

Organisms and ecosystems like programmable machines: some consequences of the mechanistic bias on nature

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Papers on theoretical aspects of this theme:

– <https://www.di.ens.fr/users/longo/download>

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Fantastic new **mechanical devices** for *moving* bodies and fluids

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Galileo permanent reference: the constructions by the artisans in Venice and Florence

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Descartes : « the **universe is a machine** where there is nothing else at all to consider than the figures and movements of its parts » (Les principes de la Philosophie, IV, 188)

Bacon : we have “to **drive nature** as a machine through action”
(quoted by a pioneer of **bio-technologies**: H. Hartley, "Agriculture as a source of raw materials for industry", *Journal textile institute*, 28, 1937)

XIX-XX century Physics, in one slide

Laplace, Fourier, 1820: mechanicism transposed into mathematics:

“any “reasonable” system of equation (any physical dynamics) can be **decomposed linearly** (the sum of the elementary and simple)”

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Physics, though, *moved away from* ... “the complex as (linear/mechanical) stacking of the simple”:

- **Poincaré, 1892**: Three Bodies (in their gravitational field):

Almost never one can give a linear approximation: the geometry of dynamical system (today's “theories of complexities”)

- **Quantum Physics**: indetermination, entanglement ..

- **Relativity Theory**: continuous deformations of space-time

XX century genetics, following Morgan, Huxley ...

« The cell is ... a **Cartesian Mechanism**, autonomous, exact, independent from external influences ... **Necessarily stereospecific** molecular interactions explain the structure of the code ... a boolean algebra, like in computers. »

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« ... if we could **create better human beings** through the addition of genes (from plants or animals), why deprive ourselves of them? What is the problem? »
J. Watson, Nobel Price, 1962

« The surprise is that the genetic specificity is written, not with ideograms as in Chinese, but with an **alphabet** »

F. Jacob, Nobel Price, 1965

(Still today's terms: gene-**editing**)

DNA as driving organisms in the ecosystem

Once decoded the DNA we will be able to transfer it on a CD-rom and say: “**Here is a human being, this is me**”

W. Gilbert, 1992, HGP

« we have caught the first glimpse of our own **instruction book**, previously known only to God »

F. Collins, June 2001

“Personalized medicine” (DNA on a DVD and use Big Data to cure)

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Core principles of genocentrism (the uni-directional and exact transmission of information):

- Exact **stereospecific** (form and chemical affinity) macromolecular correspondence (“necessary for transmitting and elaborating information”, Monod); the “**key-lock**” metaphor (late XIX century)

- The **Central Dogma** of Molecular Biology: ...

Exact, (stereo-)specific molecular correspondences

“The key-lock, hand-glove paradigms in molecular biology ... exact transmission and elaboration of biological information”

“gears of life”

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Against evidence and known to be false since 1960s:

"Even more radically ... proteins never do fold into a particular shape, but rather remain unstructured or “disordered” ... In mammals, about 75% of signaling proteins and half of *all* proteins are thought to contain long, disordered regions, while about 25% of all proteins are predicted to be “fully disordered” ... Many of these intrinsically unstructured proteins are involved in regulatory processes, and are often at the center of large protein interaction networks"

Jörg Gsponer and M. Madan Babu, “The Rules of Disorder Or Why Disorder Rules,” *Progress in Biophysics and Molecular Biology* (2009).

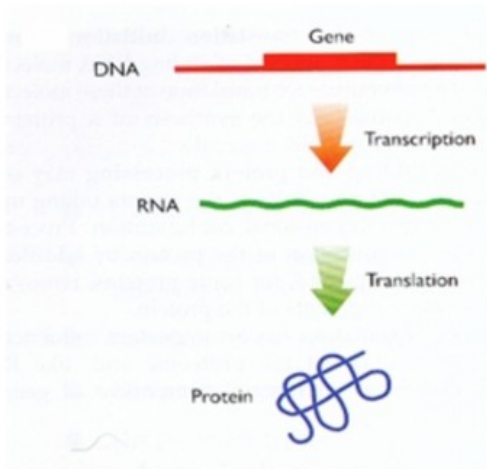
Central Dogma of Molecular Biology, Crick, Watson, 1958-62:

In University and High Schools textbooks, today

GMOs: direct children of the Central Dogma

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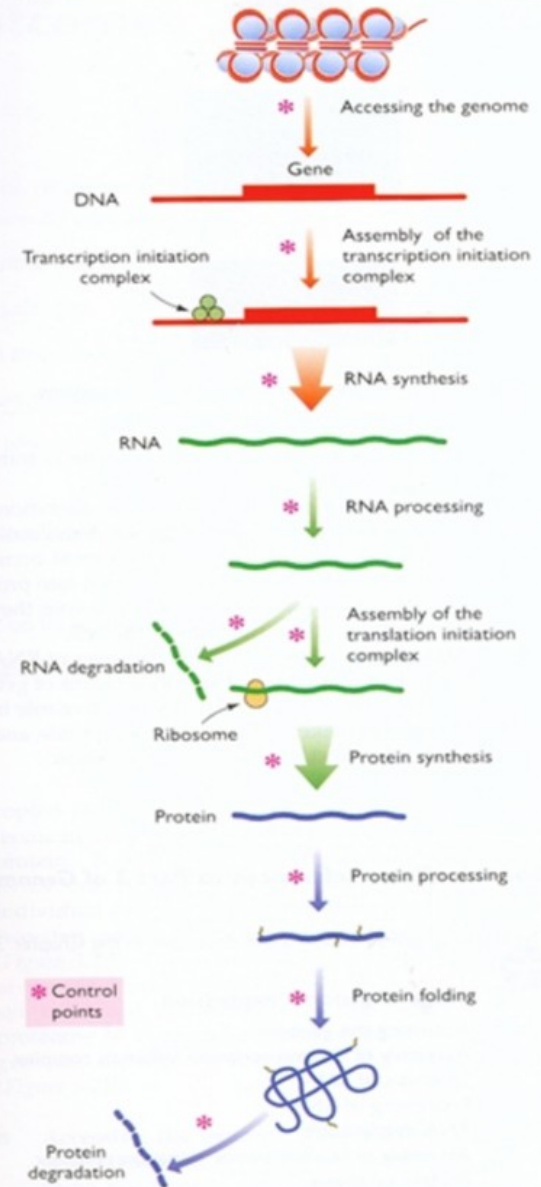
En 1960



(d'après Brown, 2002, in *genomes*)

En 2000

Transcription
Traduction



In University and High Schools textbooks, today

What is a gene ?

The notion of gene changed five times in the XX century

E. Fox-Keller, The century of the gene, 2001

« We expect to find 80,000 genes »

F. Collins, Head of HGP, **1999** (!) (Head of NIH)

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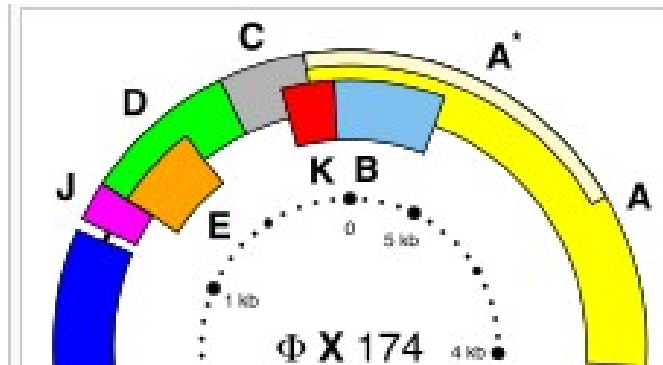
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Now: Stochastic gene expression, alternative splicing, overlapping genes ...



Bacteriophage ΦX174 genome: Genes E, K, B overlap with genes D, C, A.

Sanger, F. et al. (1977). "Nucleotide sequence of bacteriophage ΦX

SARS-CoV-2 was “*decoded*” in January 2020

Fantastic knowledge for an evolutionary (historical)
perspective

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What does the virus do in a “context” ?

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What does the virus do in a “context” ?

COVID-19 : « Symptoms can range from nil to mild to severe, to having to go to hospital, to being on life support, to death. Some people recover quickly, others take many months of rehabilitation to recover. Some never seem to fully recover – e.g. lungs may be so scarred that they may never fully recover. »

Judy Carman, former Senior Epidemiologist, Communicable Disease Control
Branch, Adelaide.

Neural damages: stroke, brain haemorrhage and memory loss

M. Marshall, *Nature*, Sept. 15, 2020

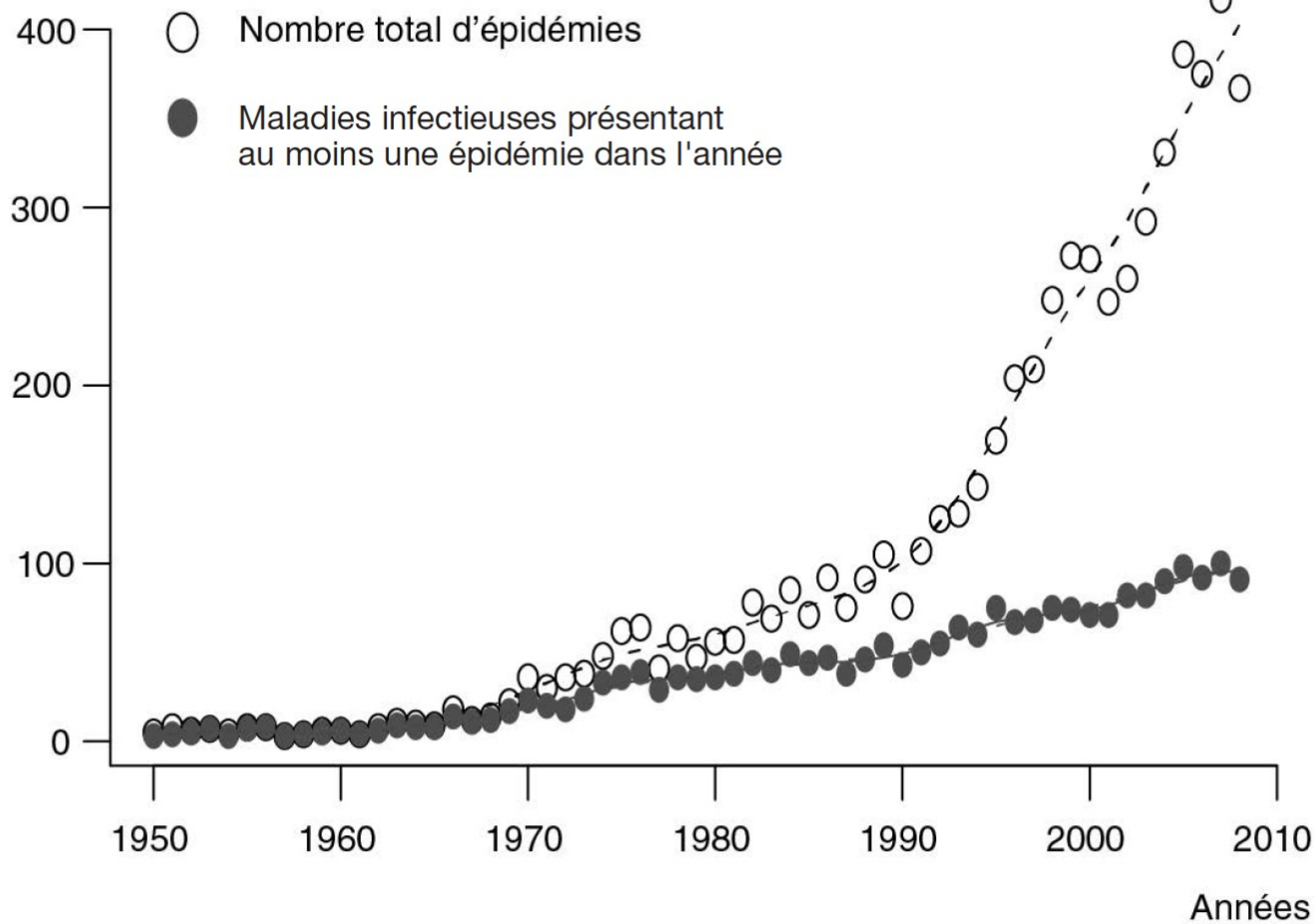
Note: SARS-CoV-2 seems to contain a high number of **overlapping genes** ... *thus* (?), its “functions” are highly context dependent

A zoonosis?

Number of *epidemics* from 1950 to 2010 (Morand, Figuié (coord.) 2015).

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Figure 2. Évolution du nombre d'épidémies de maladies infectieuses dans le monde de 1950 à 2010.



About 70% are **zoonoses**

D'après Morand, 2015.

SARS-CoV-2 / Covid19

Has **SARS-CoV-2** been artificially edited ? No idea, but ...

Fantastic technologies: chemistry, crystallography, electronics, informatics ... are in the hands of **geno-centric** fanatics

Analogy: give a rocket capable to reach Mars to people following the Ptolemaic, **geo-centric** perspective ...

Precaution and alternative theories

Principle of Scientific precaution:

GMO's, gene-editing, gene-driving ... are grounded on the

- **Central Dogma**

- The **key-lock** metaphor (**exact stereospecific** macromolecular interactions ...)

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Major relevance of the DNA (!): the chemico-physical trace of the evolution, *continually used* by the cell, in a context.

E.g.: The cave-fish: *hybrid offsprings with eyes* [Gatenby, 2011]

Molecular Biology gave us fantastic data and **mechanisms**

Cf. Ptolemaic Astronomy: the **Alfonsine Table** (XV century)

G. Longo, M. Mossio. *Geocentrism vs genocentrism: theories without metaphors, metaphors without theories* <https://hal.archives-ouvertes.fr/hal-02963836/document>

Towards new principles

Towards new principles

“Macromolecular interactions are stochastic, they must be given in probabilities and these probabilities depend on the context”

Somehow known since 1983: see Paldi and Kupiec papers in <https://ojs.uniroma1.it/index.php/Organisms/issue/view/1521/showToc>

see (Elowitz et al., 2002)

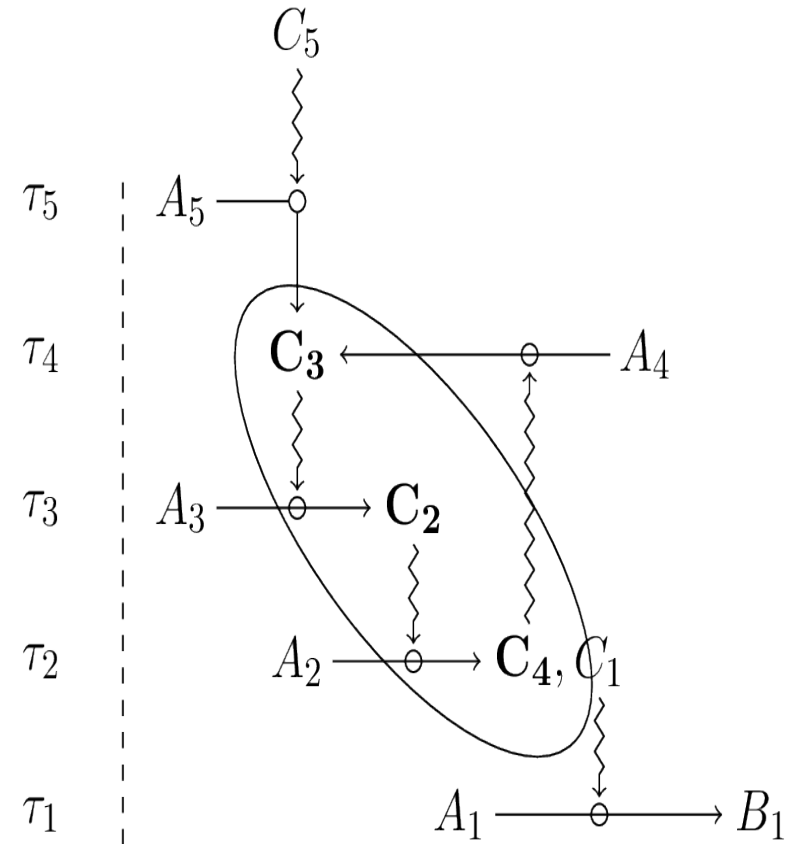
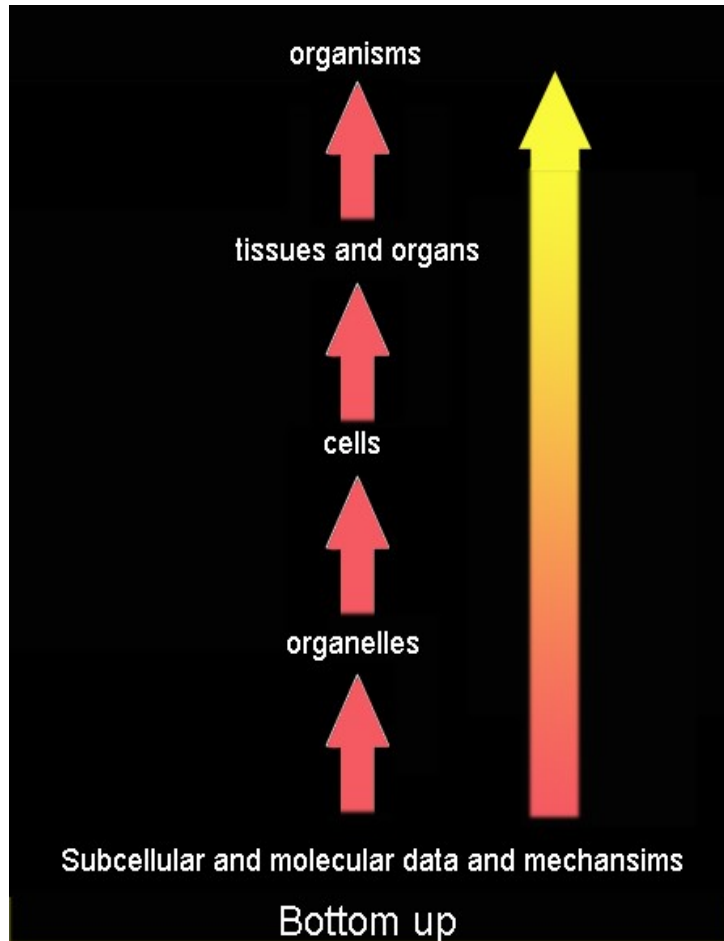
“Almost all, most common phenotypes *use* almost all DNA”

Almost all of the DNA is used/expressed in almost all cells, (Paldi, 2020)

The cell, the organism and the ecosystem strongly canalize, **constrain** and **select** macromolecular interactions, starting with gene expression.

Soto A., Longo G. (eds.) "**From the century of the genome to the century of the organism: New theoretical approaches**", a *Special issue* of *Progress in Biophysics and Molecular Biology*, Vol. 122, Issue 1, Elsevier, 2016

Move from *Central Dogma* to *Closure of Constraints*



Montévil, Mossio, *Theor. Bio.*, 2015
Soto A., Longo G. (eds.), *PBMB*, 2016

Some readings

Fox Keller, E. **The century of the gene**, Harvard U. P., 2000.

Kupiec JJ., Sonigo P. **Ni Dieu, ni gène**, Seuil, 2003

Noble D. **The Music of Life. Biology Beyond the Genome.**
Oxford: OUP, 2006.

Montévil, M., Mossio, M.: *Biological organisation as closure of constraints.* **J. Theor. Biol.** 372, 179–191, 2015.

Some *downloadable* papers: Search: Giuseppe Longo, Paris
<https://www.di.ens.fr/users/longo/>

- Longo G., Montévil M., **Perspectives on Organisms: Biological Time, Symmetries and Singularities**, *Springer*, Berlin, 2014.
- Soto A., Longo G. (guest eds), **From the century of the genome to the century of the organism: New theoretical approaches** *Special issue of Progress in Biophysics and Molecular Biology*, 122, 1, 2016.

Longo G.. *Confusing biological twins and atomic clocks. Today's ecological relevance of Bergson-Einstein debate on time. "What is time? Einstein and Bergson 100 years later"*, April 4-6, 2019 (in print, Campo, Ronchi eds)

Unpredictable interactions

“Doses” of Chemicals in the Ecosystem

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Unnoticed Endocrine disruptors:

82,000 artificial molecules produced in the XX century

(FDA Rep Congress, 2008)

Do not worry: **small doses** *and* **not stereo-specific**

The myth of the “genetic program”:

In order to carry information, de-program the genetic program
molecular interactions *necessarely stereospecific* (key-lock) ...

[Monod, 1970], [Maynard-Smyth, 1999]

- *No:*

- **non-linear** effects, **low** chemical affinities

- **varying** association/dissociation constants, **contextual**

- to be given in **probabilities**, depending on the **context** [Elowitz, 2002]

Some Data on Endocrine Disruptors

- **Endocrine target organs, cancer general increase (1994 – 2012) :**
breast 26% ; testis 56% ; prostate 94%
thyroid cancer (+285% in 30 years, till 2012)

S. De Coster, N. van Larebeke, Endocrine-disrupting chemicals, **J. Environ. Public Health** 2012.

N. Howlander, et al, SEER Cancer Statistics Review, 1975–2012,
National Cancer Institute.

- **The case of asbestos (Maltoni '70s; Huang, 2011)**

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National Cancer Institute.

- **The case of asbestos** (Maltoni '70s; Huang, 2011)
- **Lowering by 50% (!) of human spermatozoa density** since 1950's

E. Diamanti-Kandarakis et al. *Endocrine-disrupting chemicals: an Endocrine Society scientific statement.* **Endocr Rev** 30:293-342, 2009

N. Skakkebaek, *Sperm counts, testicular cancer, environment,* **BMJ**, 2017

- **GMOs: children of the Central Dogma: programming the plant ...**
(Buiatti, 2002)

The GMO's: a direct consequence of the *Central Dogma*

Remember: the **completeness of the DNA coding** of an organism
« the organism: a mere vehicle ... », « once the DNA fully decoded
... on a CD-rom... this is a man, this is me» (Collins, Gilbert, Guyon,...)

- Indirect consequences of **pesticides resistance** (absorption, transfer ...)
- *Major modifications of microbial flora and fauna* (fungi, roots, soil)
 - G.A. Kowalchuk et al., 2003. Assessing responses of soil microorganisms to GM plants. **Trends in Ecology and Evolution** 18, 403–410.
 - M. Castaldini, et al, 2005, Impact of Bt Corn on Rhizospheric and Soil Eubacterial Communities and on Beneficial Mycorrhizal Symbiosis in Experimental Microcosms, **Applied and Environmental Microbiology**, 71: 6719-29
 - M. A. Badri et al., 2009, Unintended molecular interactions in transgenic plants expressing clinically useful proteins..., **Proteomics**, 9: 746–756.

Hints to Cancer Research, after 2001

« ... genetic therapies for eliminating suffering and death due to cancer by 2015» (van Eschenbach, 2003): diagnosis, prognosis ... in a few years

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« tumors without mutations » (Versteg, 2014)

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« most human carcinogens are actually not mutagenic» (Weinberg, 2014)

« hybridation of different species of **Cavefish**, which evolved from a “normal” fish, yield fishes with functional eyes » (Gatenby, 2011)

Longo G. (2018c) Information and Causality: Mathematical Reflections on Cancer Biology. In *Organisms. Journal of Biological Sciences*, vol 2, n.1.

Some references (papers *downloadable*: Google: Giuseppe Longo ENS)

- Longo G., Montévil M., **Perspectives on Organisms: Biological Time, Symmetries and Singularities**, *Springer*, Berlin, 2014.
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Buiatti M., Longo G. *Randomness and Multilevel Interactions in Biology*, **Theory of Biosciences**, vol. 132, n. 3:139-158, 2013.

Bravi B., Longo G. *The Unconventionality of Nature: Biology, from Noise to Functional Randomness*. Invited Lecture, Auckland (NZ), 31/8 - 4/9/2015, proceedings in **Springer LNCS**, Calude et al. (Eds.), 2015.

Calude C., Longo G. *Classical, Quantum and Biological Randomness as Relative Unpredictability*. Special issue of **Natural Comput**, 15:2, Springer, 2016.

Longo G. *How Future Depends on Past and on Rare events in Systems of Life*, in **Found. Sci.** 2017 (en français, Berthoz ed., **Odile Jacob**, 2019)