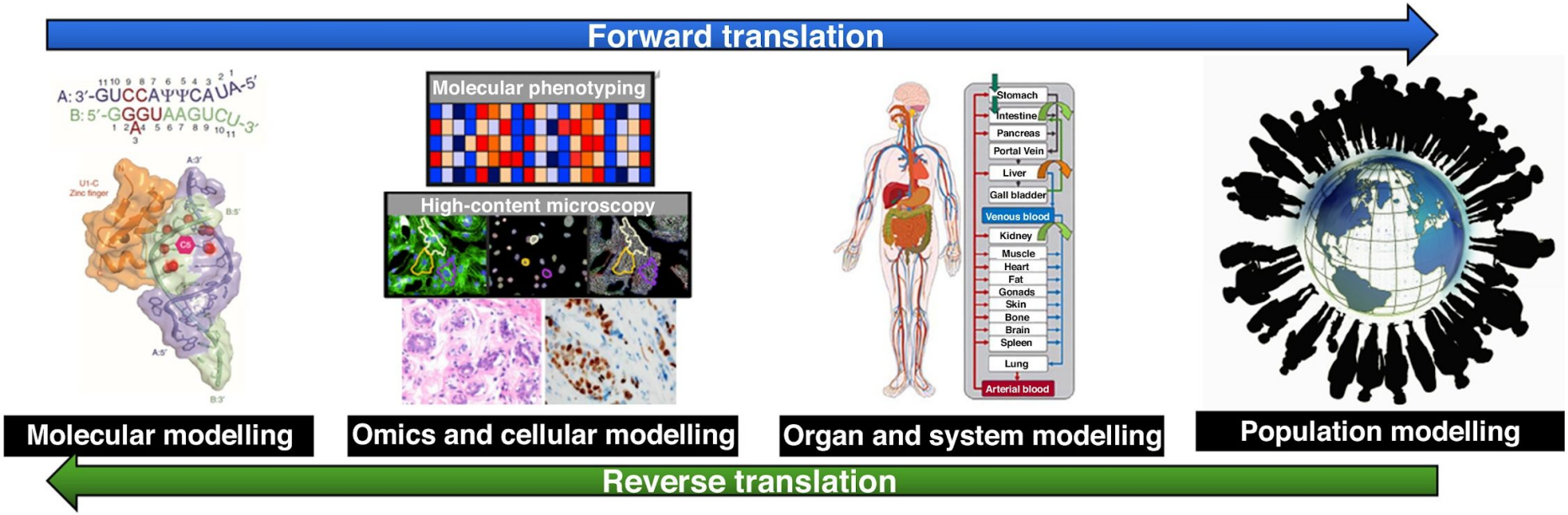
Chroma: a generative model for proteins and protein complexes learning from evolution



Propositions about the course

1. Human (disease) biology is a hierarchical complex adaptive system.
2. Drug discovery aims at identifying *new agents* that change the system's behaviour with acceptable benefit and risk profiles.
3. We use mathematical and computational biology to study the system in order to predict and study the effect of modulation.

A multiscale-modelling view of drug discovery



Drug Discovery Today

Skipped in the class

Complementary views of biological systems

- Metabolism
- Energy
- Information machine
- Evolution
- Computing machine
- Network
- ...

Skipped in the class

An example of complementary views

We want to work on hepatocarcinoma (liver cancer) and have the following information about a potential target X:

- X is a receptor expressing on the surface of most cell types;
- Upon binding ligands, X activates innate immune response;
- Gene sequence of X is conserved in primates but *not* in rodents;
- Protein X interacts with protein Y, which is essential, namely Y knockout causes lethal embryos;
- Asian population has a unique genetic variant in the non-coding region of *X*;

Discussion: what are the consequences of having these information?

Skipped in the class

Exercise

Right target

- Strong link between target and disease
- Differentiated efficacy
- Available and predictive biomarkers

Right tissue

- Adequate bioavailability and tissue exposure
- Definition of PD biomarkers
- Clear understanding of preclinical and clinical PK/PD
- Understanding of drug–drug interactions

Right safety

- Differentiated and clear safety margins
- Understanding of secondary pharmacology risk
- Understanding of reactive metabolites, genotoxicity and drug–drug interactions
- Understanding of target liability

Right patient

- Identification of the most responsive patient population
- Definition of risk–benefit for a given population

Right commercial potential

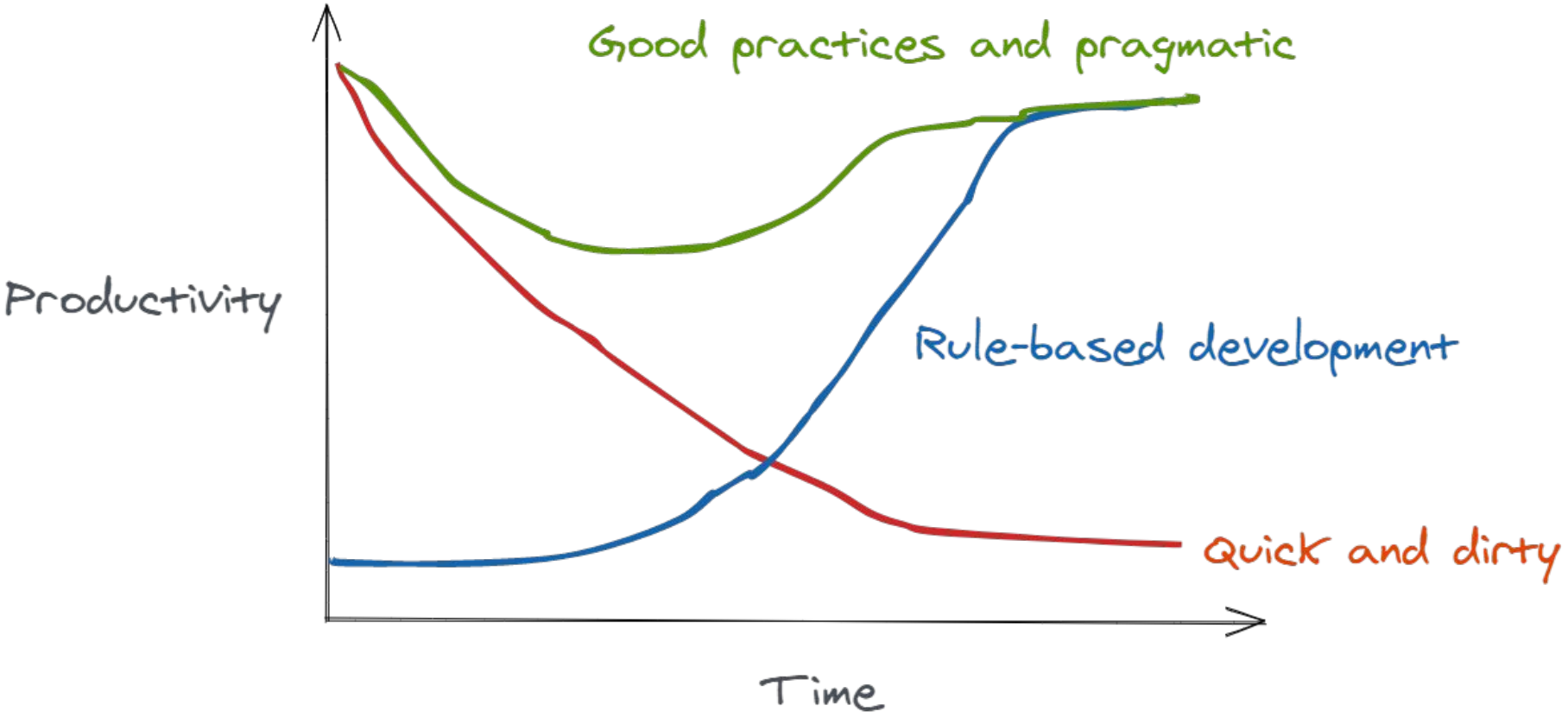
- Differentiated value proposition versus future standard of care
- Focus on market access, payer and provider
- Personalized health-care strategy, including diagnostics and biomarkers

Where do you think mathematical and computational biology will make a difference?

Nature Reviews | Drug Discovery

Nine steps toward reproducible research

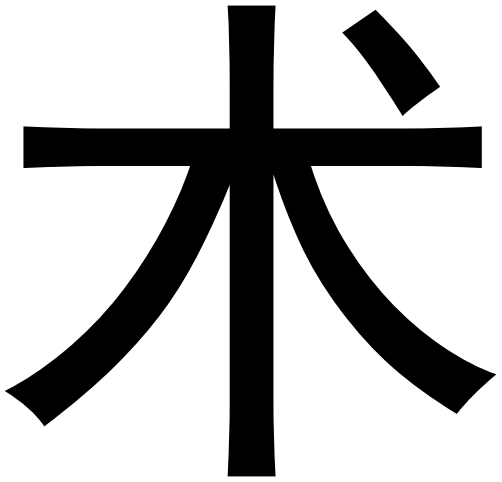
1. Version control (*git*)
2. Don’t Repeat Yourself (DRY)
3. Keep It Simple, Stuipid (KISS)
4. Automatic testing (*pytest/Hypothesis*, *testthat*, *GitHub Actions*)
5. Documentation (*sphinx, pkdown*)
6. Dependency Management (*conda*, *packrat*)
7. Containerization (*Docker/Singularity*, *Bioconda/conda-forge*)
8. Pipelining (*Snakemake*, *NextFlow*, *drake*)
9. Self-reporting analysis (*Jupyter Notebook*, *Rmarkdown*)


Good practices and pragmatic
Productivity
Rule-based development
Quick and dirty
Time

Arguments for reproducible research

- Egoism and altruism
- *You will have to do it again*
- Sustainable long-term work

Tao, Path, or Way



Shu, Technique, or Art

Contact the author