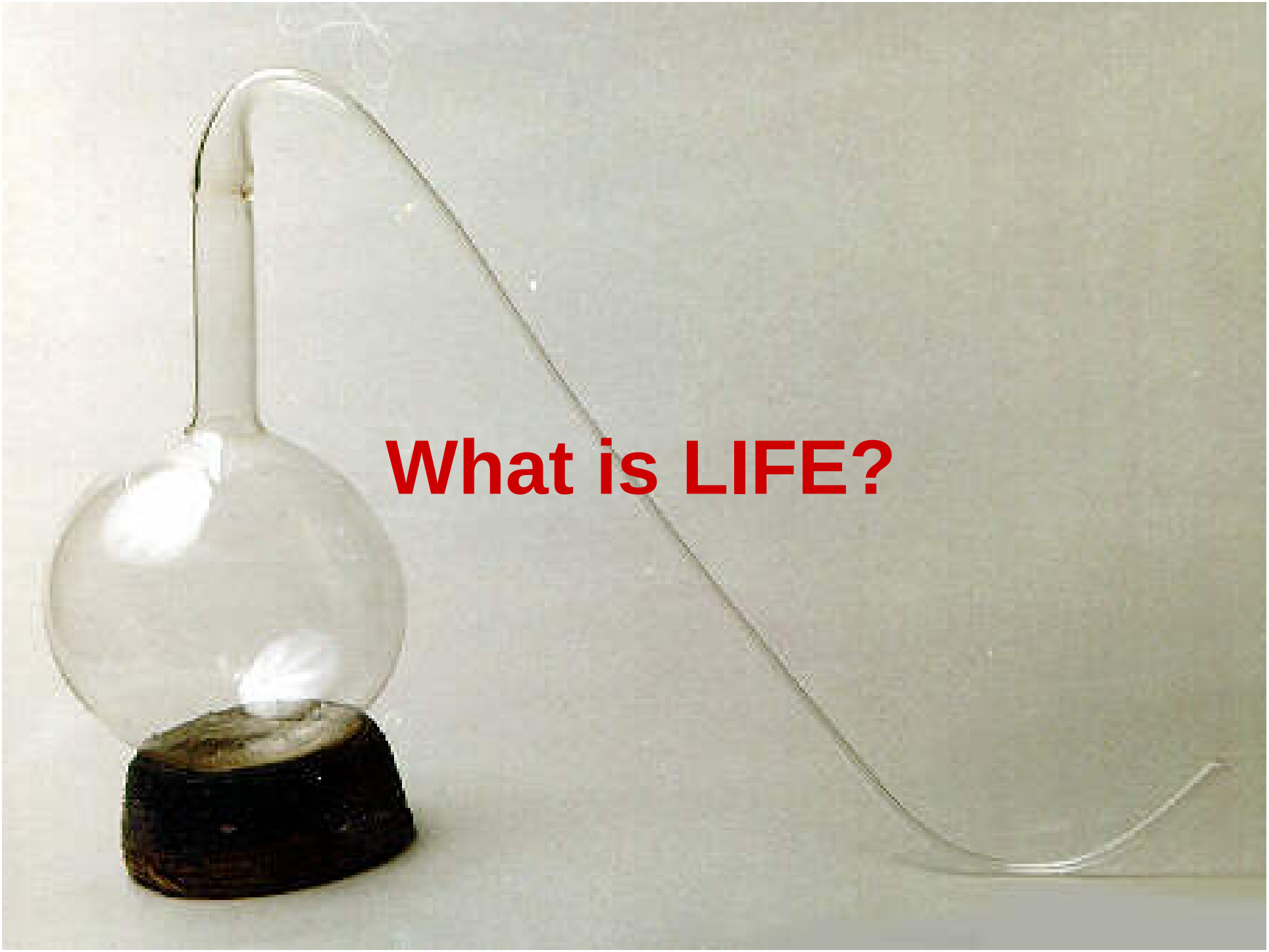
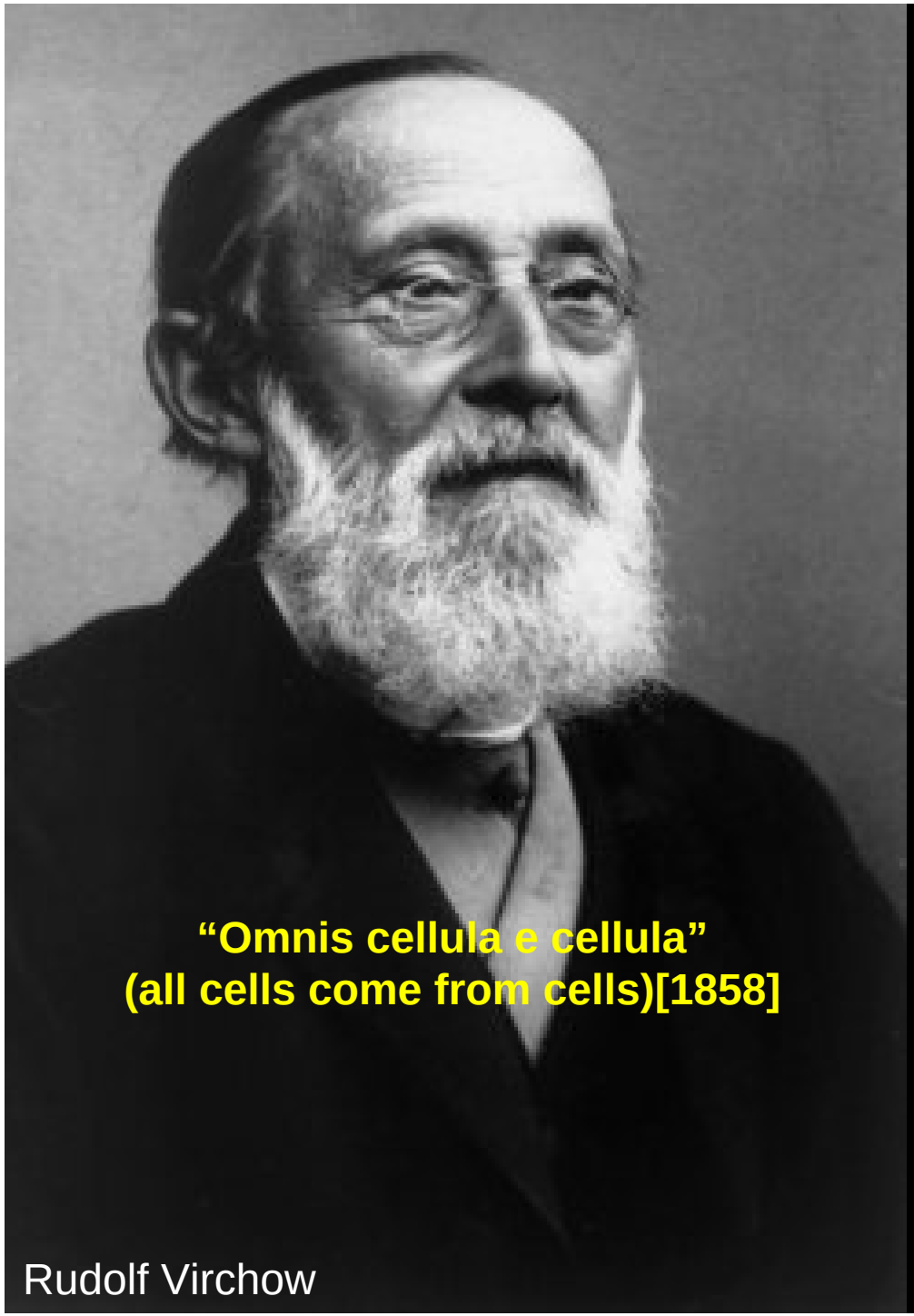
生命システム解析・構成のための次世代シミュレーション

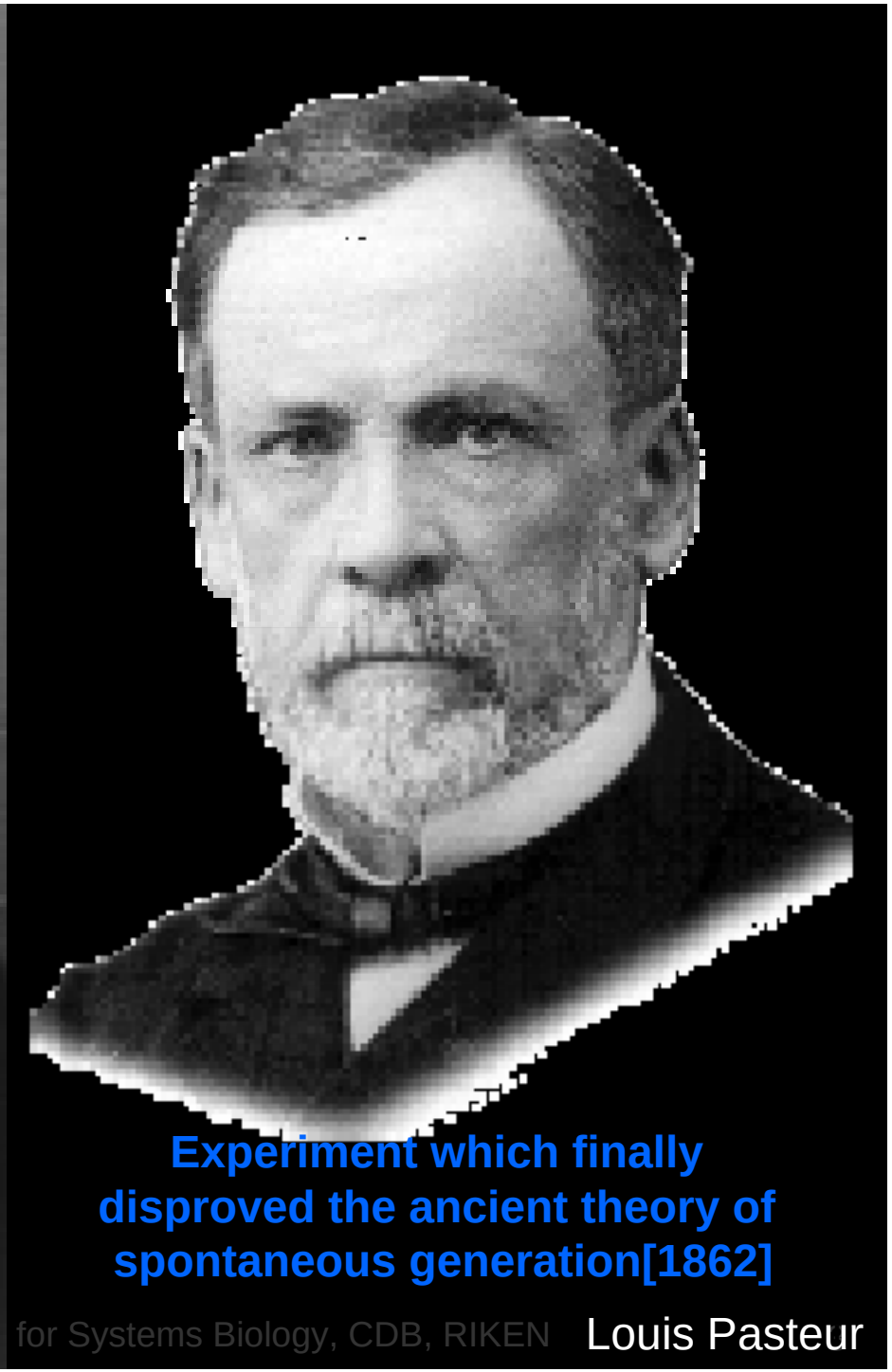
Hiroki R. Ueda
Center for Developmental Biology
RIKEN @ Kobe, JAPAN


What is LIFE?



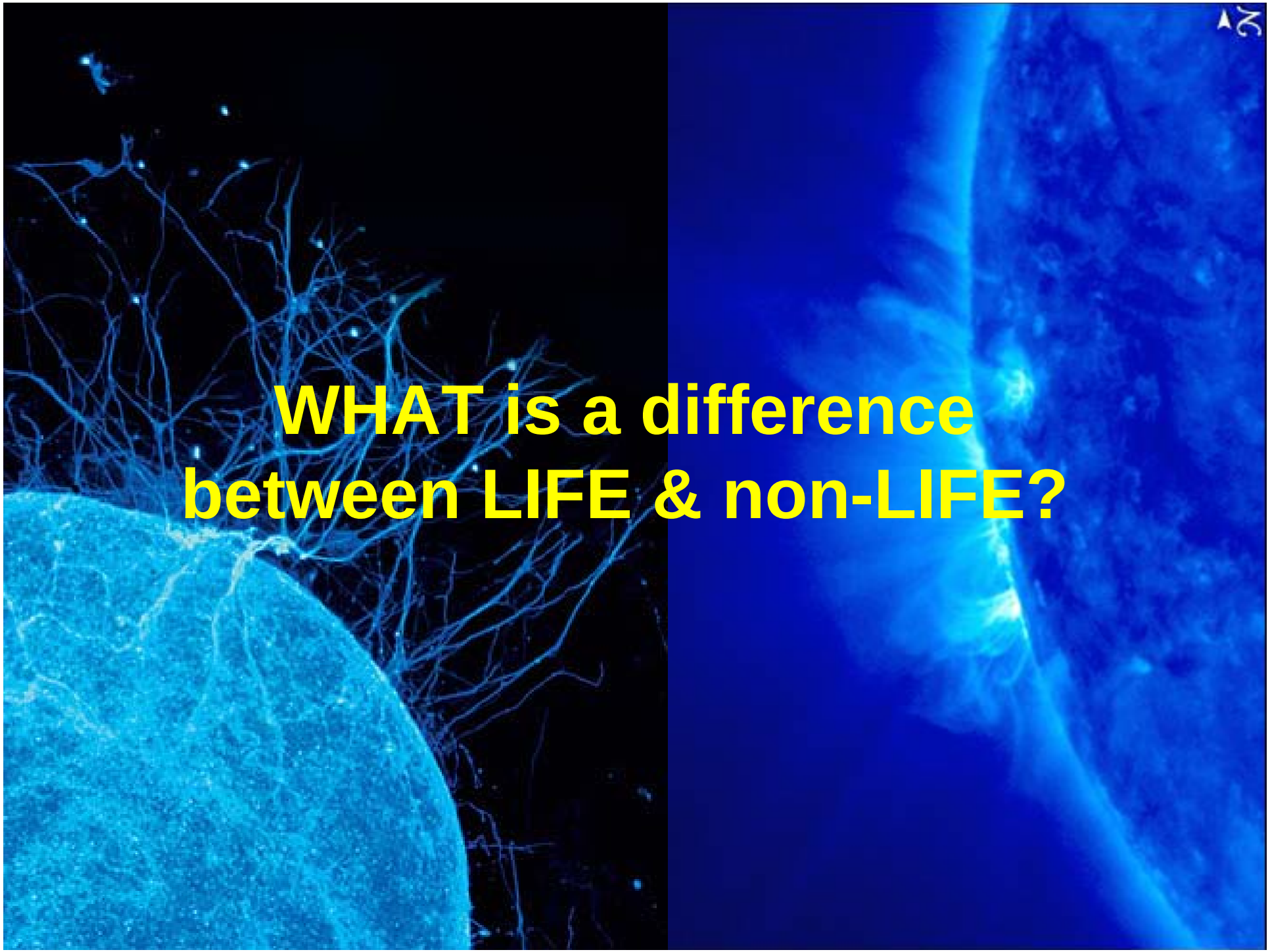
“Omnis cellula e cellula”
(all cells come from cells)[1858]

Rudolf Virchow



Experiment which finally disproved the ancient theory of spontaneous generation[1862]

Louis Pasteur


WHAT is a difference
between LIFE & non-LIFE?

"Understanding of Living Systems"
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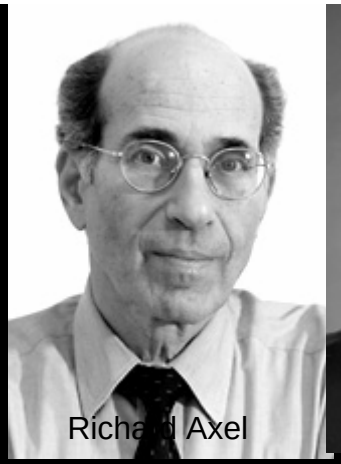
Center for Developmental Biology, RIKEN

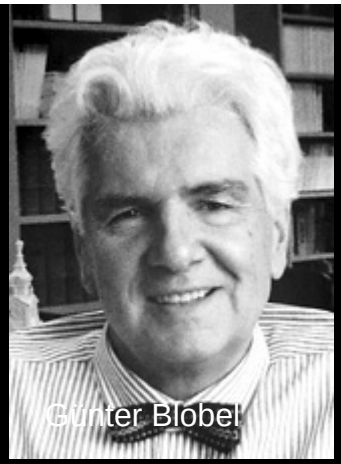
How to understand/define LIFE?


Andrew Z. Fire


Craig C. Mello


Richard Axel

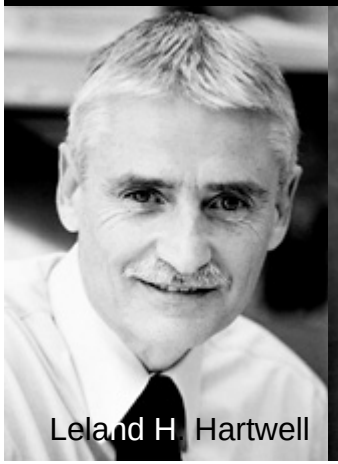

Linda B. Buck

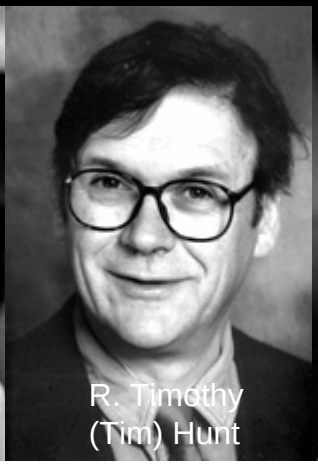

Günter Blobel

If you were BIOLOGIST…

Especially, Molecular Biologist, Geneticist…

Scientist interested in identification of "components" of system…


Leland H. Hartwell


R. Timothy (Tim) Hunt


Sir Paul M. Nurse


Sydney Brenner


John E. Sulston


H. Robert Horvitz

Understand Biological Systems

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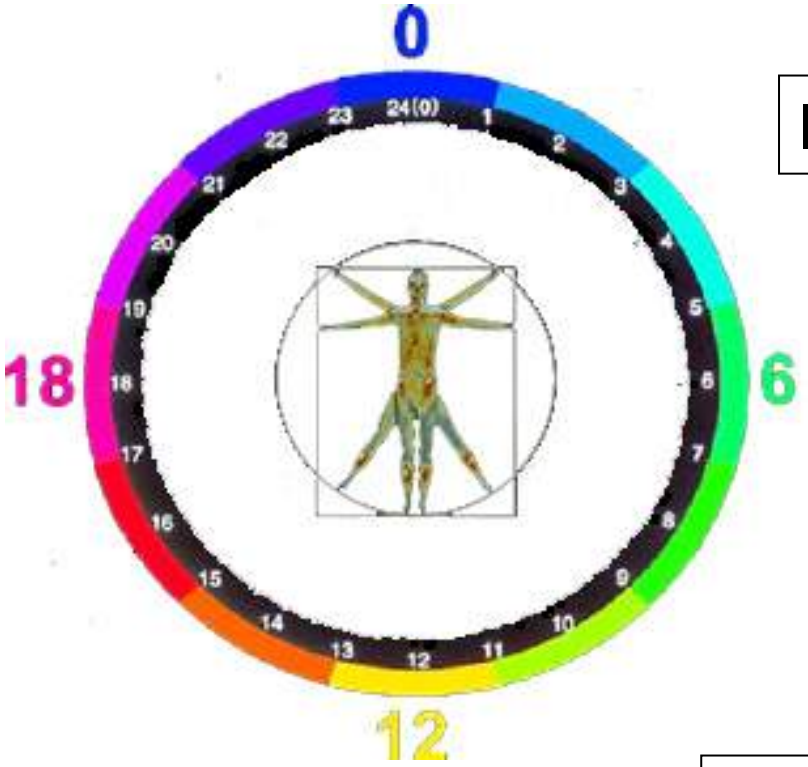
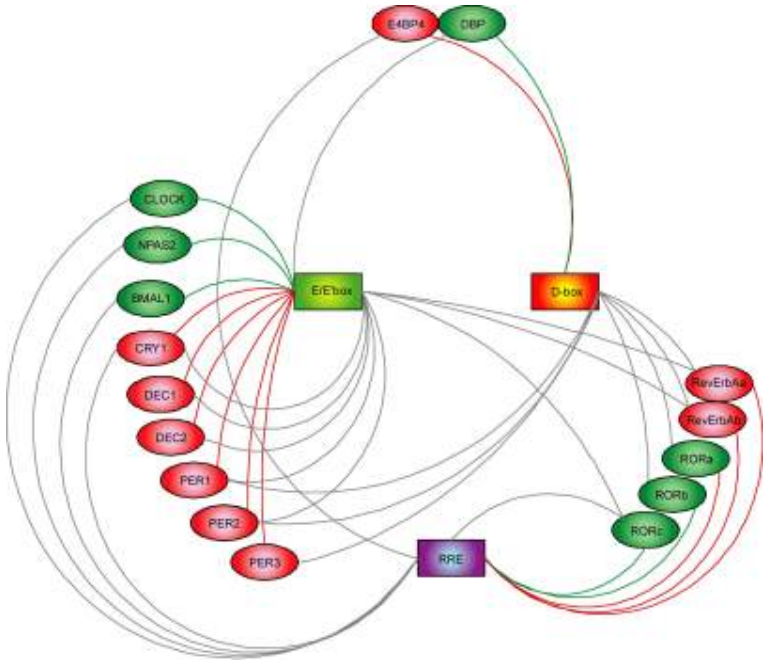
1. Identification

To completely identify system components and their interactions



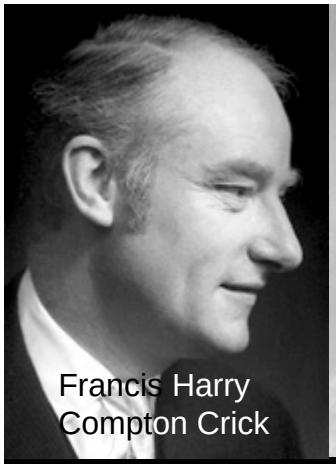
Human Circadian Clock

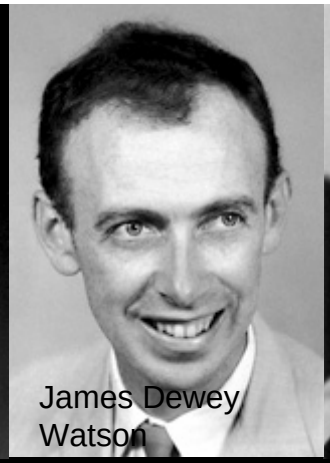
Identify



Mammalian Clock Circuits

Molecular Biologist's View

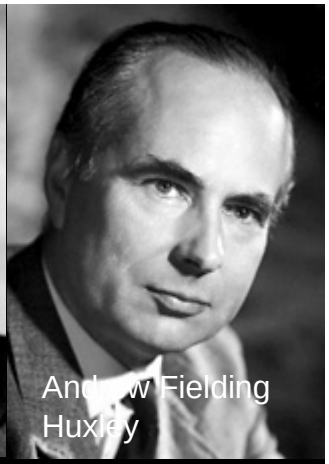

Francis Harry Compton Crick


James Dewey Watson


François Jacob


Jacques Monod


Alan Lloyd Hodgkin


Andrew Fielding Huxley

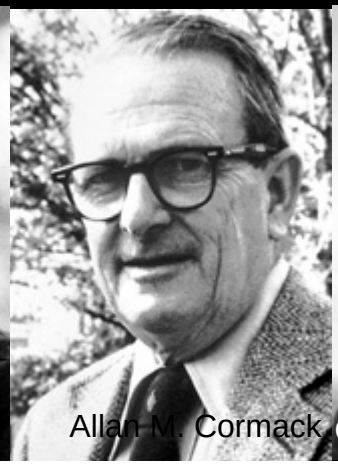
If you were PHYSISIT…

Mathematician, Physiologist,
Systems Biologist, Analytical Chemist…

Scientist interested in design principles of systems…


Erwin Neher


Bert Sakmann


Allan M. Cormack


Godfrey N. Hounsfield


Paul C. Lauterbur


Sir Peter Mansfield

Understand Biological Systems

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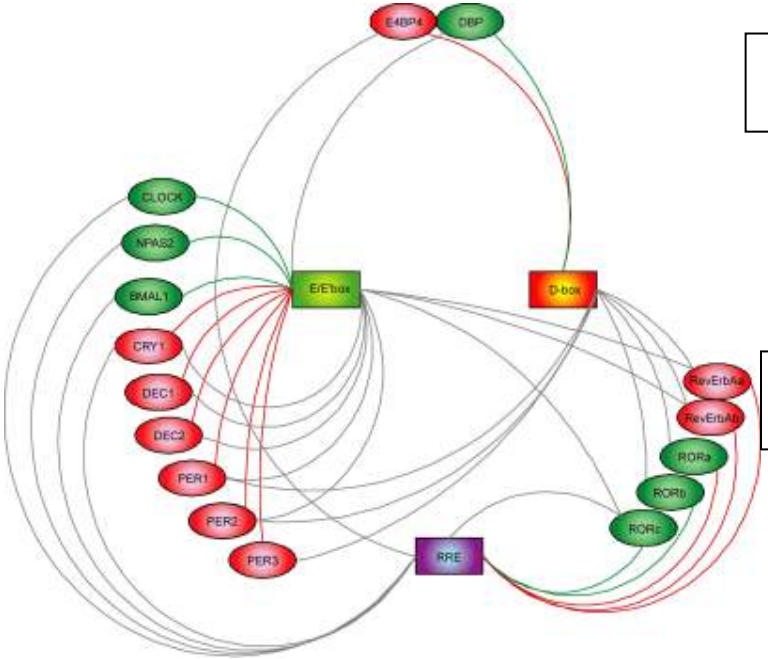
Center for Developmental Biology, RIKEN

2. Analysis

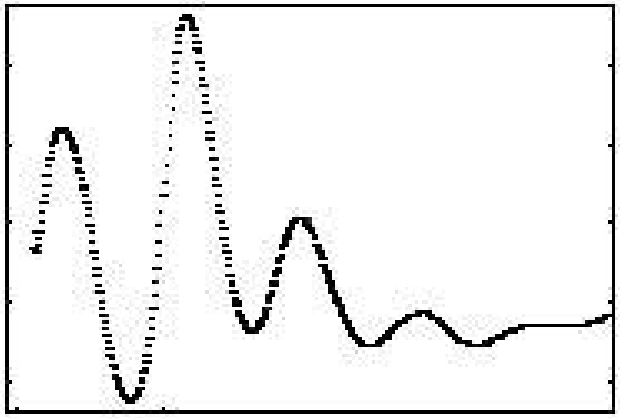
To quantitatively measure properties of components and predict the behaviors of biological systems



Mammalian Clock Circuits

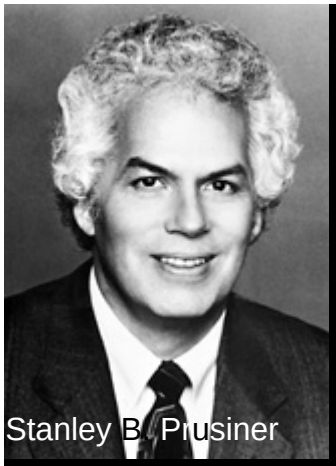
Measure

Predict

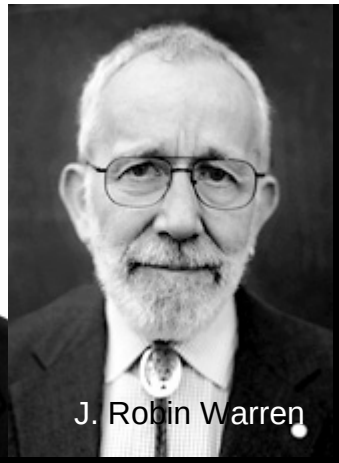


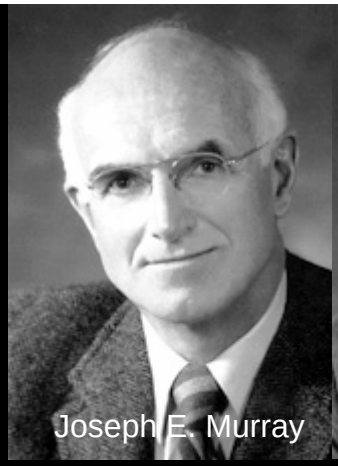
Cellular Circadian Rhythm (Bioluminescence)

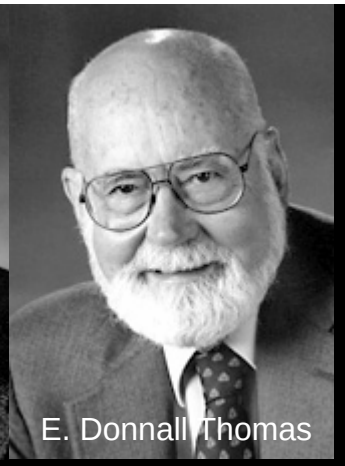
Physicist's View


Stanley B. Prusiner


Barry J. Marshall


J. Robin Warren


Joseph E. Murray


E. Donnall Thomas

If you were MEDICAL DOCTOER…

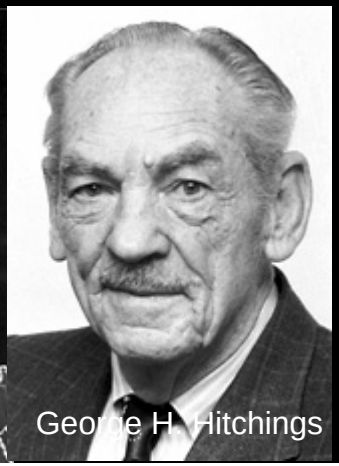
Scientist working on disease, Pharmacologist, Chemical Biologist…

Scientist interested in “controlling” systems…


Ferid Murad


Sir James W. Black


Gertrude B. Elion


George H. Hitchings

Understand Biological Systems

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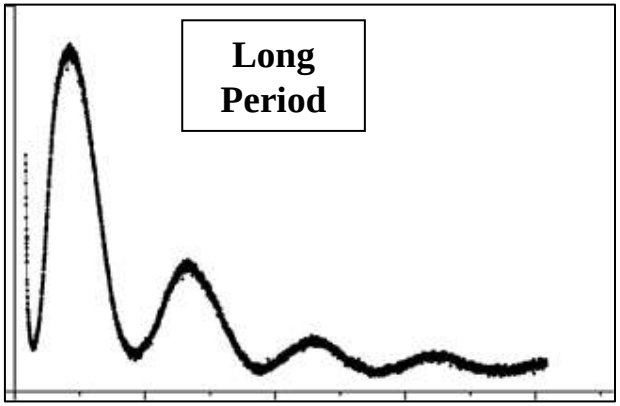
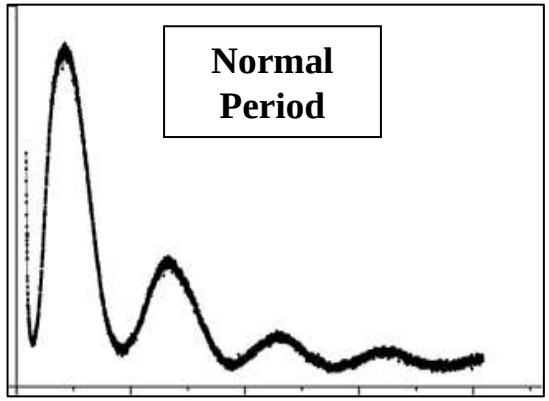
3. Control

To quantitatively perturb properties of components and direct the behaviors of biological systems

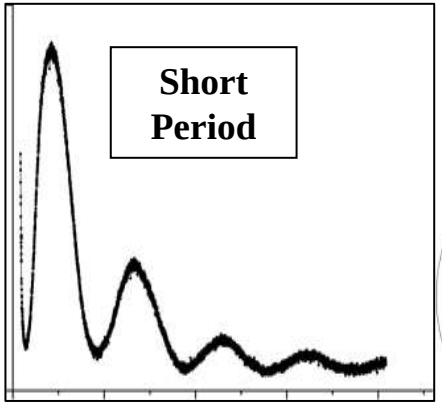


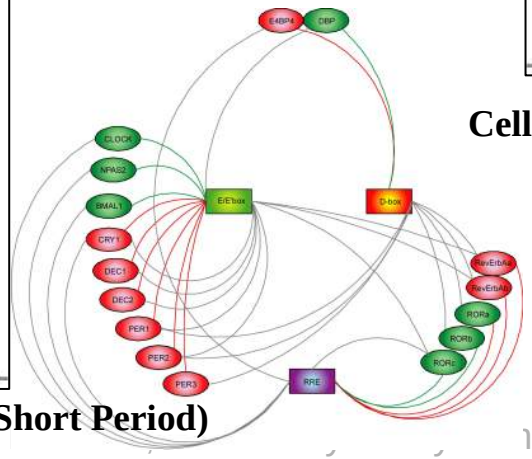
Perturb

Direct



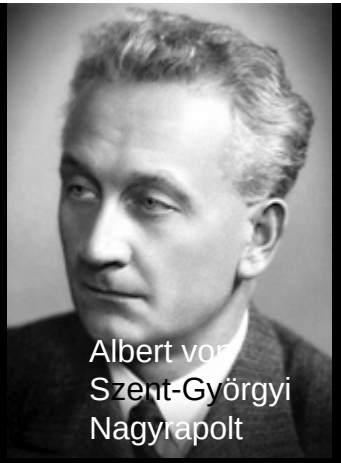
Cellular Circadian Rhythm (Normal Period)





Cellular Circadian Rhythm (Long & Short Period)

Medical Doctor's View



If you were CHEMIST…

Engineer, Computer Scientist, Synthetic Biologist…

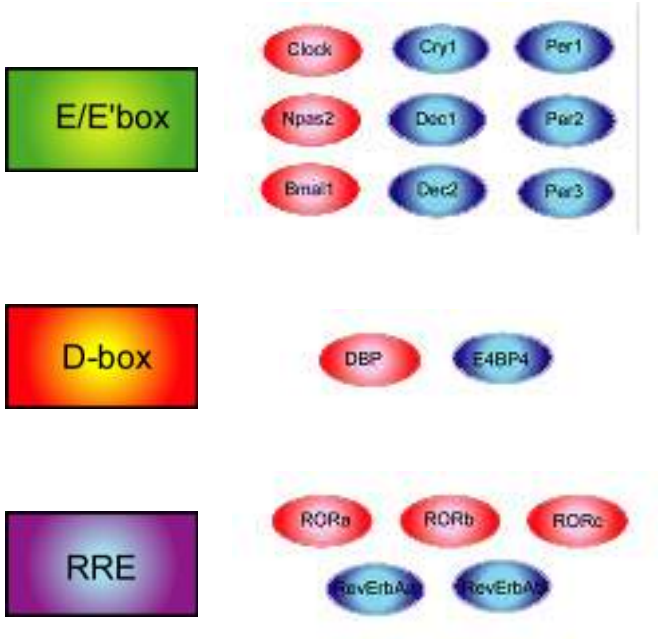
Scientist interested in “designing” systems…

Understand Biological Systems

"Understanding of Living Systems"
Laboratory for Systems Biology,
Center for Developmental Biology, RIKEN

4. Design

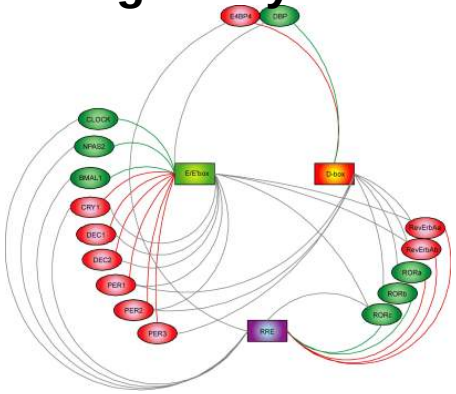
To design and implement artificial circuits with identified structure and observed dynamics of biological systems



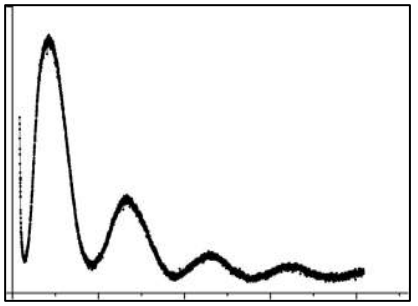
Artificial Clock Components

Design

Implement



Artificial Clock Circuit



Cellular Circadian Rhythm with Artificial Clock Circuit

Chemist's View

Understanding of Biological Systems

Analysis of "life as it is"

1. Identification

To completely identify system components

2

Systems Biology

To quantitatively measure properties of components and predict the behaviors of biological systems

3. Control

To

Synthetic Biology

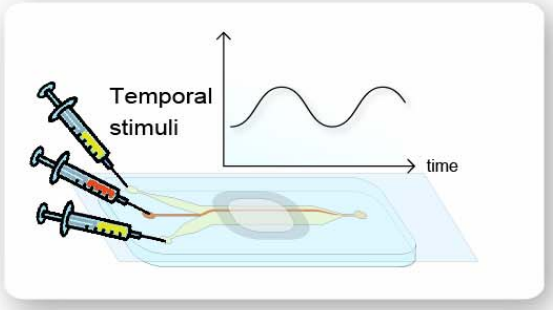
4. Design

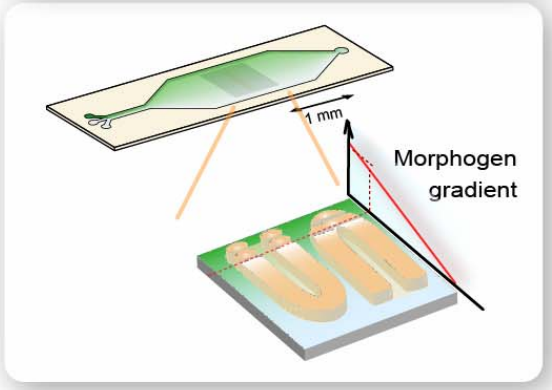
To design and implement artificial circuits with identified structure and observed dynamics of biological systems

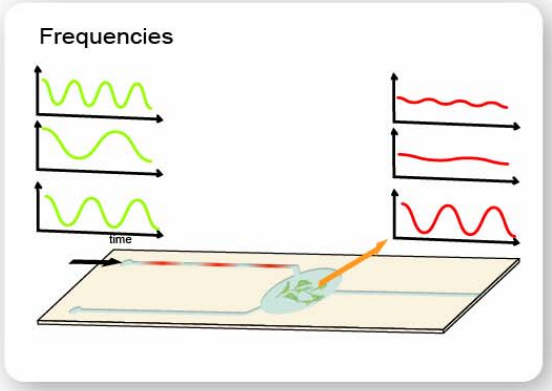
Synthesis of "life as it could be"

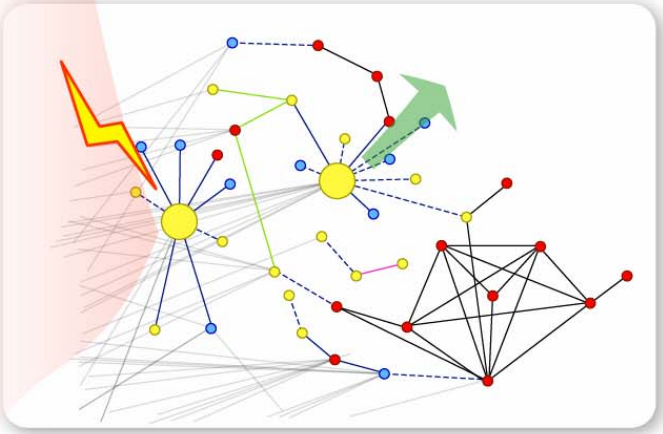
Escher , M.C. (1948) "Drawing hands"

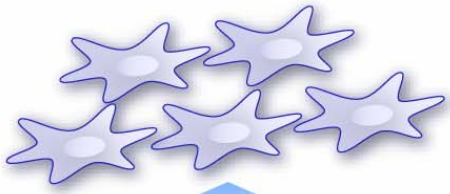
Quantitative Measurement Perturbation for Design Principles

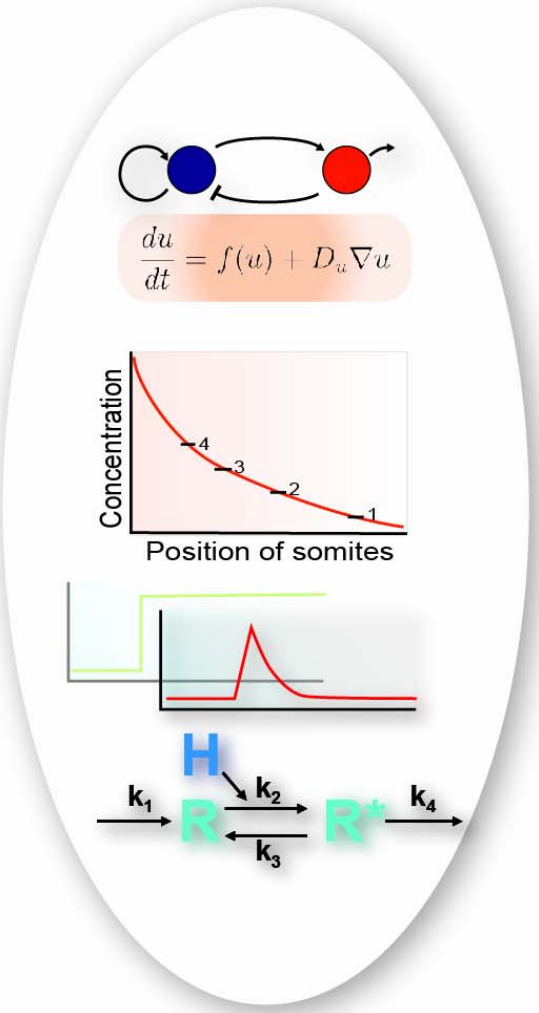










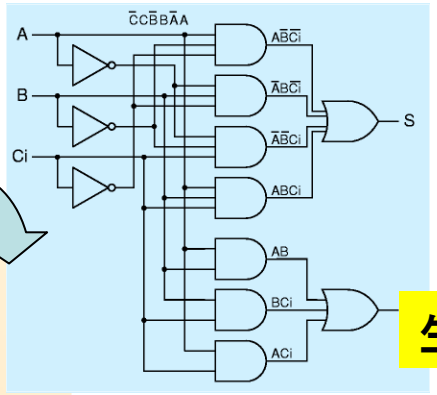


細胞運命を制御するシグナル伝達ネットワークのモデル化とシミュレーション

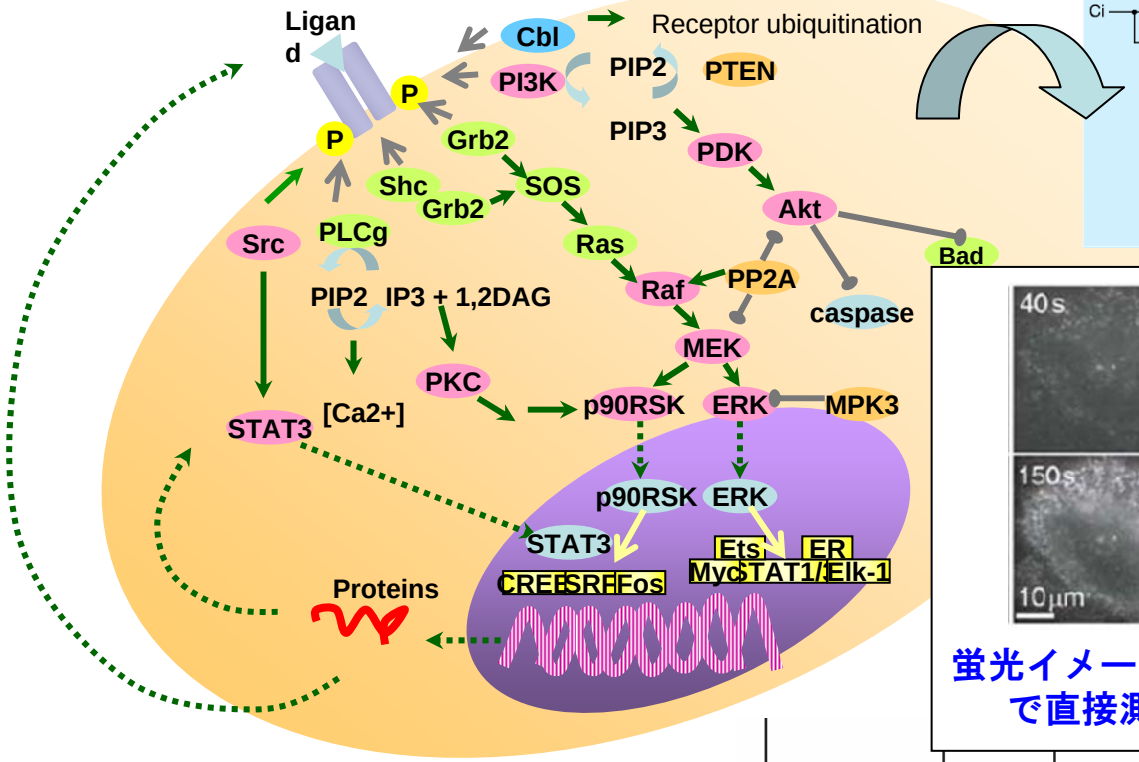
（理研/畠山・佐甲・黒崎ら、鳥取大/木村、九産大/仲）

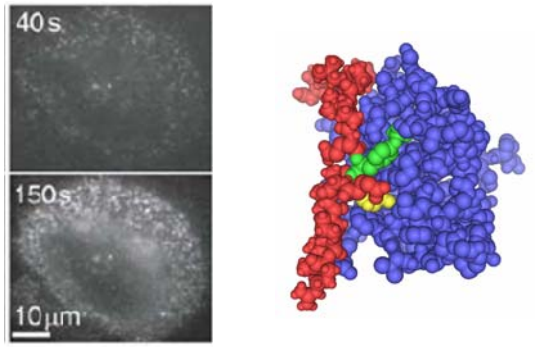
数理モデル

$$S = A + B$$



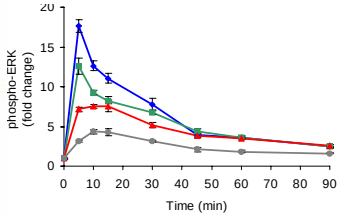
生物パラメータ



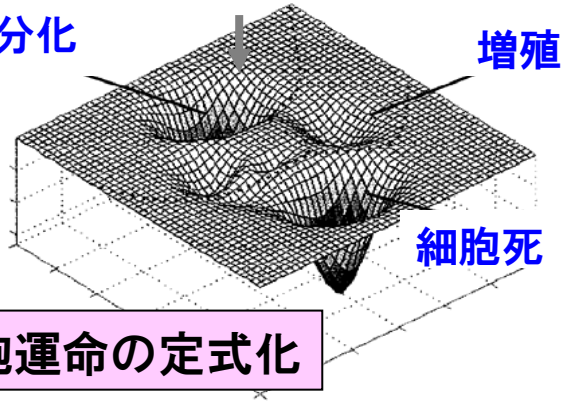


蛍光イメージングで直接測定

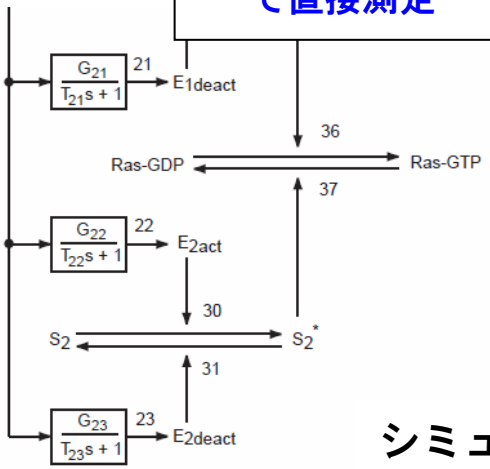
立体構造を元にした計算予測

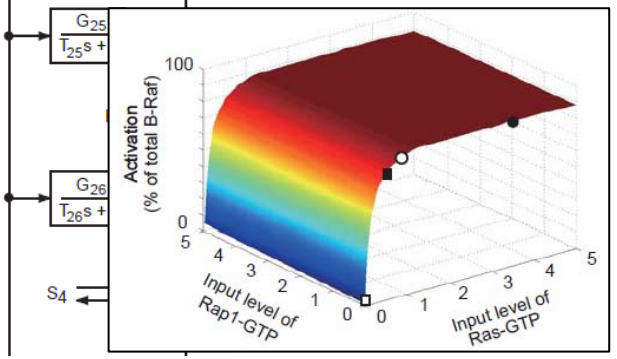


時系列定量データからの計算予測



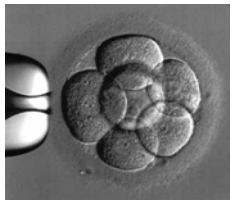
細胞運命の定式化





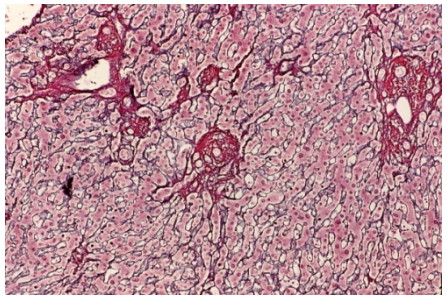
シミュレーションによる分子活性化予測

多細胞システムの形と機能の決定機構(理研/大浪)

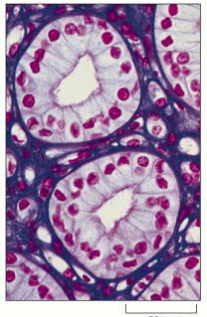


ヒト受精卵

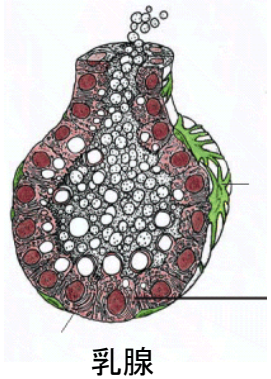
形と機能の決定



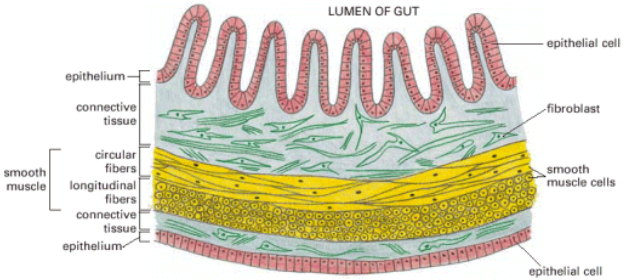
肝臓



腎臓



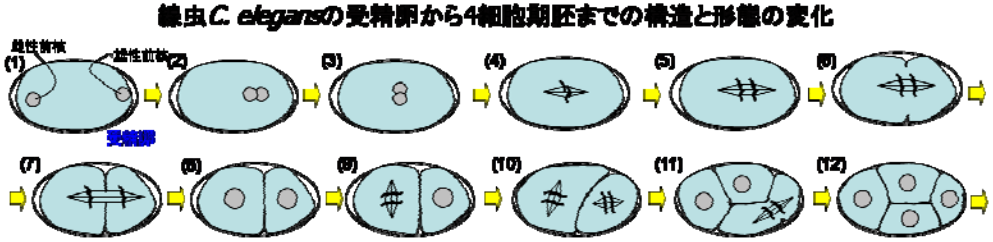
乳腺

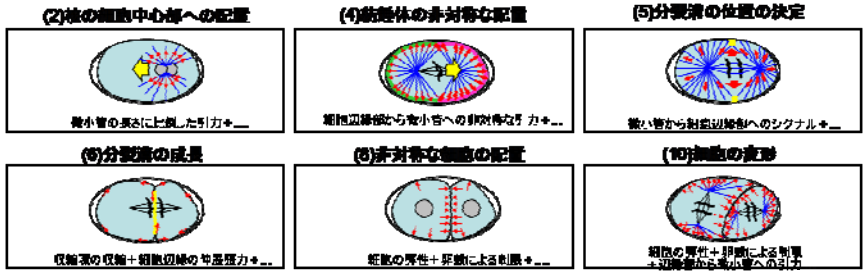


小腸

脳

正常な機能のためには正しい形が必要



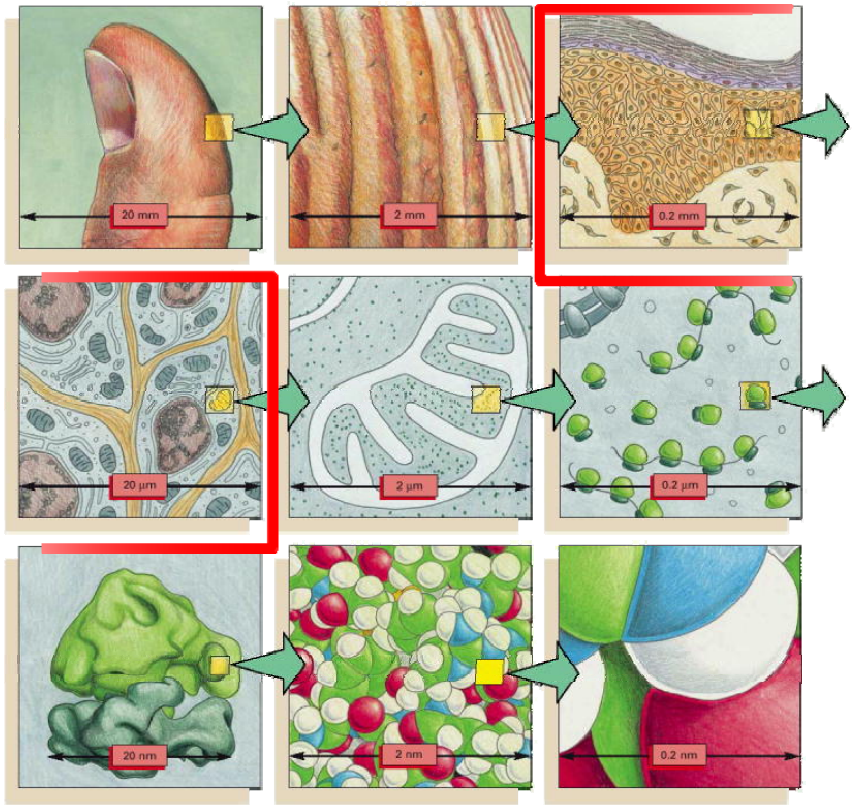


生物物理学モデル:　細胞間に働く力、細胞の変形

生化学モデル:　遺伝子発現制御ネットワーク、細胞間シグナル伝達

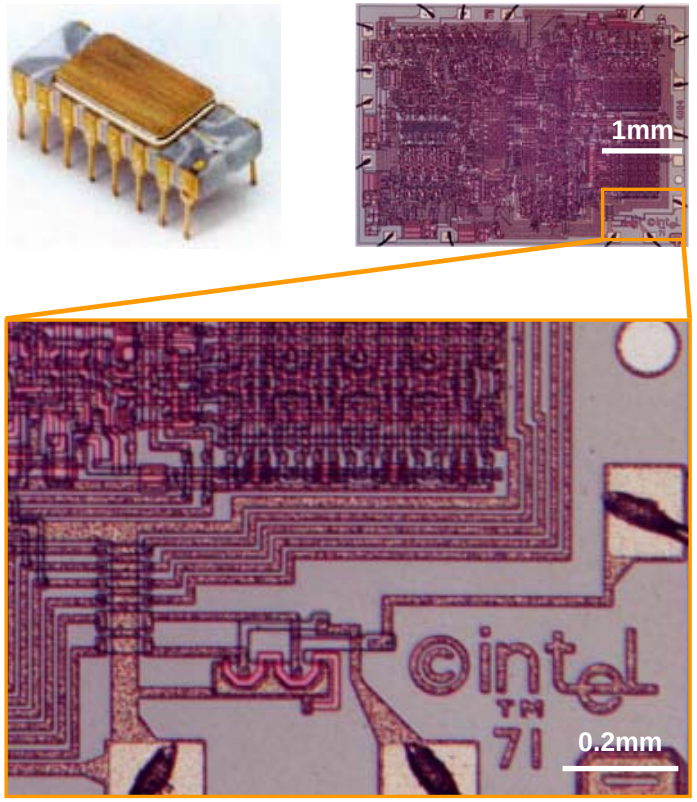
Technology for fabrication at cellular/tissue resolution

Scale between living cells and atoms



Molecular Biology of the Cell

World's first commercial microprocessor:
2300 transistors fabricated at 10μm process rule

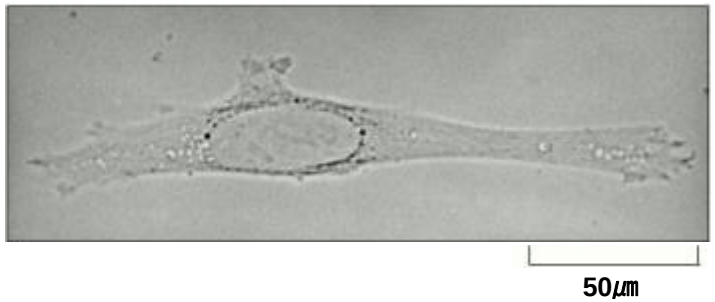


Intel Museum (*http://www.intel.com/museum/index.htm*)

Semiconductor technology for cellular resolution

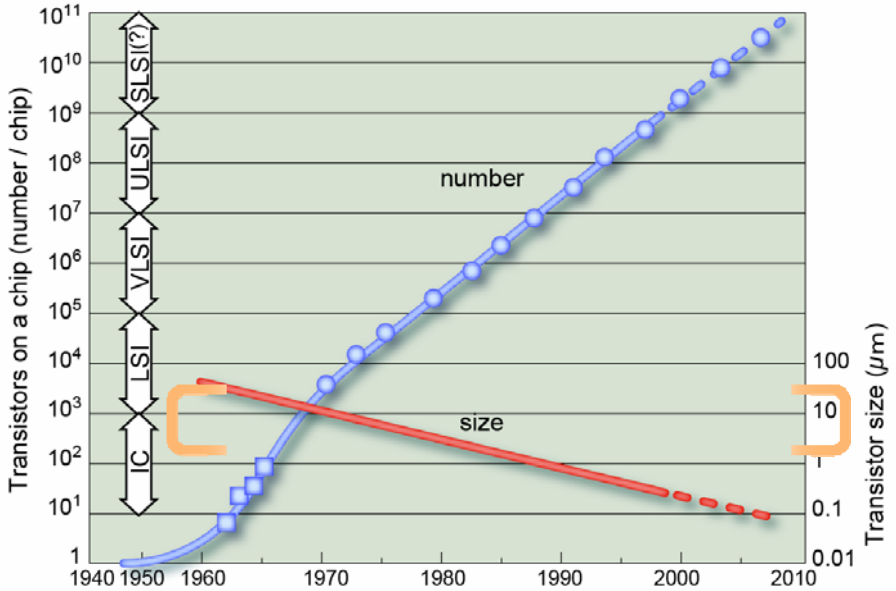
Cell size ~ Transistor size

Fibroblast cell in culture



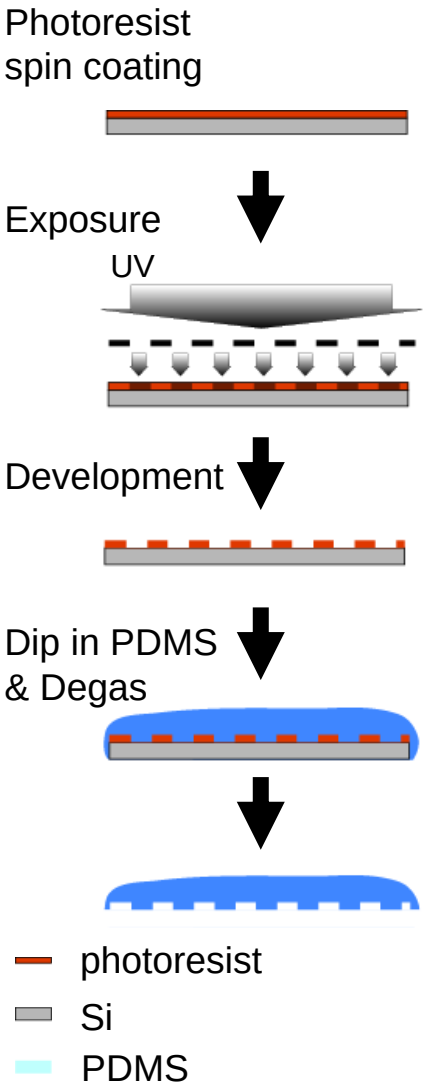
Molecular Biology of the Cell

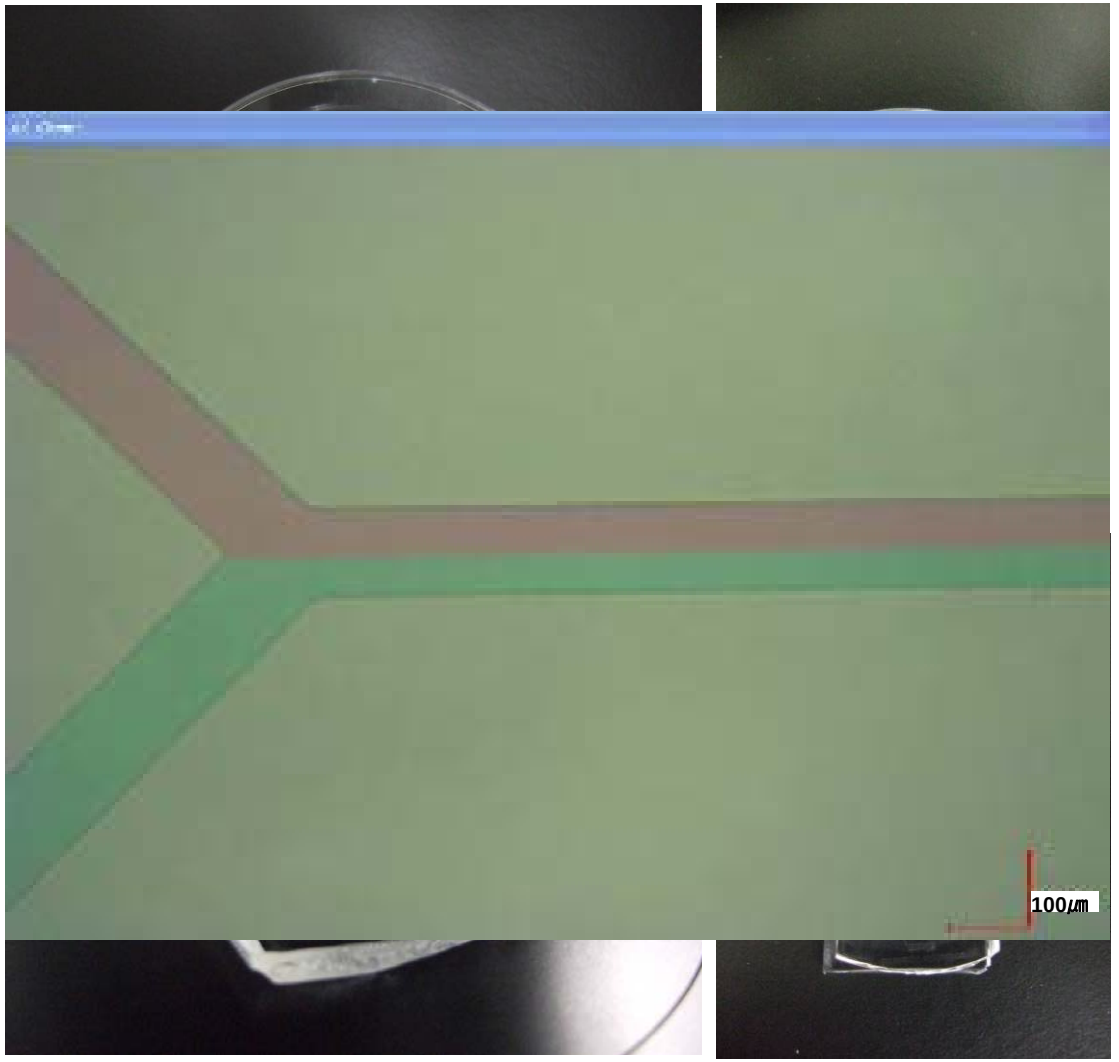
Density of transistors on a chip



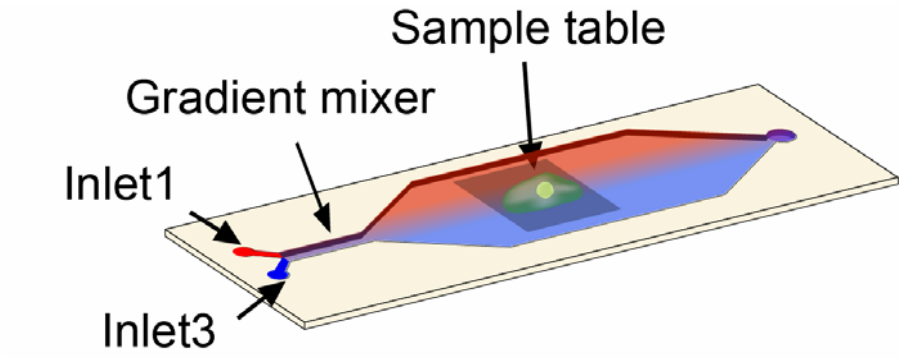
Modified from “微細加工の基礎 麻蒔立男 日刊工業新聞社”

Photolithography for micro-structure



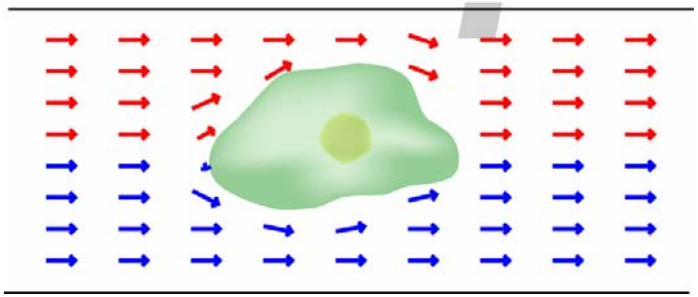


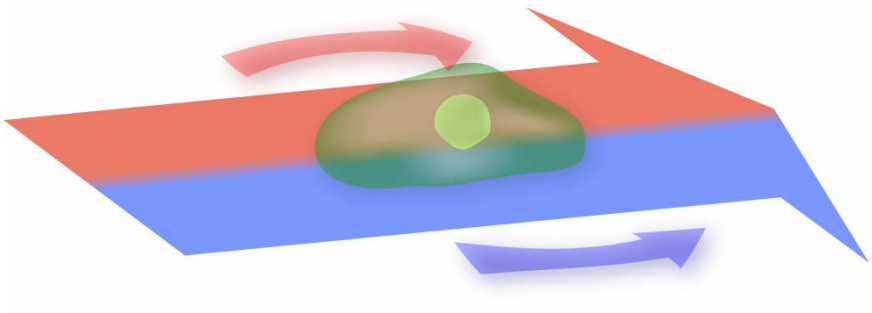
Bio-MEMS with fluidics simulation



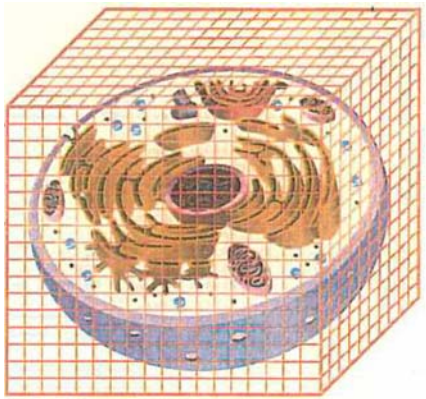
Detailed flow is unclear because of

- Complex cell shape
- Physical properties
- Micro-scale

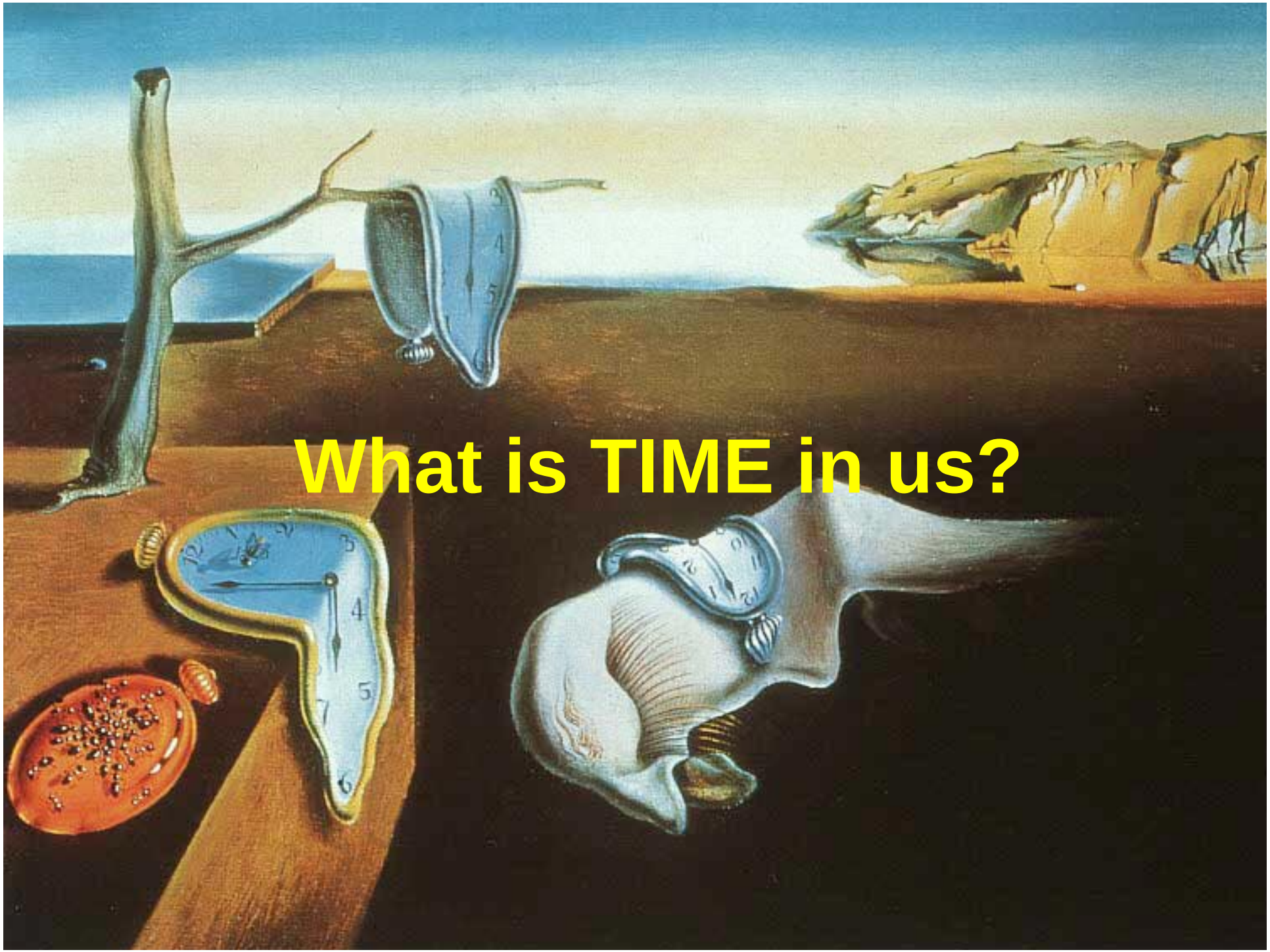


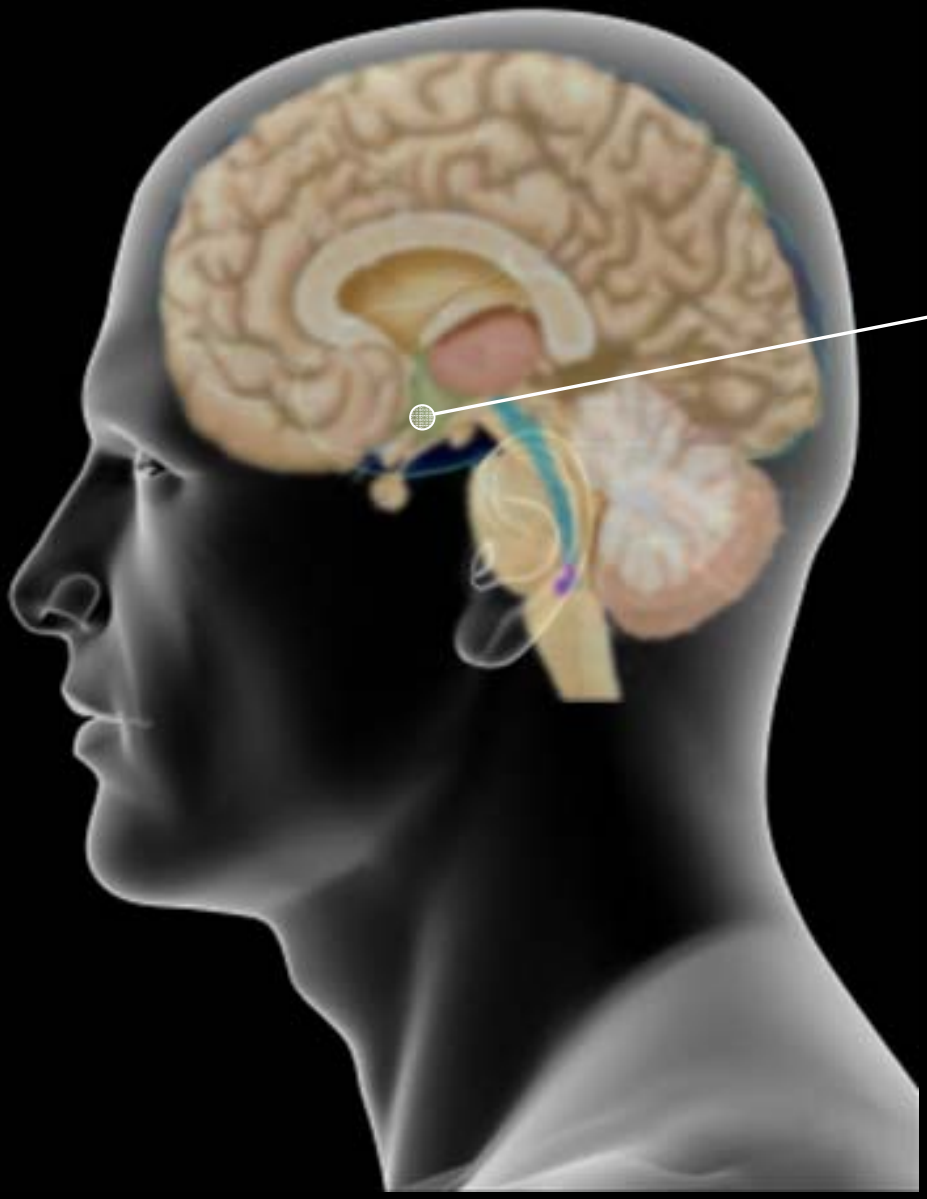


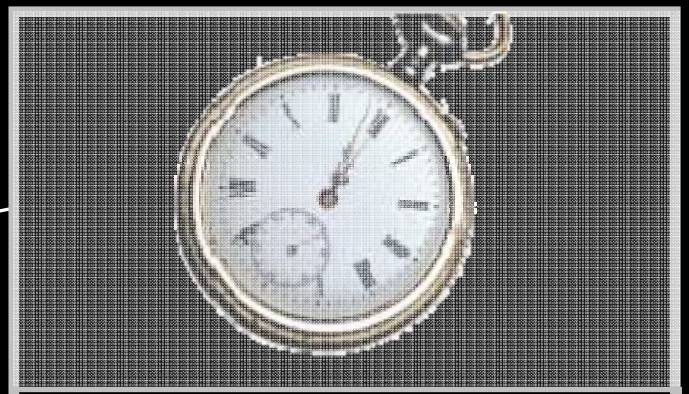
VCAD project (RIKEN)



- Cell shape
- Internal structure
- Physical property

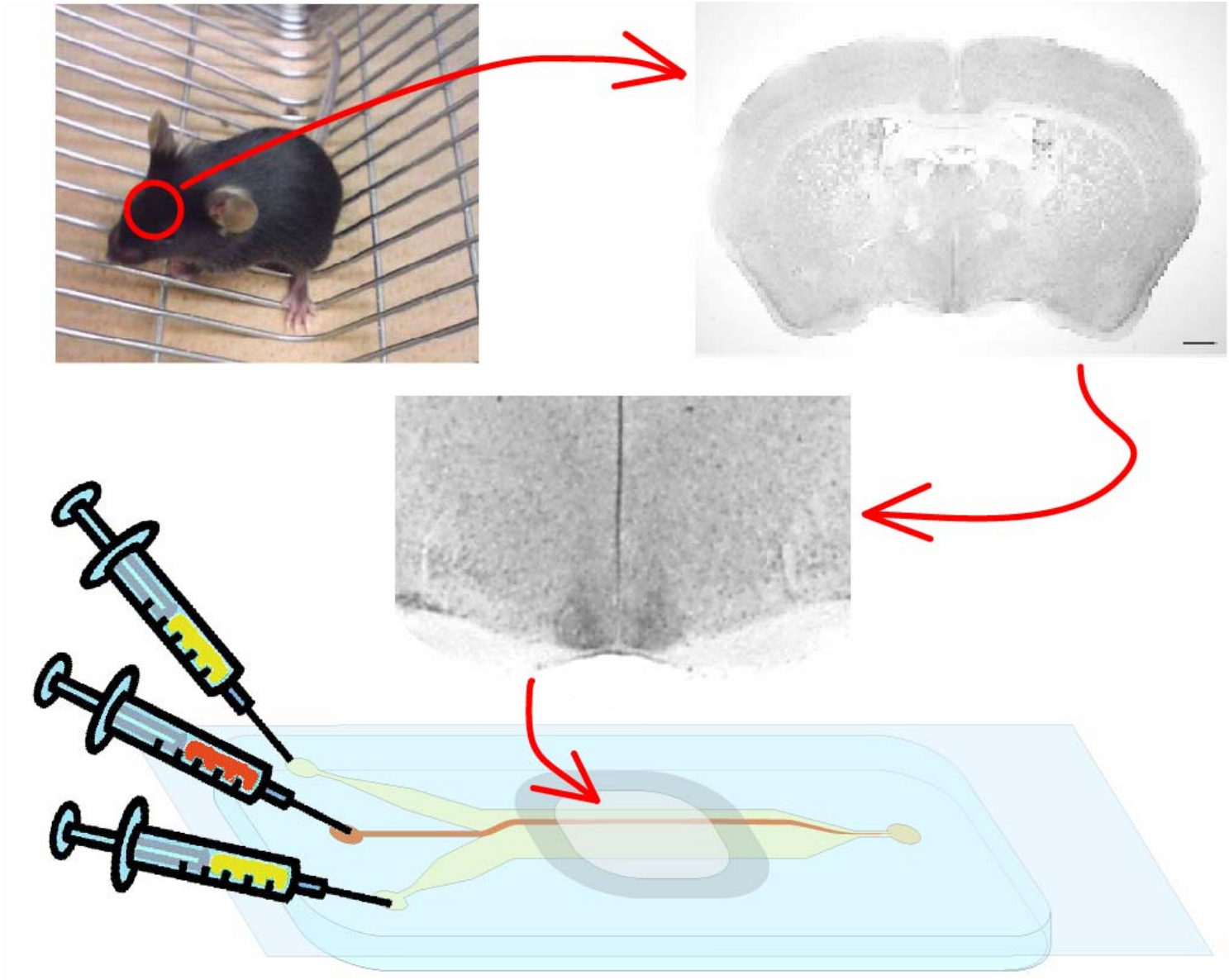

What is TIME in us?



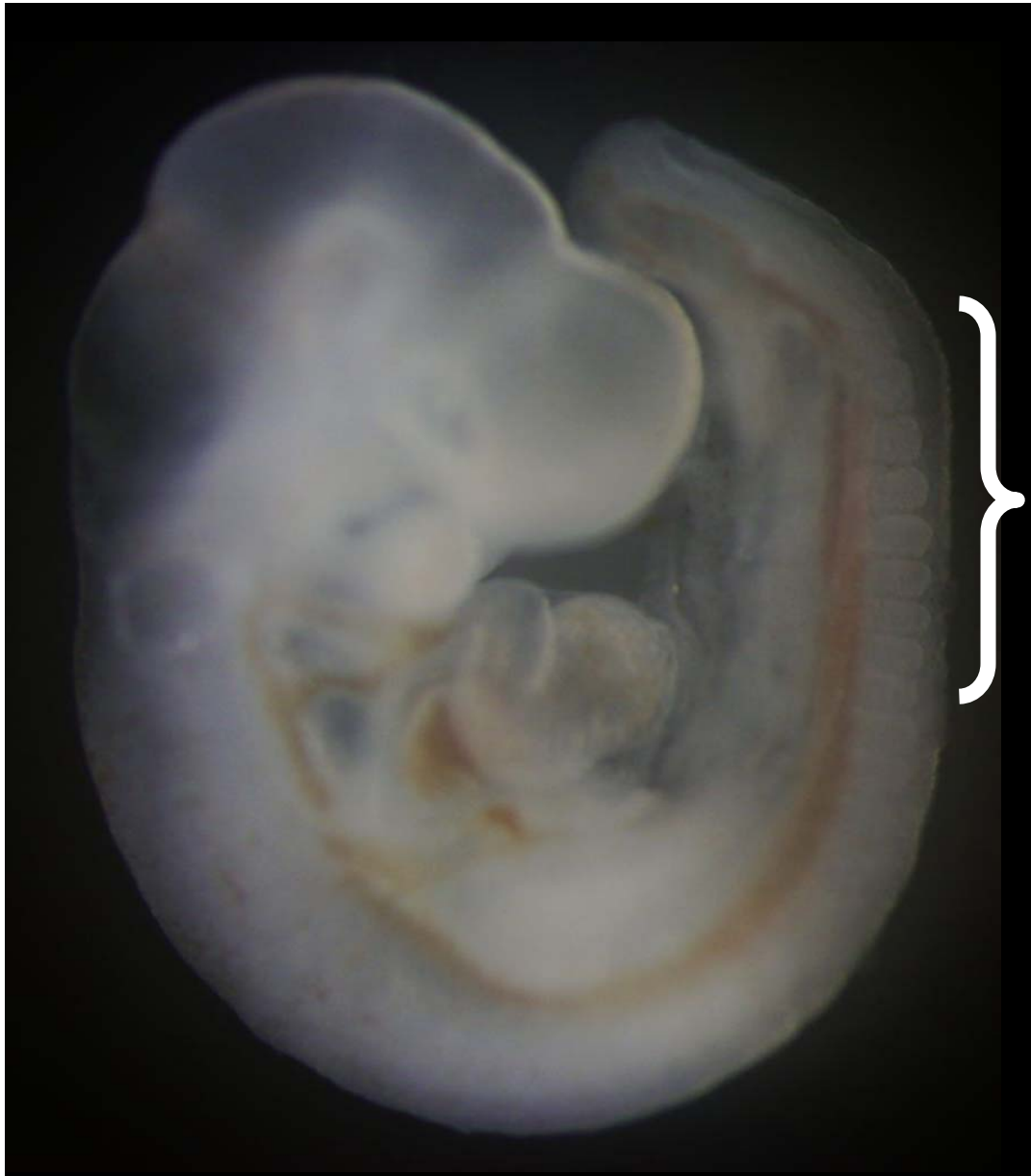


Center of human clock : SCN
Suprachiasmatic nucleus

Bio-MEMS for SCN

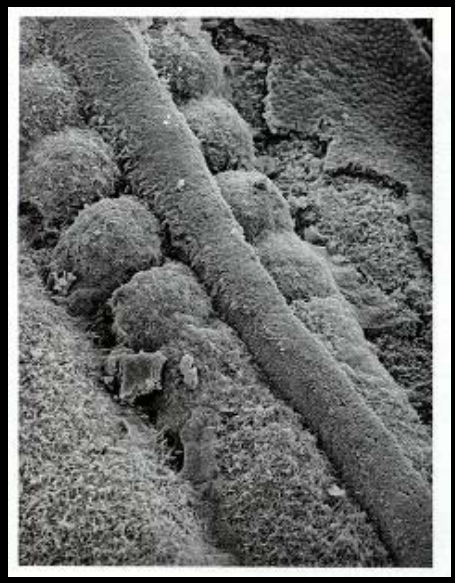



What is SPACE in us?



E9.5 Mouse embryo

Photograph by Kaori Tsujino
at Laboratory for Systems Biology

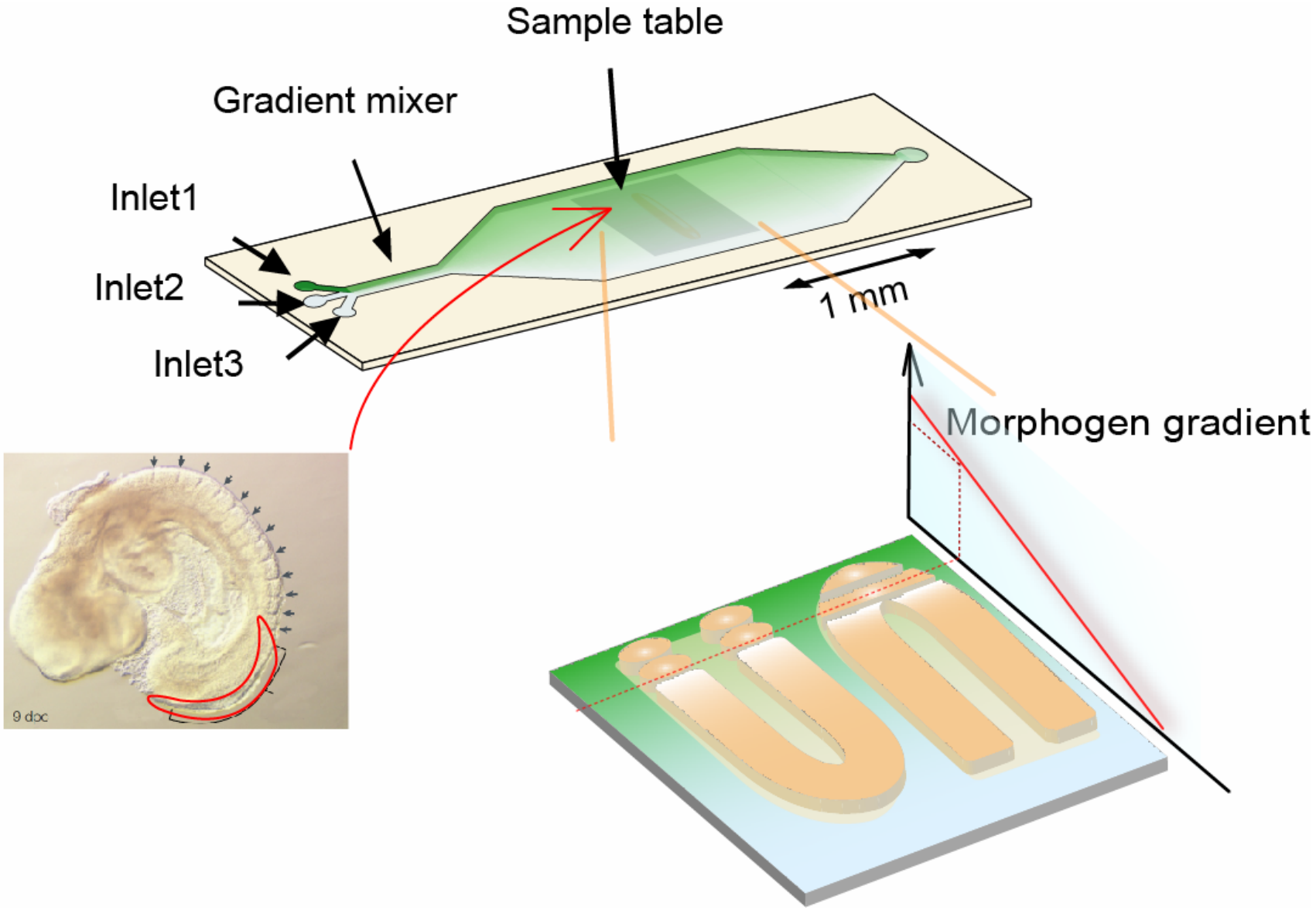


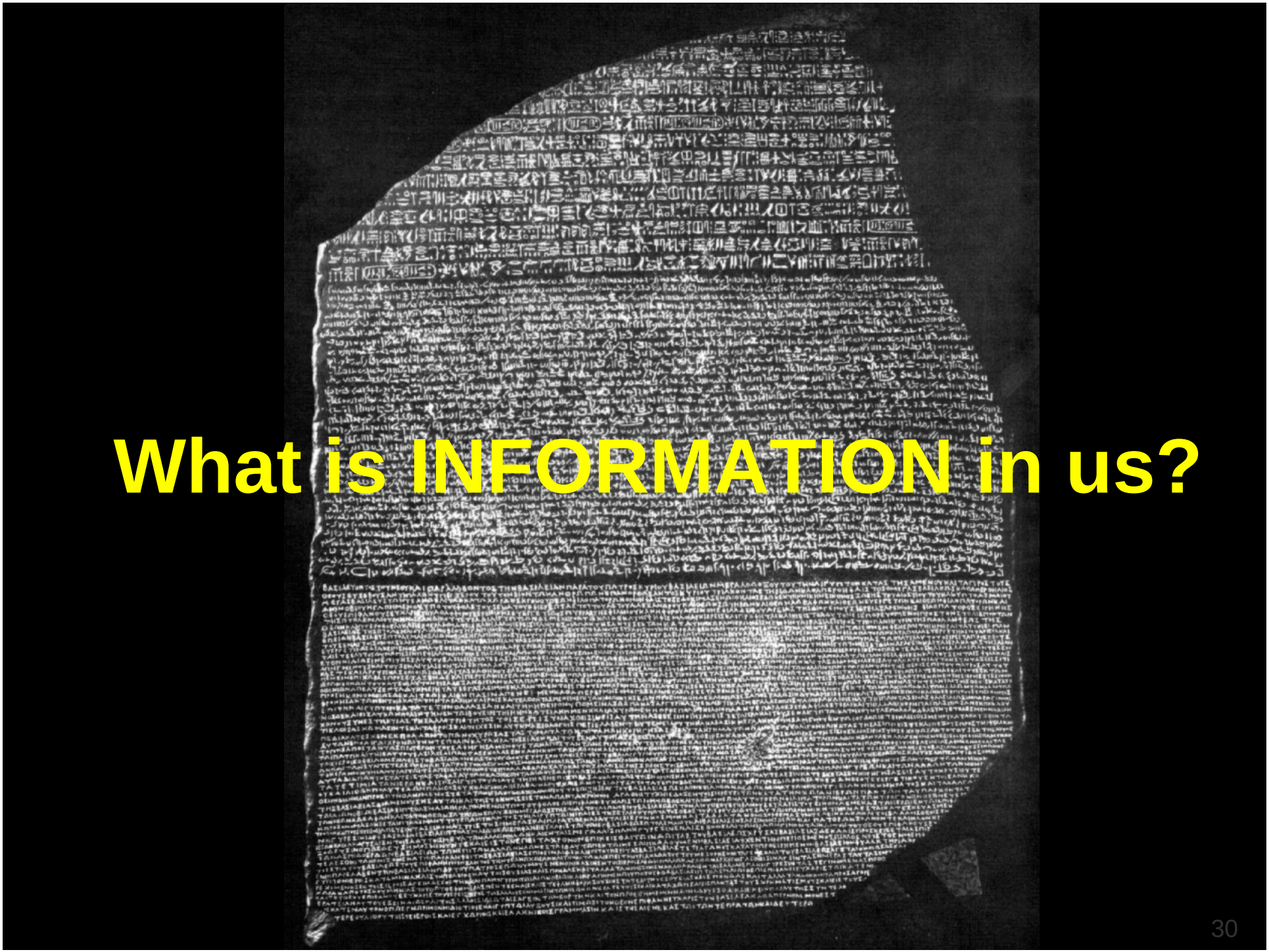
Neural tube and somites. (Scanning electron micrograph)

Developmental biology, Scot F. Gilbert -- 6th ed.
SINAUER ASSOCIATES, INC., Publishers

Masamizu et al., *PNAS*, 2006

Bio-MEMS for Somite

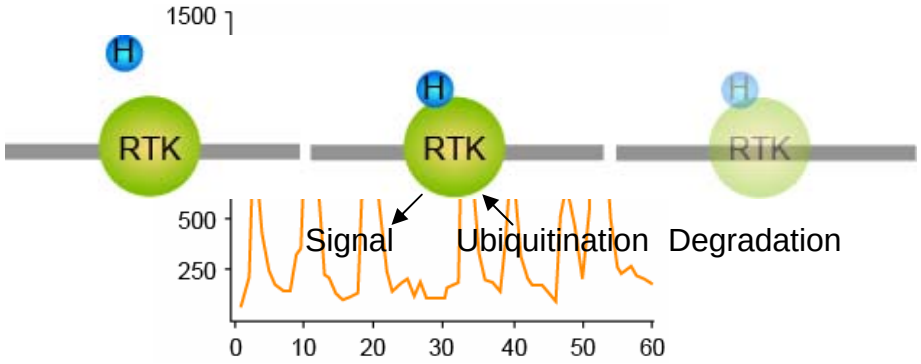




What is INFORMATION in us?

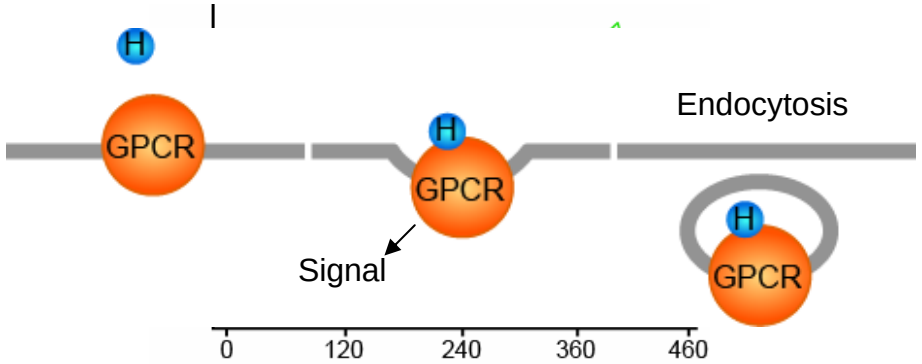
Pulsatile Secretion of Hormone

Insulin



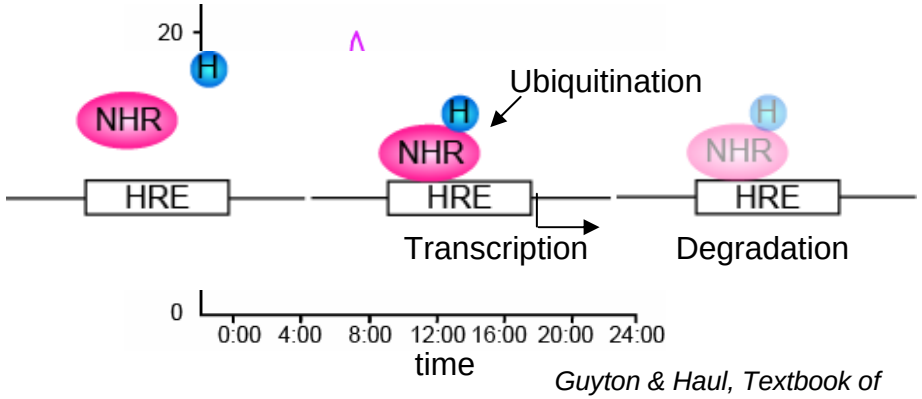
Porksen, Diabetologia, 2002

Luteinizing hormone (LH)

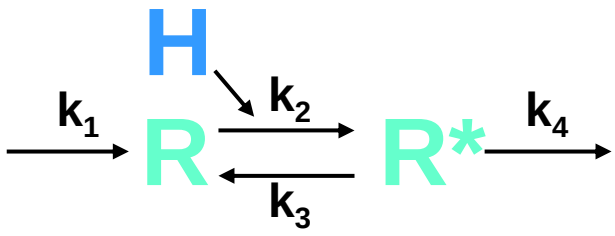


Guyton & Haul, Textbook of Medical Physiology, 2005

Cortisol



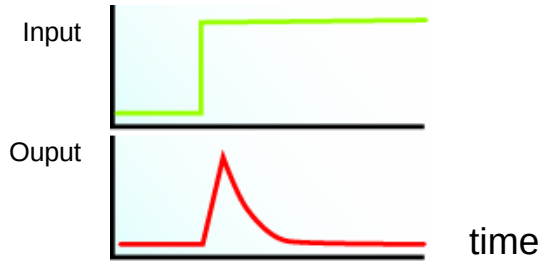
Guyton & Haul, Textbook of Medical Physiology, 2005

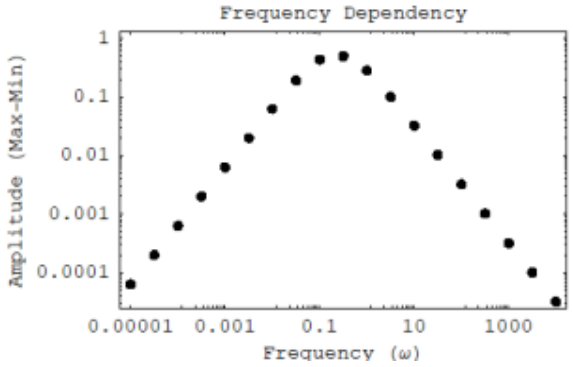


Activity-dependent Inactivation of Hormone Receptors

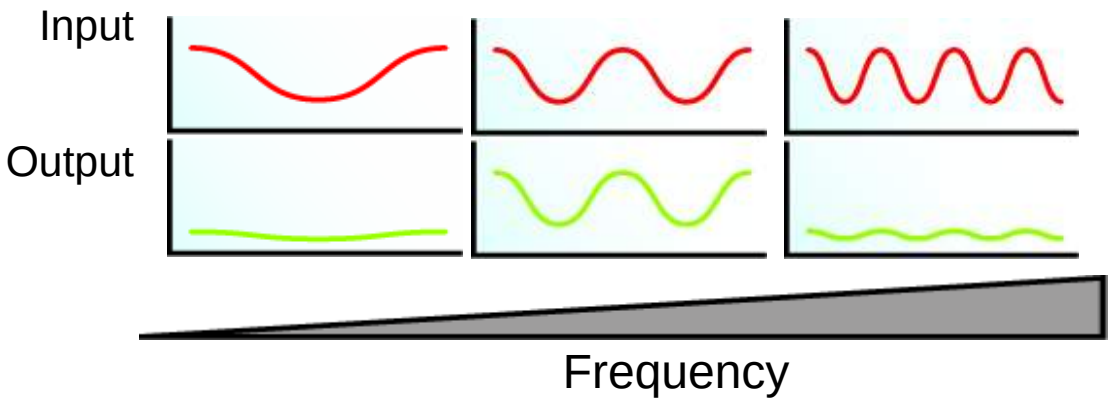
Hormone is secreted pulsatily

Expected Response of Hormone Receptor





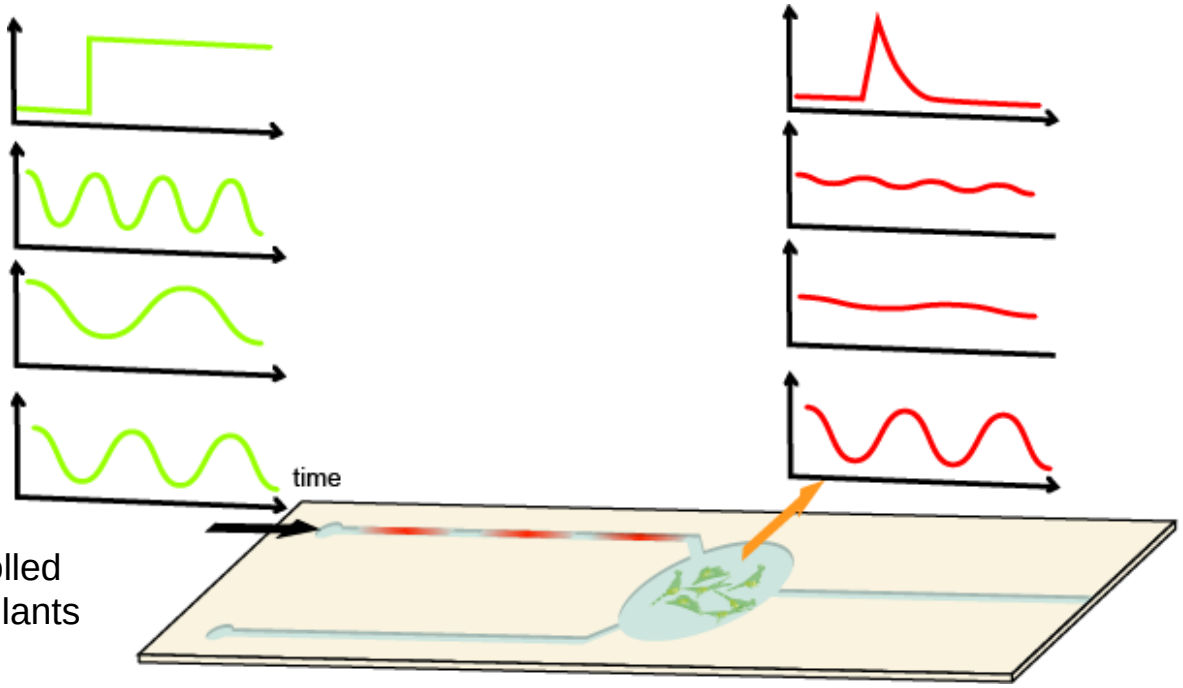
Ueda et al unpublished results



Hormone Receptors decode the information encoded in the frequency of signal (i.e. change of signals not strength of the signal)

Quantitative Perturbation by BIO-MEMS

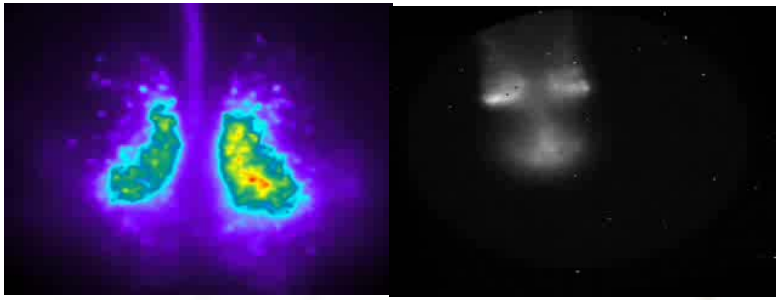
Computer-controlled
injection of stimulants

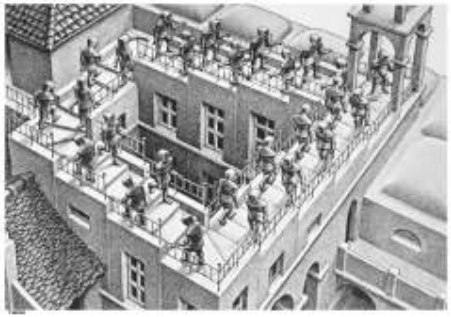


System-level Analysis of Cellular Response to the Various Stimulation

Triangle of Technologies

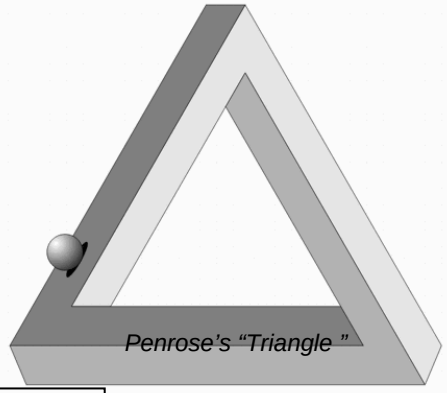
Biological Experiment





Escher , M.C. (1960)
"Ascending & Descending "

Wet

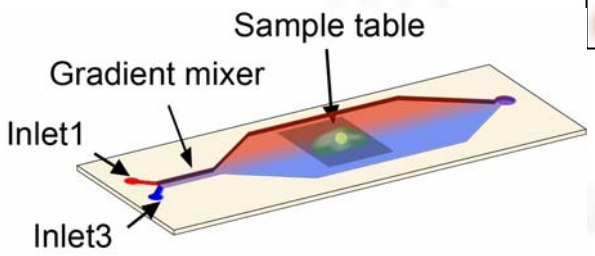


Penrose's "Triangle "

Hard

Soft

Bio-MEMS



Fluidics Simulation

Understanding of Biological Systems

Analysis of "life as it is"

1. Identification

To completely identify system components

2

Systems Biology

To quantitatively measure properties of components and predict the behaviors of biological systems

3. Control

To

Synthetic Biology

4. Design

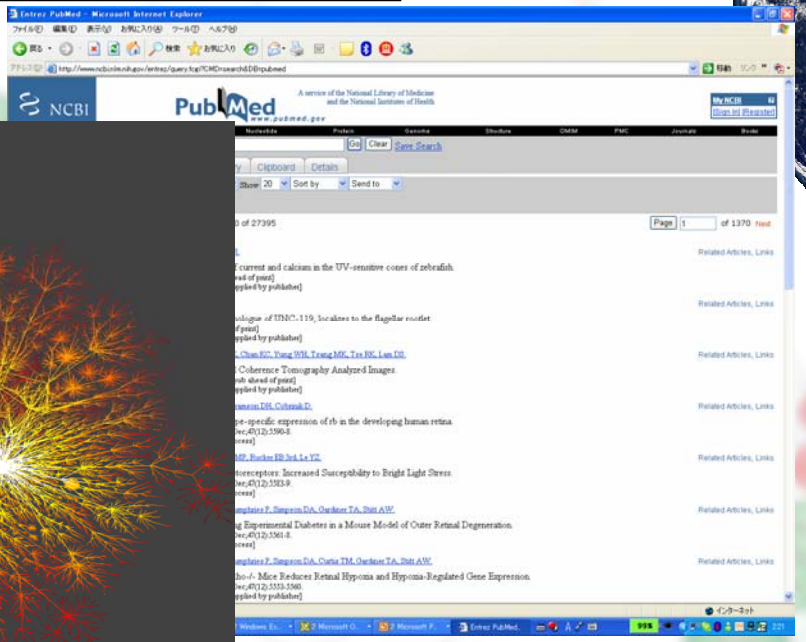
To design and implement artificial circuits with identified structure and observed dynamics of biological systems

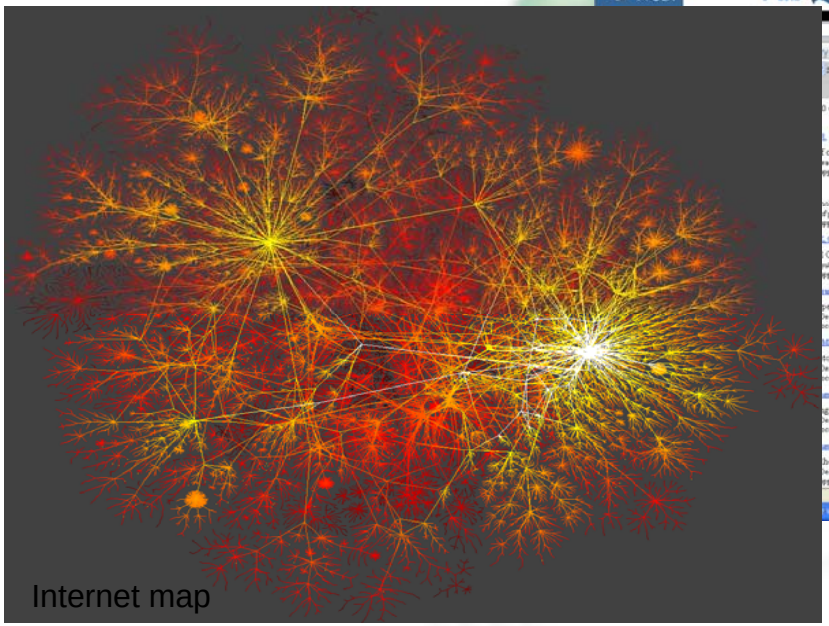
Synthesis of "life as it could be"

Escher , M.C. (1948) "Drawing hands"

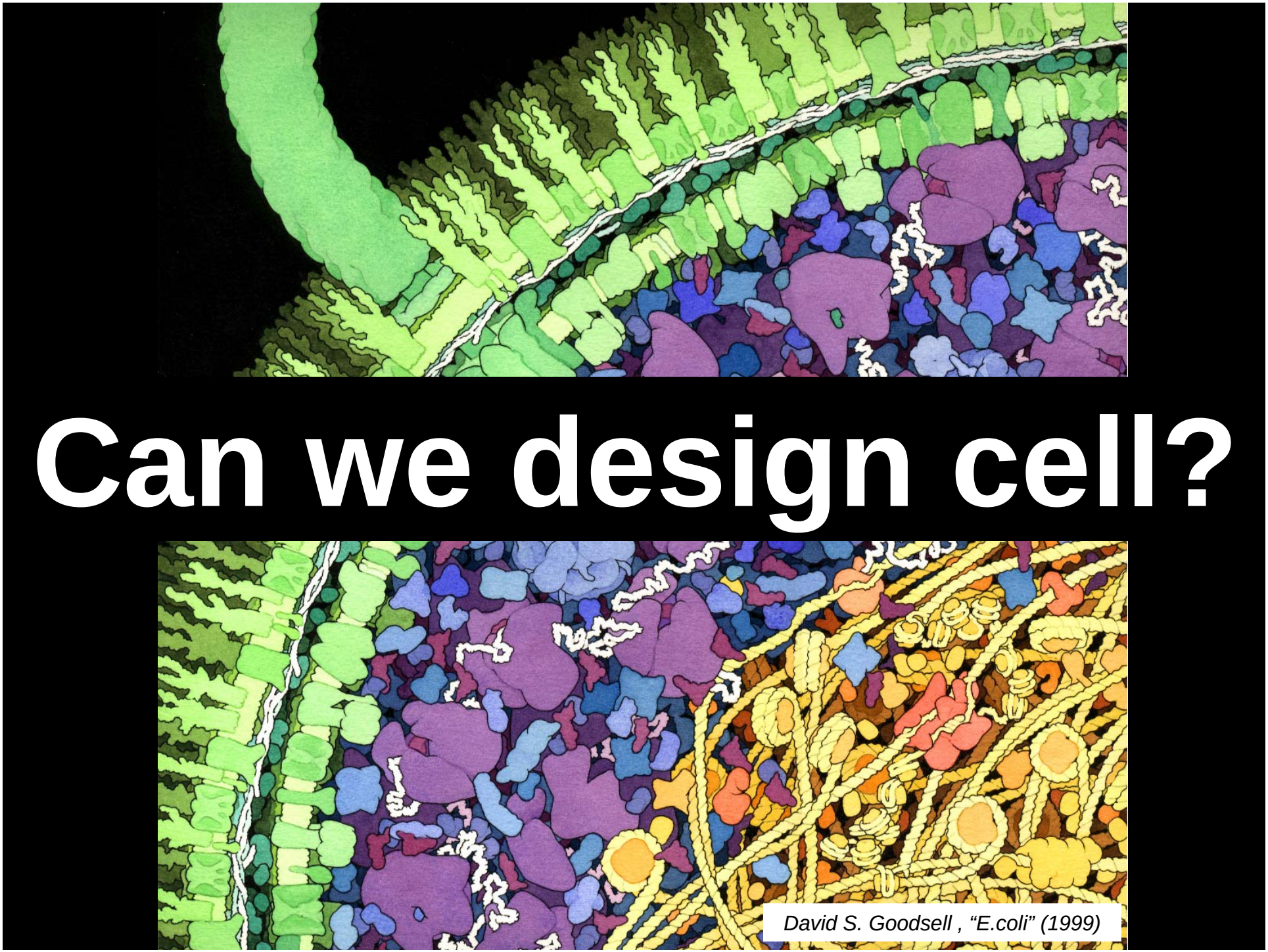
世界規模での遺伝子情報の蓄積と共有

世界中の生命科学研究によって得られた
分子生物学的知識（遺伝子情報）は
データベースに蓄積され、
インターネットを通じて共有されている。




Internet map

生命⇒機能⇒物質⇒情報



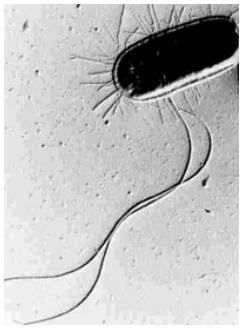
Can we design cell?

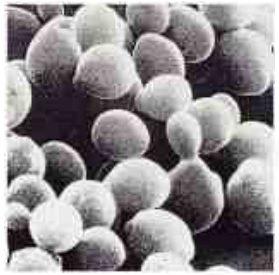
David S. Goodsell , “E.coli” (1999)

遺伝子情報:ゲノム配列情報

E.coli K12 (1997)

E.coli O157:H7 (2001)





S. cerevisiae (1997)

D. melanogaster (2000)

H. sapiens (2001) (2003)

Oryza sativa L. ssp. Indica (2002)

Oryza sativa ssp. japonica (2002)

S. pombe (2002)

C. elegans (1998)

R. norvegicus (2003)

M. musculus (2002)

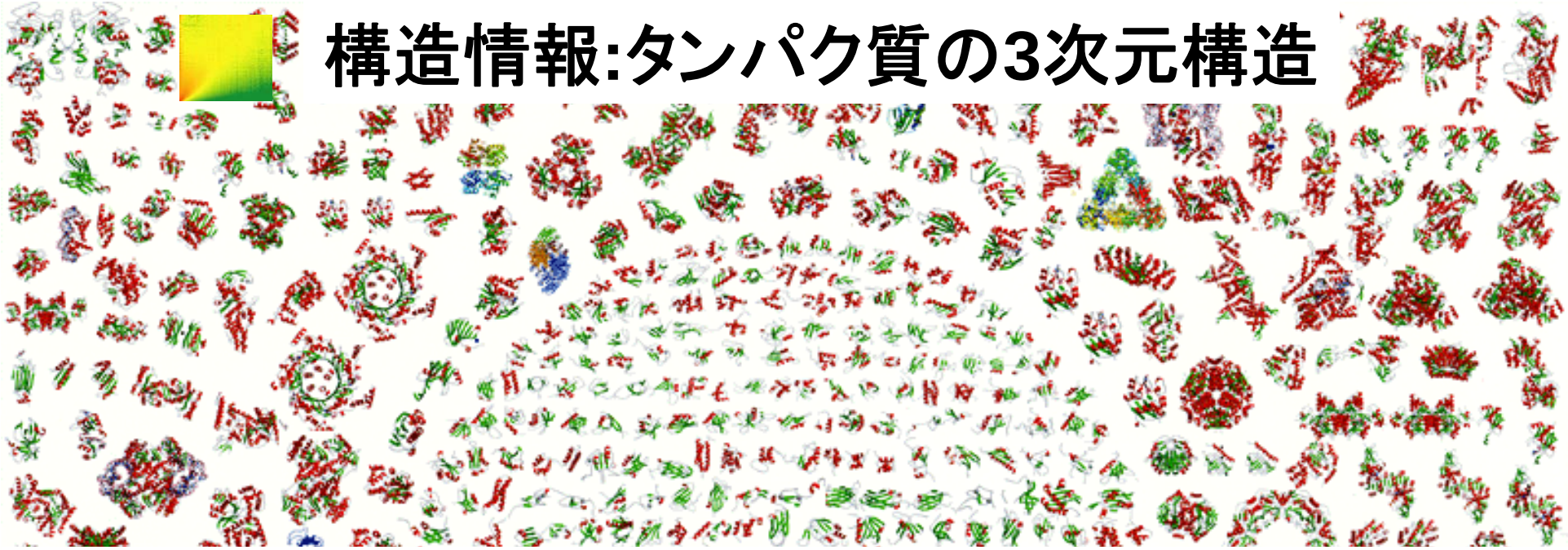
***Nature** websites*

A. thaliana (2000)

2006.11.25
Published **460**
Ongoing 998(Bacteria)
Ongoing 631 (Eukaryote)
Ongoing 56 (Archaea)
Total **2,208**

情報⇒物質⇒機能⇒生命

構造情報:タンパク質の3次元構造



Molecular Structures have been resolved

47,805 structures in Protein Data Bank in 2007

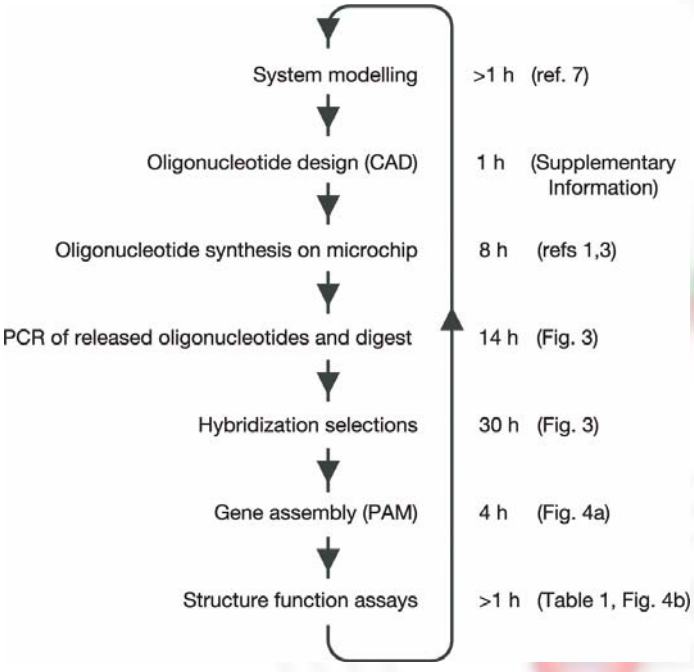
情報⇒物質⇒機能⇒生命

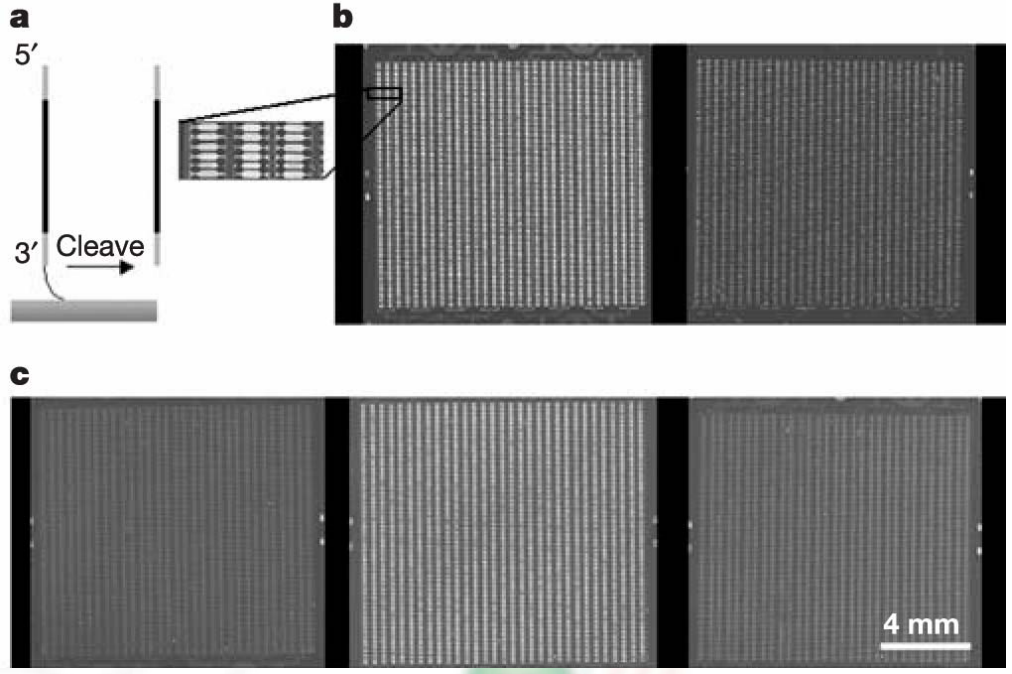
http://www.riken.jp/r-world/research/lab/genome/protein/result.html

情報から物質（遺伝子）へ:遺伝子合成

ゲノム合成は現段階では難しいが複数の遺伝子を人工的に効率よく合成できるようになってきた

光によって多種類の短いDNAを人工合成する技術が基盤技術。短いDNAを長いDNAを作るための素材として用いて遺伝子・ゲノムの人工合成を目指す。

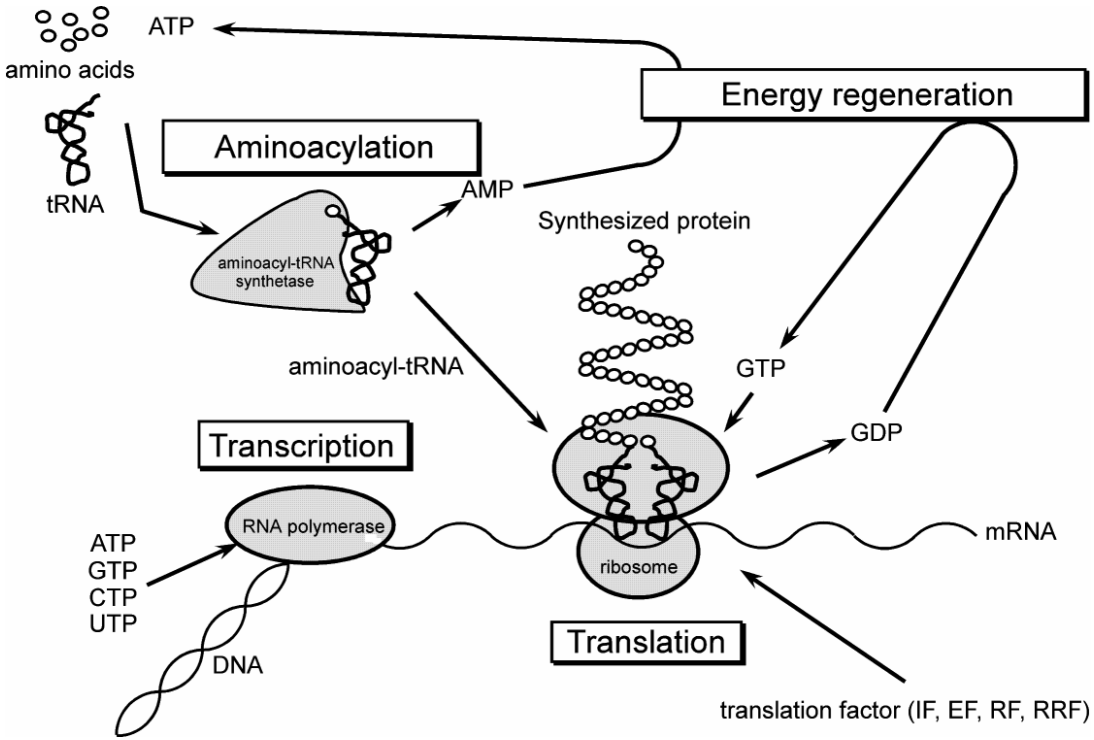




Nature 432, 1050-4. (2004)

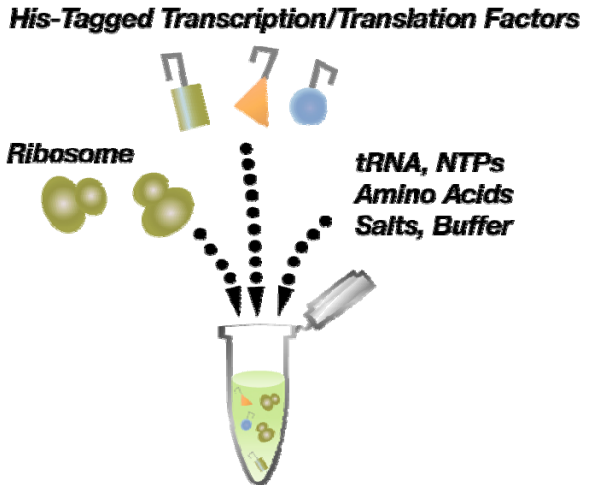
情報⇒物質⇒機能⇒生命

物質から機能へ：無細胞蛋白質合成系



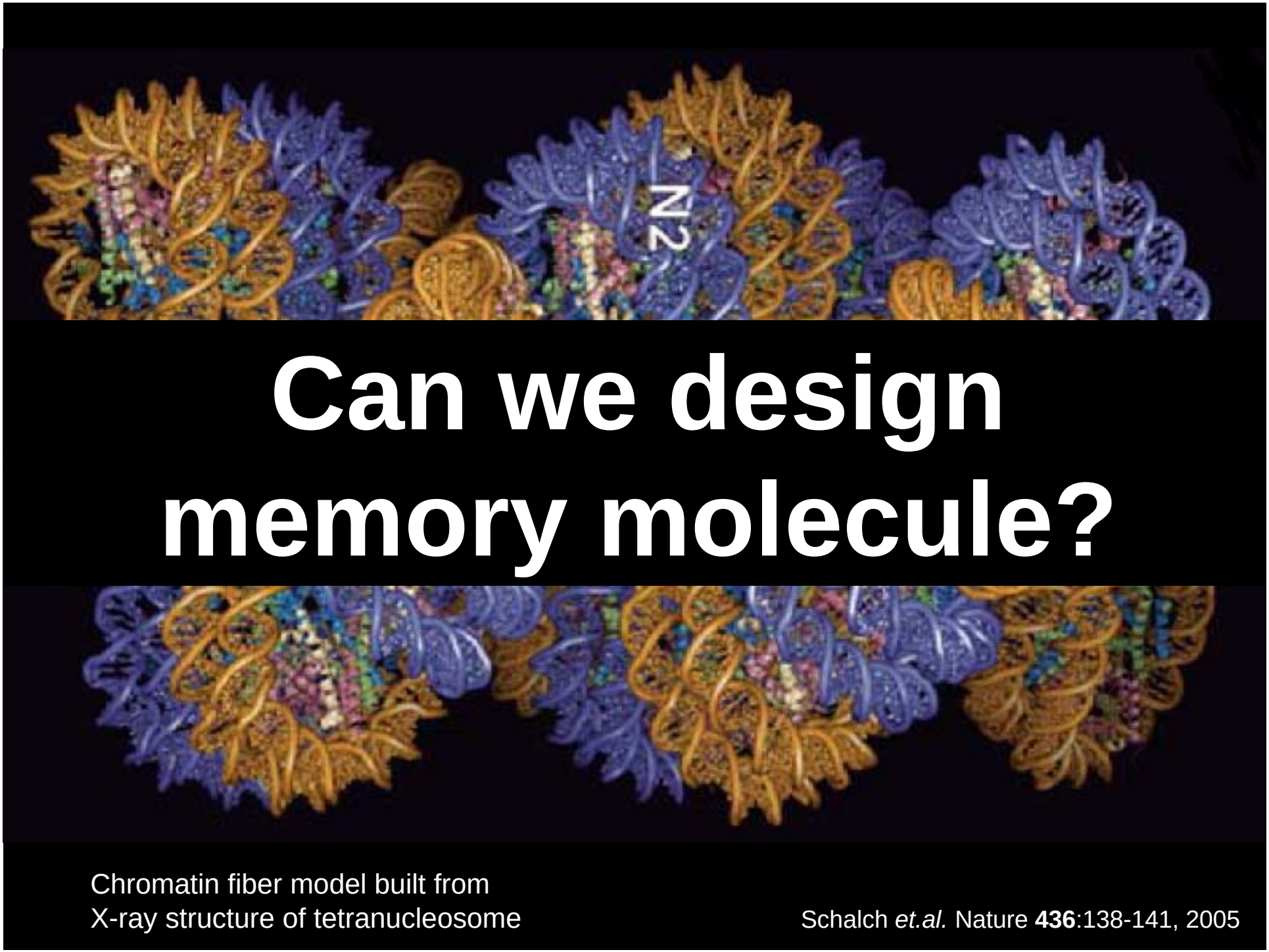
PURESYSTEM®

Protein synthesis using recombinant elements System



Shimizu Y. *et al.* (2001) *Nature Biotechnology*, vol.19, p.751-755.

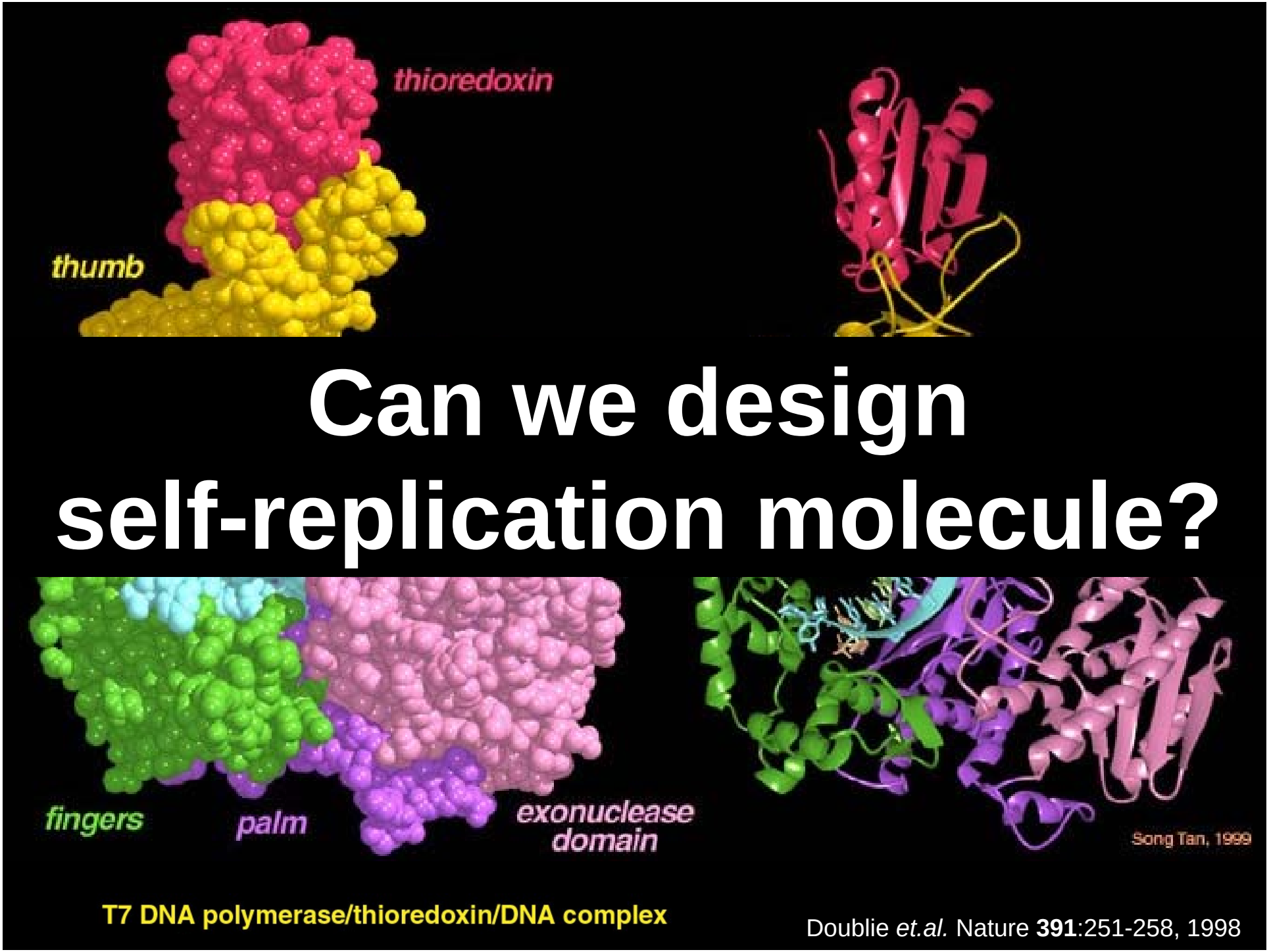
情報⇒物質⇒機能⇒生命



Can we design memory molecule?

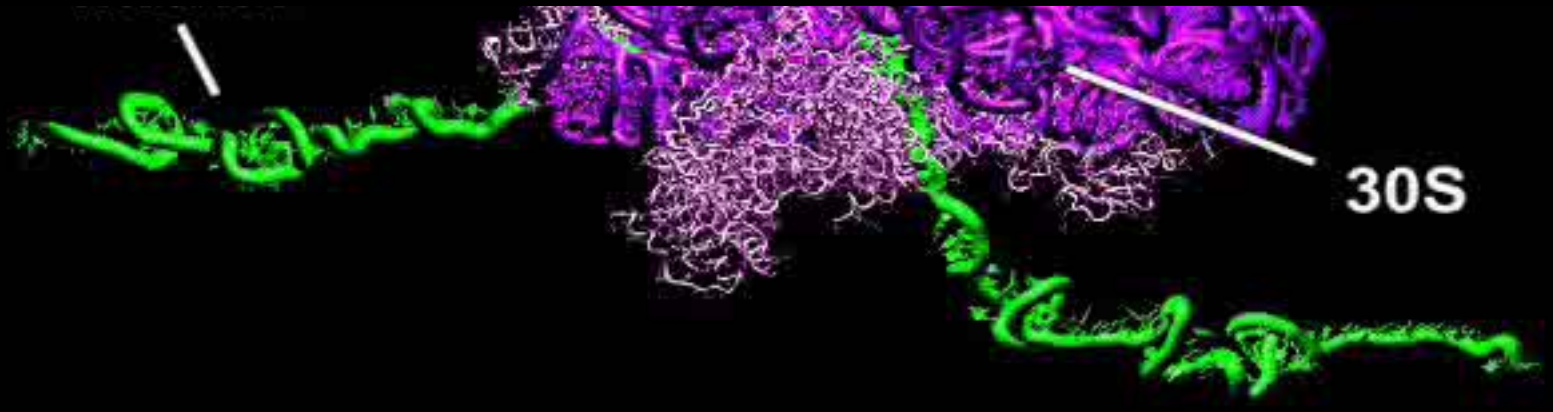
Chromatin fiber model built from
X-ray structure of tetranucleosome

Schalch *et.al.* Nature **436**:138-141, 2005



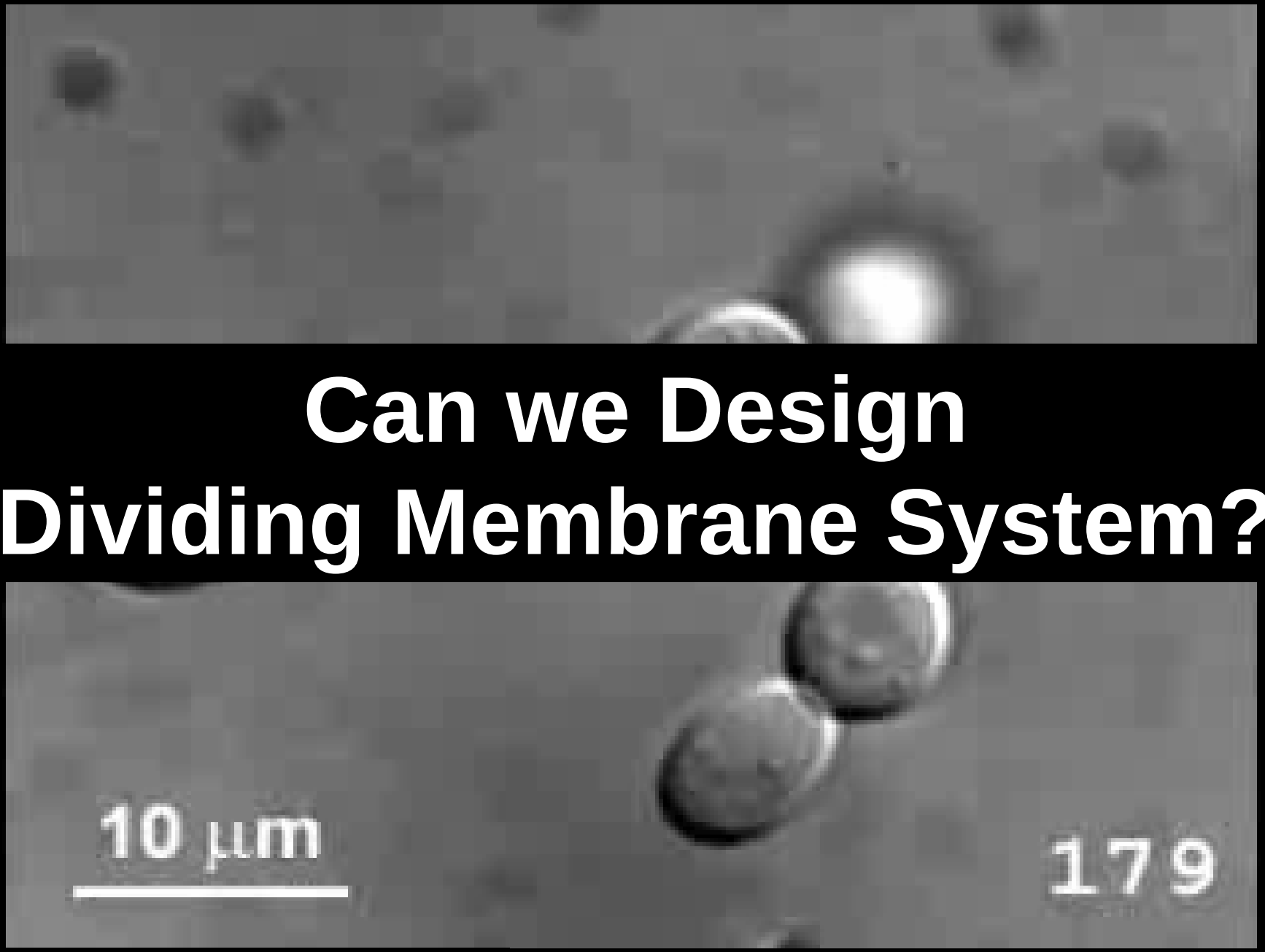
Doublie *et.al.* Nature **391**:251-258, 1998

Can we Design Protein Synthesis Molecule?



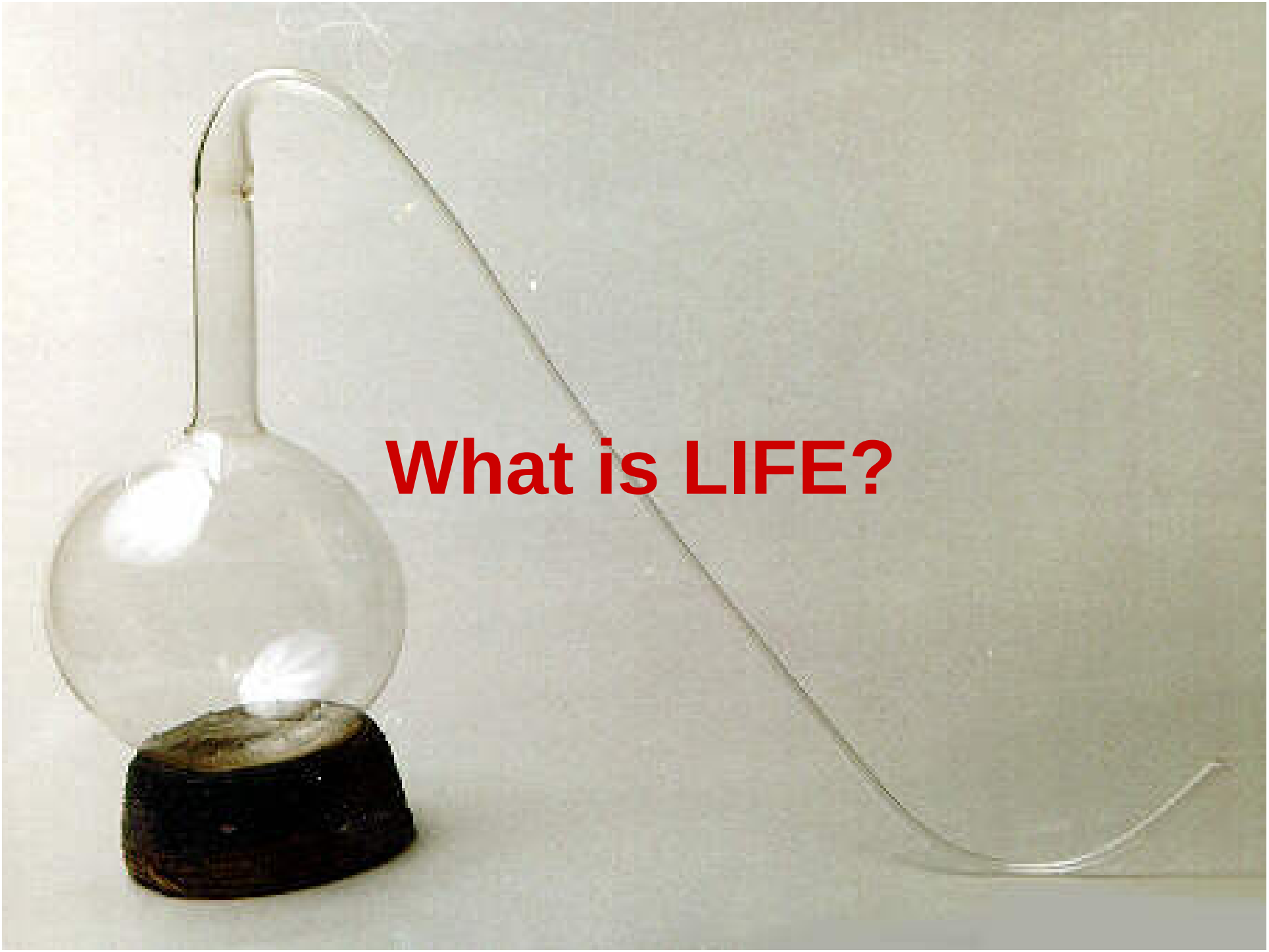
Thermus thermophilus 70S ribosome

Sanbonmatsu *et.al.* PNAS **102**:15854-15859, 2005



Can we Design Dividing Membrane System?

Growth and division of budding yeast http://www.marietta.edu/~spilatrs/biol202/budding_yeast.mov


What is LIFE?