to viral infection. The aim of systems virology is the identification and characterization of key network components or connections, and their interplay in the virus–host interaction network as a whole. Using model analysis, systems virology aims to identify load- and choke points of viral infection and replication processes, which can be used as potential new targets for antiviral drug design. Ultimately, the promise of systems virology is to provide profound knowledge about the complex virus–host system, and to translate this knowledge into predictive, preventive, and personalized medicine to combat viral infection.

To achieve these objectives at a systems level, large-scale experimental data sets are required. Systems virology, therefore, benefits greatly from major advances in molecular virology and from the development of high-throughput experimental techniques and associated data processing and analysis methods in the recent years. These include microarray-based functional genomics, high-throughput and high-content siRNA screening, live cell imaging, high-throughput protein interaction measurements using Yeast-2-Hybrid screens, automated mass spectrometry and protein arrays, and next generation sequencing (Peng et al. 2009). These technological developments are paralleled by novel developments in data processing, data integration, and data analysis techniques in the fields of statistical data analysis, bioinformatics, data mining, and machine learning, which are employed to reconstruct virus–host interaction networks and develop a basis for more detailed, quantitative, and dynamic models of virus–host interactions.

Systems virology typically proceeds in an iterative cycle, consisting of systematic and large-scale perturbation of individual entities in the virus–host system, measuring the outcome using high-throughput technologies, and then trying to relate the change at the molecular level to global properties of the system during the infection, using modeling and simulation, followed by the design of further experiments to fill the knowledge gap highlighted by the difference between the model simulation and the real system (Kitano et al. 2002). As an example strategy, large-scale siRNA screens to identify new host factors involved in viral replication are followed by live cell imaging and more detailed biochemical characterization of identified host processes to develop quantitative, dynamic models of analysis of virus–host systems. Modeling and data analysis are then carried out using a combination of machine learning approaches for the data-driven reconstruction of virus–host networks, bioinformatics annotation and database queries, and forward modeling using knowledge-based approaches and based on differential equations. Ultimately, all these approaches are mapped onto one, virus and host cell type–specific, integrated model of virus–host interactions. Such models integrating viral and host processes can then be used to identify critical points in the infection cycle, to design new drugs with optimal efficiency and minimizing side effects, and to gain a better understanding of host immune response and thus vaccines development.

Cross-References

► Systems Immunology

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Systems, Autopoietic

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Definition

The authors' definition of the autopoietic system has evolved through the years. One of them states that *an autopoietic system is organized (defined as a unity) as a network of processes of production (transformation and destruction) of components that produces the components which: (1) through their interactions and transformations regenerate and realize the network of processes (relations) that produced them; and (2) constitute it (the machine) as a concrete unity in the space in which they exist by specifying the topological domain of its realization as such a network* (Varela 1979, p. 13). Nearly the same formula was earlier used to define an *autopoietic machine* (Maturana and Varela 1973/1980, 1984/1987, p. 135).

Characteristics

The Chilean biologists H. Maturana and F. Varela proposed the term *autopoiesis* in the early 1970s to account for the organization of individual living beings, characterized as a process by which they produce their own identity in a mechanistic way. The autopoietic approach to life is very different from that of the Theory of Evolution and Molecular Biology: On the one hand, instead of reproduction or evolution, the theory focuses on autonomy and identity to naturalize them as marks of life; on the other hand, it considers that all system components have the same status to explain the self-referent dynamics by which they produce a unity; that is to say, living phenomenology is not explained in terms of some components being information carriers.

Autopoietic systems, also called initially *autopoietic machines*, explore the general relational scheme common to all living systems as the configuration of transformative processes whose result is the configuration itself, so that identity and activity, producer and product coincide. Unlike *Turing machines*, set by external programmers (thus being *heteropoietic*) to compute problems referring to issues other than the system itself (thus being *allopoietic*), *autopoietic machines* realize a self-defined identity in a space of interactions. Already in 1974 (Varela et al. 1974), the authors presented their account of living organization with a computational model in cellular automata which was later rehearsed by Barry McMullin (in Di Paolo 2004).

Some of these distinctions, for example, between autopoietic and heteropoietic, already appear in Canguilhem's *La connaisance de la vie*. In fact, the autopoietic approach belongs to a systemic tradition focused on the problem of the relational unity of the living, associated to Kant's understanding of organisms in the *Critique of Judgment*, Claude Bernard's concept of *milieu intérieur*, and the organicist tradition that considers life as organization (G. Canguilhem, H. Jonas, J. Piaget among others, see Weber and Varela 2002), and opposed to the mainstream of the time, such as some of the views of Jacob´s *La logique du vivant*. Other clear associations are with the cybernetic movement, especially with second-order cybernetics. The influence of the autopoietic approach has been significant in theoretical Biology (especially on work on the definition of life and origins and organization of minimal living systems), Artificial Life, and Cognitive Science. In contrast, it has had no comparable effect on mainstream biology (e.g., Molecular and Evolutionary Biology), although it appears to be more present in Systems Biology, whose approach is less centered on master molecules and information.

The Main Conceptual Development

Autopoietic systems aim to grasp what makes an organism be a unity of a specific kind, that is to say, how a system appears out of a continuous flux of transformations at the level of its components.

The system is characterized by its *organizational closure*, a notion that provides a reinterpretation of the cybernetic notion of *circular self-stabilization*, which instead of considering single regulatory processes in isolation and then coupling them together (as homeostatic machines, acting on internal variables, behave) refers to the whole living system: The autopoietic system is organized in such a way that it does not only maintain the interval of stability of some variables, but also the global organization is kept invariant.

Some of the main concepts of the theory refer to distinctions, such as the following:

- *Organization and structure*: This emphasizes that an organism is not characterized by its material or physicochemical processes, but by how the interactions are related to produce and maintain the integrated biological unity they belong to. The *structure* refers to the variant aspect of a living system: to its physical realization, whereas the notion of *organization* aims to grasp the invariant one: the topology of the relations that constitute it. Thus, the authors embrace a particular form of *multiple* *realizability* between organization and structure, as the autopoietic organization is proposed as a main invariant underlying the diverse biological phenomenology, that is conserved through the ontogenetic and phylogenetic changes.

- *Openness and closure*: Whereas living systems are open to the exchange of matter and energy at the level of structure, the network of processes that constitutes their organization is closed in the form of a global cyclical process that determines and regenerates itself. Rosen developed a similar view independently and expressed it mathematically in the notions of the system being *open to material causation* and *closed to efficient causation* (Letelier et al. 2006). The distinction between open structure and closed organization can be also found in Piaget's *Biologie et connaissance*, complemented by an internal mechanism of adaptation to perturbations in terms of Waddington's *assimilation* and *accommodation*.

Another characteristic feature of the theory is its internalism, present through the notion of *structural determinism*. In each time step, the system interacts and changes in a way totally determined by its structure, which specifies the set of all possible changes to effective perturbations. The latter do not define, but only trigger structural changes. Thus, environmental perturbations do not have intrinsic meaning, their effect depends on the structure of the receiver: Unlike in input-output relations, the same stimulus can cause different alterations. F. Varela (in Varela et al. 1991) showed this peculiarity through a cellular automata model called Bitorio. Similar to this is the idea that in the communication between two systems, there is no transmission of information but a *structural coupling*.

In this framework, evolution is reinterpreted in neutralist terms as a natural drift. The idea of adaptation as optimization of the organism's traits by natural selection is replaced by one of conservation of adaptation, as the maintenance of a specific form of coupling between the living system and its environment (Maturana and Varela 1984).

Further Developments

Developments of the autopoietic theory have particularly been connected with the definition of life and autonomy and with agency and cognition. Finally, some have tried, without success so far, to extend the notion of autopoiesis from the cellular level to that of multicellular organisms and social systems.

- *Definition of life as autonomy*. The main influence of autopoietic systems has been in fields related to the definition of life and its organization, such as *Artificial Life*, *Synthetic Biology*, *Astrobiology* or, in general, *Systems Biology*. The main impact of the autopoietic theory in these areas has been through the notion of autonomy as an ingredient of the definition of life.

  The goals of the initial approach to *Artificial Life* were congenial to the theory of autopoietic systems in the significance of form above matter, but very different in what concerns the nature of life, which was there thought to be connected to reproduction and evolution by the mainstream, not to autonomy or organization as the autopoietic theory maintains. Nevertheless, for some authors, it is problematic to consider the operations of the living only at a formal abstract level, without considering the complexities of material and historical realizations of life as we know it. For example, the formal account of autonomy fails to meet the thermodynamic criteria required to realistically maintain the state of activity of any candidate system in its environment, and this has been one of the main developments of the original theory by researchers who, accepting the relevance of autonomy, would not want to explore it only in formal models but related to material constraints.

  Similarly, in the *Origins of Life* field, the theory of autopoiesis has been particularly influential among those pursuing the cellular origins of life (as opposed to molecular origins) in the generation of self-maintaining and self-reproducing systems (Luisi 2006).

  In *Systems Biology*, autopoietic theory has revealed itself promising as a theoretical guideline in developing a notion of system as a integrated unity, in modeling the cellular metabolism as a closed and intertwined network of processes, in reinterpreting the role of the genomes in the cell in a more ecological fashion, and in pointing out the relevance of self-regulation at different hierarchical levels (Boogerd et al. 2007).
- *Agency and cognition*. From the autopoietic perspective, cognition is the system's capability to

provide meaning to the world, a property connected, if not coincident, with life. An increasingly relevant issue raised in the investigation of cognition is the one concerning how to characterize the specific mechanism of self-maintenance instantiated by biological metabolism in its basic form, being the notion of self-production insufficient to account for agency as the ability to act in the environment. There have been proposals to expand the definition of self-production through the introduction of active mechanisms of self-regulation.

With respect to the impact on the study of cognition in the conventional sense, autopoietic theory has provided an analysis of the biological roots of knowledge by considering human observers as structurally determined systems. In doing so it has pointed out the limits of the notions of representation and objectivity and contributed to the development of an epistemological perspective known as “radical constructivism” according to which the natural world emerges as coherences in the coupling between the observer and its medium. In cognitive sciences, the autopoietic theory has pointed to the need to develop embodied and situated accounts to characterize autonomous agents, by inaugurating the so-called *enactive approach* (Varela et al. 1991).

- *Other levels of organization.* As autopoietic systems define life at the cellular level, multicellular living systems and social ones – respectively defined as autopoietic systems of the second and third order – are considered as derivative, even if not trivially, with respect to the properties of cellular ones. But satisfactory criteria for this operation of expansion of the theory have not been provided in the original formulations.

In spite of these acknowledged difficulties, the notion of autopoiesis brings forth a relevant scenario for inquiry about the nature of life, providing an intuitive idea of what it means to be alive, autonomy, which is lacking in other approaches.

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Cross-References

▶ Autonomy
▶ Closure, Causal
▶ Organization
▶ Self-Organization
▶ Synthetic Biology, Predictability and Reliability

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