Lecture 1
A Quest Towards a Mathematical Theory of Living Systems

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Five Lectures by
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From a Mathematics of Living Systems

to Modeling Virus Pandemics

P.1. Plan of the Lectures

Nicola Bellomo **Lecture 1. A Quest Towards a Mathematical Theory of Living Systems**

Diletta Burini **Lecture 2. Mathematical Tools of the Kinetic Theory of Active Particles**

Nicola Bellomo, Diletta Burini and Nisrine Outada **Lecture 3. Towards a Mathematical Theory of Virus Pandemics - Models with Mutations, Variants and Vaccination Programs**

Damian Knopoff **Lecture 4. Heterogeneity and Networks**

Pietro Terna **Lecture 5. Agent Methods to Modeling Virus Pandemics - A quick reference to complexity**

Pietro Terna **Closure, Description of the material support to the Lectures, Acknowledgments**

P.2. Aims and Motivations

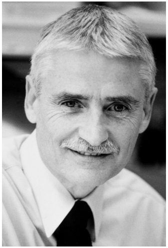
These lectures attempt to show how the broad variety of tools, delivered by mathematical sciences, can contribute to describe the dynamics of living, hence complex, systems.

The contents are developed within an interdisciplinary, multiscale framework, looking at the rich plurality of sciences.

The COVID-19 outbreak and the subsequent pandemic, has brought to almost all countries across the globe huge problems affecting health, safety, economics, and practically all expressions of collective behaviors in our societies.

The mathematical theory is applied to modeling various phenomena of the virus pandemics.

1.1. A quest towards a mathematical theory of living systems



This first Lecture presents some reasonings proposed as a very first step of a quest towards the ambitious goal of developing a mathematical theory of living systems. We start with a conceptual and philosophical background. Subsequently, we propose a strategy in the search of mathematical frameworks suitable the capture the complexity features of living systems. This Lecture contributes to the derivation of mathematical tools in Lecture 2.

1.2. A quest towards a mathematical theory of living systems

Conceptual and philosophical background

• **Immanuel Kant 1724–1804**, *Living Systems: Special structures organized and with the ability to chase a purpose.*
* I. Kant, **Critique of the Power of Judgement**, Cambridge University Press, (2002).

• *Scientists often critically analyze the specific features of different sciences arguing about a rough division between the so called "hard" and "soft" sciences. The approach to hard sciences is based on rigorous assumptions supported by theory and experiments, while a certain amount of heuristic bias is needed in the approach to soft sciences.*

• **Auguste Comte, (1798–1857)** *A certain hierarchy exists in a classification where physics and chemistry are the hardest sciences, sociology belongs to the softest, while biology is in the middle. What about mathematics?*
* A. Comte, **Cours de Philosophie Positive**, Hermann, Paris, (2012).

1.3. The quest towards a mathematical theory of living systems

A quest to a physics of living systems

- **Erwin Schrödinger (1887–1961)** firstly observes that

  Living systems have the ability to extract entropy to keep their own at low levels

Schrödinger developed some pioneering ideas on a systems approach in biology, where the dynamics of cells is driven by the dynamics at the molecular scale, motivated by the study of mutations (some of them also induced by external actions such as radiations). This concept is nowadays a fundamental hint to the interactions between mathematics and biology, where understanding the link between the dynamics at the molecular scale of genes and the functions expressed at the level of cells is the key strategy to derive a bio-mathematical theory.

***** Schrödinger, **What is Life? The Physical Aspect of the Living Cell**, Cambridge University Press, (1944).

Human behaviors and behavioral dynamics:

Ilya Prigogine (1917–2003) contributed with Herman to the modeling human behaviors in the modeling of vehicular traffic on roads.

* I. Prigogine and R. Herman, **Kinetic Theory of Vehicular Traffic**, Elsevier, New York, (1971).

> *The interpretation that Prigogine's model is a technical modification of the Boltzmann equation is definitely unfair, as he proposes new concepts on the modeling of interactions between vehicles by tools of probability theory and on the modeling of heterogeneous behaviors. The great conceptual novelty is that the overall state of a large population is described by a distribution function over the micro-scale state of interacting entities and that the output of interactions is delivered by probability rules rather than by the deterministic causality principle.*

1.5. A quest towards a mathematical theory of living systems

A forward look

• Nobel Laureate Lee Hartwell (born 1939) has well in mind that the mathematical approach to the description of the dynamics of the inert matter cannot be straightforwardly applied to living systems:

> *Biological systems are very different from the physical or chemical systems of the inanimate matter. In fact, although living systems obey the laws of physics and chemistry, the notion of function or purpose differentiate biology from other natural sciences. Indeed, cells are not molecules, but have a living dynamics induced by the lower scale of genes and is organized into organs.*

This statement directly looks forward a challenging research perspective whose first step consists in acknowledging that the mathematics used for the inert matter fails when applied to the living matter.

***** H.L. Hartwell, J.J. Hopfield, S. Leibler, and A.W. Murray, From molecular to modular cell biology *Nature*, **402**, c47–c52, (1999).

1.6. A quest towards a mathematical theory of living systems

• **Life, evolution, selection:** Giovanni Jona–Lasinio, (born 1932), where a free translation from Italian language is:

> *Life represents an advanced stage of an evolutive and selective process. It seems to me difficult understanding living entities without considering their historical evolution. Population dynamics is based on a rather primitive mathematical theory, on the other hand it should explain the emergence of individual living entities by selection.*

1.7. A quest towards a mathematical theory of living systems

Motivations

• Modeling, qualitative analysis, and numerical problems of systems of many interacting living entities is definitely one of the important mathematical challenges of this century. Applications refer to a broad variety of possible fields, for instance modeling of social dynamics, financial markets, dynamics of multicellular systems, immune competition, individual and collective learning, crowds and swarms.

• The scientific community widely shares the idea that one of the great scientific targets of this century is the attempt to link the rigorous approach of hard sciences, to the study of living, hence complex, systems. Indeed, this fascinating objective requires and motivates the invention of new mathematical methods by a development of the several theoretical sources that mathematics can offer towards new conceptual ideas.

* P. Ball, **Why Society is a Complex Matter**, Springer-Verlag, Heidelberg, (2012).

Strategy (first step)

• We suggest replacing the definition of Soft sciences with

Science of Living Systems

and then developing a strategy to take into account that the support field theories is not available for living matter.

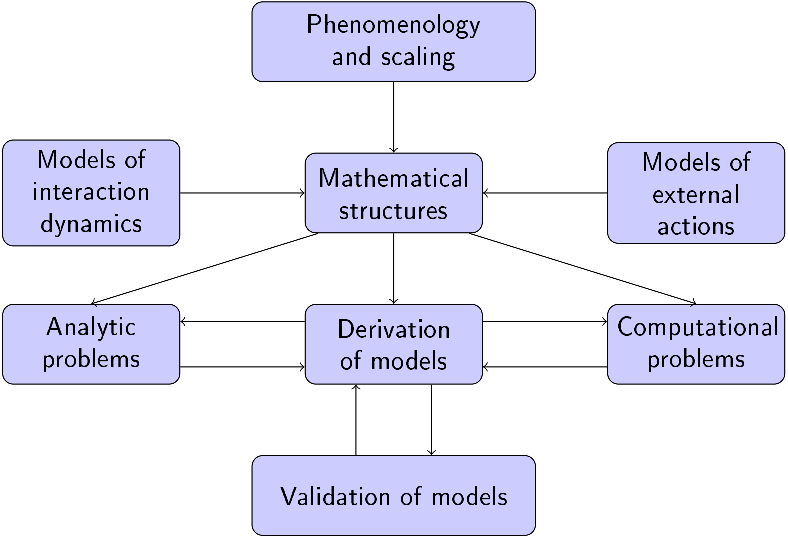
• ***The strategy consists in replacing the field theory by a mathematical structure (say mathematical theory) suitable to capture, as far as possible, the complexity features of living systems. This structure defines the conceptual framework for the derivation of models in different fields of soft sciences.***

* N. Bellomo, A. Bellouquid, L. Gibelli, and N. Outada, **A Quest Towards a Mathematical Theory of Living Systems**, Birkhäuser-Springer, New York, (2017).

Strategy (details)

- Understanding the links between the dynamics of living systems and their complexity features;
- Derivation of a general mathematical structure, consistent with the aforesaid features, with the aim of offering the conceptual framework toward the derivation of specific models;
- Design of specific models corresponding to well defined classes of systems by implementing the said structure with suitable models of individual-based, micro-scale, interactions;
- Validation of models by quantitative comparison of the dynamics predicted by them with that one delivered by empirical data. Models are required to reproduce qualitatively emerging behaviors.

1.10. A quest towards a mathematical theory of living systems



1.11. A quest towards a mathematical theory of living systems

Five common features as sources of complexity

1. Ability to express a strategy: Living entities are capable to develop specific *strategies* and *organization abilities* that depend on the overall state of the surrounding environment.

2. Heterogeneity: The ability to express a strategy is not the same for all entities. Indeed, the *expression of heterogeneous behaviors* is a common feature of a great part of living systems.

3. Nonlinear interactions: Interactions are nonlinearly additive and involve immediate neighbors, but in some cases also distant entities.

4. Learning ability: Living systems receive inputs from their environments and have the ability to learn from past experience.

5. Darwinian mutations and selection: Birth processes can generate entities more fitted to the environment who, in turn, generate new entities again more fitted to the external environment.

1.12. A quest towards a mathematical theory of living systems

Understanding living systems

• ***Multiscale aspects:*** Modeling always needs a *multiscale approach*, where the dynamics at the large scale needs to be properly related to the dynamics at the low scales.

• ***Role of the environment:*** The environment evolves in time, in several cases also due to interactions with the internal living system.

• ***Large deviations:*** Emerging behaviors often present large deviations although the qualitative behaviors is reproduced. In this case, small deviations in the input create large deviations in the output.

• ***Individuals within a certain population can aggregate into groups of affinity:*** Communications and subsequent dynamics can take advantage (or disadvantage) from the said aggregation by creating a new communication network.

• ***Birth and death imply evolution and selection.***

1.13. A quest towards a mathematical theory of living systems

What is the Black Swan?

It is worth detailing a little more the expression **Black Swan**, introduced for indicating unpredictable events, which are far away from those generally observed by repeated empirical evidence. According to the definition by Taleb a Black Swan is specifically characterized as follows:

"A Black Swan is a highly improbable event with three principal characteristics: It is unpredictable; it carries a massive impact; and, after the fact, we concoct an explanation that makes it appear less random, and more predictable, than it was."

***** N. N. Taleb, **The Black Swan: The Impact of the Highly Improbable**, Random House, New York City, 2007.

Mathematics should also develop strategies for the study of not predicable events.

1.14. A quest towards a mathematical theory of living systems

The fantasy of Escher is founded on reality, but where is the tower?

How far the Metamorphosis represents the complexity of living systems? Looking for: *Heterogeneous ability to express a strategy; Nonlinear Interactions; Learning ability; Darwinian selection and time as a key variable; Complexity in the interpretation of reality; The Black Swan.*

1.15. A quest towards a mathematical theory of living systems

Let us give freedom to our fantasy and look at Escher's metamorphosis focusing on the right hand-end part where the landscape evolves going first from a geometrical village made of similarly looking houses to a real village with an heterogeneous distribution of houses' shape.

- *The evolution is related to interactions, definitely multiple ones. Is nonlinearity somehow expressed?*
- *The evolution is selective as shown by the transition from essential shapes to an organized village, where all available spaces are well exploited.*
- *The presence of a church, that takes an important part of the space and a somehow central position, indicates the presence of a cultural evolution.*
- *This might even reflect a multiscale dynamics. In fact, it results as the output of the action from the micro-scale of individuals to the macro-scale of the village.*

1.16. A quest towards a mathematical theory of living systems

Escher founded his fantasy on reality, but where is the tower? Suddenly the landscape changes from a village, turning into a chess plate, the only connections being a Bridge and a Tower. Can this sudden change be interpreted as a "Black Swan?"

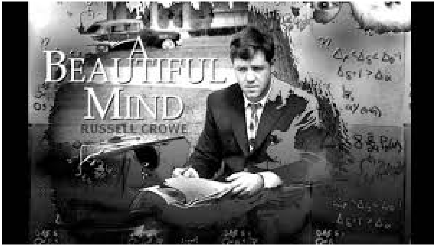
We can interpret the tower as an early signal that an extreme event is going to happen. The various changes in the picture can be interpreted as predictable emerging behaviors, while the last one is a not predictable event. Escher has gone through the experience of two world wars, the two armies of the chess plate transformed a peaceful village into a battlefield.

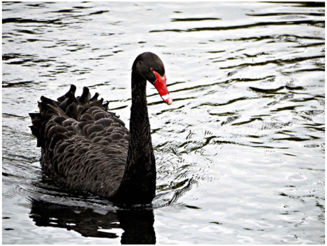
The village exists in reality (it is in the Mediterranean coast immediately on the South of the village of Amalfi) does the Tower truly exists? The village looks at the sea, while the tower cannot be observed looking at it from the front as in the picture, but it appears from the rear it is possible to observe a tower on the cape in front of the village.

1.17. A quest towards a mathematical theory of living systems

1.19. A quest towards a mathematical theory of living systems

Mathematics should try to discover also what is not predictable.





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