The logico-causal *incompleteness* of Programming Theory in Molecular Biology

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- **Part I:**

  The logico-causal incompleteness of the programming "model" (metaphor?) in Molecular Biology: a critique from the point of view of Physics and Logic.

  (With P.E. Tendero)

- **Part II** (hints):

  A systemic approach: Extended Criticality

  *(With **Francis Bailly*** [1], Chap. 6*)*

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

[1] Bailly F., Longo G. **Mathématiques et sciences de la nature. La singularité physique du vivant.** *Hermann, Paris, 2006.*

Current *causal* analysis in Molecular Biology
(a common empirical tool)

- In Biology, a **differential analysis:**

(induced/observed) genomic variations (mutation) and their phenotypic "consequences"

- A ***comparative analysis*** *with Physics*: the case of Thermodynamics

- Differential methods in *Logic* or *Programming Theory*?

The Differential Method: General Principles
from a physicalist perspective

A paradigmatic example

- ***Perfect gas***: $pV = KT$ equilibrium law,
  first obtained by the differential, but later
  derived within a **systematic-theoretical determination**
  (general construction principles):

The Differential Method: General Principles
from a physicalist perspective

A paradigmatic example

- ***Perfect gas***: pV = KT equilibrium law,
  first obtained by the differential, but later
  derived within a **systematic-theoretical determination**
  (general construction principles):

7. Least polynomial (a mathematical principle)

- Symmetries and geodetics (gas: kinetic analysis, ***next…***):

pV = KT as a *causal* model

It describes **general causal** dependencies *and*

it **may be** *uniquely* **derived** from the *principles* of **Statistical Physics** (jointly to the principles of Thermodynamics):

- an analysis of particles' kinetic energy (T) and shocks on walls (p)
- take the sum (integral - the *thermodynamic limit*) of individual trajectories, as **geodetics** (a paradigmatic reduction)

A **systematic-theoretical determination** which *justifies* the differential method, grounded on major **conservation principles.**

(That is: ***symmetries*** and ***least action*** *principles).*

In Molecular Biology:

Is the “programming paradigm” a

systematic-theoretical determination ?

Does it rely on

- a similar paradigm as in Physics or
- on a similar theoretical approach as in Computer Science (e.g. within the ***semantics*** of Programming Languages) ?

Claim:

“Per se”, a differential analysis (teratogenic) ***does not provide*** a *direct* **causal** link (for the normal processes - the wild gene) in ***absence*** of a *systematic-theoretical determination* ***as in Physics*** (**geodetics** and **symmetries** as underlying the causal structure)

Very Relevant differential information

- **Pathologies** (no physical sense):

Robust evidence for the origin as *mutations* of some (**rare**!) ***genetic*** deseases:

Tay-Sachs, Huntington, cystic fibrosis, thalassemy…

But… how to go from the mutation to the *wild gene*?

An example of *improper use*: **phenyl-cetonury**:

Mutation (two alleles mutated) $\Rightarrow$ idiot child…

- *For decades*: ***there*** is the gene of intelligence, it encodes the structure of brain!

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Mutation (two alleles mutated) $\Rightarrow$ idiot child…

- *For decades*: ***there*** is the gene of intelligence, it encodes the structure of brain!

- *More recently*: the mutation produces an *inactive enzyme* which affects *brain metabolism* during early stages of life

([Dumaret, Stewart, 1989], [Stewart, 2004])

From mutation to the wild gene ? ***(more)***

- *Another example-abuse*:

The *gene-program of* ***marital fidelity***:

can it be derived from the differential analysis, as claimed in

Young et al., **Nature**, 400, 766-788, 1999 ?

(within Theory of Programming…)

From mutation to the wild gene ? *(more)*

- *Another example-abuse*:

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Predestination in Protestantism…

A short list of “genes-as-programs” in the letterature

The gene of:

- Longevity
- Obesity (N.Y. Rockfeller Center, 2000: 20 million dollars?)
- Teaching skill
- Sociability
- Seduction
- Mathematics
- **Academic freedom** (??)

[Charles Auffray, Qu’est-ce qu’un gène?, 2004]

Entangled causality

[Goldschmidt, 1938]:

Consequences of the displacement of a **homeotic gene** in *drosophyla* : eyes → legs, wings → legs… (and viceversa)

Later observed:

the **pressure** or the local intensity of the **electromagnetic field**, as parameters of the ecosystem ("norms of reaction") *may induce the same phenotypic consequences*

(in particular: ***pressure on embryo*** shifts wings ↔ legs)

[Stewart, 2004; Fox Keller, 2004]

What causes what, in absence of general theoretical principles?

The theoretical(-causal) frame of Programming

Physical Determination (Classical)

Laplace's view:

1) determination $\Rightarrow$ predictibility

and

2) determination $\neq$ randomness

[Laplace, Philosophie des Probabilités, 1786]

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

Poincaré (1890):

classical randomness = unpredictable determinism (classical physics) by "sensitivity to border conditions"…

but determination $\not\Rightarrow$ predictibility

(physical measure is an interval + non-linearity!)

The theoretical(-causal) frame of Programming
The originality of the machine

Turing Machine:

- a **Logic Computing Machine**: a man in the least act of computing-thinking (1936)
- a ***Discrete State Machine***, since 1948

(a physical perspective: *what about* ***determination*** *and* ***causality***?)

The laplacian nature of **Turing's Discret State Machine**

- *[Turing, 1950; p. 47]:*

" In a **Discret State Machine (**DSM)... it is always **possible to predict** all future state …" by the ***discrete*** *data types* and computational *environment*

" This is reminiscent of **Laplace's** view ... "

- *[Turing, 1952]:*

  A **non-linear *(continuous)* system for Morphogenesis**: main property "***exponential drift***" (i.e. sensitivity to initial conditions, a ***theoretical*** *property*), which yeilds umpredictibility.

- *[Turing, 1950]:*

  "It is an essential property of ...[DSMs] that **this phenomenon does not occur**. Even when we consider the actual physical machines instead of the idealized machines,..., **prediction is possible**".

- Reason: **discrete** data types ⇒ perfect **iteration** (a translation symmetry)

  AND **exact measure**

[Longo, 2007: "Laplace, Turing… the impossible geometry …"]

Shroedinger, What is life? (1944)

- « In calling the structure of the chromosomes a *code-script*, we mean that the all-penetrating mind, **once conceived by Laplace**… could tell from their structure how the egg would develop… . » p. 22-23.

- Today, the code-script has been fully decoded…

Where is the program?
The changing notion of ‘gene’

1 - [Mendel, 1907]: *no attempted structural definition nor location;*
a ***functional unit of recombination*** (of assortment and segregation)

2 - Morgan (1905) and Muller [Morgan, 1926]: a *structural unit of mutation*; hypothetical location in **chromosomes** of the determination of phenotypic (observable) ***characters.***

3 - [Watson and Crick, 1953, Crick, 1957]: *characterization in terms of molecular biology* (the chemical structure of DNA: stable, organised, “rigid”); loci of determination of **proteins**.

And then: the **“central dogma”** :

a *direct-causal* and *one-way* relationship from genes,
as *portions of* DNA, to proteins.

Weakening the central dogma

Reduced to the

"**one gene one enzyme hypothesis**" [Perutz, 1987]

Later shown to be false [Brett et al. 2001; Bartel, 2004]:

One* gene – *many* proteins** ***vs. ***one* protein - *no* genes**:

Massive polymorphisms and pleiotropy:

- ***one* gene – *many* proteins** :

- the same portion of DNA may engender different proteins;

- almost isomorphic portions of DNA may produce similar effects.

- ***one* protein - *no* genes** :

the primary structure of proteins may depend on the transfer activity of RNA within cytoplasm eukaryotic cells (e. g. by *"alternative splicing" %)*

But… where are genes?

- "… the *transcripts* come from regions of DNA previously identified as holding protein-coding genes. *But many do not.*
- … the descriptions of proteins encoded in DNA ***know no borders*** — each sequence reaches into the next and beyond."
- "The more scientists become in molecular genetics, the less easy it is to be sure about *what, if anything, a gene actually is*."

[Helen Pearson, **Nature**, May 2006]

[Fox Keller, 2007]

[D. Brett; H. Pospisil; J. Valcárcel; J. Reich; P. Bork "Alternative splicing and genome complexity". *Nature Genetics* **30**, 2001].

In summary, up to now:

- No structural determination of what a gene is *(part of DNA? It includes RNA transfer activities?…)*

Reasons (from Physics) *for the abuse:*

- No way to deduce from a *differential analysis* a **direct causal** link, *without general theoretical principles*

Can these principles be derived from Logic or Computing?

Differential Methods in Logic or Programming Theory?

- **Theory of Programs**:

  Given a program: understand its “semantics” (that is the *computed function*) by inducing “mutations”?

Differential Methods in Logic or Programming Theory?

- **Theory of Programs**:

  Given a program: understand its "semantics" (that is the *computed function*) by inducing "mutations"? **No way!**

- *Analogy*: the **"Böhm-out" technique**

  [Hyland, 1976; Barendregt, Longo, 1980; Barendregt, 1984].

Böhm's theorem (1967):

"Two different terms of lambda-calculus in normal form cannot be consistently equated"

Once *given* the operational semantics!! (the "compiler" and… Church-Rosser) or certain mathematical (denotational) domains of interpretation (a *direct* "causal/deductive structure").

More on **Differential Methods in Logic and Computing**

- Formally: given M and N *terms* in normal form (programs),

$$M \neq N \quad \Rightarrow \quad [M]_E \neq [N]_E$$

***in any already given semantic environment* $[-]_E$,**

i.e. in any mathematical meaning of programs.

- This result, which may be considered of the "differential" type, ***does not*** provide the semantics of a program (or of a lambda-term), its "phenotype".

- It may instead help to characterizes syntactically the terms having *the same* (or different) *semantics*, within an ***already given*** mathematical structure.

[Hyland, 1976; Barendregt, Longo, 1980]

New paradigms in Programming ?
(concurrency in networks)

- **Message-passing**, *doesn't model protein cascades*, as it doesn't support ***re-combination*** and ***decay*** (moreover, no distinction seems possible between a message and a process, in genomics)
- **Data-flow** doesn't support loops (proteins'-enzymes cycles)
- **Synchronous and asynchronous automata** badly handle the omnipresent ***feedbacks*** in the cell
- Proteins processes are ***inhibited*** and this is not described by term-rewriting or **Petri Nets**
- **In operator algebras** the ***gates' output is predetermined***, it cannot be a function of the input, as it seems to be in molecular dynamics.

(this is only in reference to *biochemical cascades*;

yet, the "**compiler**" is the the ***global coherence structure*** of the cell - and of the organism, their *organisation* and *stability*…)

The Differential Method from a physicalist perspective *summary**

The causal **incompleteness** of the Programming Paradigm (*model/metaphor*) as ***physical incompatibility*** with respect to

- the context (dynamical, thermodynamical… *to say the least)*
- the differential method:

  in Physics: **finite number of experiences** *interpolated* by geodetics in an *intended continua:*

  - **isolate** one *parameter* (or develop a close analysis of correlations)
  - the *conceptual frame* (optimality criteria, e.g. simplest polynomial)
  - the *mathematical frame* (geodetics) are ***continuous*** - at least in variational contexts.
  - large numbers treated as **integrals** (sums: e.g. perfect gas)

Finalism and the Program

- The need for *finalism* in biologists:

  - a program is ***made for***, it is the result of an explicit ***aim*** and an ***intelligent design***;

  - it **follows the law** : Galileo, Descartes, Newton… concept of *normative* physical law - written by God: we are God to the machine *and* the machine is the result of an **intelligent design**.

About terminology:

Consider a slope, a **cavity**, a (water) **turbolence**….

A further cavity engendered by the first….

A program? The first cavity contains the information for the second?? *Modern* Physics goes otherwise.

Conclusion of Part I

Molecular Biology:

- An **extraordinary experimental richness**

  (remarkable empirical correlations between the *modifications* of genotype and of phenotype)
- No ***causal theory*** (genotype $\Rightarrow$ phenotype)
- Highly unsatisfactory use of notions from Programming.

Hints to Mathematics in Biology

Remarkable mathematical work at

different levels of organization:

- **Morphogenesis, phyllotaxis** … since D'Arcy Thompson, Waddington, Turing, Thom… : mostly organs (loci of *energy exchange* - e. g. geodetics : fractal structures…)

- **Networks** (Von Neumann, Hopfield… G. Parisi…): neural, cellular… (intercellular exchange - *grandient of energy*)

- Different mathematical methods for *different levels of organisation (no* dialogue…)

Issue: the *systemic unity* of an organism (and its structural stability)

Can they only depend on the **organisation** and **stability** of DNA?

One of the many issues:

In a cell (an organism) almost everything is ***causally correlated*** to almost everything (how to de-correlate variables?),

The structural stability (coherence structure) **of the cell (**and/or the organism), *(causally) contributes* the **organisation** and **stability** of proteins' cascades from DNA.

Our perspective: this coherence structure is

a "**physically critical state**", yet not pointwise, but ***extended…*** not treated by current physical ***Theories.***

Some Philosophy

A **theoretical**/epistemic separation (not **ontological**)

Example: **Quantum Mechanics**:

- Non-separability
- Non-locality (entanglement)
- No trajectories in space-time

Bohr, 1932 (*Light and Life*, revised, 1962):

« … no way to understand the **stability of the atom** in terms of classical or relativistic physics… similarly, there is no way to understand the **stability of the cell** in terms of current physical theories »

Within Physics: **unification *not* reduction** (of theories) !

(*sole case:*

Thermodynamics → Statistical Physics as *well constructed theories*)

Logic in Biology: challenges

- Part of Mathematics as a **science of invariants** and *invariance preserving* **transformations**.

- Computer Science: *also* a science of **iteration**
  (*from* primitive recursion *to* portability of software);
  different symmetries and symmetry breaking.

- Biology: a science of **structural stability** *and* **variability** (the main invariant?).

The physical singularity of life

Extended Critical Situations

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

Bailly F., Longo G. **Mathématiques et sciences de la nature. La singularité physique du vivant.** *Hermann, Paris, 2006***.**

*(**chapter 6**: downloadable english translation)*

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Some references

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

- Bailly F., Longo G. **Mathématiques et sciences de la nature. La singularité physique du vivant.** *Hermann, Paris, 2006.*

- Longo G., Tendero P.-E. . *The causal incompleteness of Programming Theory in Molecular Biology*. Downloadable (A preliminary and longer french version will appear aux actes du colloque **"Logique, informatique et biologie"**, Nice, à paraître chez DeBoeck, Paris, 2008.)

- Longo G.. *Laplace*, *Turing and the "imitation game" impossible geometry: randomness, determinism and programs in Turing's test*. *In* Epstein, R., Roberts, G., & Beber, G. (Eds.). **The Turing Test Sourcebook**, 2007.

- Bailly F., Longo G. *Schèmes géométriques pour le temps biologique*. Draft.

Project*: life phenomena as *singularities* of physics or as *extended critical situation

A theoretical/epistemic separation (**not ontological**)

A methodological paradigm: Quantum Mechanics:

6. Non-separability
7. Non-locality (entanglement)
8. No trajectories in space-time

Physical Singularity of Life Phenomena

- Physical variation vs. **Variability (individuation)**

- Physics: *generic* (invariant) objects and *specific* trajectoires (geodetics)

  Biology: ***generic trajectories*** (compatible**)** and ***specific objects***

- Physics: determistic impredictibility or quantum indetermination within a given phase space (entangled probabilities)

  Biology: Intrinsic **indetermination** due to change of the phase space - phylogenesis

- Physics***:*** **energy** as operator**, time** as parameter;

  Biology*: **time** as operator* (Prigogine), ***energy** as parameter*

- **Biology: Extended critical situation** (from physical criticality)

Bailly F., Longo G. **Mathématiques et sciences de la nature. La singularité physique du vivant,** *Hermann, Paris, 2006.*

Some concepts from Physics of Criticality

– *Example:* *crystal and a gas*: opposite of the scale, as for order

– ***Phase transition***:

along a state change (e.g. gas ⇒ liquid ⇒ crystal...):

•passage through a ***critical state***

•(sudden) change of the correlation length

– ***Correlation length***:

a coherence structure (in some cases: distance of (possible) causal relations):

•in a perfect gas, particles interactions

•order of magnitude of the crystalline structure

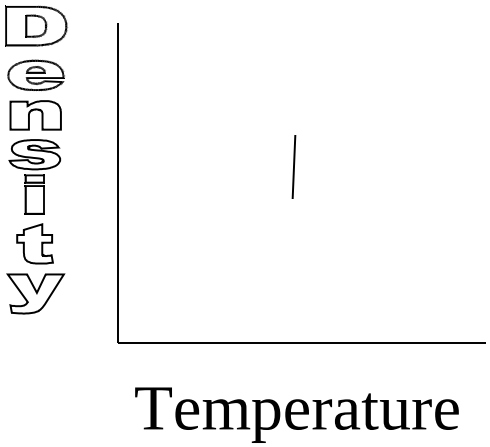
– ***State change****:*

- the ***global*** structure (may be) involved in the activities of the single particle
- the ***local*** situation depends on (correlates to) the global.

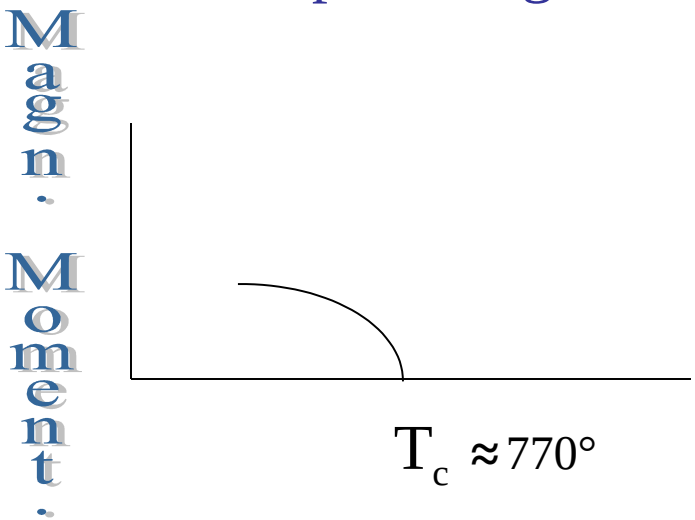
First and second order singularities

- Singularities *in* Physics: critical states: phase transitions…
  Examples:

fluid - gaz



ferro - para-magnetic



First and second order singularities

- Singularities *in* Physics: critical states; phase transitions…
  Examples:

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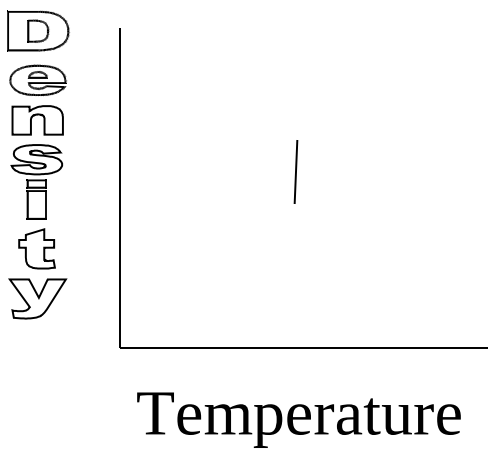

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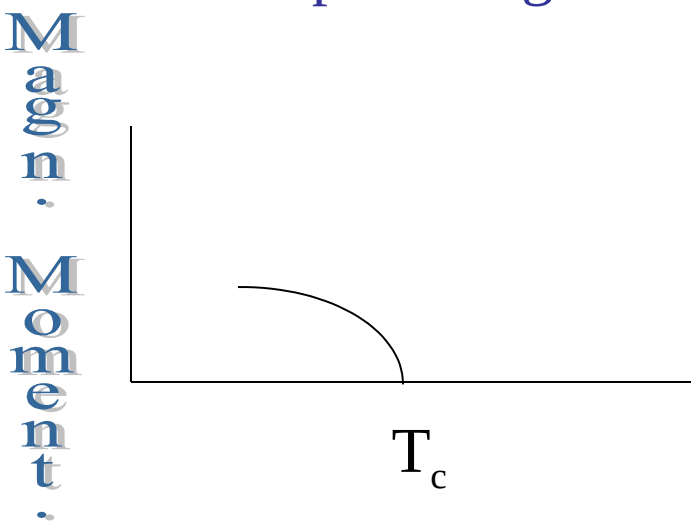
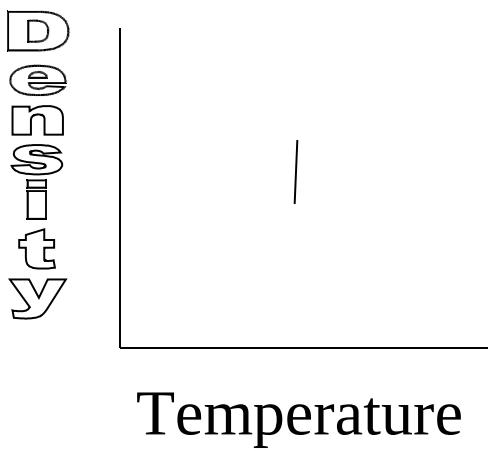


Critical phenomena (read backwards: ←)
- a passage from ***statistical*** to ***geometric*** properties, e.g. order (and viceversa: →)
- **divergence** of correlation length; from **local** *to* **global**: ….

First and second order singularities

- Singularities *in* Physics: critical states; phase transitions…
  Examples:

fluid - gaz



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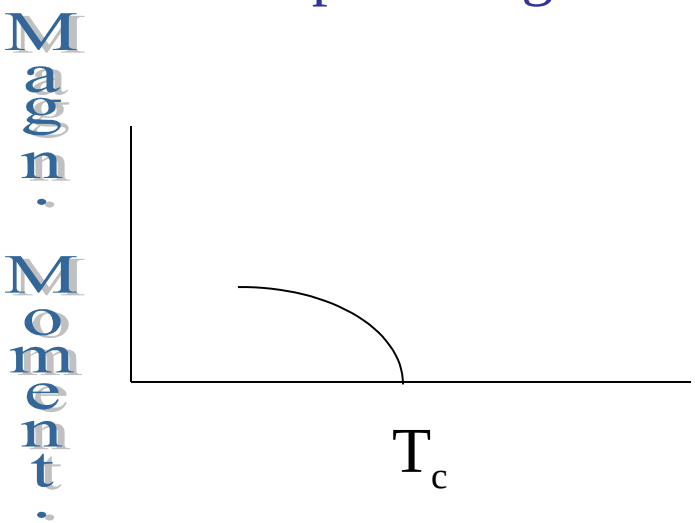
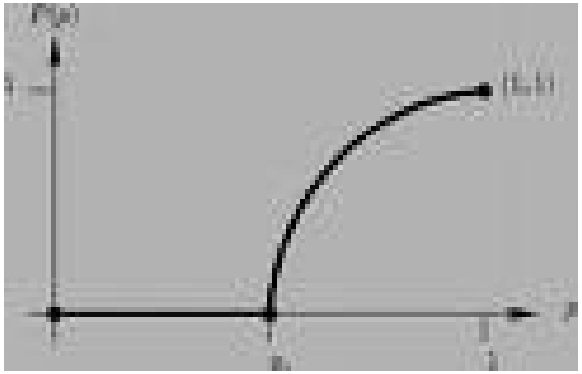


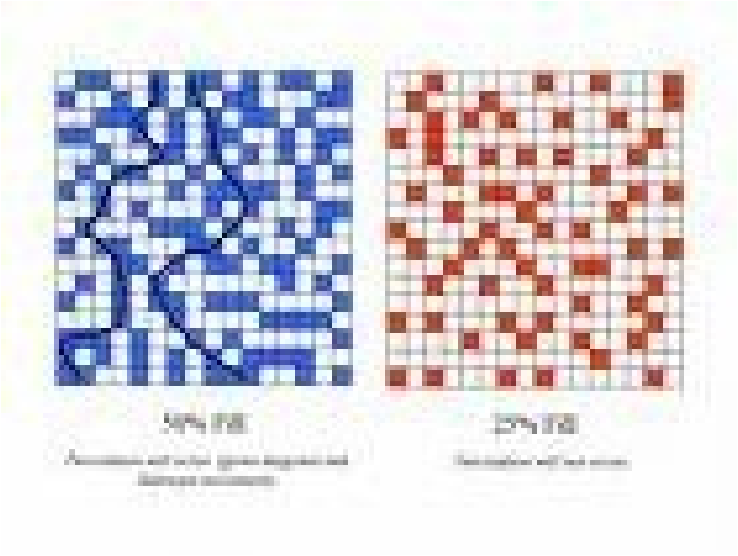
Correlation length: $L = (T/T_c - 1)^{-\nu}$

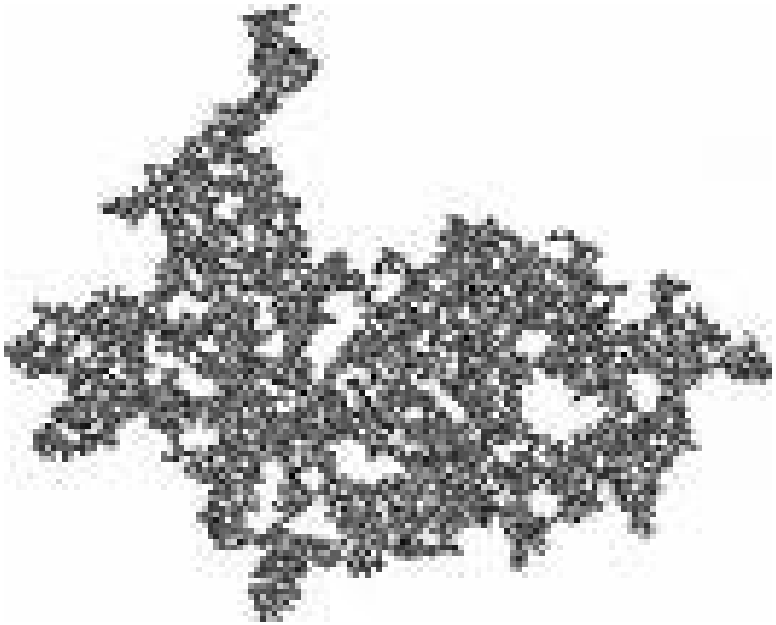
Local to global: *L goes to infinity at T_c (one point!)*

Entropy *decreases* (when *lowering* "←" the temperature)

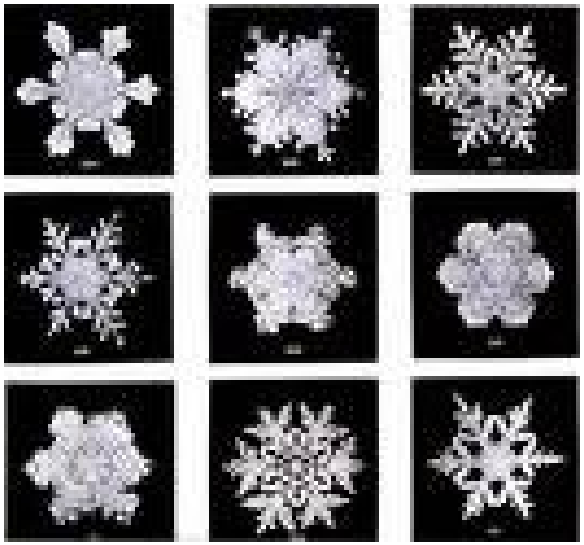
Percolation:







Snowflakes



From themodynamic potential (possible molecular links),

to a ***sudden*** and ***local,*** **decrease** of entropy

(in view of a slow-down of the brownian motion)

- Nicolis G., Prigogine I., **Self-organization in non-equilibrium systems: from dissipative structures to order through fluctuations**, Wiley, New York, 1977.

  (cascades of bifurcation, as transitions towards chaos)

- Bak P., C. Tang C. and Wiesenfeld K. "Self-organized criticality". **Physical Review** A 38: 364--374, 1988.

  (the sand pile: a critical angle)

- Kauffman S.A., **The origins of Order**, Oxford U. P., 1993. *("order for free"; **metabolic nets**)*

A critical state, in *Physics*

•An **isolated** point: a **singularity** in a process (or a bifurcation or a Thom's catastrophe, if irreversible).

•**minor fluctuations**, possibly below the level of observability, may lead towards radically different evolutions.

•*different* from "being far from equilibrium" (which does not imply *possibly different evolutions* of the system (bifurcations))

The *Mathematics* of criticality:

– **infinitesimal** variations yield **finite** changes (or finite variations lead to infinite changes, mathematical)

– instantaneous process as **divergence** of some functional descriptions (intended parameters);

– **maximality of complexity**, which also yields instability.

Life phenomena as *singularities* of physics or as *extended critical zone*

Physics (critical states, phase transitions…), *summary*:

- a **coherence structure** (order) may appear;
- **local to global** correlation length
- **isolated points** (0 measure) of the parameter(s);
- some **diverging** observables.

*Living matter as **extended critical zone***:

- far from **equilibrium**
- **local to global**: internal correlation length *extended over time*: "same" order of the system itself (critical phenomena)
- **fluctuations** within *extended* limits (several control parameters)
- **infinite physical complexity** (in view of divergences)
- Mantained into criticality by **autopoiesis** and **homeorhesis**
- Nesting and coupling of **levels of organization**.

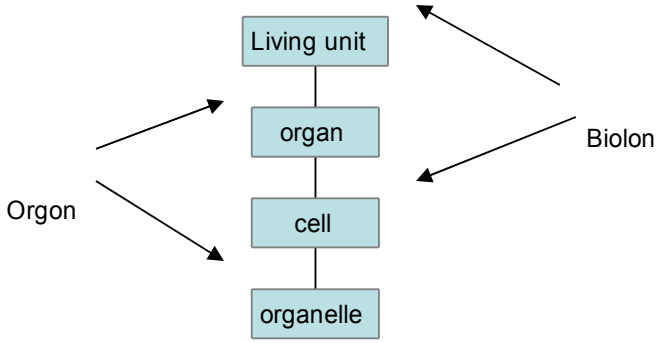
A possible meaning of a dynamics in an "extended critical situation"

- To be a **dissipative** process, **far from equilibrium**, as maintaining the internal organization requires energy exchanges, an **abnormally low entropy** w.r. to the equilibrium

  (global flux entropy, in all dimensions = the sum of all Lyapounov exponents (Ruelle) ≠ Shannon-Kolmogorov-Sinai entropy = information flux, only positive exponents (Lesne))

2. To form a **unity in space and time** (at least locally), where
   - **correlation lengths** at the various level of organization, at least one of the size of the system itself (the new object pertinent to the critical state)
   - **characteristic times**: within a stability (attracting) zone, exhaustive paths correspond to existence time.
   - **two dimensions of time**: a thermodynamical arrow of time, a compactified internal time (endogenous rhythms)

- To have an **internal organization**, given by the **interaction of the various levels** of organization, corresponding to dissipation constraints (dissipative structures) and to **organization loops** (e.g., autopoïetic and sensory-motor loops). Alternating levels of organisation: organelles, cell, organ, living unit



(orgon: typical *fractal structures*)

4. A **volume**, not just a space of parameters (like in Physics), within a semi-permeable **membrane** (regulating energetic exchanges).

Integration, regulation and causal regimes

– Within *the borders of the extended critical state*, **phase transitions, changes in correlation length, passages through singularities** ... ***occur continually*** (e.g. pathologies), but, within within the borders of criticality, they are dealt with by the regulatory activities.

– ***Integration*** is the (upward-*causal*) presence of the local into the global structure:

Integration may be understood as the *correlations of variables* that give unity to a given system of equations; or, also, as the *organizing role of singularities* in their solutions.

– ***Regulation*** is the global structure that *causally* affects (downwards) local ones:

Regulation may play the role of the *initial or border conditions* on global behaviors of the solutions of equation systems (differential or at finite differences).

Causality and complexity

Physics:

Causal relations are local; global only in the sense of a field (by propagation of *local* interactions; i. e. by transitivity) or of the global determination (by equations).

Biology:

local causality may *differ* radically from **global** correlations, yet it *cannot be isolated* from the latter: integration and regulation, typically, *causally affect* local interactions

(e.g. local bio-chemical exchanges may be regulated by cascades of hormones or neural signals of an entirely different nature).

Time: the product a compactified dimension (the loops) and a physical arrow.

More on the intelligibility of life phenomena

On complexity:

Elementary $\Rightarrow$ **Simple** (the cartesian myth)

vs.

Elementary & Complex (todays challenge)

(strings (Physics); cells; cognitive units)

Our proposal: Life phenomena as **an extended critical states:**

- continual phase transitions (over an interval)
- global unity of new entity (causal entanglement)
- infinite (physical) measure of complexity

Biological units live in a state of **maximal** (infinitary), physically unstable (even: *physically unsuitable*), **state of complexity**:

an extended critical situation

(a dynamical interference of global and local causality)

The **physical paradigms** helped us to formulate this notion, which is **not** internal to physical ***theories***.

Summary: Physical Singularity of Life Phenomena

- **Biology: Extended critical situations** (from *physical criticality*)

- Physical variation vs. **Variability (individuation)**

- Physics: *Specific* trajectoires (geodetics) and *generic* objects
  Biology: *generic trajectories* (compatible**)** and ***specific objects***

- Physics: *determistic impredictibility* or *indetermination* within a given phase space
  Biology: Intrinsic indetermination due to change of the phase space - phylogenesis (ontogenesis?)

- Physics***:*** **energy** as operator**, time** as parameter;
  Biology*: **time** as operator*, ***energy*** *as parameter*

Some references

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

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