Systems Biology and Scale Relativity

Laboratoire Joliot Curie
Ecole Normale Supérieure de Lyon
March 2, 2011

Charles AUFFRAY
charles.auffray@vjf.cnrs.fr

Laurent NOTTALE
laurent.nottale@obspm.fr

Functional Genomics and Systems Biology for Health
CNRS Institute of Biological Sciences - Villejuif

Laboratory Universe and Theories
CNRS - Paris-Meudon Observatory - Paris Diderot University

Definitions of Integrative Systems Biology

Integrative: interconnection of elements and properties
Systems: coherent set of components with emerging properties
Biology: science of life (Lamarck 1809)

Field studying interactions of biological systems components
Antithesis of analytical reductionism
Iterative research strategy combining modeling and experiments
Multi- Inter- and trans-disciplinary community effort

Origins of Systems Biology in William Harvey's Masterpiece on the Movement of the Heart and the Blood in Animals
Charles Auffray and Denis Noble
(2009) Int. J. Mol. Sci. 2009, 10:1658-1669.

Definitions for Integrative Systems Biology

The (emergent) properties and dynamic behaviour of a biological system are different (more or less) than those of its interacting (elementary or modular) components

Combine discovery and hypothesis, data and question driven inquiries to identify the features necessary and sufficient to understand (explain and predict) the behaviour of biological systems under normal (physiological) or perturbed (environmental, disease or experimental) conditions

Biology triggers technology development for accurate and inexpensive global measurements (nanotechnology, microfluidics, grid and high-performance computing)

Models are (more or less abstract and accurate) representations

The Theoretical Framework of Systems Biology

Self-organized living systems: conjunction of a stable organization with chaotic fluctuations in biological space-time

Auffray C, Imbeaud S, Roux-Rouquié M and Hood L
(2003) Philos. Trans. Roy. Soc. Math. Phys. Eng. Sci. 361:1125-1139

From functional genomics to systems biology: concepts and practices

Auffray C, Imbeaud S, Roux-Rouquié M and Hood L
(2003) C. R. Biologies 326:879-882

The Theoretical Framework of Systems Biology

The analytical reductionist framework based on the Cartesian precepts of objectivity, decomposition, causality and exhaustivity has enabled identification of the stable physical scaffolding of living systems

Systemic modelling using conjunctive logic based on the precepts of contextualization, relatedness, conditionality and pertinence will help the development of system level understanding in biology

Working Hypotheses and Conjectures for Systems Biology

Living systems have the ability to organize themselves as the result of a conjunction occurring through an interface between the variable part of a relatively stable physical organization, and the stable part of a chaotic network of small fluctuations.

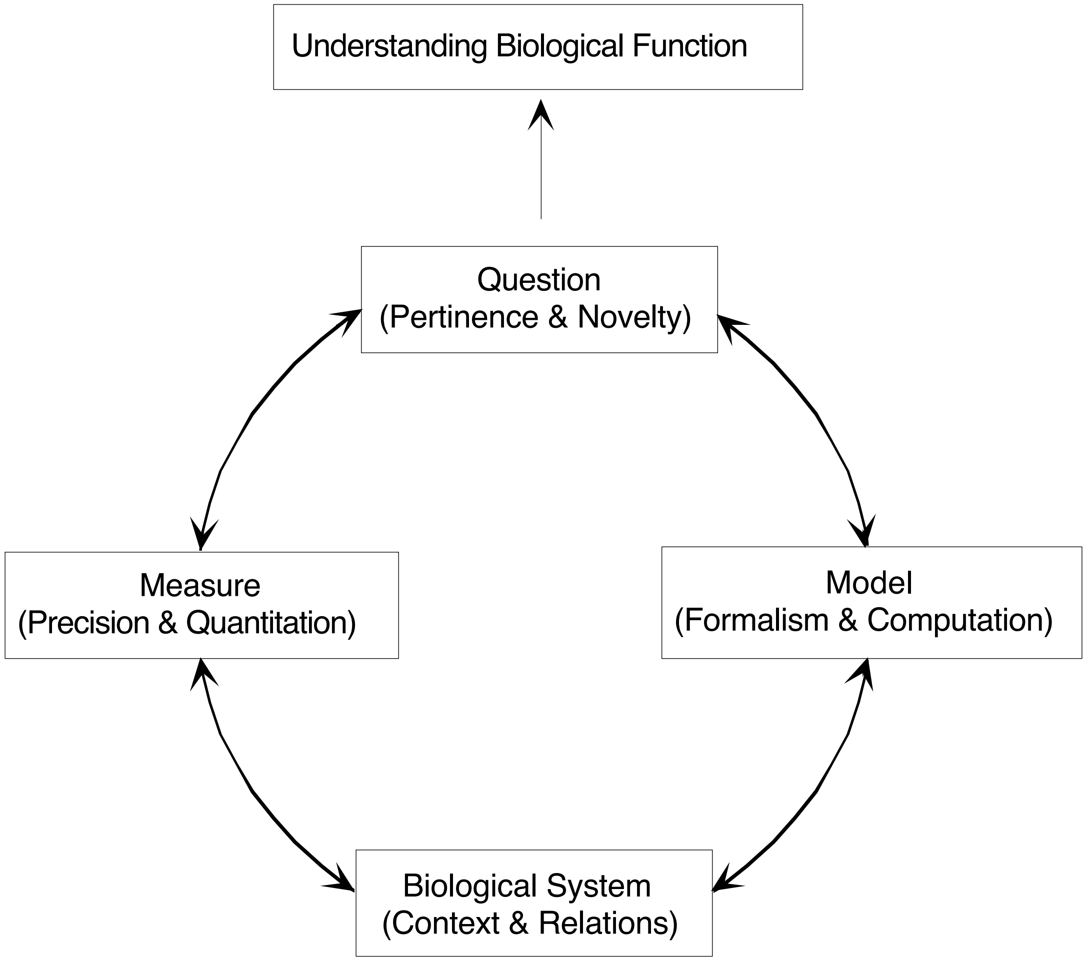
These small fluctuations, which are inaccessible to currently available tools, may be the major determinants of the behaviour of biological systems because they convey collectively the most important part of biological information.

Working Hypotheses and Conjectures for Systems Biology

Complex biological systems operate in a space with a variable number of dimensions, biological space-time.

Detection of small changes of low intensity signals will require the development of a new conceptual and practical framework combining in an iterative mode systemic modelling of biological systems, to generate hypotheses, together with a high level of standardization of high-throughput platforms enabling reliable cross comparisons, to test them.

The Iterative Process of Systems Biology



Middle-out Scheme of Inquiry on Biological Systems

The Iterative Process of Systems Biology

1- Formulate and formalize general or particular questions

2- Define components of biological system and collect relevant biochemical and genetic data

3- Use them to formulate an initial model of system

4- Perturb components of system and study results

5- Compare observed and predicted responses

6- Refine model to improve fit with experimental observations

7- Conceive and test new perturbations and competing hypotheses

8- Iterate the process until answers are obtained

Challenges of Systems Biology and Medicine

Experimental design

Multidimensional data space
Biological and technological fluctuations

Technological

Multiparameter high-precision inexpensive measurements
Single-cell, single-molecule measurements
Non-invasive imaging

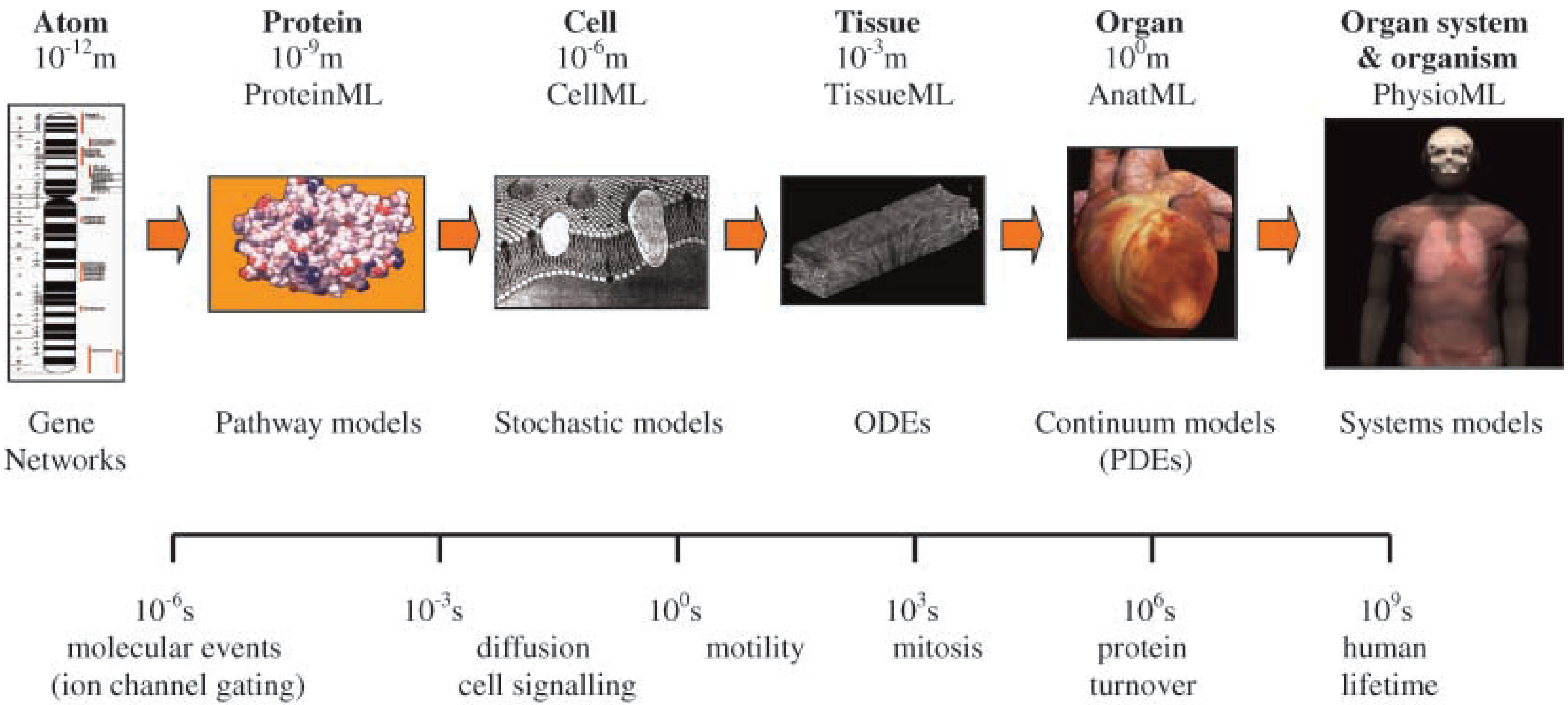
Computational

Multi-scale integration
Predictive dynamic models and simulations

Sociological

Multi, inter and trans-disciplinary culture
Mutual understanding and respect
Training, evaluation and funding

The Grand Challenge of Integrative Systems Biology: Multiscale Integration



Hunter P, Robbins P, and Noble D (2002) The IUPS human Physiome Project. Pflugers Arch 445:1-9.

The Grand Challenge of Integrative Systems Biology: Multiscale Integration

Multiple formalisms used to model biological systems
at their different levels of organization

Molecular: e.g. ordinary and partial differential equations

Cellular: e.g. logical networks, cellular automata

Organ: e.g. finite element lattices

Often based on incompatible principles

Extended mathematical framework needed to enable
multiscale integration across all levels simultaneously

Principles of Systems Biology

Denis Noble - The Music of Life - Oxford University Press

Fourth principle

The theory of biological relativity

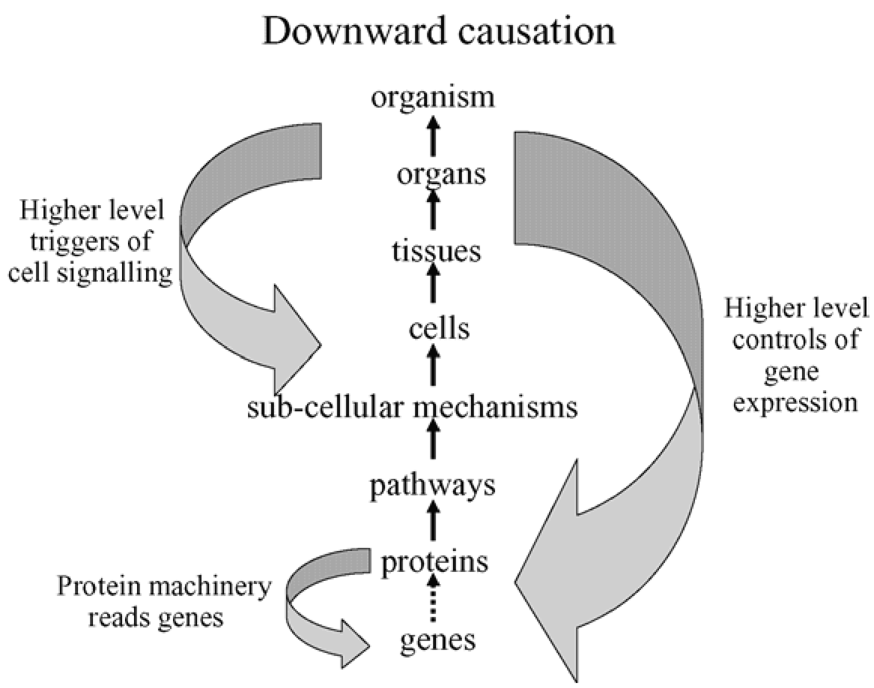
There is no priviledged level of causality. This is necessarily true in systems possessing multiple levels interacting through ascending and descending feedback loops.

The fundamental concept is that, since all levels can be the starting point of a causal chain, each can be the basis for a simulation.

In biological systems, there is no priviledged level dictating its law to the other levels. The levels are not equivalent, their relationships are not linear.

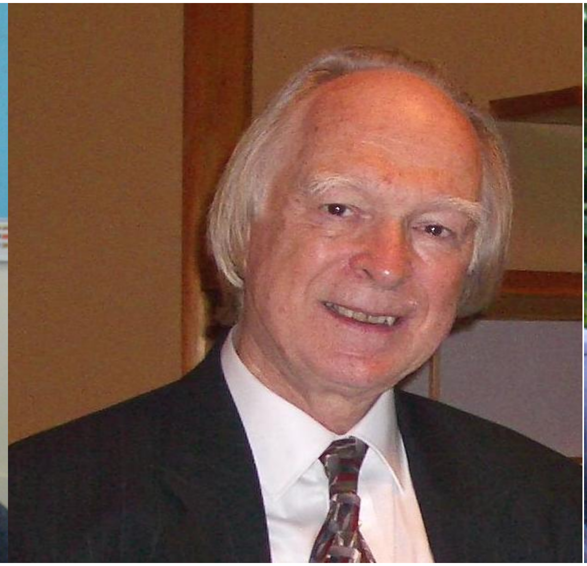
EXTENDing the Conceptual, Mathematical and Experimental Framework of Integrative Systems Biology

Formalise the principle of biological relativity



There is no priviledged level of causality

EXTENDing the Conceptual, Mathematical and Experimental Framework of Integrative Systems Biology



Charles Auffray
Qu’est-ce que la vie ?

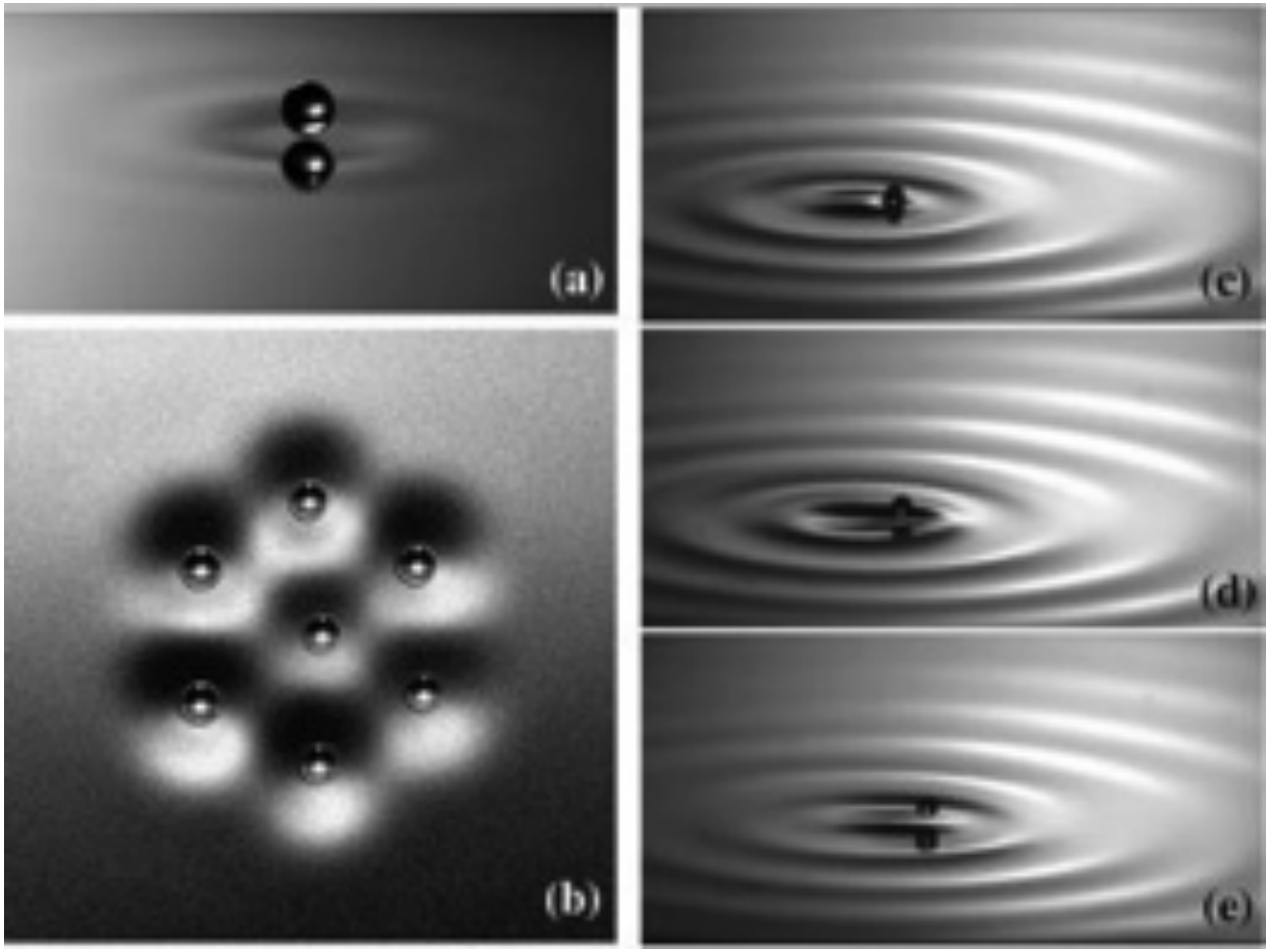
Le Pommier

Denis Noble
La musique de la vie

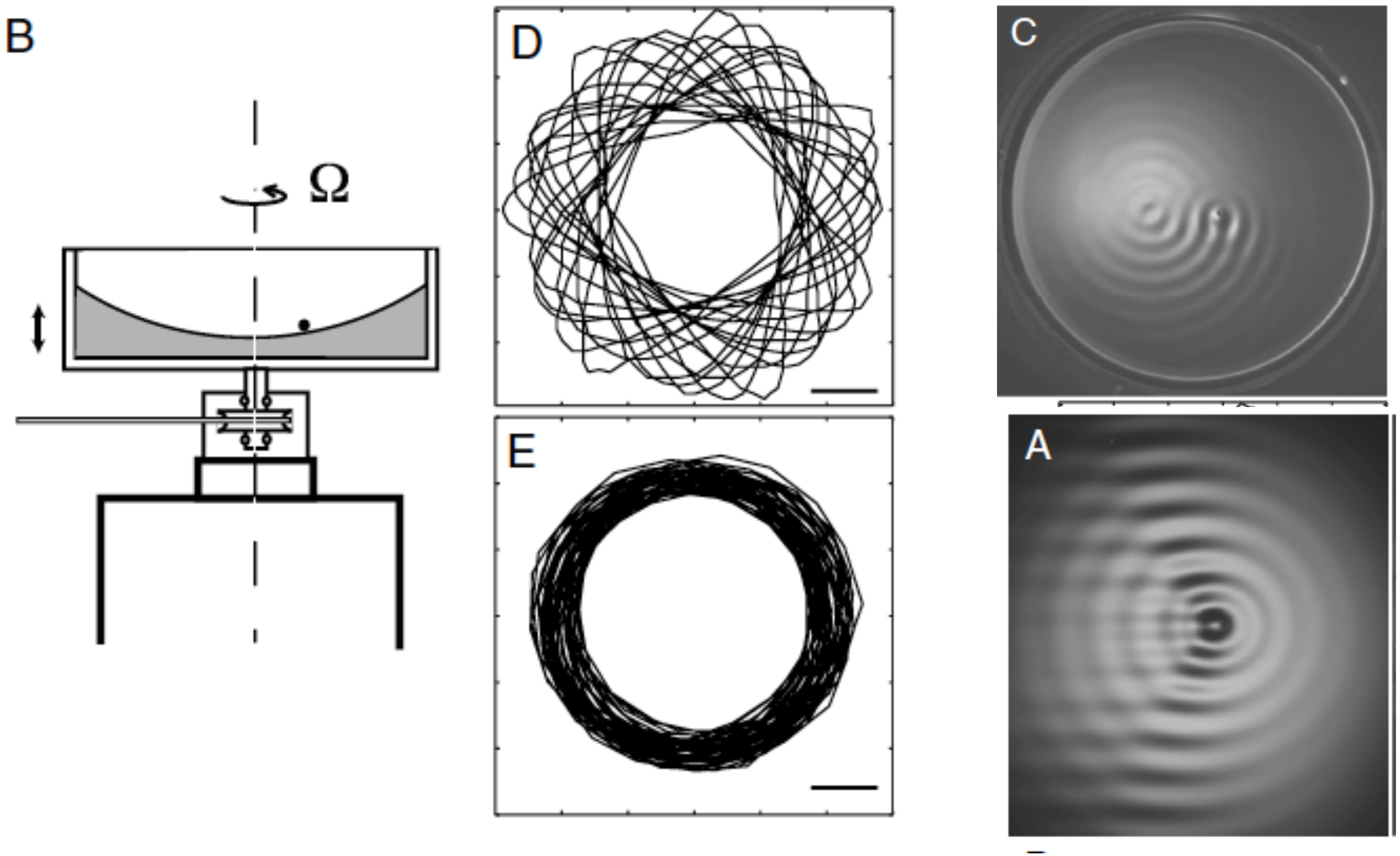
Le Seuil

Laurent Nottale
La relativité
dans tous ses états
Hachette

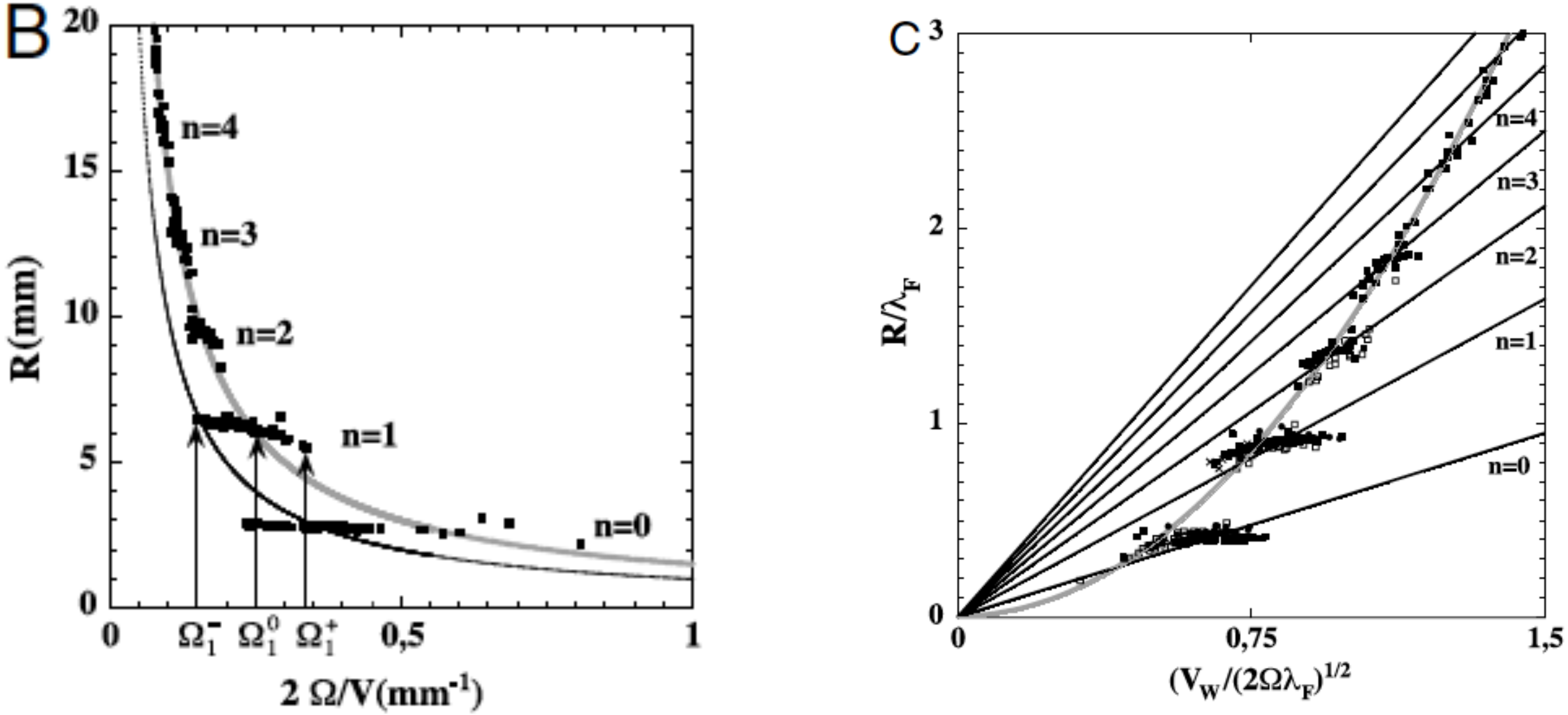
Yves Couder et al. - 2005 Nature 437:208
Dualité onde-particule à l'échelle macroscopique
billes sauteuses et marcheuses



Fort et al. 2011 PNAS 107:17515
Orbites quantifiées des billes marcheuses sur un support tournant



Fort et al. 2011 PNAS 107:17515
Orbites quantifiées des billes marcheuses sur un support tournant



Extending the Theoretical Framework of Systems Biology

Scale Relativity Theory and Integrative Systems Biology

1. Founding Principles and Scale Laws

Auffray, C. and Nottale, L.

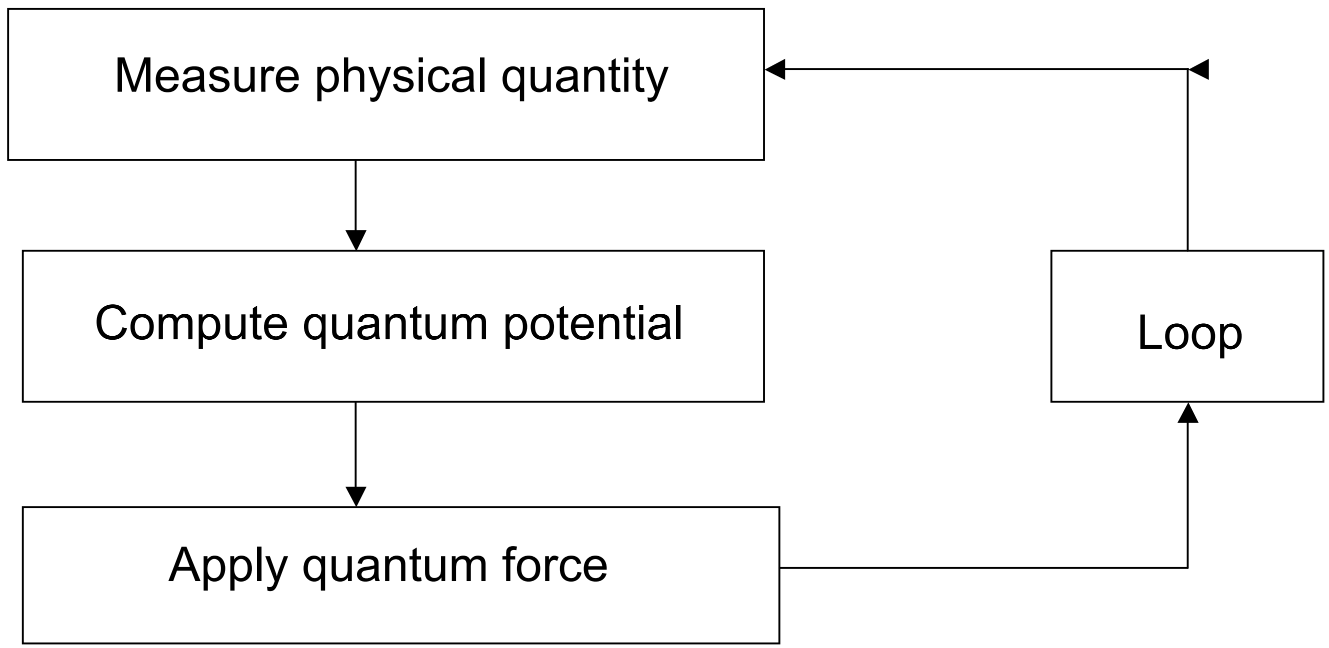
(2008) Prog. Biophys. Mol. Biol. 97, 79-114.

2. Macroscopic Quantum-type Mechanics

Nottale, L. and Auffray, C

(2008) Prog. Biophys. Mol. Biol. 97, 115-157.

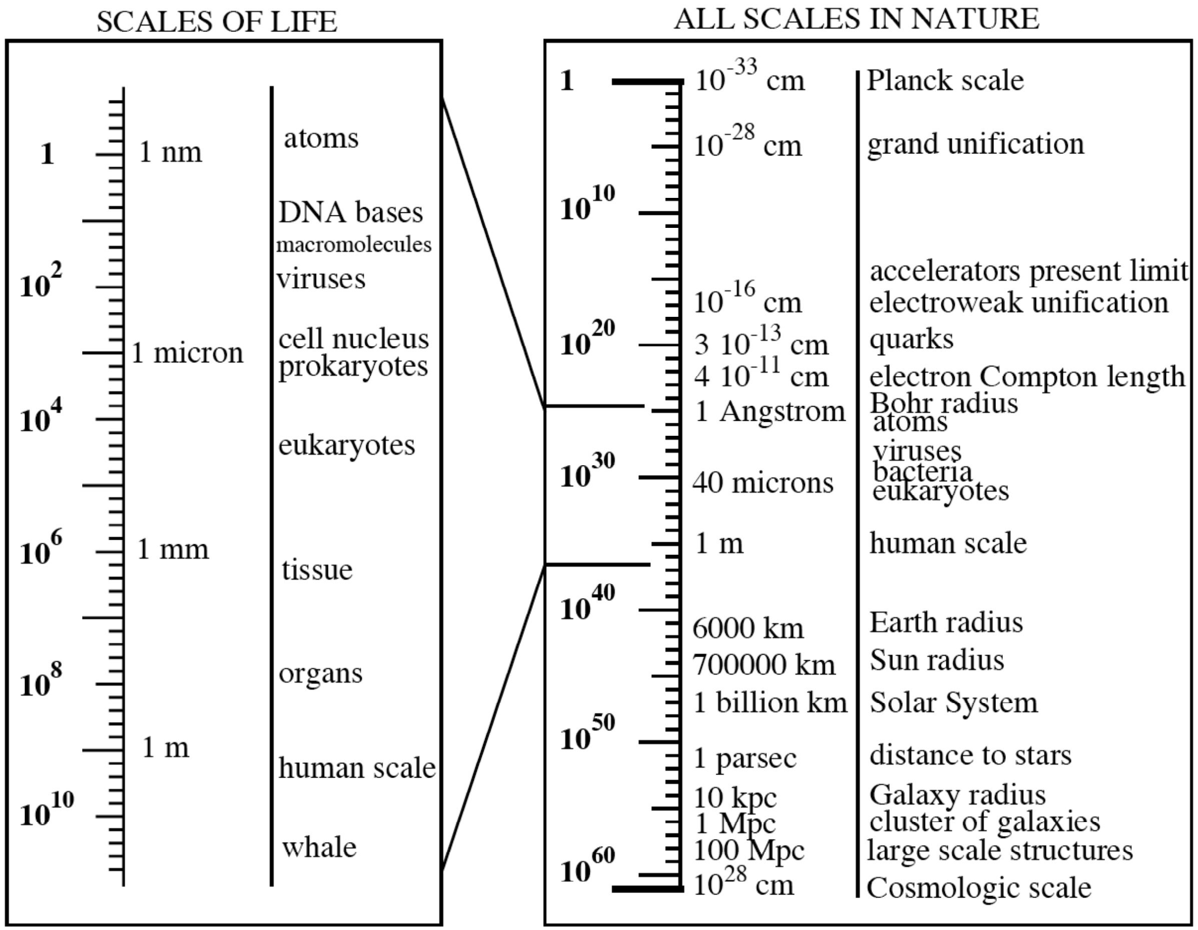
EXTENDing the Conceptual, Mathematical and Experimental Framework of Integrative Systems Biology



Experiments and devices with macroscopic quantum-type properties

The Theory of Scale Relativity

Scales in nature



The Theory of Scale Relativity

According to the principle of relativity, natural laws are valid in any system of coordinates, whatever its state.

The state of any system can be defined only relatively to another system.

Only scale ratios have a physical meaning, there is no absolute scale.

Resolution is an inherent (relative) property of space-time geometry.

According to the principle of scale relativity, the fundamental laws of nature apply whatever the state of scale of the coordinate system.

The Theory of Scale Relativity

Space-time is continuous and generally non-differentiable, therefore fractal (explicitly scale-dependent and divergent).

Therefore, there is an infinity of paths, identified with the geodesics (shortest in proper time), which are themselves fractal.

In this framework, the fundamental equations of dynamics can be integrated in the form of a generalized Schrödinger equation.

It becomes possible to derive linear and non-linear scale laws to describe the self-organization of biological structures and quantum-type behaviours.

Scale Relativity Theory and Integrative Systems Biology

Predictions of scale relativity in astrophysics

More than 50 validated through subsequent observations

Derivation of the axioms of quantum mechanics

General relativity and quantum mechanics in common (geometric) framework

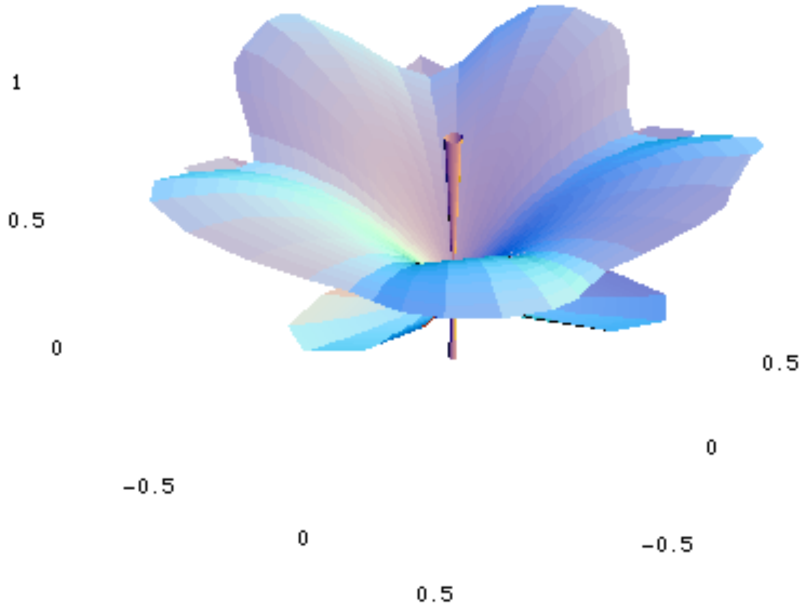
Models for self-organization of biological systems

Tree of life described by log-periodic scale laws

Morphogenesis and growth described by a macroscopic Schrödinger-type equation

Scale Relativity Theory and Integrative Systems Biology

This is not a flower



Solutions of a generalized Schrödinger equation for spheric growth (scattering) from a centre

Platycodon flower

Scale Relativity Theory and Integrative Systems Biology

Generalized and quantum scale laws could allow identification of biological fields and charges, and to measure complexergy in biological systems.

Complexergy is a measure of the complexity of a scale-structured system with entangled levels of organizatrion.

Scale Relativity Theory and Integrative Systems Biology

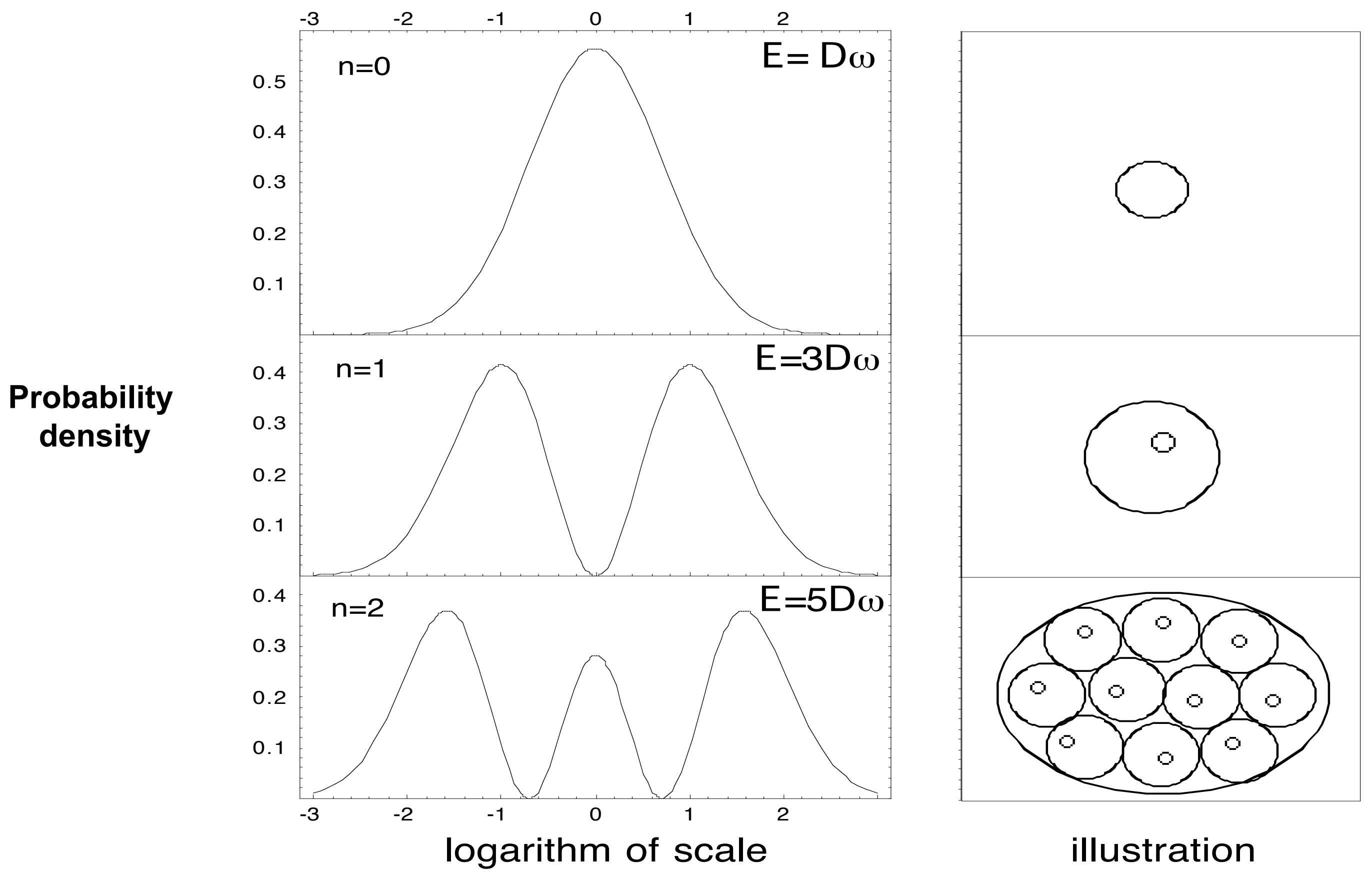


FIGURE 6. Solutions of increasing complexergy of the scale-Schrödinger equation for an harmonic oscillator scale-potential. These solutions can be interpreted as describing systems characterized by an increasing number of hierarchical levels, as illustrated in the right hand side of the figure. For example, living systems such as procaryots, eucaryots and simple multicellular organisms have respectively one (cell size), two (nucleus and cell) and three (nucleus, cell and organism) characteristic scales.

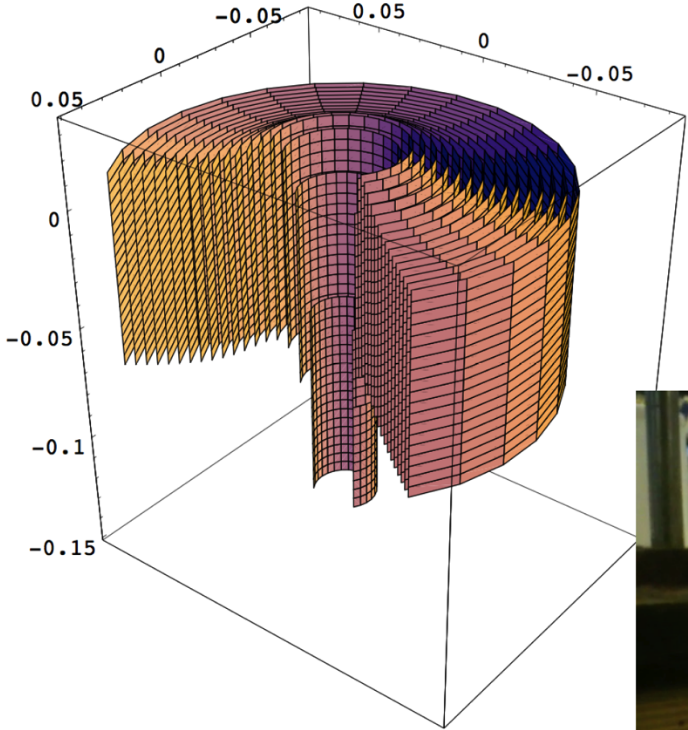
EXTENDing the Conceptual, Mathematical and Experimental Framework of Integrative Systems Biology

- Objective 1 : explore the conceptual extensions of the classical framework to derive the elements of an integrative theory of living systems from the first principles of scale relativity; define biological space-time, biological fields and charges.

- Objective 2 : extend existing models for multi-scale integration and prediction of the behaviour of biological systems: cardiac systems biology, cellular aggregation, growth of cancer cells; test and validate the extended models through computer simulations and targeted experiments.

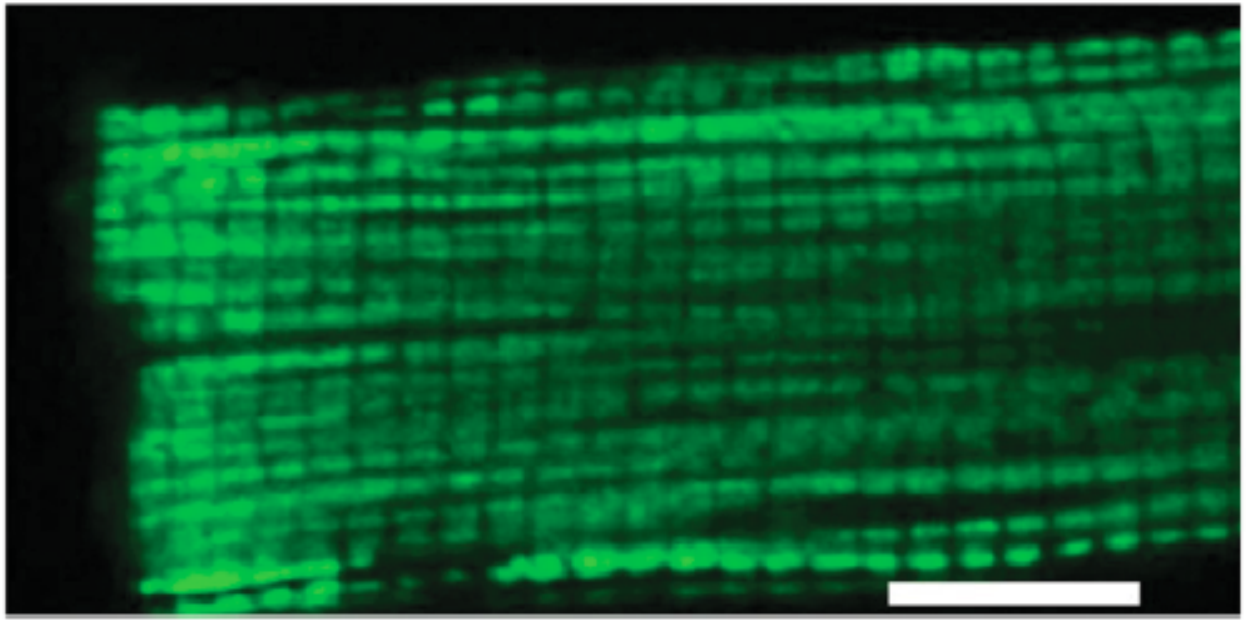
- Objective 3 : design and implement experiments using macroscopic quantum potentials, and reduce them to practice through engineering of prototype devices.

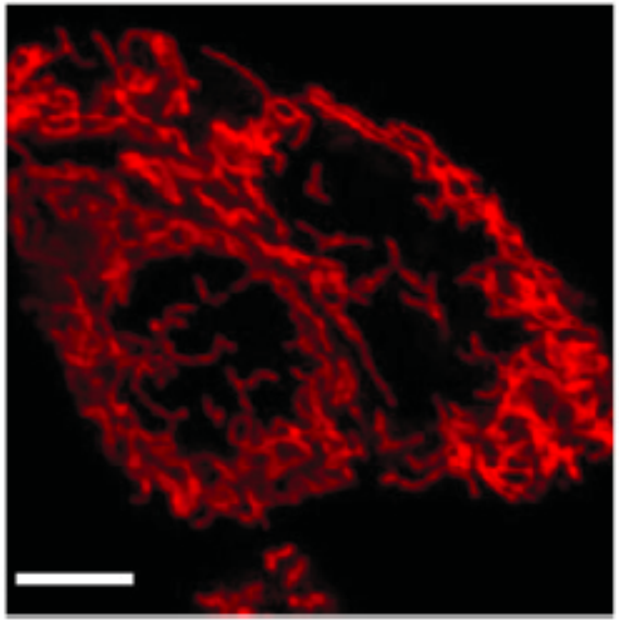
Simulation d'un potentiel quantique macroscopique



Transition
1->2 vertex

Guzun et al. 2011 BBA Epub Feb4
Mitochondrial-cytoskeleton interacions
in normal and cancer cardiomyocytes





Utilisation du bioplasmoscope pour l'implémentation de la boucle macroscopique
Françoise Argoul et Alain Arneodo - LJC