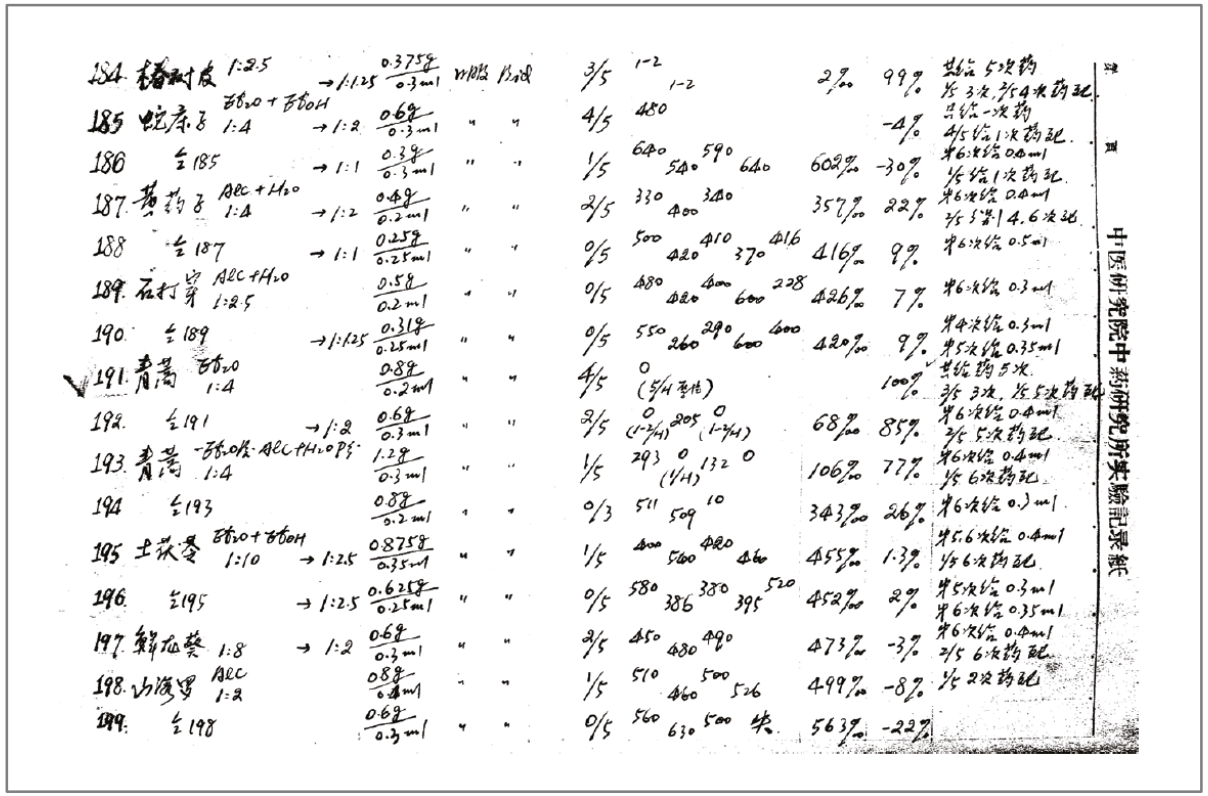
Applied Mathematics and Informatics In Drug Discovery



Copy of the original laboratory notebook record showing 100% inhibition of malaria parasites by the Qinghao neutral extract when tested on a rodent malaria model.

Artemisinin — A Gift from Traditional Chinese Medicine to the World, Youyou Tu, Nobel Lecture 2015.

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

Contact the author

Computational Biology & Biostatistics PhD
Network analysis and applications in cancer

Bioinformatics MSc
high-throughput screening data analysis

Life Sciences BSc
with German Studies as minor

STEM high school

Academia

Mathematical statistics

Theoretical Bioinfo

Mol Biol MSc

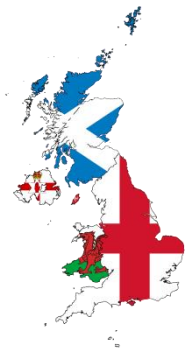
Marine Biol MSc

German Studies BSc

Sport journalist

Medicine, Chemistry, CS BSc

Computational Biologist @ Roche since 2011
Preclinical research on drug efficacy and safety



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My career path

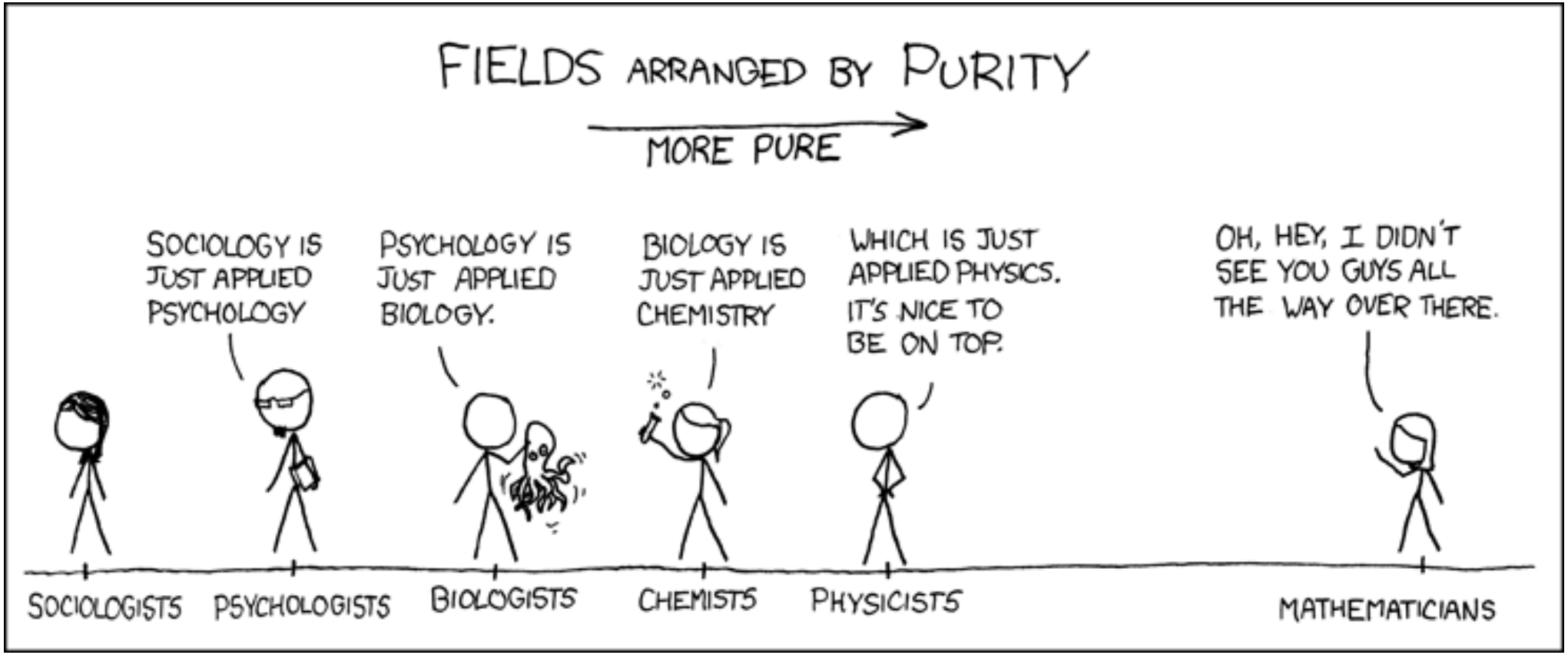
Disclaimer

- **Teaching is my personal engagement.** My opinions and views do not necessarily reflect those by F. Hoffmann-La Roche, my employer.

- **Please be aware of my biases and limitations.**
  - I am neither a mathematician nor a computer scientist by training. I am a computational biologist working in drug discovery.
  - I see my task is to share with you the mathematical concepts and computational approaches used in drug discovery that I find beautiful and useful.
  - I look forward to learning from you mathematics and other expertise that I did not know.

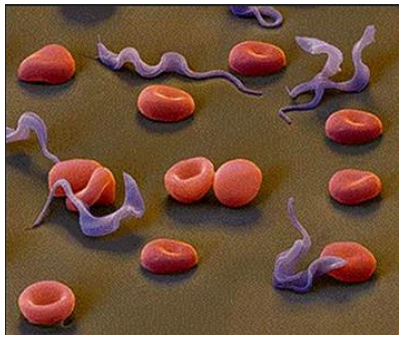
Purity

https://xkcd.com/435/

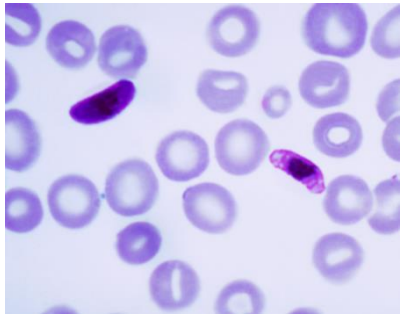


- **Now is the best time in human history to fight diseases**
- **Applied mathematics and informatics approaches are indispensable to modern drug discovery**
- **Applied mathematics and informatics will join interdisciplinary efforts to transform drug discovery in the coming decades**

The history of *Homo sapiens* is a history of living with, understanding, and fighting diseases



Trypanosomes



Plasmodium

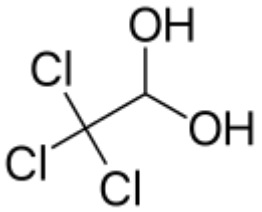
Tropical diseases

~500,000 years ago

A young patient of smallpox,
the first eradicated infectious disease

Hygiene, vaccination, and antibiotics

~250 years ago



Chloral hydrate,
the first synthesized drug

Pharmaceutical drugs

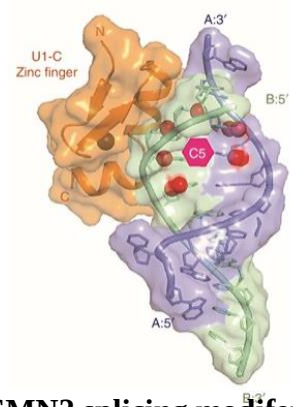
~150 years ago

Nobel prize laureates 2018,
immune checkpoints,
and drugs targeting the pathways

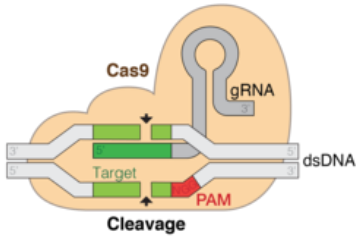
Personalized precise healthcare

~20 years ago

Now is the best time in human history to fight diseases



SMN2 splicing modifer
Naryshkin *et al.*, Science 2014; Sivaramakrishnan & McCarthy *et al.*, Nat Comm, 2017



CRISPR-CAS9 gene editing system

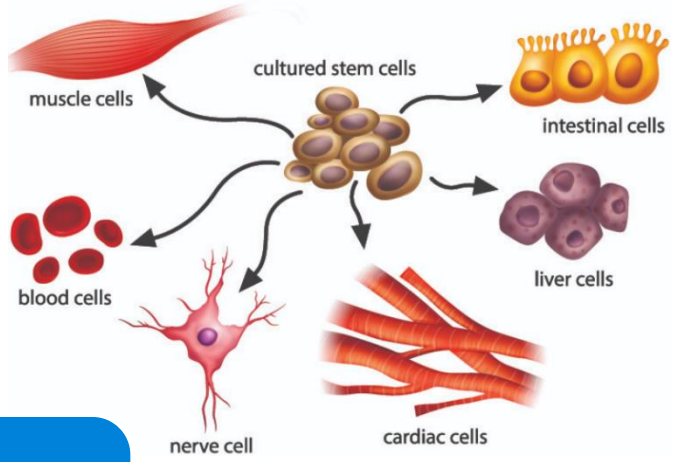
More biological, chemical, and medicinal knowledge

New disease-modelling systems

Digitalization of molecular mechanisms in living organisms

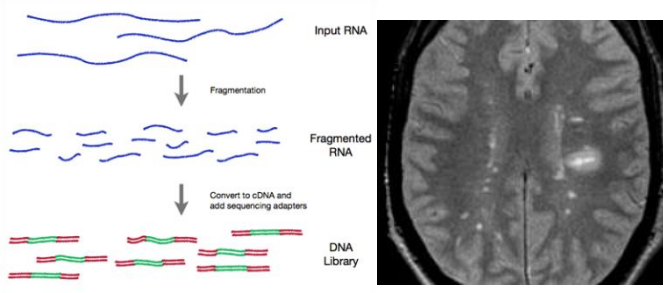
Better algorithms, models, and more computing resources

New therapeutic modalities



Stem cells

Comprehensive Sensing

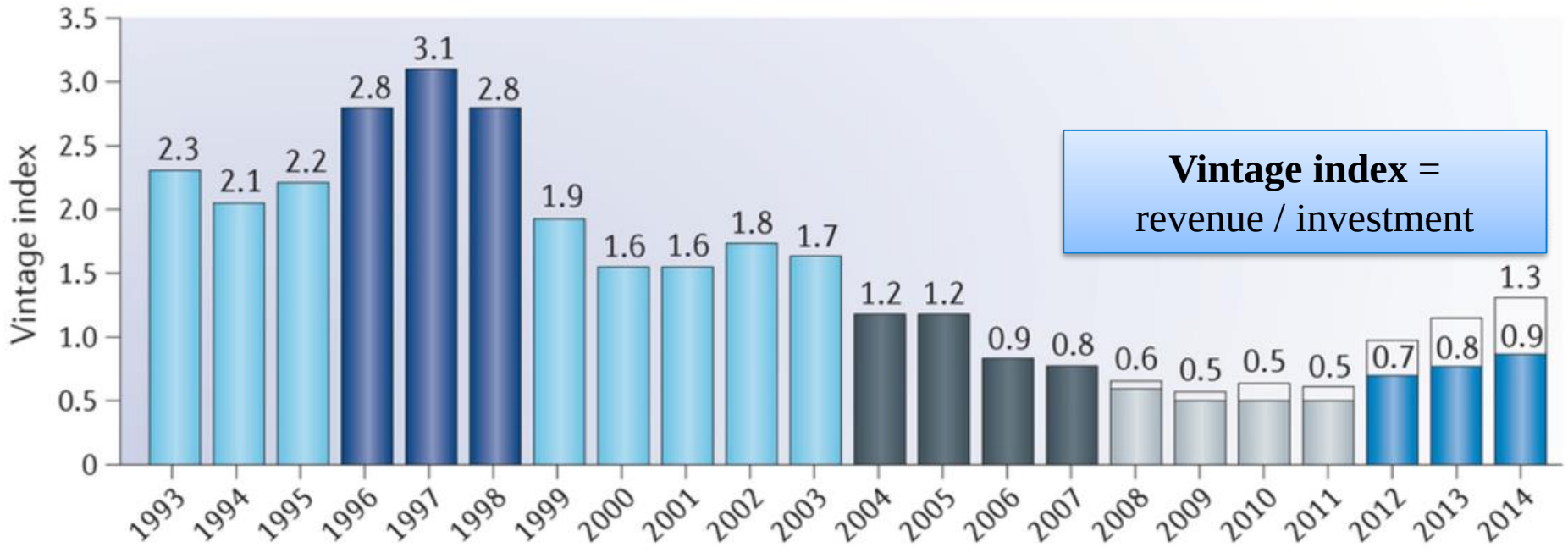


Gene expression profiling and imaging

How Do You Make A Drug?

It sounds simple, but…

Increasing cost and decreasing return of investment in drug discovery



Modified from Smietana *et al.* "Improving R&D Productivity." Nature Reviews Drug Discovery, 2015

Finding new drugs has become more challenging and expensive

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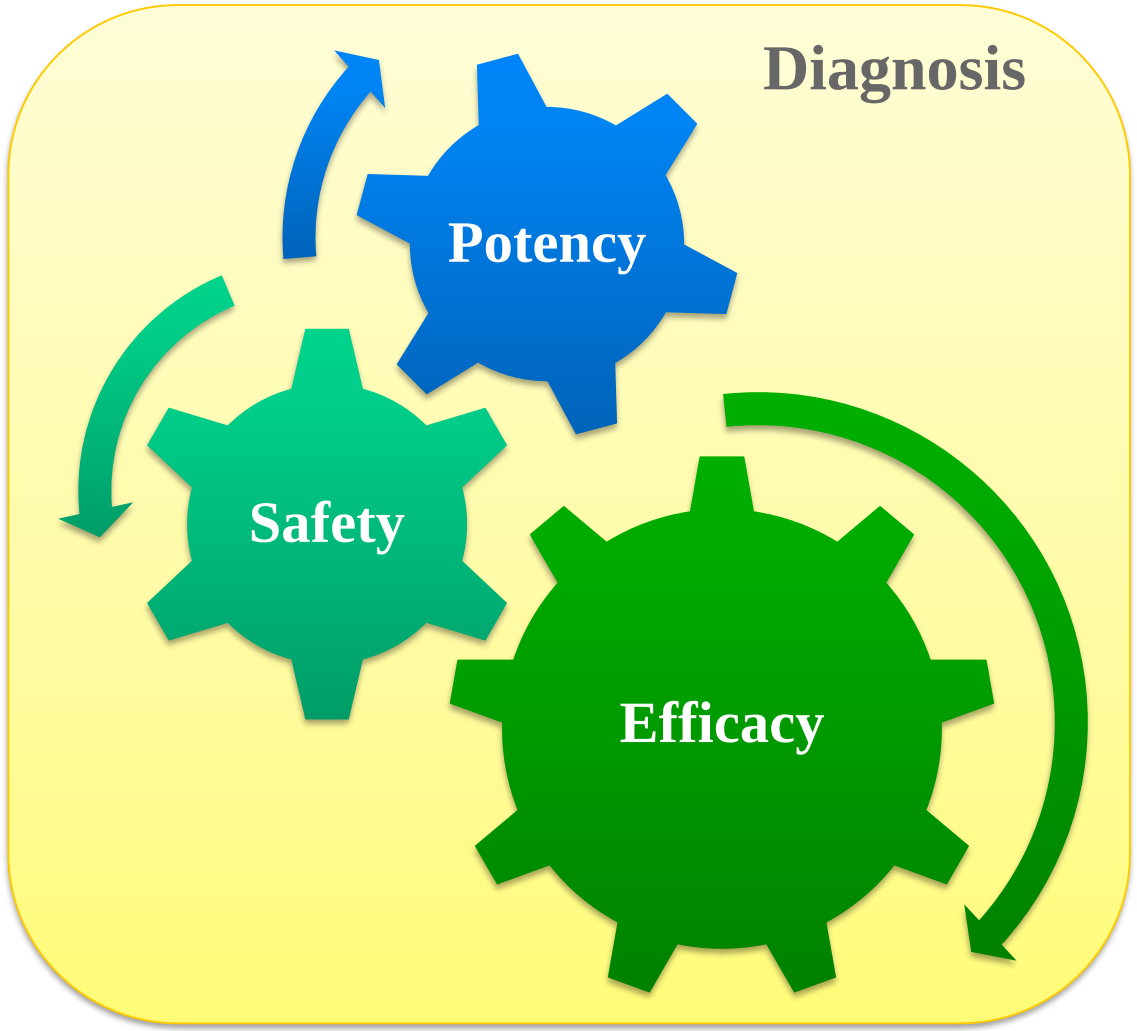
~~*n.* crisis~~

Danger + Opportunity

Prerequisites to make a good drug that works



- **Potency**
- **Safety**
- **Efficacy**
- **Diagnosis**: doctors' judgement + *biomarkers*
  - *Biomarkers* are informative features derived from measurements of patient or patient material, *e.g.* blood chemistry, genetic make-up, imaging, *etc.*
- Other criteria: commercial rationale, development ability, intellectual property, *etc.*

Success in drug discovery is determined by potent, safe, efficacious drugs and accurate diagnosis

Introduction to Applied Mathematics and Informatics in Drug Discovery (*iAMIDD*)

A new course series at DMI, Uni Basel

- **Introduction to drug discovery**
- **Bioinformatics and computational biology**
  - Biological sequence analysis
  - Omics data analysis
  - Protein sequence and structure
- **Cheminformatics and computer-aided drug design**
  - Chemical structure representation and search
  - Molecular modelling
  - Molecular descriptors and QSAR
- **Mathematical modelling**
  - Principles and applications of modelling in pharmacology
  - Pharmacokinetics (PK) and pharmacodynamics (PD) modelling
  - Clinical pharmacology and pharmacometrics
- **Statistics and machine learning**
  - Emerging biomarkers: imaging and digital biomarker
  - Clinical trials
  - From real-world data to causal analysis and inference

It is hoped that iAMIDD builds a bridge between students and quantitative aspects of drug discovery

Applied mathematics empowers drug discovery by many ways

Applied mathematics *in drug discovery*
is not a definable scientific field
but a human attitude.

Richard Courant
(1888-1972)

Statistics, Data Mining and Machine Learning	Applied Combinatorics and Graph Theory	Stochastic Simulation	Geometric Modeling
Ordinary / Partial/ Stochastic Differential Equations	Network Analysis	Dynamical Systems	Molecular, Quantum, and Continuum Mechanics

Course information

- Lecturer: Jitao David Zhang
  - jitao-david.zhang@unibas.ch (Email)
- Website: amidd.ch
- Thirteen lectures this semester
  - Introduction to drug discovery (1 session)
  - Molecular level modelling (2 sessions)
  - Omics- and cellular level modelling (2 sessions)
  - Organ- and system-level modelling (1.5 sessions)
  - Populational level modelling (1.5 sessions)
  - Case studies (1 session)
  - Invited guest speakers (2 sessions)
  - *Dies Academicus*
  - Near-end-term presentations (2 sessions)

- Fridays 12:15-14:00, two sessions of ~45 min each.
- No exercise hour yet; pre-reading and post-reading articles, as well as videos, are shared and recommended.
- We focus on interdisciplinary research with mathematics as the language and informatics as the tool.
- Both slides and board are used. Slides and notes are shared.
- The final note is given by participation (20%), presentation (30%), and an oral examination (50%).
- The oral examination will be about concepts that we learned together, and about explaining mathematical concepts (or concepts in your domain of experts) to a layman.
- **Questions**?

I am glad to share my expertise in drug discovery, and to learn from you!

Questions on the video on Herceptin by Susan Desmond-Hellmann

1. What is the **indication** of *Herceptin*? What is its generic (USAN, or United States Adopted Name) name?
2. What is the **gene target** of Herceptin?
3. In which year was the **target** of Herceptin described? When was Herceptin **approved**?
4. What was the **improvement** of Herceptin compared with earlier antibodies?
5. Why does a **biomarker** matter besides developing drugs?
6. In the clinical trial of *Herceptin* for **metastatic breast cancer**, how much improvement in the **median survival** did Herceptin achieve? And how much improvement is in the **adjuvant setting** (Herceptin applied directly after operation)?

Questions for further thinking

- Susan Desmond-Hellmann summarizes great drug development in four key concepts: (1) Having a deep understanding of the basic science and the characteristics of the drug. (2) Target the right patients. (3) Set a high bar in the clinic. (4) Work effectively with key regulatory decision markers. Where do you think mathematics and informatics play a crucial role?
- She emphasized the importance of collaboration. What skillsets do we need for that?
- How do you like her presentation? Anything that you can learn from her about presentation and story telling?

Please introduce yourself!

- **Name?**
- **Background?**
- **Which part of mathematics (or other background) are you mostly interested in? Why?**
- **What do you want to take away from this course?**

Questions on the package insert info

1. What is the **indication** of *ZYRTEC*? What is its generic name?
2. What is the **gene target** of ZYRTEC?
3. How much time does ZYRTEC reaches **maximum concentration** following oral administration?
4. How long do normal vonlunteers have to **wait** until the skin wheal and flare caused by the intradermal injection of histamine is inhibited after taking 10mg ZYRTEC?
5. What types of **adverse reactions** are observed in volunteers taking ZYRTEC?
6. Is there a **biomarker** for ZYRTEC?

Questions for further thinking

- What are the commonalities between Herceptin and Zyrtec, and what are the differences?

Acknowledgements





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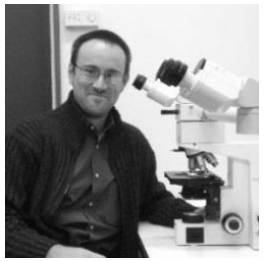

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Summary and Q&A