

LES ENJEUX DE L'ALÉATOIRE ET DU TEMPS, ENTRE MATHÉMATIQUES ET BIOLOGIE

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Papers on this theme:

- <https://www.di.ens.fr/users/longo/download-random.html>

Randomness, Unpredictability, Noise

Main **themes** of this lecture:

- Analyse Contingency or *Randomness* as *Relative Unpredictability* (w.r.to a theory):
 - no *absolute* notion of randomness in Science
 - but major *invariant relation*:
 - randomness, symmetry breaking, time irreversibility
- Compare the mathematics of **Randomness** and *Noise* in *Physics* and in *Biology*

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- Compare the mathematics of **Randomness** and *Noise* in *Physics* and in *Biology*

“Tell me how your theory deals with randomness,
I will tell your philosophy of nature (and of knowledge)”

Une brève histoire: le hasard, des hommes aux choses

- **Pacioli, Cardano, Galileo** (1400-1600): finance, cartes, dés ...
- **Pascal** (lettre à Fermat, 1654) : Méthode d'estimation d'un jeu ...
Une "modélisation" du hasard par les **probabilités**.
L'infini (le même pour le hasard) : « on en saisi *l'existence*, mais on n'en saurait connaître la **nature** »

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- **Spinoza** (Ethique, 1675): sur la « nature » du hasard :
la **rencontre de chaînes causales indépendantes**;
e. g. un tuile qui se décroche, glisse, tombe sur la tête du passant, deux parcours bien déterminés.
Pas d'analyse probabiliste, mais une proposition sur la **nature**:
imprédictibilité déterministe, très épistémique ...

The time, randomness, irreversibility in Physics vs Biology

Aristotle: “**time** is movement that is counted”

Galileo, Einstein: “time is what is measured by **clocks**”

Laplace, Kolmogorof (1930):

“**randomness** is what is measured by probability”

Boltzmann: “**time reversibility** is just a matter of (low) probability”

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This is all sound in Physics, **totally inadequate** in Biology

G. Longo *Confusing Biological Twins and Atomic Clocks: today's ecological relevance of Einstein-Bergson debate*, 2019

Classical Randomness in one slide

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1 - **Classical randomness** = *deterministic unpredictability*

Epistemic, e. g. since Poincaré (*Phase Space*: momentum x space)
« ... la complication de tous les problèmes de la dynamique où il n'y a pas d'intégrale uniforme [bifurcation, trajectoires homoclines...] » (Poincaré, 1892)

Poincaré, 1902 : « ... **et nous avons un phénomène aléatoire** »

1.1 Non-linear dynamics (*sensitivity, density, topol. trans. ...*) and

1.2 The interval of measurement (dice ... Solar System, Laskar, 1996)

- **Measurement**: the only “*access*” we have to “*reality*”

The fluctuation below measurement is “amplified” by non-linearity
e.g. thermal/gravitational fluctuation *different* from **noise** at *measurement*

Quantum Randomness in one slide

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2 - **Quantum randomness:** Objective or **intrinsic** (to the theory):

2.1 - indetermination (*non-commutative measurement*:

position/momentum or energy/time)

2.2 - **Schrödinger's** equation, probability amplitude (*Hilbert's Phase Space*)

2.3 - **Spin-up/spin-down** as pure contingency (no causes: standard interpret.)

2.4 - **entanglement** (*Bell inequalities: dice vs. entangled quanta*)

Challenge: continua and discrete *superpose* (waves *and* particles)

Different probabilities (Bell's inequalities) handled in different Phase Spaces (vs classical physics) over the **same observables** (energy, momentum ...), *incompatible theories*, in search for a unifying theory!

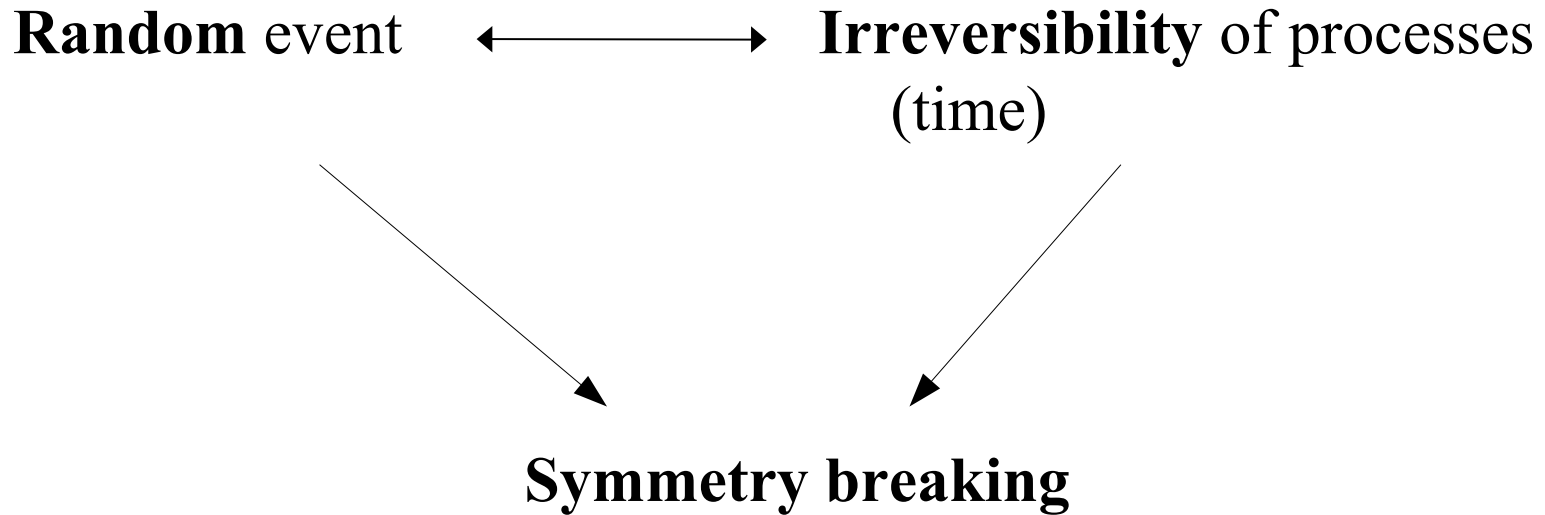
The unity of Physics

In both classical and quantum frames:

- A major symmetry: the **conservation of the Phase Space** (in each theory): thus randomness is given by probabilities (a measure on the Phase Space)
- Unifying **symmetries** (as conservation laws) and their breaking
- Each **Theory** defines Randomness, as **unpredictability**, that *differs* from “noise” at measurement (e.g. spin-up / spin-down)
- **Asymptotical Unity**, by Algorithmic Randomness (Kolmogoroff, Martin-Löf, Chaitin) *via* Computability Theory (Gacs, Calude: Hoyrup, Rojas, Abbott **Theses** 2008 et 2013)

Symmetry breaking, an invariant correlation

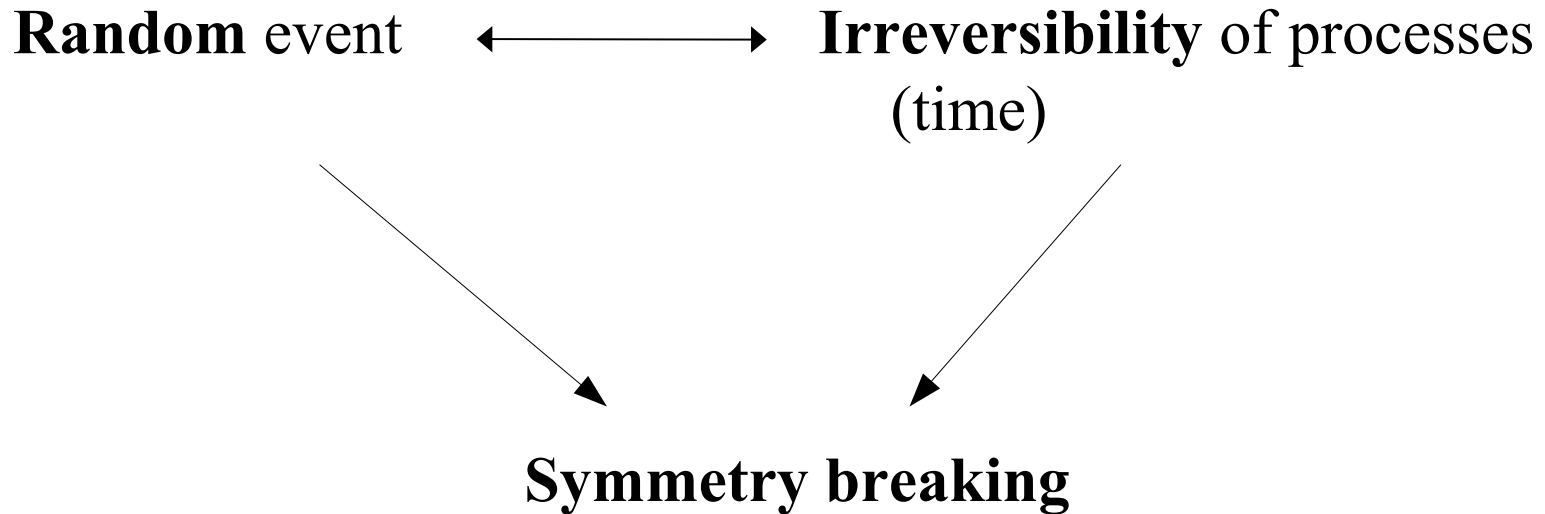
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Classical: bifurcations, critical transitions, diffusion (entropy in Thermodynamics) ...

Quantum: quantum measurement, Schrödinger ...

Biology: back to Darwin

Darwinian Evolution: some principles

Darwin's Evolution:

phylogenetic trajectories of *organisms* and *species*

Darwin's principles:

1. **Descent** *with* **modification** (cf. Buffon, Lamarck)
2. **Selection** (of the incompatible; i.e. death)

Thus the pertinent observables *change*:

the **phenotype** (beginning with the **cell**:

the *elementary, yet complex* component of life)

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*Note: 1. is a **non-conservation principle** (cf. Hamilton)*

Darwin on randomness

Variation is omnipresent: “no case is on record of a variable organism ceasing to vary under cultivation” (Origin, chap.1)

As for “the causes of variation ... there are two factors; namely, the nature of the organism, and the nature of the conditions. ... nearly similar variations [of the organism] sometimes arise under, *as far as we can judge*, dissimilar conditions; and, on the other hand, dissimilar variations arise *under conditions which appear to be nearly uniform* ... we may infer that variability is thus induced, partly from the fact of *this system being extremely sensitive to any change in the conditions*” (my italics). (Origin, chap.5)

A reference also for Boltzmann (1890) ...

Physical Determination and Randomness

Laplace's view:

A) determination \Rightarrow predictability

B) determination \neq randomness

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[J. Monod, Le hasard et la nécessité, 1970]

“The cell is ... the molecular processes are a *Cartesian Mechanism*, autonomous, exact, independent from external influences ... Necessarily **stereospecific** molecular interactions ... a boolean algebra, like in computers ... Genes **define completely** the tridimensional folding of proteins, the epigenetic environment only excludes the other possible foldings. ... **Evolution originates in noise, imperfections**” (J. Monod, 1971)

The constitutive role of randomness in Biology

One of the crucial « changes of perspective », in Biology:

- Not noise,
- No “stochastic” stability (large numbers), but

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Randomness *implies* variability *implies* diversity

An essential component of **structural stability**, by “low” numbers

Compare: Randomness as intrinsic to Quantum Mechanics:

it changes measurement and the “structure of determination”
(Schrödinger equation).

Take an analogous, not homologous conceptual step ...

Biological relevance of randomness

Randomness in molecular activities:

Each cell reproduction (elementary *and* fundamental):

Asymmetric partitions of proteomes; *differences* in DNA copies; *changes* in membranes ...

In multicellular organisms: varying reconstruction of tissues' matrix (collagen structure, cell-to-cell connections ...), a **symmetry breaking** (a new coherence, a *critical transition*)

[Bailly, Longo, Montévil, 2006 – 14]

Consequence: **intrinsic irreversibility** in phylo-onto-genesis:

- The construction of organization (e.g. embryogenesis) joins a production of slight disorder: **don't even dream to reverse it!**

Which form of randomness ?

The cellular core of randomness in Biology

Randomness in molecular activities ... more :

Each cell reproduction (elementary *and* fundamental):

- *asymmetric* partitions of proteome;
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- *changes* in membranes ... **adaptivity** in unicellular organisms

Do random events "average out" in (large) *clonal populations*?

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Do random events "average out" in (large) *clonal populations*?

No! « two yeast cell populations derived from a *single steady-state mother population* and exhibiting a similar growth phenotype in response to an environmental challenge, displayed *diverse expression patterns* of essential genes » (10^8 - 10^{10} cells)

E. Stolovicki, E. Braun, PLoS ONE, June 2011, vol.6- 6
Bury-Moné, Sclavi, "Stochasticity ... epigenetics in bacteria", *Microbiology*, 2017

Inside the Cell

Quantum and Classical Randomness

Quantum Randomness in Biology

... with phenotypic consequences:

Quantum tunneling: non-zero probability of passing any physical barrier (cell respiration, Gray, 2003; destabilizing tautomeric enol forms – migration of a proton: Perez, 2010)

Quantum coherence: electron transport (in photosynthesis and in many biological processes: Winkler, 2005)

Proton transfer (quantum probability): RNA mutations (G-C pairs: Ceron-Carrasco, 2009)

REFERENCES IN:

Buiatti M., Longo G. *Randomness and Multilevel Interactions in Biology 2013*

Classical Randomness in Biology

Non linear affects (molecular level):

- Macromolecular **enthalpic oscillations** (quasi)-turbulent in the cytoplasm of *Eukaryote* cells
- **Brownian motion**

(see also J.-J. Kupiec, T. Heams, A. Paldi ... Elowitz et al., *Science*, 2002)

Hydrodynamics: *Fluidity* and *incompressibility* in *continua* (its role of permeability of membranes):

“*water QED coherence*”: empowered **metabolic stochasticity**
(Del Giudice, 2005; Plankar, 2011)

Classical *and* Quantum Randomness in Biology

Molecular level:

non linear dynamics (classical)

and quantum processes *superpose*

That is:

They happen *simultaneously* and *interfere*

Moreover:

a quantum effect may be **amplified** by a (classical non-linear)
dynamics

Contingence, hasard, ergodicité, stochasticité, probabilité ...

Biological **contingency**: Spinoza's "*being there*", plus

1. Result of a history, as a "**cascade of symmetry breakings**"
2. which (**highly**) **constrain random** events

The path is **not ergodic** (*physical meaning*: asymptotic exploration of the entire space of possibilities; molecules of 200 amino acids by 10^{80} interacting atoms at Planck time, in 10^{30} lives of Universe).

Constrained Probabilities as for molecular events (stochastic gene expression, macromolecular interactions)

Next:

No probabilities outside molecular events (phenotypes dynamics)

Physical Forms in Pre-given Spaces of Forms

Phase Space: pertinent **observables** and **parameters**

In Physics:

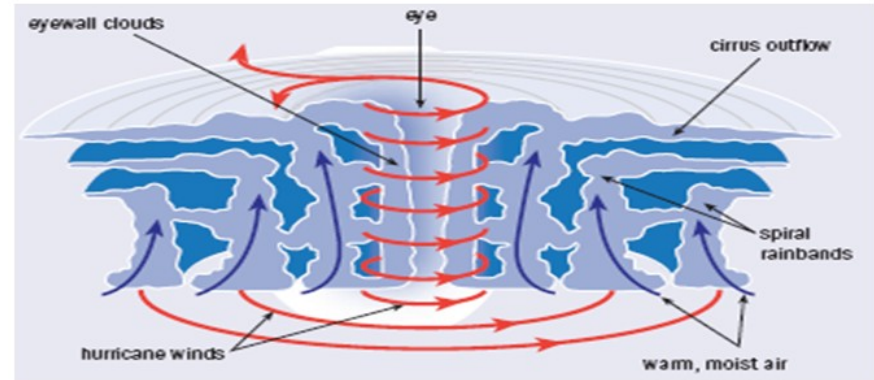
handling randomness by probabilities, within pre-given phase spaces

Einstein: “it is the **theory** that fixes the observables”

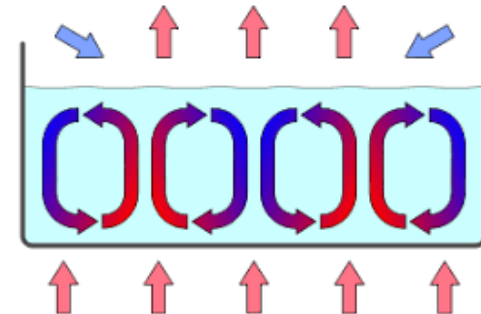
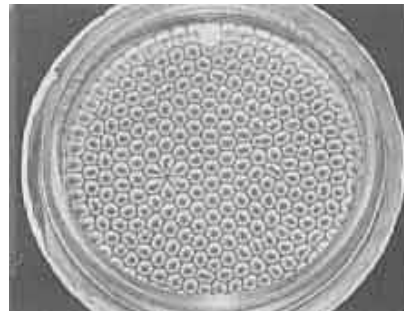
Physical Forms in Pre-given Spaces of Forms
(far from equilibrium (flows): *a time of processes*)

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- Hurricanes:



- Benard Cells:



Every surface and path is **optimal** (a geodetic): just physical forces acting on **inert molecules**, that “follow the flow”.

Inert Matter in Biology

- Beehive (ruche):



- Shells:



Inert matter
produced by
organisms:

physical forces
dominate, in a
given context

Every surface and path is **optimal** (a geodetic)

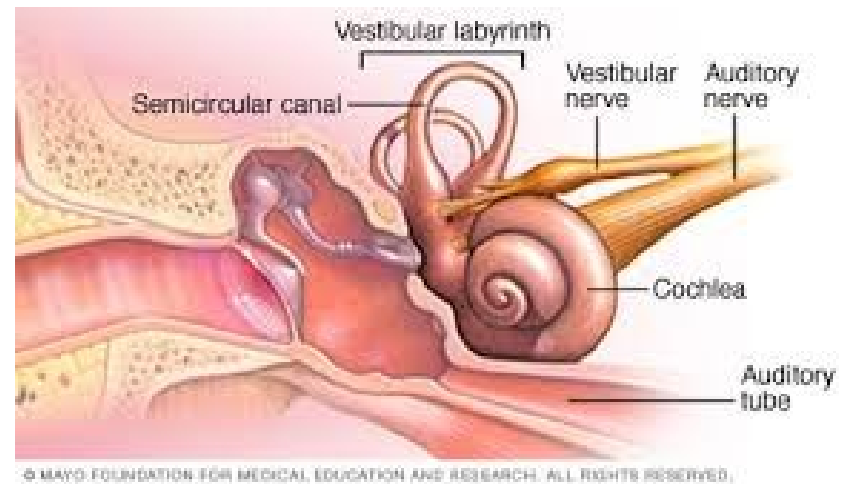
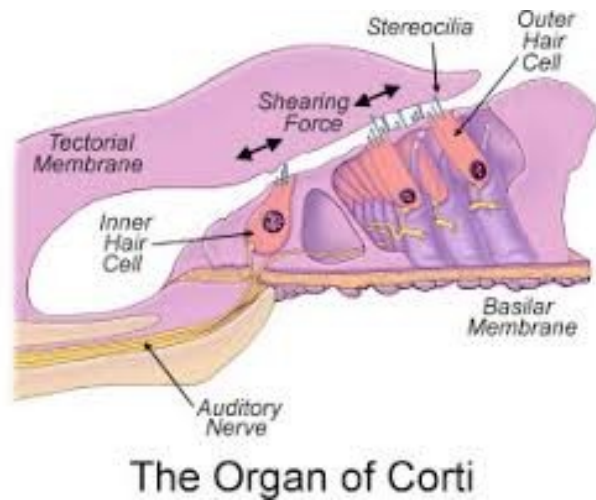
Changing Phase Spaces: The Historical Time of Biology

Re-used traces of the past: ex-aptation

New forms under *Constraints*

Re-used traces of the past: ex-aptation

Vertebrates **internal hear** (*vestibular system*) :

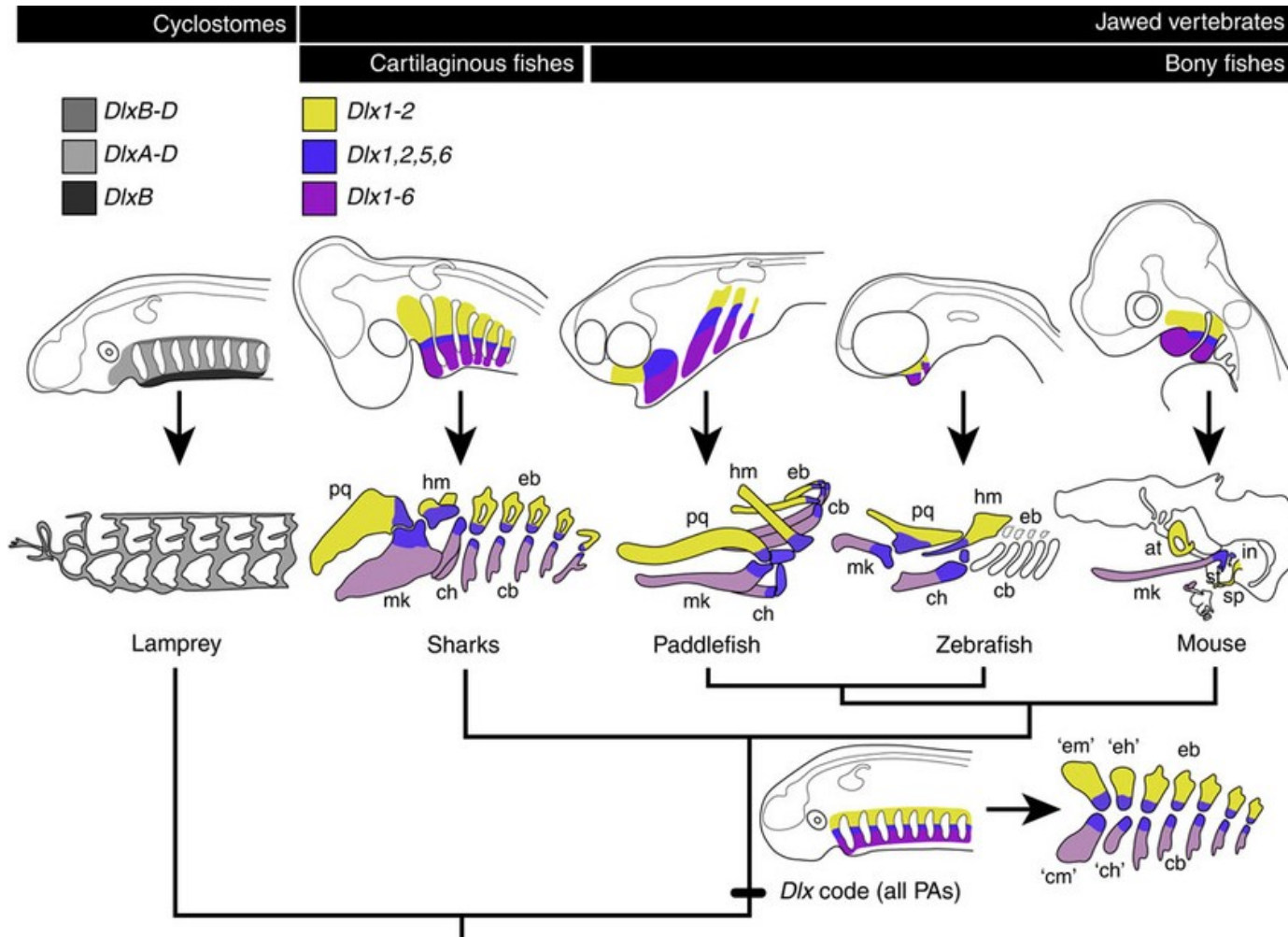


Origin: Devonian vertebrates (gnathostomes)

S.J. Gould, 1980-2002

Re-used traces of the past: ex-aptation

The **double jaw** in Devonian vertebrates (gnathostomes) yield the **bones of the median ear** of amphibians (stegocephalia), then:



Re-used traces of the past: ex-aptation

New Forms under *Constraints*

Evolution:

homologous *vs* analogous structures

Examples of Homology:

Bats' wings with (our) hands,

Birds' wings, with (our) arms



S.J. Gould, 1980-2002 ; E. Jablonka, M. Lamb, 2008 ; M. West-Eberhard, 2003

Re-used traces of the past: ex-aptation

Irish Elk's antlers (bois): *allometric* properties **constrain** morphogenesis: elongated neural spines of **shoulders'** vertebrae (also: **Darwin's correlated variations**), a “spandrel” for **hair**, *sex-appeal*



Gould, S.J. *The origin and function of "bizarre" structures: antler size and skull size in the "Irish Elk," Megaloceros giganteus.* **Evolution** 28: 191-220, 1974.

Re-used traces of the past: ex-aptation

Co-costruction of a new observable (phenotype)

A change in the phase space (the space of possibles)

" ... it is like re-using the chassis of an old chair to construct the **box of a radio**" (F. Jacob, on "bricolage", Science, 1977)

Not optimal, but ... *overloading*

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Historical sciences : *unpredictability without probabilities*

A variation on a them by Stuart Kauffman :

Marconi's used his *grand-father's* metal **screw-drive** as an **antenna**, in 1900, for the first radio transmission

Which were the *probabilities*, in 1820, that that screw driver was going to find that use ?

DNA, constructed in *and* used by the context

DNA and its use **change**:

- **Horizontal gene transfer** (now known in multicellular Eukaryotes as well [Keeling, Palmer, 2008])

Knowledge of the *present* or of the *possible future* role of these genes may require knowledge of their origin (*placenta* vs *marsupial*).

- “**Cryptic genetic variations** (CGV) are invisible under normal conditions, but they can *fuel evolution when circumstances change* ... CGV can represent a massive cache of *adaptive potential*”
[Paaby, Rockman, *Cryptic genetic variation: evolution's hidden substrate*, **Nature Reviews Genetics**, 15, 247–258 (2014)]
- **Cave fishes**: brain "vicariance", *hybrid offsprings with eyes* [Gatenby, 2011] **Knowledge (measure) of the past**

Re-used traces of the past

“the origin of species differences, and of novel phenotypes in general, involves the **reorganization of ancestral phenotypes** (developmental recombination) followed by the genetic accommodation of change”.

For example, the **leaf forms of *Monstera dubia*** “have been developmentally duplicated, deleted, and recombined in a multitude of ways during the evolution of the genus *Monstera*, giving rise to a variety of species-specific ontogenies” (and forms) ...



(West-Eberhard, 2005)

Bacteria that have lost their flagella through deletion of the relevant DNA sequence can evolve the regulatory networks required to restore flagella and so **restore motility in response to a stressful environment within just four days.**

Taylor, T.B., G. Mulley, A.H. Dills, *et al.* (2015) Evolutionary resurrection of flagellar motility via rewiring of the nitrogen regulation system. *Science* **347**:1014–1017

Cavefish : « hybridation of close but different species of this eyeless fish, which evolved from a “normal” fish, yield fishes with functional eyes »

(Gatenby, 2011)

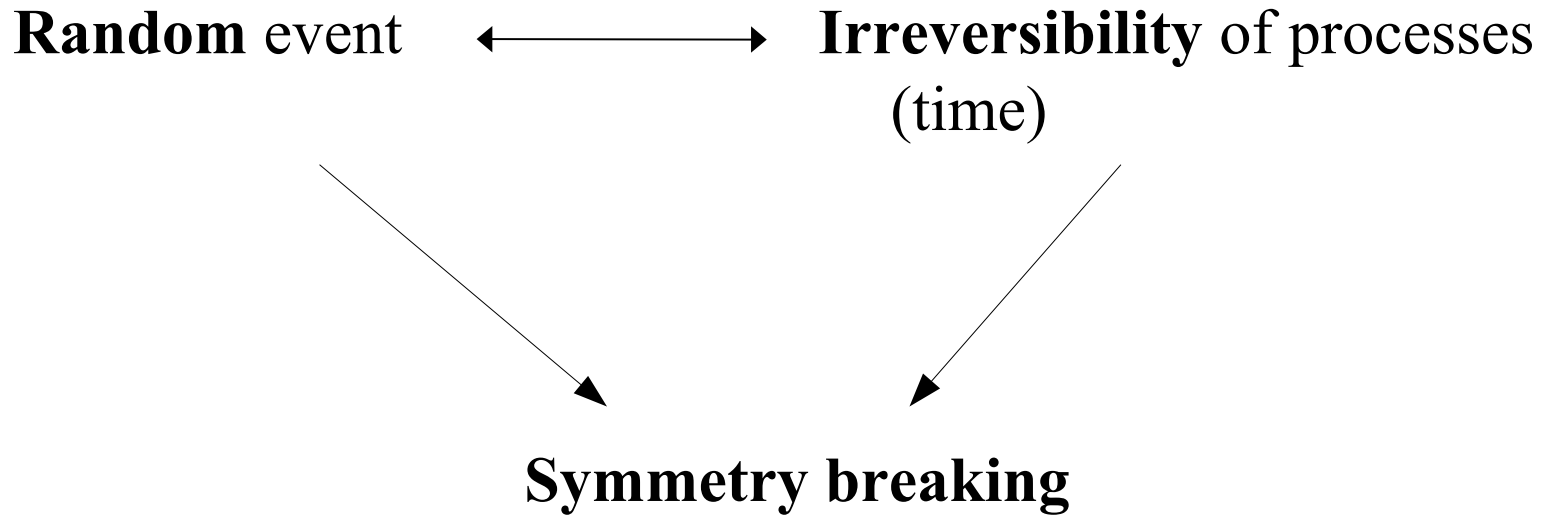
Re-used traces of the past (*re-interpreting the past*)

In summary:

- **Past contexts** may **shape** today's forms, e.g. the predecessors of homologous organs *or* DNA ... by a *then* (not now) *relevant* way.
- Yet, traces of the **past** (possibly below measurement) **contribute to shape the future *observables***, or :
- *Synthetically*: Any tentative determination/knowledge of **both** the *present* and the *future*, requires knowledge (*measurement*) of the past – the way an **organ** or **DNA** was constituted and possibly used
- *Synchronic* and *diachronic* measurement, a challenge

RECALL: Symmetry break, an invariant correlation

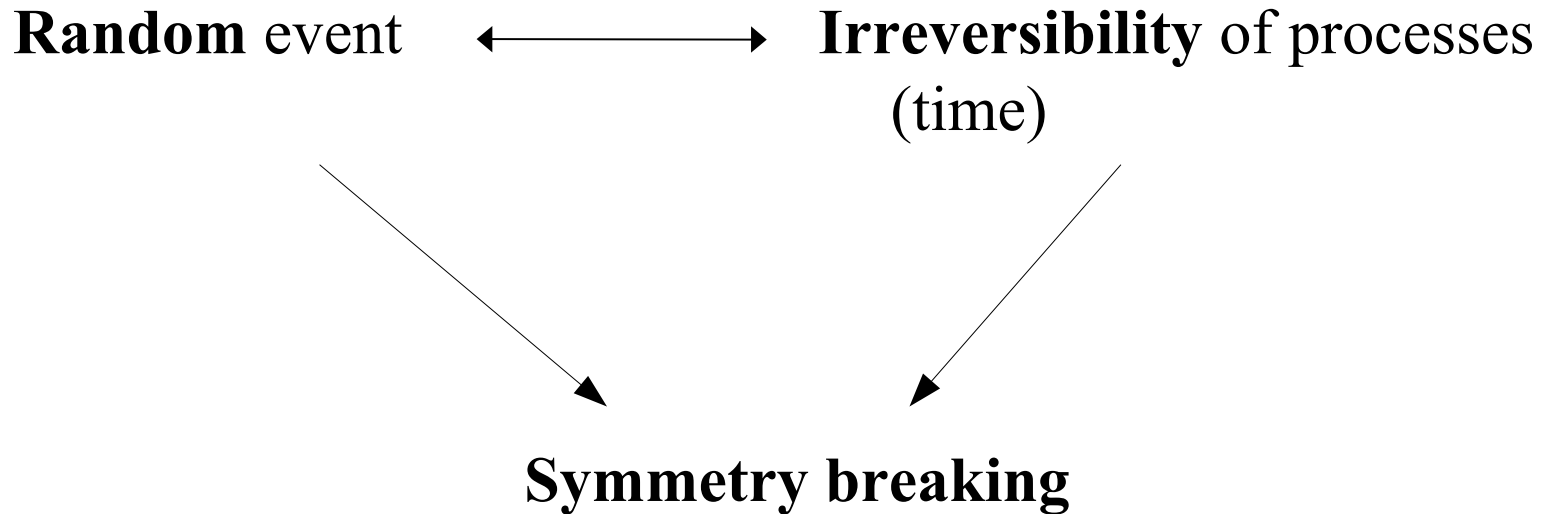
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Fundamental symmetry break:

the non conservation of the phase space

Historical vs Processual *Time*

In **Biology**:

1 – *if phenotypes are the relevant **observables**, then **time dynamics** include the **changes** of the **phase space***

2 - *rare events crucially contribute to history: e.g. **speciation** by a **hopeful monster** (no averaging-out [Bravi, Longo, 2015])*

(rare: speciation, variation or allopatry: placenta, lost eyes, wings ...)

Open issue: find a right **mesoscopic level** for dealing with biological randomness, from molecules to cells in organs (Giuliani, Huang...)

A distinction between:

3 - *time of processes vs. time of history*,

as different observable times in the same physical dimension:

e.g. flames, hurricanes, micelles ... **processual time** in a given phase space, *no historical* changes: all lines and surfaces are geodetics

Historical time includes **1** and **2** above

Challenges of Randomness in Biology

Physics: probabilities: *all* within a given **phase space** (the *possible* states – observables and parameters).

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A proper notion of **biological randomness**, at finite *short/long* time?
Due to the **superposition** of the two physical notions?

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Randomness: Physics/Computing/Biology

- **Physics:** two forms of randomness (different probability measures)
- In *Concurrency*? In Computers' *Networks*? *A lot of work...*
- **Biology:** the sum of all forms? What can we learn from the different forms of randomness and (in-)determination?
- ... but with **small numbers** (vs Statistical Physics)

No pre-given Phase Space

- **R. Thom** in (Amsterdamski, 1990):

in all dynamical systems, the mathematical phase space pre-exists to the randomness (“noise”) affecting the system (p. 270); *thus*,

“it is the lack of the definition [of the virtual possible] that affects - very seriously – the scientific nature of Darwin's Theory of Evolution.” (p. 271).

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Sarti, A, Citti, G, Piotrowski, D “Differential *heterogenesis* and the emergence of semiotic function”. *Semiotica*. Vol 2019, Issue 230

« Unlike usual differential calculus in mathematical-physics, heterogenesis is based on the assemblage of **differential constraints** that are different from point to point. The construction of differential assemblages yields the heterogeneity of the differential constraints and of **the associated phase spaces, that are continuously changing in space and time ...** »

The “relativistic” role of time in Biology

Recall a major epistemic lesson of Einstein’s RT, as for the key role of **space**:

The geometry of relativistic spaces is a tissue of interactions: when deforming these interactions, the tissue and its geometry change; conversely, a deformation of the geometry changes the interactions, their tissue.

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The key role of **time** in biology and its permanent deformations may be analogously synthesized:

The time of an ecosystem is a tissue of interacting rhythms and frequencies: when deforming these interactions or their tissue, rhythms, frequencies and their relative timing change; conversely, a deformation of rhythms or frequencies and of their relative timing, modifies the tissue, the time of the ecosystem. <https://www.di.ens.fr/users/longo/download.html>

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]

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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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- **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

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.
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DNA and phenotypes, after 2001

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

« Myriad mutations afflicting individual cancer cell genomes» (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)

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

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

Re-used traces of the past: ex-aptation

In any historical science: **physical forces** provide *only* constraints

Insufficient to intelligibility

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In any historical science: **physical forces** provide *only* constraints
Insufficient to intelligibility

Historicity: 1920 : a radio antenna at the top of San Peter's dome:



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

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