L'importanza del "modello standard" per l'Informatica come scienza, contro lo scientismo del "tutto è informazione"

Giuseppe Longo

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- Simone Martini 60th birthday conference, January 2020

Martini's notion of "Standard Model"

"**Despite** some early insights of some of the pioneers **(Turing, von Neumann, Curry)**, programming the early computers was a matter of fiddling with small **architecture-dependent** details"

"The **standard model** was not born together with the general purpose electronic computer—it is rather the **result of a deliberate research agenda** of the end of fifties and the early sixties of the last century"

(Martini, 2019)

"A mathematical theory of computation”

Böhm (1954!), McCarthy, Landin (1960’s) …. Scott (1969) ….

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Alfonso **Caracciolo**:
"Some remarks on the syntax of symbolic programming languages".
Commun. ACM 6(8) (**1963**)

Fig 4.6: Official inauguration of the CEP (1960): Alessando Faedo on the extreme left side, President Gronchi at centre and Alfonso Caracciolo at his left (1960)

Why a mathematical theory of computation?

Boltzmann: “There is nothing more practical than a good theory”

Turing, 1947: “there will be much more practical scope for logical systems than there has been in the past.”

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Kreisel, 1971: “Some reasons for generalizing Recursion Theory”

Kreisel: Four letters to G.L. (1982-83)

https://www.di.ens.fr/users/longo/download.html

- Making **explicit** the (intended) **principles**
- Taking a step **aside**
- **Changing** the principles of knowledge construction

Theories and Knowledge Construction

In Science, thinking differently,

- novelty grounded on ***critical*** *thinking* and *proposal*

Explicit principles: awareness of the **limits** of knowledge construction, always an **interpretation**, a perspective (a friction on, canalized by "reality")

The relevance of **Negative Results**

Poincaré, Gödel, Einstein (Longo, *Interfaces of Incompleteness* 2010-19)

Thanks to **F. Bailly**, T. Paul, M. Mugur-Schachter (*physics)*
M. Montévil, **A. Soto**, M. Buiatti … (*biology*)

Next ...

- **Science** *vs* **Scientism (**G. Cardano)
- **"All is information"**: DNA (the genetic program)
- **Some consequences in Biology** (cancer research, GMO)
- **The myth of Big Data**, in spite of their relevance
- **Framing causality** in Physics and Biology

Science *vs* **Scientism**

Scientism, *some properties*:

- **occupy** reality with existing tools (possibly one: e.g. “Information”)

- projecting the **latest machine** on the world (brain, DNA …)

- make intelligible and *govern* the world by **optimization methods**

- **science for control**: flatten on one dimension, “*follow the rule”*

Focus on some ***Biases on Knowledge*** posed by scientism
(and its promises: “Pourquoi tant de promesses?” Audétat, ed.,’15)

Science *against* **Scientism**

Association "**G. Cardano**" http://cardano.visions-des-sciences.eu

"Science against Scientism"

The role of human *"**interpretation** and **meaning**" in* **Mathematics,**
against "unique and optimal paths" and "follow the rule"

With:
N. **Bouleau** (stochast), M. **Montévil** (bio), A. **Sarti** (morphogenesis)

We " … mathematical invention and construction of understandings
rather than purely *quantitative analyses* and *reductionism* …
for *knowledge construction* more than for *control*"

Big Data

Calude, Longo, *The deluge of spurious correlations in Big Data*, 2016

How did people get to Big Data in Cancer Biology?

By the failure of the prevailing *theories* of cancer

Collaboration since 2008 with the
Soto Lab, Boston
Ana Soto, Carlos Sonnenschein

(*endocrine disruptors and their carcinogenetic effects*)

The myth (and the disaster) of the DNA as "**genetic program**" and the **Central Dogma** of Molecular Biology

From **des-embodied biology** to a **dehumanized** science:

How to "re-program the de-programmed DNA"

Nixon's **War on Cancer**: re-program DNA, 1971 - 1976

Just **data**, give-up **understanding**

The myth of the "genetic program"

- ***J. Monod**, 1970:* "[in cells] … the molecular processes are a **Cartesian Mechanism**, autonomous, **exact**, **independent** from external influences …

  Oriented transmission of **information** …

  || ***Necessarely stereospecific*** || molecular interactions explain the structure of the code … a boolean algebra, **like in computers**"

  Compositional-linear thinking, Laplacian (chance/necessity)

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  False: since '50s: largely **stochastic**, probabilities, context
  - **changing** affinity constants
  - large enthalpic **oscillations**, non-linear interactions
  - **context** dependence (Kupiec 1983 … Elowitz 2002 ...)

  - Main stream keyword: **signal** ... *a gradient ? information ?*

  Apothosis (deprivation), *reproduction* (estradiol) (Sonigo, Soto ...)

The myth of the “genetic information”

Two major theories of Information :

Elaboration (Turing-Kolmogorof) and
Transmission (Shannon 1948, Brillouin 1956, see (Longo, ‘19))

Key difference : co/contra-variance of **complexity** with **entropy**

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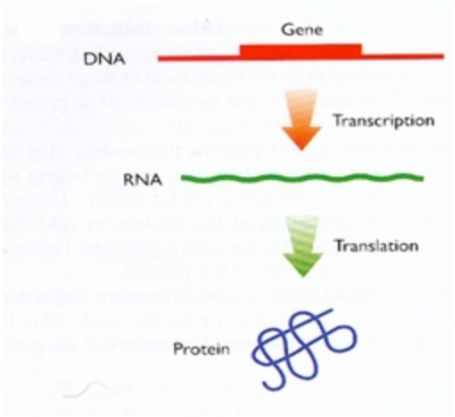
Main stream Molecular Biology :

- Vague references to **common sense** notions;
  "*It is difficult to prove a vague theory false*" Feynman

- **Wrong** references to Turing vs Shannon theories
  Maynard-Smith J. *The idea of Information in Biology.*
  The Quarter Rev of Bio 74, 1999
  Gouyon, **2002** ; *Danchin*, **2006** ; Stanford Enc. Bio, **2016**. (Longo et al., 2012; 2018)

The Central Dogma still resisting: causality replaced by "coding"

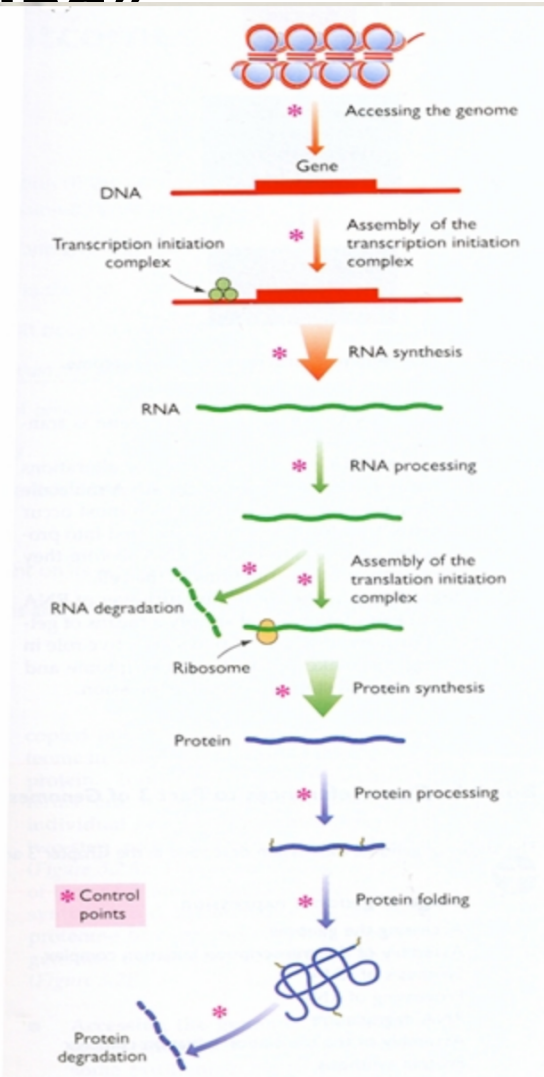
En 1960



Transcription

Traduction

En 2000



(d'après Brown, 2002, in *genomes*)

Till now (Peter&Davidson, *Genomic Control Process*, 2015 & 2019)
Cancer research: **onco-gene, proto-onco**-gene, **onco-suppressor-**gene...**GMO**

A **non-mecanicist** genetics marginalised

Waddington, McClintock: **epigenetics** (1930-50)
Kauffman's **gene-networks expression** (1970's)
Prusiner: **prions** (1980)
Kupiec: **stochastic gene expression** (1983) …

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Kupiec: **stochastic gene expression** (1983) …

Little attention by molecular biologists to:

Physics of the Cell:

Lesne et al. **Torsion and pressures for gene expressions** (2005)
Del Giudice et al. **Quantum hyper-coherence of water** (1990: increasing stochastic molecular interactions)

Process calculi for molecular interactions: **holistic** approaches (beyond the "compositional" attitude of main stream Molecular Bio)

“Doses” of Chemicals in the Ecosystem

The myth of the “genetic program”:

In order to implement the genetic program macro-molecular interactions are ***necessarely (stereo-)specific*** **(key-lock**: E. Fisher**)**

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Unnoticed **Endocrine disruptors:**

82,000 artificial molecules produced in the XX century

(FDA report, **USA Congress, 2008)**

Till then: Do not worry: **not stereo-specific** *and in* **small doses**

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No:

- **low** chemical affinities matter, **non-**linear and **cocktail** effects,
- **context dependent** association/dissociation constants,
- to be given in **probabilities**, depending on the **context** [Elowitz, 2002]

Major carcinogens … %

Some Data on Endocrine Disruptors and Cancer

- **endocrine target organs,** cancer general increase (1994 – 2012) :

brest 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**.

- **BisphenolA** (Soto et al, 1992)

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- **BisphenolA** (Soto et al, 1992)

- **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

- **GMOs**: children of the Central Dogma: programming the plant: %

GMO's: the direct heritage of the *Central Dogma*

"Drive the plant in the ecosystem from the DNA"

- 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 »

[many authors, see Longo, 2018]

GMO's: the direct heritage of the *Central Dogma*

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- 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 »

[many authors, see Longo, 2018]

Besides indirect consequences of **pesticides resistence** (absortion, transfer …), thus more ***endocrine disruptors,*** also:

Major modifications of **microbial symbionts** (fungi, roots, soil)

- G.A. Kowalchuk et la., 2003. Assessing responses of soil microorganisms to GM plants. **Trends in Ecology and Evolution** 18, 403–410.
- M. A. Badri et al., 2009, Unintended molecular interactions in transgenic plants expressing clinically useful proteins..., **Proteomics**, 9: 746–756.

Biology: genes and … public opinion

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"Being Rich and Successful Is in Your DNA"
(*Guardian*, July 12, 2018);

"A New Genetic Test Could Help Determine Children's Success"
(*Newsweek*, July 10, 2018);

''Our 'Fortunetelling Genes' make us''
(*Wall Street Journal*, Nov. 16, 2018).

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''Our 'Fortunetelling Genes' make us''
(*Wall Street Journal*, Nov. 16, 2018).

Longo, Mossio ''*Geocentrism vs genocentrism*", 2020
Longo, Vianelli, *''On the differential Method''* (revised), in prepar.
Böhm-out?

DNA decoding, 2000-01 (fantastic technological achievement)

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R. Weinberg, 2002: « **Cancer biology, now an exact science** »
A. Von Eschenbach, director Nat. Cancer Inst. 2003: ‘‘to eliminate the suffering and death from **cancer**, and to do so by 2015”
Diagnosis and **prognosis** within two or three years … *NO WAY !*

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C. Venter, interview for the *Spiegel, July 29, 2010*:
Title: « **We have learned nothing from the genome** »
« ... ***phonies*** … the ill-founded belief that those who know the DNA sequence also know every aspect of life. This nonsense ... »

http://www.spiegel.de/international/world/spiegel-interview-with-craig-venter-we-have-learned-nothing-from-the-genome-a-709174.html

Yet, **we did learn a lot**: *the case of cancer* ..

Cancer and the DNA decoding

From the massive DNA decoding of cells in cancer tissues:

1 - Gene-expression *signatures* for **benign** and **malignant** cancer may coexist in the same tumor.

2 - DNA sequencing does not help in distinguishing a **primary** from a **metastatic** cancer (80 % of letal cancer).

(Imielinski et al., 2012 ; Gerlinger, 2012 ; ...)

G. Longo. **Information and Causality: Mathematical Reflections on Cancer Biology**, 2018.

« most human carcinogens are **not mutagenic** » ... « most mutations are **followers**, not drivers » (Weinberg, 2014)

See also: Abestos (Maltoni, 1980);
R. Gatenby "***Of cancer and cave fish***", **Nature**, 2011

M. West-Eberhard, 2003; E. Jablonka, M. Lamb, 2008

Cancer and Big Data

Since … « myriads of **unexpected** mutations » (Weinberg, 2014)

« tumors **without** mutations » (Versteg, 2014)

« cancer cells that display … a **mutational burden** similar to and perhaps *even lower* than that of adjacent normal cells » (Gatenby, 2017).

Liver: Duncan AW., Aneuploidy, polyploidy and ploidy reversal in the liver. *Semin. Cell Dev. Biol*., Apr;24(4):347-56, Jan 16, 2013

- *All considered "hallmarks of cancer"...*

From a Mechanics of Organisms to a Mechanics of Thougth

Microsoft ‘‘Computing Cancer Project’’ 2016
http://news.microsoft.com/stories/computingcancer/

> “… we debug the DNA program and ***it is a solved problem***”

- A bias on research funds.

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R. Weinberg, 2014: the debacle :

« Never confuse cancer biology with science »

Yet another possible answer to the “debacle”:

mechanize thinking, **use Big Data**!

Cancer and Big Data

Since the ‘‘DNA centered’’ **War on Cancer is lost** ...

*Then **forget science***: let’s predict and act on the grounds of Big Data!

Big Data Driven cancer research (-omics):
diagnosis, prognosis … by correlations on Big Data :

- **Cancer Institute**, Oregon Health & Sci. Univ. & Intel, 2016:

http://www.informationweek.com/big-data/big-data-analytics/can-big-data-help-cure-cancer-/d/d-id/1326295

- Many Biology University Labs & **IBM**, 2016:

http://www.businessinsider.in/IBMs-Watson-can-now-do-in-minutes-what-takes-cancer-doctors-weeks/articleshow/47168413.cms

Big Data and The Market

- In spite of capitulation from Venter to Weinberg, Big Decoding Data still guide Biology ? *« We do not have enough data ! »*

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After the Human Genome Project, HGP, 2001 *(from 2006 to '15)*:

1 - **ENCODE**: decode 80% of human DNA considered "junk" DNA

2 - **Genome Wide Association Study**: correlate all common genetic variants and phenotypes (diseases)

3 - **Human Microbiome Project**: decode DNA of (all) symbiotic bacteria and fungi (some 3 million different genotypes)

4 - **Human Cancer Genome Atlas Project**: examine all *primary* cancer-related mutations (in 5 then 10 years, since 2006, 100 Mn$)

Big Data and The Market

Earth BioGenome Project :

It is asking for US$ **4.7 billion** to sequence all 1.35 million known eukaryotic species over the next 10 years

8 NOVEMBER 2018 | VOL 563 | **NATURE** | 155

What for ? In Which theory ? cf. **Evolution** ….

Big Data and The Market

S. Brenner (biologist, Nobel Prize) « this 'omic' science has corrupted us. It has created the idea that if you ***just collect a lot of data***, it will all work out » [quoted in Parrington, 2015]

R. Weinberg (2014) « **Generating large data sets** became an **almost-addictive** undertaking », then collect all « "**omics**" ... genomes, transcriptomes, proteomes, epigenomes, methylomes, glycomes ... »

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S. Rajan (2006) « Genomics allows the metaphor of life-as-information to become ***digital data*** that can be ***commodified*** … life in informational terms that can be packaged, turned into a commodity, and sold as a database » (p. 16)

From [Kowalski, Mrdjenovich, *in* American J. of Clin. Experim. Medicine, 2017]

Biology and Data

The data can be **marketed**!

In biology: decrypt, pack and sell ...

Hegemony of the **everything is information**:
software/hardware dualism *against* the **radical materiality of life**

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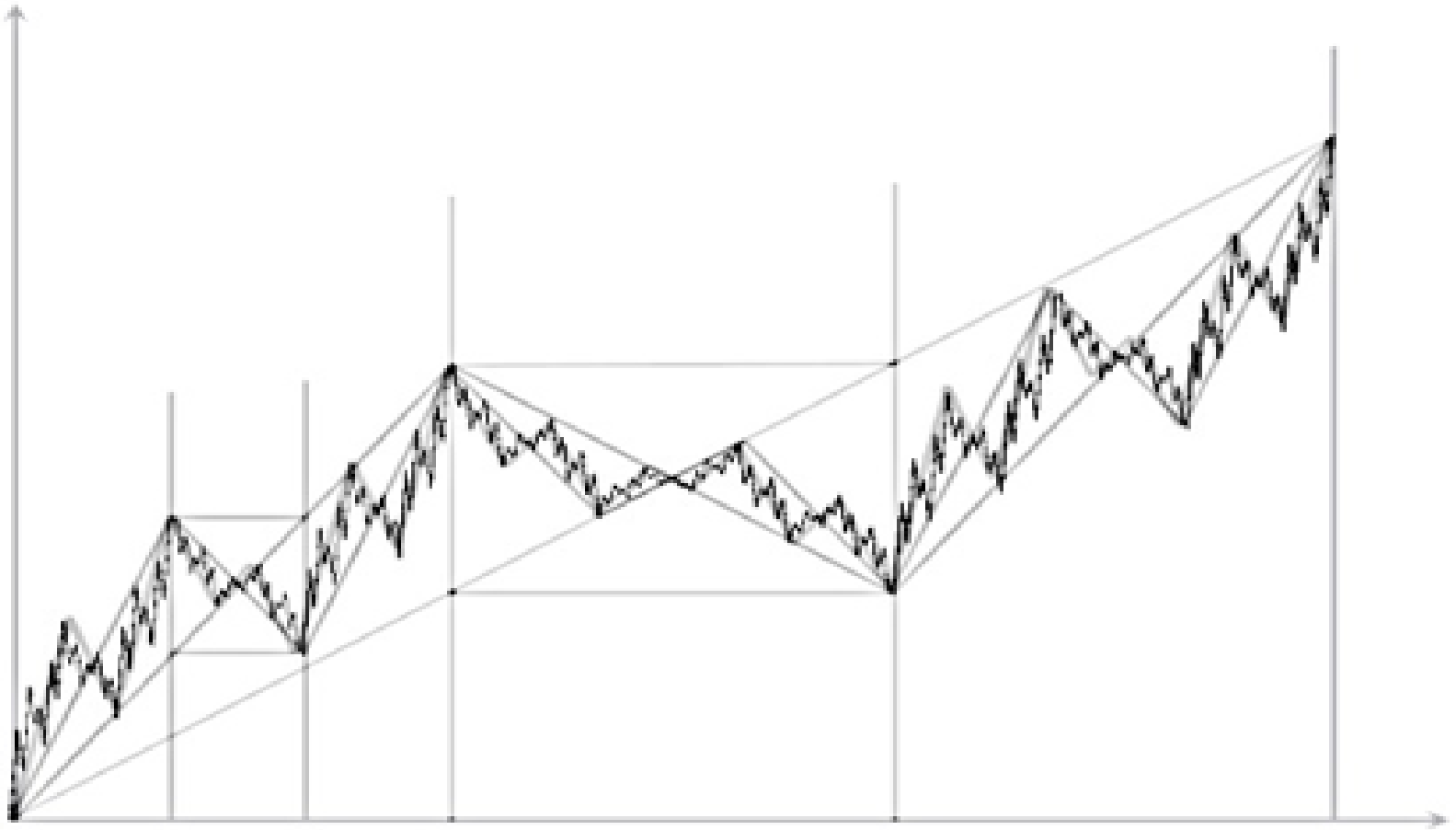
Economic value of information:

- **Huber** and **Rbnb** etc. only sell information:
packaging, encrypting and decrypting…
- The **stock market** evaluates information (**Hayek**, 1944)
Underlying "Value"? *Foodstuffs*: less than 50% (**S. Biasoni**)
"Value-labour"?

Fast Trading: gains on oscillations, forget trends



N. Bouleau, the stock-market's "fog" on trends,
http://cardano.visions-des-sciences.eu/fr

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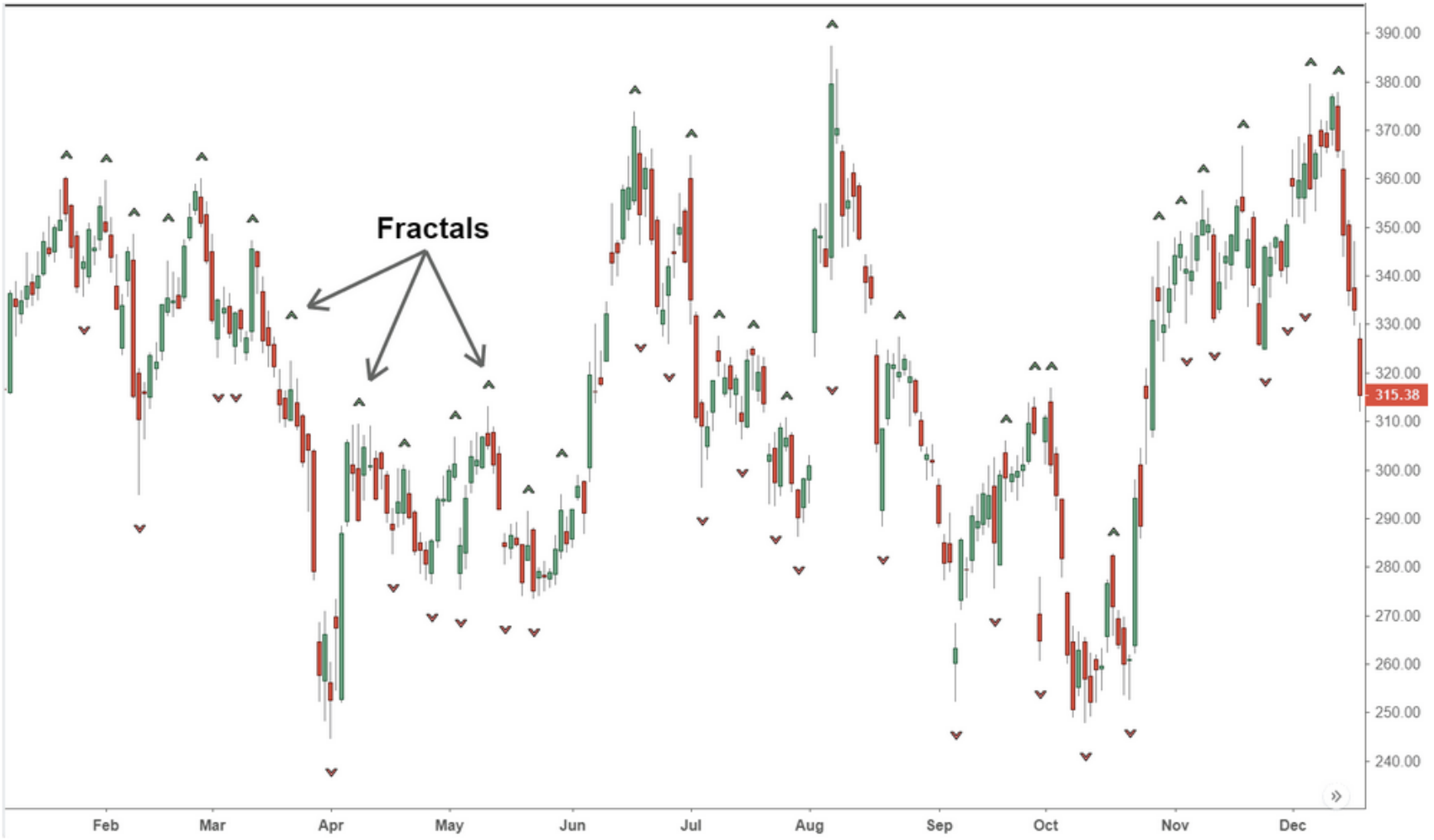

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Recovering Sense:
the Role of Causality in Biology

Big Data, a fantastic opportunity for science

Greek observations and speculation further enriched by

Experimental method (Galileo),
Mathematics (Descartes, Newton),

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Greek observations and speculation further enriched by

Experimental method (Galileo),
Mathematics (Descartes, Newton),
Big Data (if soundly used …)

Negative results: Pythagora, Riemann, Poincaré, Gödel, Einstein...

Presence of randomness in **Big Data** *is correlated to*
Concrete Unprovability (1978 - …), as negative results:
a form of **Feymann's awarness of ignorance**

Longo, Palamidessi, Paul, *On Randomness and determination,* 2010
Calude, Longo, *The deluge of spurious correlations in Big Data*, 2016

Do we need “causes”?

Modern Physics may avoid “causality” *(or “frame” causes)*:

1 - **Noether’s** theorems (1920): **Conservation** properties (momentum, energy) are ***continuous* symmetries** (in the equations)
2 - By the **Hamiltonian** variational method (Lagrangian): from conservation properties **derive** (**Newton**, Einstein, Schrödinger) trajectories
3 - thus falling bodies, **Kepler’s properties**, quantum dynamics (**Schrödinger’s** equation: probability amplitude) …

Causality not forgotten, but **framed** in (very) robust Theories:

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Causality not forgotten, but **framed** in (very) robust Theories:

“A **body falls**, a planet moves… ***for symmetry reasons”*** (Longo, ‘18)

Discrete/programming frame: **written instruction** (Wolfram, 2012)

Conclusion and Opening: Organismal Biology

Causality framed within proper principles:

Darwin's **first principle**, *applied within the **organism***:

- Reproduction with variation *and* motility (default state)
- Enablement (Longo, Montévil, Kauffman 2015)

Sound **causal** analysis: e.g. the "causes" of a pneumonia (a bacterium *enabled* by …), of **cancer** (unconstrained reproduction with variation)
and **enablement (**carcinogenes, disrupting control of reproduction – e.g. *asbestos not mutagenic*)

Soto A., Longo G. (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, Elsevier,2016.

Some references (*downloadable:* Google: Giuseppe Longo Paris)

Bailly F., Longo G. **Mathematics and the Natural Sciences. The Physical Singularity of Life.** *Imperial College Press*, London, 2011

Longo G., Montévil M., **Perspectives on Organisms: Biological Time, Symmetries and Singularities**, *Springer*, Berlin, 2014.

Soto A., Longo G. (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,** Vol. 122, Issue 1, Elsevier, 2016.

Calude C., Longo G. *The deluge of spurious correlations in Big Data*, *in* **Foundations of Science**, 1-18, March, 2016

Longo G. *Information and Causality: Mathematical Reflections on Cancer Biology*, **Organisms, J. Biology,** 2018.

Auguri Simone!

Allieva recente: Bijou, Piombino 2019