Department of Physics

UNIVERSITY OF OXFORD

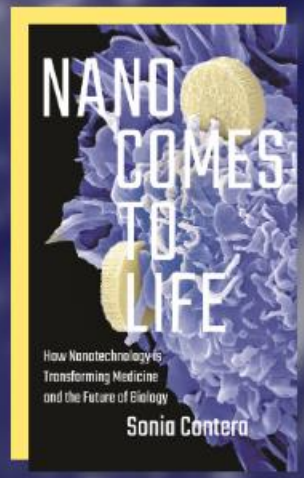
Nano comes to life:

How nanotechnology ushers physics in to biology, transforming medicine and the future ot technology

Prof Sonia Contera

Professor of Biological Physics and Associate Head of the Department of Physics for Equity, Diversity and Inclusion

Author of *Nano comes to Life*



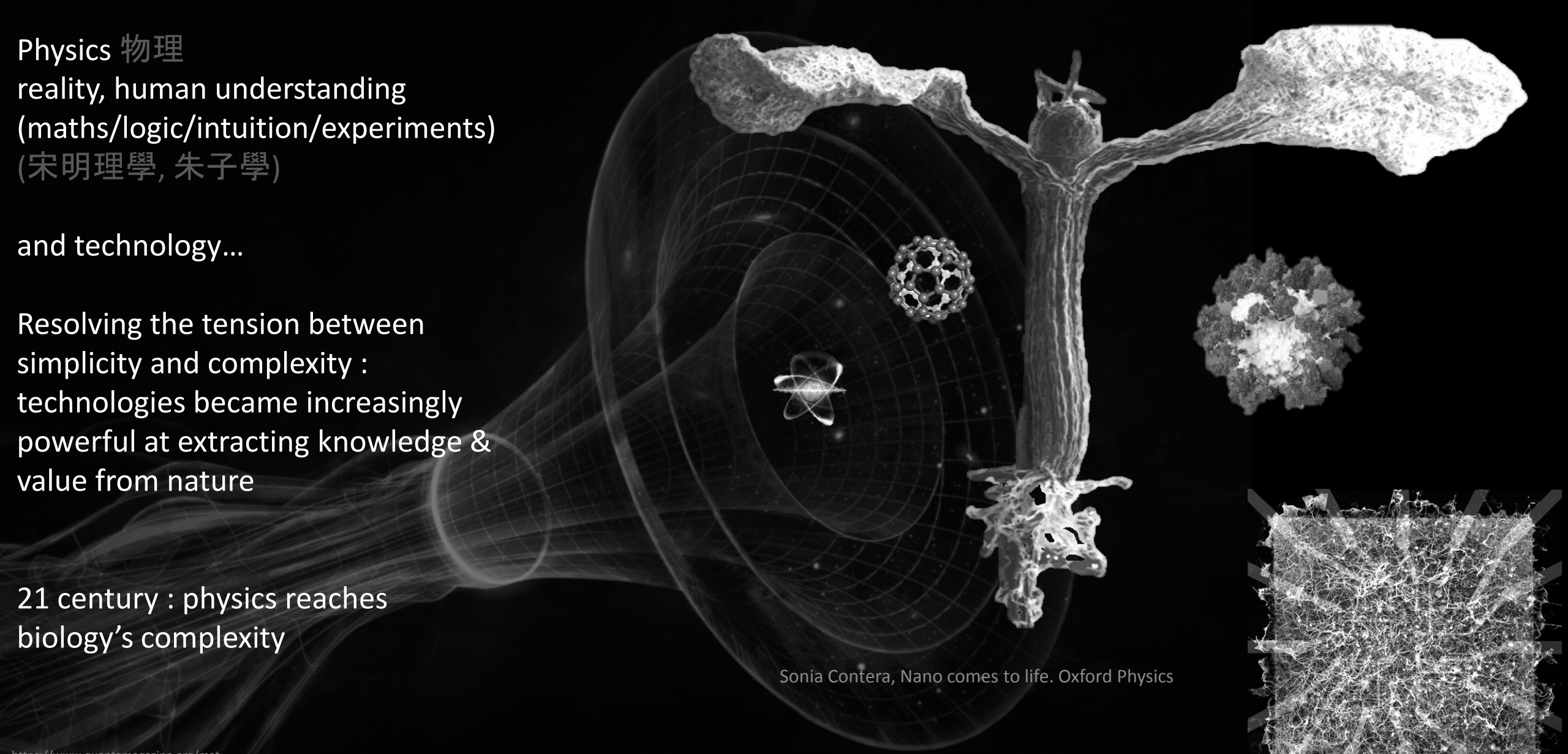
Follow Prof Contera on Twitter or Instagram @SONIACONTERA

Physics 物理
reality, human understanding
(maths/logic/intuition/experiments)
(宋明理學, 朱子學)

and technology…

Resolving the tension between simplicity and complexity : technologies became increasingly powerful at extracting knowledge & value from nature

21 century : physics reaches biology's complexity



Sonia Contera, Nano comes to life. Oxford Physics

Gimzewski neuromorphic computing

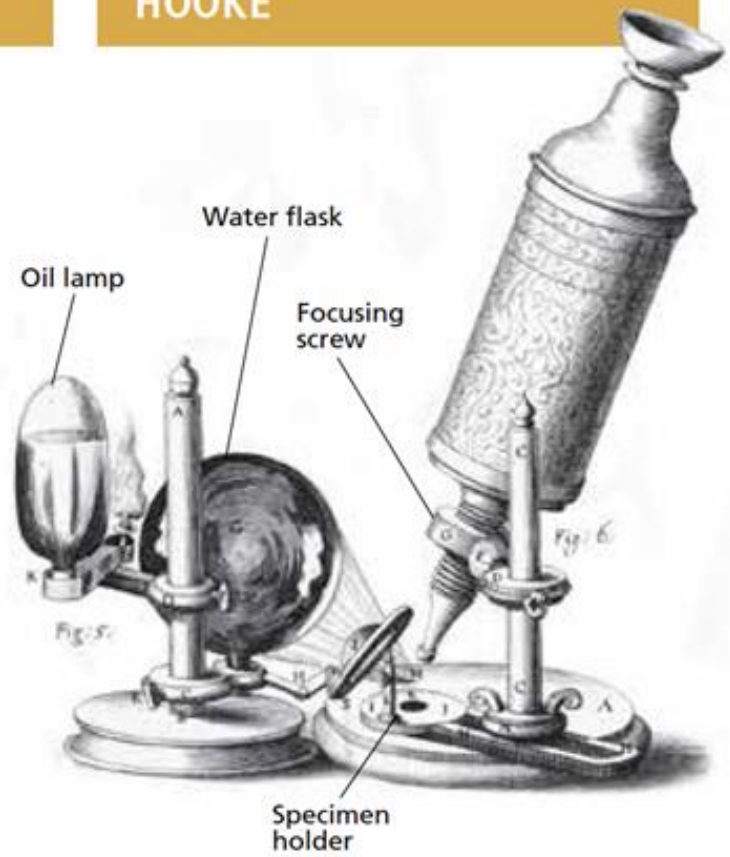
https://www.quantamagazine.org/mathematicians-disprove-conjecture-made-to-save-black-holes-20180517/

30/08/2021

GALILEO

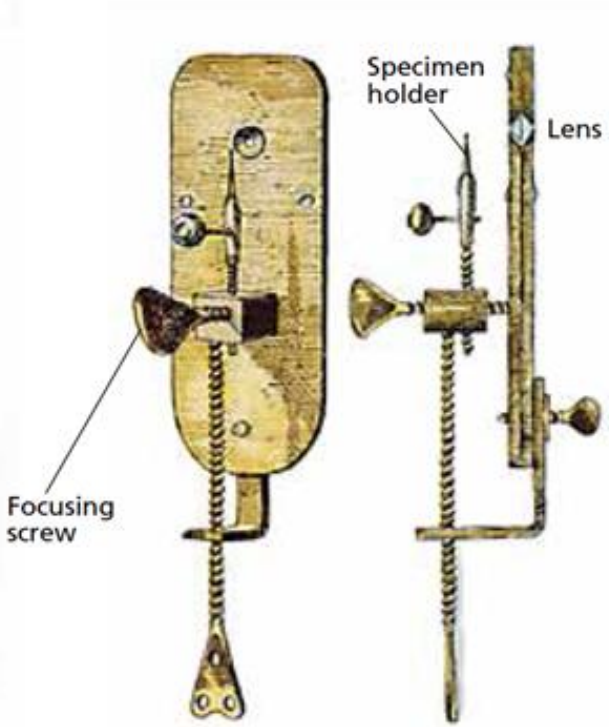
An early example of a microscope, which many historians believe was invented by Galileo in the 17th century.

HOOKE



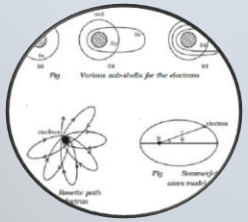
Hooke's illustration of his own microscope, published in *Micrographia*. His model had a magnification of about twentyfold.

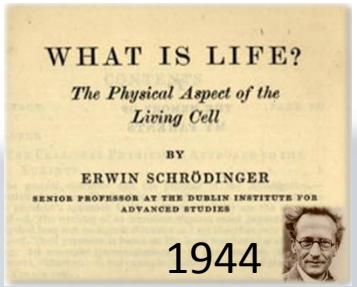
LEEUWENHOEK

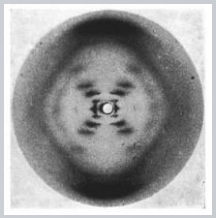


An illustration of one of Leeuwenhoek's microscopes. Surviving models from his collection can magnify more than 200 times.

Elemental particles
Quantum mechanics
1900-1920s

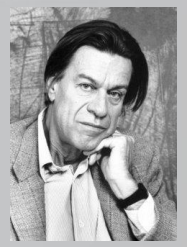






Photograph 51
Franklin
(1953)

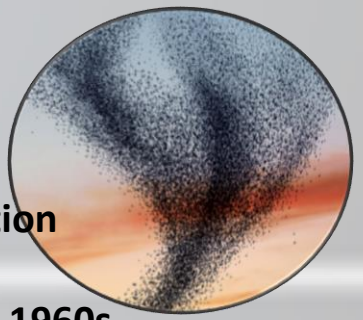
Pierre-Gilles de Genes



Solid State Physics
(Superconductivity 1937….)

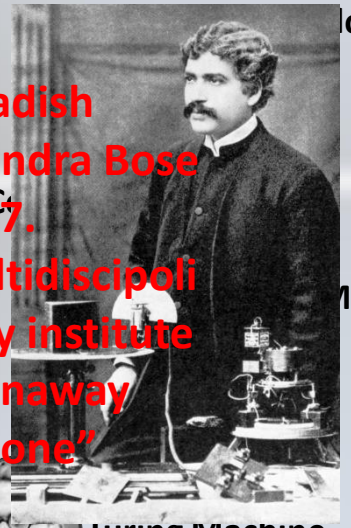
Soft Matter Physics 1960…

"there is plenty of room at the bottom"



Self-organisation
Fractals
Chaos Theory 1960s
(Lorentz , using computers)

Jagadish Chandra Bose 1917. Multidiscipolinary institute "Runaway cyclone"



Torahiko Terada Earthquake Institute 1926

1947

Lars Onsager

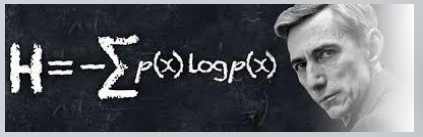
Ilya Prigogine

John Horton Conway
Game of Life
1970

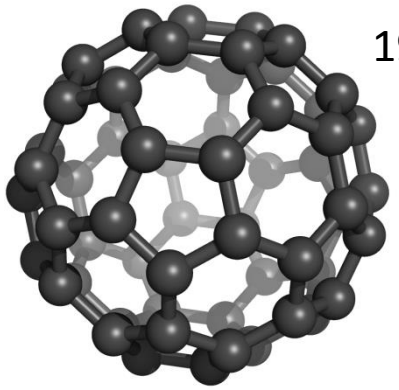
1940s

Turing Machine
1936

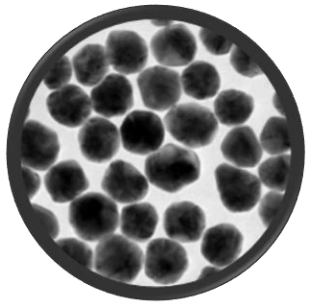
Goedel's incompleteness theorems
1931

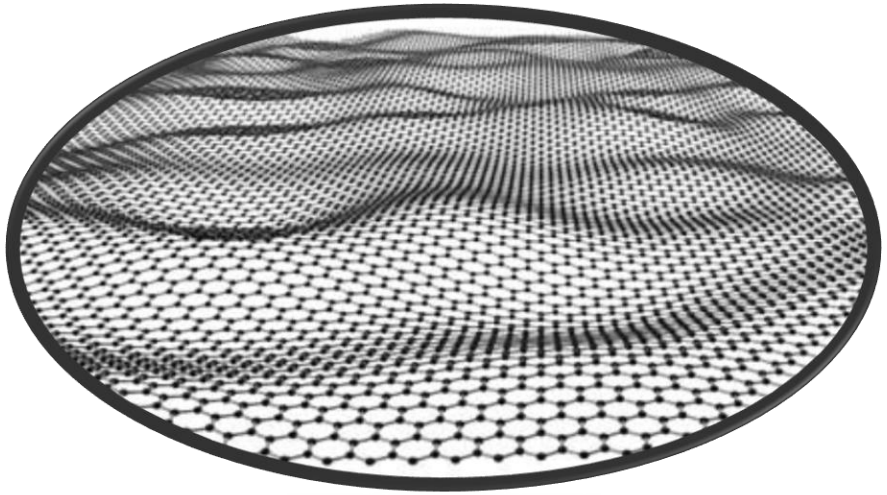


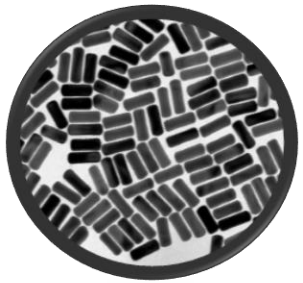
Claude Shannon
"A mathematical theory of communication"
1948

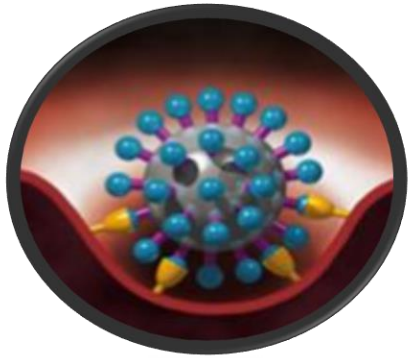


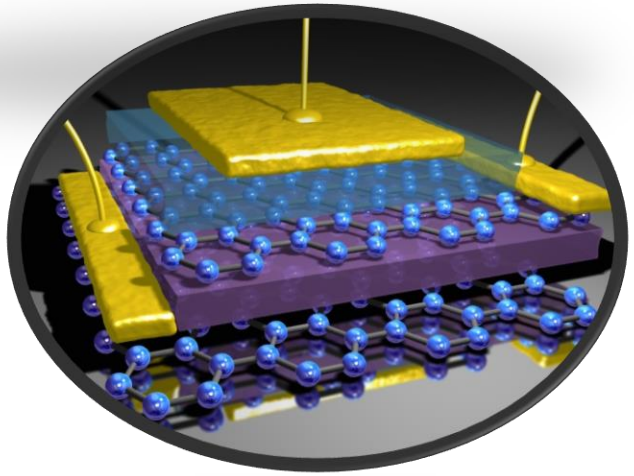
1985, Fullerene





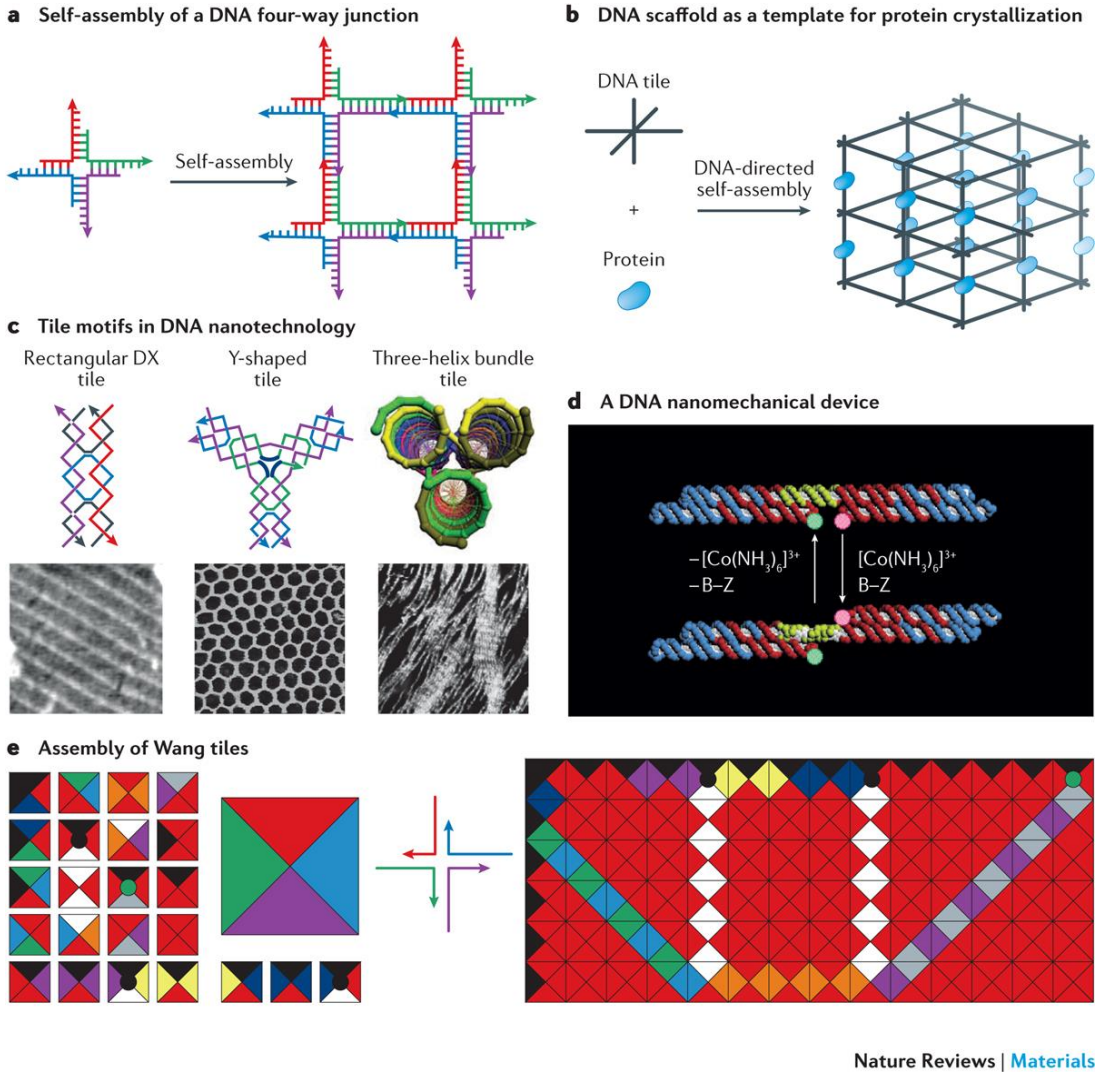




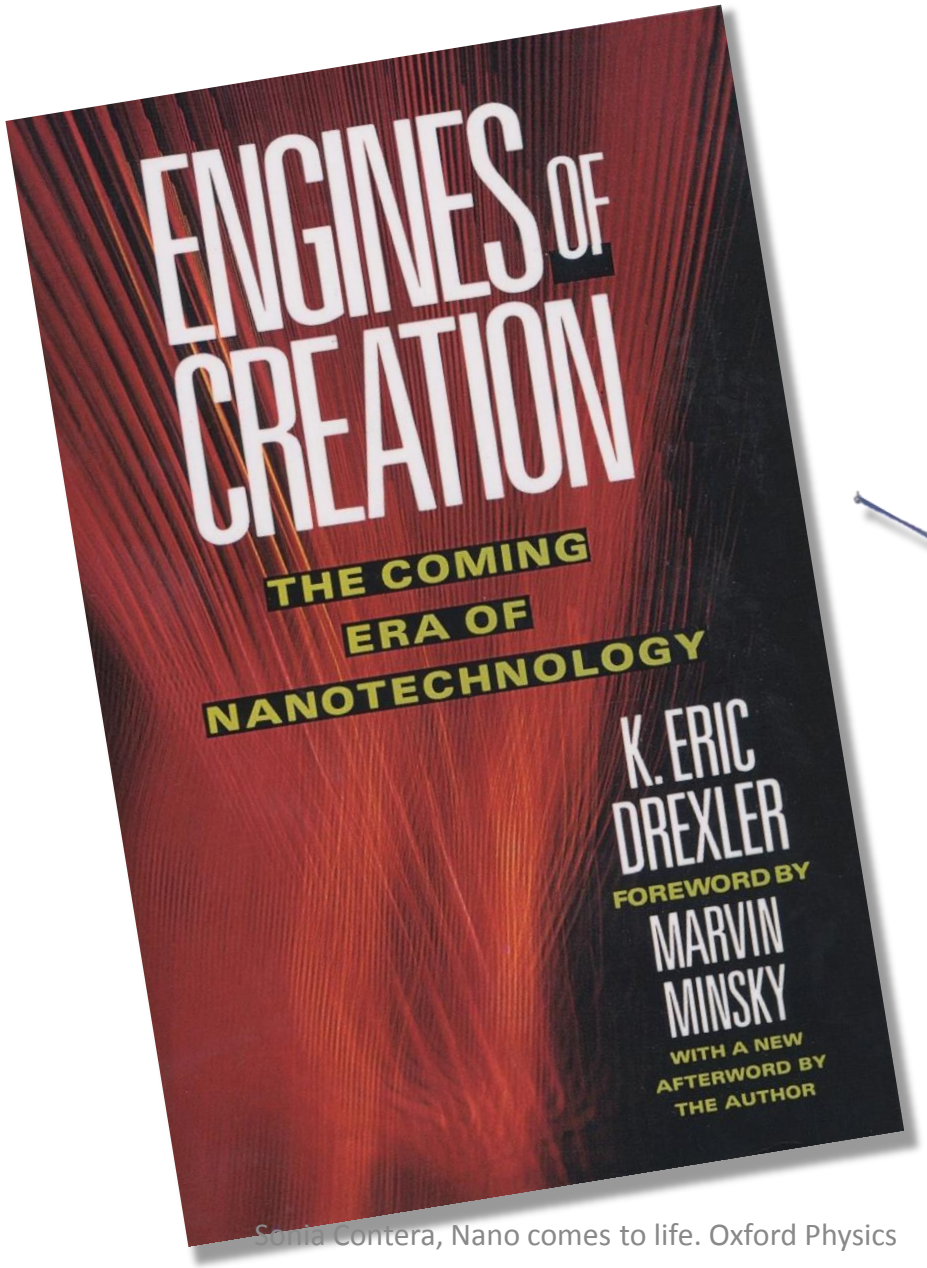


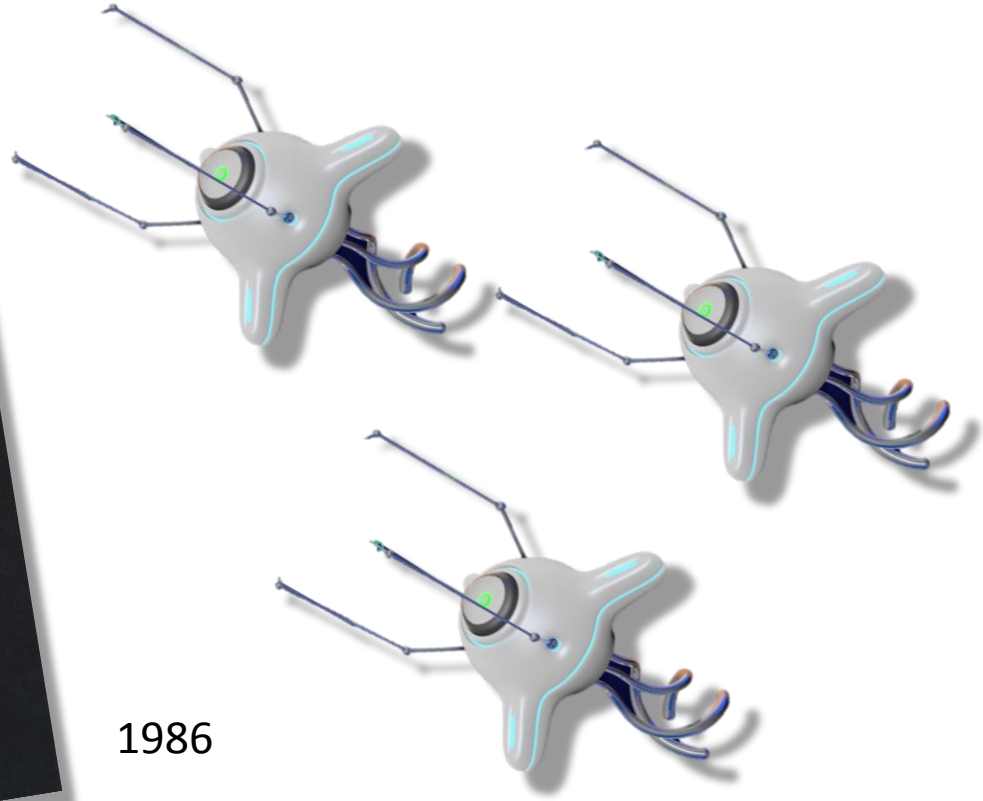
nanomaterials

DNA nanotechnology



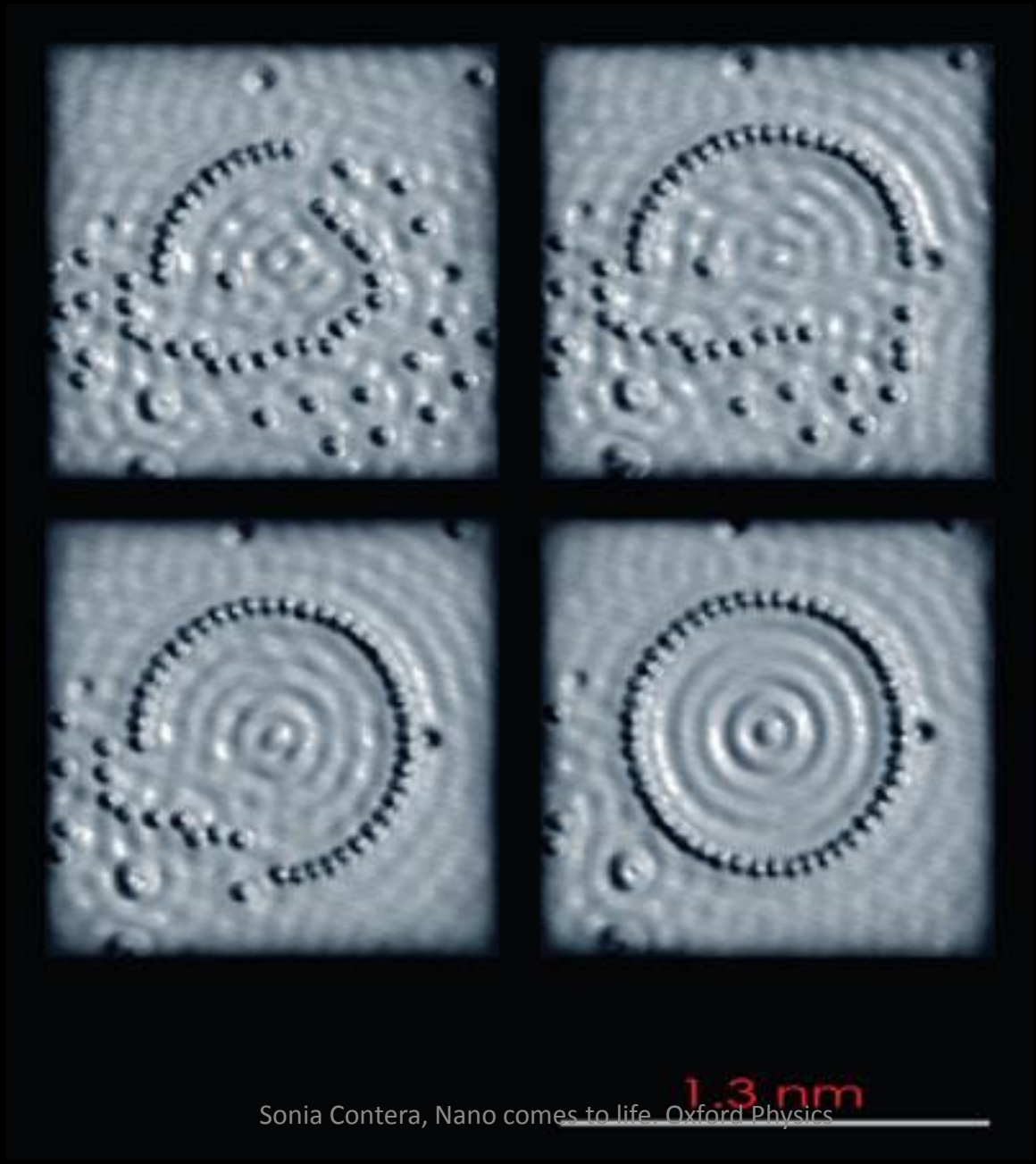
Seeman, N. C. & Sleiman, H. F. (2017) DNA nanotechnology
Nat. Rev. Mater. doi:10.1038/natrevmats.2017.68

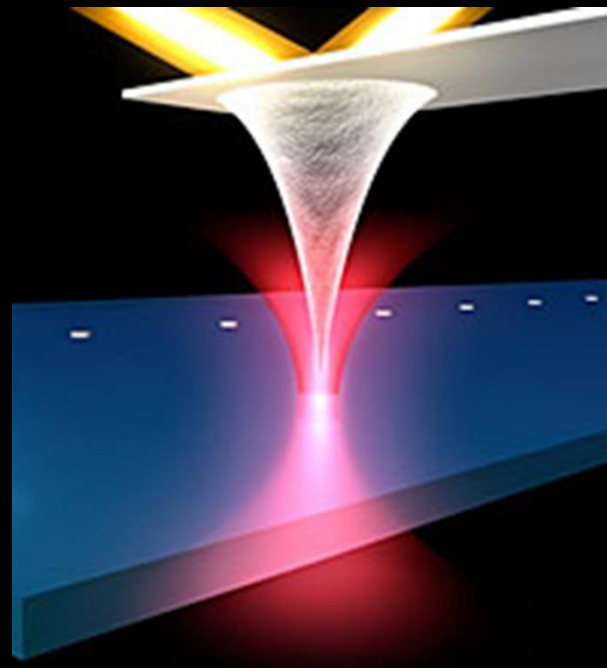

ENGINES OF CREATION
THE COMING ERA OF NANOTECHNOLOGY
K. ERIC DREXLER
FOREWORD BY
MARVIN MINSKY
WITH A NEW AFTERWORD BY THE AUTHOR



1986

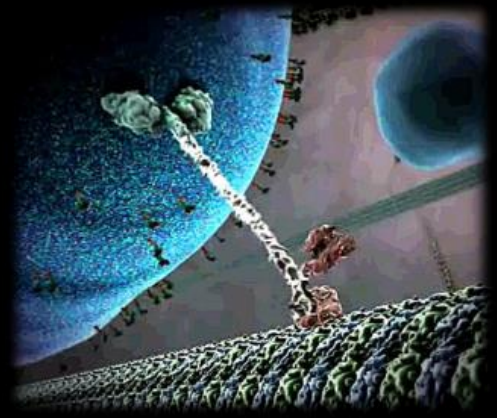
SCANNING PROBE MICROSCOPES



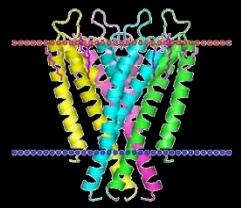


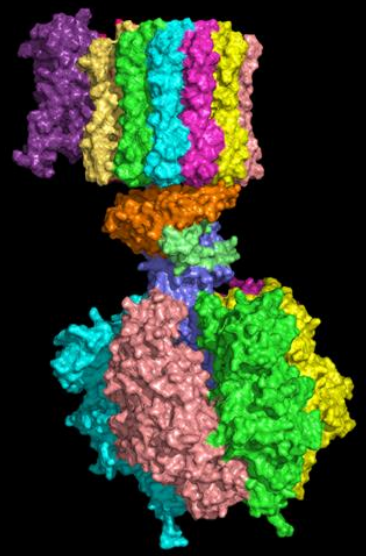
1980s-90s

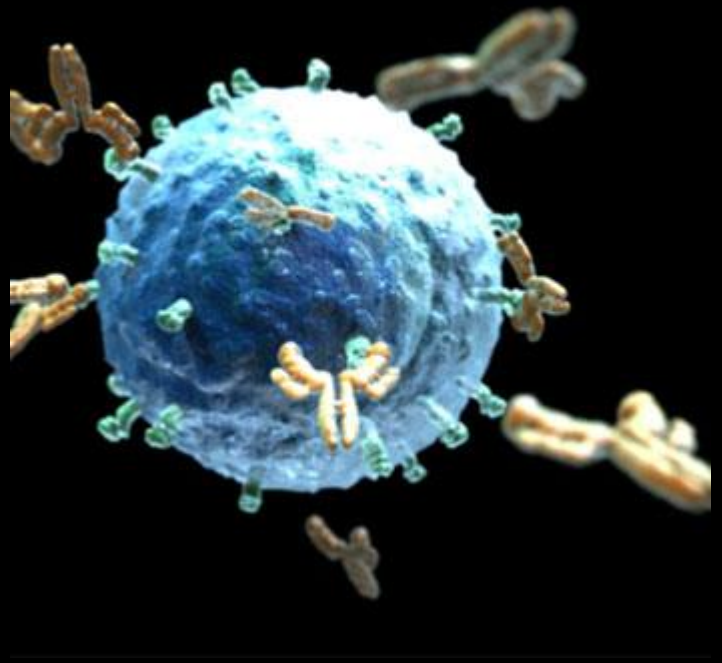
Proteins :molecular motors, crystal structures. Cartoons.



kinesin



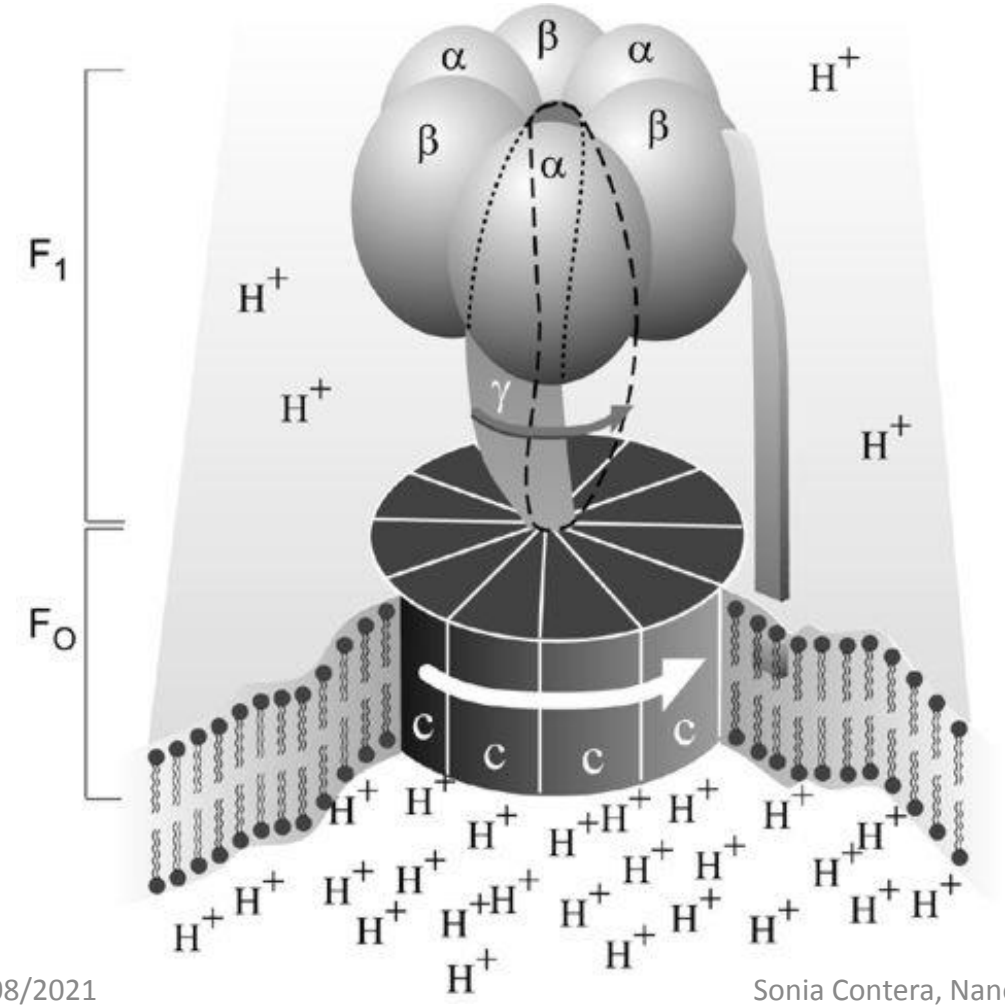


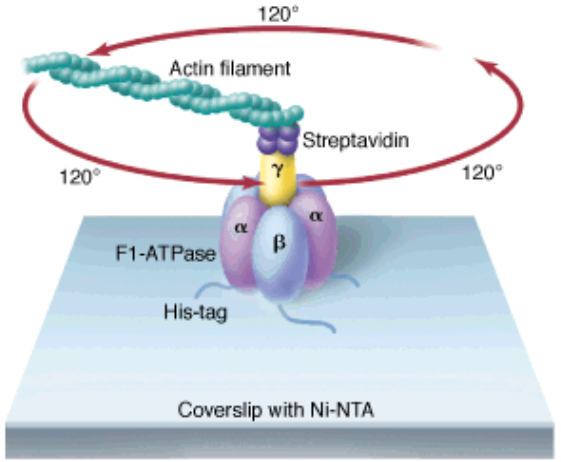


The Nobel Prize in Chemistry 1997

Paul D. Boyer, John E. Walker, Jens C. Skou

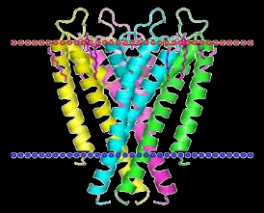
MOLECULAR MOTORS



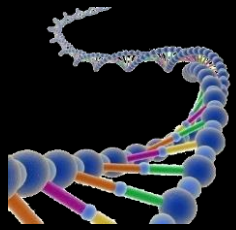


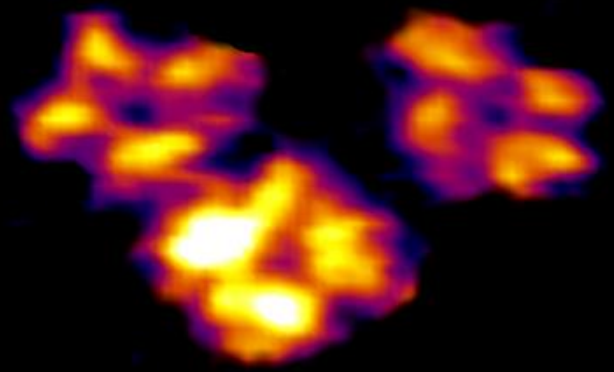
Noji, H.. Science **282**, 1844 (1998)
Copyright (1998) American Association for the Advancement of Science

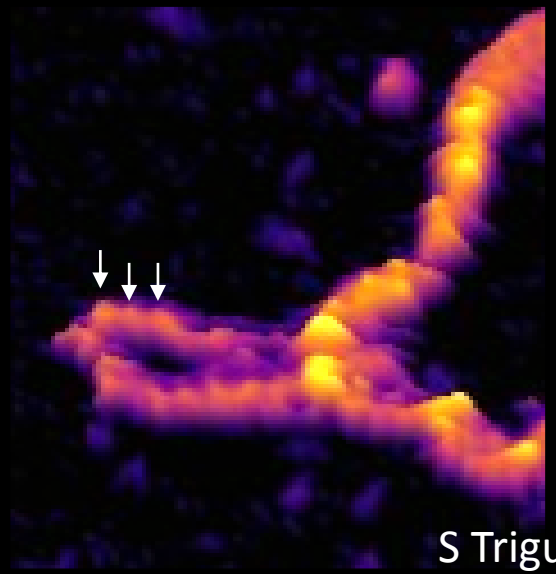
Hiroyuki NOJI- Tokyo University
（東京工業大学、木下和彦）



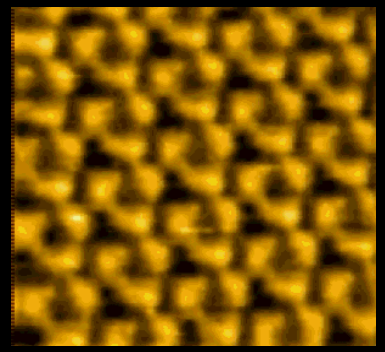
ATOMIC FORCE MICROSCOPY







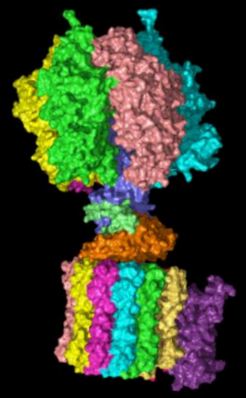
S Trigueros, S Contera,

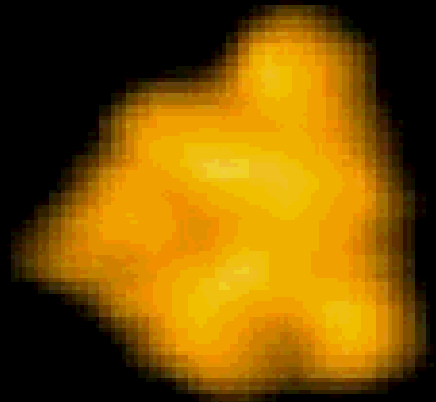


We were moving from cartoons
To images, to movement, to physics…..

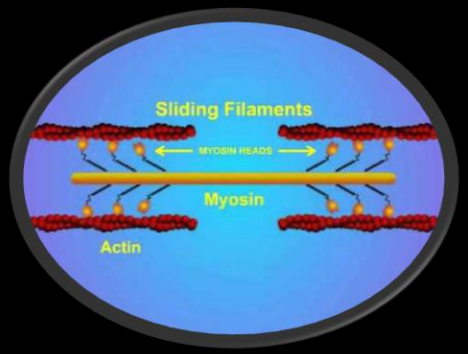
Contera, Voitchovsly, Ando, Uchihashi, et al Kanazawa University

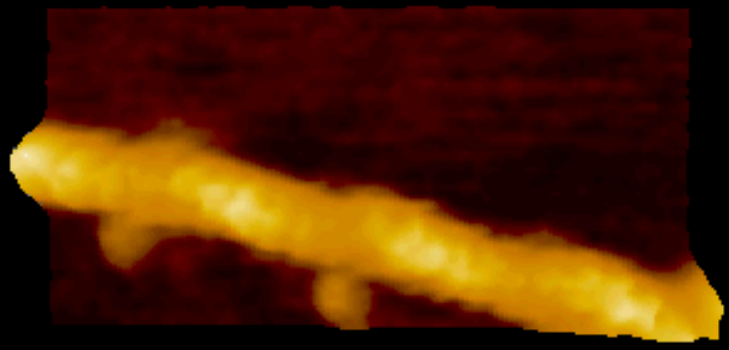
WHY is BIOLOGY NANOsize???





Iino, Noji (Tokyo Uni) Kodera, Ando, Uchihashi, … Kanazawa University

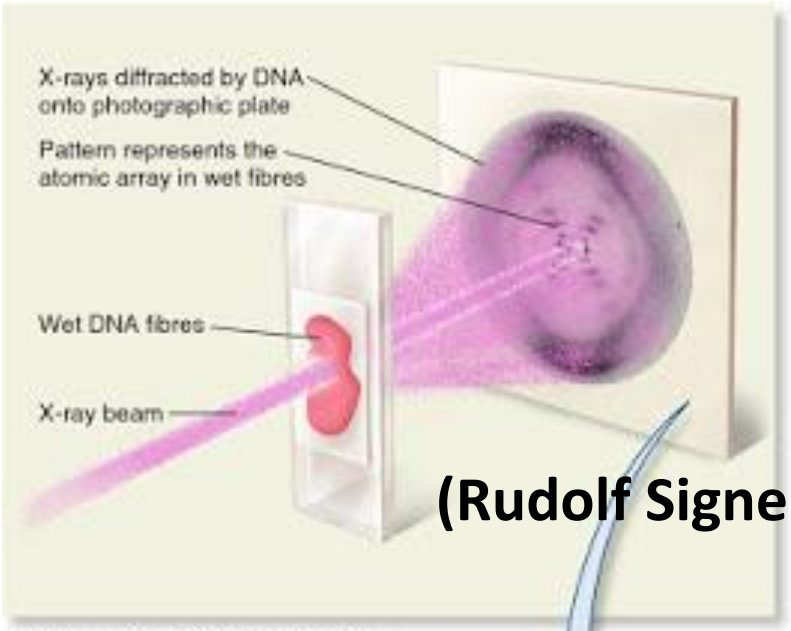




Kodera, Ando, Uchihashi, … Kanazawa University. 2000s

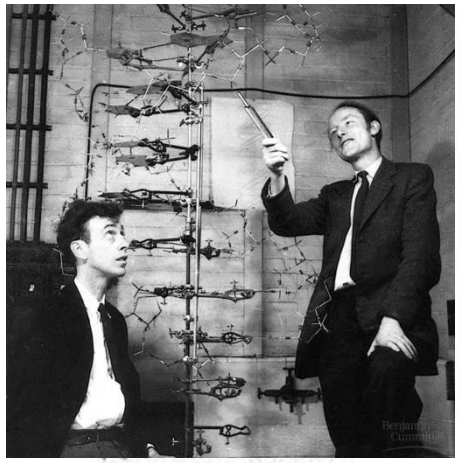
Rosalind Franklin
Maurice Wilkins and Ray Gosling

1953

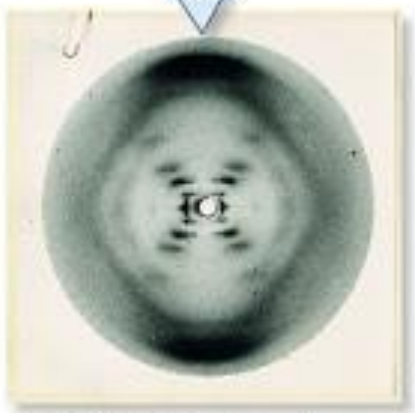


(a) The method of X-ray diffraction

(Rudolf Signer)



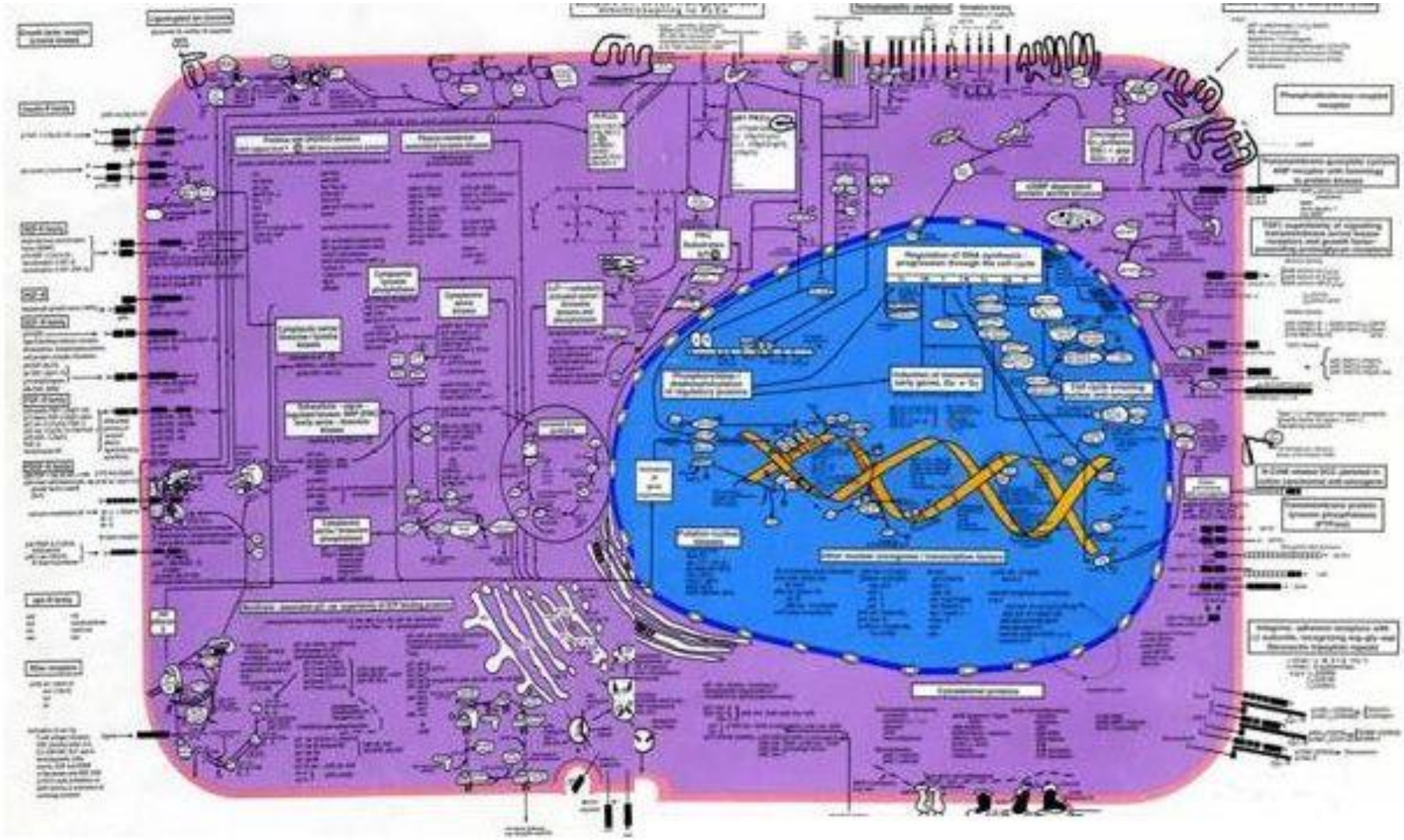
Watson and Crick

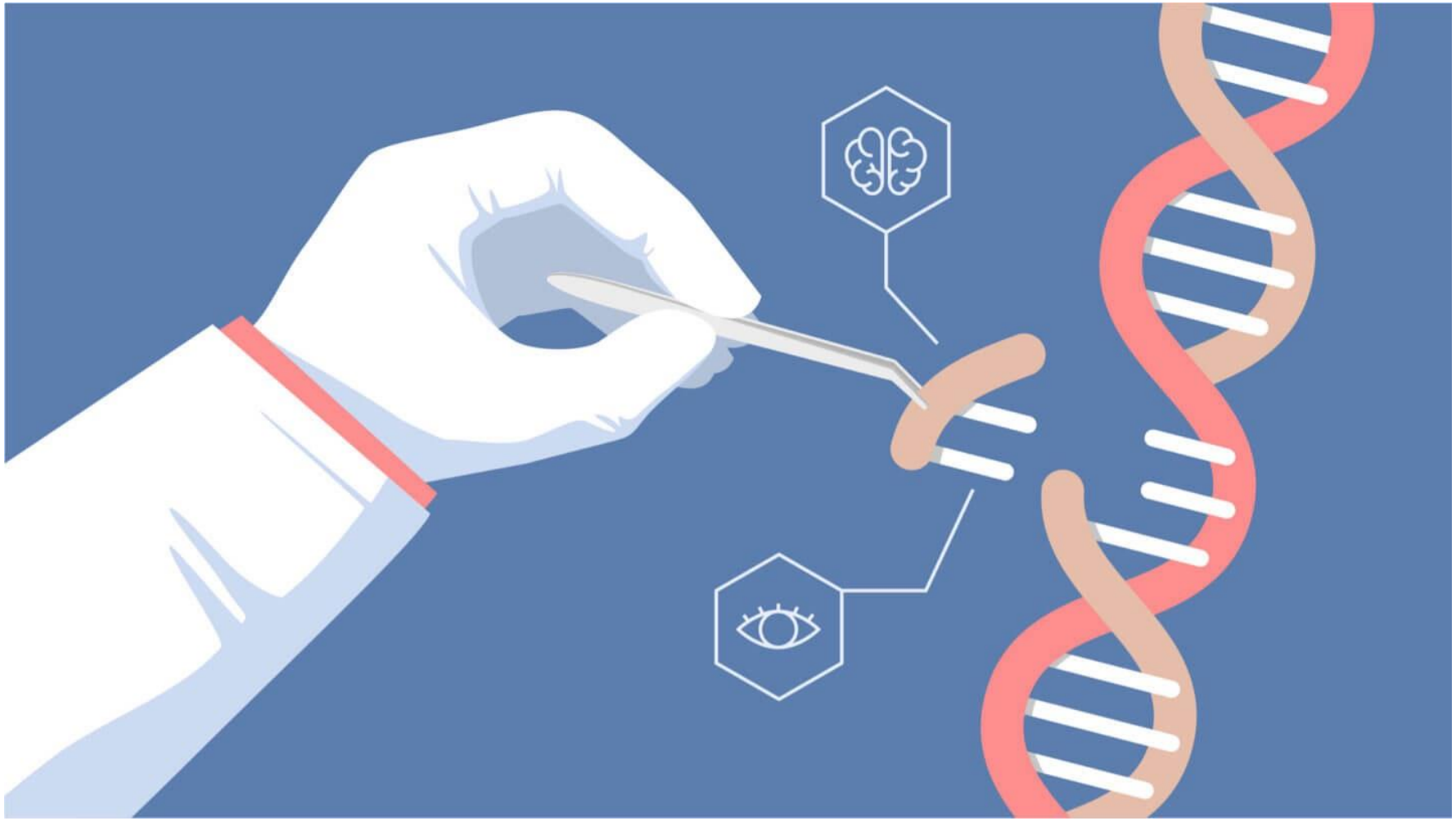


(c) Franklin's X-ray diffraction pattern of wet DNA fibres

Photograph 51

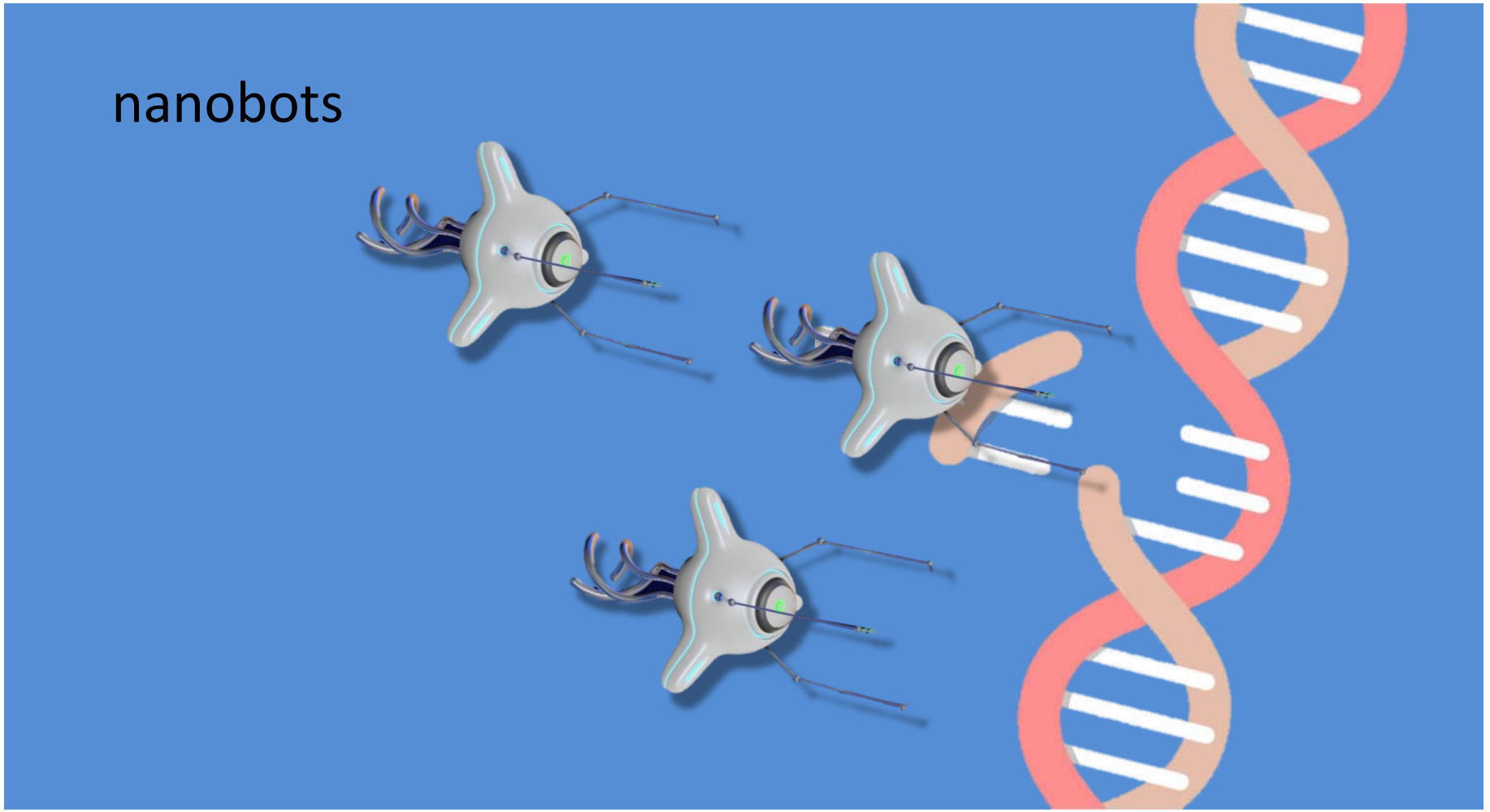
LIFE: IS IT REALLY AN ALGORITHM WRITTEN IN GENES????





https://medium.com/@barmstrong/the-pros-and-cons-of-genetically-engineering-humans-49973778c349

nanobots

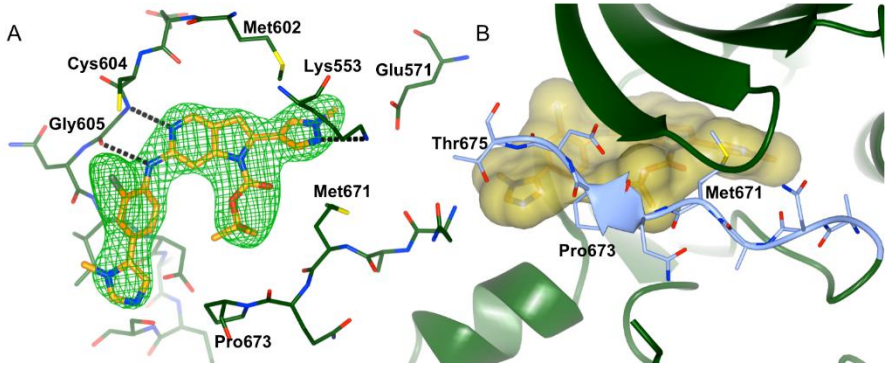


Why are drugs- failing to improve cancer treatment?

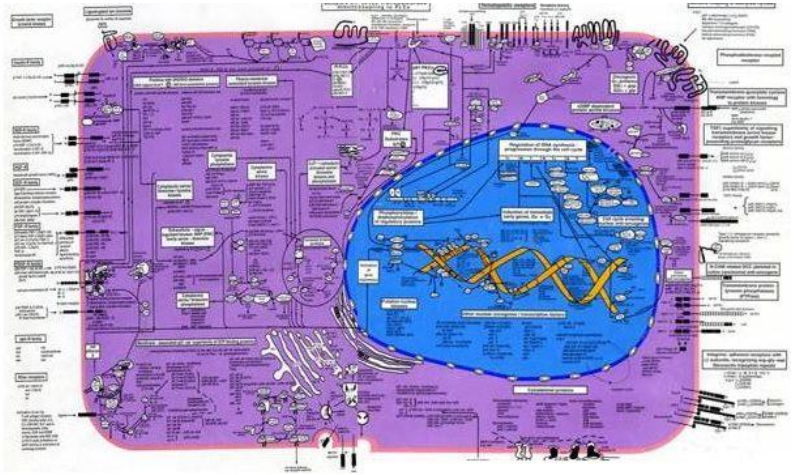
….the reductionist approach to treating disease was justifiably fuelled by decades of revolutionary drug discoveries – antibiotics, chemotherapy and other ‘miracle drugs’ – that led to steep improvements in life expectancy. However, this century has seen a sharp decline in the number of effective new medicines produced. **Between 2002 and 2014, a total of 71 new cancer drugs appeared, of which only 30 have gained approval from the US Food and Drug Administration.**

They were found to prolong life in patients with solid tumours by an average of 2.1 months, compared with older drugs –

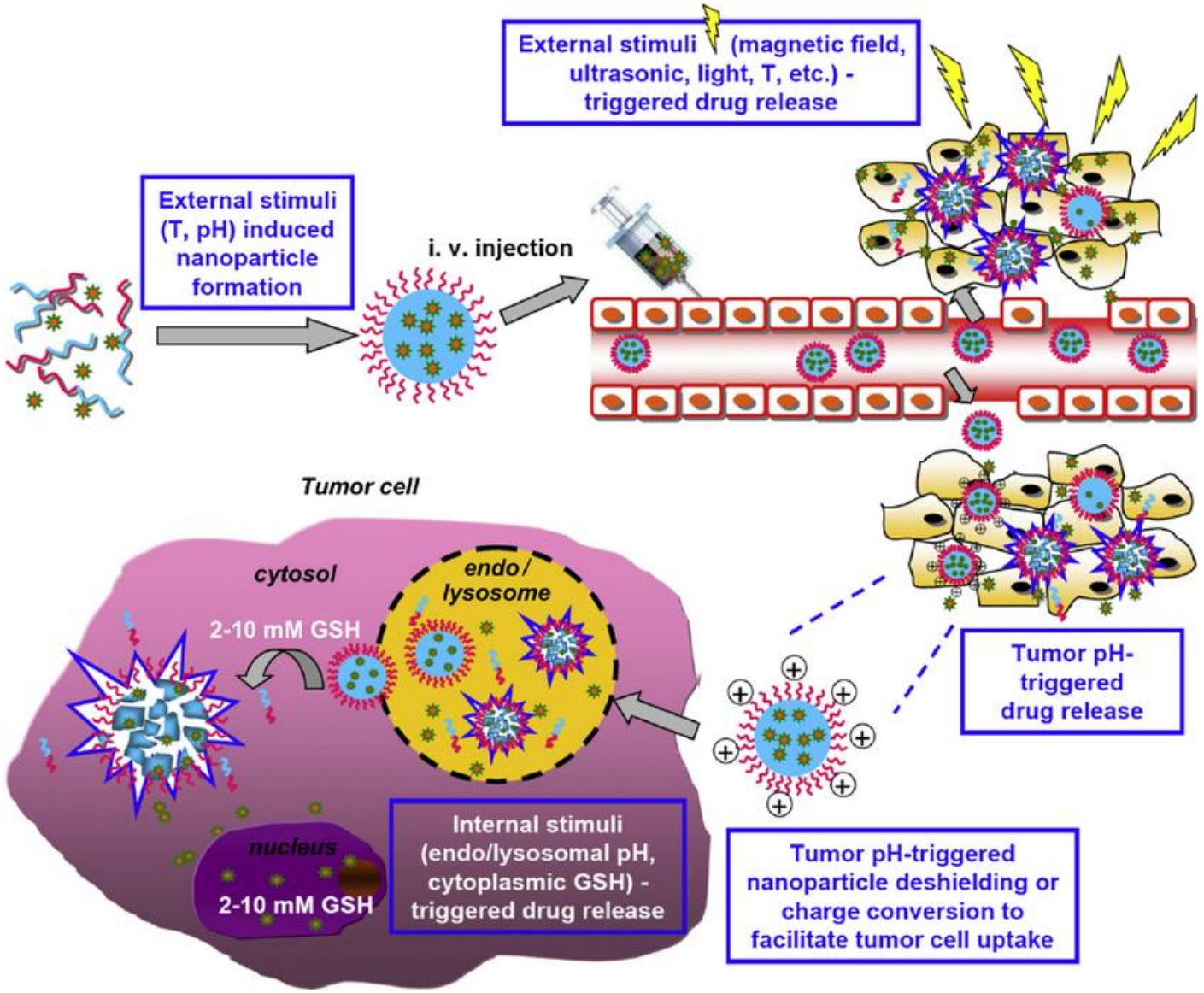
The costly and largely ineffective trial-and-error methods used to identify new drugs, and the difficulty of conducting clinical trials, were partly responsible for this downward turn.



https://www.icr.ac.uk/our-research/research-divisions/division-of-cancer-therapeutics/hit-discovery-structural-design/research-projects/structure-based-drug-design-of-cancer-drugs

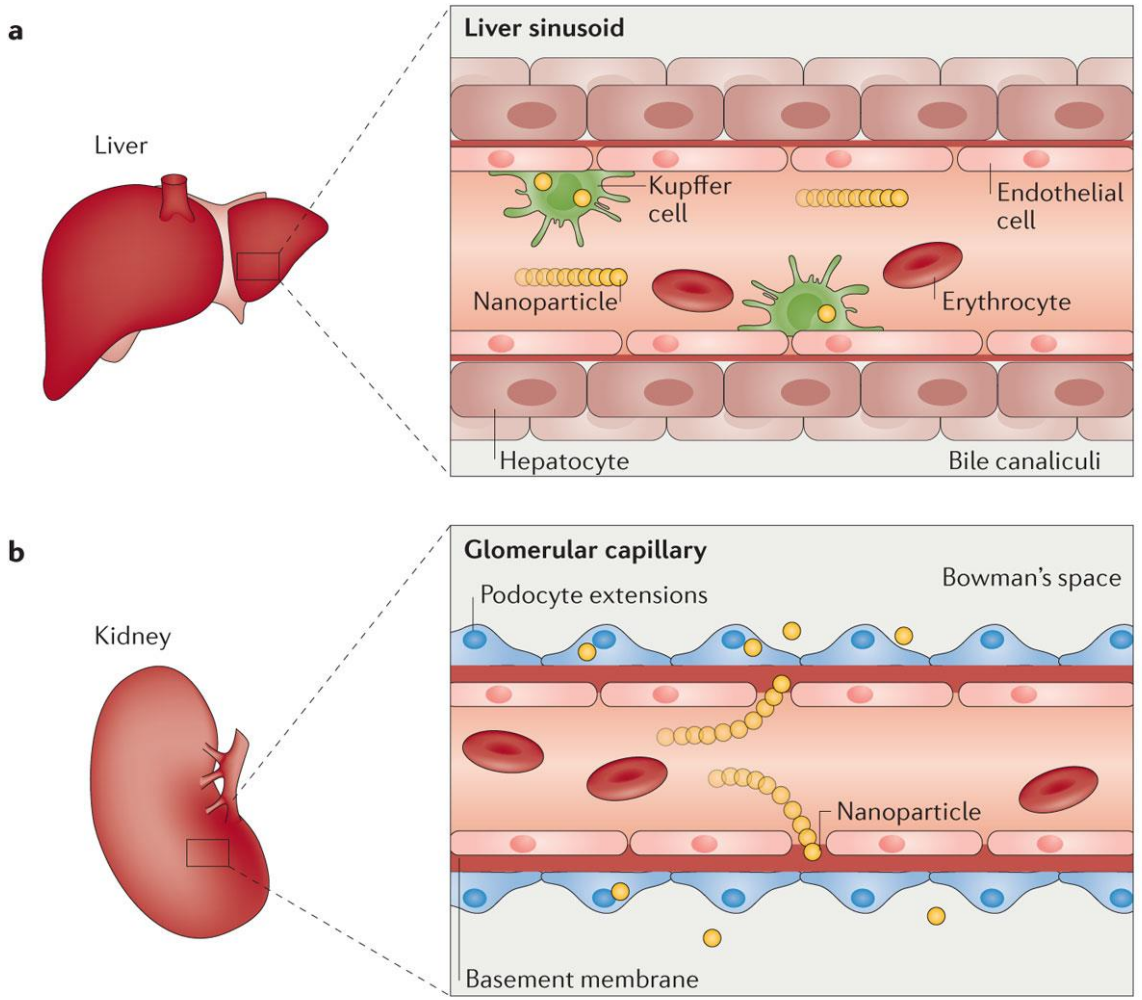


Sonia Contera, Nano comes to life. Oxford Physics



Translational cancer research 2013
DOI:10.3978/j.issn.2218-676X.2013.08.11
Tumor microenvironment and nanotherapeutics.
Meenakshi Upreti, Amar Jyoti, Pallavi Sethi

The body clears nanoparticles

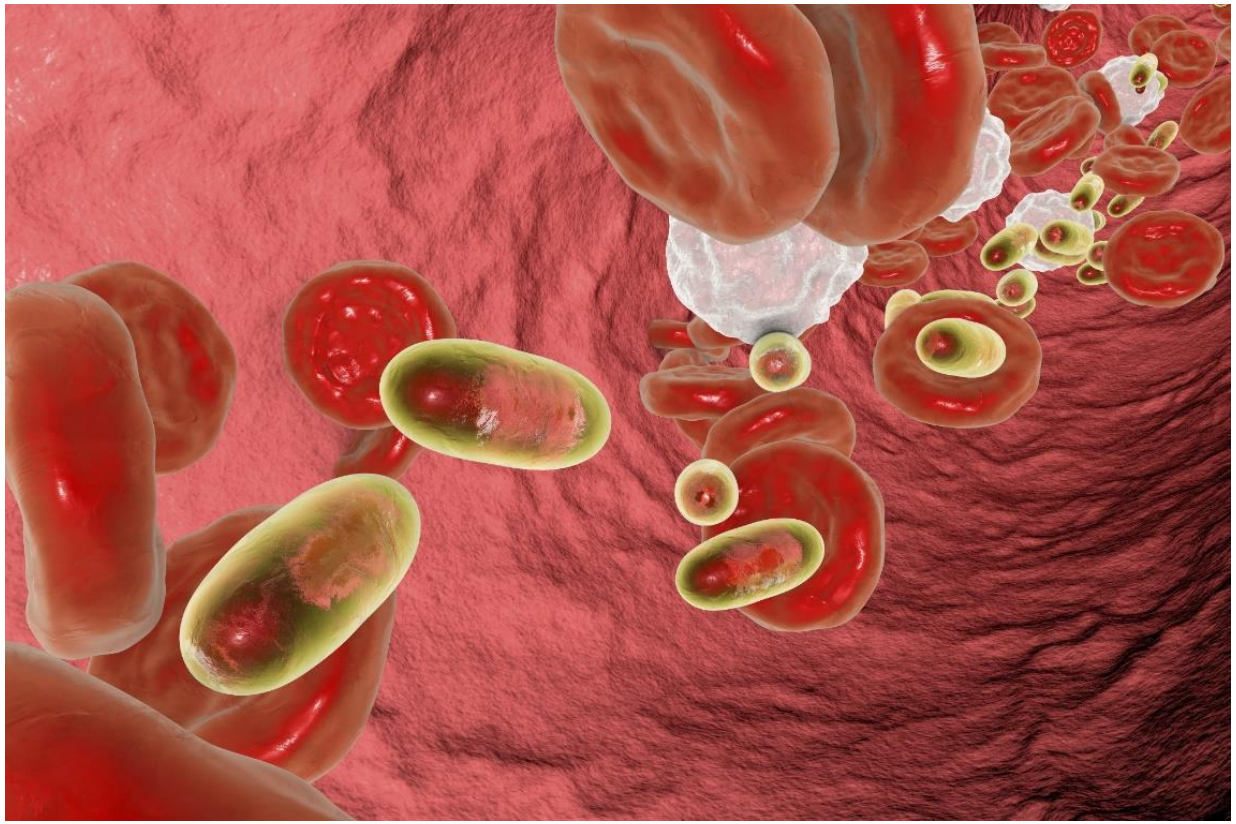


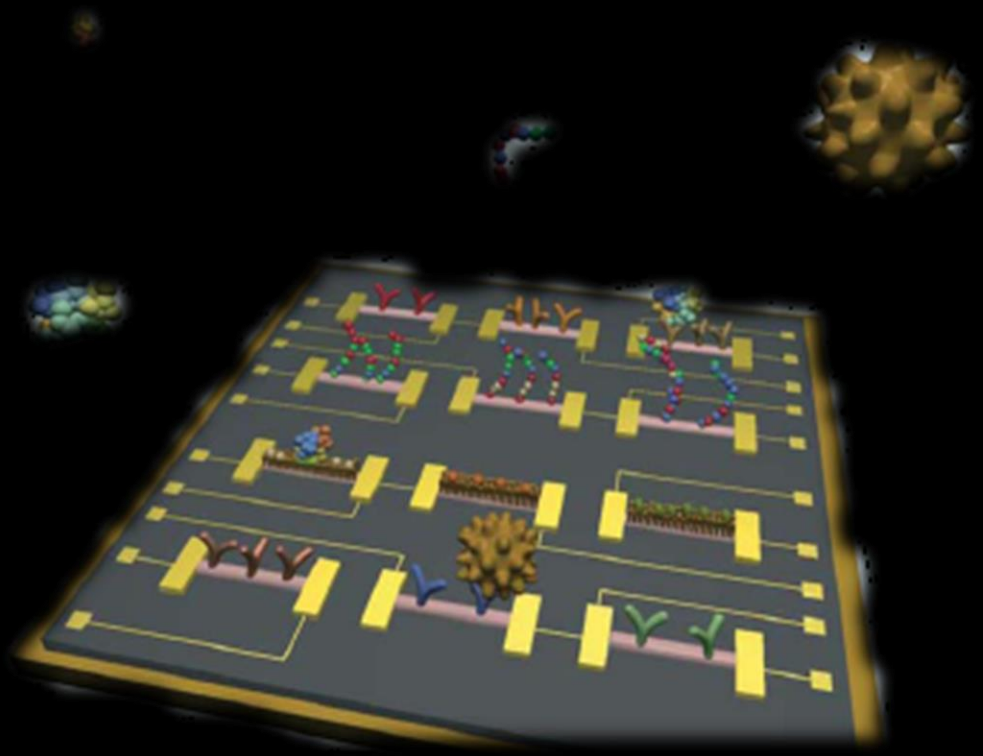
Nature Reviews | Materials

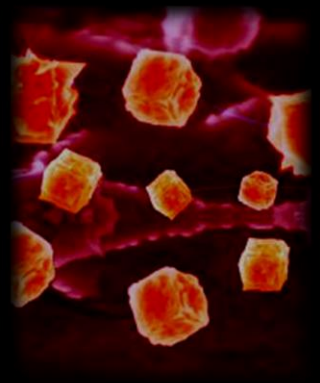
Figure 4 Mechanisms for nanoparticle elimination from the bloodstream

Wilhelm, S. *et al.* (2016) Analysis of nanoparticle delivery to tumours
Nat. Rev. Mater. doi:10.1038/natrevmats.2016.14

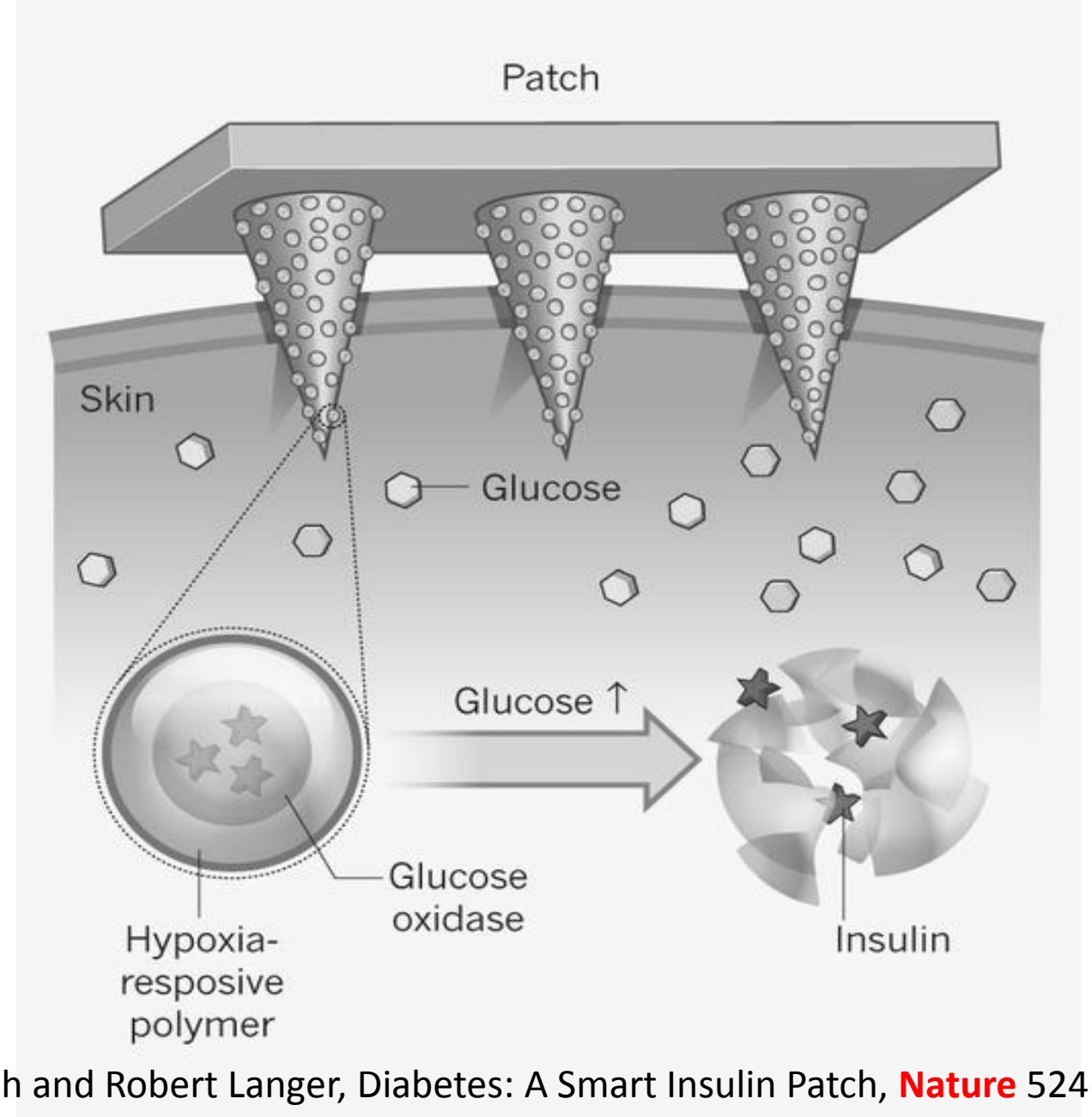
The field, instantly dubbed ‘nanomedicine’, grew rapidly. But expectations didn’t live up to the hype: currently fewer than 20 nanomedicines have been approved for use in cancer treatment. Seeking nano-powered magic bullets and lucky shortcuts to cure disease, while overlooking the complexity of the biology involved, has not proven especially fruitful. By mirroring the strategies of pharmacology, nanomedicine largely reproduced its failures.



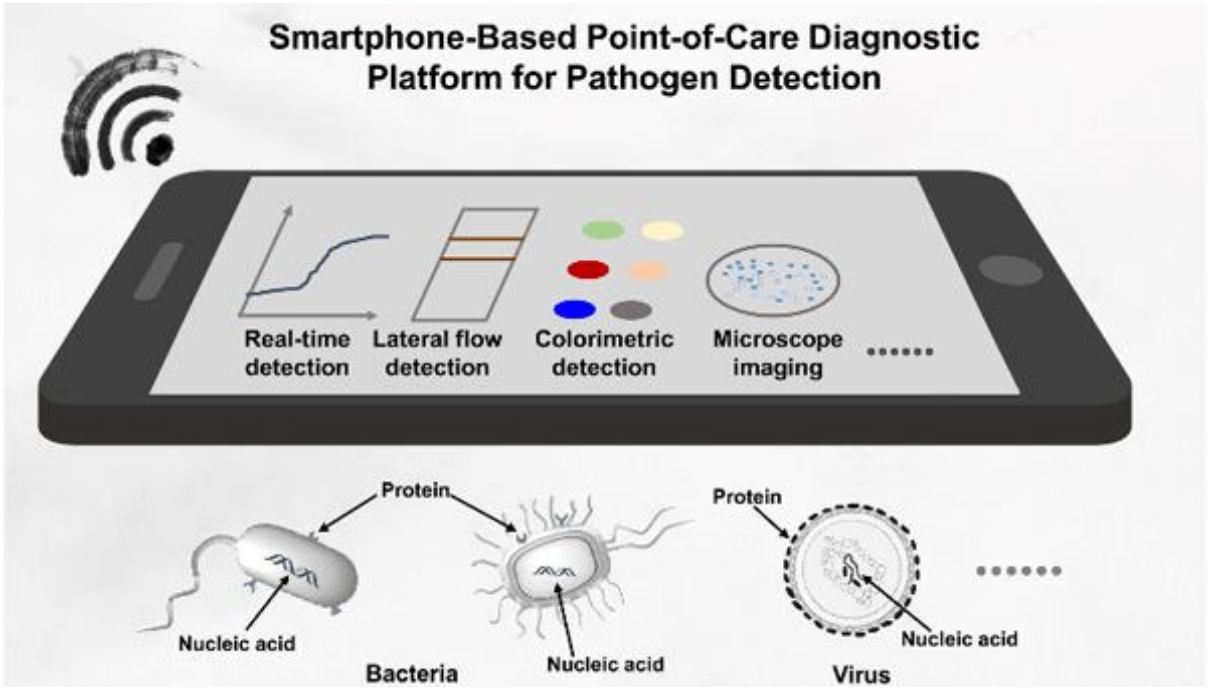


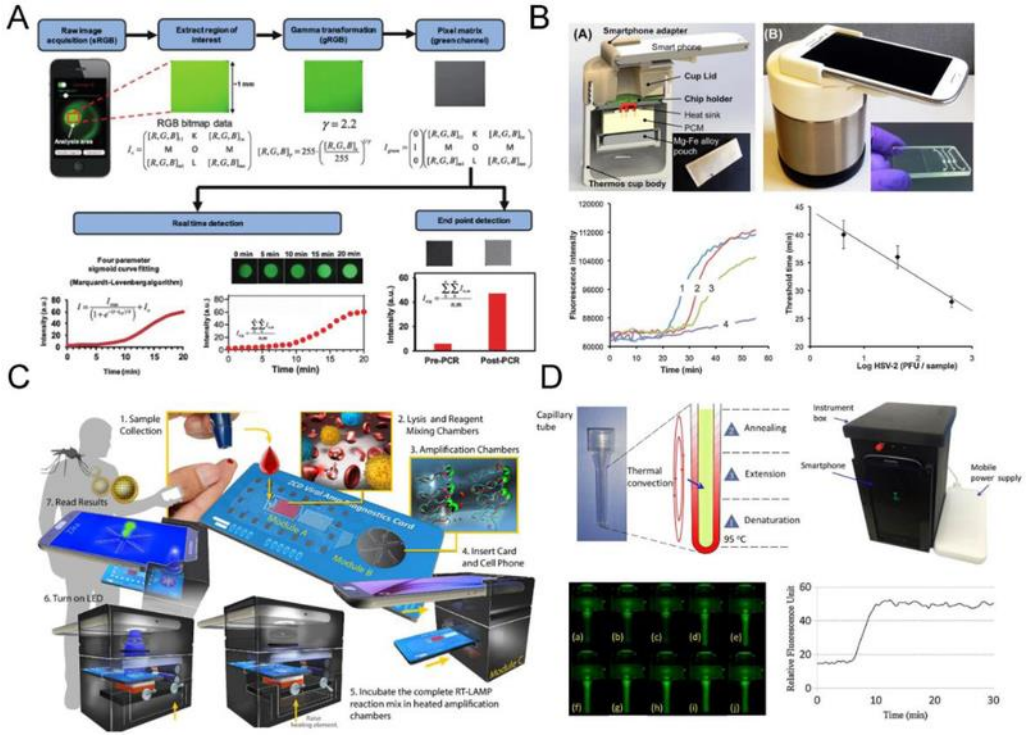


Biosensing



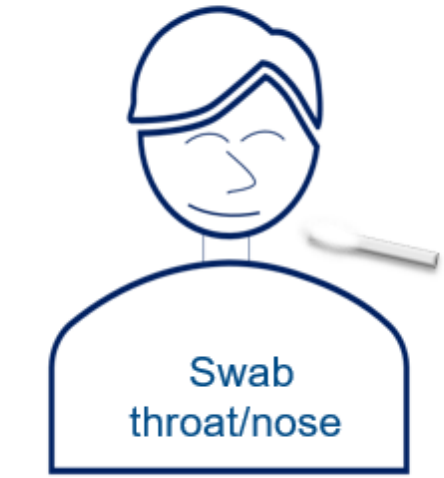
Omid Veiseh and Robert Langer, Diabetes: A Smart Insulin Patch, **Nature** 524 (2015) 39-40





Analytical Chemistry, 03 Dec 2018, 91(1):655-672

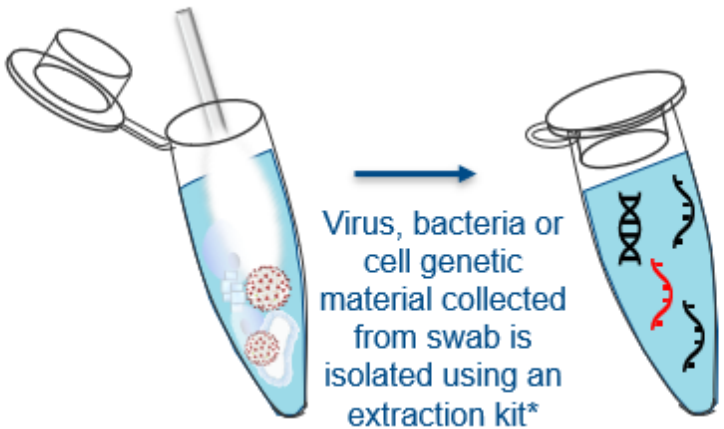
Using IDT Primers and Probes for COVID-19 Testing



IDT PRIMERS recognize SARS-CoV2 DNA

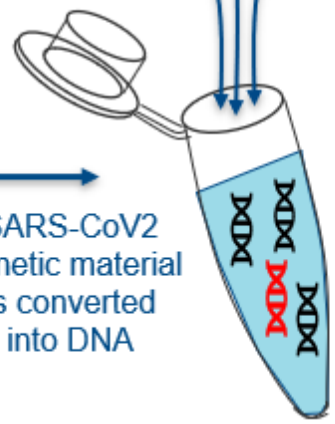
IDT PROBES recognize SARS-CoV2 DNA

Master mix*

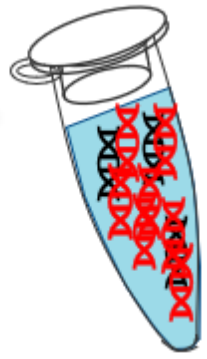


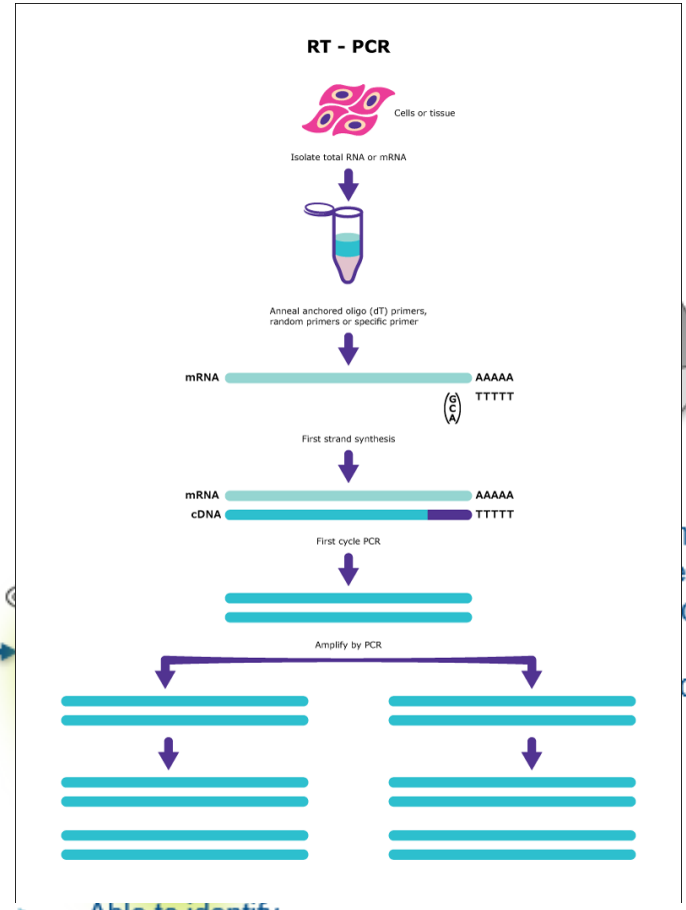
Virus, bacteria or cell genetic material collected from swab is isolated using an extraction kit*

SARS-CoV2 genetic material is converted into DNA



Unable to identify SARS-CoV2 DNA





Able to identify SARS-CoV2 DNA

IDT PRIMERS and master mix work together to make billions of copies of SARS-CoV2 DNA

IDT'S SARS-CoV2 PROBES release fluorescence when SARS-CoV2 DNA is present

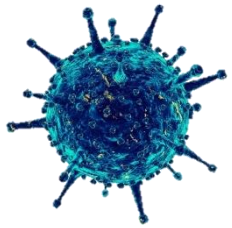
IDT does not manufacture or sell a diagnostic test for coronavirus.
IDT manufactures primer and probe kits that may be used as a component of the COVID-19 test.

* Not supplied by IDT

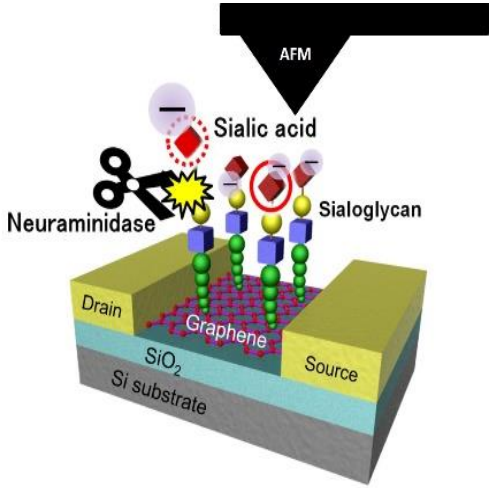
IDT INTEGRATED DNA TECHNOLOGIES

Testing antiviral drugs and molecular interactions with a graphene field effect transistor

Kaho Kamada, Ryota Hayashi, Calum Gabbutt, Sonia Contera, Kazuhiko Matsumoto, OSAKA UNIVERSITY



Influenza virus



納豆

Lab-on-a-graphene-FET detection of key molecular events underpinning influenza virus infection and effect of antiviral drugs

T. Ono, K. Kamada, R. Hayashi, A. R. Piacenti, C. Gabbutt, N. Sriwilaijaroen, H. Hiramatsu, Y. Kanai, K. Inoue, S. Nakakita, T. Kawahara, Y. Ie, Y. Watanabe, Y. Suzuki, S. Contera*, K. Matsumoto*

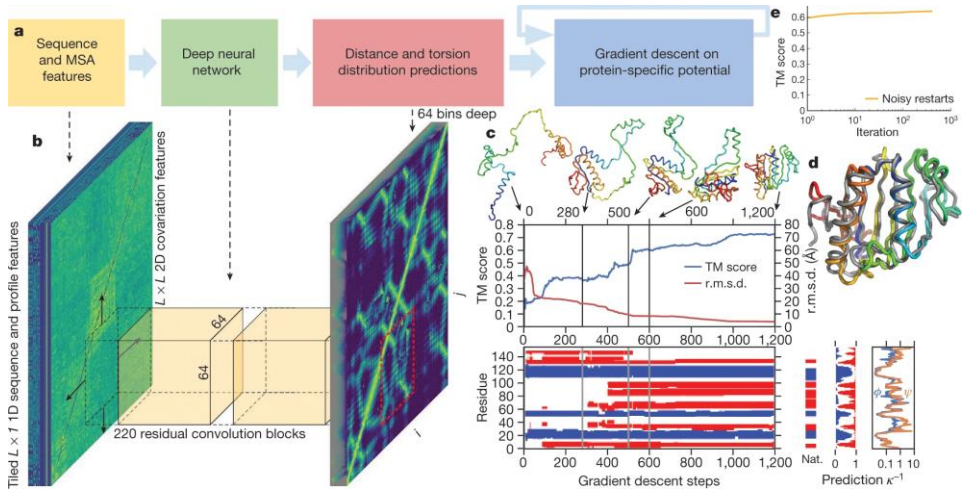
Bioarxiv

doi: https://doi.org/10.1101/2020.03.18.996884

Ryota, Sonia and Kaho

New synthesis methods,
Protein designers,
Drug synthesis using DNA nanotechnology

WE HAVE LEARNT TO DESIGN AND CONSTRUCT MATERIALS WITH ATOMIC PRECISION

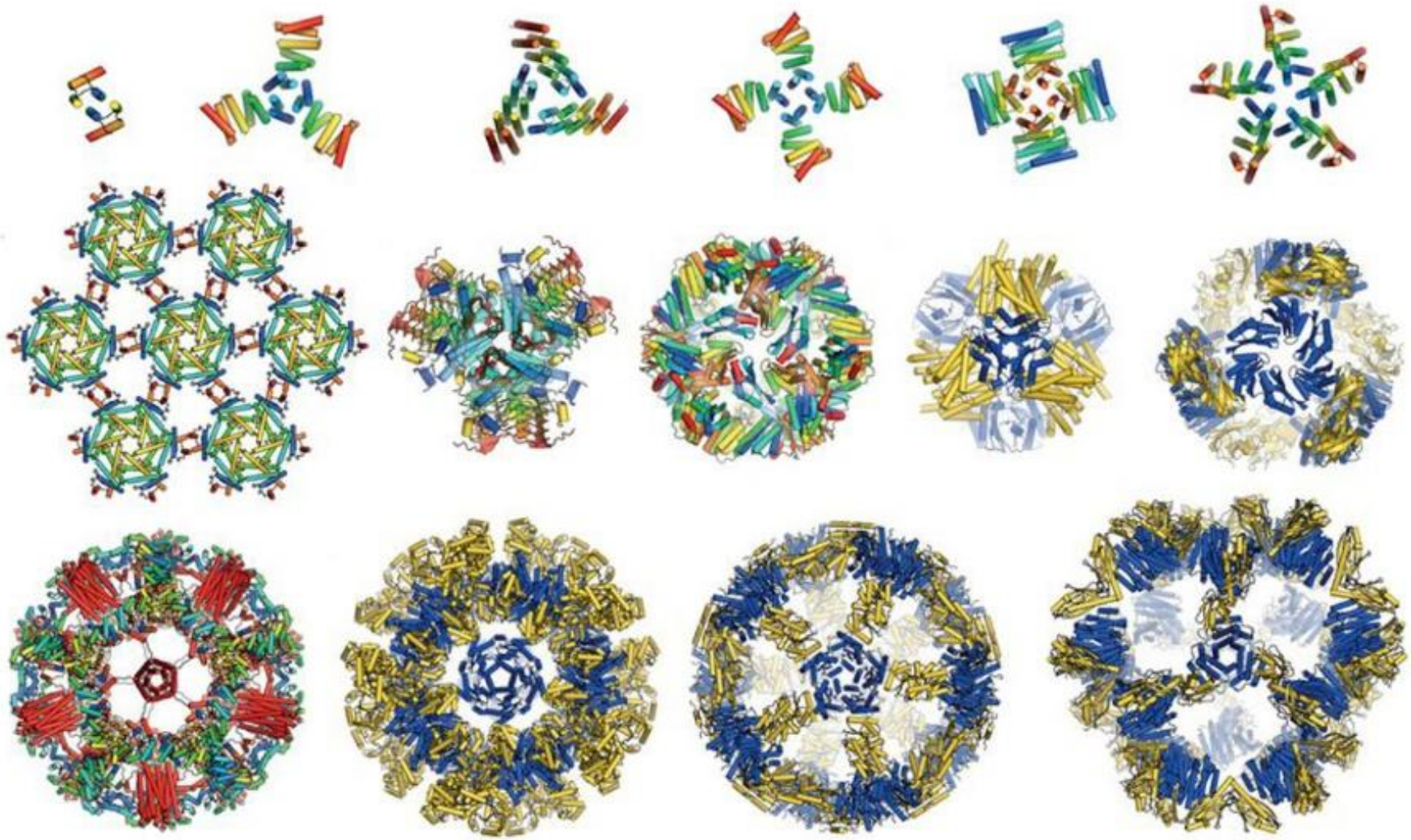


Social Interface
Collaboration
Artificial Intelligence
Crowdsourcing

Free
Available

David Baker, Protein design September 2016 NATURE.

Improved protein structure prediction using potentials from deep learning
Nature **volume 577**, pages706–710(2020)



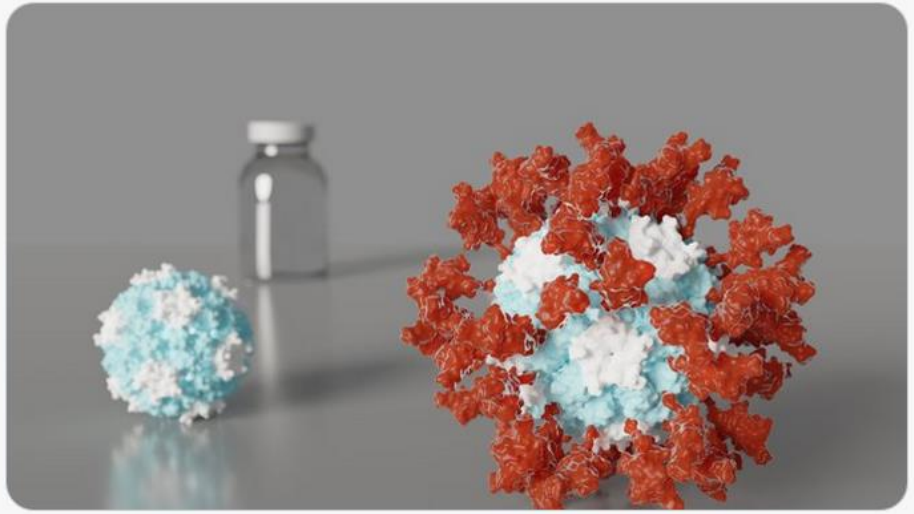
BUT THIS IS NOT A REDUCCIONIST APPROACH……It uses cells to produce the proteins
The evolutionary history of life contained in the fabrication process

King Lab @KingLabIPD · 23h

It's a historic day for the lab: Our candidate nanoparticle #SARSCoV2 vaccine has been injected into humans — the first in-person test of our immunogen design platform.

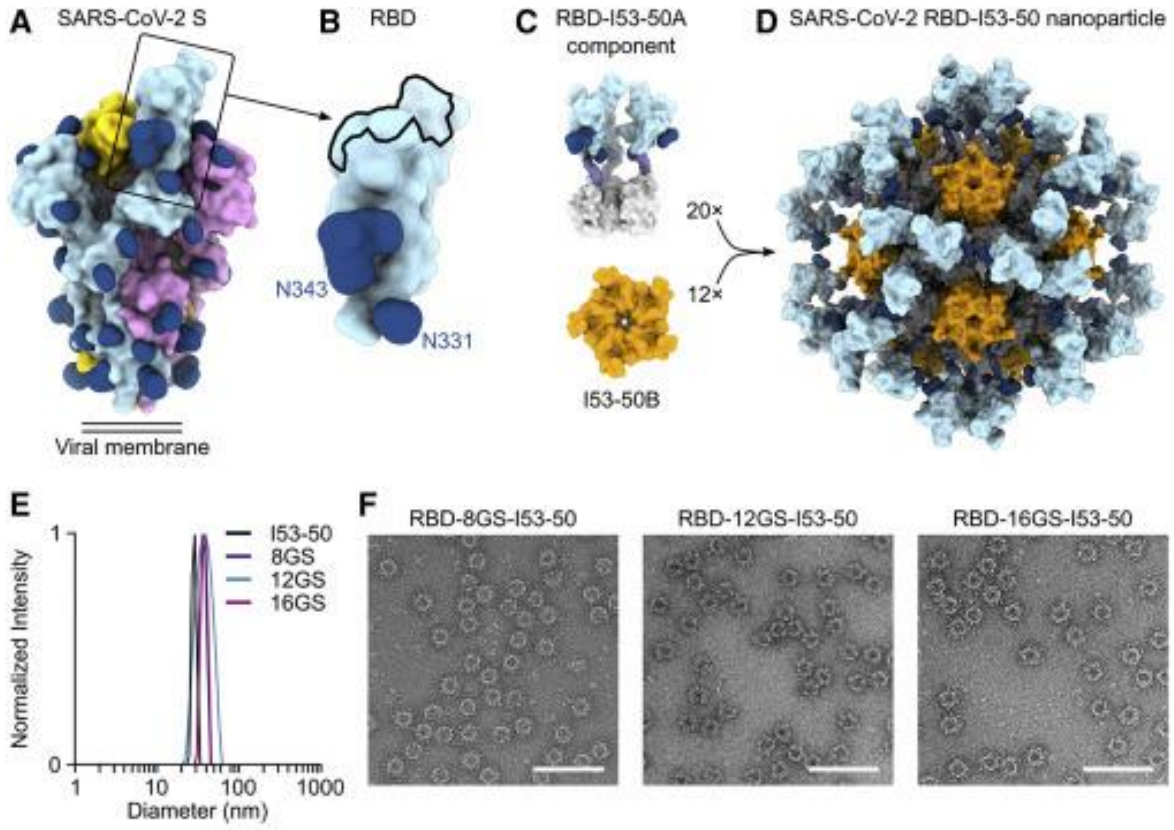
Thanks to SK Bioscience 🇰🇷 for leading this Phase 1 trial.

cell.com/cell/fulltext/...



The Veesler Lab and 3 others

12 124 608



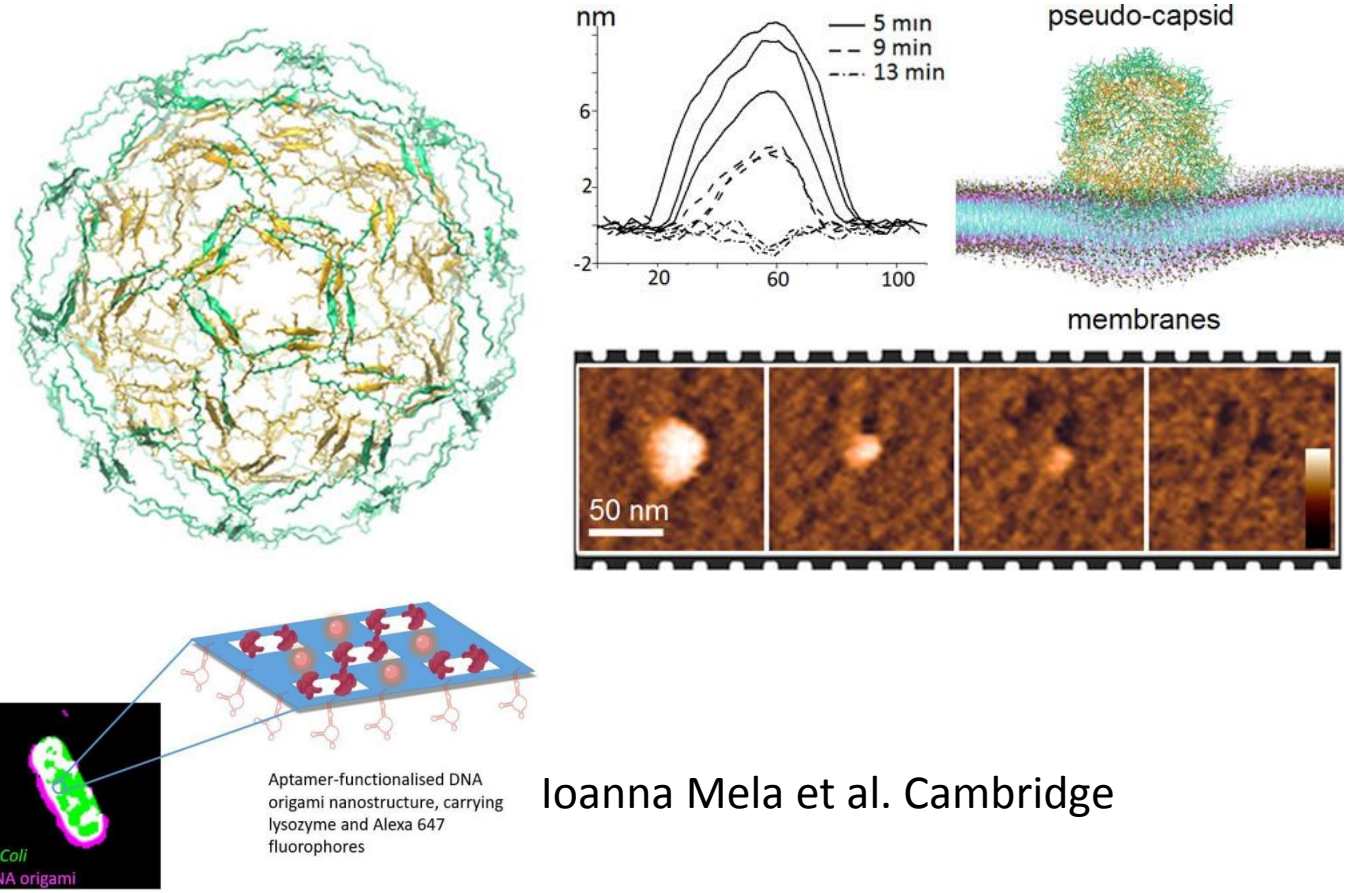
Elicitation of Potent Neutralizing Antibody Responses by Designed Protein Nanoparticle Vaccines for SARS-CoV-2

King Lab https://www.cell.com/cell/fulltext/S0092-8674(20)31450-1

Harnessing biological evolution in technology

Engineering Chirally Blind Protein Pseudocapsids into Antibacterial Persisters

Inspiration from viruses



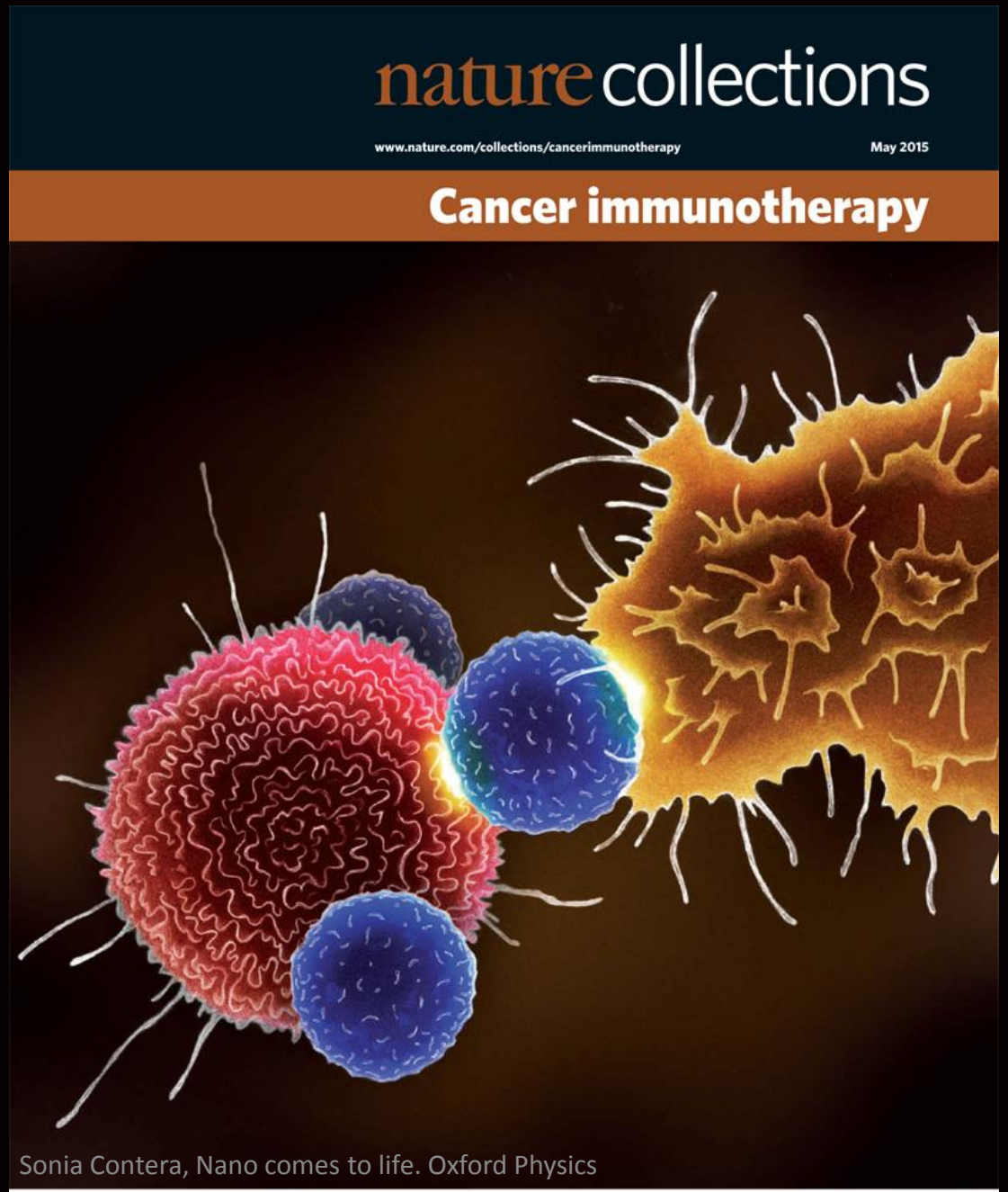
Ioanna Mela et al. Cambridge

The success of Ryadnov's approach relies on a combination of skills: understanding protein structure, and the physics of protein assembly, being familiar with the biology of bacteria and viruses, and the biomedical techniques needed for assessing the effectiveness of antibiotics, with computational simulations and microscopy techniques from physics. It also points the way forward to a future where scientists can adopt evolutionary strategies (developed over time in our own immune systems) to overcome medical problems by engineering new versions of those strategies at the nanoscale.

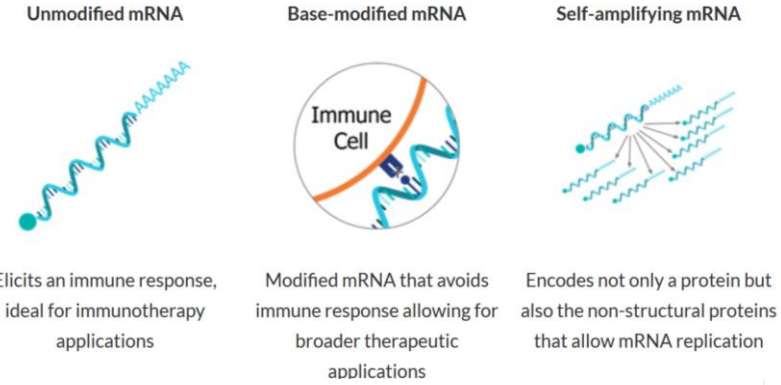
Published in: Ibolya E. Kepiro; Irene Marzuoli; Katharine Hammond; Xiaoliang Ba; Helen Lewis; Michael Shaw, Smita B. Gunnoo; Emiliana De Santis; Urszula Łapińska; Stefano Pagliara; Mark A. Holmes; Christian D. Lorenz; Bart W. Hoogenboom; Franca Fraternali; Maxim G. Ryadnov; *ACS Nano* Article ASAP
DOI: 10.1021/acsnano.9b06814; Copyright © 2019 American Chemical Society

In biomedicine too… things are starting to move away from reductionism:

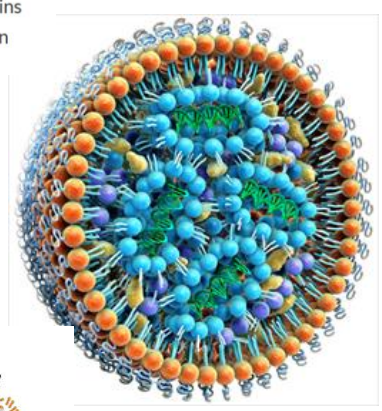
IMMUNOTHERAPIES!

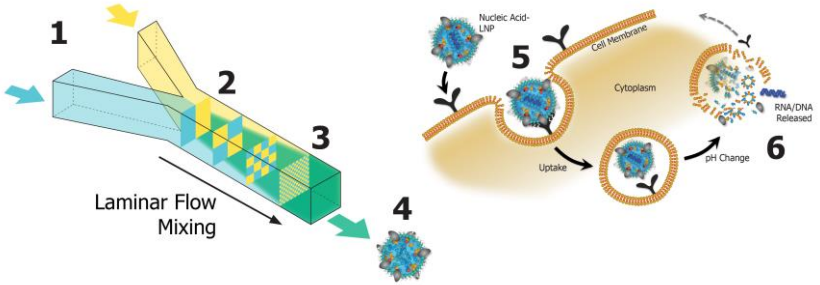


Sonia Contera, Nano comes to life. Oxford Physics

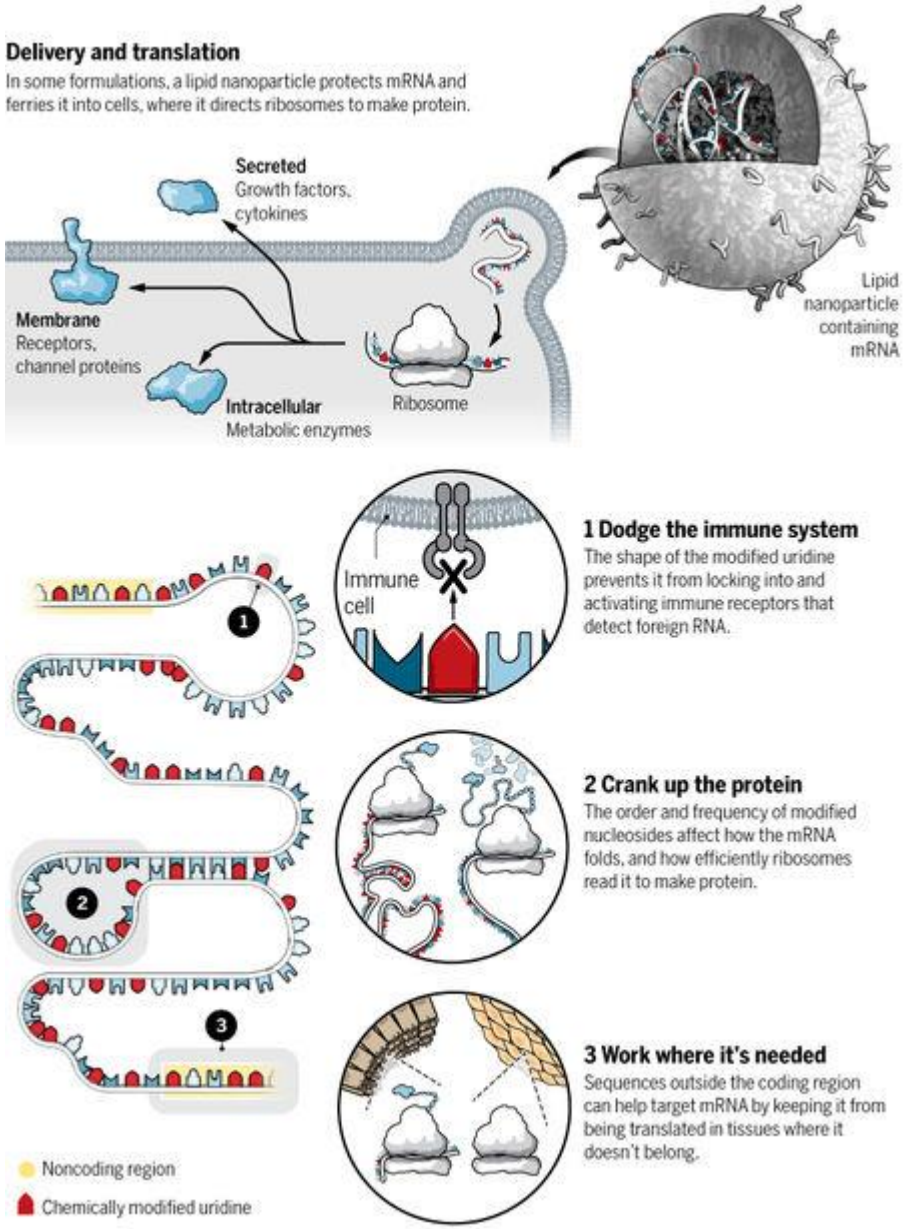


Nanotech vaccines





https://www.precisionnanosystems.com/



https://www.sciencemag.org/news/2017/02/mysterious-2-billion-biotech-revealing-secrets-behind-its-new-drugs-and-vaccines?utm_campaign=news_daily_2020-03-25&et_rid=54900386&et_cid=3259035#

The nanotech covid vaccines

N1GEL

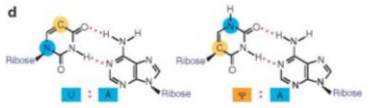
ionizable (cationic) lipid; cholesterol; DSPC (phospholipid) and PEG2000-DMG (conjugated anti-aggregation lipid). The percentages of the four components in the formulation of mRNA-1273 were not disclosed.

ACUITAS HAS SUED MODERNA

Derrick Rossi, Langer, Afeyan

Moderna

Karikó and Weissman RNA modification, ACUG

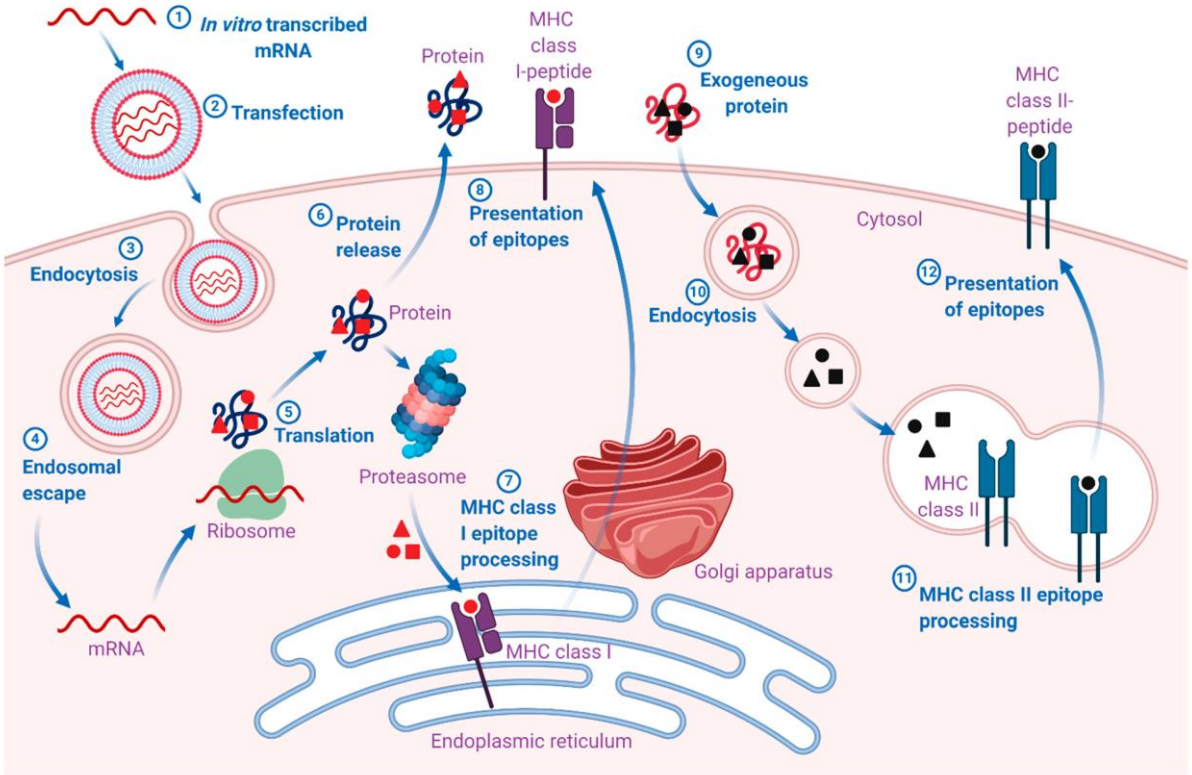


Mol Ther. 2008 Nov; 16(11): 1833–1840.

BioNTech

(K Kariko, U Sahin) self-amplifying mRNA technology (SAM)

The nanoparticle material is provided by companies such as Canada's **Acuitas Therapeutics** and is then processed in preapproved facilities owned by Pfizer and BioNTech across the US and Europe. Those facilities will be able to produce a combined 1.35bn doses by the end of next year, the companies have said.
(FT)



Pharmaceutics **2020**, *12*(2), 102; https://doi.org/10.3390/pharmaceutics12020102

Two classes of mRNAs, i.e., non-replicating and self-amplifying mRNA, are commonly used as vaccine vectors. Non-replicating mRNA encodes only the protein antigen(s) of interest, while self-amplifying mRNA also encodes proteins enabling RNA replication

SARS-CoV-2 mRNA Vaccine Development Enabled by Prototype Pathogen Preparedness
doi: https://doi.org/10.1101/2020.06.11.145920

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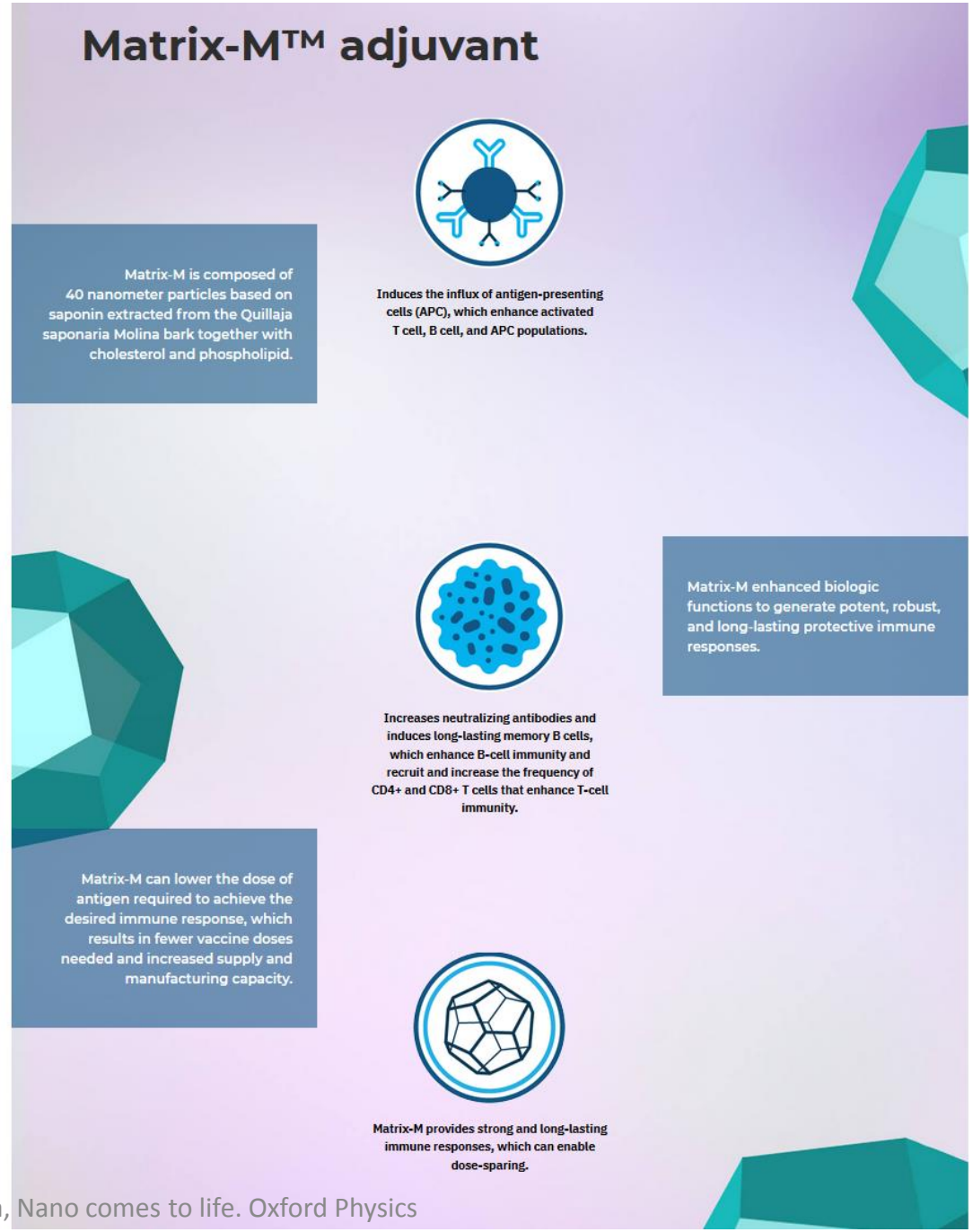
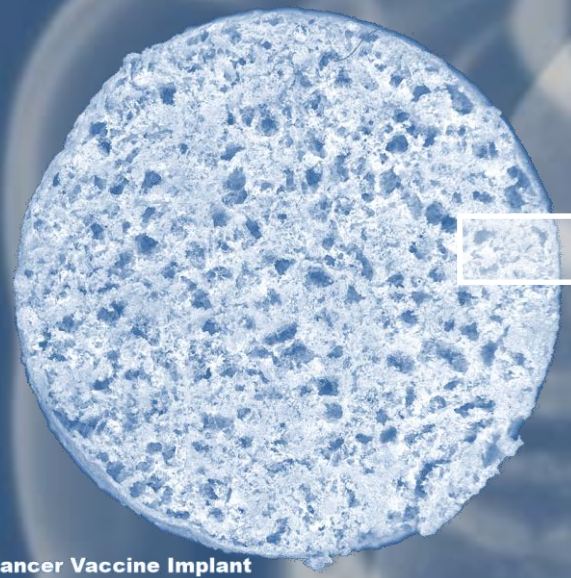
UK | England | N. Ireland | Scotland | Alba | Wales | Cymru | Loc

Covid-19: Novavax vaccine shows 89% efficacy in UK trials

24 minutes ago

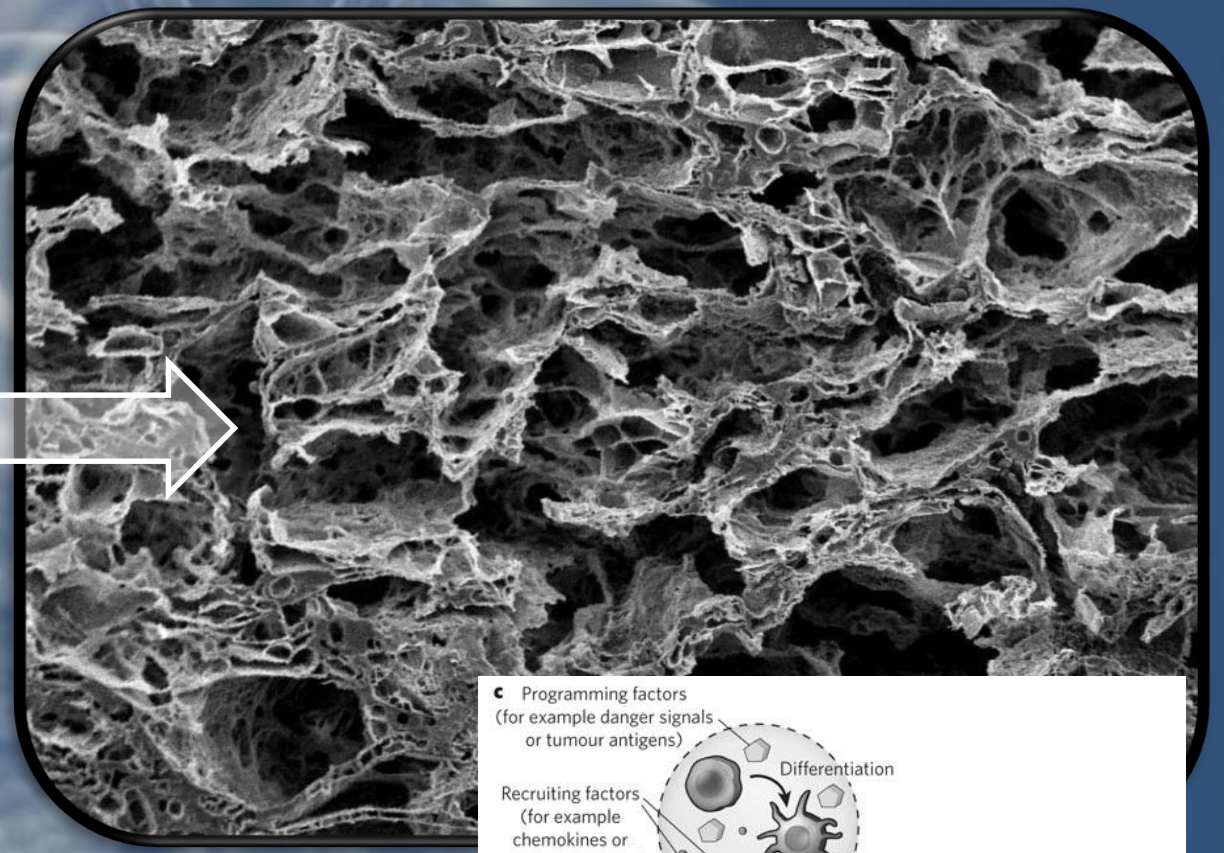


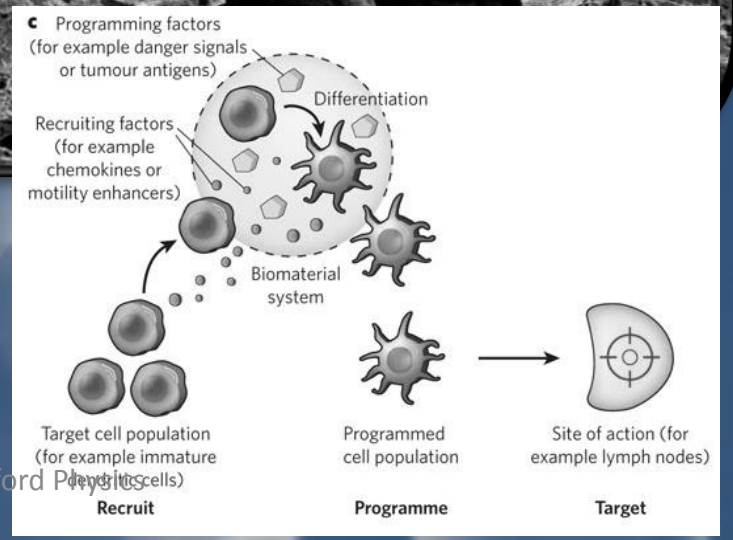
Implantable cancer vaccines



Cancer Vaccine Implant

Mooney Lab Harvard



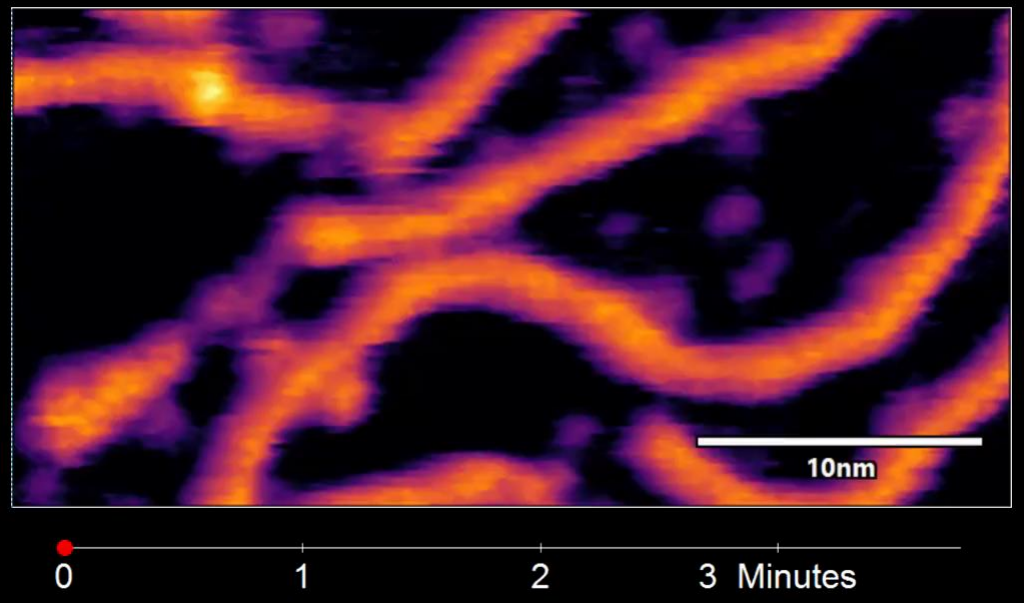


Biological physicists , complexity scientists, etc .were becoming more ambitious, and starting to challenge the paradigm
What are the limits of the molecular biology paradigm?...
Why are we made of nanostrings?
Why medicine fails?

Slowly they started to put biology in a wider context……. THE PHYSICS OF LIFE

DNA Double Helix imaged at 1 frame per second with AFM

Lambda digest imaged in $NiCl_2$ buffer with Cypher VRS Video-Rate AFM



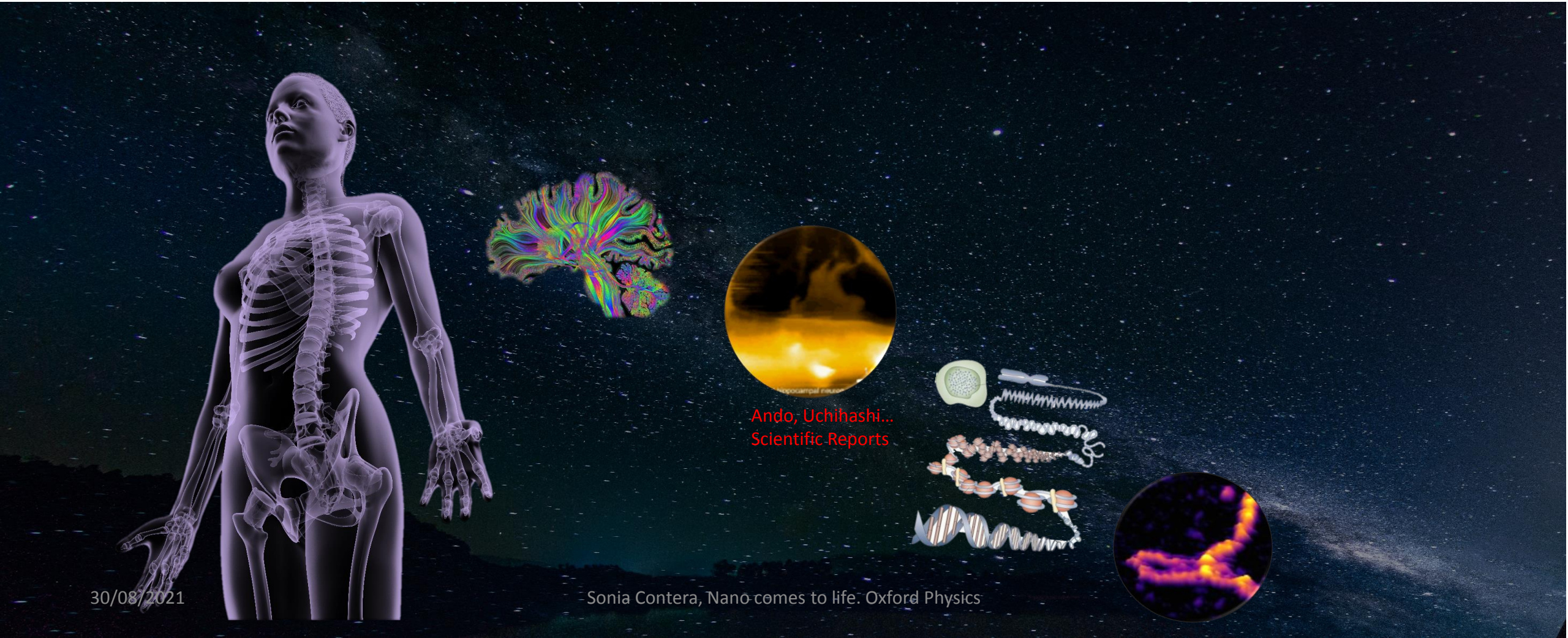
Asylum Research, Santa Barbara, CA

Embracing (at last!) biology's complexity

From the central dogma's reductionism to

COMPLEXITY, EMERGENT PHENOMENA, HIERARCHICAL STRUCTURES IN BIOLOGY

MATHEMATICAL MODELLING, SIMULATION….. And new computing paradigms!!!

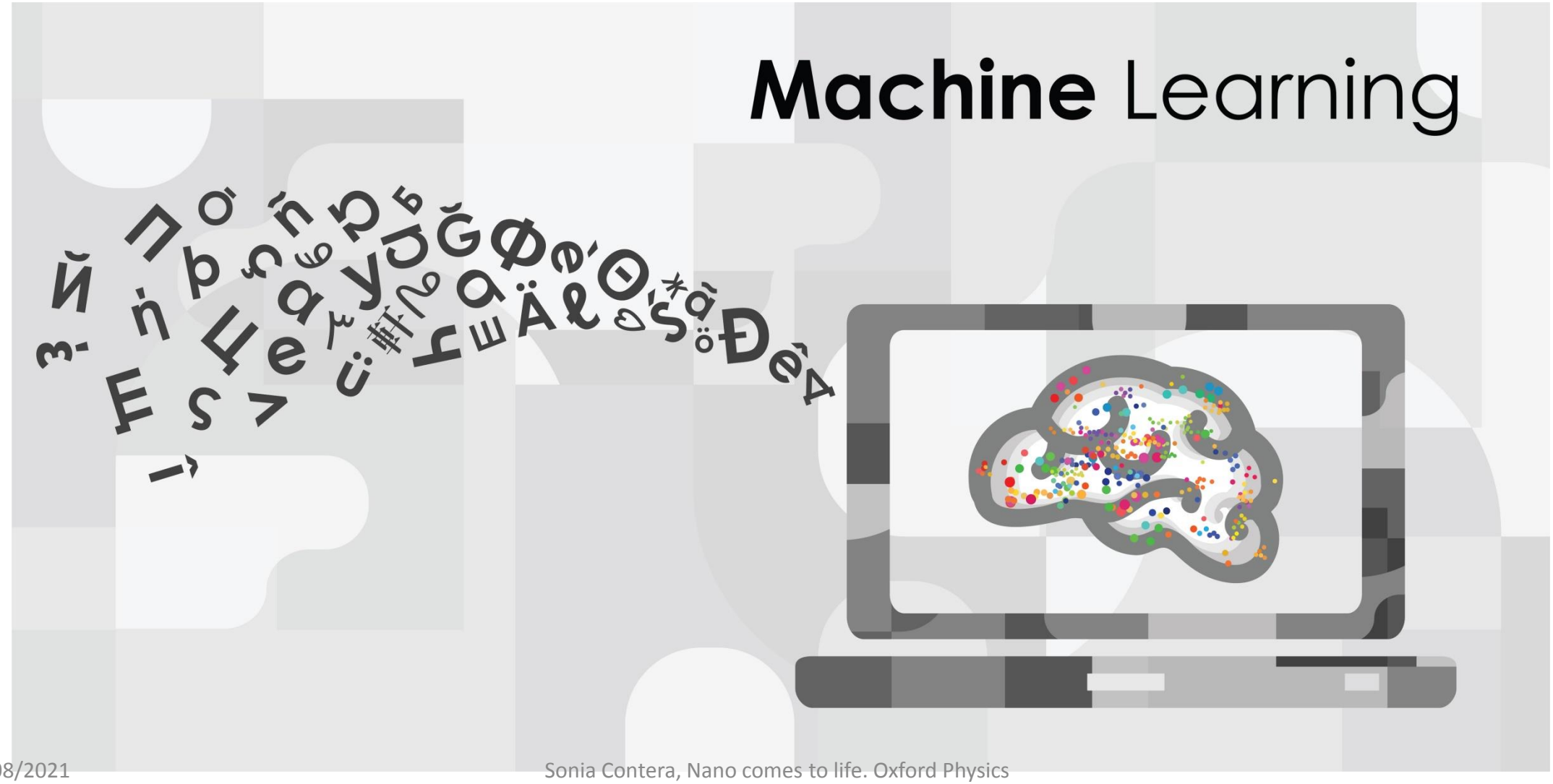


Ando, Uchihashi…
Scientific Reports

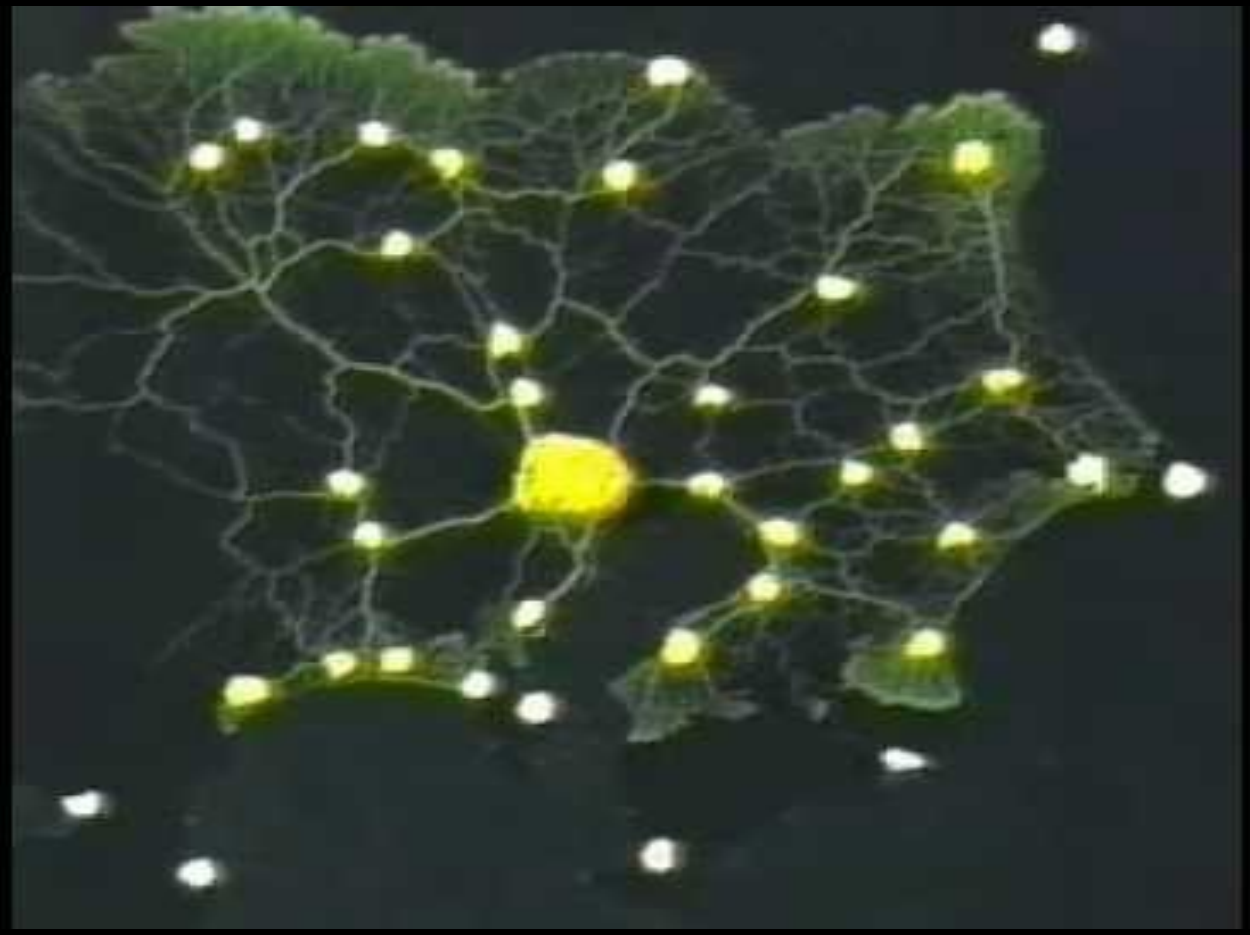
Sonia Contera, Nano comes to life. Oxford Physics

Meanwhile in computer depts….. There were other people interested in the complexity of biology

Neural networks, and AI…..

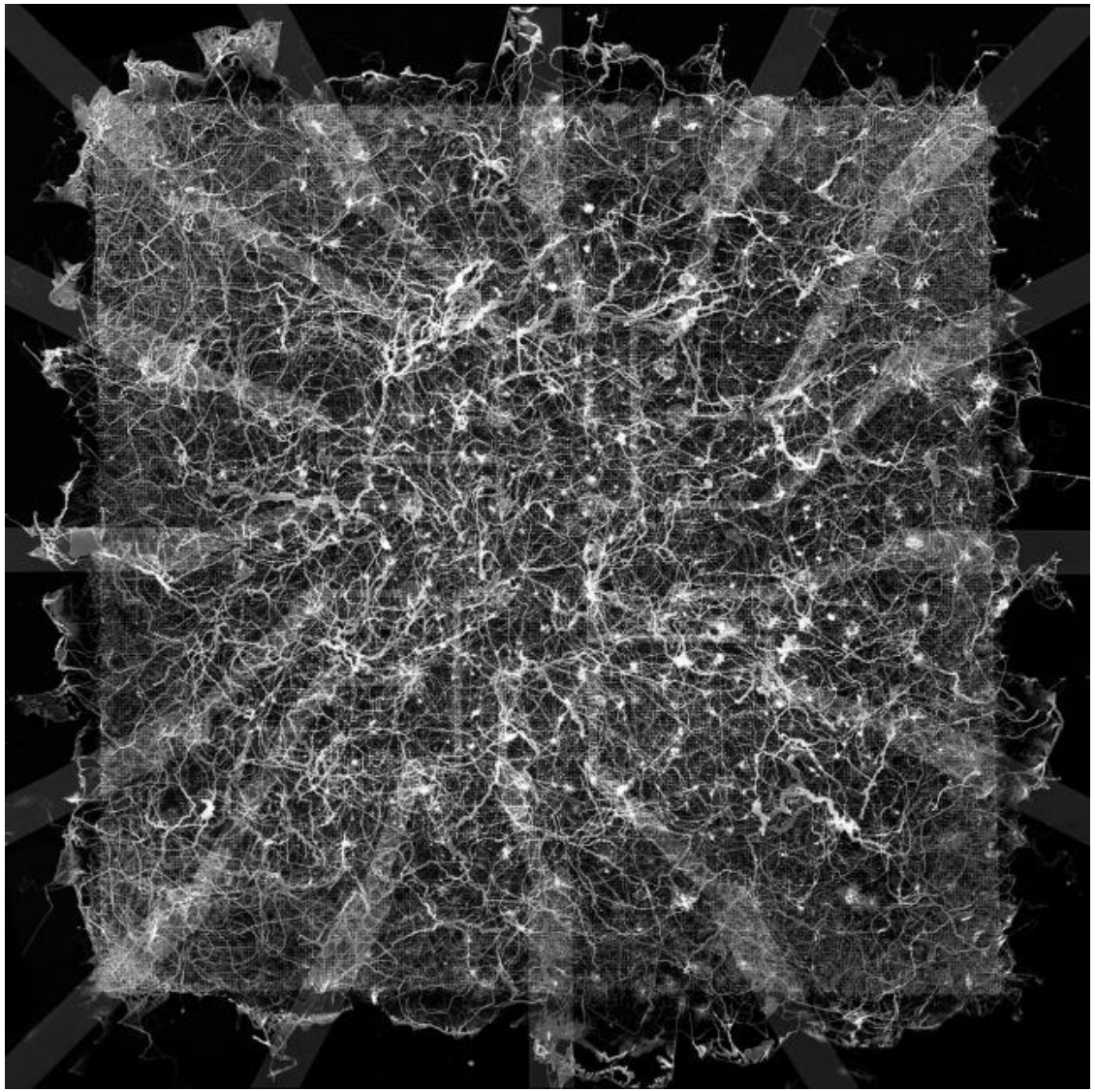


Simple organisms computational power :SLIME MOULD

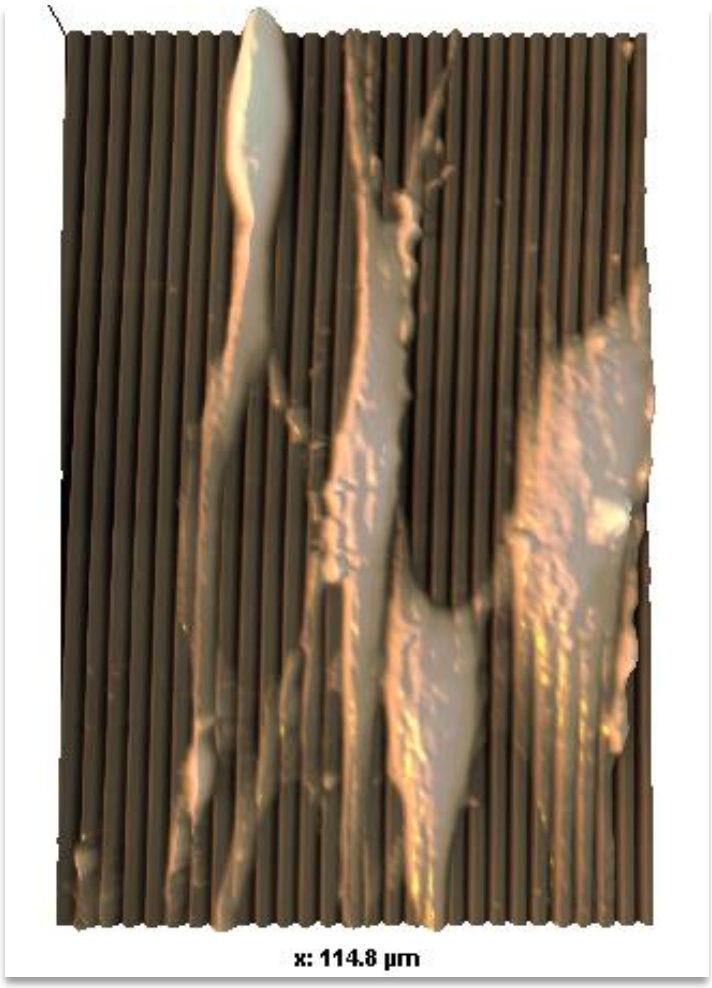


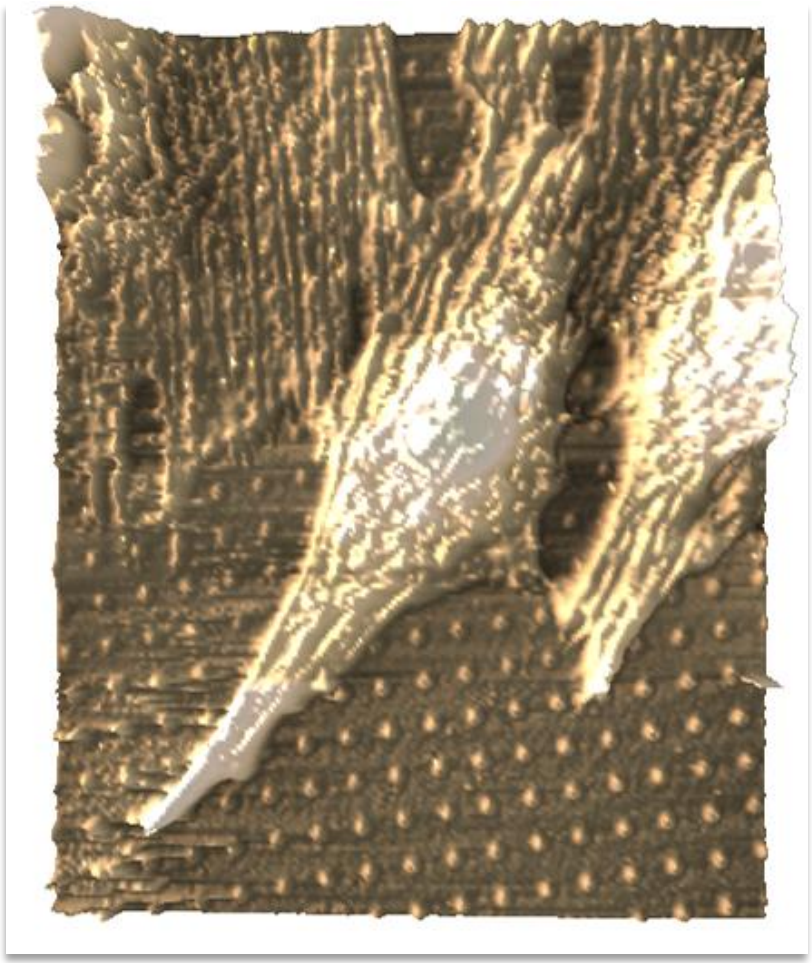
COMPUTING AND LIFE: Neuromorphic computing

Jim Gimzewski

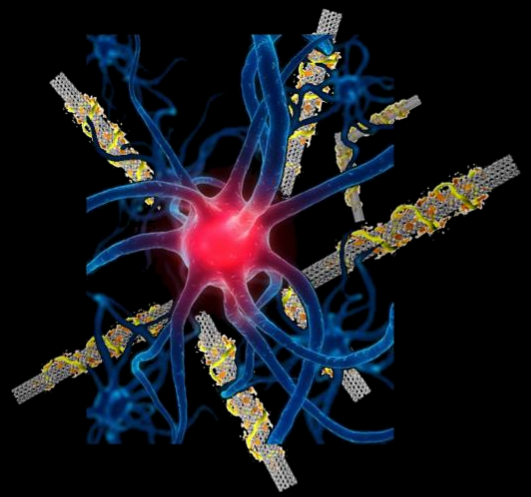


.Per Bak, the Danish physicist who died in 2002, first proposed power laws as hallmarks of all kinds of complex dynamical systems that can organize over large timescales and long distances. Power-law behaviour, indicates that a complex system operates at a dynamical sweet spot between order and chaos, a state of "criticality" in which all parts are interacting and connected for maximum efficiency.



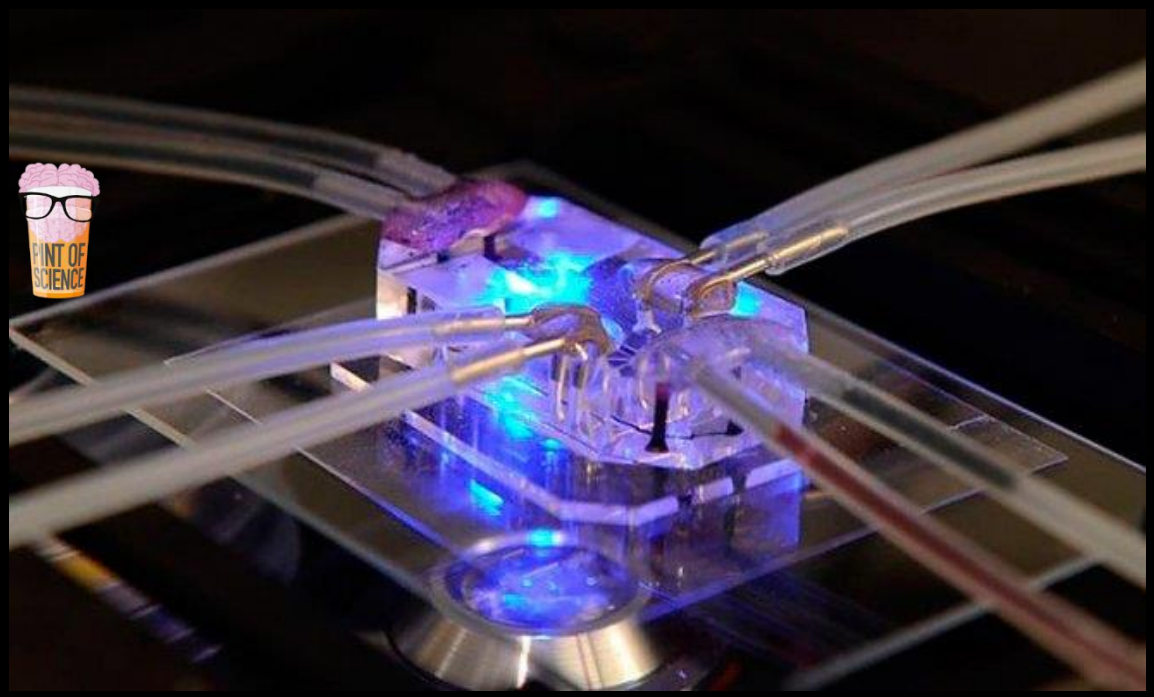


From Contera et al. AFM images of living pre-osteoblasts . Unpublished .



3D printed organs

Organ in a chip



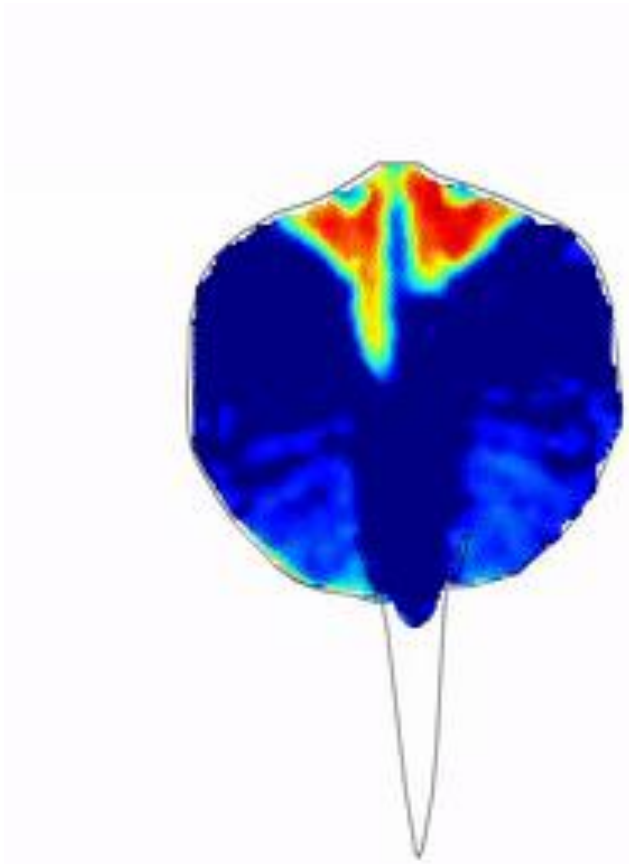
Kolesky, Homan, Skypar-Scott and Lewis, WYSS institute, Harvard.

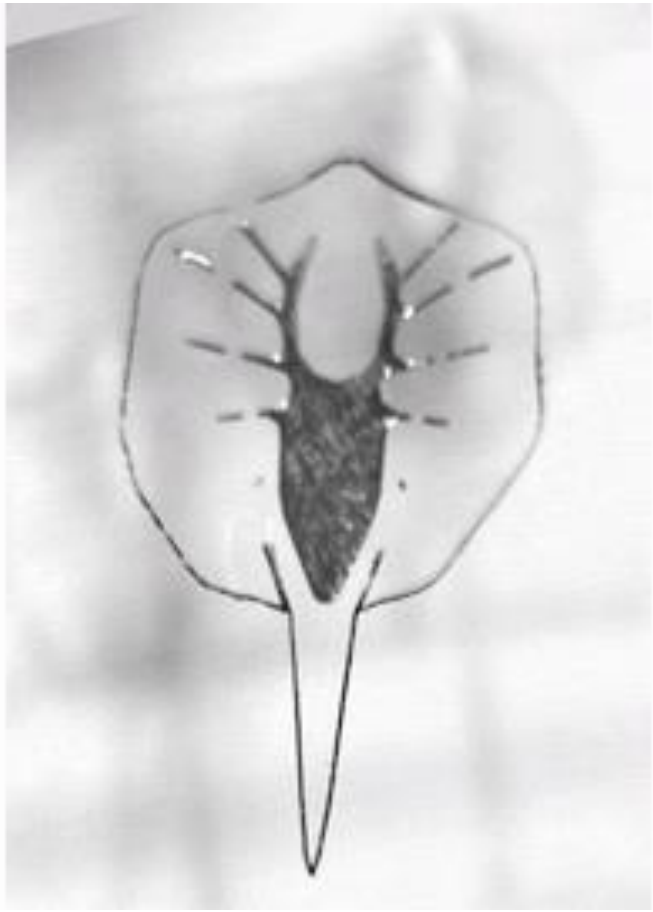
Quantitative real time measurement, combination of nano and probably cells, combining reductionist with emergent approaches

SMART MATHEMATICAL MODELLING
AI
and simulations

Somehow we get closer to the dream of traditional medicines---
(Topic for another talk)…

TRANSMATERIAL FUTURES

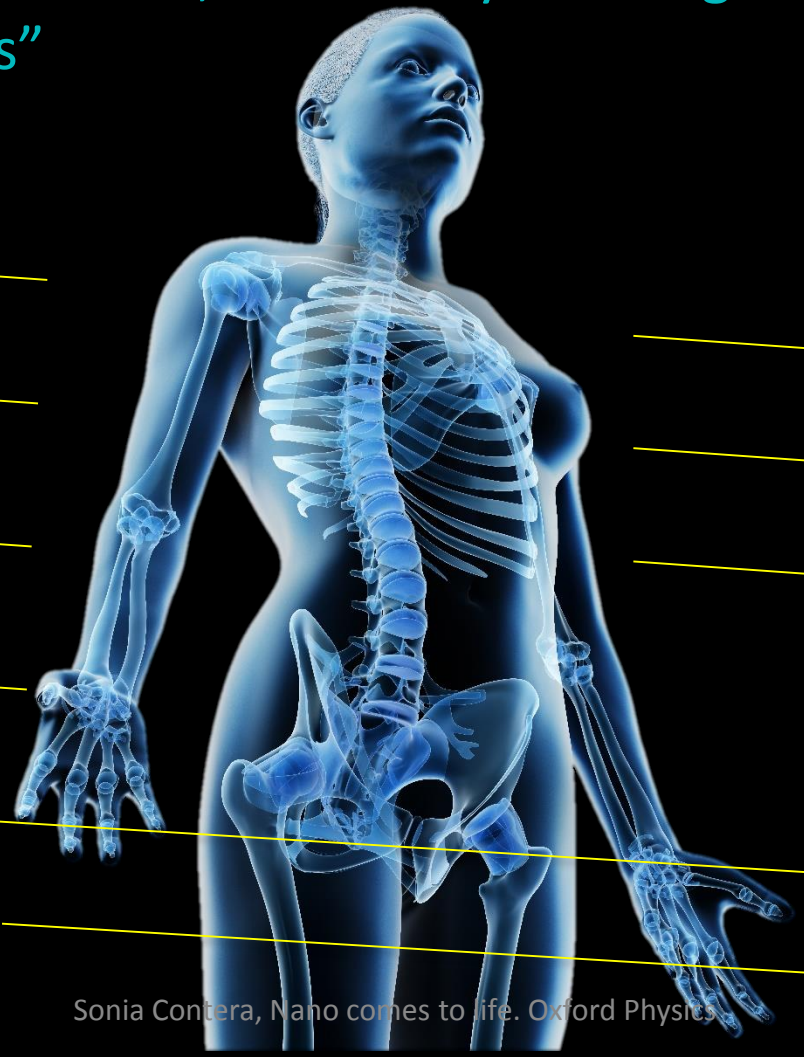




CYBORG STINGRAY

(Kit Parker, Harvard's Wyss Institute, 2016)

The convergence of sciences and technologies
Erosion of the boundaries between material and biological sciences, new medical treatments, better algorithms…
MERGING WITH COMPLEXITY, a new way of doing technology
“transmaterial futures”



Nanotechnology

Biology

Physics

Engineering

(Quantum) computing

Big Data

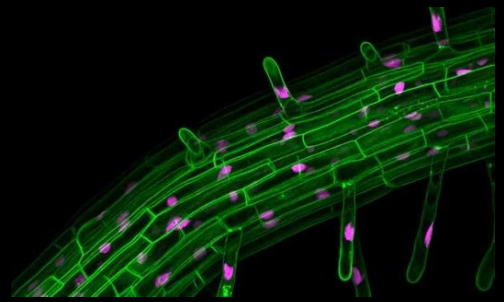
Algorithms

Artificial Intelligence

Mechanical properties of plant cell walls

Ian Moore (Plant Sci) , Charlotte Kirchhelle, JACOB SEIFERT

A Jerusalem (Eng Sci)

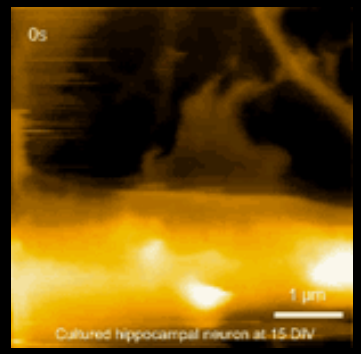


Funded by the Leverhulme Trust

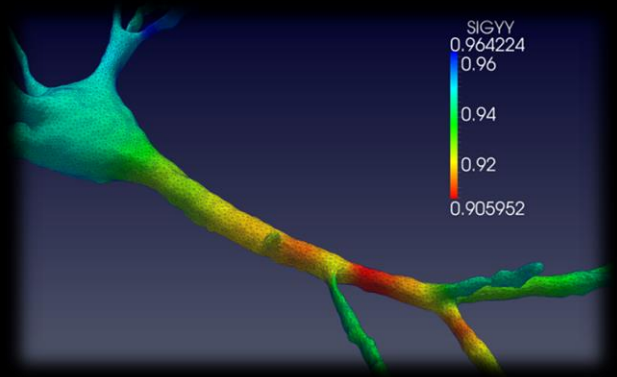
Electromechanical coupling of neurons with AFM

(Antoine Jerusalem, Eng Sci, Ari Ercole Cambridge),

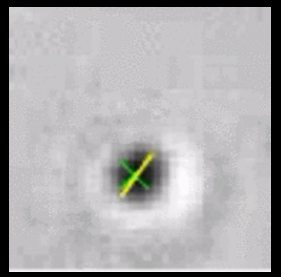
Casey Adam, Sarah Waters: ELECTROMECHANICAL coupling IN BIOLOGY

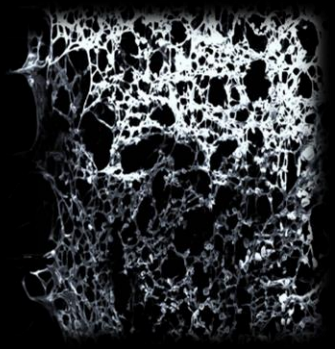


AndoLab.SciRep



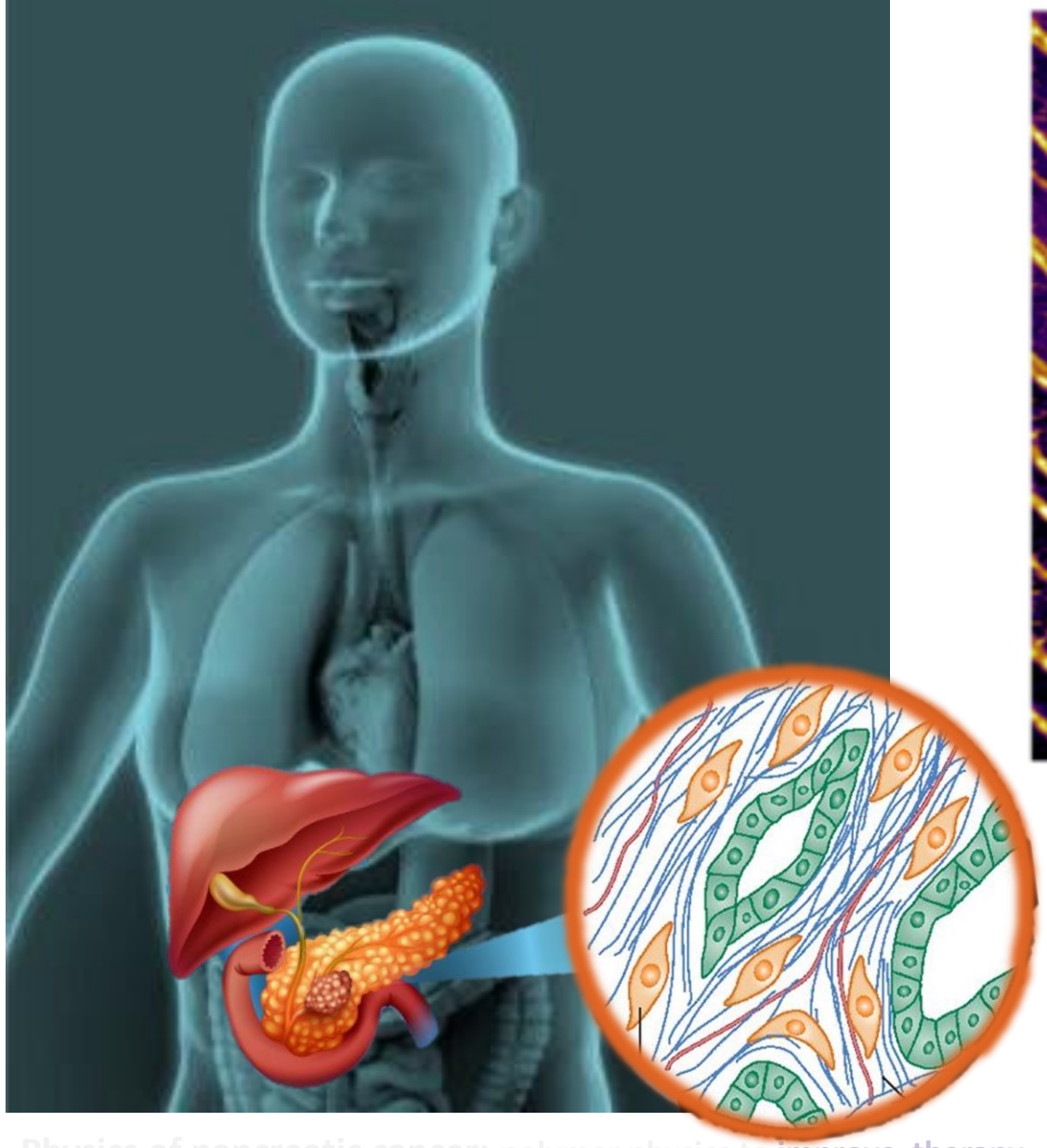
Biomimetic magnetic materials for tissue engineering and drug delivery

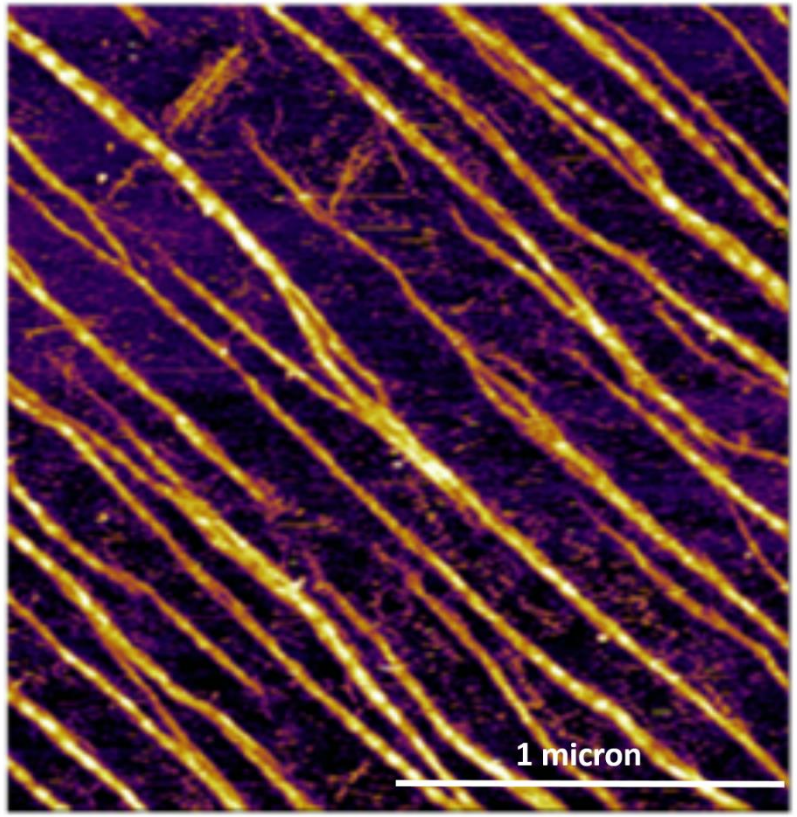




Cryopreservation
Sarah Waters

Physics of pancreatic tumours (A Gordon-Weeks Sarah Waters, Casey Adam)

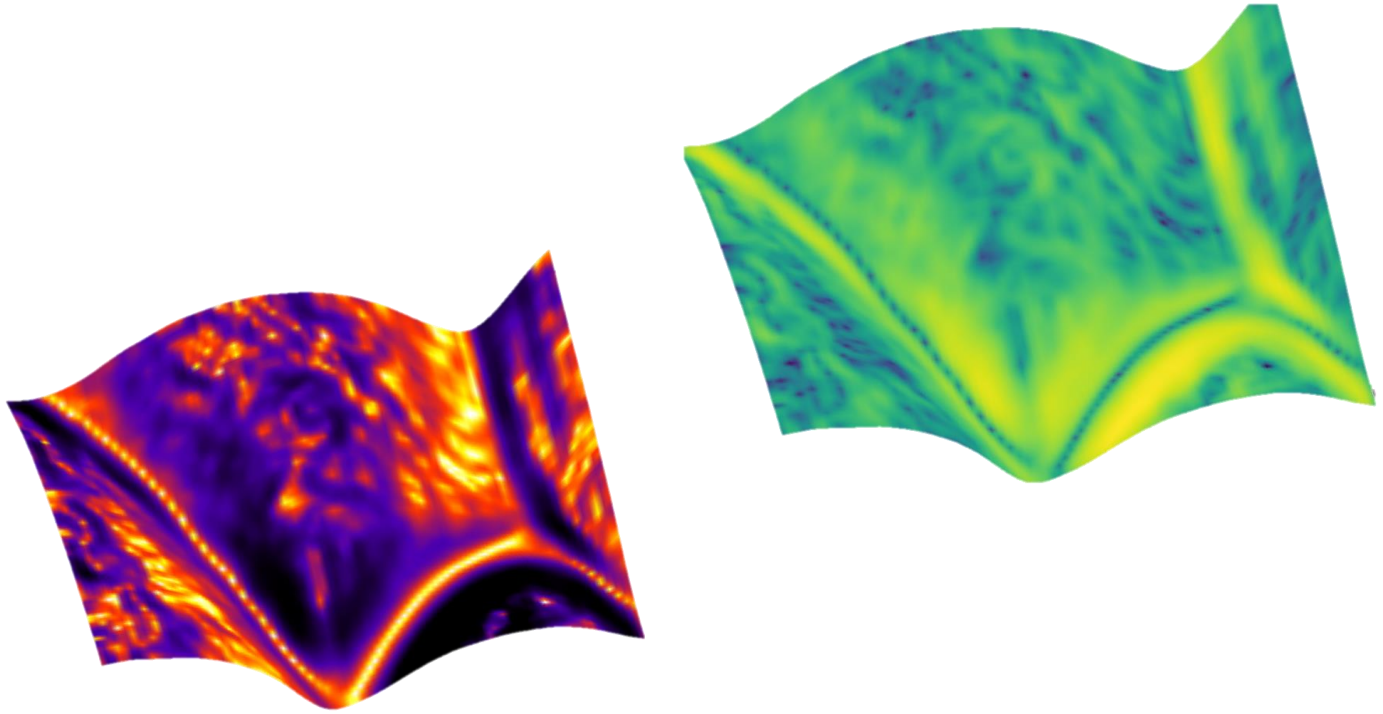




Physics of pancreatic cancer: polymer physics to improve therapy

Casey Adam(Physics), Alba Piacenti (Physics), Sarah Waters (MATHS), A Gordon-Weeks (MEDICINE) A Jerusalem (Eng Sci) and Sonia Contera (Physics)

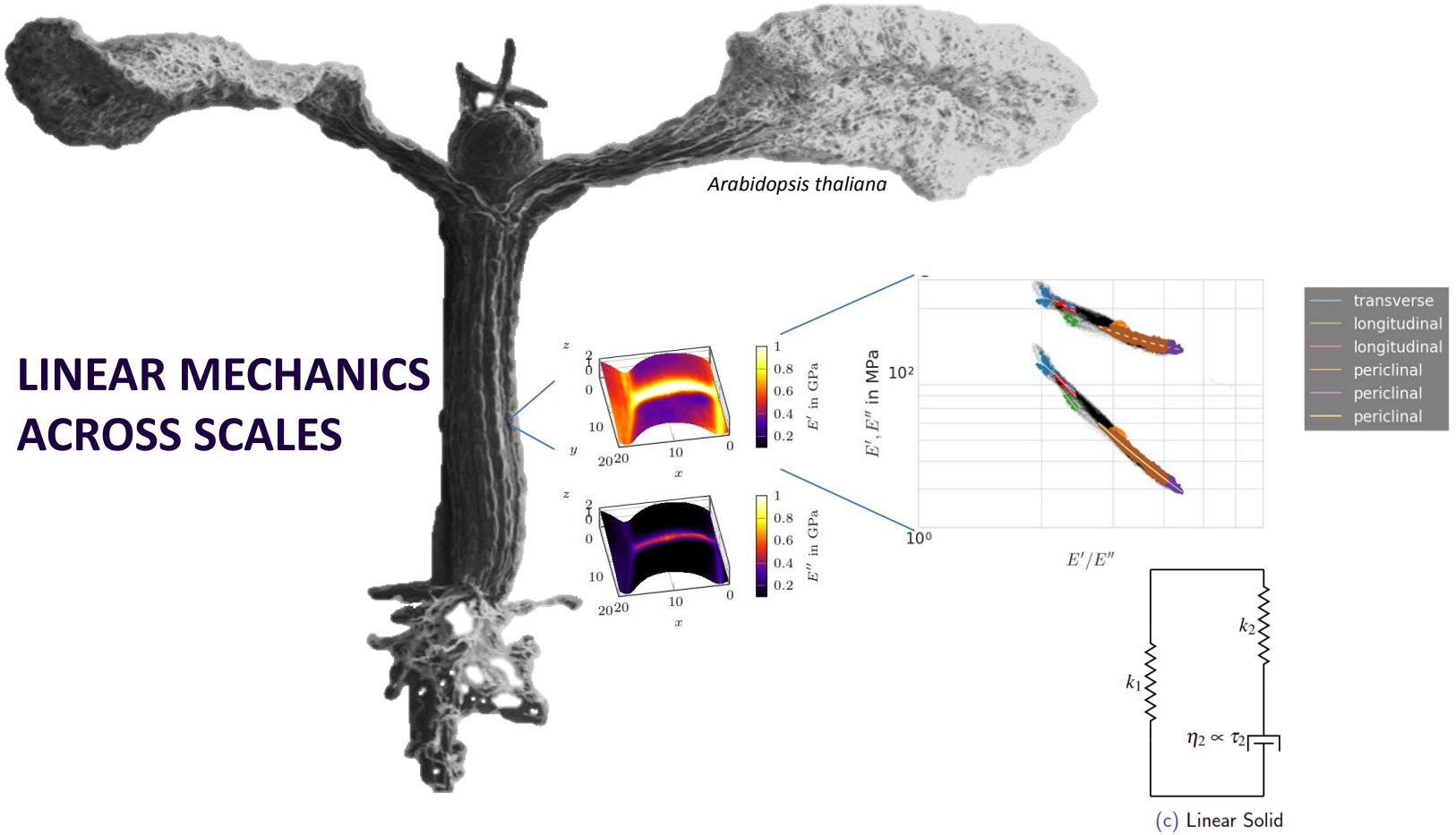
GROWTH, FORM and LIFE



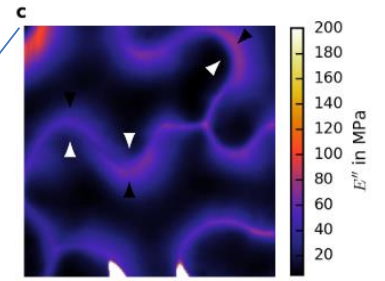
Oliver Hamant

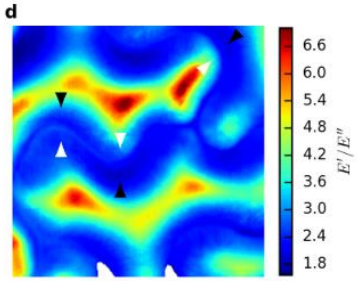
Jacob Seifert, Ian Moore, Sonia Contera

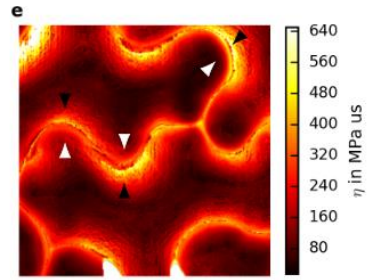
LINEAR MECHANICS ACROSS SCALES

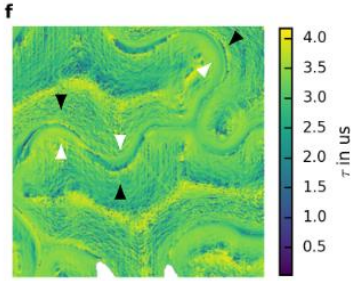


Jacob Seifert, Ian Moore, Sonia Contera*, 2019

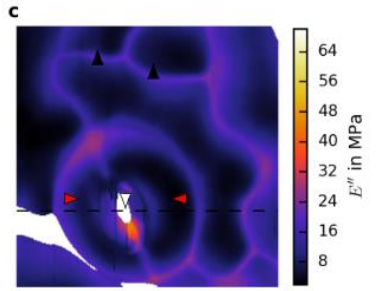


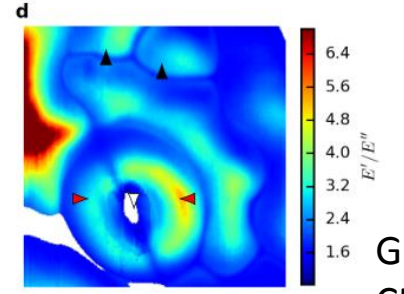






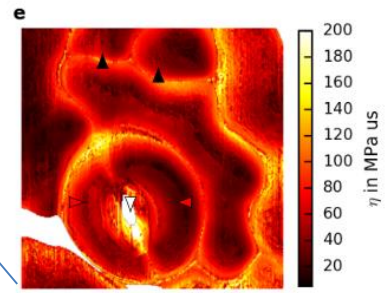
PAVEMENT CELLS

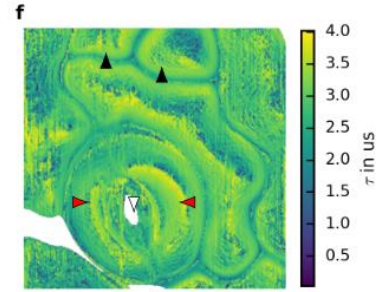


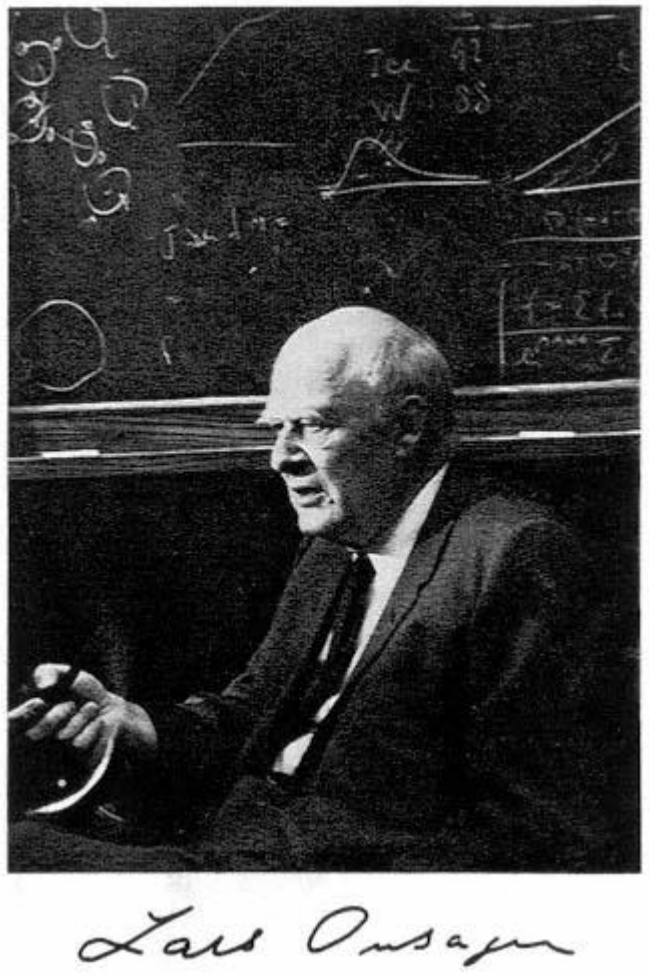


GUARD CELLS

stoma



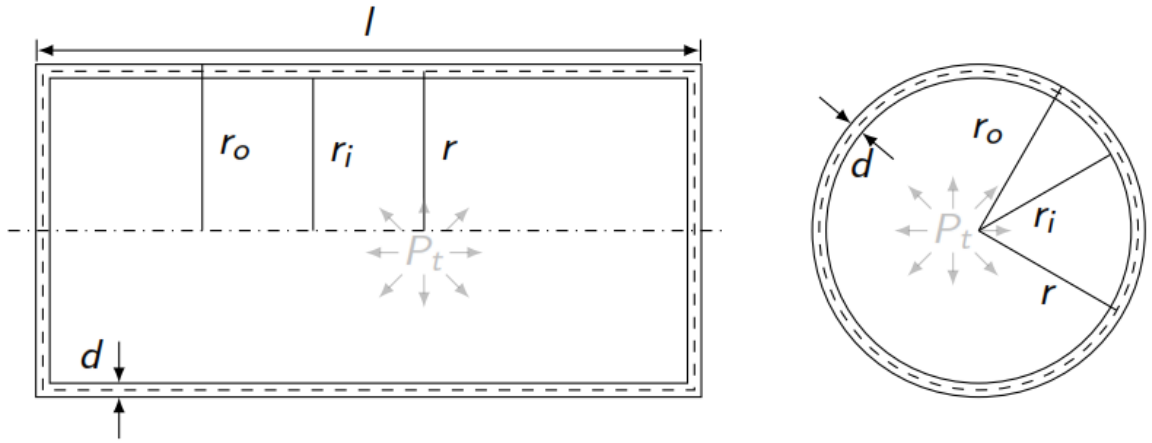




Non-equilibrium thermodynamics

Lars Onsager analysed mathematical equations for various irreversible thermodynamic processes and in 1931 found the connection that led him to formulate equations that came to be known as **reciprocal relations**. This allowed a complete description of irreversible processes.

Non-equilibrium thermodynamics to understand growth : EXPERIMENTALLY????



$$\frac{1}{l}\frac{\mathrm{d}l}{\mathrm{d}t} = \frac{r_i^2}{2dr}\frac{1}{\eta}\left(P_t - \frac{2dr}{r_i^2}\sigma_w\right)$$
$$= \Phi(t)\,(P_t - Y)$$

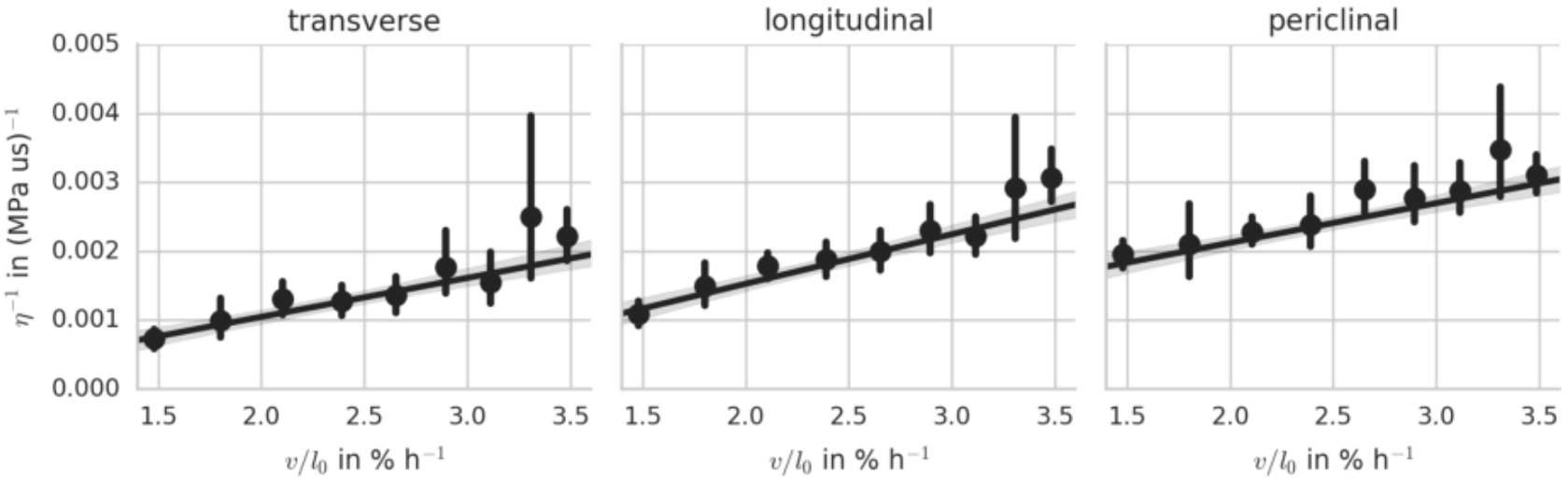
Seifert, Moore, Contera, in preparation

Nanoscale Viscosity Correlates with Plant Growth

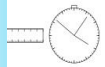
From the Onsager principle it can be shown that:

$$\Phi = \frac{1}{\eta} \frac{r_i^2}{hr}$$

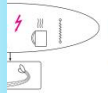
r_i ... inner radius
r ... radius of stress neutral plane
h ... wall thickness



The growth rate of individual cells correlates with their viscose response



Describes growth at **any** length- and time-scale → bridges scales.



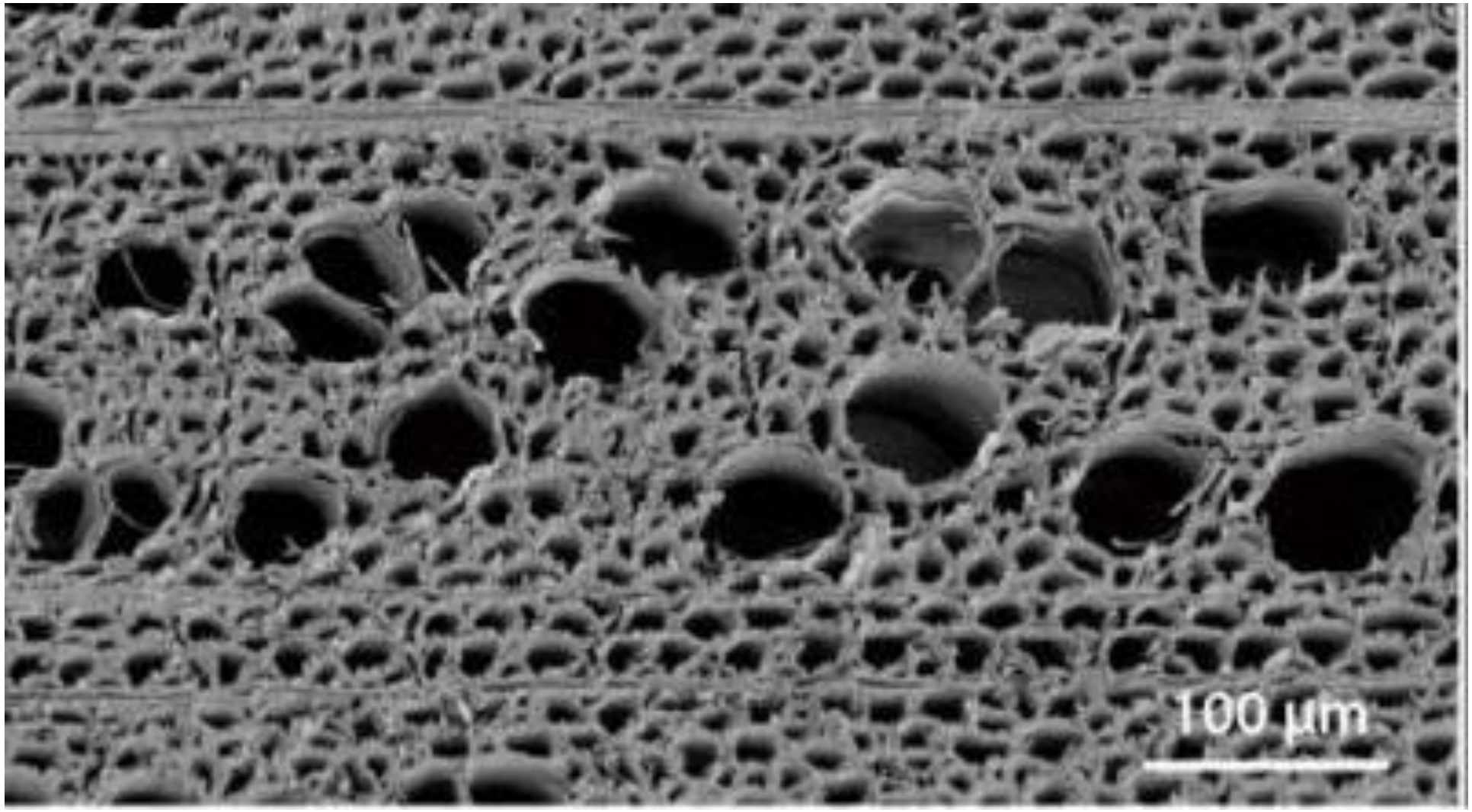
Provides **energy approach** for growth → links chemical, mechanical, electrical, and thermal energy to biological growth.

Energy uptake must be $> \mathcal{D}$.

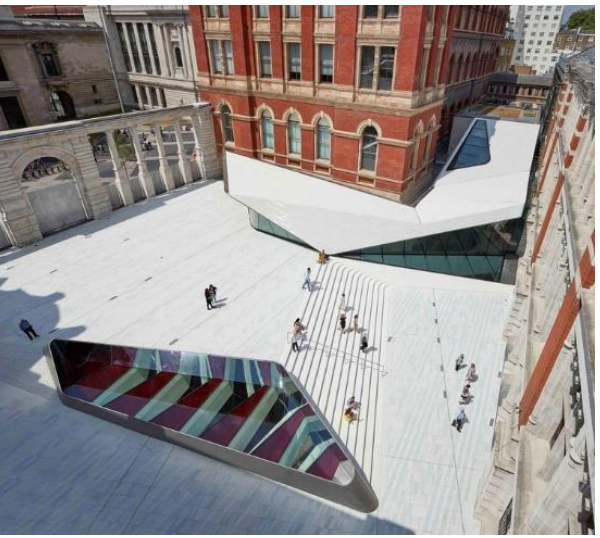
?

Is the Onsager principle a **sufficient** or **necessary** condition?

Environmental conditions must be **stable** over the time-scale of growth.


100 µm

la Biennale di Venezia
di Architettura



30/08/2021

V&A Museum

https://www.ala.uk.com

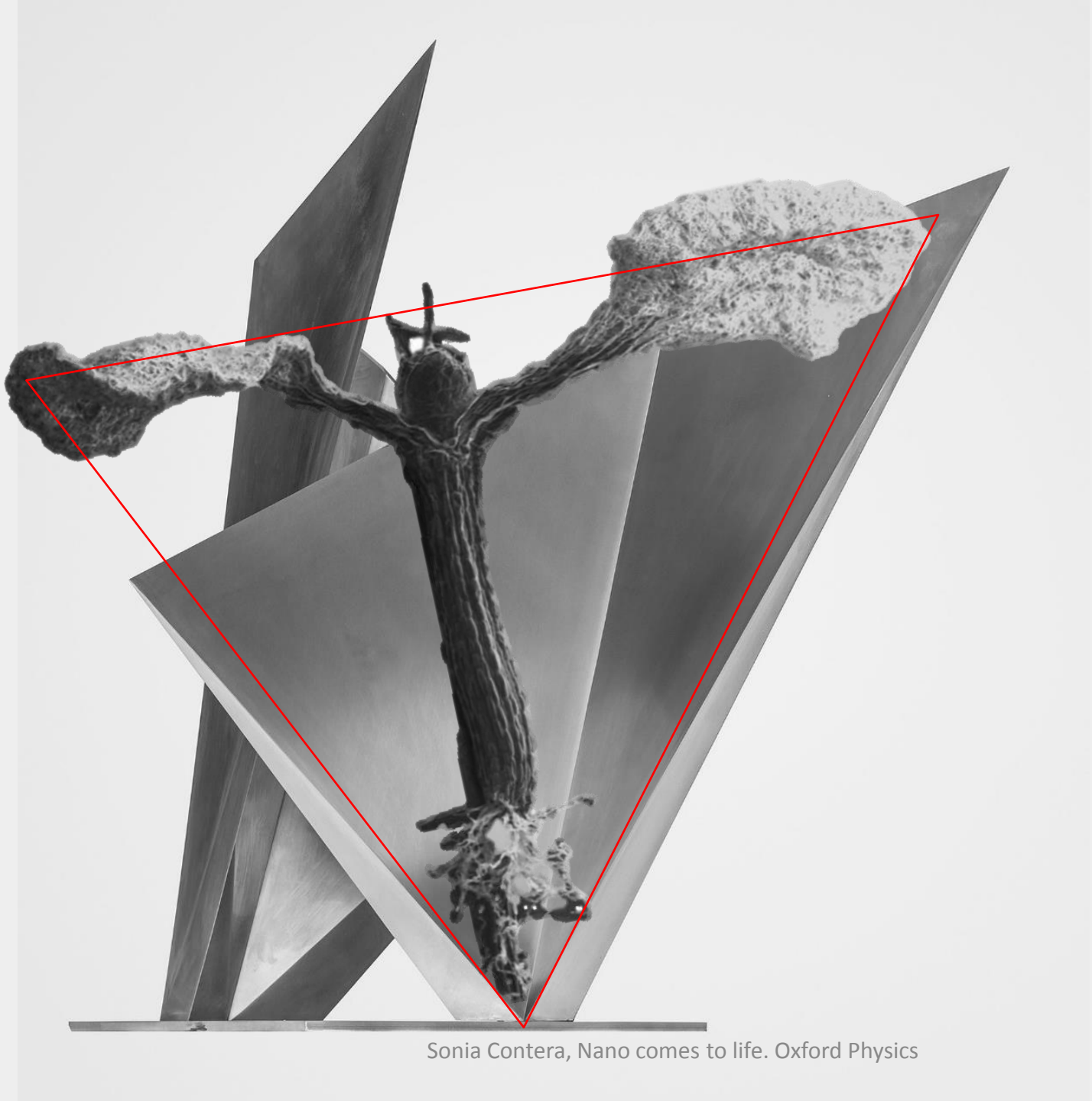
AL__A

Oxford Physics

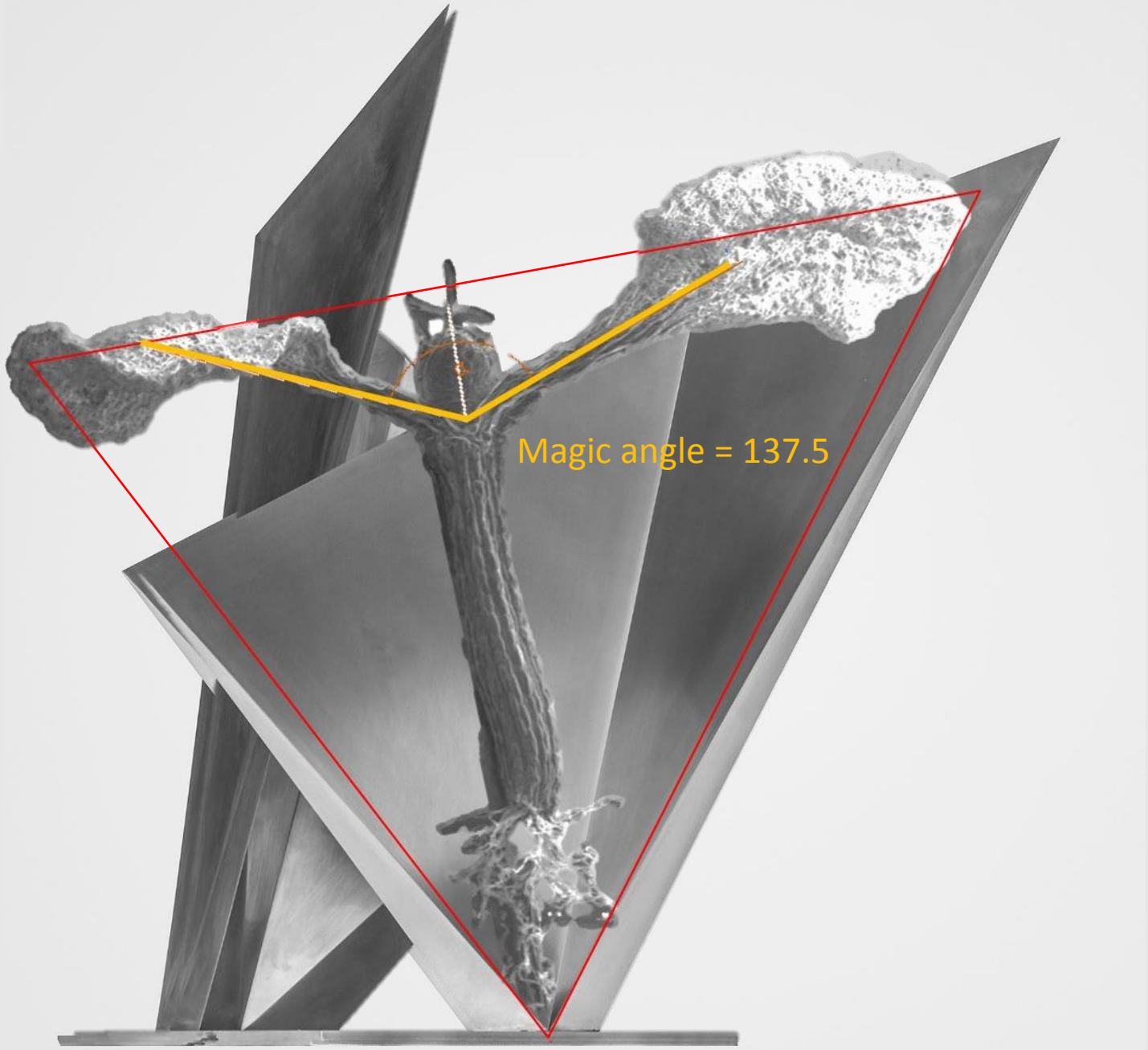
And moving on???
Where does nano go from here….

ARTURO BERNED
www.berned.com

ぐりんぐりん 福岡



Sonia Contera, Nano comes to life. Oxford Physics



Sonia Contera, Nano comes to life. Oxford Physics

Where physics is not computational (coherent quantum mech)

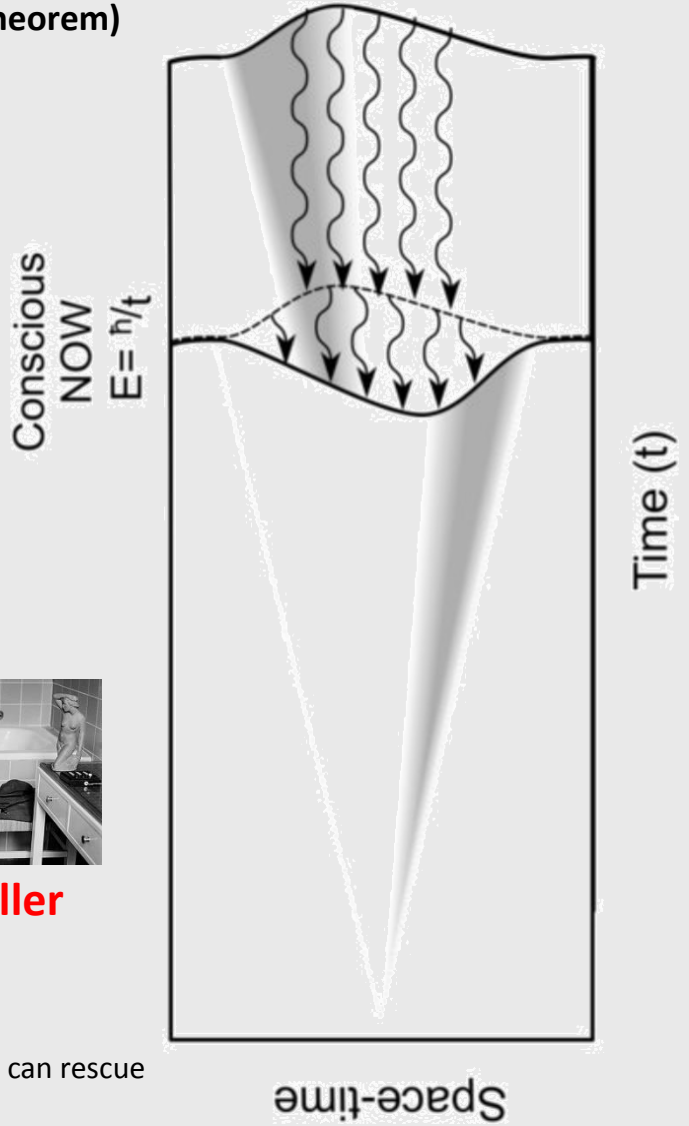
(logic is not enough, Goedel incompleteness theorem)

Gödel

?

Penrose

Lee Miller



How quantum biology can rescue conscious free will
Stuart Hameroff
DOI: 10.3389/fnint.2012.00093

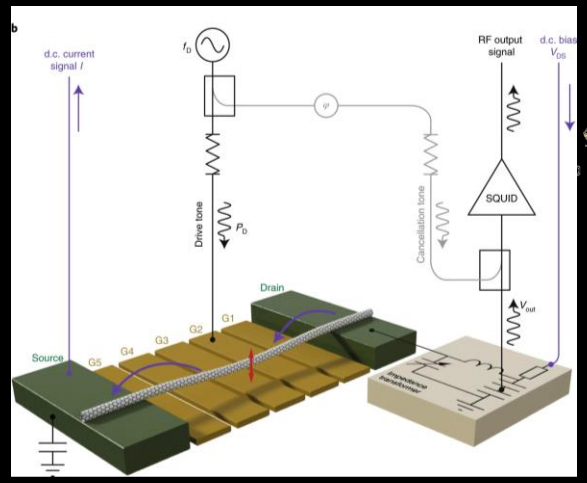
QUANTUM COMPUTATION AT HIGH TEMPERATURE/ BIOLOGY

At the interface of nano and quantum devices

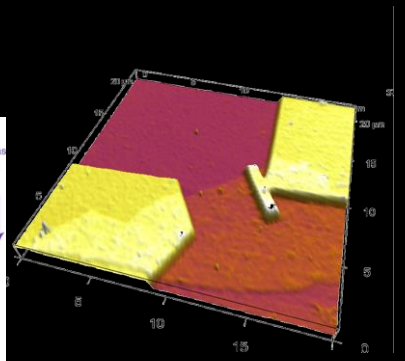
Orchestrated objective reduction

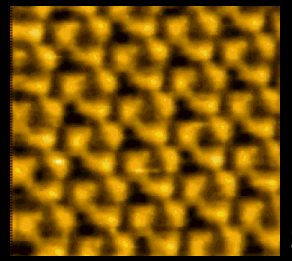
Roger Penrose

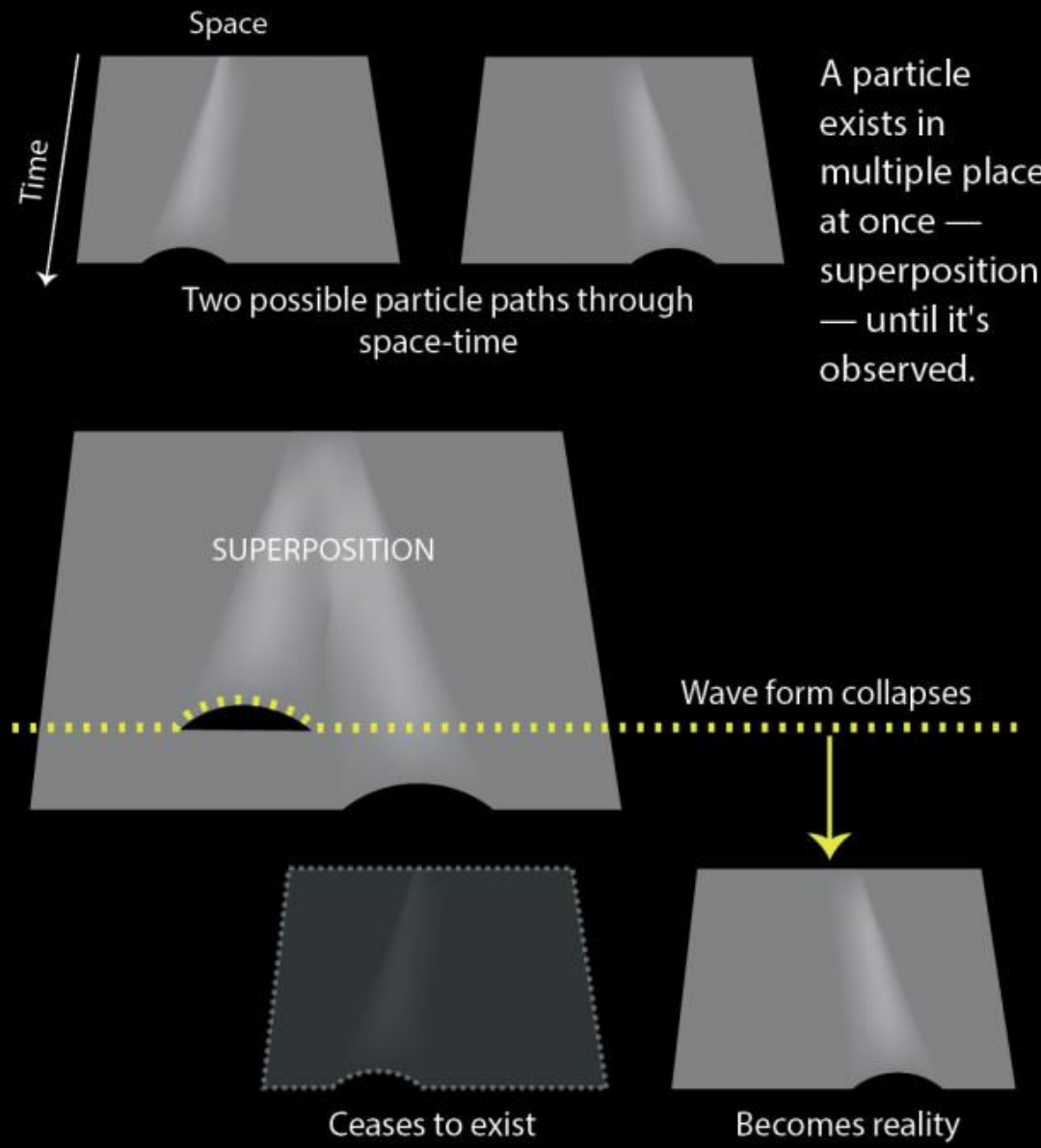
where quantum reality meets Classical reality



A coherent nanomechanical oscillator driven by single-electron tunnelling
Yutian Wen, Andrew N. Cleland, T. Pei, G. A. D. Briggs & E. A. Laird
Nature Physics **volume 16**, pages75–82(2020)



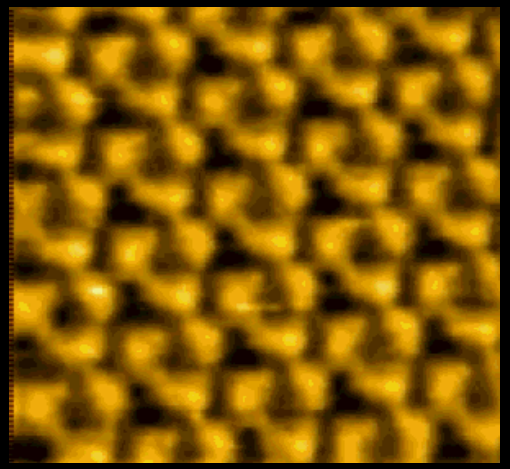


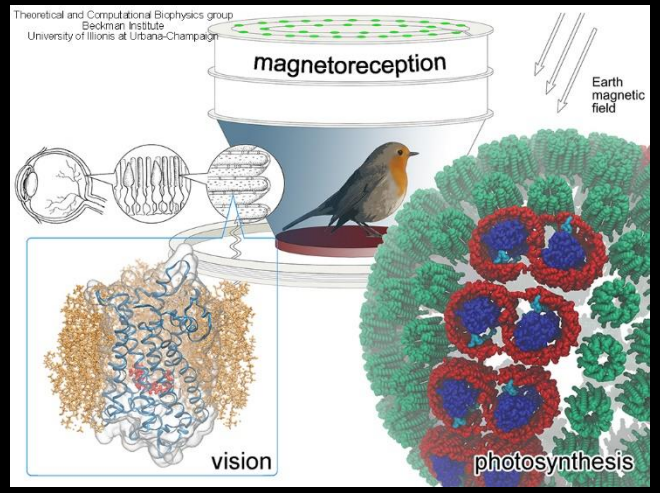


Sonia Contera, Nano comes to life. Oxford Physics

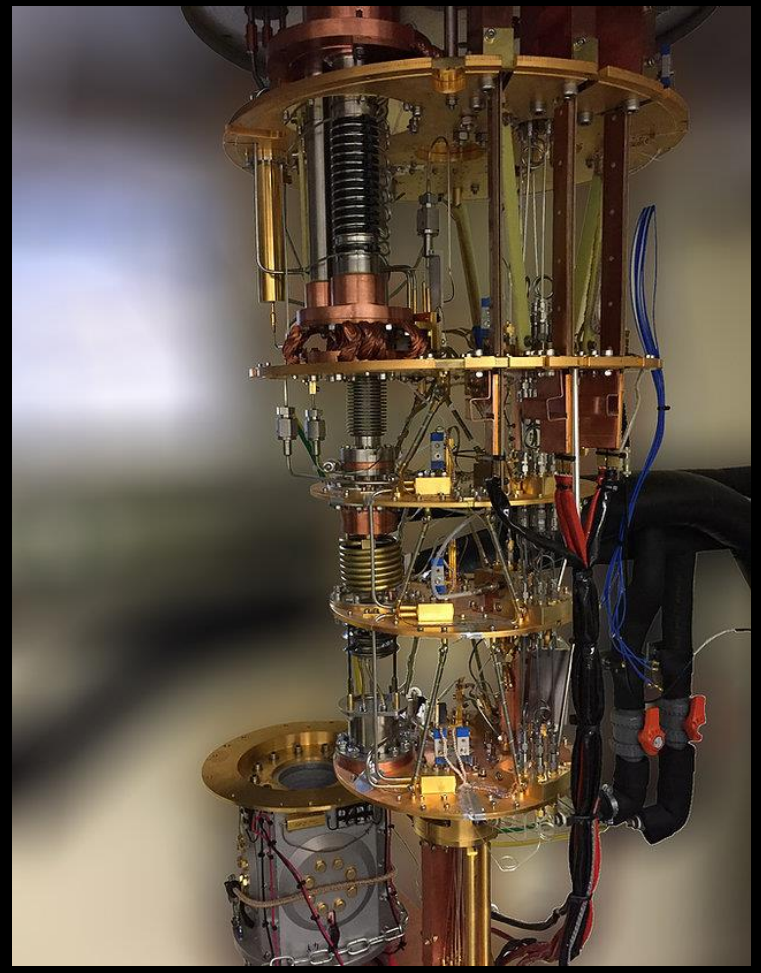
Information, thermodynamics, time and shape
Origin of life, evolution, intelligence… and indeed intuition

Classical, biological reality



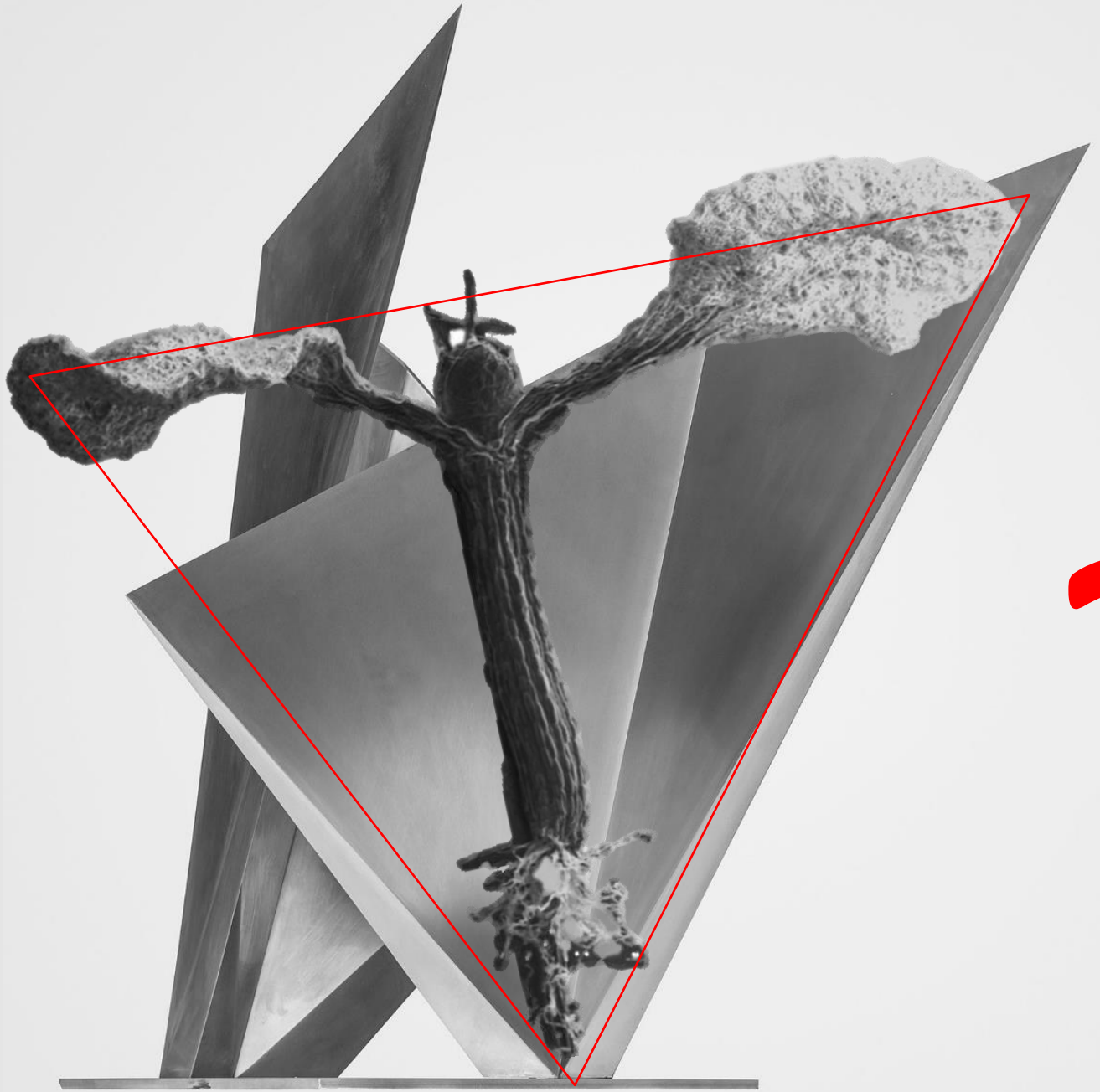


Quantum biology



Natalia Ares's lab, Oxford Materials

Quantum devices/computers



?

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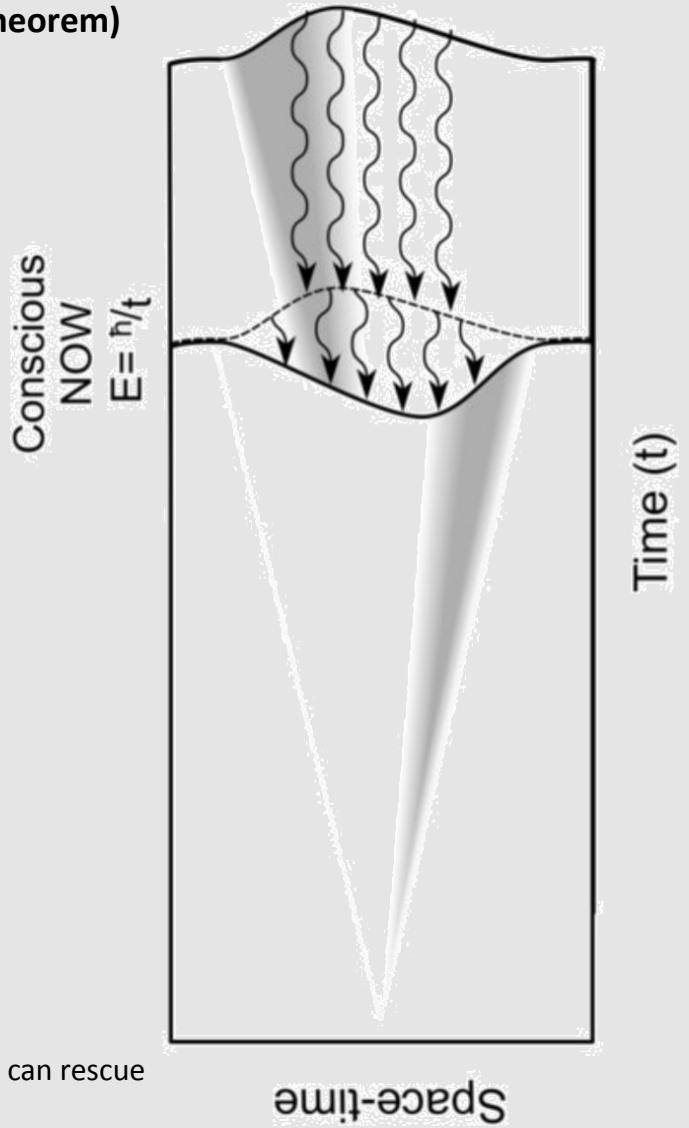

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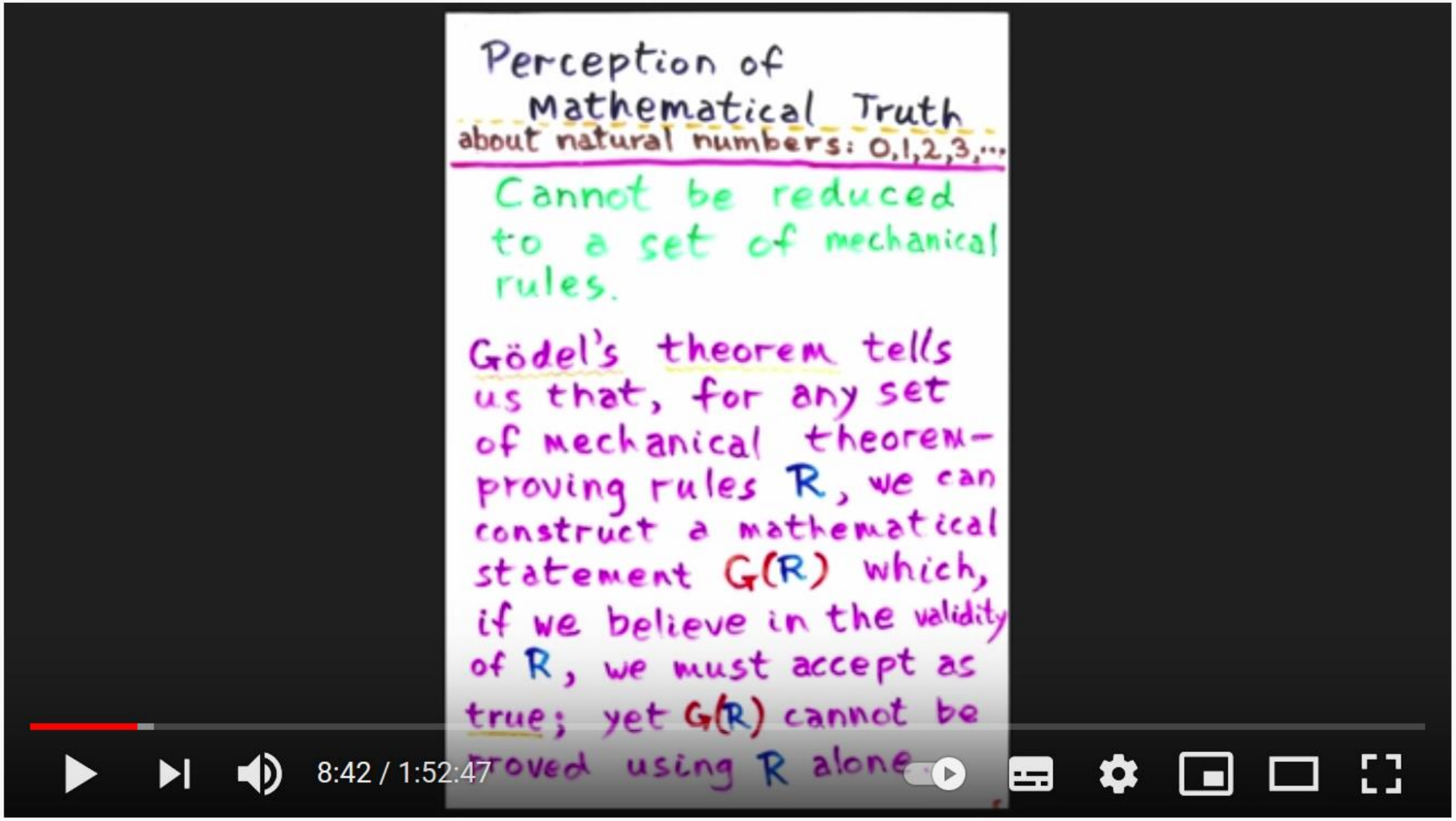
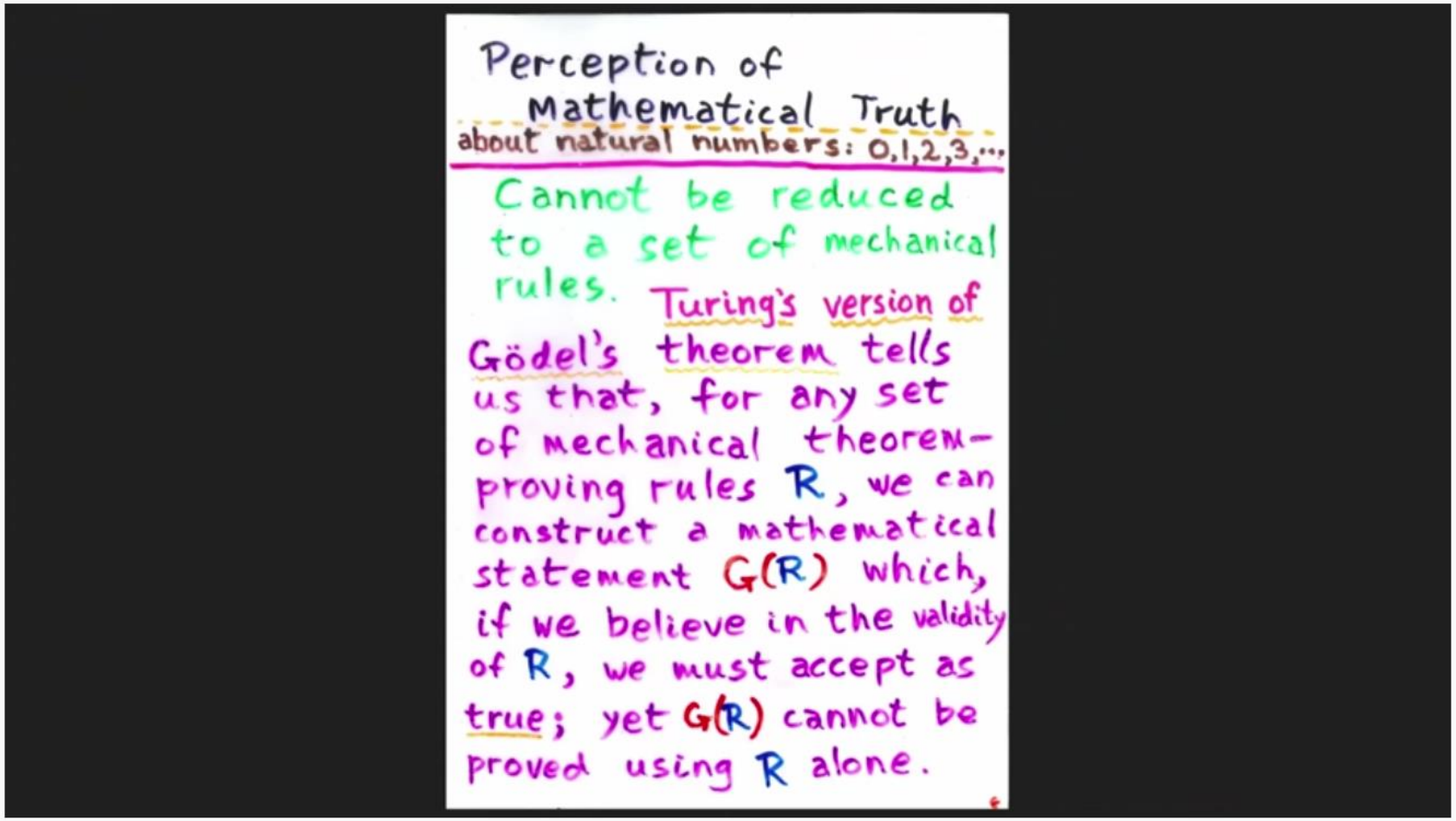


Sir Roger Penrose & Dr. Stuart Hameroff: CONSCIOUSNESS AND THE PHYSICS OF THE BRAIN



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