Maxwell's demon's genes:

Towards a cell factory or towards a living synthetic cell?

Antoine Danchin 唐善・安東

European Science Foundation

Sant Feliu de Guixols, March 31st, 2009

Goals of Synthetic Biology

• **Reconstructing and understanding.** Forgetting the "black box" SB reconstructs life to explore whether we understand what life is and learn missing entities from our failures

• **Abstracting.** SB keeps the laws defining life, and applies them using objects of a different physico-chemical nature

• **Engineering.** SB designs and standardises « biobricks » to construct a « cell factory » with Man's interests drive

• **Evolving.** SB combines design and evolution to use (poorly understood) principles that drive adaptation

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However, here is the symmetrical situation …

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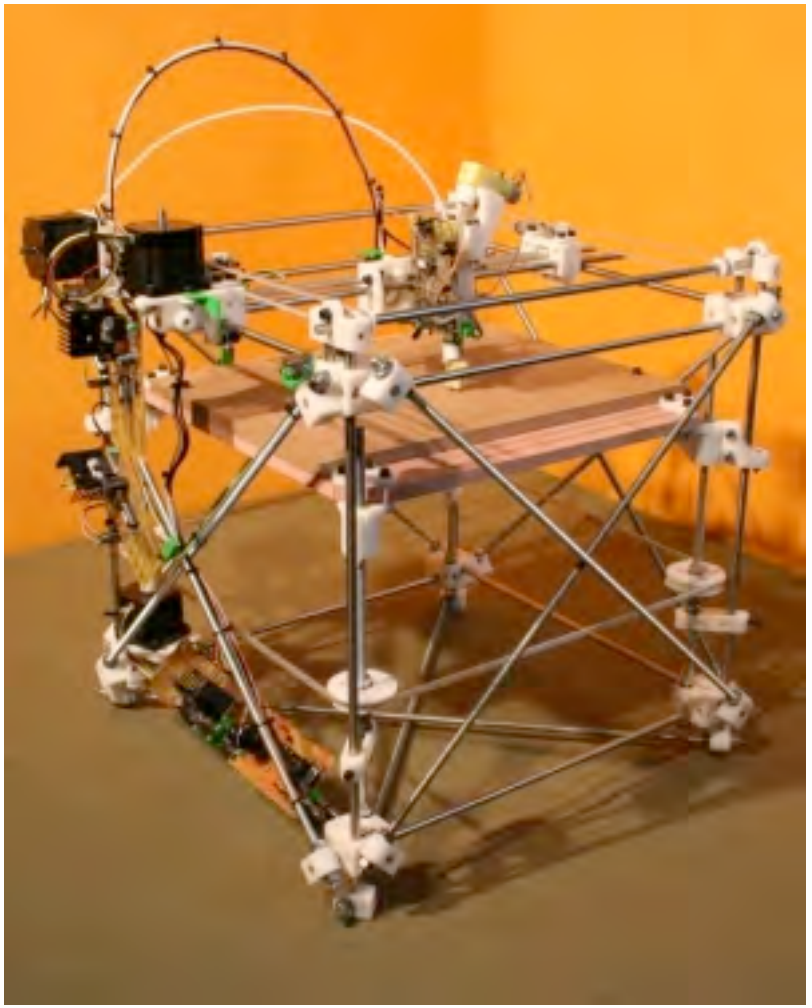
A 3D self-reproducing printer

Project RepRap (Replicating Rapid-prototyper, 2004) **aims at creating a laser 3D self-reproducing printer :**

- **The machine produces most of its components (= “biobricks”)**
- **What is missing :**
  - **The program**
  - **The assembly (managing space and time - sequence of events, and specific functions such as lubrication)**

http://reprap.org/



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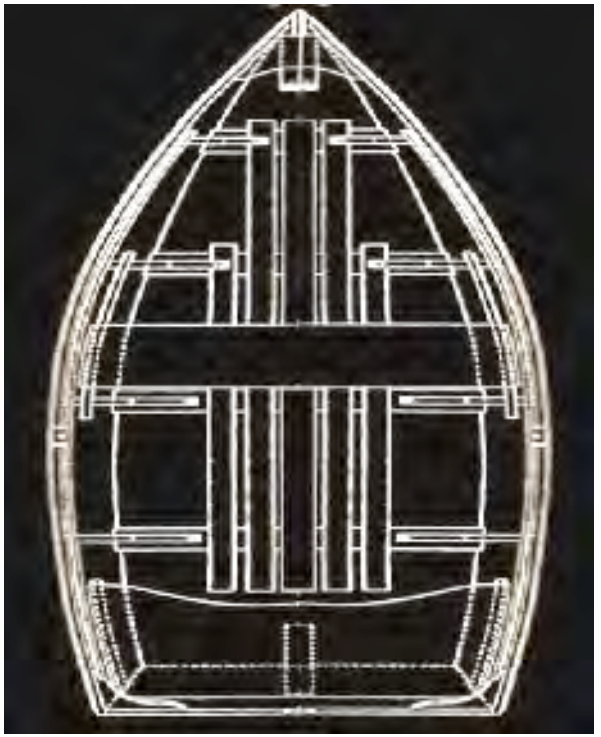
Biology is « symplectic »

• Biology is a science of relationships between objects

• It is **symplectic** (**συν** together, **πλεκτειν**, to weave), same as « complexus » in Latin; used here to avoid unfortunate contradictions linked to the word « complexity »; used in fairly arcane Geometry, this will have no bad consequences…

• It is an information that expresses what is conserved in the boat, not the matter of its planks !



A. Danchin The Delphic Boat, Harvard University Press, 2003
La barque de Delphes, Odile Jacob, 1998

V. de Lorenzo, A. Danchin Synthetic Biology: discovering new worlds and new words 9: 822-827. EMBO Reports, 2008

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Beyond usual categories

Historically, much of fundamental physics has been concerned with discovering the fundamental particles of nature and the equations which describe their motions and interactions. It now appears that a different programme may be equally important: to discover the ways that nature allows, and prevents, information to be expressed and manipulated, rather than particles to move

Andrew Steane (1998) Oxford University

Engineered biological systems have been used to manipulate information, construct materials, process chemicals, produce energy, provide food, and help maintain or enhance human health and our environment

Drew Endy (2005) MIT

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Making information concrete: infotaxis

Saturnia pyri

http://pdubois.free.fr/

How does a moth find a partner one kilometer away?

Climbing up a chemical gradient is impossible at such a distance (air turbulence, obstacles…)

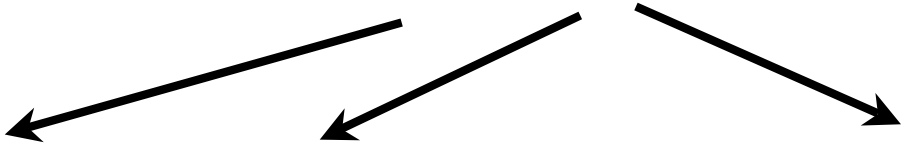
Vergassola and co-workers have shown that maximising information collection permits reaching that goal…

'Infotaxis' as a strategy for searching without gradients
Vergassola M, Villermaux E, Shraiman BI
Nature (2007) **445:** 406-409

Information, a fifth category of Reality?

Classical Physics

$E = mc^2$



energy matter space/time

Quantum Physics

$\Delta x \Delta p \geq h/4\pi$

indeterminacy = lack of information

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A fifth category of Reality

Matter / Energy / Space / Time

- Classical physics
- Quantum physics
- Chemistry
- Biology
  - Development
  - Neurobiology
  - Linguistics
- Mathematics

Information

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What life is

Life requires:

- **A machine (chassis) allowing the program to be enacted (reproduces)**
  - **1. Metabolism (a dynamic process**
  - **2. Compartmentalisation (defining an inside and an outside)**

- **A program (a "book of recipes", which replicates)**
  - **3. Recursive information transfer and trapping => coding from one level to a second one as an essential element**

The cell is the atom of life

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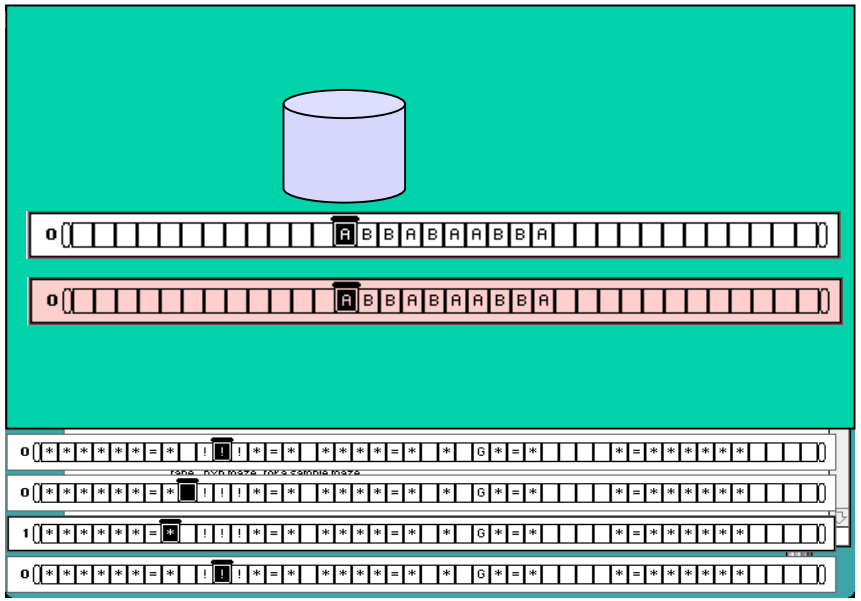
What computing is

Two entities permit computing:

- A machine able to read and write
- A program on a physical support, split by the human mind (not conceptually!) into two entities:
  - Program (providing the "goal")
  - Data (providing the context)



The machine is distinct from the data/program

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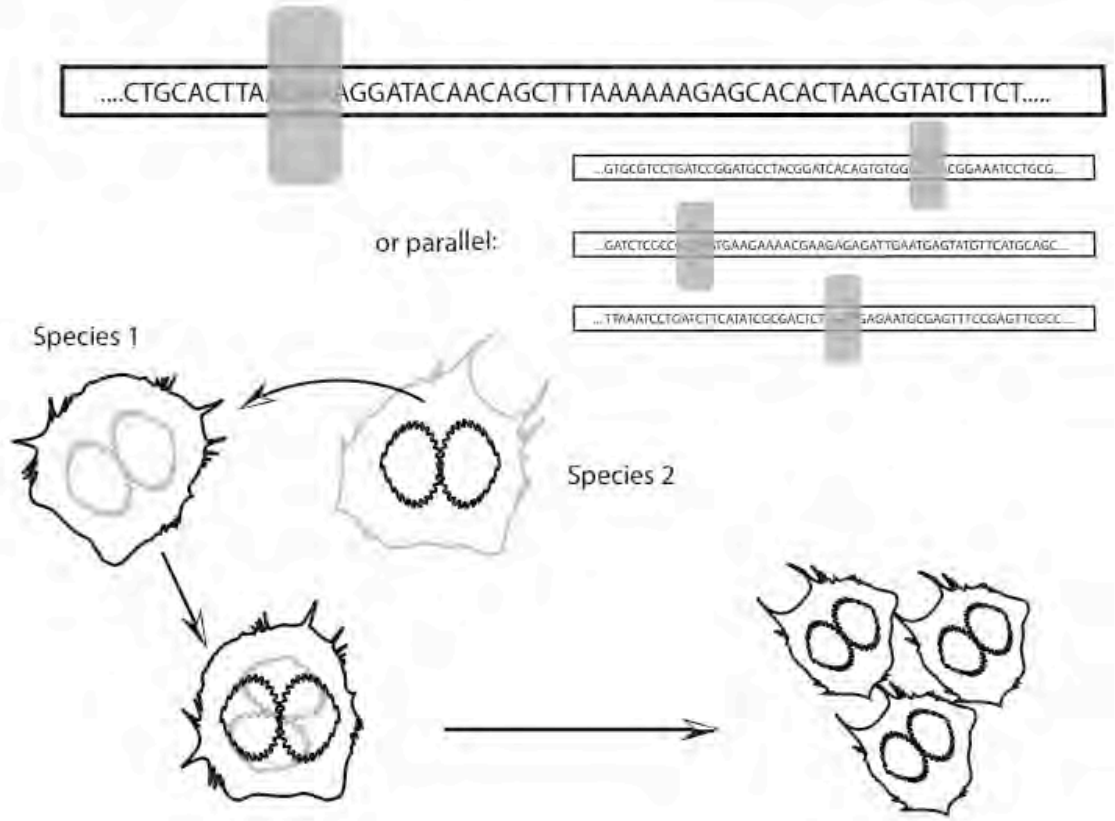
Lartigue-Venter's demonstration

The Turing machine

May exist in a parallel set up



Genome transplantation

Genome transplantation in bacteria: changing one species to another
Lartigue C, Glass JI, Alperovich N, Pieper R, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC
Science (2007) **317:** 632-638

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Objection to the computer model of the cell

“Beside the genetic program, the cell carries a considerable amount of information…”

TRUE: but in a computer as well. This requires construction of an entirely novel theory of “machine-information”

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Even in authentic computers, mind the physical support!

It is not enough to have a DNA molecule with the right sequence, it needs to be correctly folded!

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Babies are born very young!

- **The machine reproduces**
  - Reproduction can improve over time: it is always an aged organism that gives birth to a young one (this implies creation of information)

- **The program replicates**
  - Replication keeps accumulating errors

Which genes permit accumulation of information?

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Looking for ubiquitous functions

Variation / Selection / Amplification

↳ Stabilisation ↱

Evolution

↓ *creates (information comes in)*

Function

↓ *captures (recruits)*

Structure

↕ *codes*

Sequence

Functional ubiquity does not imply structural ubiquity

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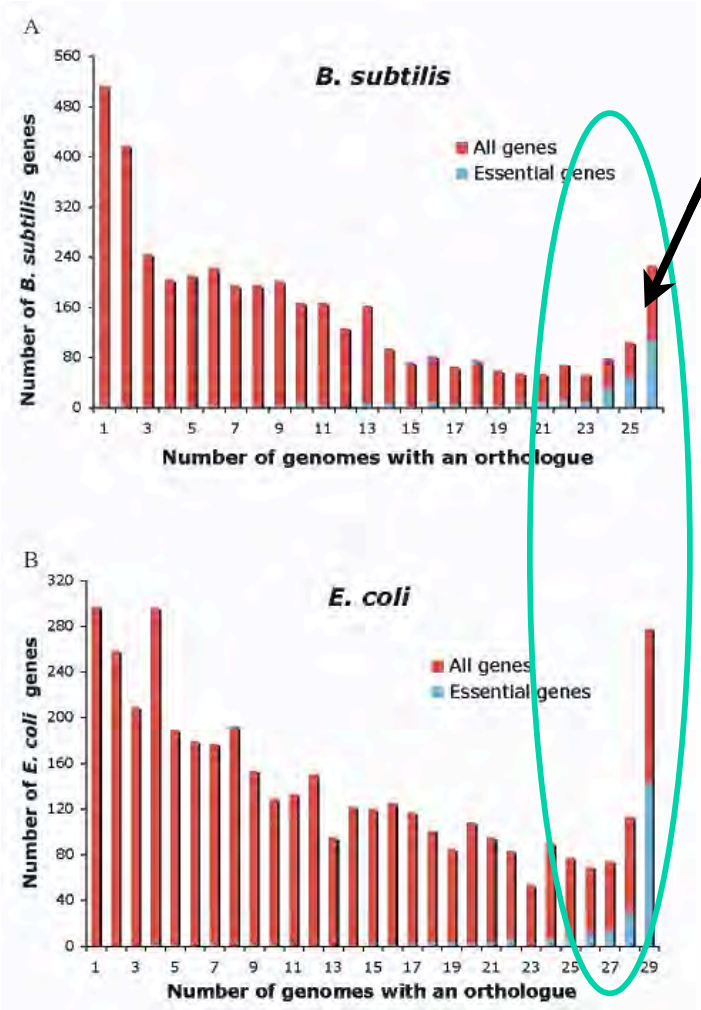
Gene persistence: too many genes



Persistent genes

Essential genes and ….

Stress, maintenance and repair

Energy-dependent degradation

Metabolic patches (serine effect)

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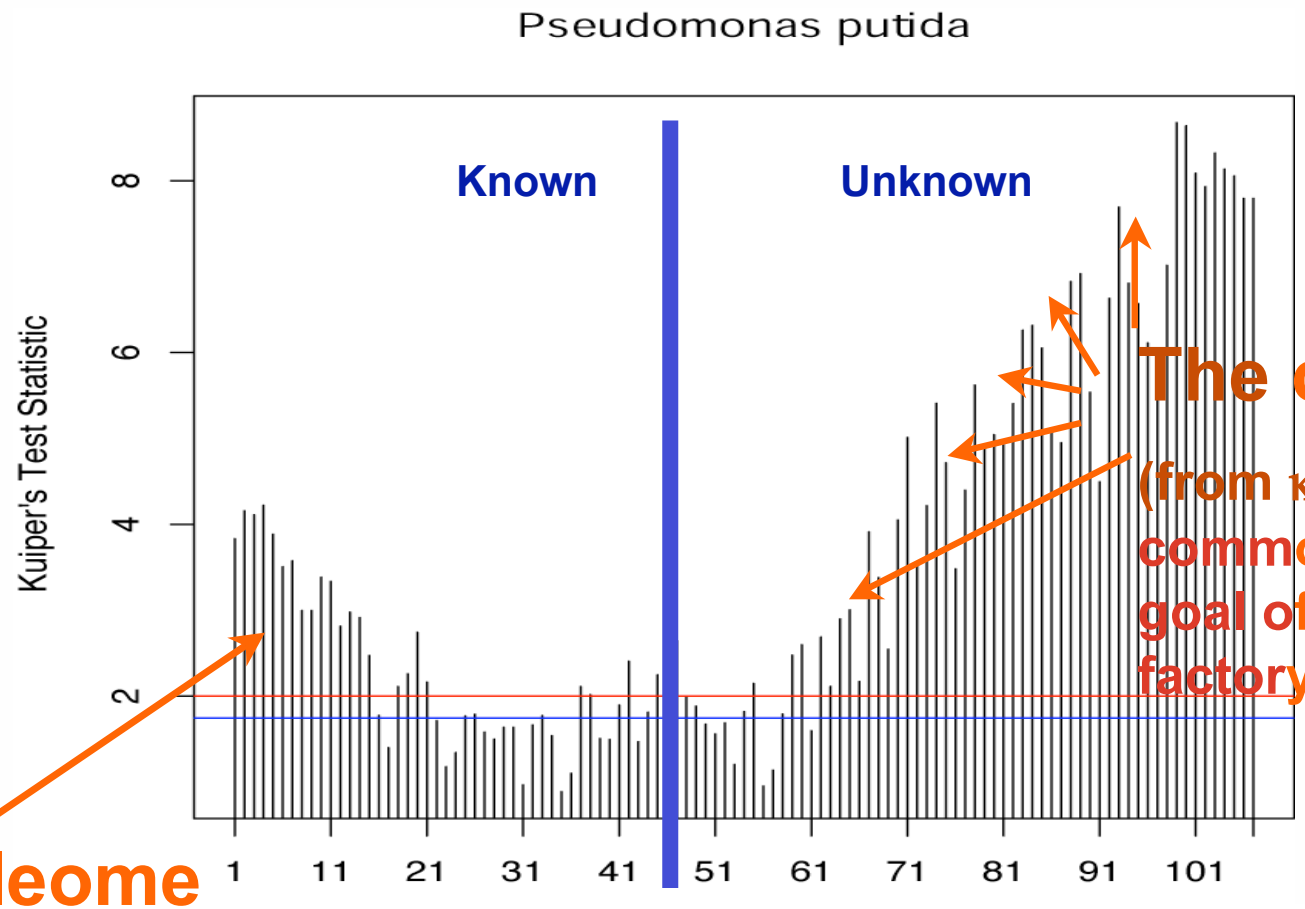
Organisation of bacterial genomes



The cenome

(from κοινος, common): the goal of the cell factory

The paleome

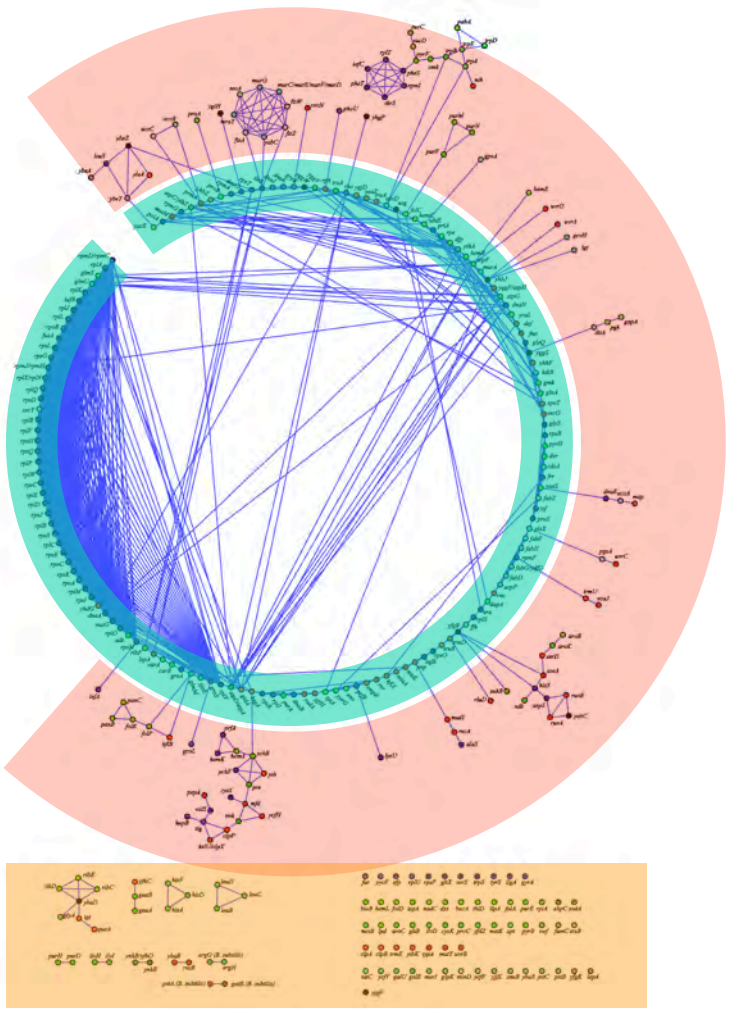
(from παλαιος, ancient): the cell factory

Genome core
<2,000 genes

Variable genes
already > 50,000 genes

Persistent genes recapitulate the origin of life

The external network, made of genes of intermediary metabolism (nucleotides and coenzymes, lipids) is highly fragmented; the middle network is built around class I tRNA synthetases, and the inner network, almost continuous, organized around the ribosome, transcription and replication manages information transfers



A Danchin, G Fang, S Noria
The extant core bacterial proteome is an archive of the origin of life
Proteomics. (2007) **7**:875-889

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Twice too many persistent genes

Functional ubiquity does not imply structural ubiquity

Yet, efficient objects tend to persist through generations:

- Looking for « persistence » permits identification of (most) ubiquitous functions
- Is « ubiquitous » a synonym of « essential »?

~ 500 genes persist in bacterial genomes, forming the paleome; only ~250 are essential

A variable number permits to occupy a niche (cenome)

The paleome and the cenome

- The structure of the paleome
  - Essential functions; the gene expression machinery as the « operating system » of the cell-as-a-computer
  - Energy-dependent degradation
  - Sulfur metabolism (anabolism, salvage, catabolism)
  - Chemical frustration (metabolic « patches »)

- The cenome
  - Horizontal Gene Transfer
  - Occupation of a particular niche
  - From commensalism to virulence

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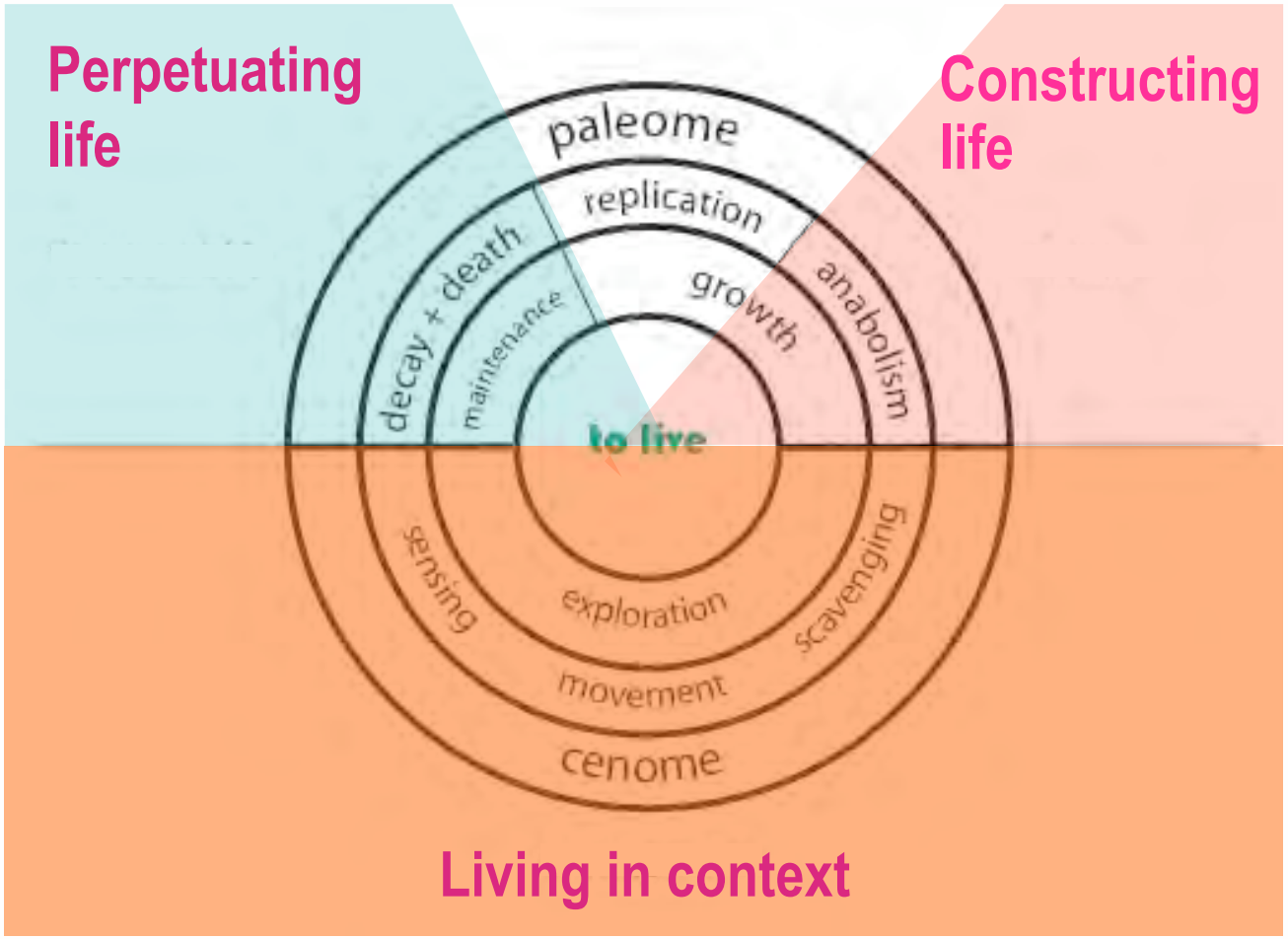
A tale of two genomes

metagenomics



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A split paleome

- **Paleome 1 (essential genes)**
  - **Constructor**: DNA specifies proteins which form the machine that constructs the cell (reproduction)
  - **Replicator**: DNA specifies proteins that replicate DNA (replication)

- **Paleome 2 (persistent non-essential genes)**
  - Perennisation of life, energy-dependent degradation
  - Metabolic patches (chemical frustration)

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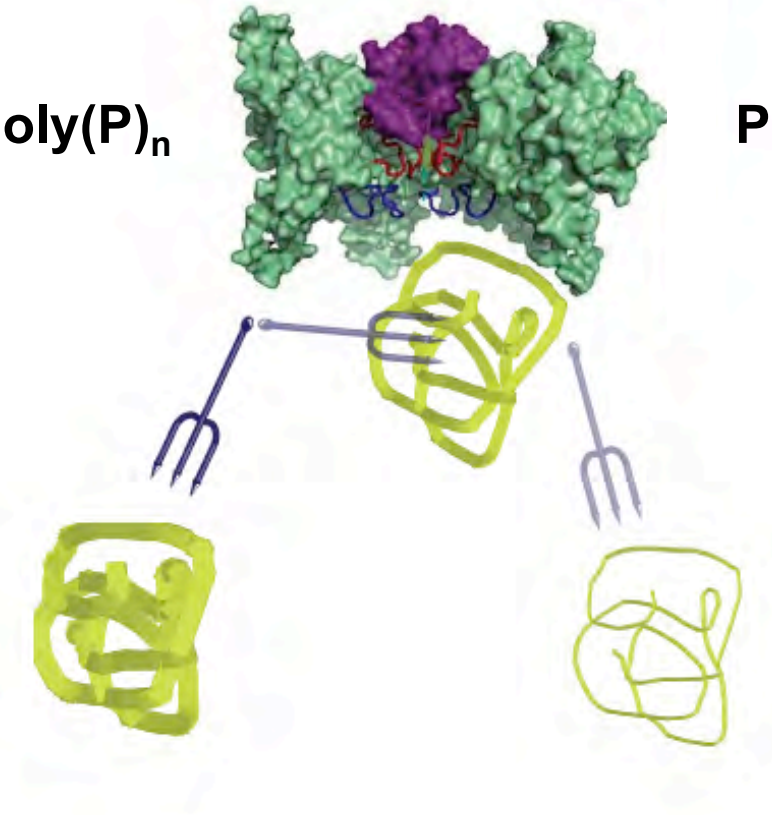
Revisiting information

Intuition tells us that creation of information requires energy. Yet, in an endeavour to calculate the limits of practical computation, Landauer demonstrated that creation of information is reversible (*i.e.* does **not** require energy: Landauer, 1961; Bennett, 1982, 1988); however, accumulating information requires an energy-dependent process to make room for this ratchet-like accumulation.

Open question: if « making room » is needed to accumulate information, how is it obtained? Can we identify in genomes the genes coding for the functions required to put this process in action? Can we find a ubiquitous and stable energy source?

Maxwell's demon's genes

Poly(P)$_n$



Poly(P)$_{n-1}$

The degradation machinery uses energy to reject a functional entity

Non functional entities are recognised and degraded

Maxwell's demon's genes

- Energy-dependent degradative processes make room for newly synthesised entities; energy is used to **prevent** degradation of functional entities
- This process accumulates information, whatever its origin, in a ratchet-like manner
- As this process is ubiquitous, we expect that the corresponding functions are encoded in the paleome, including management of the major energy sources postulated here

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Conjecture: polyphosphates

- Synthesis and turnover of poly-P is coded for in the set of persistent non-essential genes; this process is still poorly known and associated to RNA degradation

- Poly-P is a **mineral**, hence extremely stable; it is present in all known cell types

- NTPs can be regenerated starting from NMP and poly-P; Protease Lon can use poly-P instead of ATP; NADP (anabolism) may be generated from NAD and poly-P…

Putting the conjecture to test: Adaptive mutations

Construction of "intelligent" bacteria

Placed to grow on a medium with limited nutrient supply. Form colonies of approximately 10^8 bacteria. The medium also contains nutrients that they cannot use

After a few weeks time, papillae appears that begin to grow and invade the medium, using the supplied "unusable" nutrients. They derive from adaptive mutations

These mutations did not pre-exist, and this supposes creation of information

Natural selection traps information

- Energy-dependent degradative processes make room for newly synthesised entities; energy is used to **prevent** degradation of functional entities

- This process accumulates information, whatever its origin, in a ratchet-like manner

- Because the process is ubiquitous, the corresponding functions are expected to be coded in the paleome, including the possible energy source

- This process is **myopic**: it cannot have any grand design, hence the “tinkering” feature of the evolution of life

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A synthetic cell?

- The engineering view of SB precludes innovation in synthetic cells
- It is possible to exclude genes permitting accumulation of information
- The consequence is that, as factories, cell factories will age and have to be systematically reconstructed
- This has the considerable societal advantage that the associated risks are minimised

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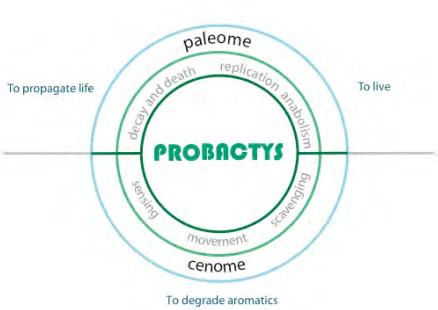
Funding



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