

# **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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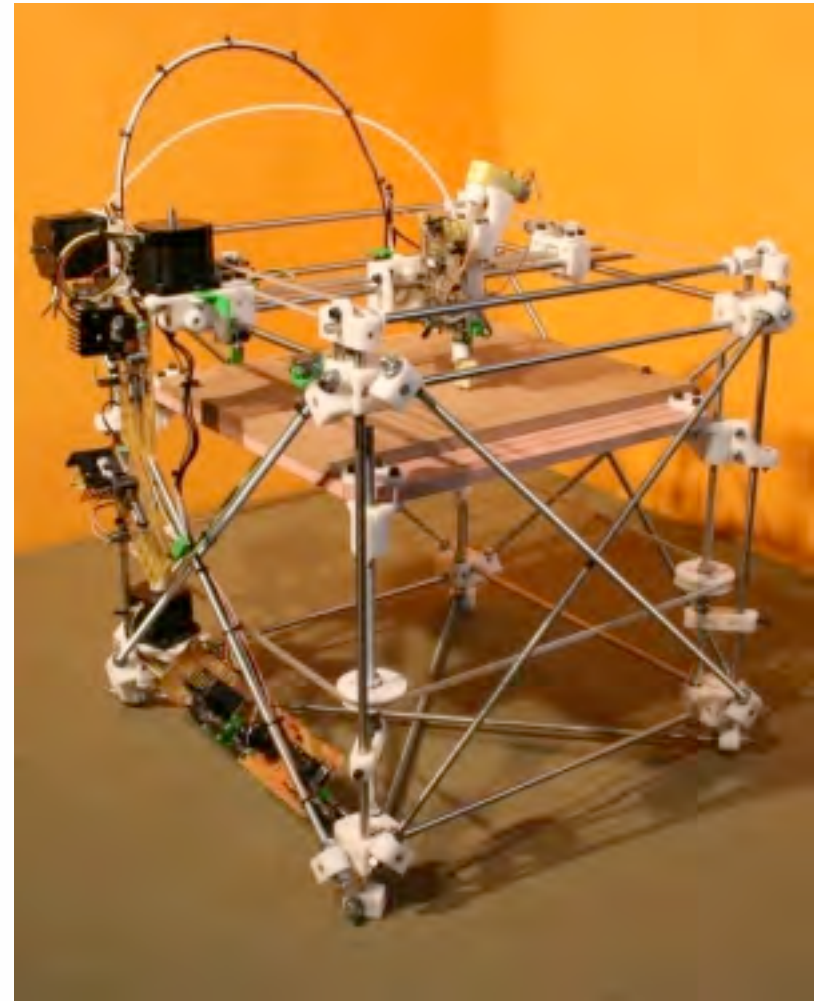
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# A 3D self-reproducing printer

**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/>

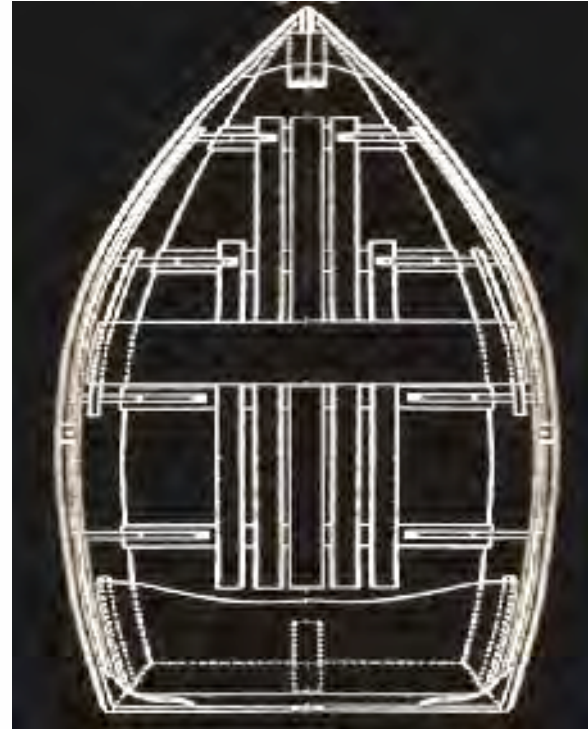


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# Biology is « symplectic »

- 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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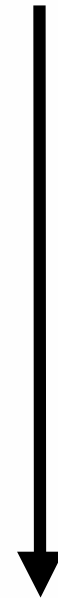
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# A fifth category of Reality

## 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**

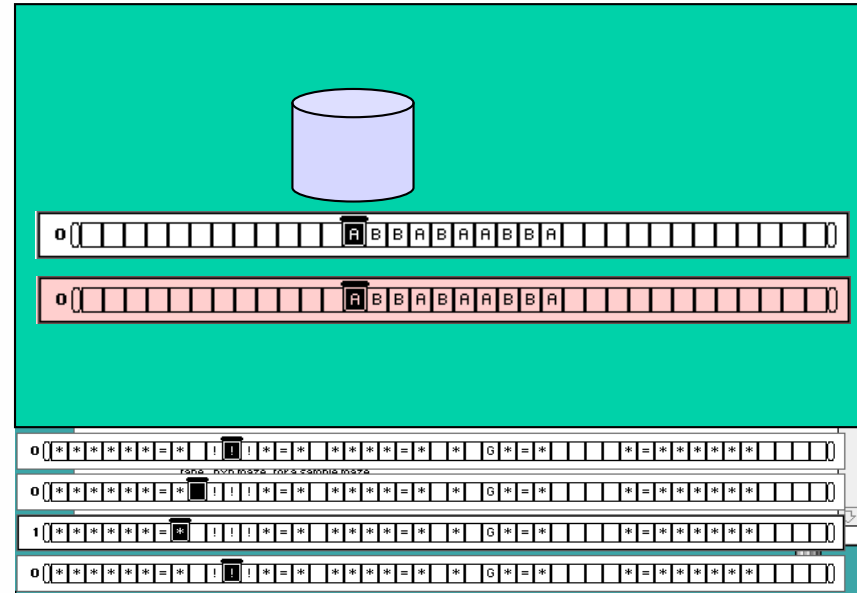
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# What computing is

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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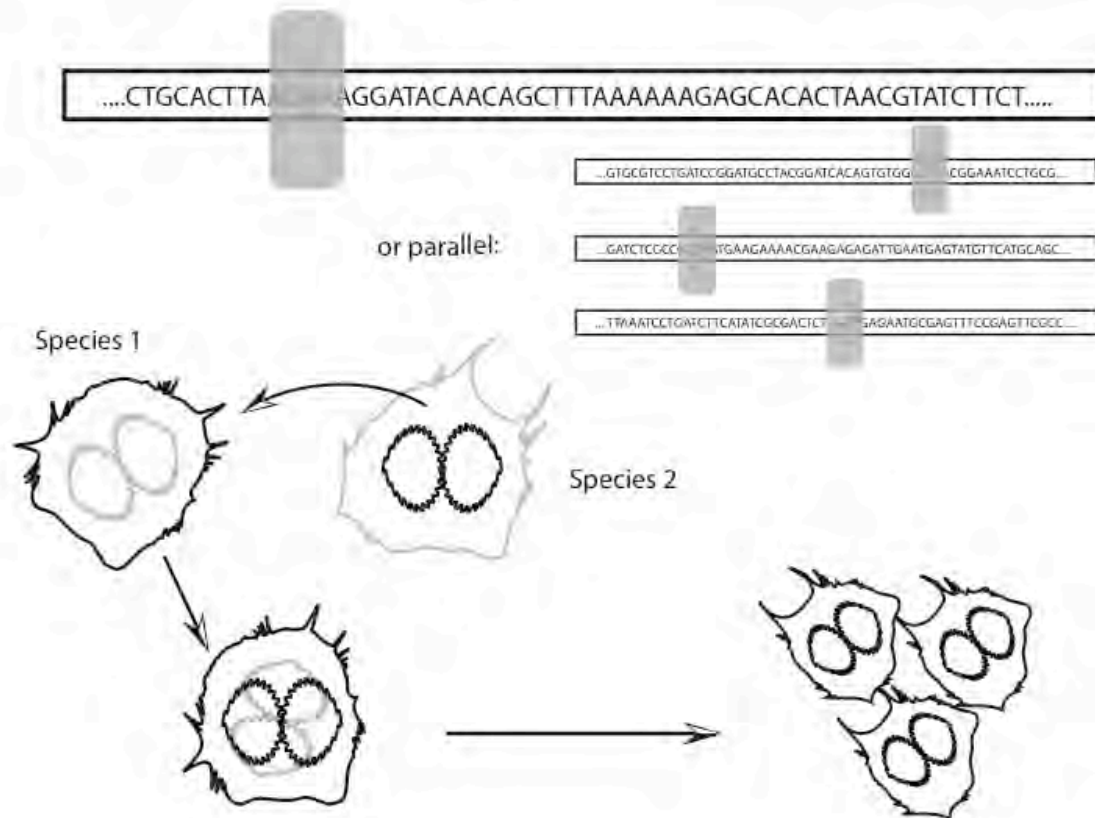
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# Lartigue-Venter's demonstration

## 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 »?

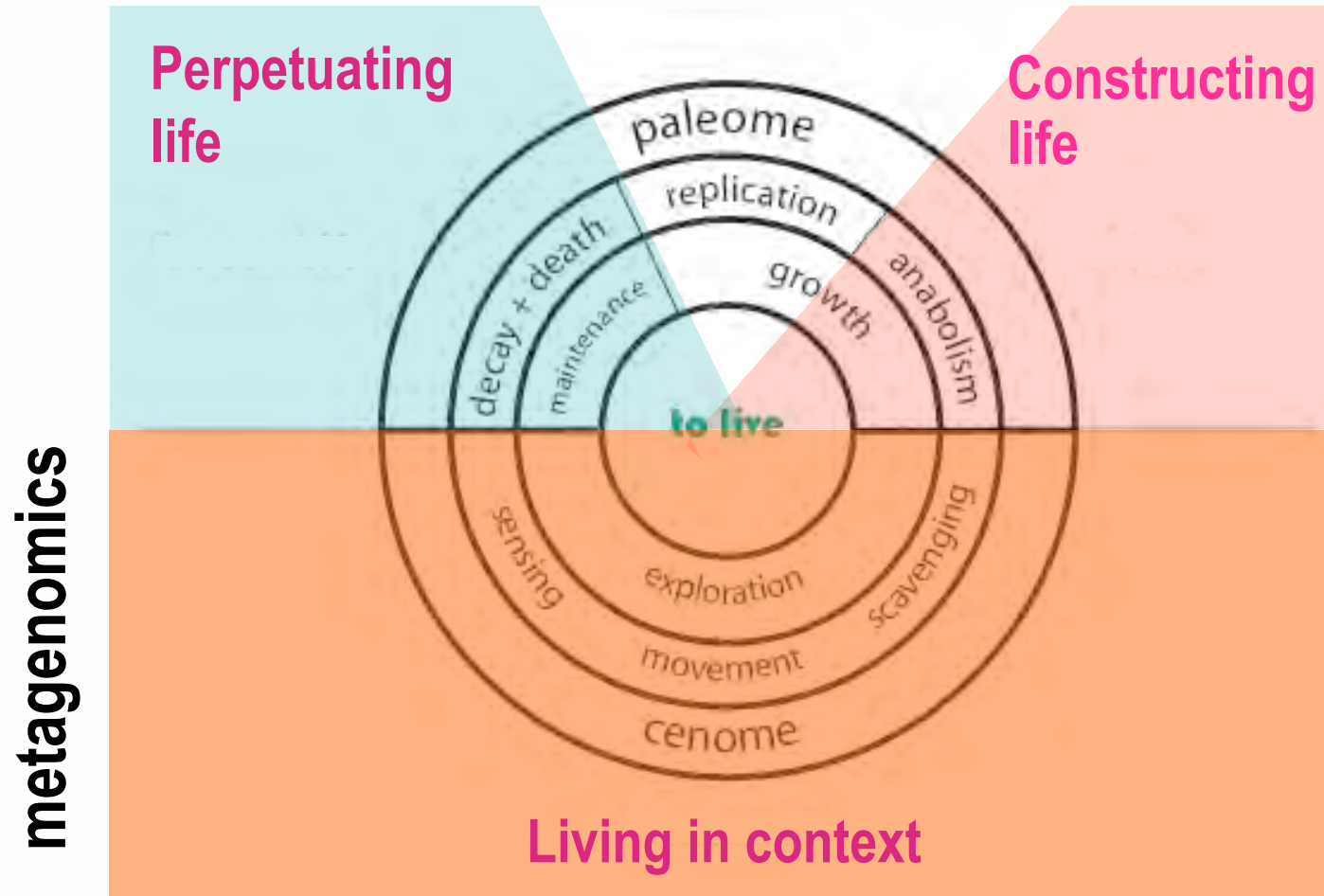
~ 500 genes persist in bacterial genomes, forming the **paleome**; only ~250 are essential

A variable number permits to occupy a niche (**cenome**)

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# A tale of two genomes



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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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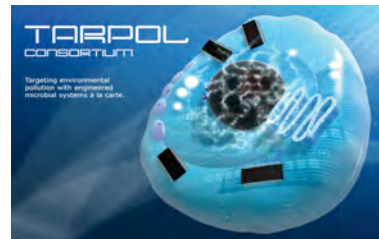
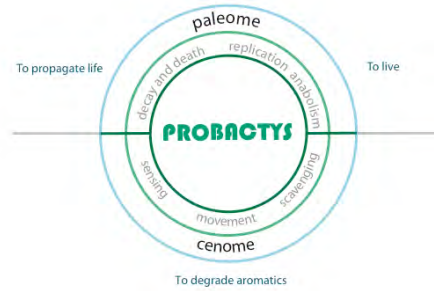
# A synthetic cell?

- 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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POUR LE RAYONNEMENT DE LA BIOLOGIE

