Self-organization, Emergence and Systems Biology

SYSTEMS BIOLOGY IS THE STUDY OF AN ORGANISM, VIEWED AS AN INTEGRATED AND INTERACTING NETWORK OF GENES, PTOTEINS AND BIOCHEMICAL REACTIONS WHICH GIVE RISE TO LIFE. INSTEAD OF ANALYZING INDIVIDUAL COMPONENTS OR ASPECTS OF THE ORGANISM.

SYSTEMS BIOLOGY HAS BEEN AIDED BY POWERFUL NEW RESEARCH TECHNOLOGIES, AND THE INFUSION OF SCIENTISTS FROM OTHER DISCIPLINES, e.g. COMPUTER SCIENTISTS, MATHEMATICIANS, PHYSICISTS AND ENGINEERS.

BIOLOGISTS, GENETICISTS AND DOCTORS HAVE HAD LIMITED SUCCESS IN CURING COMPLEX DISEASES SUCH AS CANCER, HIV AND DIABETES BECAUSE TRADITIONAL BIOLOGY GENERALLY LOOKS AT ONLY A FEW ASPECTS OF ANY ORGANISM AT A TIME.

A FOCUSED, YET GLOBAL, INVESTIGATION OF HOW MOLECULAR INTERACTIONS ENGENDER PROPERTIES BECOMES MORE TRACTABLE AND, EXPERIMENTS CAN NOW BE PERFORMED ROUTINELY BECAUSE WE KNOW THE GENOMIC SEQUENCE.

THE INTERACTIONS OF PROTEINS WITH ONE ANOTHER AND OTHER SMALL AND LARGE MOLECULES WILL GENERATE THE PROTEIN NETWORKS AND REGULATORY NETWORKS.

PREVENTATIVE AND PERSONALIZED MEDICINES WILL BE THE MOST OBVIOUS IMPACT. OTHER TRANSFORMATIONS, SUCH AS THE DEVELOPMENT OF ALTERNATE FOOD AND ENERGY WILL OCCUR. THERE WILL ALSO BE A DEEPER UNDERSTANDING OF THE BIOLOGICAL BASIS OF HUMAN BEHAVIOR AND EFFORT TO PREDICT AND CONTROL IT.

Systems Biology: Molecular Docking, Folding, Motoring, Consciousness

Entropy is disorganization?

No bearing on systems with a small number of particles or an infinite number of particles.

Boltzmann dealt with transition from the microscopic to the macroscopic level in physics.

2nd Law states that entropy in an isolated system always increases. Unlike in Newton's Law of Gravity this is not always applicable.

Parallels of Boltzmann’s theories with Darwin’s.

A random number of fluctuations lead to irreversible change, one in the form of biological evolution, the other in the dissipation of energy, and evolution towards disorder.

A living cell is a self-organizing system that survives by taking in energy in the form of food and excreting energy in the form of heat and waste

There are patterns in Nature. Decay and Growth. Life and Death.

So, Creative Laws lie elsewhere than thermodynamic entropy.

The creation of amino acids, of microorganisms, of self-reproducing plants and animals, of complex information systems like the brain?

Those do not refer to only isolated systems. Prigogine's new interpretation of Boltzmann's theories are far wider and radically different.

In living systems, catalysts called enzymes are decisive in the emergence of life on earth. At a critical point, quantity suddenly becomes transformed into quality.

Living organisms combine order and activity.

Non-equilibrium is the rule. The emergence of life is not simple and linear. A living cell cannot be kept in a state of equilibrium or it would die.

Communication is very important. Dissipative structures simplify communication.

"Order through fluctuations" models introduce an unstable world where small causes can have large effects.

"Self-organization" can consolidate so that it affects the whole system.

Irreversible processes are necessary for Life.

The 2nd Law leads to a new concept of matter.

In a state of non-equilibrium , order emerges.

“Non-equilibrium brings order out of chaos.”

The origin of order

- **Classical physics: order can be built only rationally, by application of a set of fundamental laws of physics**
  - **Order needs to be somehow created by external forces**
- **Darwin: order can build itself spontaneously, e.g. Evolution**
  - **Spontaneous "emergence" of order.**
- **Classical physics: splitting the atom and observing distant galaxies**
- **Darwinian approach: focus on the evolutionary process that gradually built the universe the way it is**
- **Physics today: study how things are modified when a force is applied**
- **Darwinian approach: study how things modify themselves spontaneously**

The origin of information

- **Order is directly related to information**
- **Entropy is therefore related to information**
- **Classical physics: a study of forces**
- **Darwin's theory: the creation of information**
- **Classical physics: a study of gravitation or electricity**
- **Darwinian approach: a study of information**
- **Classical physics: differential equations**

The origin of organization

- **Darwinian approach: algorithms**
- **Algorithms are discrete, occur in steps, and can refer to themselves**
- **A science based on algorithms would be inherently different from a science based on equations.**
- **Darwinian approach: explain organization**
- **The concept of organization is deeply rooted in the physical universe.**
- **Darwin's treatise on the origin of species was indeed a treatise on the origin of order**

Design without a designer

- **Why do all living things have to grow?**
- **Why do all living things have to evolve?**
- **Darwin's intuition: the target can be reached not by designing it and then building it, but by taking a primitive object and letting it evolve**
- **The target object will not be built: it will emerge**
- **Everything in the universe was not built, it developed slowly over time**
- **How they happen to be the way they are depends to some extent on the advantages of being the way they are and to some extent on mere chance**

The math of nature

- **Nature is able to obtain far bigger and more complex structures than humans can ever dream of building by design**
- **Nature uses much simpler mathematics**
- **Humans have developed a system that is much more complex than anything nature has ever dreamed of using**
- **Another self-organizing systems that grows: the brain**
- **The algorithm is such that every time it ends it somehow remembers the result of its computation and will use it as the starting point for the next run**

Chaos and complexity

- **A mathematical model of phenomena of emergence (spontaneous creation of order)**
- **A physical justification of their dynamics (which violates physical laws)**
- **Poincare`'s "chaos" theory: a slight change in the initial conditions results in large-scale differences**
- **Derrida: a system goes through a transition from order to chaos if the strength of the interactions among its parts is gradually increased**
- **Very "disordered" systems spontaneously "crystallize" into a higher degree of order**

Chaos and complexity

- **Complexity: a system must be complex enough for any property to “emerge” out of it**
- **Complexity can be formally defined as non-linearity**
- **The world is mostly nonlinear**
- **Chaos theory = nonlinear dynamics**
- **Strange attractors: shapes that chaotic systems produce in phase space**

The science of emergence

- Processes of emergent order and complexity
- How structure arises from the interaction of many independent units
- At every level of science, the spontaneous emergence of order, or self-organization of complex systems, is a common theme
- Koestler and Salthe: complexity entails hierarchical organization
- Von Bertalanffi's general systems theory
- Haken's synergetics
- Prigogine's non-equilibrium thermodynamics
- A unifying view of the universe at different levels of organization

Systems Theory

- **Von Bertalanffy's "organized complexities" consist of interacting parts**
- **General systems theory**
  - **Looks for an isomorphism of law in different fields**
  - **Studies "wholes", which are characterized by such holistic properties as hierarchy, stability, teleology**
- **A living organism is a hierarchical order of open systems, where each level maintains its structure thanks to continuous change of components at the next lower level**

Hypercycles

- **Manfred Eigen's cyclic reaction networks**
  - **Focus on very fast chemical reactions**
  - **A hypercycle is a cyclic reaction network, i.e. a cycle of cycles of cycles**
  - **Life is the product of a hierarchy of hypercycles**
    - **Basic catalytic cycles can be organized into an autocatalytic cycle, i.e. a cycle that is capable of self-reproducing**
    - **A set of autocatalytic cycles gets, in turn, organized into a catalytic hypercycle**
    - **This catalytic hypercycle represents the basics of life**

Hypercycles

- Manfred Eigen's cyclic reaction networks
  - The dual process of unity (due to the use of a universal genetic code) and diversity (due to the "trial and error" approach of natural selection) in evolution started even before life was created
    - Evolution of species was preceded by an analogous stepwise process of molecular evolution
  - Natural selection is a mathematical consequence of the dynamics of self-reproducing systems

Dissipative systems

- **Ilya Prigogine's non-equilibrium thermodynamics**
  - **Classical physics: the world as a static and reversible system that undergoes no evolution, whose information is constant in time**
  - **Classical physics is the science of being**
  - **Thermodynamics describes an evolving world in which irreversible processes occurs**
  - **Thermodynamics is the science of becoming**
  - **Irreversible processes are an essential part of the universe**
  - **Furthermore, conditions far from equilibrium foster phenomena such as life that classical physics does not cover at all**
  - **Irreversible processes and non-equilibrium states may turn out to be fundamental features of the real world**

Dissipative systems

- The science of being and the science of becoming describe dual aspects of nature
- “Conservative” systems vs “dissipative” systems (subject to fluxes of energy and/or matter)
- Dissipative systems give rise to irreversible processes
- Order can come either from equilibrium systems or from non-equilibrium systems that are sustained by a constant source (by a persistent dissipation) of matter/energy
- All living organisms are non-equilibrium systems
- The distance from equilibrium and the nonlinearity of a system drive the system to ordered configurations, i.e. create order

Dissipative systems

- **Non-equilibrium and non-linearity favor the spontaneous development of self-organizing systems, which maintain their internal organization, regardless of the general increase in entropy, by expelling matter and energy in the environment**
- **Nonlinear systems driven away from equilibrium can generate instabilities that lead to bifurcations (and symmetry breaking beyond bifurcation)**
- **When the system reaches the bifurcation point, it is impossible to determine which path it will take next: chance**
- **Once the path is chosen, determinism resumes**
- **The multiplicity of solutions in nonlinear systems can be interpreted as a process of gradual "emancipation" from the environment**

Catastrophe theory

- **Rene' Thom's catastrophe theory**
  - **General laws of form evolution**
  - **A form is defined, first and foremost, by its stability: a form lasts in space and time**
  - **Life itself is, ultimately, creation, growth and decaying of form**
  - **Every physical form is represented by a mathematical quantity called "attractor" in a space of internal variables**
  - **If the attractor satisfies the mathematical property of being "structurally stable", then the physical form is the stable form of an object**
  - **Changes in form, or morphogenesis, are due to the capture of the attractors of the old form by the attractors of the new form**
  - **All morphogenesis is due to the conflict between attractors**

Catastrophe theory

- The universe of objects can be divided into domains of different attractors
- Such domains are separated by shock waves
- Shock-wave surfaces are singularities called "catastrophes"
- A catastrophe is a state beyond which the system is destroyed in an irreversible manner
- In a 4-dimensional space there exist only 7 types of elementary catastrophes
- The form of an object is due to the accumulation of many of these "accidents"

Complex systems

- **Stuart Kauffman's self-organizing systems**
  - **The fundamental force that counteracts the universal drift towards disorder**
  - **“Candidate principle”: organisms change their interactions in such a way to reach the boundary between order and chaos**
  - **Systems on the boundary between order and chaos have the flexibility to adapt rapidly and successfully.**
  - **Living organisms are a particular type of complex adaptive systems.**
  - **Natural selection and self-organization complement each other: they create complex systems poised at the edge between order and chaos, which are fit to evolve in a complex environment**

There are several models of the cell. Pathways or Signal Transduction, by which the arrival of a chemical signal at the cells turn on a new pattern of gene expression, are every bit as important as the application of network models.

Cellular processes occur on timescales from nanoseconds to days. This challenges predictive models of cell dynamics. Self-organization (Turing 1952) and the fact that it must must occur when the system is far from equilibrium (Prigogine) led to multiple scales in the network of transport processes.

In the same way (kinetics) that I used a program to describe combustion or environmental species concentrations, the cell modeler now calculates cell species concentrations except that such calculations are at constant temperature and diffusion is used:

$$\partial C/\partial t = D\nabla C$$

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C6H5NO NITROSO-PHENYL or NITROSO-BENZENE  CALCULATED BY BOZZELLI USING GROUP
ESTIMATES. EXTRAPOLATED TO 6000 K USING WILHOIT'S POLYNOMIALS. HF298=48.0 KCAL
REF=Choo, Golden & Benson, Int. J. Chem Kinet 7,(1975),713. Max Lst Sq Error
Cp @ 1500 K 0.36%.
C6H5NO              T 7/95C   6H   5N   1O   1G   298.150  5000.000  F 107.11184 1
 0.15129273E+02 0.20169394E-01-0.79009702E-05 0.14240839E-08-0.96649392E-13    2
 0.17118219E+05-0.56899184E+02 0.20849489E+01 0.34489960E-01 0.27707248E-04    3
-0.65460444E-07 0.29821820E-10 0.21870293E+05 0.15898367E+02 0.24154400E+05    4

C6H5O  PHENOXY RADICAL  SIGMA=2  STATWT=2  IA=14.8396  IB=30.4574  IC=45.297
NU=3087,3063,3027,1603,1501,1261,1168,1025,999,823,526,958,817,409,973,881,751,
686,503,225,3070,3049,1610,1472,1343,1277,1150,1070,619,403  REF=BURCAT,
ZELEZNIK & MCBRIDE HF298=47.698 KJ  MAX LST SQ ERROR CP @ 1300 K 0.81 % .
PHENOXY RAD         L12/84C  6.H  5.O  1.   0.G   300.000  5000.000  B  93.10490 1
 0.13833984E 02 0.17618403E-01-0.60696257E-05 0.91988173E-09-0.50449181E-13    2
-0.69212549E 03-0.50392990E 02-0.18219433E 01 0.48122510E-01-0.46792302E-05    3
-0.34018594E-07 0.18649637E-10 0.42429180E 04 0.33526199E 02 0.57367379E 04    4
```

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ELEMENTS
C H S
END
SPECIES
CH4 H CH3 C2H6 H2 C2H5 C2H4 C2H3 C4H6 C2H2 C4H3 C4H2 C5H12 CH2 CH4S C2H6S C2H
C4H10 C3H8 C3H6 H2S I*C3H7 N*C3H7 C3H5 C3H4 C4H8 BUTENE2 OCTENE* IC4H10
N*C4H9 S*C4H9 C4H7 P*C4H9 C6H6 C6H5 C12H10 C3H3 ETBENZENE OCTANE CUMENE
TOLUENE TMBEN* OXYLENE MXYLENE PXYLENE C6H12 C6H14 ISOOCTANE HEPTANE STYRENE
END
REACTIONS
CH4+M=CH3+H+M           2E17          0.0       88000.
CH4+H=CH3+H2            2.24E4        3.0        8750.
CH3+CH3=C2H6            1E13          0.0           0.
CH3+CH3=C2H5+H          7.94E14       0.0       26520.
CH3+CH3=C2H4+H2         1E16          0.0       32000.
CH3+M=CH2+H+M           1.95E16       0.0       91600.
C2H6+CH3=C2H5+CH4       5.49E-1       4.0        8280.
C2H6+H=C2H5+H2          5.37E2        3.5        5200.
C2H5+M=C2H4+H+M         2E15          0.0       30000.
C2H5+C2H5=C4H10         7.94E12       0.0           0.
C3H8=C2H5+CH3           1.7E16        0.0       85840.
C3H6=C2H3+CH3           6.31E15       0.0       85800.
C2H5+C2H3=C4H8          8.91E12       0.0           0.
C2H3+C2H3=C4H6          8.91E12       0.0           0.
C2H4+M=C2H2+H2+M        9.33E16       0.0       77200.
C2H4+M=C2H3+H+M         6.31E18       0.0      108720.
C2H4+C2H4=C2H3+C2H5     5.01E14       0.0       64700.
C2H3+M=C2H2+H+M         7.94E14       0.0       31500.
C2H4+H=C2H3+H2          1.51E7        2.0        6000.
C2H3+H=C2H2+H2          2E13          0.0         250.
C2H3+C2H4=C4H6+H        1E12          0.0        7300.
```

Biochemical reaction

One example of biochemical reactions is shown in Eq.1.

$$\mathbf{S + E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{SE} \xrightarrow{k_2} \mathbf{P + E} \qquad \textbf{Eq.1}$$

This is known as Michaelis-Menten equation, in which substrate S binds enzyme E

$$S + E \xrightarrow{k_1} SE$$

$$SE \xrightarrow{k_{-1}} S + E$$

$$SE \xrightarrow{k_2} P + E$$

In 1952 Alan Turing published a very influential paper in Philosophical Transactions of the Royal Society, entitled *The Chemical Basis of Morphogenesis*. In that article Turing proposed a possible solution to the problem of how developing systems can become heterogeneous, spatially organized entities starting from an initially homogeneous state (Turing 1952, Meinhardt 1982, Murray 1989, Lengyel and Epstein, 1992). Turing showed that an appropriate compromise between local reactions and long-range communication through diffusion could generate macroscopic spatial structures. The interplay of both components was described in terms of a system of partial differential equations, so called *reaction-diffusion* (RD) equations, namely a set

$$\frac{dC_i}{dt} = \Phi_i(C_1, ..., C_n) + D_i \nabla^2 C_i$$

$$R_1 + g_1 \xrightarrow{k_1} 2g_1$$

$$R_2 + g_2 \xrightarrow{k_2} 2g_2$$

$$g_1 + g_2 \xrightarrow{k_3} 2g_0$$

$$\frac{\partial c_{g_1}}{\partial t} = k_1 \cdot c_{R_1} \cdot c_{g_1} - \rho_1 \cdot c_{g_1} - k_3 \cdot c_{g_1} \cdot c_{g_2} + D_{g_1} \cdot \nabla^2 c_{g_1}$$

$$\frac{\partial c_{g_2}}{\partial t} = k_2 \cdot c_{R_2} \cdot c_{g_2} - \rho_2 \cdot c_{g_2} - k_3 \cdot c_{g_1} \cdot c_{g_2} + D_{g_2} \cdot \nabla^2 c_{g_2}$$

$$\frac{\partial c_{g_0}}{\partial t} = 2 \cdot k_3 \cdot c_{g_1} \cdot c_{g_2} - \rho_3 \cdot c_{g_0} + D_{g_0} \nabla^2 c_{g_0}$$

$$\frac{\partial c_{R_1}}{\partial t} = R_{1_0} - k_1 \cdot c_{R_1} \cdot c_{g_1} + D_{R_1} \nabla^2 c_{R_1}$$

$$\frac{\partial c_{R_2}}{\partial t} = R_{2_0} - k_2 \cdot c_{R_2} \cdot c_{g_2} + D_{R_2} \nabla^2 c_{R_2}$$

3D morphology

A-Cell v5.1 includes A-Cell-3D functions, which gives functions of generating cellular or subcellular morphological models and embedding models constructed by A-Cell. Thus A-Cell v5.1 is unified software of A-Cell and A-Cell-3D of previous version. A-Cell-3D is not required if A-Cell v5.1 is installed.

Two examples of generated morphologies, pyramidal cell (a neuron) and spine/dendrite are shown in Fig.2.

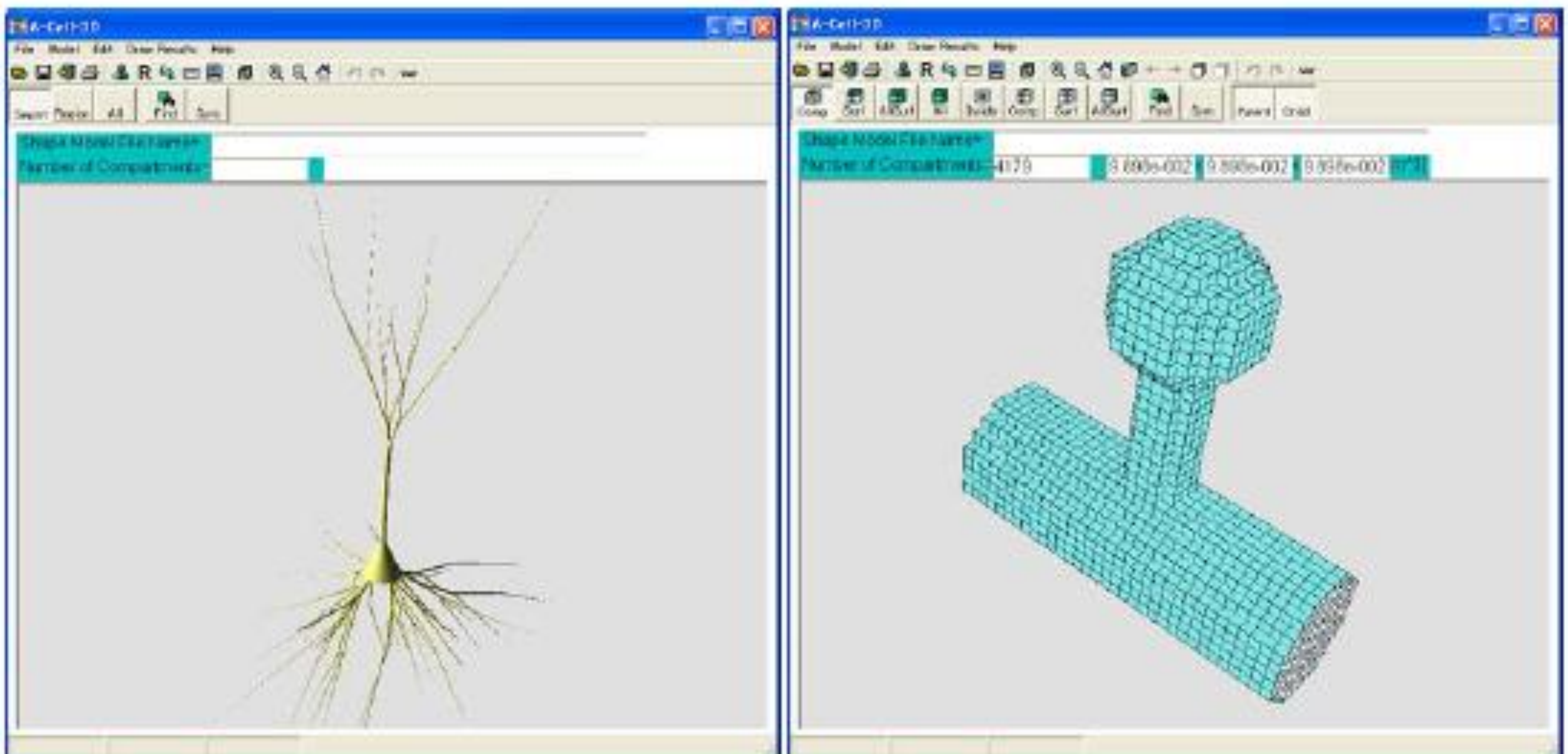

Fig.2 Generated morphologies of a neuron and a spine/dendrite

DISCUSSION TOPICS

1. BIO FRONTIER PHYSICS

2. GENE REGULATORY, PROTEIN & METABOLIC NETWORKS

3. SYSTEMS BIOLOGY

4. FOLDING & DOCKING

5. NANOMACHINES

6. SYNTHETIC BIOLOGY, MORPHOGENETIC FIELDS & LAB ON A CHIP

7. RESONANT RECOGNITION MODEL & NEW DRUGS

8. MEMORY & CONSCIOUSNESS

9. CANCER (SIGNALLING, TARGETS & METASTASIS)