Will we be able to construct a synthetic cell?

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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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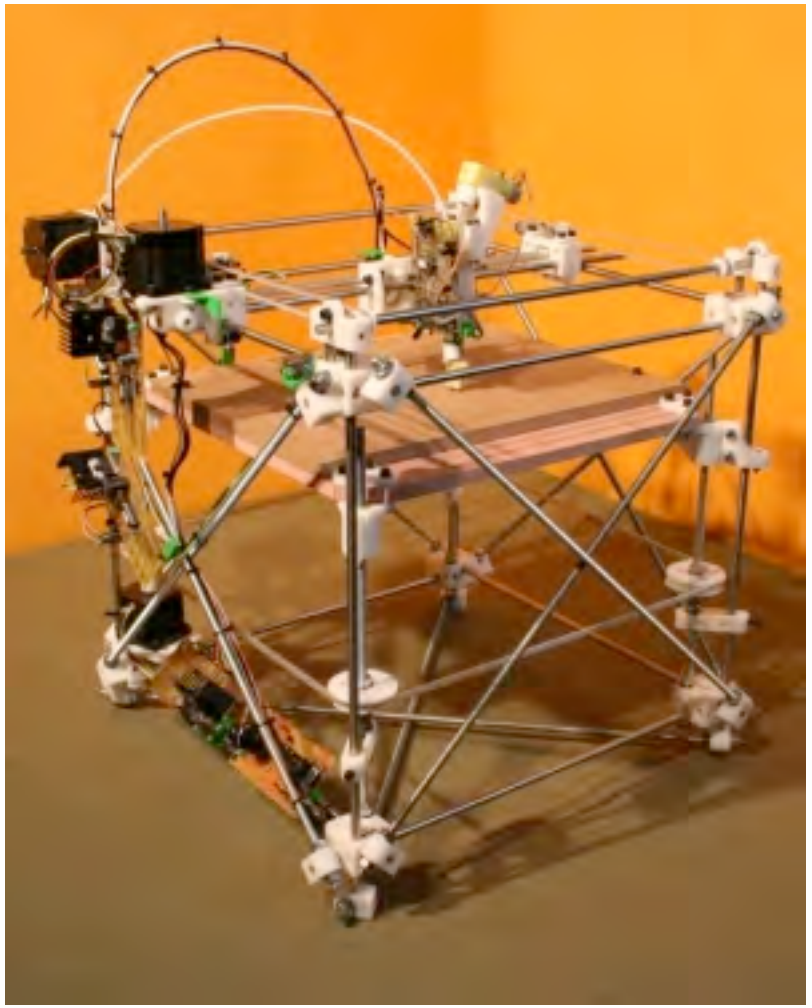
A 3D self-reproducing printer

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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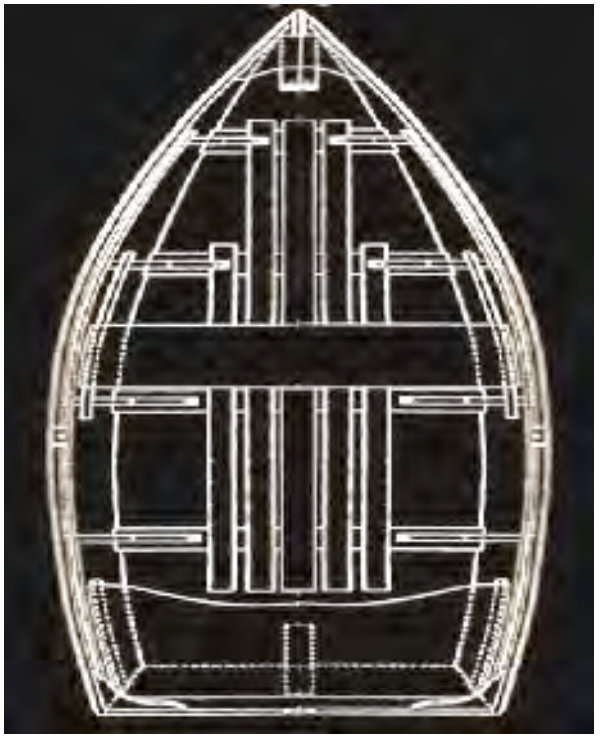
Biology is « symplectic »

• 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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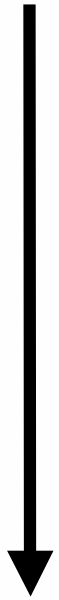
A fifth category of Reality

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 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 => coding from one level to a second one as an essential element**

The cell is the atom of life

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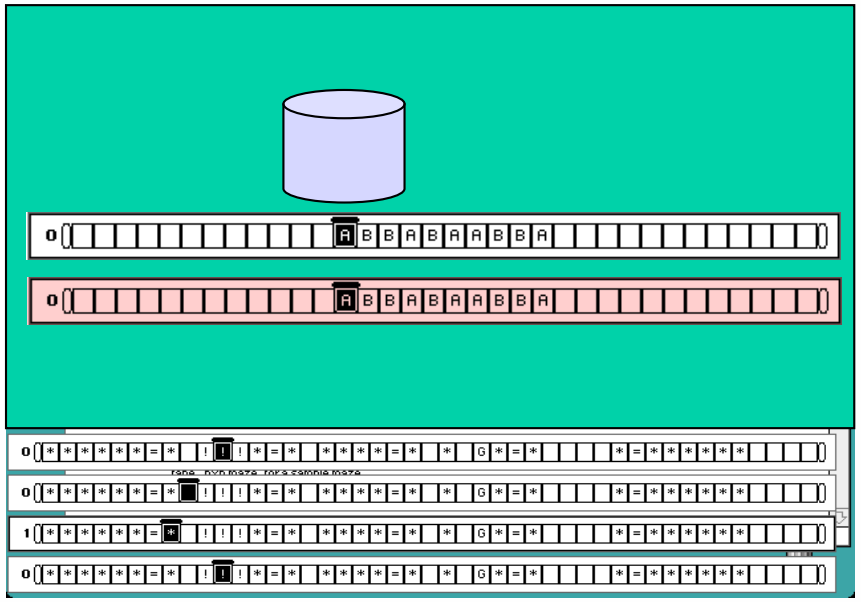
What computing is

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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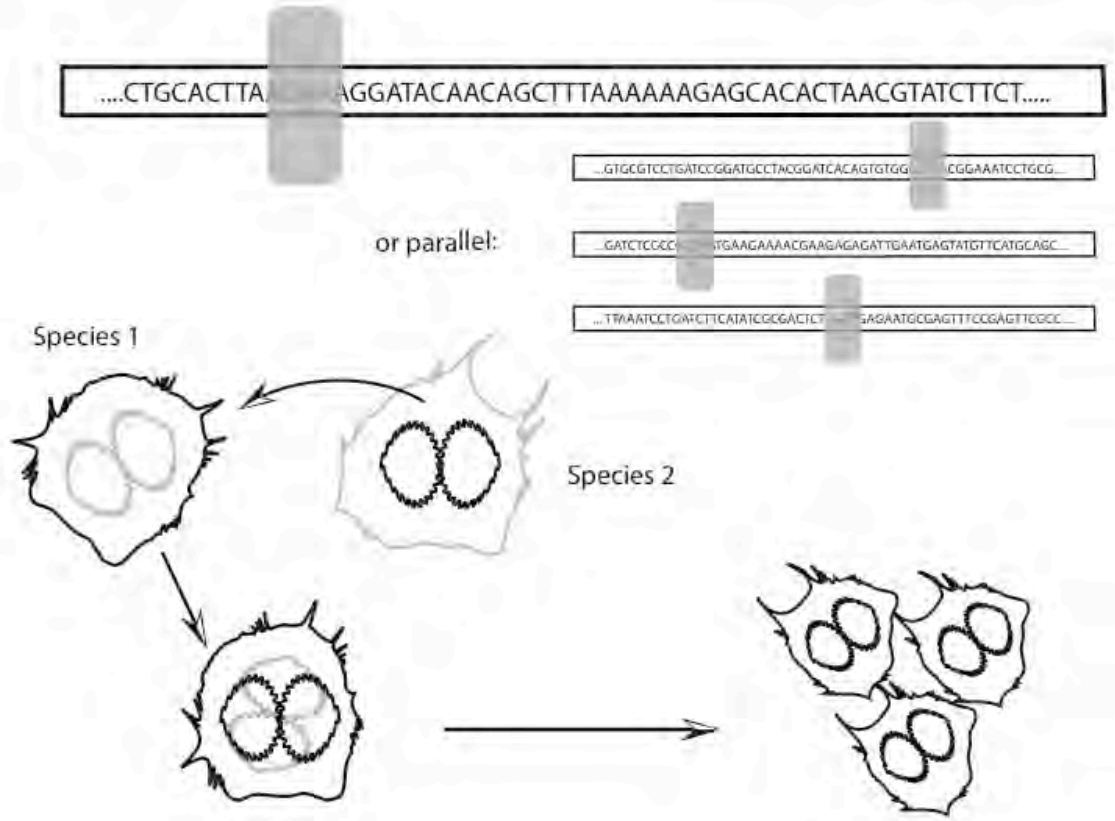
Lartigue-Venter's demonstration

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…”

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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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Twice too many persistent genes

Functional ubiquity does not imply structural ubiquity

Efficient objects tend to persist through generations:

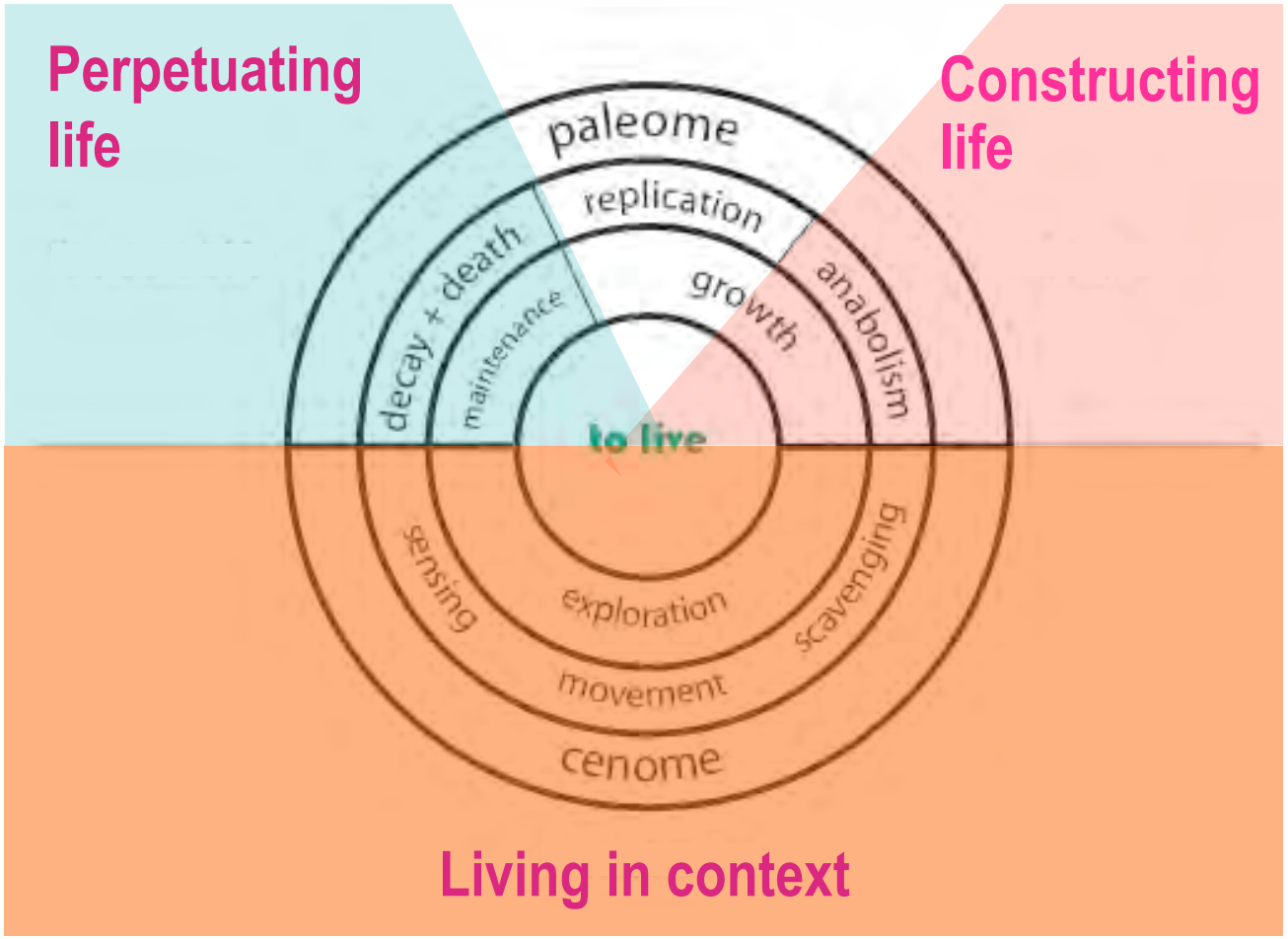
- Looking for « persistence » permits identification of (most) ubiquitous functions
- Is « ubiquitous » a synonym of « essential »?

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

A variable number permits to occupy a niche (cenome)

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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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

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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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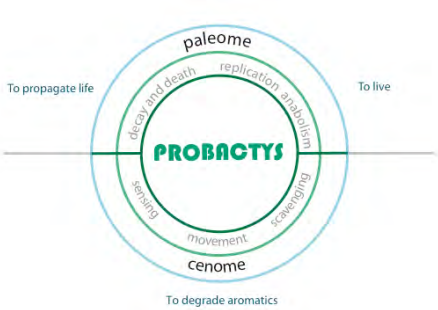
Funding



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