

# Mathematical and Computational Biology In Drug Discovery (2023)

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### Administrivia

- Please fill <u>the pre-course survey</u>.
- 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?**

p(TS)



Discovery Development

### Failure analysis: 2013-2015



### 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.

### Investment and collaboration are necessary



# **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<sup>2</sup> (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



### **Propositions about the course**

- 1. Human (disease) biology is a hierarchical complex adaptive system.
- 2. Drug discovery aims at identifying *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 modulate it.

### **Complementary views of biological systems**

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

### 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?

## 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?

Target identification & assessment

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

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

### **Common modelling approaches**

- Statistical modelling
- ODE/PDEs (compartment & transport models)
- Agent-based models (particle models)
- Networks (graphical and boolean models)
- Evolutionary game theory
- Fractional calculus

### A multiscale-modelling view of drug discovery



Drug Discovery Today

### 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

### 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.
- 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?
- 3. Read 'Improving target assessment in biomedical research: the GOT-IT recommendations' by Emmerich *et al.* (NRDD, 2021). Think about the question that we will discuss next time: what is a good drug target?

### References

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- 10. Sturm, Gregor. 2020. "Hallmarks of Good Scientific Software". https://grst.github.io/bioinformatics/2020/07/16/hallmarks-scientific-software.html

## **Backup and License**

### 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)

## 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

### Learn more about reproducible research

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

# Mathematical and computational biologists are part of an interdisciplinary team



### **One-compartment model, oral dosing**

For oral dosing, an extra gut compartment (right) is often sufficient to model the absorption phase

$$\frac{dA_{gut}}{dt} = -K_a \cdot A_{gut}$$

Suppose rate the absorption of the drug is faster than the elimination process (Ka > K), we can model the concentration in the central compartment as



In reality, we cannot easily assess the concentration of drug in the gut. Is it possible to derive the relationship between central-compartment concentration *A* and time *t* given the initial condition?

Yes: we can find the expression of *A*(t) analytically in a closed form using *Laplace transform*, which translates a function of a continuous variable (*e.g.* time) to a function of a complex variable (frequency) (see backup).





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