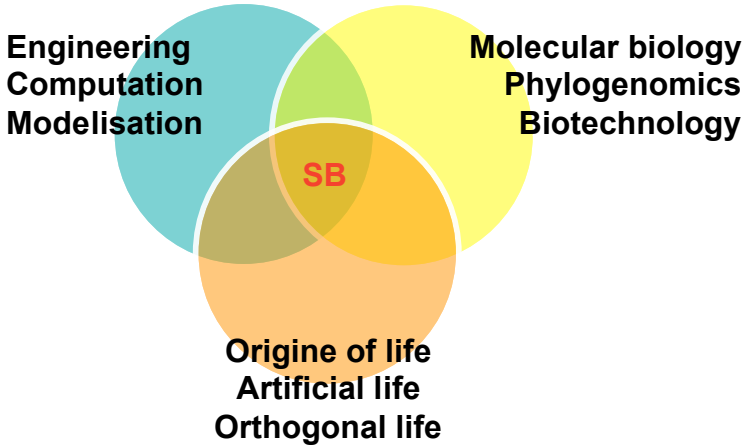
Life and perpetuation of life of a synthetic bacterium



Antoine Danchin 唐善 安東
Director, Department Genomes and Genetics, Institut Pasteur
EMBL, november 7th, 2008

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Goals of synthetic biology

- A first aim of SB is to reconstruct life, in an endeavour to explore whether we understand what life is and learn missing entities from our failures
- A second aim is to keep the laws defining life, and to apply them using objects of a different physico-chemical nature
- A third aim is to see life from an engineering standpoint, trying to class and normalise « biobricks » to construct a « cell factory »

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However, here is the situation …

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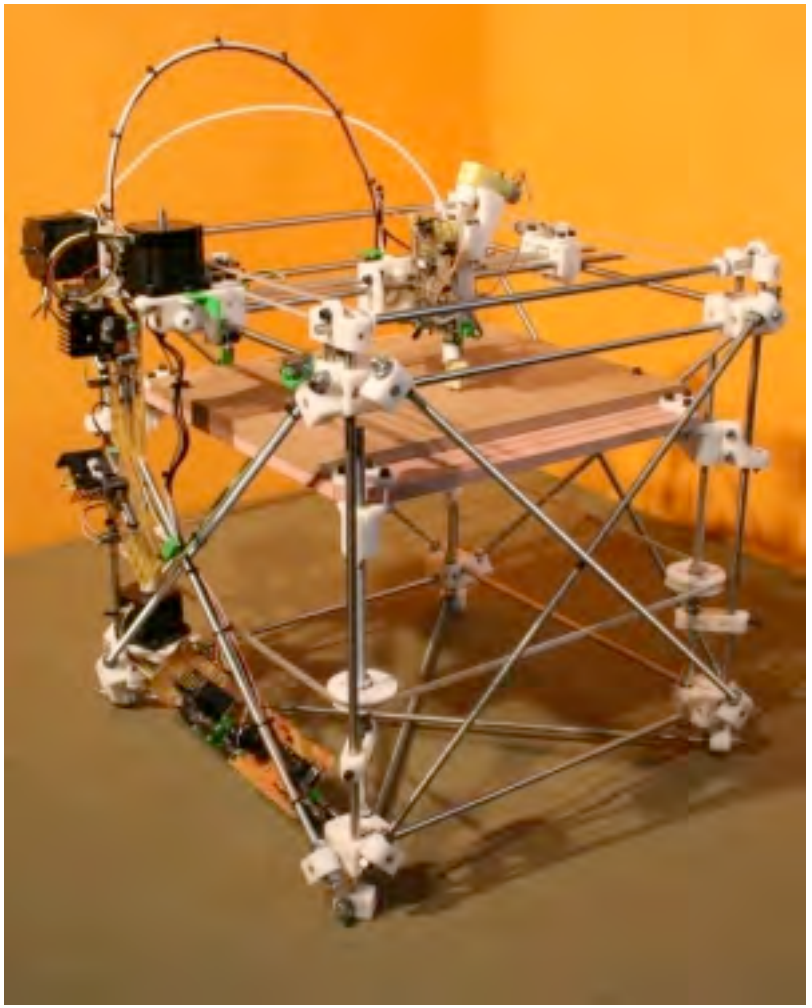
A 3D self-reproducing printer

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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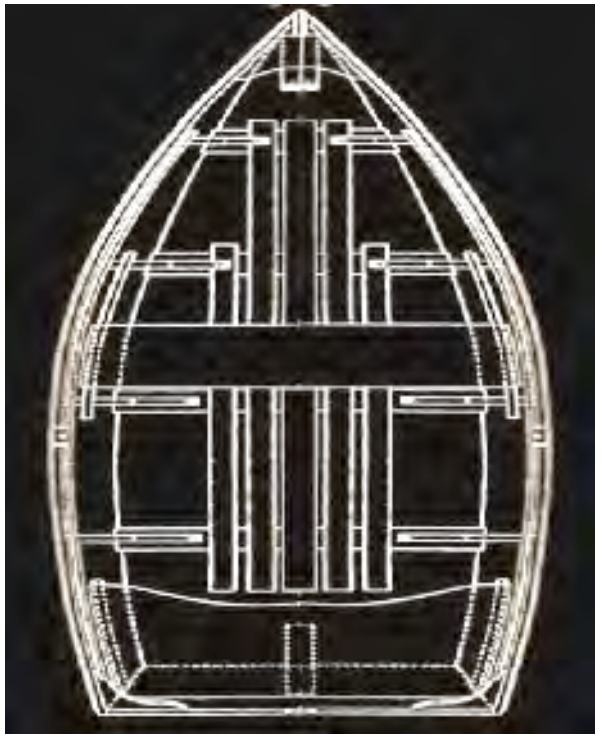
Biology is « symplectic »

Biology is a science of relationships between objects:

It is **symplectic** (συν together, πλεκτειν, to weave) the same word as « Complex » in Latin;

If the matter of the boat is of minor importance, what is the relevant category of Nature involved in the function of the boat?



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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The relevant category is “Information”

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

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Four or five categories of Nature?

Classical Physics

$E = mc^2$

energy matter space/time

Quantum Physics

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

uncertainty = lack of information

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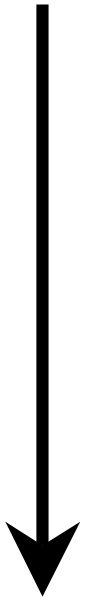
Revisiting the hierarchy of the sciences

Matter / Energy / Space / Time

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

Information



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Reconsidering 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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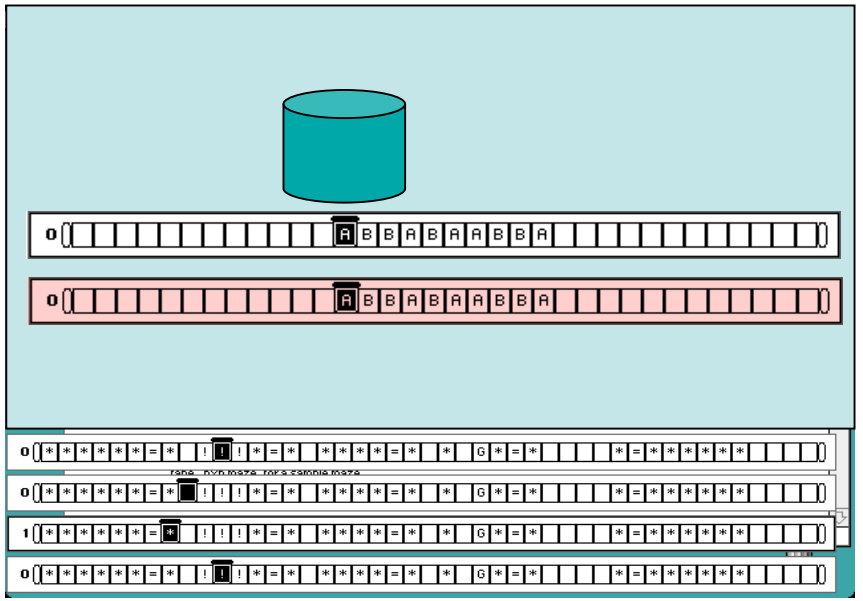
What computing is

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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Cells and computers

Genetics rests on the description of genomes as texts written with a four letter alphabet: do cells behave as computers?

Horizontal Gene Transfer

Viruses

Genetic engineering

Direct transplantation of a naked genome into a recipient cell with subsequent change of the recipient machine into a new one (2007)

all points to separation between

«Machine» (the cell factory) and «Data/Program» (the genome)

CONJECTURE: living organisms are information traps, and we can identify the concrete processes permitting accumulation of information

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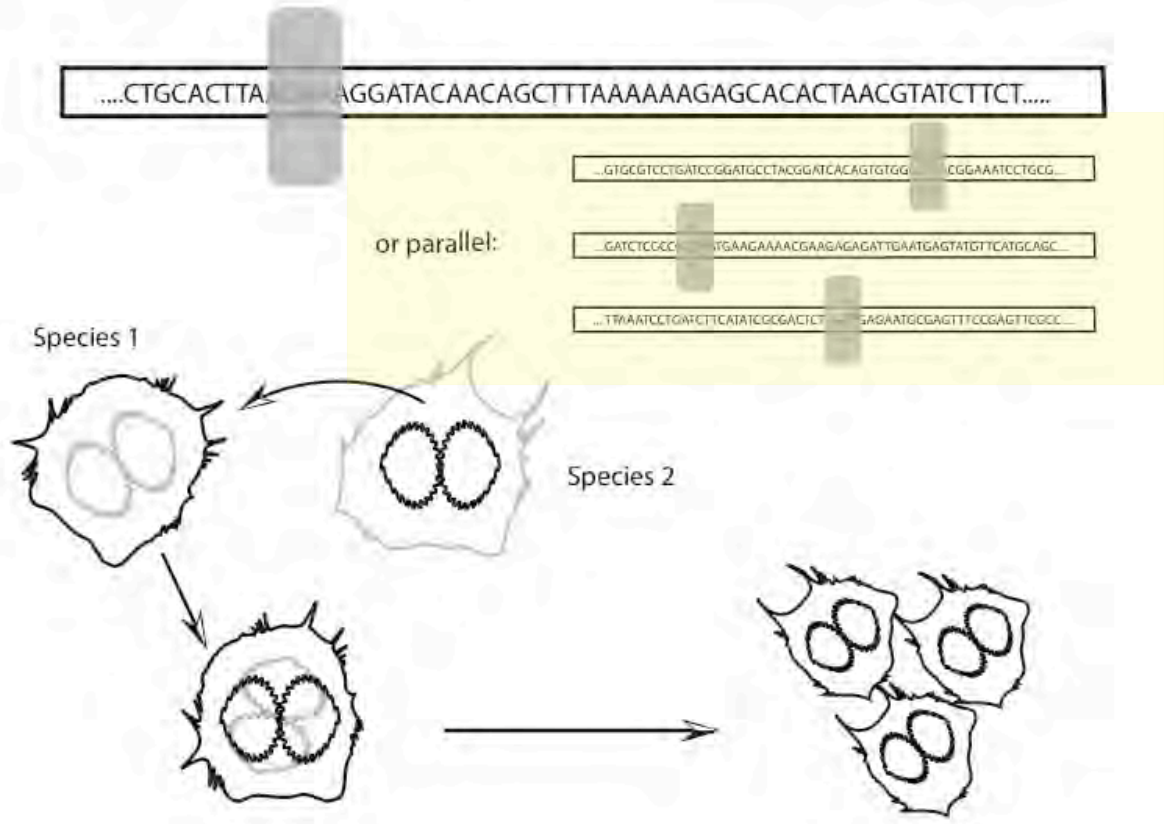
Venter's demonstration: the program

The Turing machine

May exist in a parallel set up



Genome transplantation

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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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Constructing the machine and the program

- The program *replicates*
- The machine *reproduces*

- Replication accumulates errors
- Reproduction can improve over time

- **This process implies creation of information**
- **This is widely different from what is expected from a factory**

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Everything ages

Ageing is a ubiquitous constraint in the genome, in the proteome, in metabolism…

Yet « babies are born very young » !

This implies that creation of information is a ubiquitous process of life; resting on ubiquitous functions

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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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From functional ubiquity to gene persistence

Functional ubiquity does not imply structural ubiquity. Fortunately, efficient objects tend to persist over generations:

- Looking for « persistence » permits identification of (most) ubiquitous functions
- Is « ubiquitous » a synonym of « essential »? **NO**

~ 500 genes persist in bacterial genomes; about 250 cannot be inactivated without loss of capacity to live; what about the other half?

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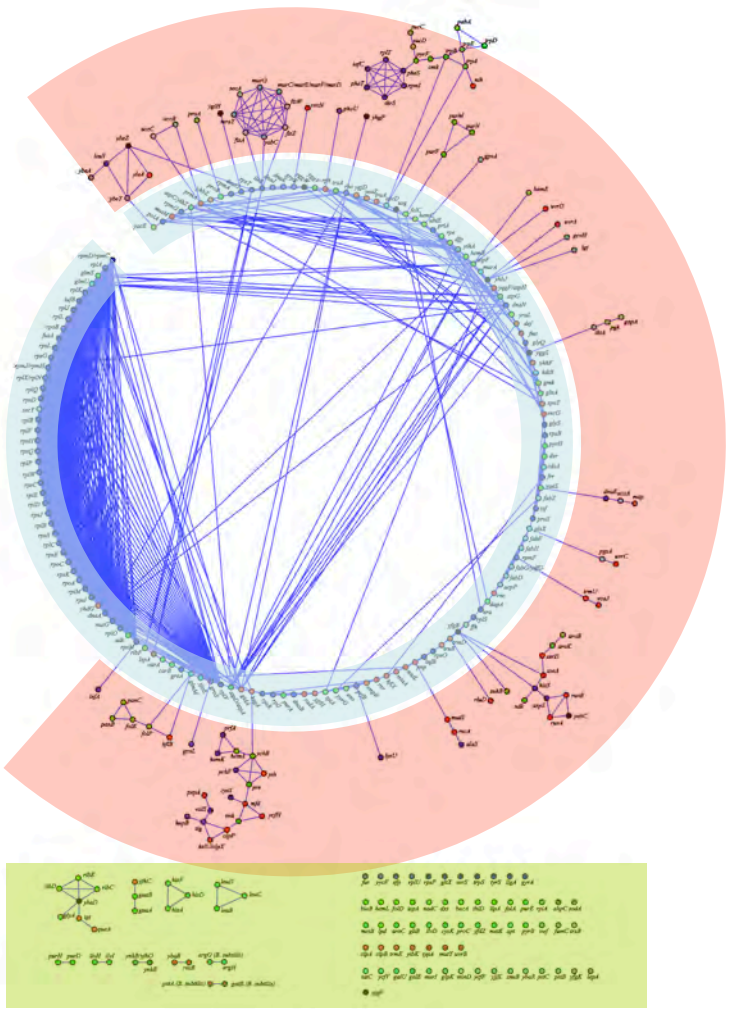
Persistent genes recapitulate the origin of life

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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Persistent genes are clustered together

Persistent genes are functionally defined. Depending of their tendency to remain clustered in genomes they form three families that reflect a scenario of the origin of life. This group of core genes form the paleome (from παλαιος, ancient)

The rest is highly variable and form the cenome (from κοινος, common, to mark their role in permitting occupation of a common niche)

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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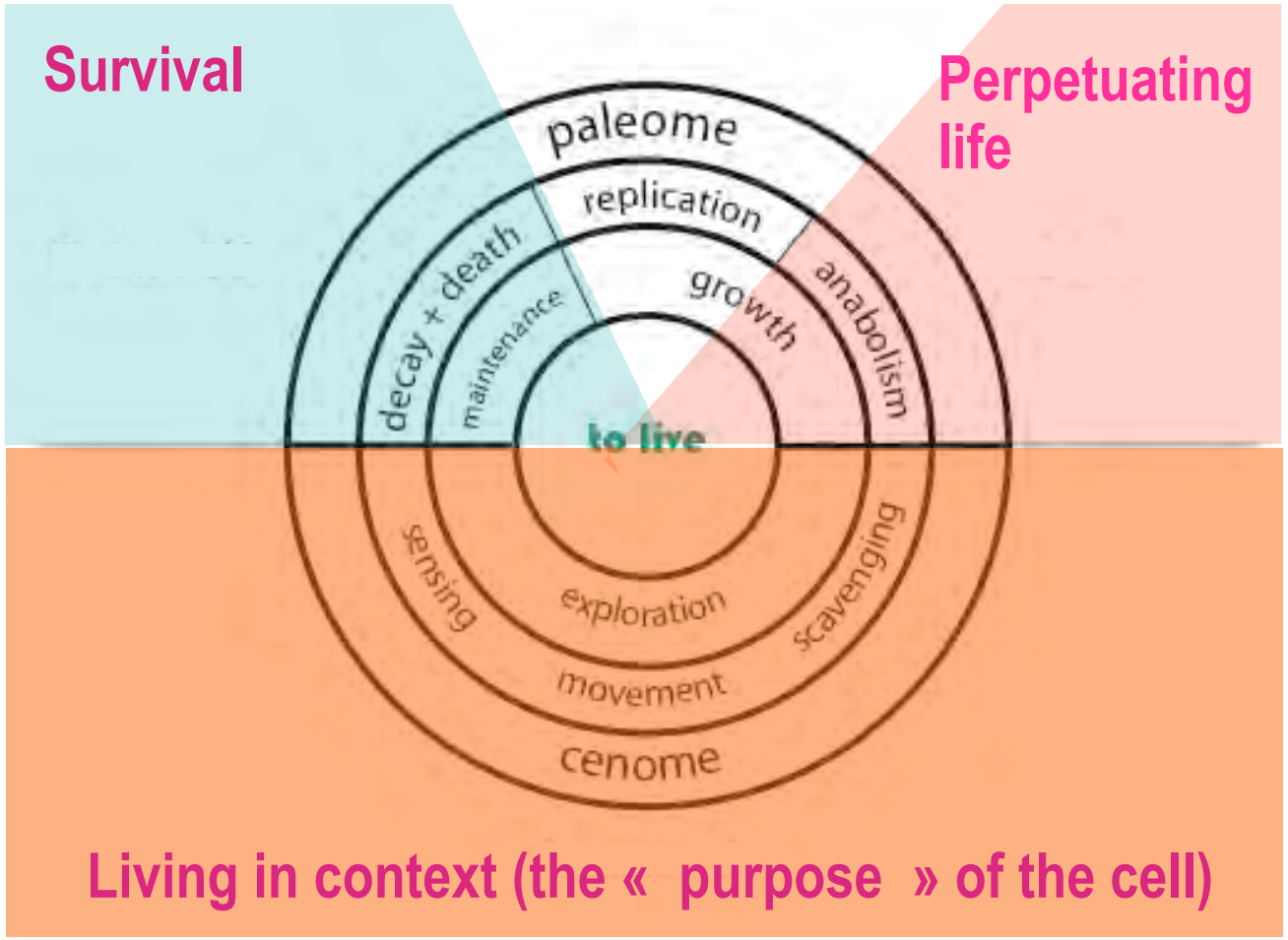
A tale of two genomes

metagenomics



Σ = {pan-genome}

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Reproduction and replication again

- **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?

Is the process permitted by physics?

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Revisiting information

Intuition tells 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 information: 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?

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Too many persistent genes….

- **Paleome 1 (genes that are essential for a synthetic bacterium)**
  - **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 processes, preventing degradation of functional entities
  - Metabolic patches (chemical frustration)

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Provisional conclusion

- Information theories and biology are reconciled via the common requirement for degradation processes requiring energy to avoid destroying what is functional
- Living organisms accumulate information, whatever its origin: they are information traps
- This accounts for their « tinkering » features and the constant increase of complexity over time
- The process must be general, and needs also to account for cell differentiation (metamorphosis) and learning and memory

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Construction of a synthetic cell

- Construction of a minimal genome with the genes of the constructor and the replicator in a minimised host cell
- Addition of specific genes to fulfill the goal of the cell factory (fine chemicals, biofuels, depollution…)
- Engineering requires omission of the genes permitting creation of information

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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 a considerable societal advantage, as the risks associated to spontaneous innovation are minimised

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