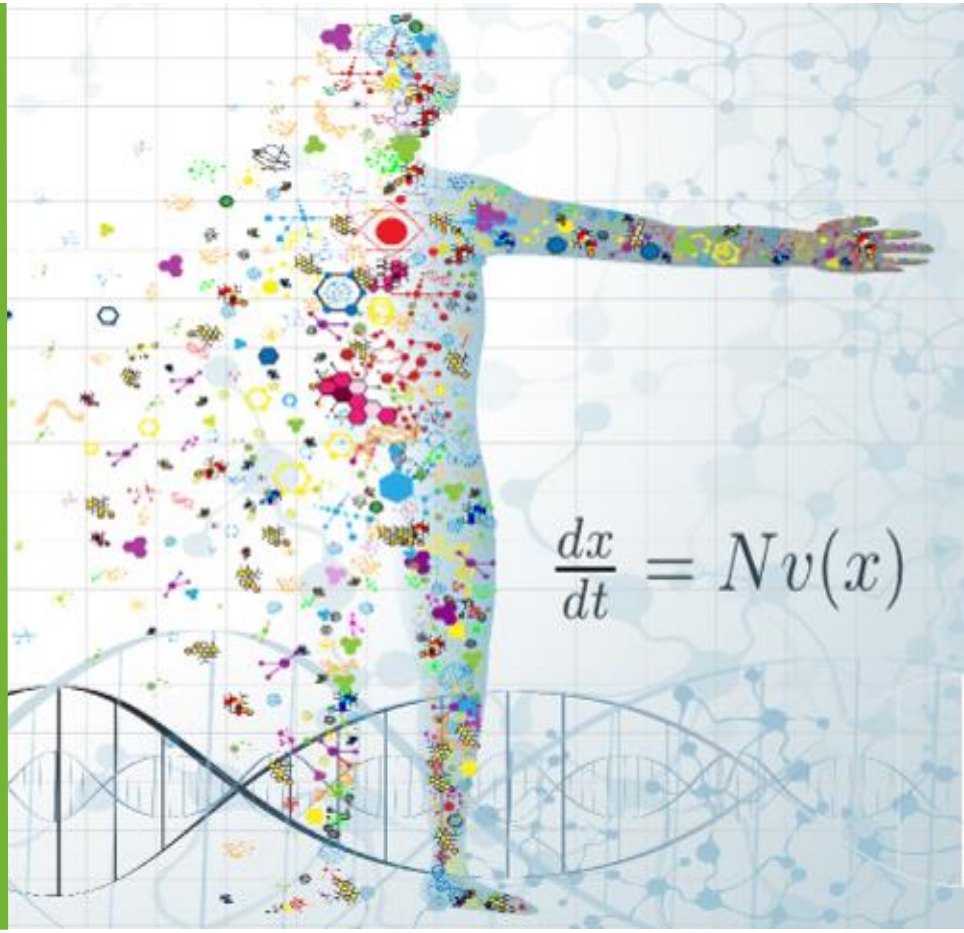
Why do biology & medicine need modelling and what can we explain by modelling?



Walter Kolch

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Dublin 4, Ireland
Phone 00353-(0)1-716 6303
Email: walter.kolch@ucd.ie
http://www.ucd.ie/sbi/

SYSTEMS BIOLOGY IRELAND

UCD DUBLIN

Biology as it used to be

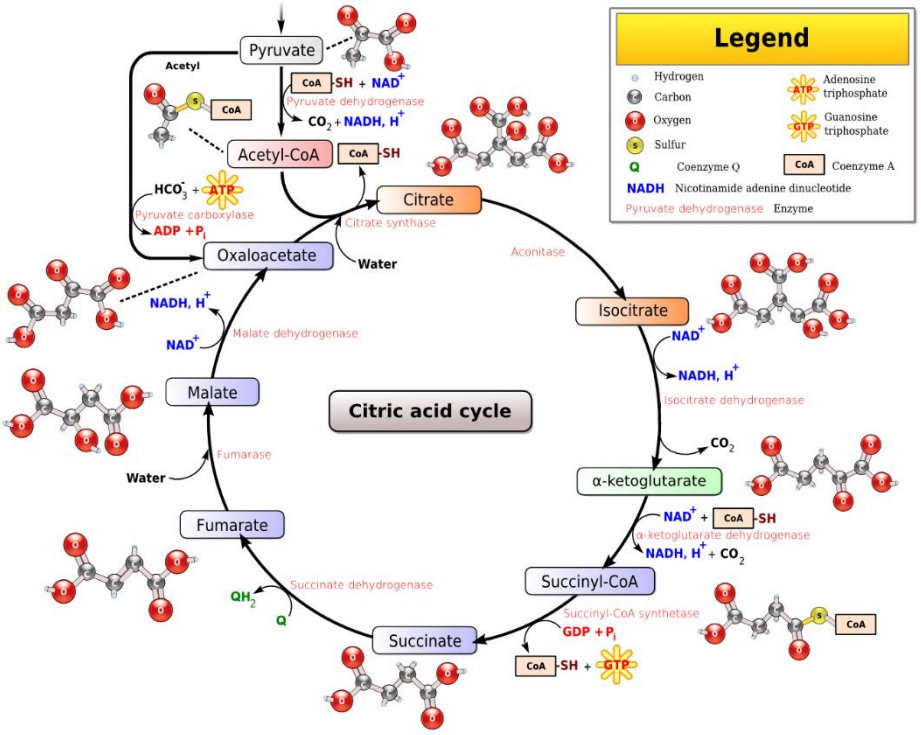
Hans Adolf Krebs in his lab

Walter Kolch as postdoc

Biology as it used to be

Grind and find

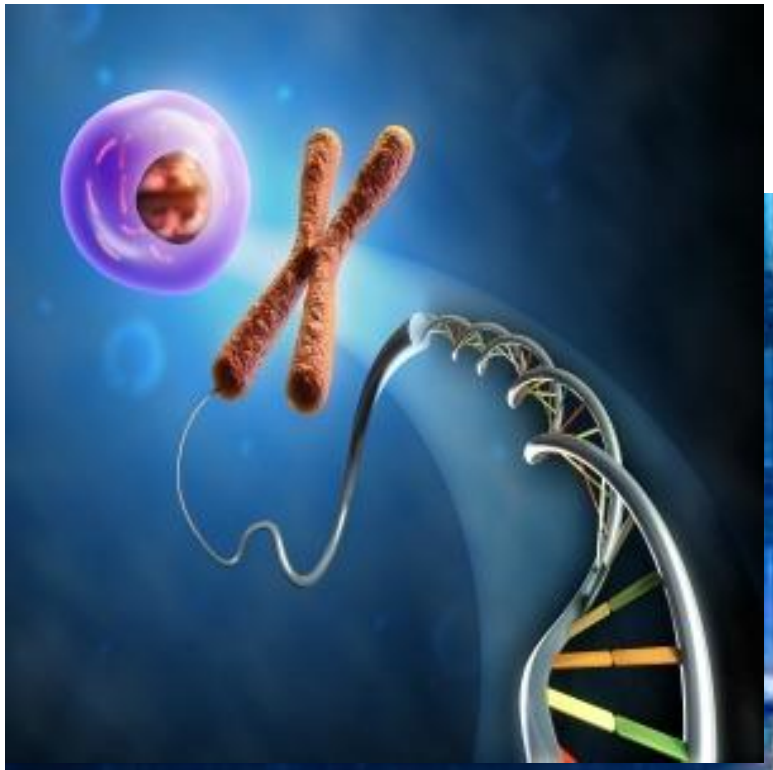
The results were amazing



And the key to success was quantitative measurements

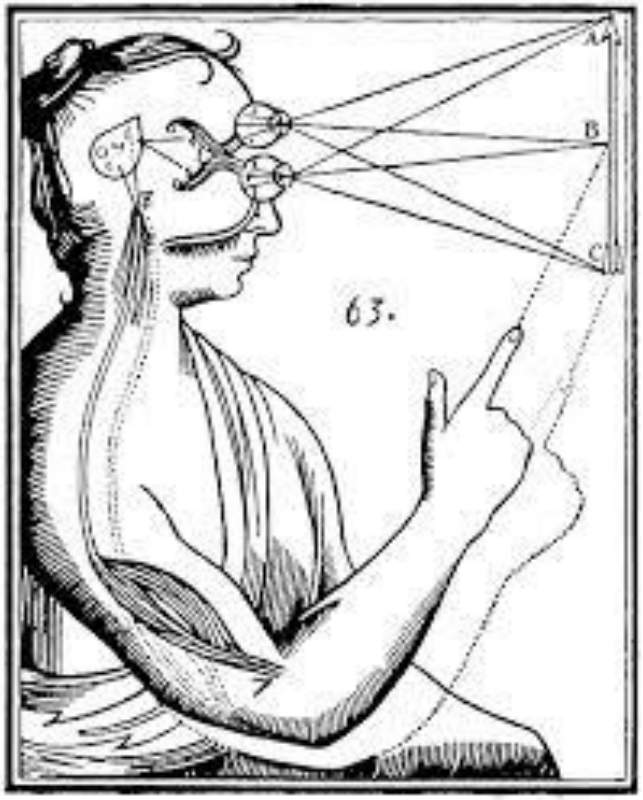
https://www.youtube.com/watch?v=JPCs5pn7UNI

Biology even got better – it become molecular



… and qualitative

Reductionism works



... the body works like a machine

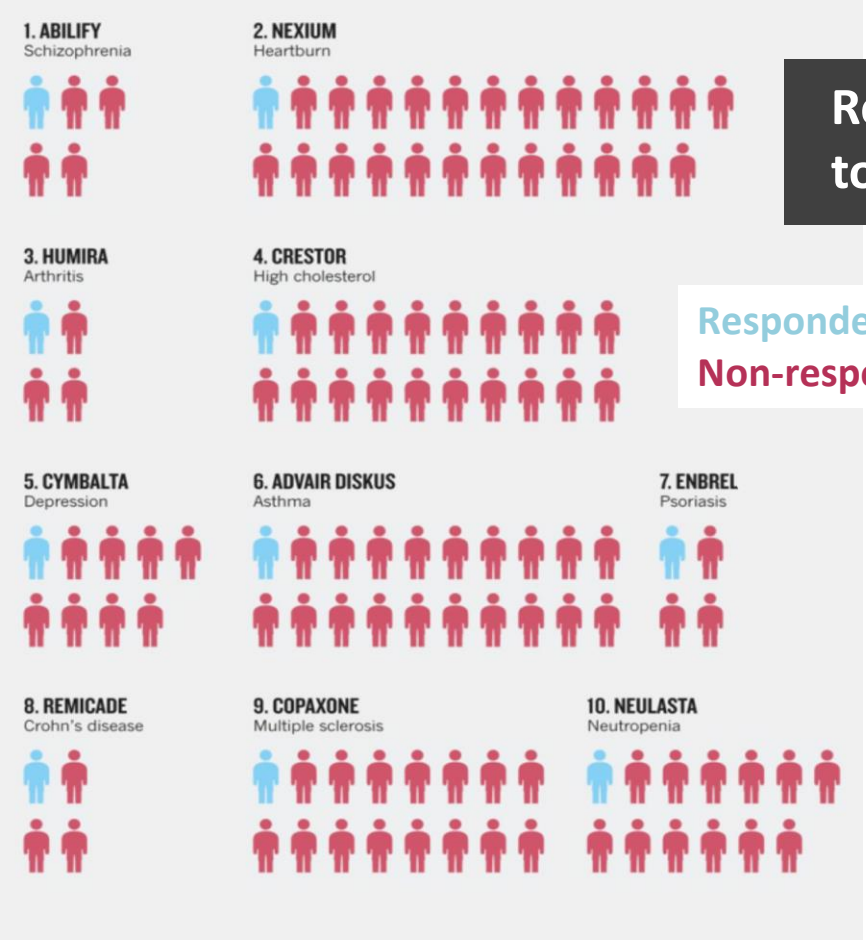
Reductionism works – or does it?

Do we really work like machines?

When we get sick, can we be repaired like machines?

Houston, we have a problem

If you are sick, current therapies most likely will not help you

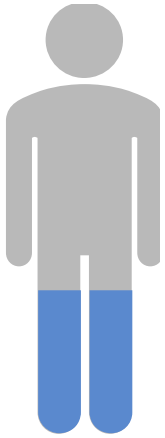


Response rates to the top 10 selling drugs

For example…

The HSE currently spends per year

But only 30% of patients respond to these drugs



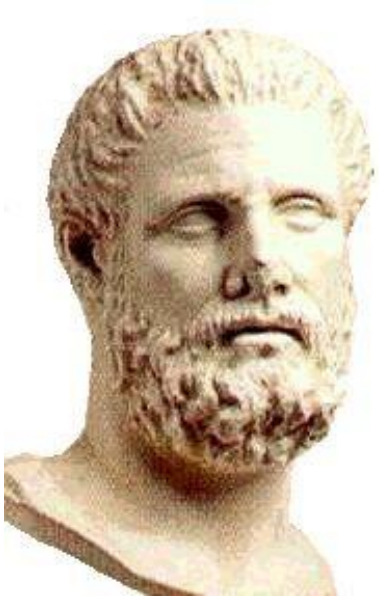
€80m injected into patients who derive no benefit

We need

- Right diagnosis
- Right drug
- Right dosage

…for the right person

A brief diversion into history



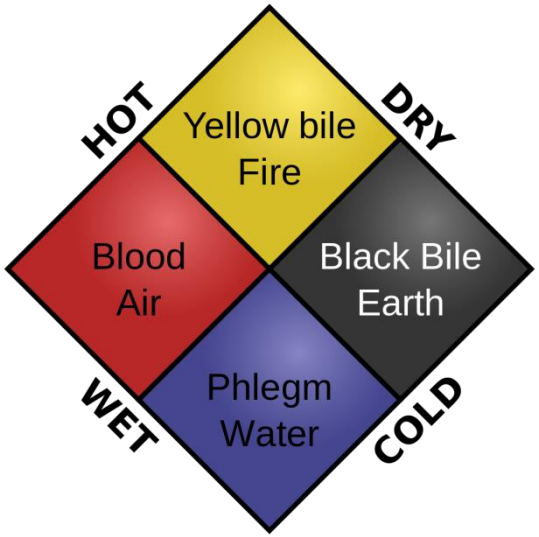
"It is more important to know what sort of person has a disease than to know what sort of disease a person has."

Hippokrates (c. 460 – c. 370 BC)

A brief diversion into history

From Hippokrates for the next 2000 years ...

Humorism



"The Human body contains blood, phlegm, yellow bile and black bile. These are the things that make up its constitution and cause its pains and health. Health is primarily that state in which these constituent substances are in the correct proportion to each other, both in strength and quantity, and are well mixed. Pain occurs when one of the substances presents either a deficiency or an excess, or is separated in the body and not mixed with others”

A brief diversion into history

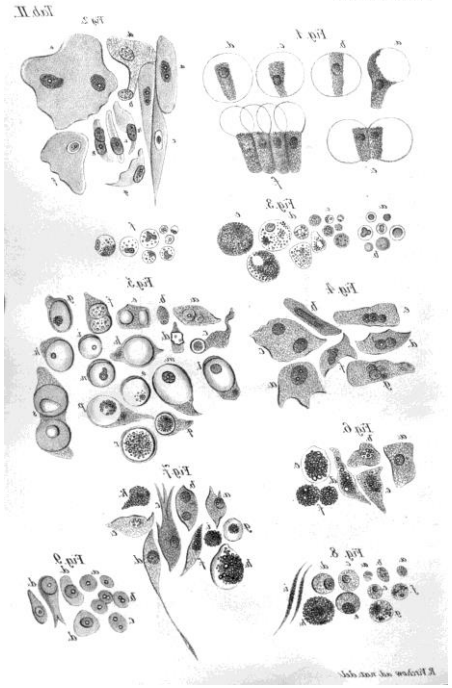
Rudolf Virchow (1821-1902)

Cellular Pathology (1858)

Omnis cellula e cellula

(everything originates from cells)

The human body is a “republic of cells”



Life itself is but the expression of a sum of phenomena, each of which follows the ordinary physical and chemical laws.

Disease is not something personal and special, but only a manifestation of life under modified conditions, operating according to the same laws as apply to the living body at all times, from the first moment until death.

A brief diversion into history

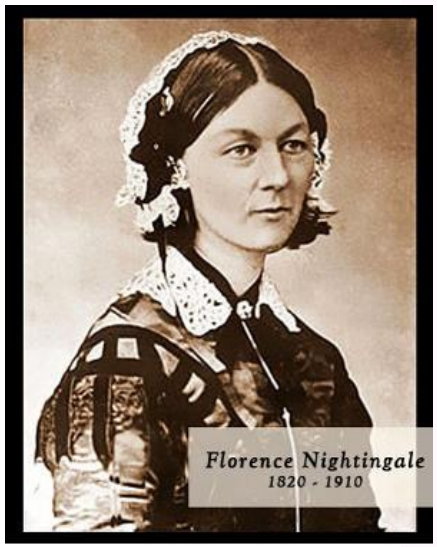
Otto von Bismarck

Virchow opposed Bismarck's excessive military budget, which angered Bismarck sufficiently to challenge Virchow to a duel in 1865. Virchow, having been the challenged and therefore entitled to choose the weapons, selecting two pork sausages, a normal sausage and another one, loaded with *Trichinella* larvae.

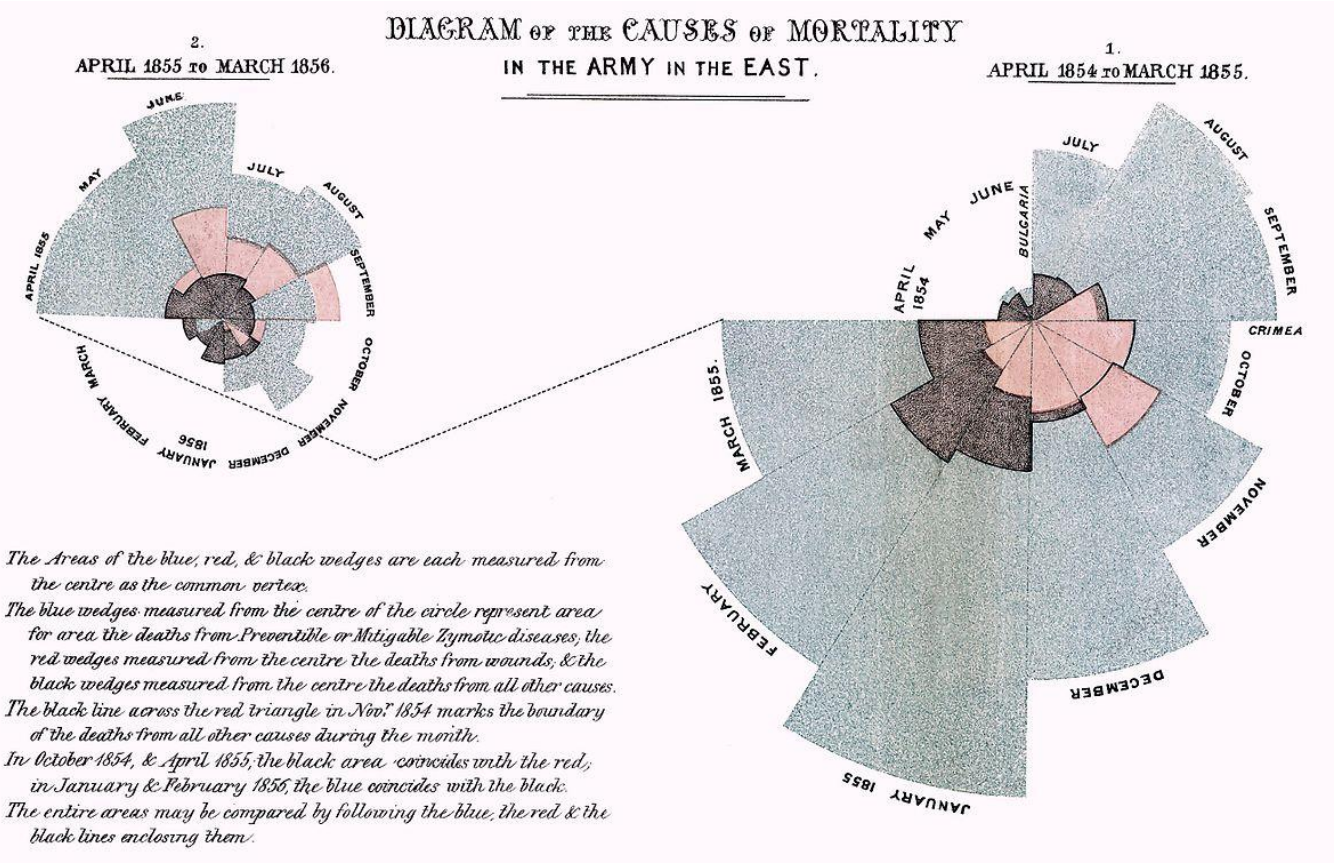
Rudolf Virchow

A brief diversion into history

The live-saving introduction of statistics into medicine



Florence Nightingale



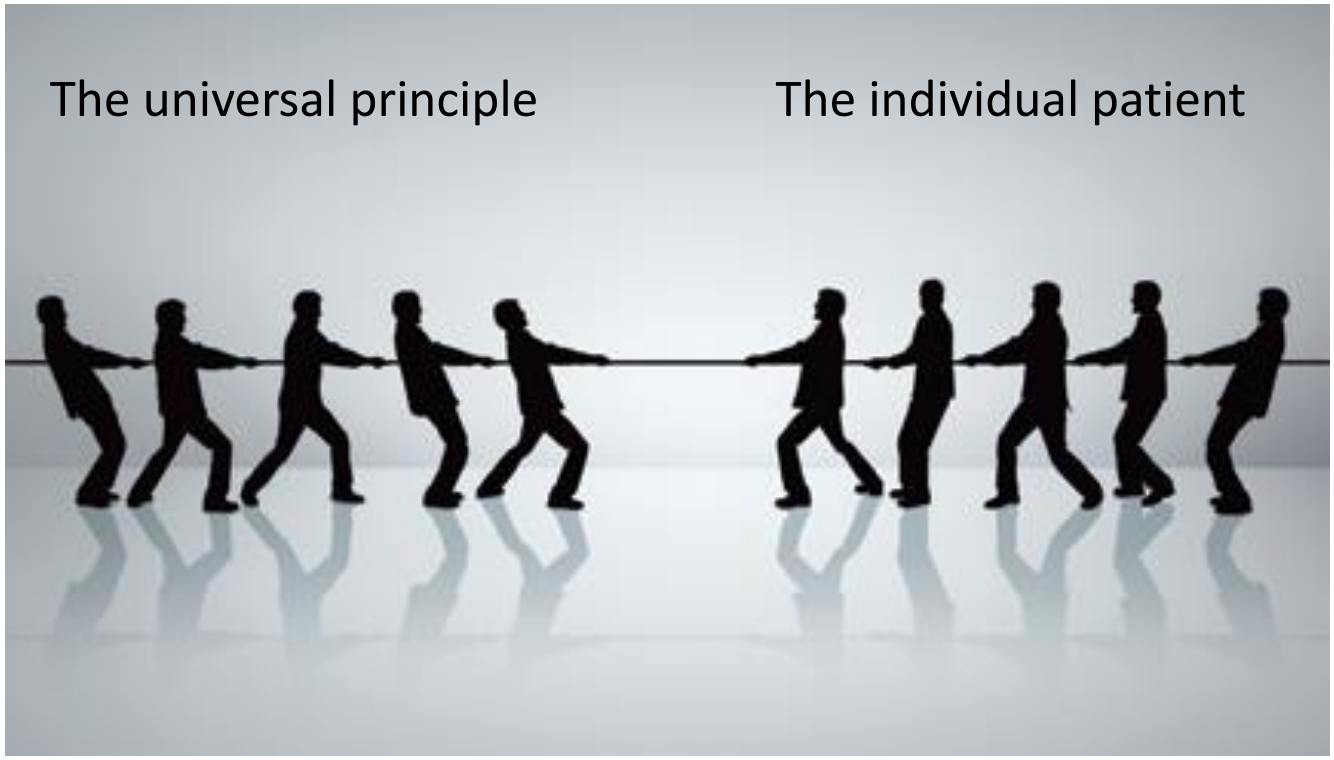
A brief diversion into history

Sir William Osler (1849 – 1919)
The father of modern medicine; one of the 4 founders of Johns Hopkins Hospital; introduced residence training

"The good physician treats the disease; the great physician treats the patient who has the disease."

"Medicine is a science of uncertainty and an art of probability."

A brief diversion into history

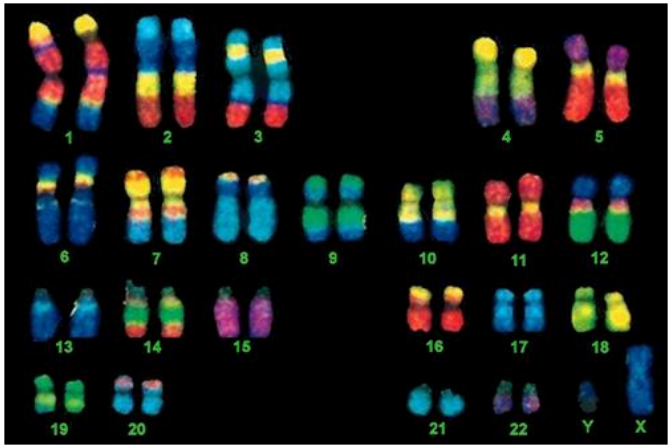


Now we have the technologies to realise this vision

For the first time we can diagnose, prevent & treat diseases according to their molecular causes

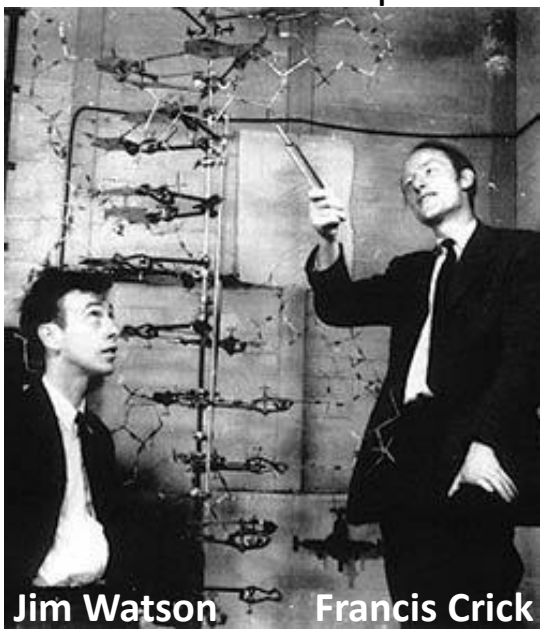
The human genome

A landmark feat of the success of molecular dissection approach was the deciphering of the human genome sequence published in 2003



24 chromosomes

3.2 billion base pairs

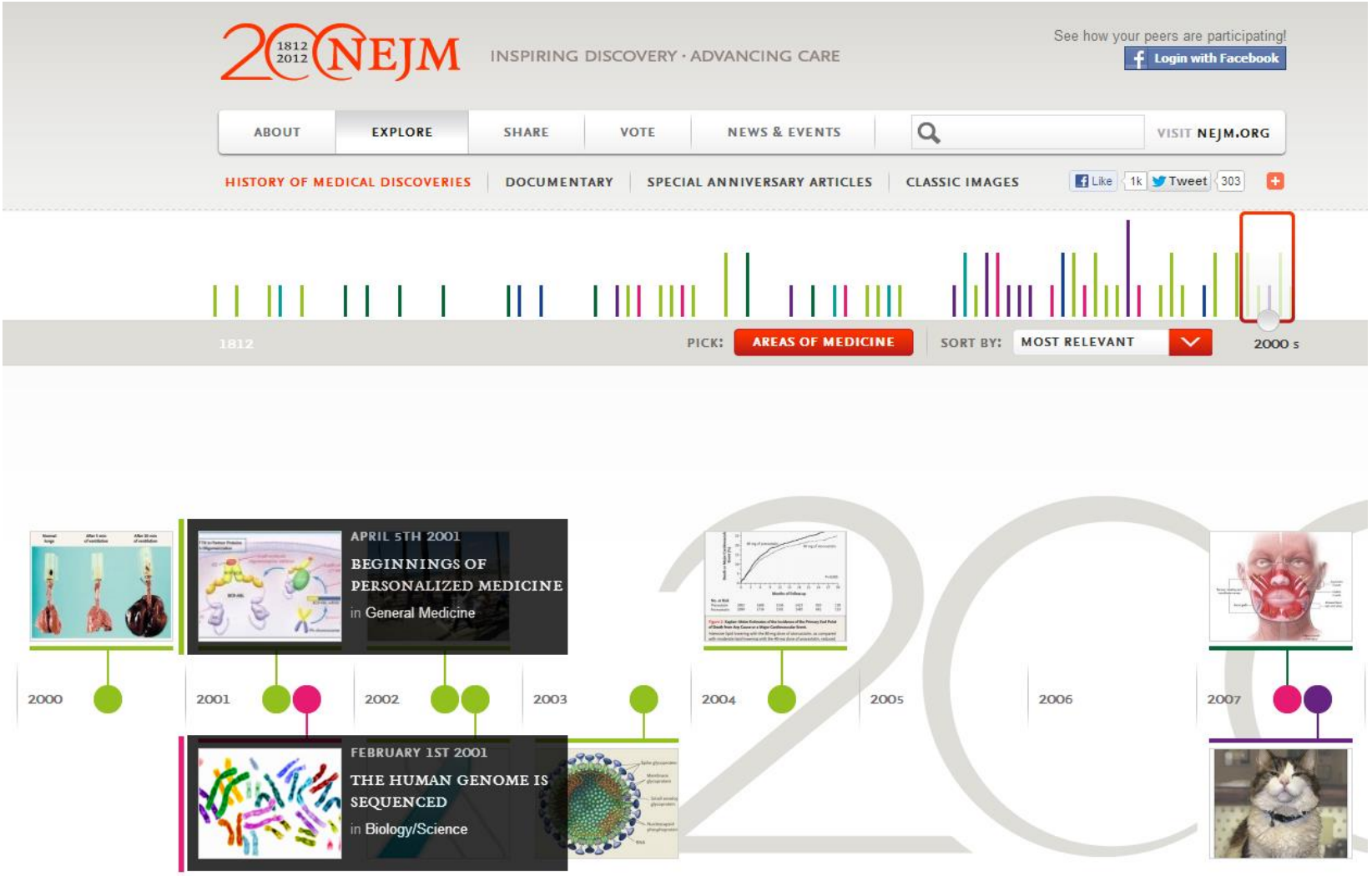


If the genome sequence was published as a book it would have ~1 million pages

This corresponds to ~1000 copies (or ~100 metres) of Tolstoy's "War and Peace"

How has genome sequencing advanced medicine?

The history of medical discoveries (New England Journal of Medicine)



How has genome sequencing advanced medicine?

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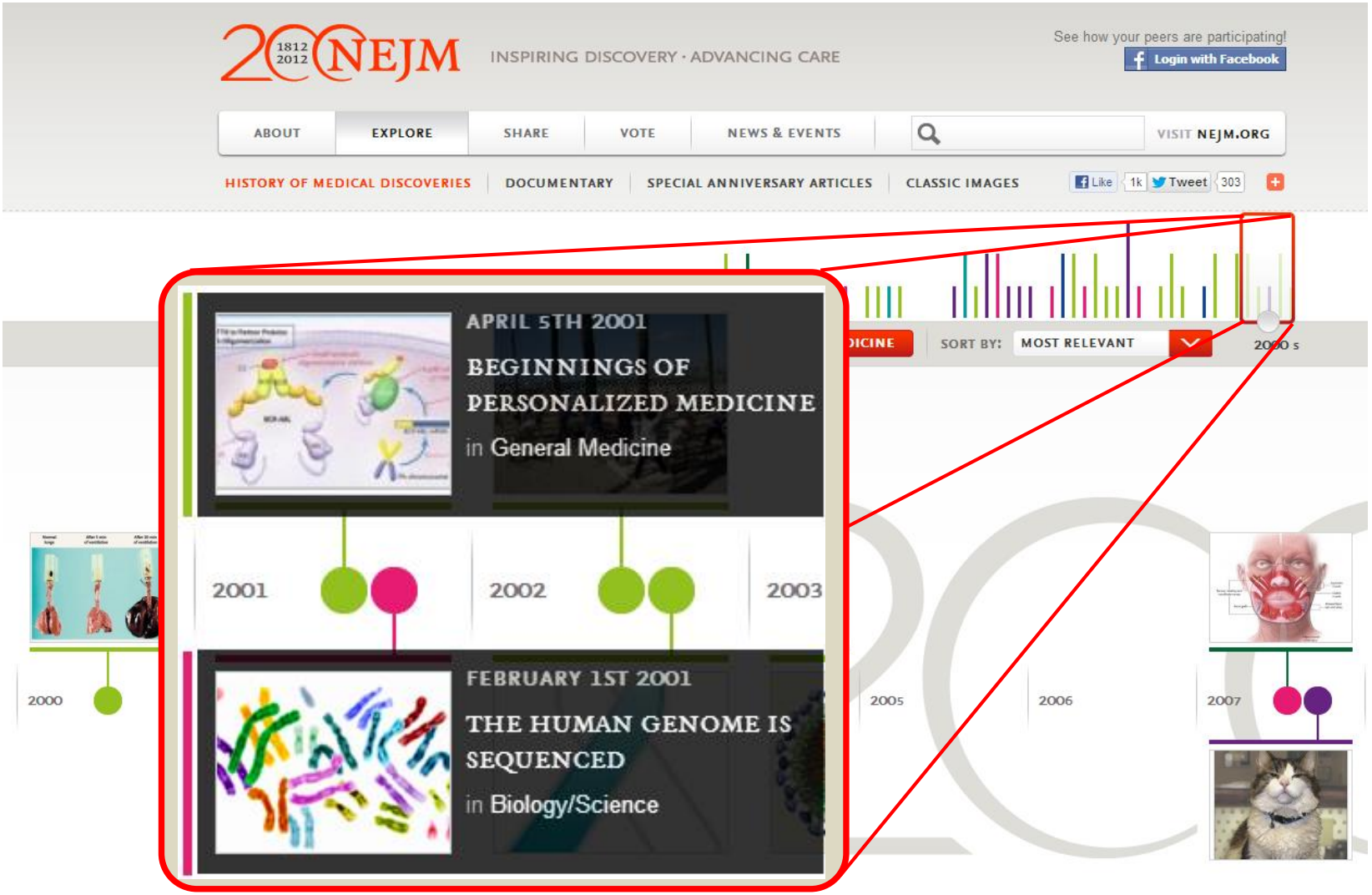
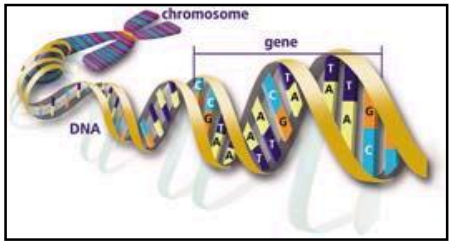
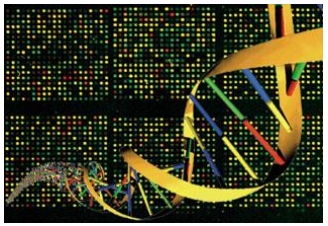


And more –omics technologies are available

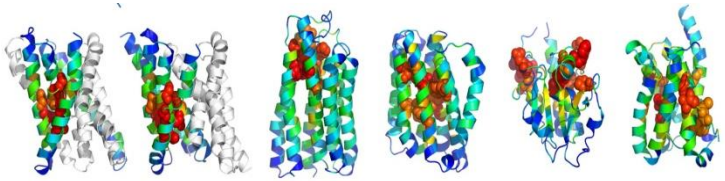
Genome ~20,000 human genes



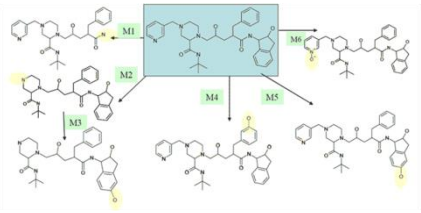
Transcriptome ~100,000 mRNAs



Proteome >500,000 proteins



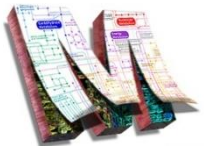
Metabolome >5000 metabolites



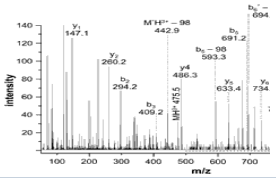
How will we use all these data?

We can produce more data on patients than ever before

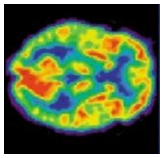
Metabolomics data



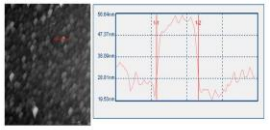
MS-data



Images



Biochemical data

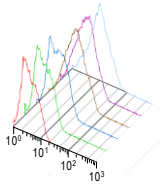


Metabolomics | Proteomics | Imaging | Clinical laboratory

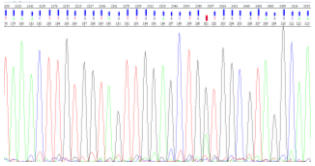
Pathology & Biomarkers | Cell Biology & Molecular Biology | Genomics & Transcriptomics

Technology Platforms

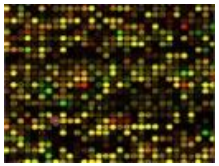
Tissue microarrays



FACS data



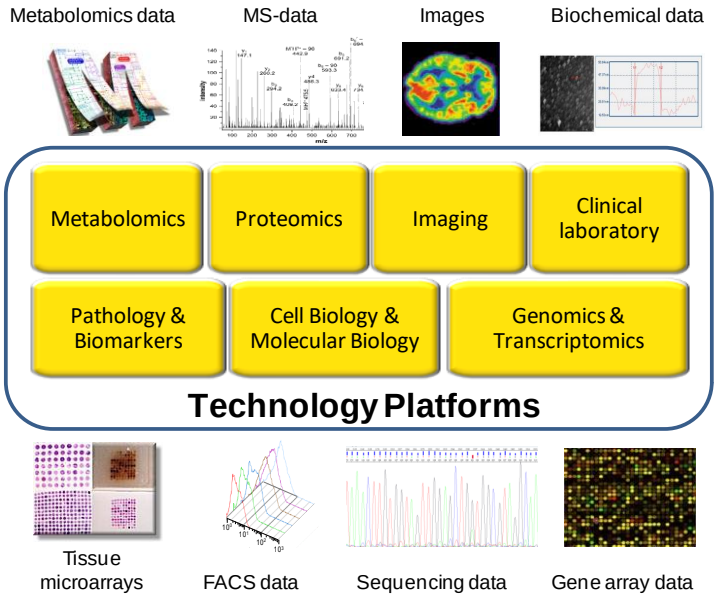
Sequencing data



Gene array data

The grand challenge

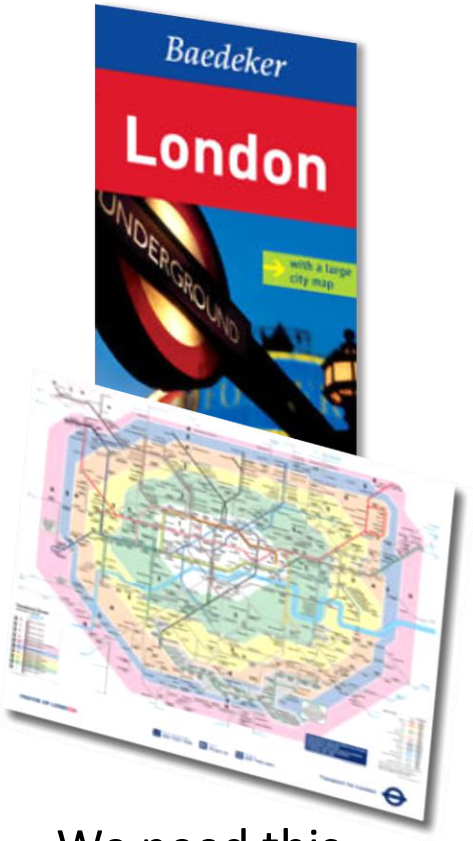
Turning data into knowledge



The –omics dilemma

We got that

We proceeded



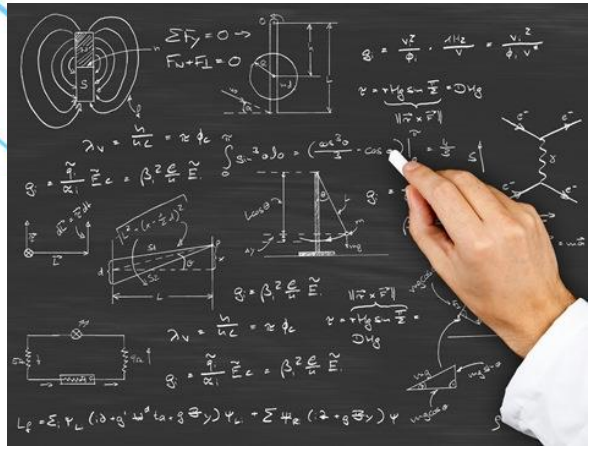
We need this

How do we turn a phonebook into a map?

Systems Biology makes the connections

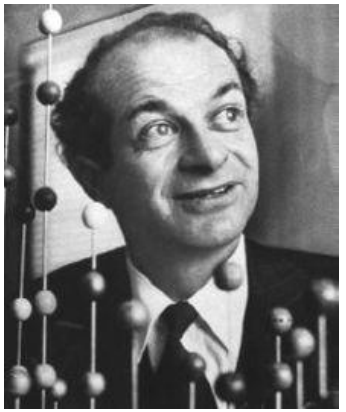
Systems Biology

uses mathematical & computational modelling to describe and analyse biological and biomedical processes



Life is a relationship among molecules and not a property of any molecule.

Linus Pauling
(won 2 Nobel Prizes)



SYSTEMS BIOLOGY IRELAND

~60 staff
>20 nationalities
~1 publication/week

Wet and dry under one roof

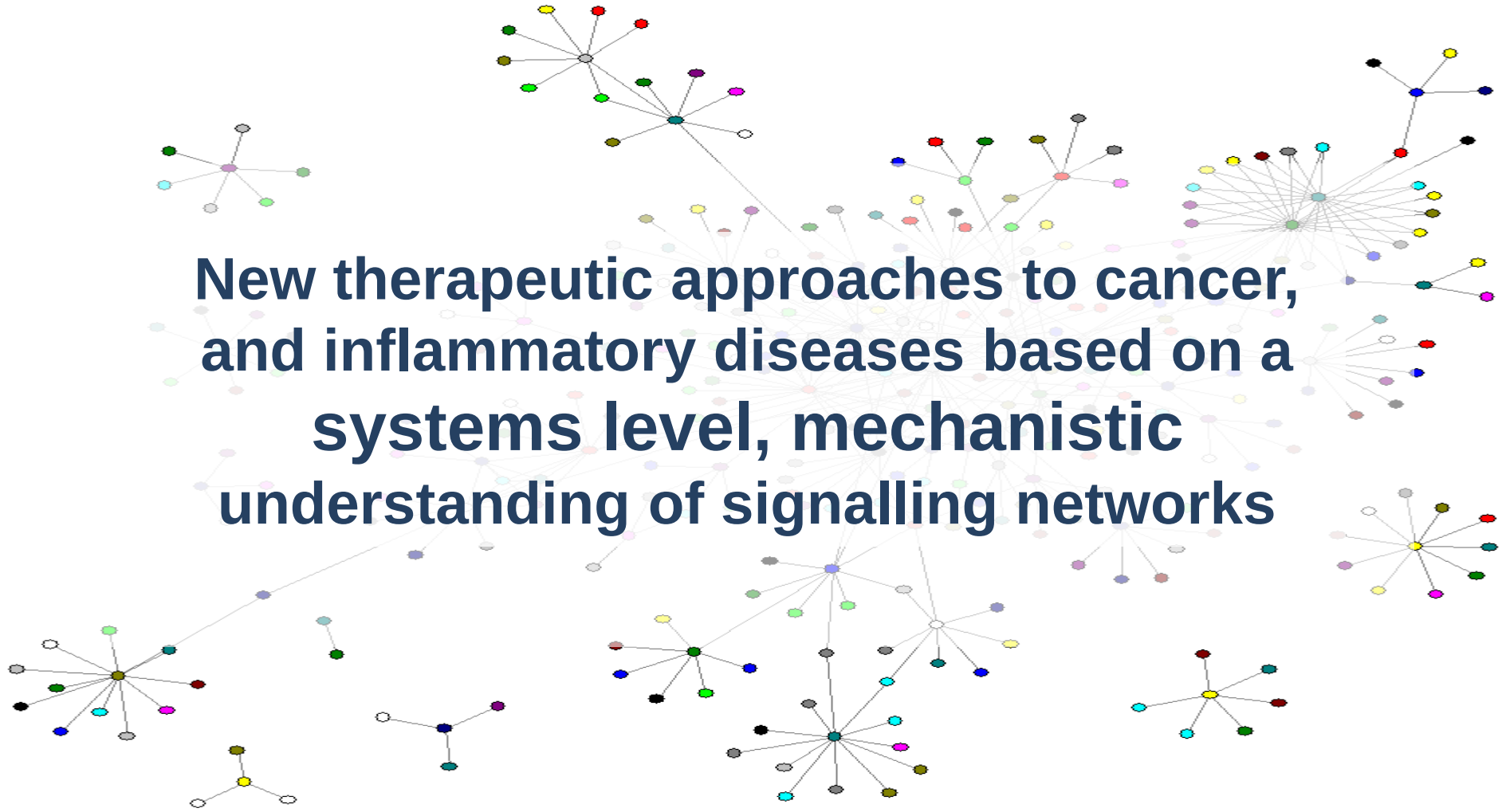
SBI is "... one of the top five Systems Biology Centers in the world"

From the report of an SFI appointed international review panel, November 2014

SBI

sfi
Fondúireacht Eolaíochta Éireann
Science Foundation Ireland

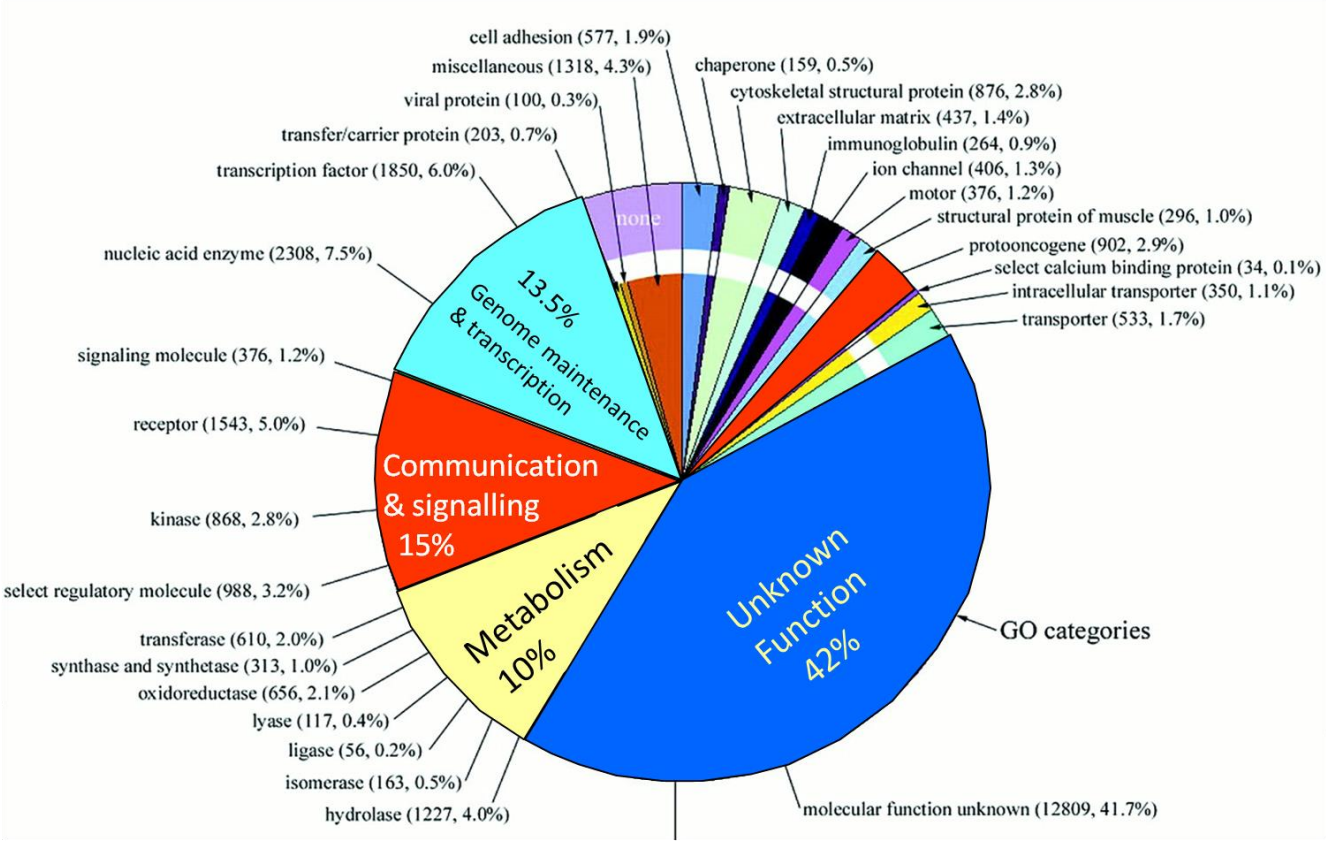
THE SYSTEMS BIOLOGY IRELAND VISION



New therapeutic approaches to cancer, and inflammatory diseases based on a systems level, mechanistic understanding of signalling networks

Why focus on signal transduction networks?

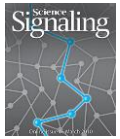
Signal transduction networks provide the **communication** within and between cells. **15% of our genes** are dedicated to **communication.**



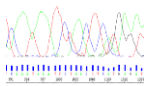
A vision for personalised medicine

Evidence & data

Pathway literature



Mutation data

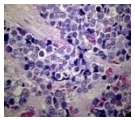


Pathway mapping

Patients' samples

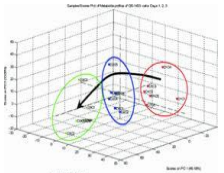
Clinical literature

Clinical samples

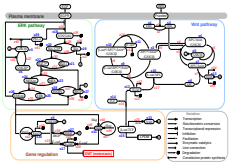


Multidimensional inputs

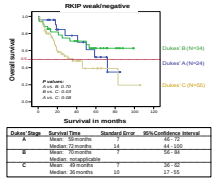
Omic profiles



Signalling networks

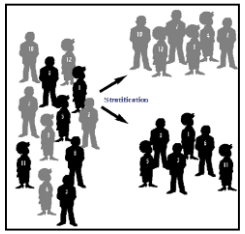


Clinical data

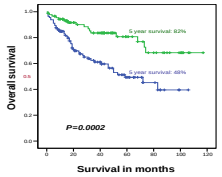


Computational models

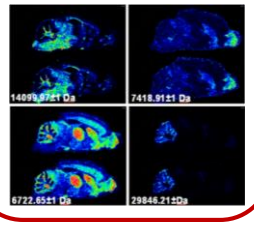
Patient stratification



Prognosis



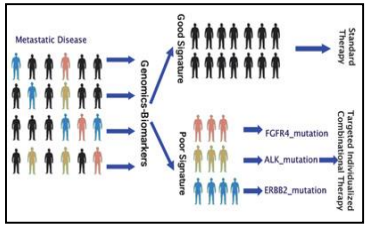
Therapy response



Virtual patients

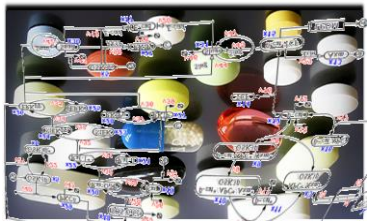
Improved diagnostics & therapies

Personalised diagnostics



&

Personalised therapies



Validation

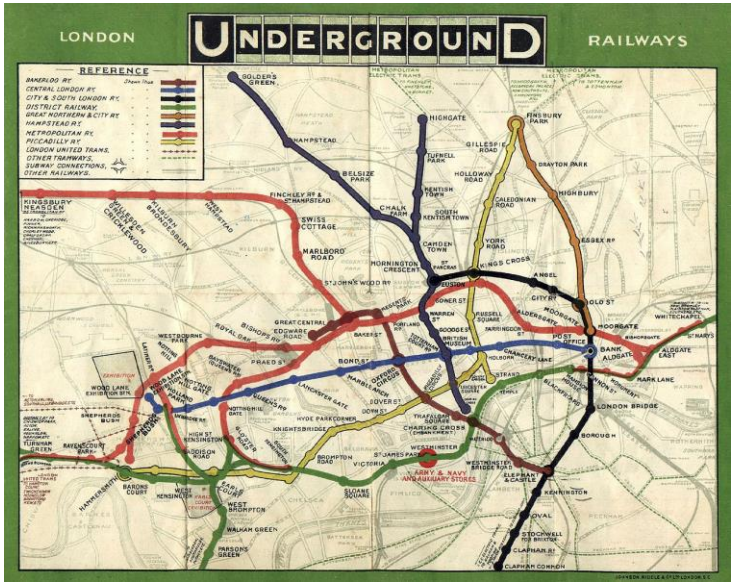
What does a model do?

A model is a representation of a system that allows for investigation of the properties of the system and, in some cases, prediction of future outcomes.

Investorwords.com

Models are not reality.
Models are useful abstractions that allow us to understand complex realities

A very useful network map



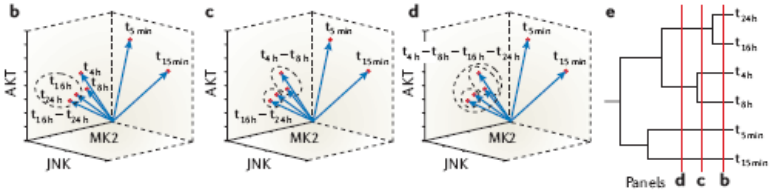
1908

Harry Beck's Underground Map of 1933

Common modelling approaches

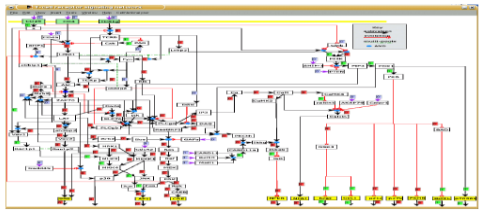
Data driven modelling

- Analysis of large datasets



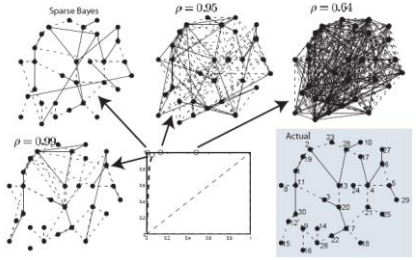
Rule based modelling

- Interaction networks (proteins, pathways, cells)
- Petrinets, Boolean Networks, automata, …



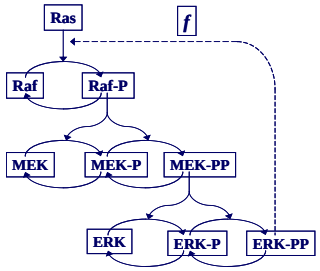
Stochastic & statistically based modelling

- Interaction networks (proteins, pathways, cells)
- Markov chains, Bayesian Networks, …



Mechanistic modelling

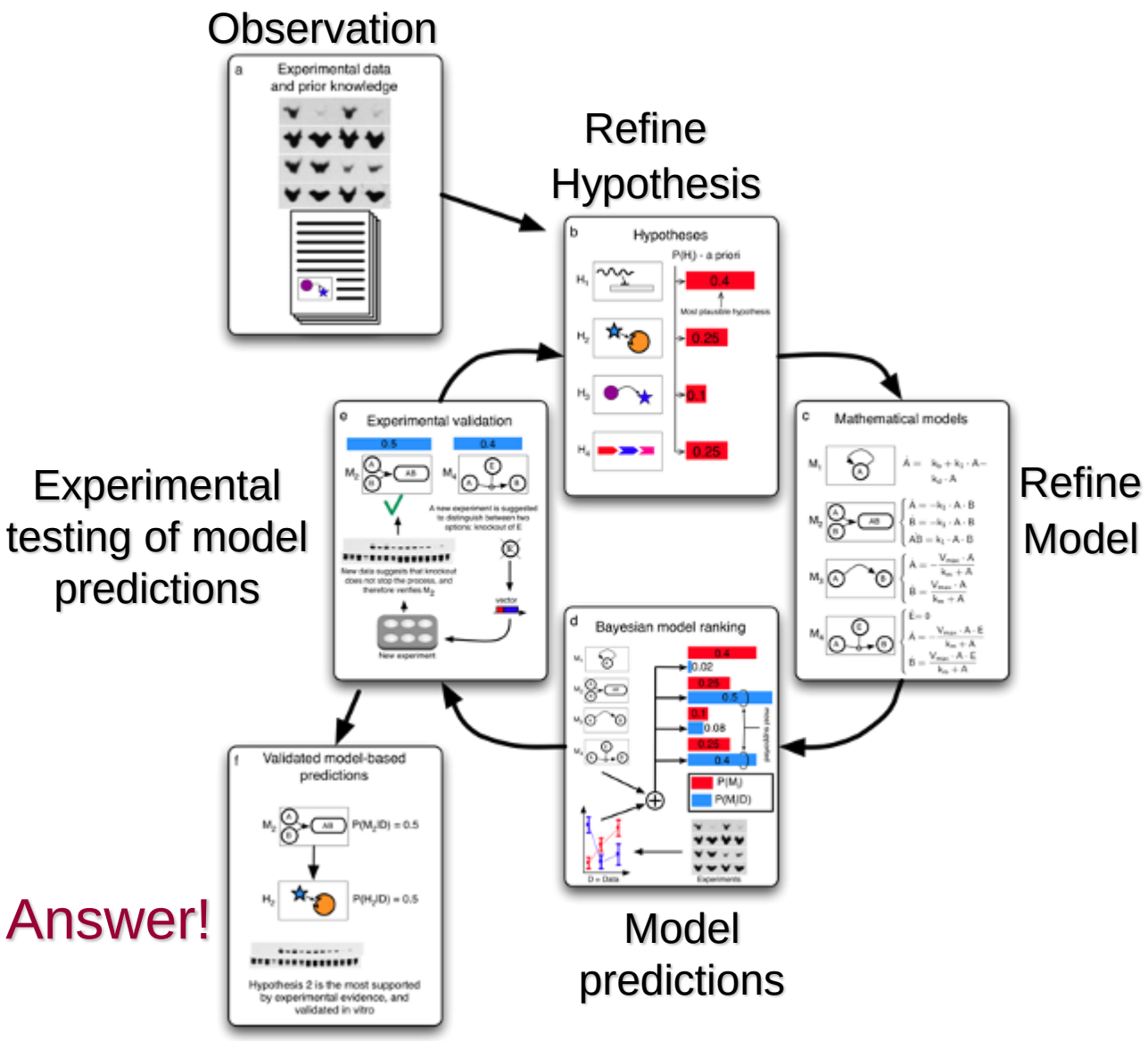
- Reactions, diffusion, gradients
- Consider time
- Can consider space
- Typically based on differential equations



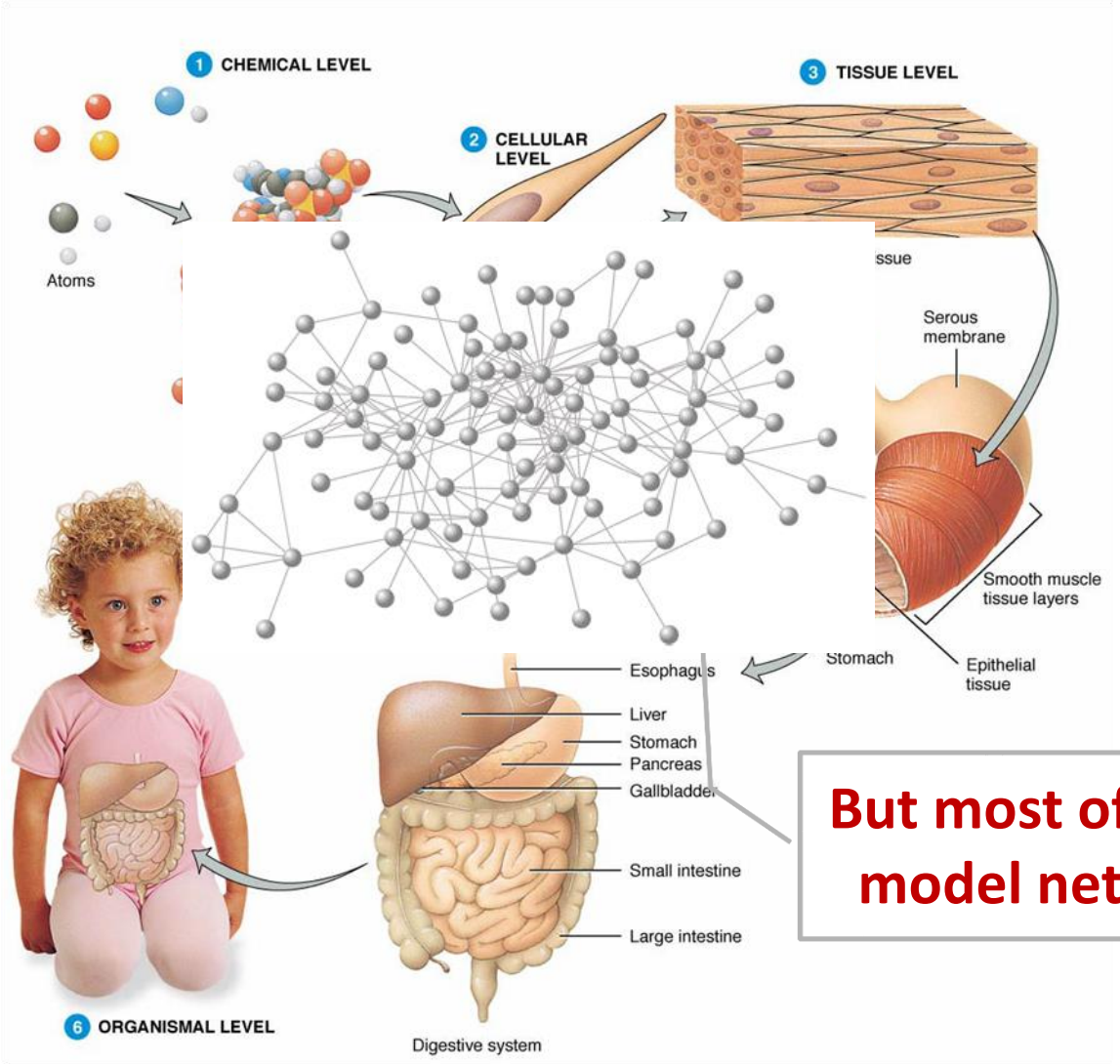
$$v_{kin} = \frac{k_{kin}^{cat} E_{kin} M}{(K_{m1} + M)} \cdot \frac{(1 + AM_p / K_a)}{(1 + M_p / K_a)}$$

$$\frac{dM_p}{dt} = v_{kin} - v_{phos}$$

Making models is an iterative process



Models can be across scales

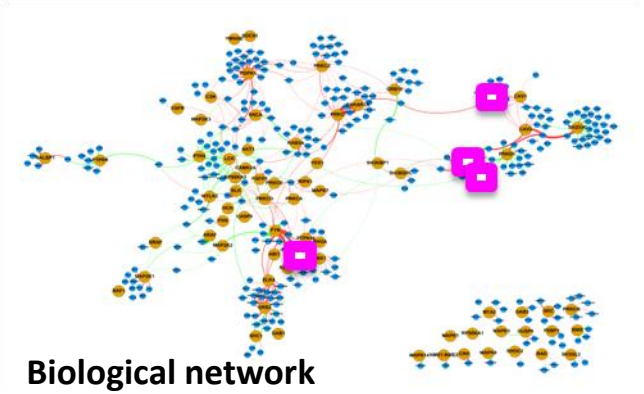


But most often we model networks

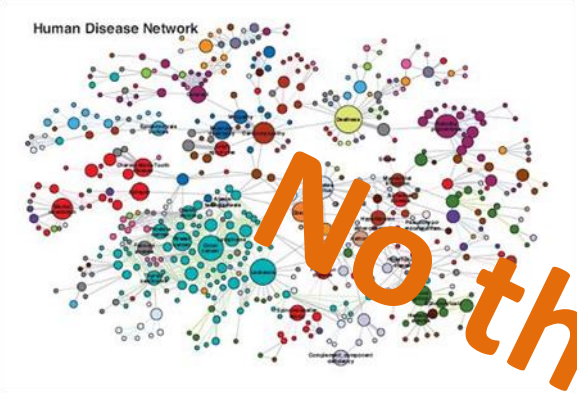
What is a network?

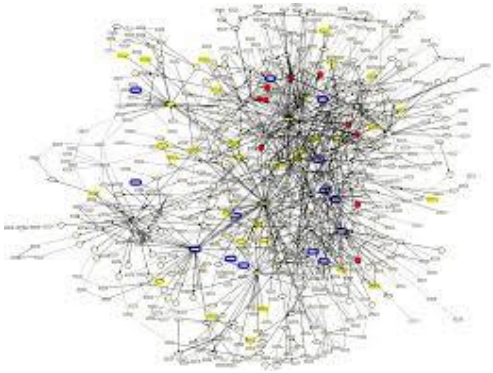
Real world networks

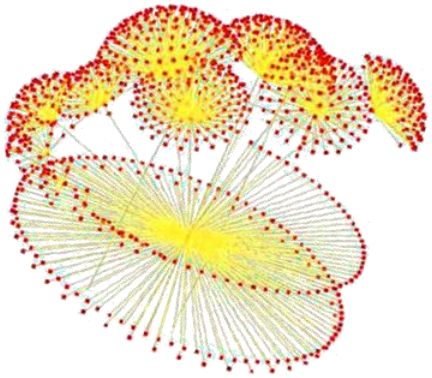
They all look alike

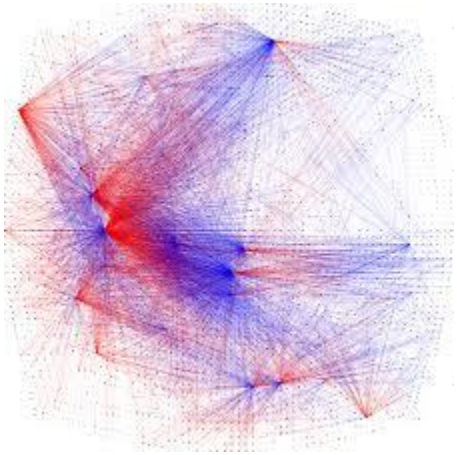


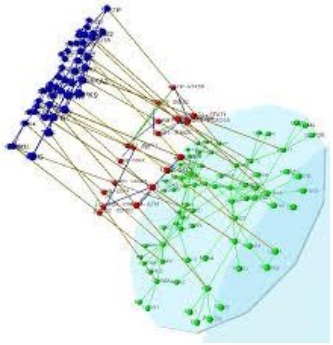
Biological networks

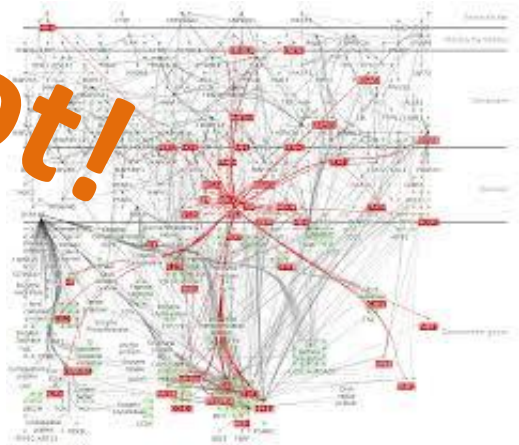






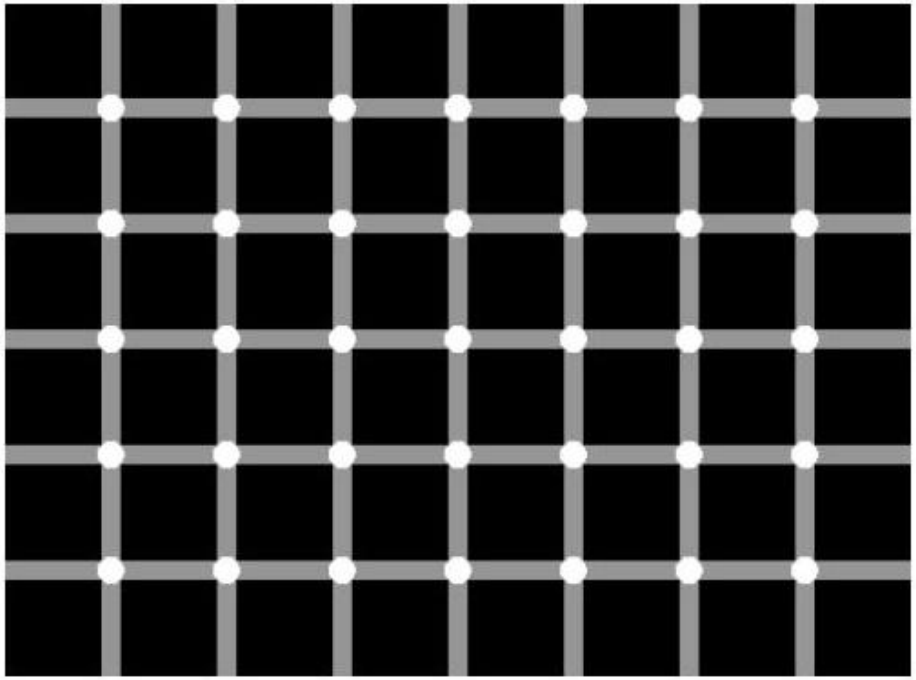






No they do not!

Count the black dots

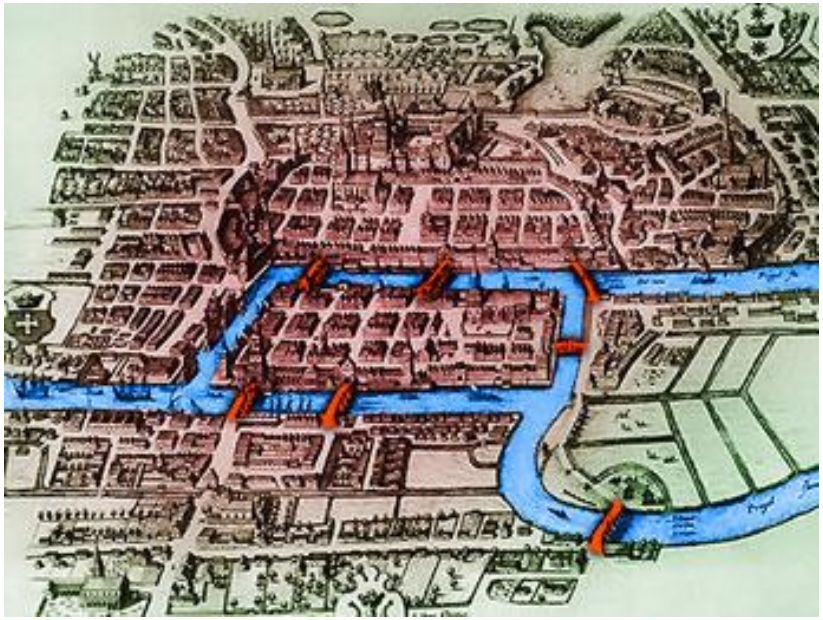


How much is our concept of networks determined by our perception?

Are networks what we think they are?

The Network Concept

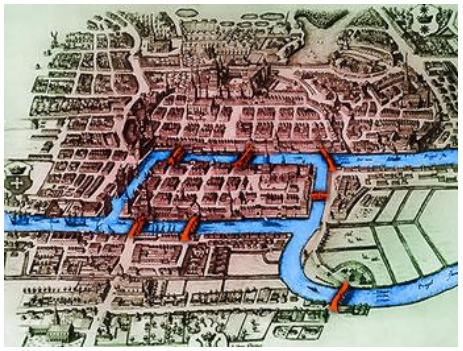
The 7 Bridges of Königsberg (1736)



Can you walk through the city by crossing each bridge once and only once?

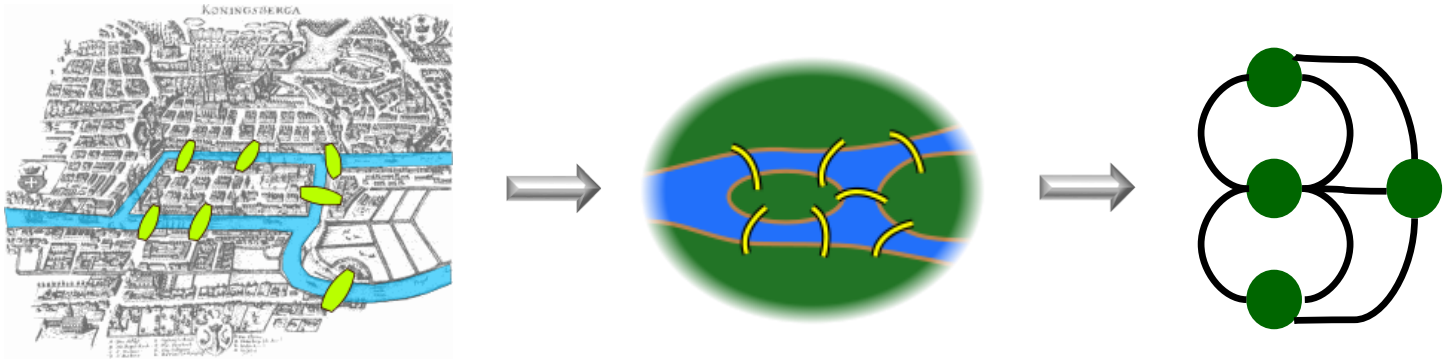
Leonard Euler

The 7 Bridges of Königsberg – birth of the network concept

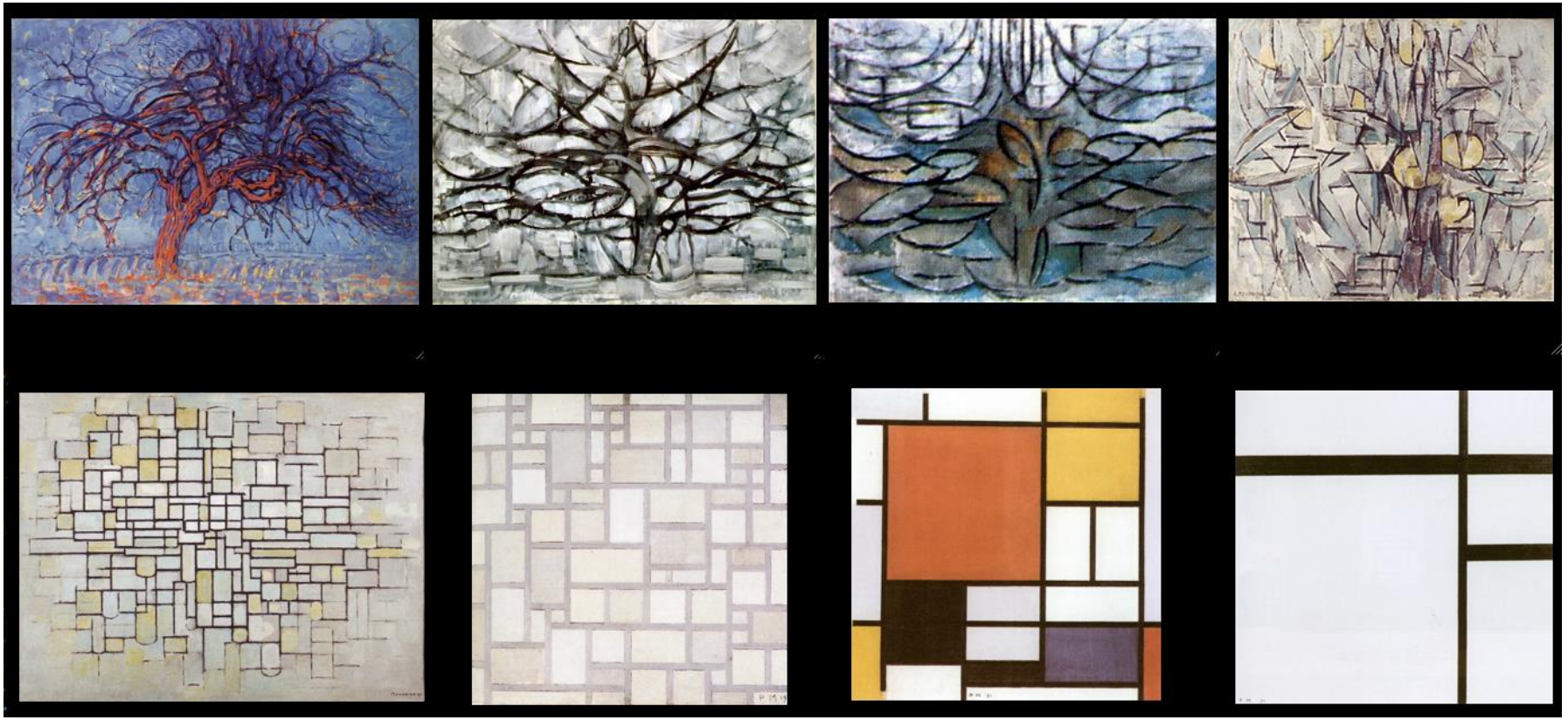


Can you walk through the city by crossing each bridge once and only once?

1) The choice of route inside any quarter of the city is irrelevant.
2) To find the best route only the sequence of bridges crossed is important.
3) Therefore, one only needs to retain the bridges and a representation of the city quarters. All other features can be eliminated.
4) This leads to the representation as a network graph: a city quarter becomes a "vertex" or “node”, and a bridge becomes an "edge“



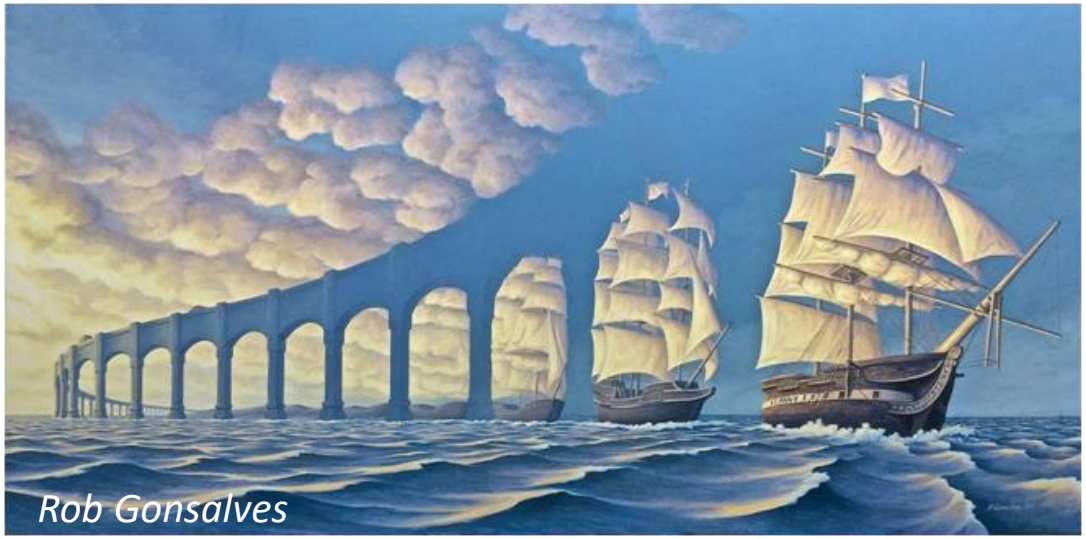
A network is an abstraction



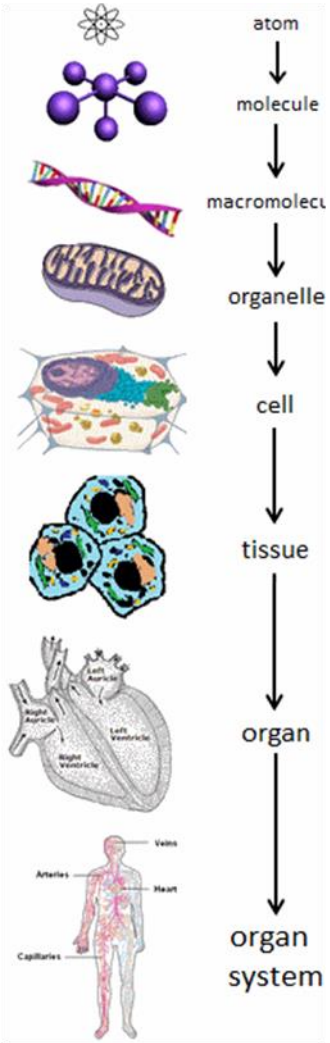
Piet Mondrian (1872-1944)
Abstraction of a tree

A network is an abstraction

What reality do we abstract?
For what purpose?
What does the abstraction tell us?
Can we go back from abstraction to reality?



What reality do we abstract?



Maps of organisation

Components
- Molecules
- Molecular machines

Relationships
- Spatial
- Temporal

Functions
- Alone
- In self-context
- In interaction with environment

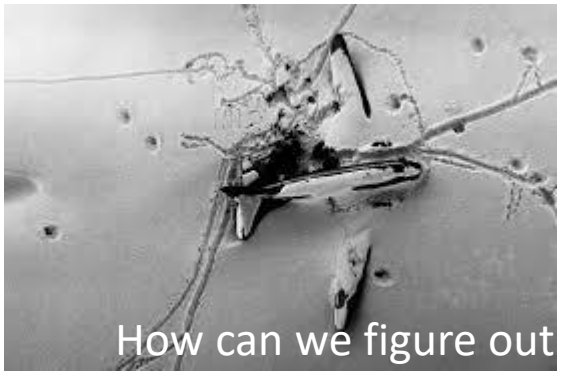
Design
- Can we reproduce it?

For what purpose?

Why do we need abstractions?

Our approach is “grind and find”

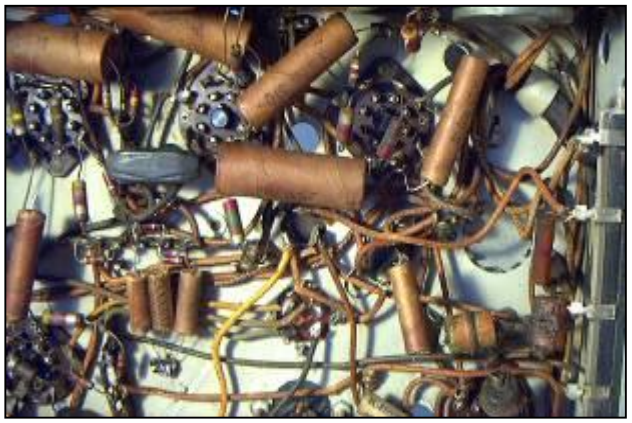
We have learned the structure of biological systems mainly by breaking them up into the smallest components.



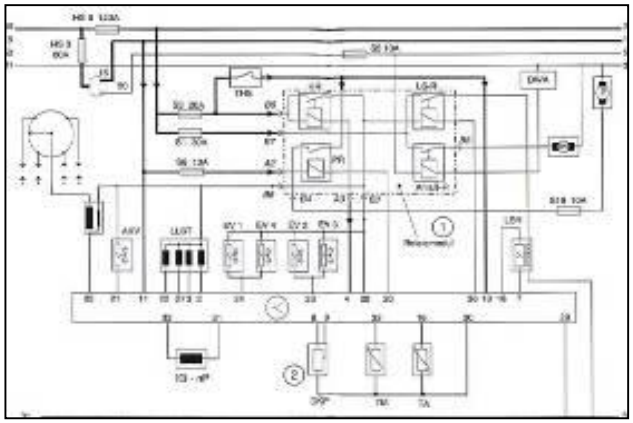
How can we figure out the original function from analysing wrecks?

For what purpose?

What we can see

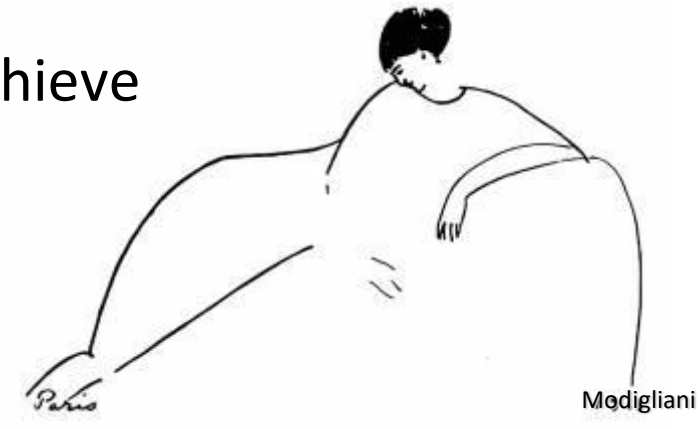


What we would like to see



What we can achieve

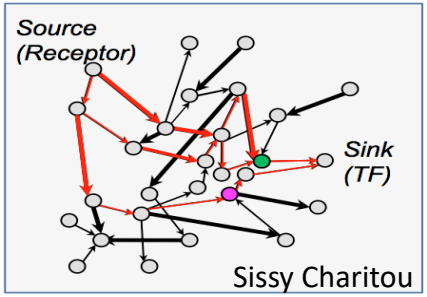
Models are useful abstractions



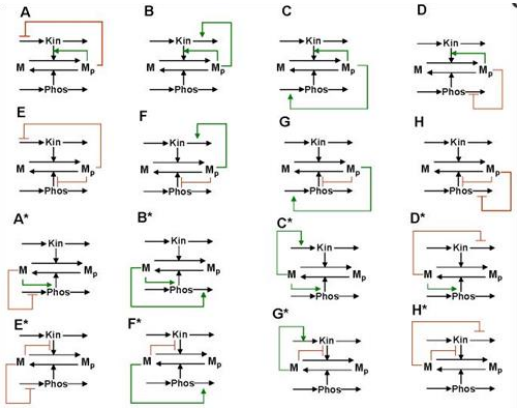
What does the abstraction tell us?

Emergent properties

Information flow

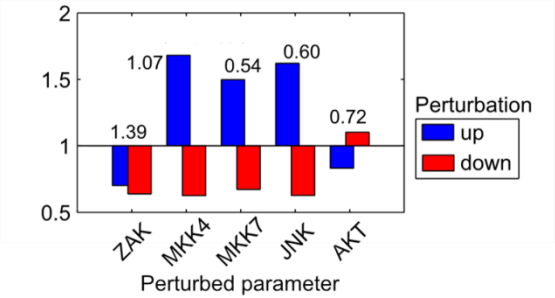


Network dynamics



Feedback designs that can turn a universal signalling cycle into a bistable switch and relaxation oscillator
B Kholodenko. Nat Rev Mol Cell Biol. 2006 7(3): 165–176.

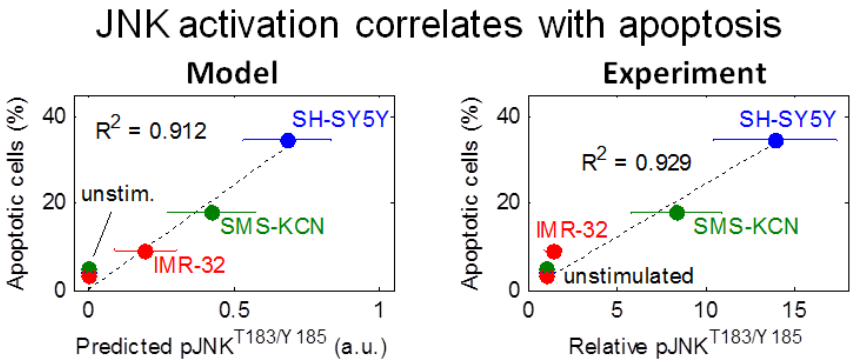
Control nodes



How can we go back from abstraction to reality?

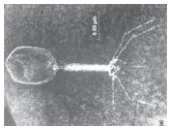
Acknowledging the limitations of biological & computational models

Firmly link model predictions with biological outcomes



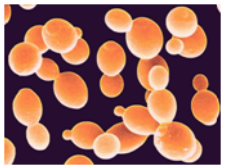
Common model systems

Single cells

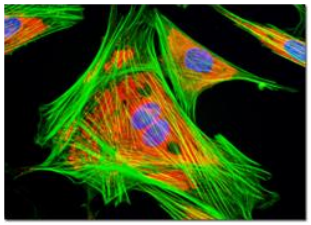


virus

bacteria

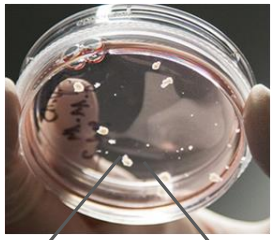


yeast



mammalian cell

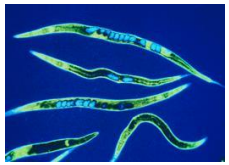
Tissue models



organoids

artificial skin model

Model organisms



C. elegans

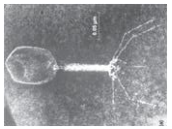
Drosophila

Zebrafish

Mouse

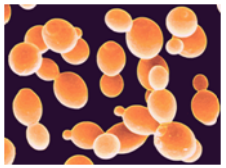
Common model systems – what have they told us?

Single cells

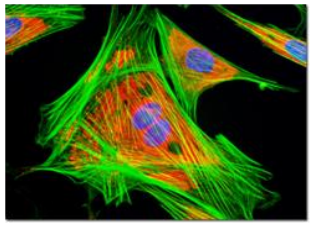


virus

bacteria



yeast



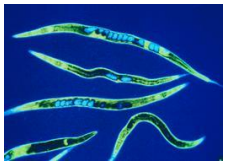
mammalian cell

- DNA replication
- DNA repair
- Gene expression
- Protein translation
- Cell cycle
- Genetic engineering

Fundamental principles

Common model systems – what have they told us?

Model organisms



C. elegans

Drosophila

Zebrafish

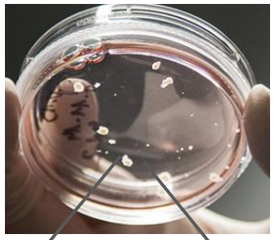
Mouse

- Apoptosis
- Development
- Cell fate decisions
- Disease models
- Metastasis
- Behavioural models

Higher order organisation

Common model systems – what have they told us?

Tissue models



organoids

artificial skin model

- Effect of mutations
- Stem cell potency
- Inductive processes
- More to come...

Principles of organisation

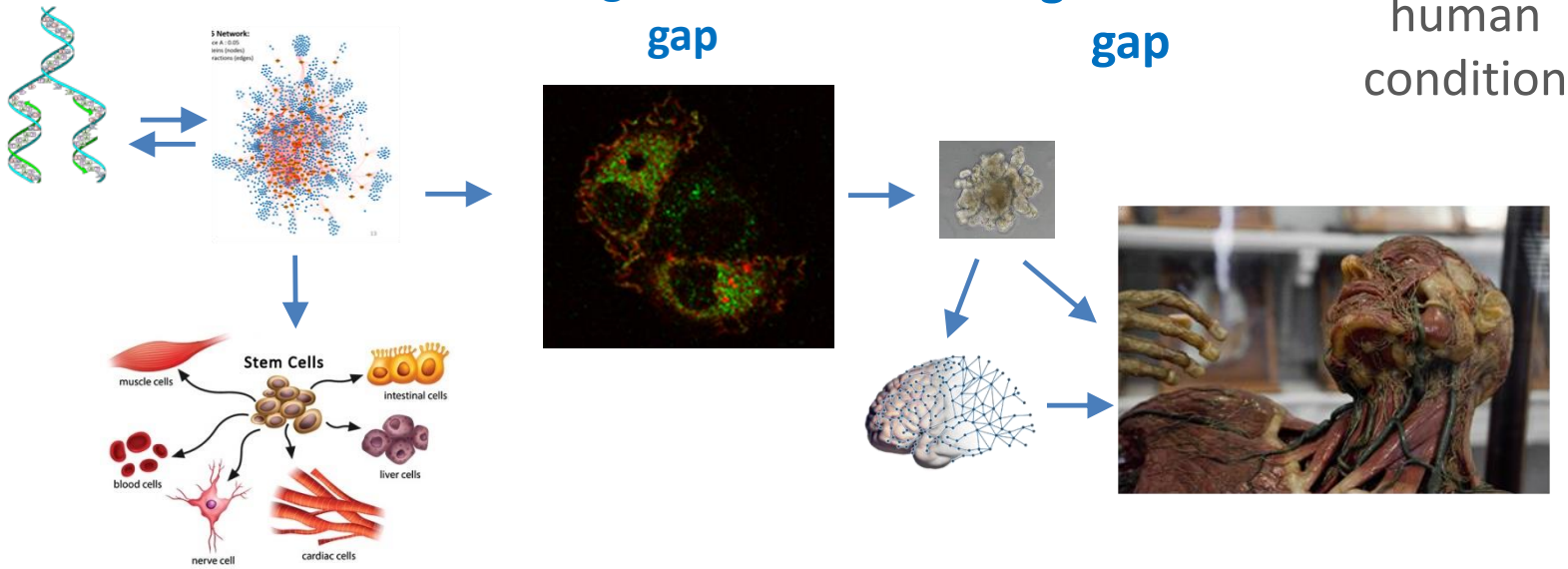
Model systems – what have they NOT told us?

Fundamental principles

Principles of organisation

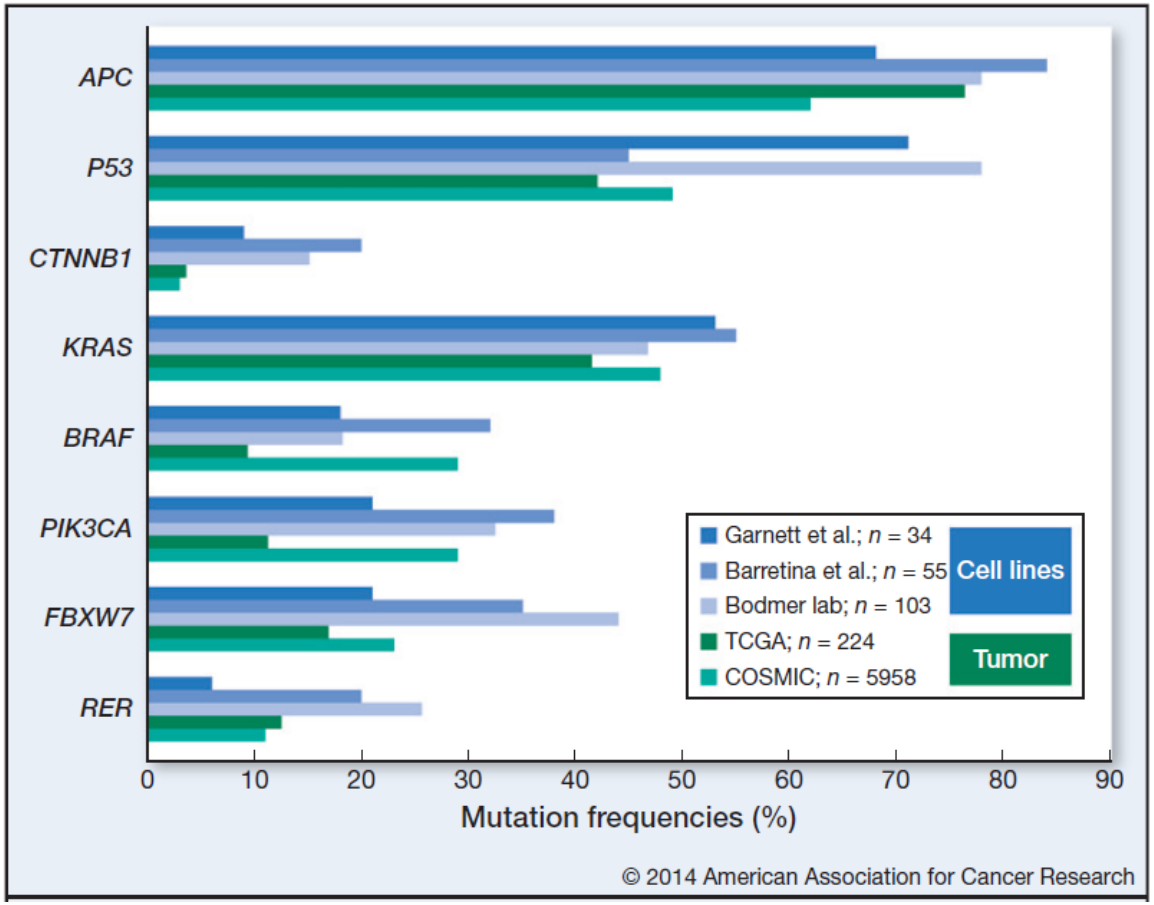
Higher order organisation

The emerging human condition



What is the best model for the human?

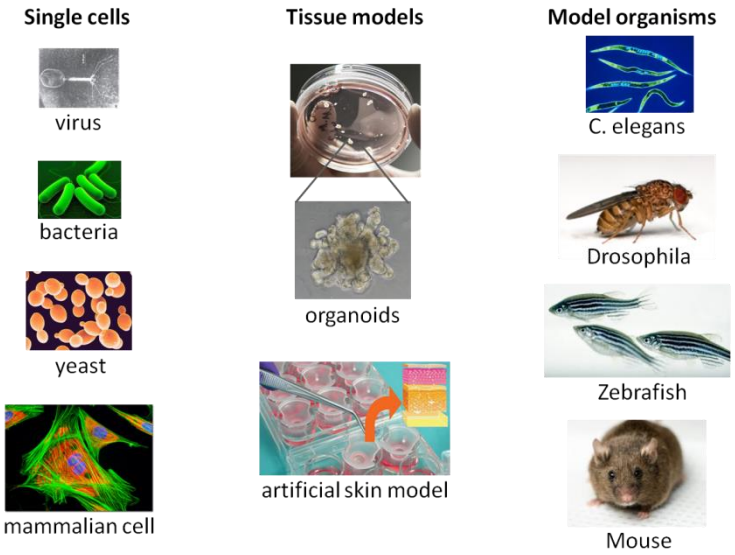
Cell lines are not too bad



Correlation between the frequencies of commonly mutated genes in colorectal cell lines versus primary cancers.

Jennifer L. Wilding and Walter F. Bodmer. **Cancer Cell Lines for Drug Discovery and Development.** *Cancer Res 2014;74:2377-2384.*

What information can we get from model systems? What model system should we use?

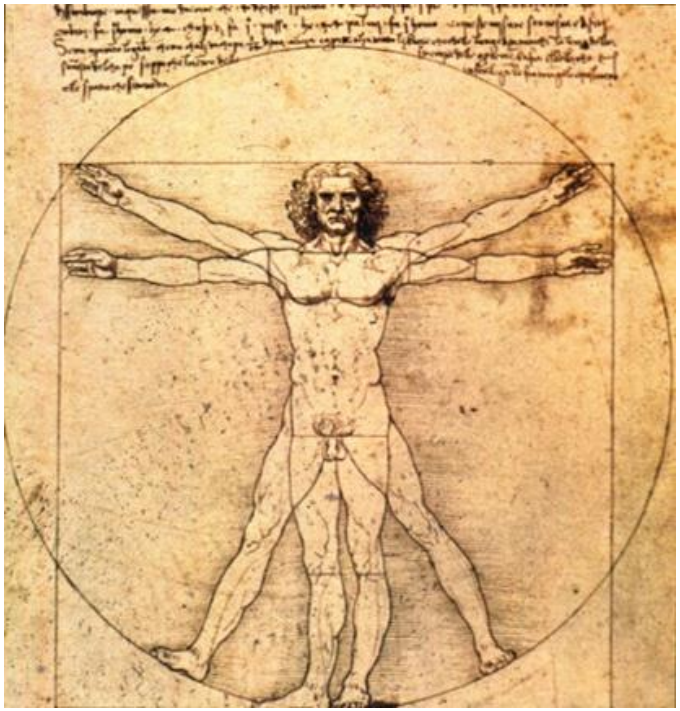


"Experience is a question of instinct about life" *(Oscar Wilde)*

"An instinct about life is a question of experience " *(Porto)*

There is no perfect model

The model needs to be adequate to the question

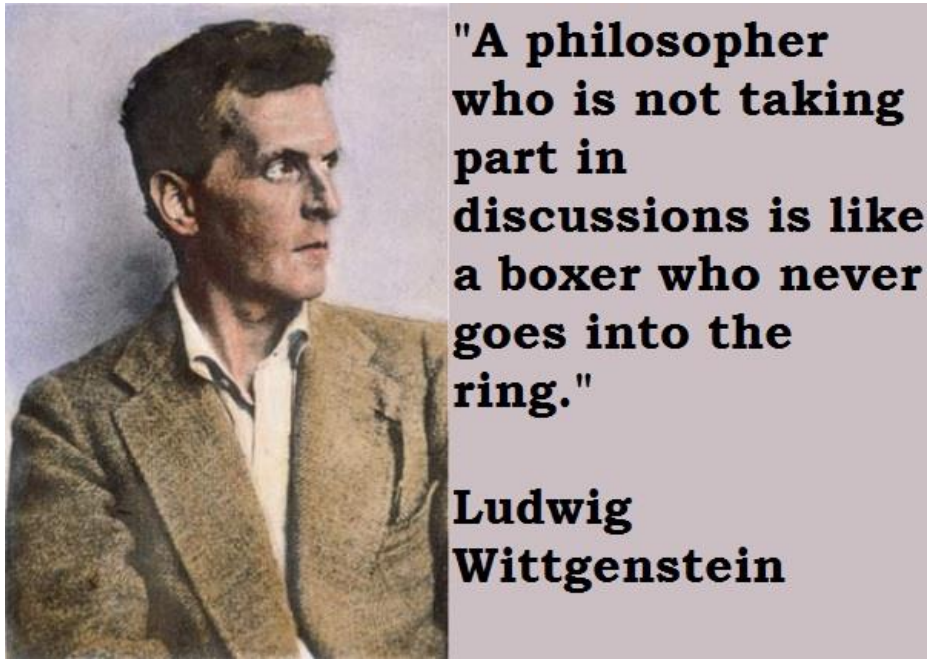


Leonardo da Vinci

You cannot square the circle,
but you can approximate it.

“If people never did silly things nothing intelligent would ever get done.”

Ludwig Wittgenstein, Philosopher of Science (1889-1951)



Thank you

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