Contingency and diversity in biology: from anatomical complexity to functional organization

Giuseppe Longo

Centre Cavaillès, République des Savoirs, CNRS, Collège de France et Ecole Normale Supérieure, Paris, and

Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, Boston

http://www.di.ens.fr/users/longo

Chance? Determination? In Biology …

"Science has dealt poorly with the concept of contingency"

(S.J. Gould, **Wonderful Life**, 1989; p. 10)

Index

1 – Randomness *vs.* determination in **Physics**

2 – Randomness in **Biology**

3 – **Superposition** of different forms of randomness in an organism

4 – Is "**organismal complexity**" increasing along Evolution? Gould's analysis

5 – Hints to the mathematics of **phenotypic complexity** *vs.* **organization** (the case of cancer)

Physical Determination (Classical)

Laplace's view:
A) determination *implies* predictibility

and

B) determination *opposes* randomness

[Laplace, Philosophie des Probabilités, 1786]

Physical Determination (Classical)

Laplace's view:

A) determination *implies* predictibility (**false**: Poincaré, 1890)

and

B) determination *opposes* randomness (= determ. unpredictab, ")

[Laplace, Philosophie des Probabilités, 1786]

Thus, Poincaré ***broadened*** *determinism*

by including classical randomness: a fluctuation/perturbation *below* ***measurement***, may yield an observable effect, over time:

"... and we have a random phenomenon", [Poincaré, 1902]

The "nature" of classical randomness

Physical Determination and Randomness

Laplace's view:

A) determination $\Rightarrow$ predictibility

B) determination $\neq$ randomness

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

Physical Determination and Randomness

Laplace's view:

A) determination $\Rightarrow$ predictibility

B) determination $\neq$ randomness

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

Today's consequences of the **Laplacian view**:

A process is deterministic *and* predictable

if and only if

it is **programmable**

(the "DNA is a program" theory)

Moreover, both *Turing-Kolmogorof* and *Shannon-Brillouin* "information theories", on discrete data, are explicitly Laplacian

Longo G., P.A. Miquel, C. Sonnenschein, A. Soto.
Is Information a proper observable for biological organization?
In **Progress in Biophysics and Molecular Biology**, 2012

Laplacian Determination and Randomness …. 100 years after Poincaré

"[in cells] … the molecular processes are a *Cartesian Mechanism,* autonomous, **exact**, **independent** from external influences …

Oriented transmission of information … in the sense of **Brillouin**

Necessarely stereospecific molecular interactions explain the structure of the code … 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**, 1970]*

Summary (classical): State Determined Systems

A physical system/process is **deterministic** when we have or we believe that it is possible to have a set of ***equations*** or an ***evolution function*** 'describing' the process;

i.e. the dynamics of the system is 'fully' **determined**

by its *current states* and by a '*law*'.

Classical/Relativistic systems are *State Determined Systems*:

randomness is an **epistemic** issue = unpredictability in the intended theory

(dice "know" where they go ...)

Thus, randomness, is at the **interface "**(equational) determination *vs.* (physical) process", accessed by **measurement** (its principles)

Quantum unpredictability as intrinsic indetermination

Quantum Mechanics is ***not*** deterministic (not SDS):

intrinsic/objective role of probabilities in constituting the theory:

- measure of conjugated variables [pq – qp > h] ;
- Entangled probability measurements, no hidden variables.

Quantum unpredictability as intrinsic indetermination

Quantum Mechanics is ***not*** deterministic (not SDS):

intrinsic/objective role of probabilities in constituting the theory:

- measure of conjugated variables [pq – qp > h] ;
- Entangled probability measurements, no hidden variables.

Schrödinger's idea: the **equational determination** of a "*law of probability*" in **Hilbert** sp. (thus the indeterministic nature of QM)

Quantum Mechanics: you ***can't even think*** of an infinitary daimon.

Key differences: measure of conjugate variables *and,* e.g.,

the "spin up – spin down" of an electron is ***pure contingency*** !

Against Descartes, Spinoza, Leibniz: "all events have a cause"

Recent survey/reflections: [Longo, Paul et al., 2008-09], [Bailly, Longo, 2011]

Summary: Physical Randomness

1 - Classical randomness = deterministic unpredictability

Epistemic, e. g. since Poincaré (*phase space*: momentum x space)

non-linear dynamics *and* the interval of measure (dice)

2 - Quantum randomness (*phase space*: state function, **Hilbert**)

Objective or intrinsic (to the theory):

- indetermination (position/momentum or energy/time)
- entanglement (*Bell inequalities*: dice *vs.* entangled quanta)

Different probabilities, **different** theories of randomness…

Handled in different spaces over the **same observables** (energy, momentum …)

In search for a unified theory!

Challenges for Randomness in Biology

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

Challenges for Randomness in Biology

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

Biology: *question:* intrinsic indetermination due to change of the (Darwinian) phase space, in phylogenesis (ontogenesis?) ?

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

Challenges for Randomness in Biology

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

Biology: *question:* intrinsic indetermination due to change of the (Darwinian) phase space, in phylogenesis (ontogenesis?) ?

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

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?

The constitutive role of randomness in Biology

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

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

Randomness *implies* **variability** *implies*

adaptation *and* **diversity**

An essential component of **structural stability**

The constitutive role of randomness in Biology

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

Not noise, no "stochastic" stability (large numbers), but

Randomness *implies* **variability** *implies*

adaptation *and* **diversity**

An essential component of **structural stability**

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 …. more :

Each cell proliferation (elementary *and* fundamental):

Asymmetric partitions of proteomes; *differences* in DNA sequences; *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 – 12]).

Biological relevance of randomness

Randomness in molecular activities …. more :

Each cell proliferation (elementary *and* fundamental):

Asymmetric partitions of proteomes; *differences* in DNA sequences; *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 – 12]).

Not "noise", "mistakes" from DNA to Proteins, in a "program",

but non-specificity and randomness is at the core not only of *variability* and *diversity* (the main biological invariants), but even of **cell differentiation** (in embryogenesis: sensitivity to a context in a critical transition).

Which form of randomness ?

Classical Randomness in Biology

Non linear affects (molecular level):

- **Brownian** motion (e.g. stochastic gene expression)
- Molecular **enthalpic oscillations**
- **Turbulence** in the cytoplasm of Eukaryote cells
- Empowered **metabolic random** activities by (water) "QED coherence" (Del Giudice, 2005; Plankar, 2011)

(see also J.-J. Kupiec, T. Heams, A. Paldi, B. Laforge work)

Quantum Randomness in Biology

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/sharing (in photo-synthesis and in many biogical processes: Winkler, 2005)

Proton transfer (quantum probability): double proton transfer affects spontaneous mutation in RNA duplexes, particularly in G-C base pairs (Ceròn-Carrasco et al, 2009).

REFERENCES IN:

Buiatti M., Longo G. *Randomness and Multilevel Interactions in Biology,* ***Theory of Biosciences,*** *2013*, Downloadable.

Quantum Randomness in Biology

Quantum tunneling: for the enzyme alcohol dehydrogenase, which transfers a proton from alcohol to nicotinamide adenine dinucleotide (Cha et al., 1989).

Quantum coherence: Collini et al. (2010) showed, through two-dimensional photo echo-spectroscopy, quantum coherent sharing of electronic oscillation across proteins at ambient temperature in photosynthetic algae**.**

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

REFERENCES IN:

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

Classical *and* Quantum Randomness in Biology

Molecular level:

non linear dynamics (classical)

and **quantum processes *superpose***

That is:

They happen ***simultaneously*** and ***interfere***

(not analyzed in Physics)

Moreover:

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

Proper (?) Biological Randomness 1

Randomness ***within*** other levels of organization *in an organism*:

- **Cellular dynamics** and **interactions in a tissue**
- **Developmental dynamics** (dynamic intercellular contacts: Soto et al., 1999)
- **Fractal bifurcations** (mammary gland development, *ongoing work*)

Proper Biological Randomness 2:

Recall: since Poincaré, randomness as "planetary **resonance**" …

Extended to general non-linear dynamics *at equilibrium*:

at **one level** of (mathematical) determination

(*far from equilibrium*: Pollicott-Ruelle resonance, dynamical entropy in open systems (Gaspard, 2007))

Proper Biological Randomness 2:

Recall: since Poincaré, randomness as "planetary **resonance**" …

Extended to general non-linear dynamics *at equilibrium*:

at **one level** of (mathematical) determination

(*far from equilibrium*: Pollicott-Ruelle resonance, dynamical entropy in open systems (Gaspard, 2007))

Bio-resonance (Buiatti, Longo, 2013):

Randomness ***between*** different levels of organization *in an organism*:

thus, resonance (as interference) between **different levels** of (mathematical) **determination** *(aim: analyze randomness)*

The mathematical challenge: the Mathematics (of Physics) does **not** deal with **heterogeneous structures** (of determination)

Bio-resonance

Physical resonance (at equilibrium / far from equilibrium) is related to "destabilization" (growth of entropy or disorder)

Bio-resonance

Physical resonance (at equilibrium / far from equilibrium) is related to "destabilization" (growth of entropy or disorder)

Bio-resonance includes "integration and regulation", thus

it ***stabilizes*** and ***destabilizes***

Examples (networks and *morphogenetic* dynamics*)*:

- The lungs, …
- In "colonies" of *Myxococcus Xanthus,* a prokaryote, and *Dictyostelium discoideum,* an eukaryote (Buiatti, Longo, 2013)

Aim: role of randomness in ***structural stability*** (organisms, niche, ecosystem …)

More than one hundred years after Poincaré, some dynamics at the molecular level

More than one hundred years after Poincaré, some dynamics at the molecular level

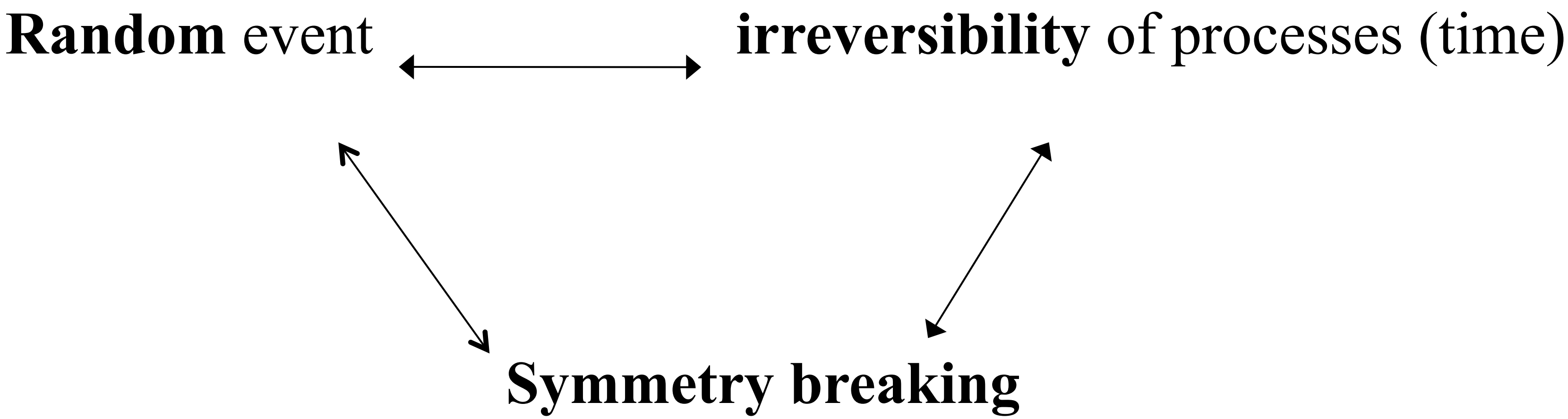
Since

• Alternative Splicing [Brett et al., 2001; Sammeth, 2008],
• The new role of methylation and demethylation [Caroll, 2008]
• Torsional constraints on chromosomes [Lesne, 2009]
• Stochastic gene expression [Heams, 2013]
• Level of nitrate in metabolism modifies plants genome, known since (Durrant, 1962) [Buiatti, 2013]

Symmetries ?

Symmetries ?

A triangular relation (*in existing physical theories*):



Longo G., Montévil M., **Perspectives on Organisms: Biological Time, Symmetries and Singularities**, *Springer*, 2013.

Back to Darwin:

A phylo(onto-)genetic trajectory is a **cascade of symmetry breakings**

Darwin’s Principles

“The Origin of Species”, **Two** Fundamental Principles:

1 – **Descent with Modification**

2 – **Selection**

The first as revolutionary as the second, which has no meaning without the first.

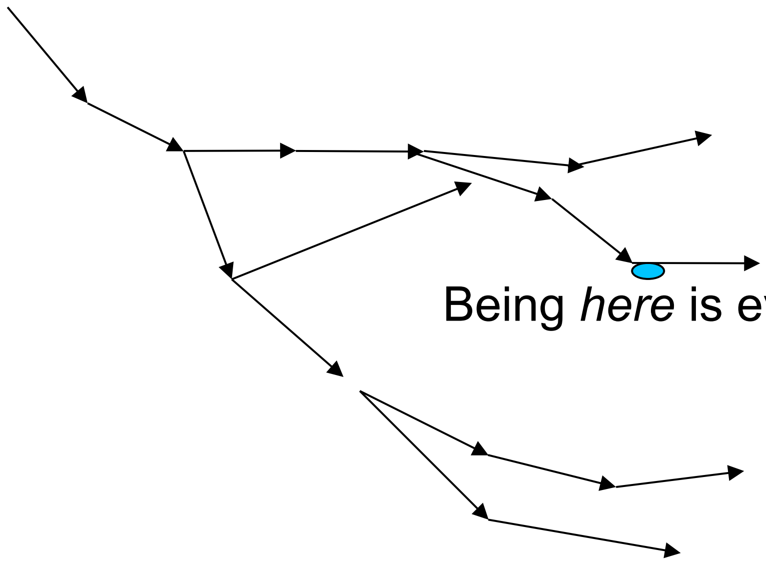
Recall: each **cell division** is a ***symmetry breaking***, it (randomly) engenders **variability** thus **diversity** thus,

jointly to **reproduction** (inheriting DNA, proteome, membrane …), by **modification** it *contributes* to structural stability

(adaptability of an organism, diversity of a population …)

Ontophylogenetic trajectories

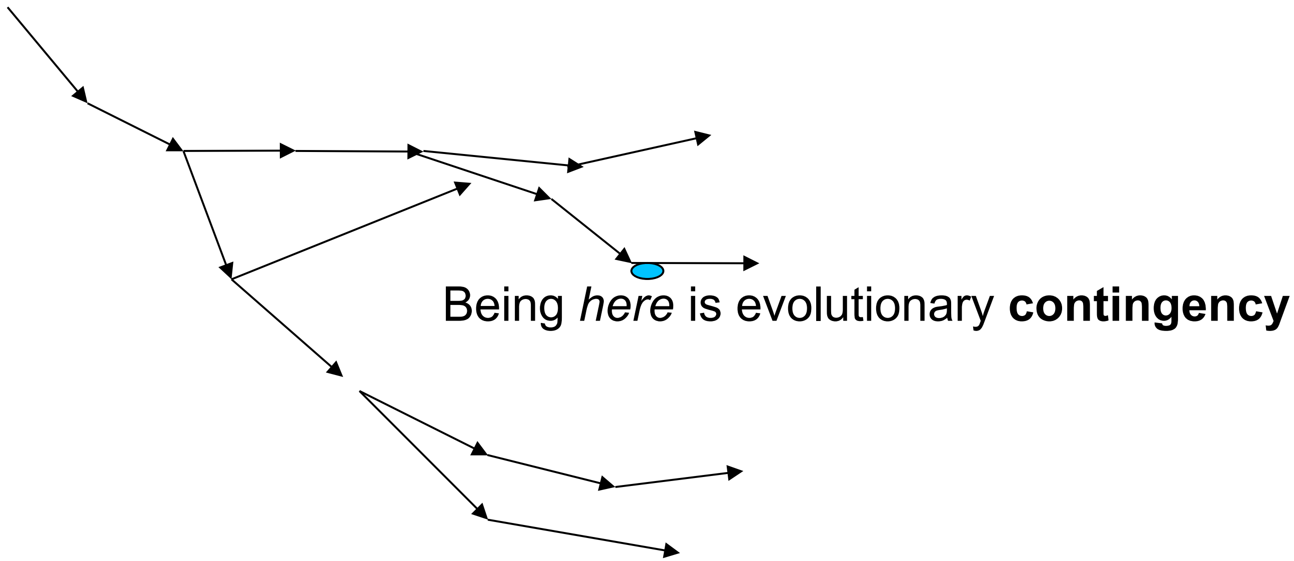
Each bifurcation is a symmetry breaking



Being *here* is evolutionary **contingency**

Ontophylogenetic trajectories

Each bifurcation is a symmetry breaking



Evolutionary **contingency** is the result of

1 - (physical and biological) **randomness** (symmetry breakings),

2 - under (historical and ecosystemic) **constraints**, and

3 – **crossing** of different causal (physical and biological) dynamics ("**Spinoza's** contingency")

Contingency, randomness, ergodicity, stochasticity, probability …

Biological **contingency**: *"being there"*

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

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

No **probabilities** outside molecular events (phenotypes dynamics)

Evolution and “Complexity”

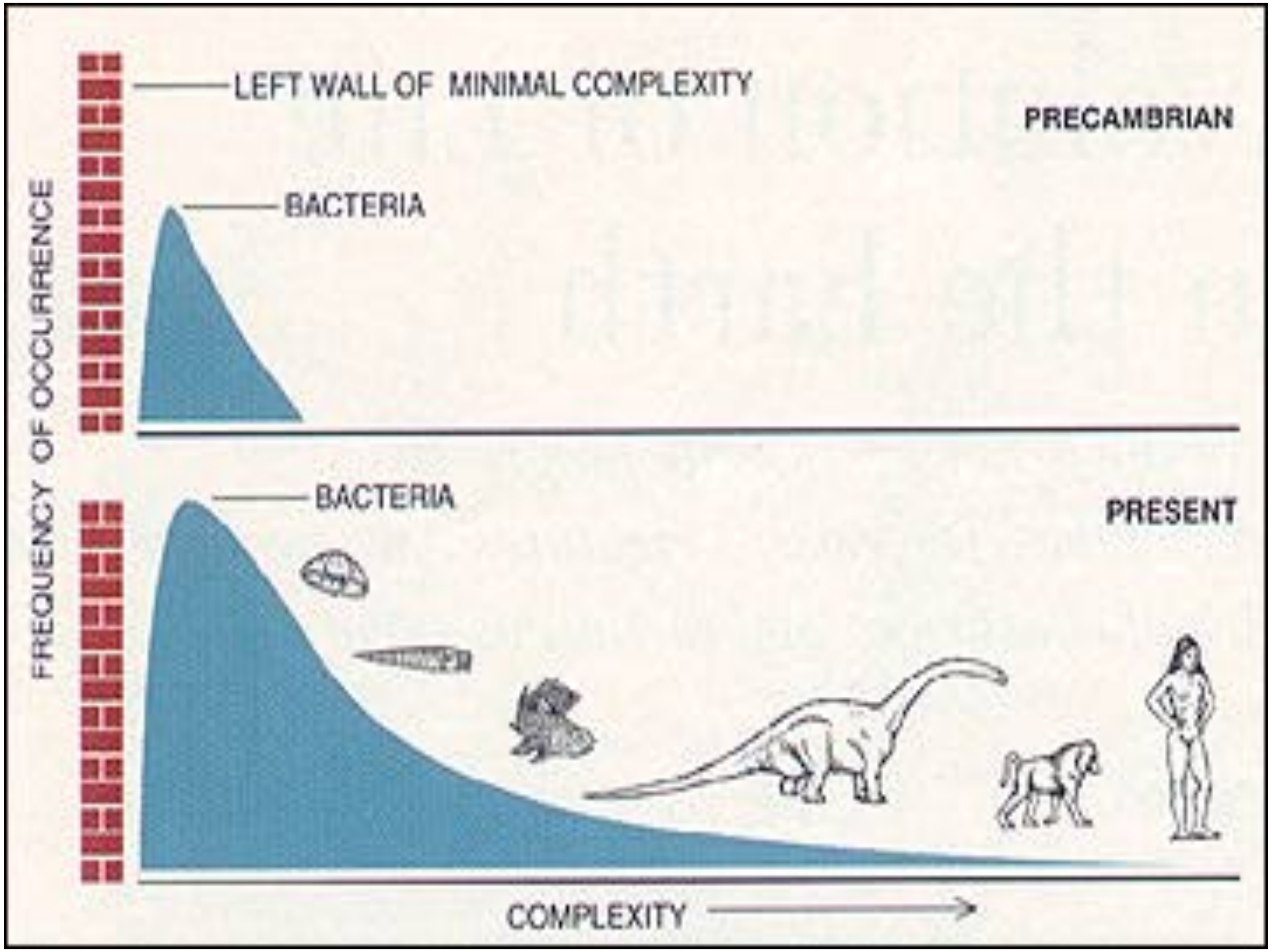
Gould’s Thesis on the Random Increase of biological complexity

Evolution and "Complexity"

The ***wrong*** image (progress?):

However: Gould's growth of "phenotypic" complexity [**Full House**, 1989]

However: Gould's growth of "phenotypic" complexity [**Full House**, 1989]



How to understand increasing complexity?

No way to explain this in terms of random mutations (only):

1. DNA's (genotype) **random mutations** statistically have probability 0 to cause globally increasing complexity of phenotype (examples: mayfly (ephemeral); equus… [Longo, Tendero, 2007])

2. Darwin's evolution is **selection of the *incompatible*** ("the best" makes no general sense)

3. Greater probabilities of **survival** and reproduction ***do not imply*** greater **complexity** (bacteria, … lizard…) [Maynard-Smith, 1969]

Gould's idea: symmetry breaking in a diffusion…

Mathematical analysis as a distribution of Biomass (density) over Complexity

Derive Gould's empirical curb from

- general (mathematical) principles,
- specify the phase space (observables and parameters)
- explicit (and correct) the time dependence

Write a suitable **diffusion equation** inspired by Schrödinger operatorial approach

Note: any diffusion is based on **random paths**!

F. Bailly, G. Longo. *Biological organization and anti-entropy*. **J. Bio-Systems,** 2009.

G. Longo, M. Montévil. *Randomness Increases Order in Biological Evolution.* **Conference in Honor of S.J. Gould**, Venice (It.), May 10 - 12, 2012.

Phenotypic Complexity along phylogenesis and embryogenesis

Specify (quantify) Gould's informal "complexity" as *phenotypic complexity* **K**

$$\mathbf{K} = \alpha K_c + \beta K_m + \gamma K_f \qquad (\alpha + \beta + \gamma = 1)$$

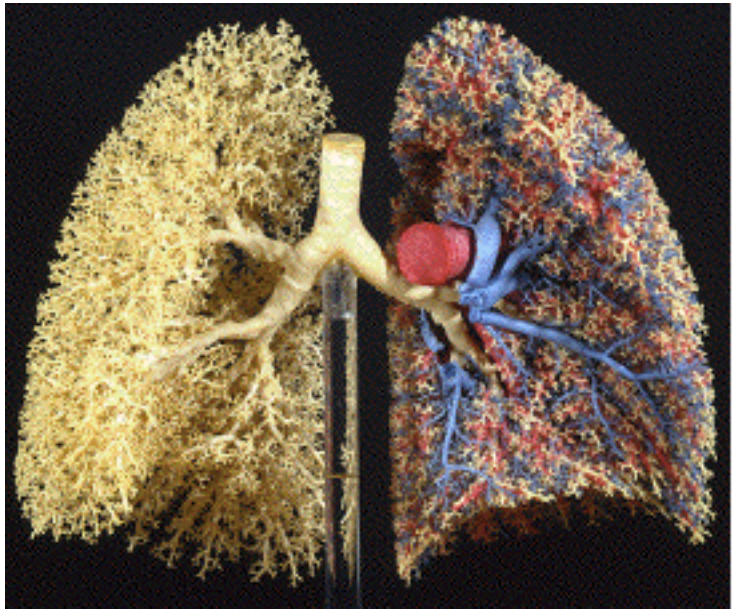
- K_c (combinatorial complexity) = cellular combinatorics as differentiations between cellular lineages (tissues)
- K_m (topological complexity) = topological forms and structures (e.g., connexity and fractal structures)
- K_f (functional complexity) = neuronal and cellular (interaction) networks

Main idea: formalize **K** as **anti-entropy** -S …

(*C.aenorhabditis elegans, see* [Bailly, Longo, 2009])

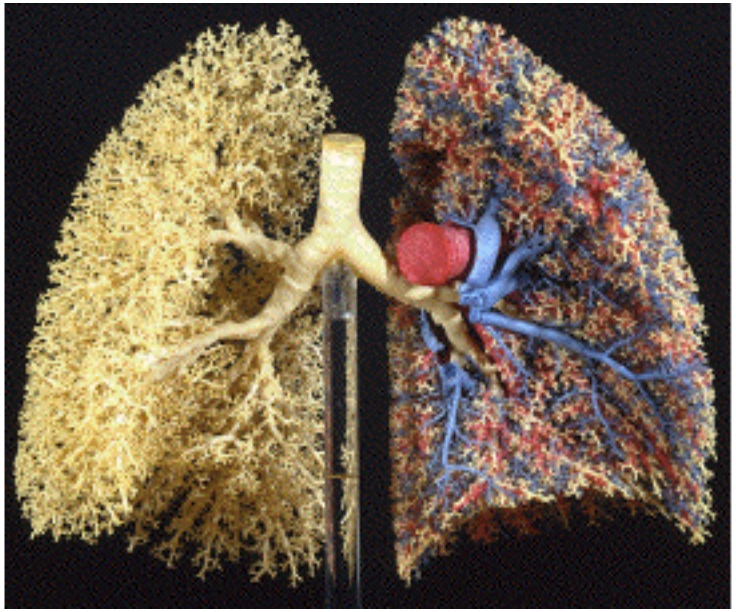
Example: Fractal or Topological Complexity

Human

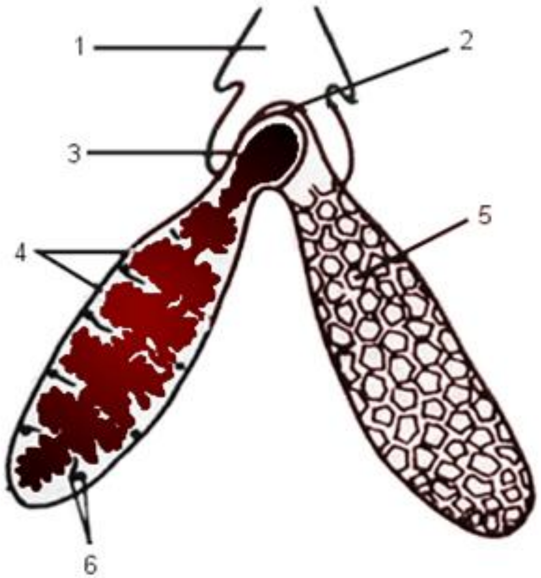


Example: Fractal or Topological Complexity

Human



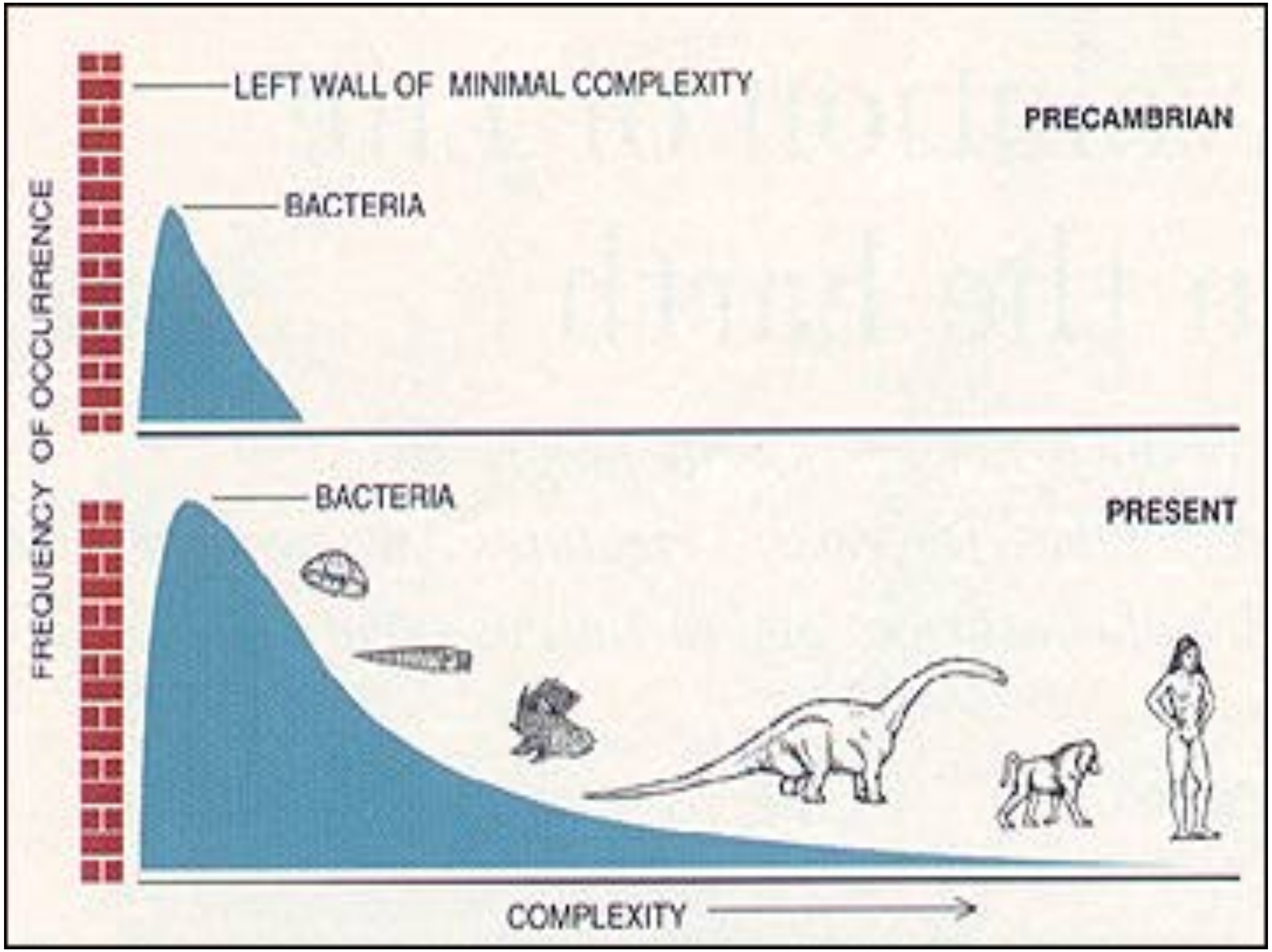
Frog



1. Hyoid apparatus 2. Glottis
3. Laryngeotracheal chamber
4. Alveoli 5. Right lung

(A) Structure of lung

How to use our "phenotypic" complexity for Gould's growth of evolutionary complexity ?



The theoretical frame: analogies

.... by a *conceptual analogy* with **Quantum Physics**:

In ***Quantum Physics*** (a "wave diffusion" in Hilbert Spaces):

- The determination is a ***dynamics*** of a ***law of probability***:

$$ih\partial\psi/\partial t = h^2\partial^2\psi/\partial x^2 + v\,\psi \quad \text{(Schrödinger Eq.)}$$

In our approach to ***Complexity*** in *Biological Evolution*:

- The determination is a ***dynamics*** of a ***potential of variability:***

$$\partial f/\partial t = D_b\partial^2 f/\partial K^2 + \alpha_b f$$

What is f ? a diffusion equation, in *which spaces*?

Random walks …

A **diffusion** equation: $\partial m/\partial t = D_b \partial^2 m/\partial K^2 + \alpha_b m(t,K)$ (3)

A **solution**

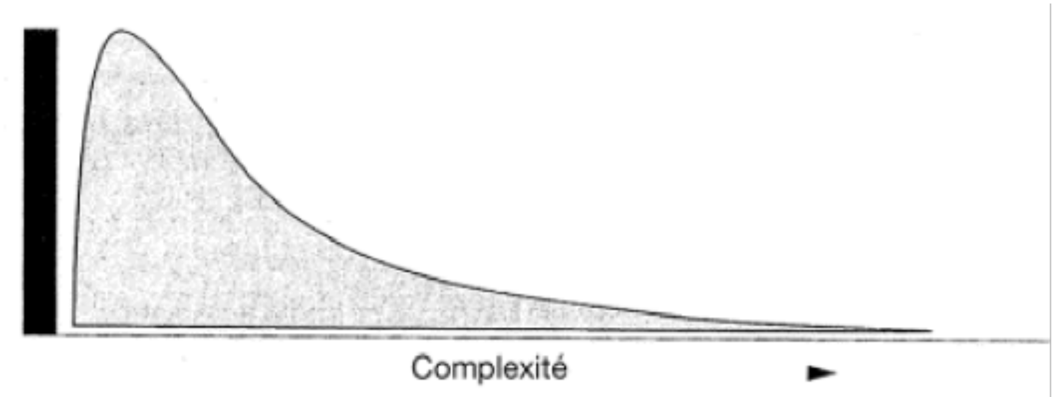
$$m(t,K) = (A/\sqrt{t})\ \exp(at)\exp(-K^2/4Dt)$$

models Gould's asymmetric diagram for Complexity in Evolution

An asymmetric diffusion by *random paths…*, ***also along t*** :

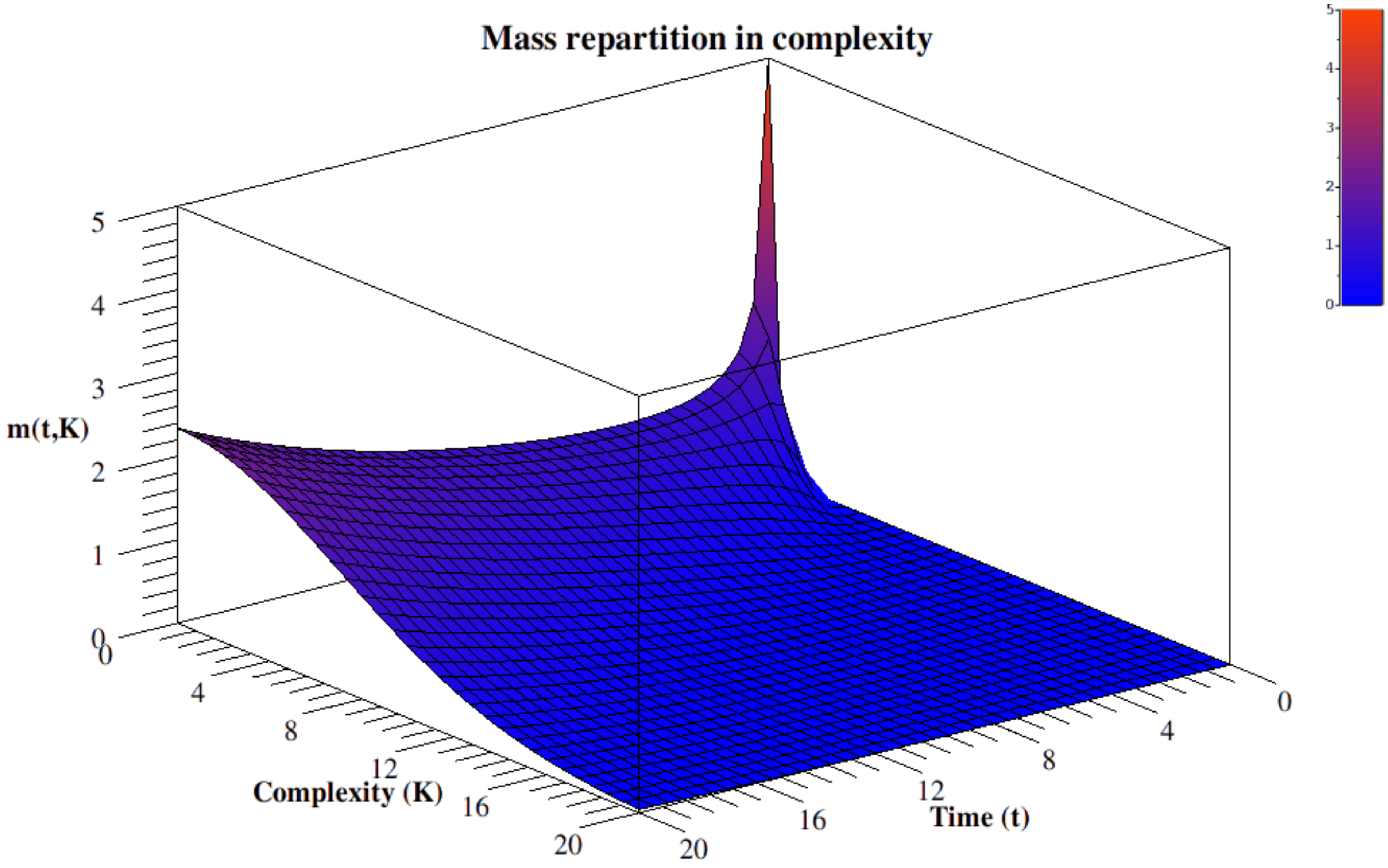
(biomass and the **left wall** for complexity, archeobacteria original formation)

↓



F. Bailly, G. Longo. *Biological Organization and Anti-Entropy…*

(Implementation by **Maël Montevil**; “ponctuated equilibria” smoothed out)



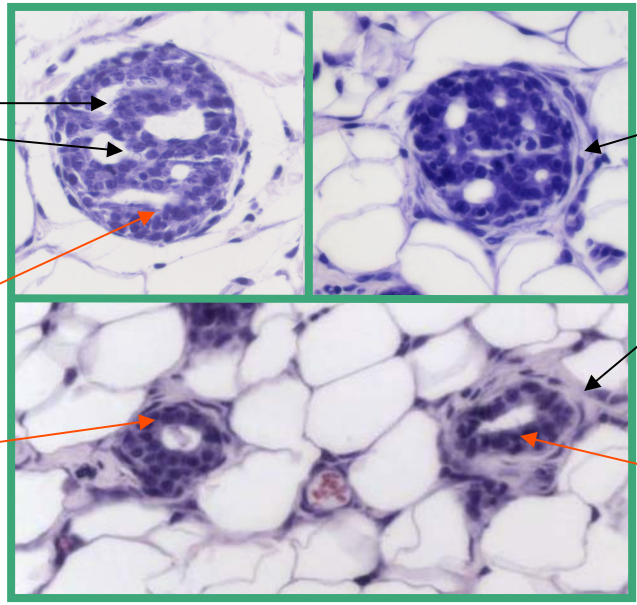
Reflections on Gould's phenotypic complexity

Ongoing discussion with
Carlos **Sonnenschein** and Ana **Soto**:

Can a notion of phenotypic (anatomic) complexity help to "singularize" cancer as a disease?

Ductal Carcinoma *in situ*, cross-section

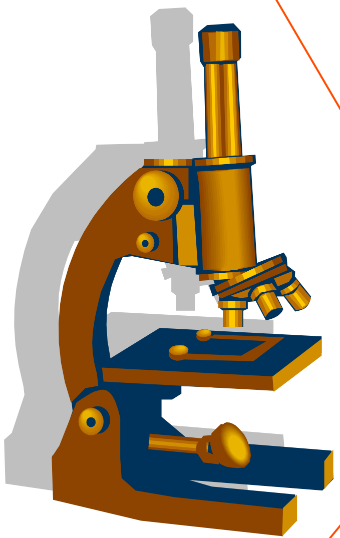
TOP: Cancer: greater topological complexity

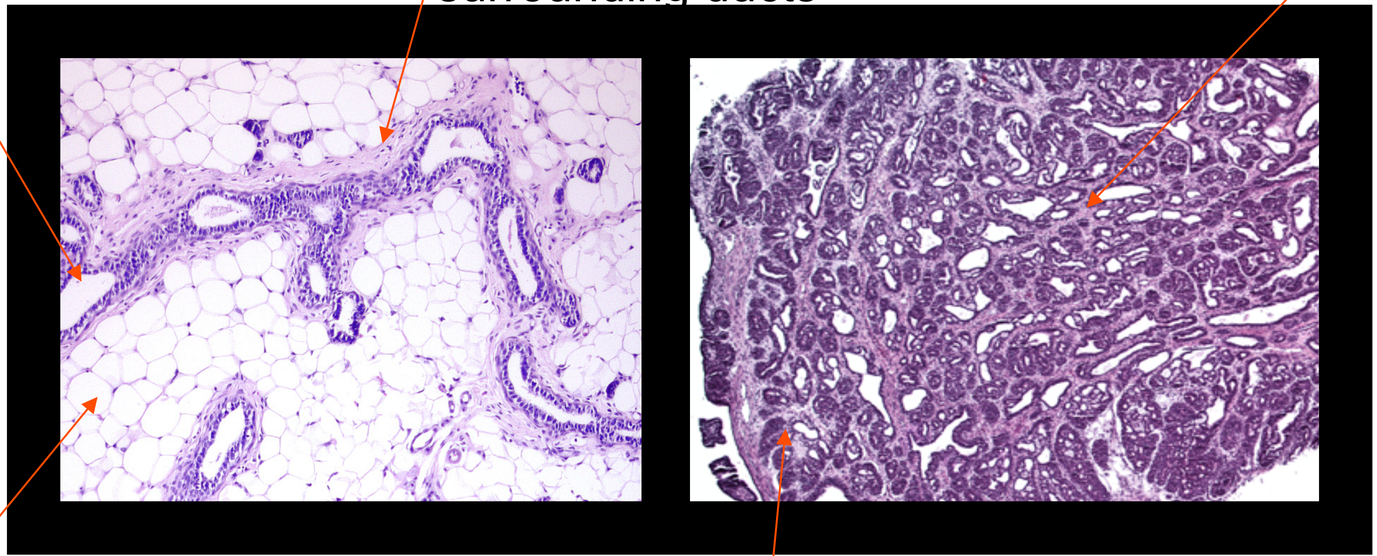


BOTTOM: control

From Murray et al 2007

What is a neoplasm?





The hallmark of neoplasms is altered tissue organization and excessive accumulation of cells. Neoplasms are diagnosed by pathologists using light microscopes.

Normal: rat mammary gland showing ducts; **tumor**: rat mammary adenocarcinoma

Conjecture:

With Carlos Sonnenschein and Ana Soto:

Cancer is (the only?) pathology that

- **increases** phenotypic (anatomic) complexity and
- **decreases** functionality (functional complexity)

Some references (*downloadable:* http://www.di.ens.fr/users/longo)

- Bailly F., Longo G. **Mathematics and the Natural Sciences. The Physical Singularity of Life.** *Imperial College Press*, London, 2011 (français: Hermann, 2006).

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

Bailly F., Longo G. *Biological Organization and Anti-Entropy*, in **J. of Biological Systems**, Vol. 17, n. 1, 2009 (revised with M. Montévil, *Randomness Increases Order in Biological Evolution,* **Gould's Conf.,** 2012)

Longo G., P.A. Miquel, C. Sonnenschein, A. Soto. *Is Information a proper observable for biological organization? In* **Progress in Biophysics and Molecular Biology**, Volume 109, Issue 3, pp. 108-114, August 2012.

Longo G., Montévil M. *Randomness Increases Order in Biological Evolution*. Invitedpaper, conference on "**Computations, Physics and Beyond**", Auckland, New Zealand, 21-24, 2012; **LNCS** vol. 7318 (Dinneen et al. eds) Springer, 2012 (Also, an invited lecture, **Conference in Honor of S.J. Gould**, Venice (It.), May 10 - 12, 2012).