Sensitive living systems: balancing disorder and complexity in holobionts for communication across ecosystems

Véronique Thomas-Vaslin[1] *and *Dominique* Pastor[2]
[1]Sorbonne Université, INSERM, Immunoregulation-Immunopathology-Immunotherapy (I3); UMRS959; Paris - France; CNRS-France
[2]IMT Atlantique, Lab-STICC, CNRS UMR 6285, Technopôle Brest-Iroise, CS 83818, Brest -France

Abstract. How do living systems sustain communication, identity, and resilience while remaining exposed to disorder and environmental perturbations? How do poly-genomic organisms integrate evolutionary history (including non-genetic transmission), development, and ecological context to generate memory and tolerance? Addressing these questions requires a paradigm shift, from reductionist descriptions toward living systems conceived as sensitive subjects, historically embedded organizations. We consider the holobiont—the host organism together with its microbiota—and the immune system as a model of multiscale living co-organization shaped by onto-phylogenesis. We show how somatic diversification, degeneracy, and stochastic interactions enable biological networks to regulate integrity and coherence, transforming variability into adaptive organization rather than noise. Across intertwined temporalities—developmental time, critical decision windows, and long evolutionary time—biological sensors detect and interpret perturbations, supporting emergent properties such as dominant tolerance, distributed memory, and resilience. We introduce the Generic Sensor-Actuator (GenSA) framework as a scale-independent, subject-centered abstraction: living systems are modeled as networks of multiscale holons that sense, integrate, memorize, and respond to distortions through energy- or affinity-based interactions, providing a common language of communication from molecules to ecosystems. Adaptation relies on probabilistic evaluation of perceived distortions through random distortion functions/tests across scales, making “memory” and “tolerance” history-dependent dynamical networks.

1 Introduction

Living systems are exposed to disorder, stochastic fluctuations, and continual perturbations, yet they maintain coherence, identity, and adaptive memory across development and evolution. Understanding how such systems infer meaningful distortions from noise, and transform variability into organized function, remains a central challenge in biology.

Over the past century, biological thought has progressively shifted from object-based, reductionist descriptions toward dynamical views emphasizing self-organization, emergence, and eco-evolutionary embedding [1-3]. Nonetheless, many systems biology and multi-omics modeling efforts continue to deconstruct living systems into molecular components, pathways, and interaction networks. While these methods have advanced the analysis of components and interactions—including in immune system dynamics, as shown in our previous work [4-7]—they remain limited in explaining how system-level properties emerge, stabilize, and persist. Specifically, they encounter challenges in accounting for learning, historical organization, and cognitive-like functions in complex living systems [8, 9].

The limitations of classical models become evident in complex holobionts, such as humans, which develop as poly-genomic organisms comprising host tissues and about 800 symbiotic microbial species. These systems must accommodate and integrate beneficial foreign partners throughout development and aging, while maintaining the capacity to initiate context-appropriate inflammatory responses and adaptive memory against pathogens. Classical models struggle to incorporate several defining characteristics of living systems: their sensitivity to energetic and molecular signals, the degeneracy and redundancy of components, the probabilistic nature of interactions, and their ability to detect novel perturbations ("distortions") in real time. Consequently, living systems cannot be described as passive entities; rather, they function as historically situated subjects that sense, interpret context, and respond adaptively.

Instead of merely buffering stochastic fluctuations, living systems actively utilize noise and variability as resources for adaptation. They can thus be conceptualized as sensitive cognitive networks that learn from interactions and exhibit emergent, distributed memory. This phenomenon is particularly evident in the immune system of higher vertebrates, where systemic memory emerges and can be lost when critical network components are transiently disrupted, revealing memory as a collective, dynamic property rather than an intrinsic cellular one [10].

Key questions.
Motivated by this perspective, we address two central questions:

(Q1) Why and how do memory, cognition-like functions, and communication emerge in multiscale living systems?

(Q2) How do living systems integrate environmental signals and infer meaningful information amid noise, thereby maintaining identity and viability across development and evolution (phylo-ontogenesis)?

To address these questions, we propose a paradigm shift in modeling living systems, building on limitations encountered in simulating immune and ecological dynamics. These efforts revealed challenges of

* **Corresponding author:** veronique.thomas-vaslin@cnrs.fr

articulating multiscale interactions, recursive signal integration, and long-term coherence within a unified framework [9, 11, 12]. A key conceptual advancement was introducing living systems as communicating holons organized across scales—from molecular networks to organisms and ecosystems—capable of recursive integration, self-assertion, and state-dependent reconfigurations driven by internal organization and environment [12]. Building on this abstraction, prior mathematical work emphasized probabilistic inference, multiple detection criteria, and degeneracy as a principle of robustness in communicating systems [13-15].

We introduce now the ***Generic Sensor–Actuator* (*GenSA*)** framework, which conceptualizes living organizations as sensitive systems that infer and respond to distortions through energy fluxes or affinity-based interactions, along with its formal counterpart, the **Generic Sensory Automaton (**GENSA). This framework focuses on principles by which self-organizing holarchies develop emergent functions such as memory, tolerance, and adaptation [12]. We argue that biological systems' intrinsic tendency to explore and self-organize—under energetic constraints—facilitates cognitive processes. Stochastic event streams are detected locally and integrated through networked interactions, enabling living systems to record history, evaluate state, and infer perturbations to maximize viability.

A landmark illustration of such *generative disorder* is the evolutionary origin of somatic immune diversification. Approximately 500 million years ago, a rare event occurred in jawed vertebrates, with the integration of a recombinase-encoding transposon (RAG) in lymphocytes. This enzyme facilitated random V(D)J gene recombination thereby generating vast antigen-receptor diversity [16-18]. This stochastic, individual-level diversification in lymphocytes reintroduces an exploratory (and therefore seemingly disordered) component to complement innate germline encoded and transmitted immunity: it allows each developing organism to “invent” new receptors and display new detector functions beyond the phylogenetically inherited, germline-encoded repertoire of innate recognition elements, which has been strongly selected and stabilized over millions of years. Adaptive immunity thus exemplifies a central principle of sensitive living systems: a functional balance between order (conserved, reliable, pre-tuned highly selected sensors) and disorder (somatic variability and degeneracy that create room for novelty, learning, and context-dependent memory), yielding robust yet creative responses to perturbations.

Collectively, these observations support a paradigm shift from object-based descriptions toward models of living organizations as sensitive subjects implementing perception–action loops (inference, memory, and context-dependent response). In this view, the order–disorder complementarity is a multi-scale, multi-temporal property (Chronos/Kairos/Aion), enabling the propagation and integration of perturbations across coupled levels—from cells and organisms to ecosystems.

Figure 1 summarizes this perspective and its formalization within the *GenSA*/GENSA framework of communicating holarchies.

Article outline. The paper develops a conceptual trajectory from biological observations to a generic theoretical abstraction and its formal counterpart. **Section 2** reconstructs the historical and conceptual shift from object-centered explanations toward living systems conceived as sensitive, historically embedded organizations, and positions the key notions of self-organization, eco-organization, and multi-temporality. **Section 3** uses the immune system (in the holobiont context) as a paradigmatic model to identify the generic properties that enable sensitivity, degeneracy, and distributed cognition-like functions. **Section 4** provides *in vivo* evidence showing how tolerance and memory emerge as system-level, history-dependent properties that cannot be reduced to isolated components or *in vitro* settings. **Section 5** then explains why classical modeling approaches fail to capture emergence, multiscale coupling, and distortion sensitivity. Building on this diagnosis, **Section 6** introduces *GenSA* as a conceptual space for sensitive living systems and GENSA as one possible formal instantiation supporting probabilistic, non-Boolean evaluation. A concise and accessible overview of this formalism is provided in the **Appendix**, while full mathematical developments are presented in a companion paper. Finally, **Section 7** discuss the interdisciplinary implications of this paradigm—semiotics, temporality, viability, and computational perspectives—and **Section 8** concludes and opens future directions.

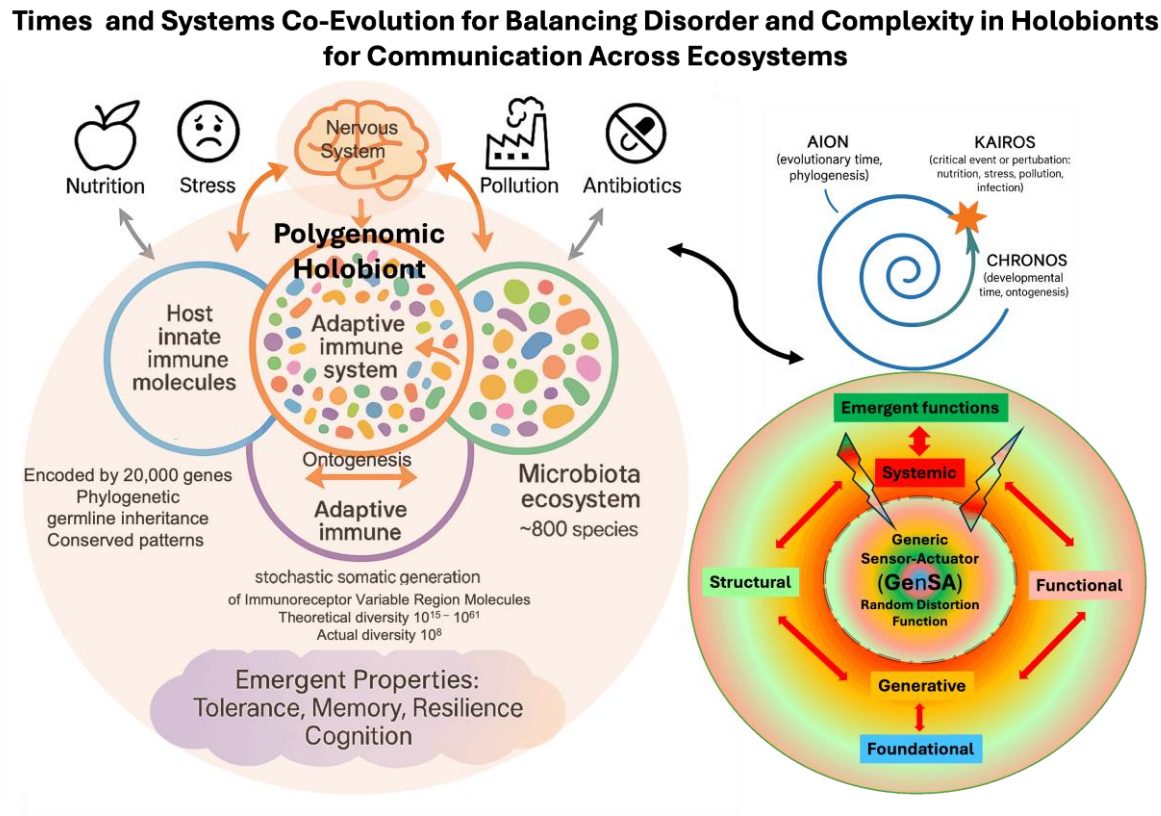

Fig. 1:Sensitive living systems and holobionts as evolving complex systems

Poly-genomic holobionts (host + microbiota) are depicted as complex living systems that continuously adapt through interactions with internal (microbiota, immune networks) and external (nutrition, stress, environment) cues. Across intertwined temporalities—developmental, critical, and evolutionary—living systems balance disorder and organized complexity, allowing the emergence of foundational, structural, functional, and systemic adaptations, allowing for emergent properties as adaptive systems with memory, tolerance and resilience to perturbations. This conceptual framework motivates a generic abstraction of living systems as sensitive sensor-actuator holarchies (GenSA) and their formal modeling through complementary approaches (GENSA).

Key elements: Left: Holobiont (host + microbiota), immune system, molecular mimicry, co-evolution: Color codes distinguish innate immunity (blue), adaptive immunity (multicolor receptors), the microbiota (complementary multicolor mimicry), Central Nervous System (orange), and environmental cues (gray) and interactions (arrows). Right: Timescales (Aion, Kairos, Chronos), emergence of properties/functions, communication across scales, abstracted by holarchies of communicating holons with GenSA, whose properties and states evolve through a spectrum of energy-like affinities leading to Random Distortion Functions

2. Conceptual and Historical Foundations: From Reductionism to Sensitive Living Systems

2.1. The Evolution of Biological Paradigms

Scientific views of living systems have evolved through several major paradigms. Newtonian mechanics introduced a deterministic, reductionist perspective: complex phenomena were explained by isolating components and applying universal physical laws. While this approach revolutionized physics, it proved inadequate for biology, where organisms exhibit non-linear, emergent, and context-dependent behaviors that cannot be deduced from parts alone.

Darwinian evolution then framed organisms as products of natural selection acting on random variations. This explained adaptation and species change, but Darwin's framework (and its application in early theoretical biology) did not fully address how novel, pre-adaptive structures arise or how spontaneous order can emerge without external selectors. It assumed variation precedes selection, without detailing what generates meaningful novelties or how higher-level organization comes about.

Human perspectives on causality and holism demonstrate significant variability. Research on cultural cognition reveals that Western analytical thinking tends to isolate objects, whereas Eastern traditions emphasize context and relationships [19-21]. These findings imply that alternative, more holistic paradigms may be essential for understanding the complexity of living systems and emergent new functions.

2.2. From Clonal Selection to Cognitive Immunology

In immunology, the shift from reductionism toward systems thinking is clearly illustrated by the historical evolution of its core theoretical frameworks. **Table 1** summarizes these paradigm shifts, highlighting how immunological thinking progressively moved from linear, object-based explanations toward network- and system-level perspectives. Notably, both Burnet's clonal selection theory and Jerne's idiotypic network theory—each awarded the Nobel Prize—embody distinct and enduring paradigms of immune organization, whose conceptual tension continues to shape contemporary debates in immunology.

Burnet's clonal selection theory [22] applied Darwinian logic at the cellular level. In this framework, the immune repertoire is composed of independent lymphocyte clones, each bearing a specific receptor; antigen exposure selectively activates responsive clones, while self-reactive clones are eliminated during development. This model successfully explained specificity and adaptive memory through somatic selection, but it portrayed immunity triggered only by external antigenic encounter. As a result, it could not fully account for phenomena such as the presence of natural auto-antibodies, preparatory immune activity in the absence of pathogens, or the active and sustained maintenance of self-tolerance.

Niels Jerne directly challenged this purely reactive view by asking, *"What precedes clonal selection?"* [23]. His idiotypic network theory introduced a major conceptual shift by proposing that antibodies (and, by extension, B- and T-cell receptors) recognize not only antigens but also each other, forming a self-referential network of idiotope–anti-idiotype interactions [24]. The *idiotope* refers to antigenic determinants within the variable region of an antibody or receptor, which can themselves be recognized by other antibodies termed *anti-idiotypes*. Through these reciprocal recognitions, immune receptors become interconnected in a network of mutual interactions. Then, Jerne push the notion of "immune system" that maintains an internal, self-referential organization sustained by ongoing idiotype–anti-idiotype interactions, even in the absence of exogenous antigen [25]. The network can thus generate and stabilize regulatory states through recursive coupling among variable regions, providing an operational basis for an "internal image" of self.

When Jerne speaks of a *generative grammar* [26], the analogy is to language: a finite set of units (idiotypes/variable regions) combined by interaction rules (affinity-based constraints and network connectivity) can generate a large set of well-formed global configurations. In immunological terms, these "well-formed structures" correspond to stable or metastable network motifs and attractors that implement context-dependent tolerance, activation, and memory—an idea that will be linked below to experimental perturbations of idiotypic cascades (e.g [27].

Jerne's ideas paved the way for the "Paris school" of immunology (Coutinho, Varela, Stewart, Vaz, and other colleagues), which further developed the concept of an autonomous immune network, questioning the cognitive paradigm [28] and explored the direction of evolution and the particularity of Variable Region Molecules (VRM) [29] for cooperative organization using free energy sources [30, 31].

Accordingly, the division between a Central Immune System (CIS)—an internal, self-referential core that first organized during early ontogeny in fetal life—and a Peripheral Immune System (PIS) that interfaces with the external world was introduced.

According to Coutinho, the CIS self-organizes through degenerate idiotypic interactions among early lymphocyte populations, generating a stable dynamical structure that embodies self-tolerance and an internal definition of "self" [32]. A central role in this process is played by multi-reactive "natural antibodies" produces by early perinatal B cells revealing, even in absence of external antigens (axenic or germ-free mice) the natural auto-reactivity in 10-20% of lymphocytes, then constitutive of the core network of the CIS. Building on these ideas, our early experimental work detailed in Section 4, showed that lymphocyte persistence, repertoire shaping, and population dynamics depend strongly on the host microenvironment and developmental context [33-36], supporting a systems-level view of dominant tolerance and memory as emergent network properties from auto-organized evolutive dynamical systems.

In this perspective, immune regulation and memory arise primarily from the internal dynamics of the receptor network, rather than from clonal expansion and deletion alone. These early idiotypic interactions then establish a dynamic regulatory network that stabilize self-identity then a form of memory of self-contents (even a diverse microbiota) to regulate tolerance [30, 37, 38].

These successive paradigms, summarized in **Table 1,** reflect how conceptual advances in immunology were repeatedly driven by tensions between reactive, selection-based models and emerging evidence for internal organization and self-reference to sustain the system.

Taken together, these developments show that conceptual innovations and *in vivo* discoveries progressed in parallel: from Burnet's clonal selection, to Jerne's proposal of immune system and self-reference, and to the experimental identification of a central autoreactive regulatory core. They collectively support the view of the immune system as a non-linear adaptive system, characterized by internal feedback loops, organizational closure, and context-dependent regulation—properties that extend beyond classical dual self/non-self discrimination and motivate more generic system-level modeling approaches.

Table 1: Evolution of concepts in biology and immunology

Conceptual Stage	Key Contributors	Core Idea / Question	Immune System Impact (Example)
Newtonian Mechanics	Newton, Laplace	Determinism; reduction of whole to parts.	Cells as mechanical objects; no context sensitivity.
Darwinian Selection	Darwin, Wallace; Burnet	External natural selection on random variation. What adapts survives.	Clonal selection (reactive paradigm) [22]: antigen-driven selection/deletion of clones; specificity and memory explained, but pre-immune organization left implicit.
"What Precedes Selection?"	Jerne (1970s)	Is the system only reactive? What organizes it beforehand?	Idiotypic network hypothesis [23]: immune activity and regulation precede antigen exposure through self-referential interactions
Generative Immune "Grammar"	Jerne (1980s)	Immune system as a language with recursive rules.	Recursive idiotype–anti-idiotype network generates internal images and meanings [26].
Autopoiesis & Self-Org.	Maturana & Varela; Capra	Living system = self-producing closed network.	Immune system seen as autonomous network maintaining itself [39]. Hidden feedback loops [40] sustain immune homeo-dynamics [41]
CIS/PIS – Immune Networks	Coutinho, Varela; Stewart	Early self-organization (CIS) vs peripheral response (PIS).	Central immune system (CIS) establishes self-reference and dominant tolerance; peripheral immune system (PIS) responds to external cues under CIS context [31, 32, 38].
Complexity & Emergence	Prigogine, Kauffman, Ulanowicz, Morin	Order from chaos; feedback and degeneracy yield new properties.	Memory, tolerance, and resilience emerge from interactions network "memory" [10], [8].

These immunological developments resonate with broader theoretical frameworks of autopoiesis, self-organization, and eco-organization, which provide a general language to describe how living systems maintain identity through internal closure while remaining coupled to their environment.

2.3. Autopoiesis, Self-Organization, and Eco-Organization

In parallel, the concept of autopoiesis by Maturana and Varela [39, 42] defines living systems through organizational closure—the closure of the network of processes that produces and maintains the system—while this closure is compatible with continuous structural openness to matter, energy, and environmental perturbations. In this perspective, biological identity does not reside in fixed components or structures, but in the persistence of an organizational pattern despite ongoing material turnover.

Yates further clarified this point by emphasizing that biological stability is neither structural nor state-determined, but fundamentally homeo-dynamic [41]. Living systems maintain their identity through functional and dynamical organization, expressed as stable trajectories or regimes of activity rather than invariant structures. Stability thus corresponds to the persistence of coordinated processes over time, compatible with variability, noise, and historical contingency, and not to the preservation of fixed configurations.

This homeo-dynamic view provides the dynamical counterpart to organizational closure: it explains how self-producing systems remain viable and coherent through continuous internal change and environmental coupling, without reducing biological organization to programmed control (as exemplified for lymphocyte dynamics [33] or purely informational feedback.

This dynamical view anticipates later systemic emphases on feedback and circular non-linear causality [40], while recalling that adaptive regulation and stability through feedback were already central to early cybernetics, particularly in Ashby's work [43].

Applied to immunology, these ideas support the view of the immune system as a dynamic network of interactions among immune cells and molecules, maintained by recursive feedback rather than independent reactions. Indeed, Stewart pointed out that natural living systems cannot be fully understood by linear cause-effect diagrams, because they involve recursive causality and emergent properties not found in artificial systems [44].

Edgar Morin's concept of eco-organization further argues that organisms evolve not in isolation but in constant interplay with their environment, necessitating interwoven networks with redundant pathways and feedback [3]. In ecosystem dynamics, Ulanowicz noted that a certain degree of redundancy

(degeneracy) in trophic networks increases an ecosystem's capacity to persist amid disruptions.

2.4. The Need for a Paradigm Shift: From Objects to Sensitive Subjects

Building on the organizational and dynamical foundations outlined above, theoretical biology progressively moved beyond strict reductionism toward process-based views of living systems.

Schrödinger's question *"What is life?"* framed living systems as open, physically constrained organizations able to maintain order through energy–matter exchanges [45]. Much later, Friston's free-energy principle formalized perception–action coupling as an inference-driven mode of regulation under uncertainty [46]. In parallel, complexity-oriented approaches emphasized that biological order and resilience can emerge from non-linear interactions without central control, as proposed by Kauffman (self-organization and attractor dynamics) and Ulanowicz (ecosystem viability, redundancy, and constraint-based resilience) [1, 2].

Box 1 — From Viability Constraints to Sensitive Organization

Resolved questions (WHAT): Previous thermodynamic, informational, and complexity-based frameworks clarify the conditions under which living systems can remain viable. These approaches identify energetic constraints, global regulatory principles, and network-level properties such as self-organization, stability regimes, and resilience.

Open questions (HOW/WHY): They do not explicitly explain how and why living systems, as historically embedded subjects, generate and diversify their sensing capacities, transform noise and distortions into sources of innovation, or stabilize memory, tolerance, and identity across development and evolution.

Paradigm shift proposed here: *GenSA* addresses this gap by focusing on *generic processes of sensitivity*: how living systems detect meaningful distortions, integrate variability through multiple detection principles, and build emergent memory and regulation via feedback. In this view, noise is not a perturbation to be suppressed, but a structuring resource through which new receptors, sensitivities, and adaptive responses are explored, selected, and transmitted across complex temporalities.

As summarized in **Box 1**, these contributions primarily specify viability constraints **(***WHAT***)**—energetic bounds, stability regimes, and network-level resilience—while leaving open the constructive dimension **(***HOW/WHY***)**: how living systems build, diversify, and transmit sensitivity, memory, and tolerance across intertwined temporalities (ontogeny/phylogeny/historicity).

The central difficulty for theoretical biology is therefore not only to state constraints, but to explain the historical construction of organization: *How and Why* systems generate detectors, stabilize regulatory regimes, and transmit functional dispositions through time. In holobionts and other multi-partner living systems, viability is not achieved by fixed variables rules or structures, but by continuously detecting and regulating meaningful distortions amid variability, while preserving identity through ongoing components renewal, reconfiguration and feedback.

While the above frameworks elucidate how organized patterns and stability regimes can emerge, they remain largely agnostic with respect to how living systems come to sense, interpret, and regulate perturbations as historically situated subjects.

The focus should therefore shift from static entities as "objects" to modeling energy and information flows in "subjects" prioritizing dynamic functions emerging within systems in response to stochastic events.

This approach recognizes the agency of organisms in harnessing diversity, as proposed by Noble [47], where biological systems actively utilize variability to their advantage. Critically, "noise" is not only a driver of macroscopic dynamics: in living systems it provides structured distortions through which new sensitivities and detectors can be explored, selected, and stabilized—thereby enabling creativity, learning, and the long-term consolidation of tolerance. Instead of viewing randomness as noise, it should be recognized as integral to these systems, potentially serving as a source of adaptive potential—precisely because distortions are what trigger exploration, learning, and the stabilization of tolerance over time.

Evidence suggests that sensing, sensitivity, (including feeling, sentience,) distributed cognition are properties of living systems for billions of years [48-52]. This ancient evolutionary heritage is reflected in the sensitivity and adaptability observed across all domains of life, from unicellular organisms to complex holobionts.

In this work, we deliberately adopt the notion of 'sensitive systems' and a ***Generic Sensor–Actuator*** (*GenSA*) abstraction. Rather than identifying a minimal scalable level at which sensitivity would reside, our approach focuses on a generic, scalable organizational abstraction.

The **Table 2** situates the ***GenSA*/GENSA** framework among major theoretical approaches to cognition and complexity, with a specific focus on whether and how degeneracy and complexity according to the Nobel prize Edelman [53] and now distortion-sensitive detection are conceptually integrated; at this stage, these frameworks are introduced only as conceptual reference points, and their detailed assumptions and limitations will be mobilized later when positioning GenSA.

Table 2: Comparison of theoretical frameworks for cognition, complexity, and distortion sensitivity

Framework / Reference	Core perspective	Cognition & memory	Distortion / degeneracy handling
Jerne (1974) – Idiotypic network	Immune system as a self-referential network of interacting antibodies	Memory and regulation emerge from network dynamics	Degeneracy implicit in network overlap; distortion not explicitly modeled
Eco (1988) – Semiotics	Systems of signs, interpretation, and meaning	Conceptual framework for meaning and interpretation	Conceptual relevance only; no biological or formal modeling
Parisi (1990) – Idiotypic network (statistical mechanics)	Spin-glass–like immune networks	Memory emerges from collective dynamics	Focus on stability and capacity; no explicit distortion detection
Ulanowicz (2009) – A Third Window	Process ecology, non-equilibrium flow networks	Resilience and memory emerge from ecosystem flows	Indirectly addresses perturbations via system-level resilience
Cohen (2000s) – Immunological homunculus	Immune system as a cognitive self-model	Distributed internal image guides responses	Distortion not formalized; emphasis on self-representation
Kourilsky (2016) – Normative self	Immune identity as dynamically regulated	Regulation viewed as inference and threshold tuning	Degeneracy and tuning conceptually present, not formalized
Ehresmann & Simeonov (2017) – WLIMES	Hierarchical, category-theoretic systems	Multi-level memory and distributed intelligence	Degeneracy implicit via co-regulators; no explicit distortion criterion
Root-Bernstein (2019) – Immune–microbiota co-evolution	Host–microbiota mimicry and cross-talk	Memory shaped by ecological interactions	Distortion implied through mimicry and misrecognition
Morin (2014) – Method of complexity	Non-linearity, emergence, eco-organization	Identity and memory as emergent properties	Degeneracy and disorder conceptually central, not operationalized
***GenSA* / GENSA (this work)**	Sensitive holarchic sensor–actuator networks	Emergent, multiscale, distributed memory and regulation	**Explicitly models degeneracy and distortion-sensitive inference**

These considerations motivate a generic perspective in which sensitivity is not reduced to cognition or sentience at a specific level, but treated as an emergent, multiscale property of living systems.

Consequently, sensitivity does not appear as an isolated property of living systems, nor as a predefined function. Rather, it emerges (as the stabilization of functional responses over time) from the interplay between stochasticity (as a source of distortions), degeneracy and diversity (as resources for exploratory detection.

However, identifying the generative origin of sensitivity does not yet explain how such properties are coordinated, stabilized, and propagated across scales.

This paradigm shift therefore implies a departure from classical element-based or component-centered ontologies. This shift does not amount to replacing one ontology by another (e.g. an ontology of processes or functions), but to adopting a non-ontological, organizational abstraction.

Living systems are no longer described in terms of predefined entities and their interactions, but in terms of historically constructed organizations sustained by the circulation of flux and coordination of processes. Thus, we consider that sensitivity, cognition, and regulation are not properties of elements, but emergent properties of organization.

2.5. The multi-level organization of properties and hierarchical modularity

Building on this process-centered perspective, the challenge is no longer to identify elementary entities, but to understand how processes are coordinated, coupled, and stabilized across scales and dimensions.

The *GenSA* framework is positioned as a unifying approach addressing the limitations of prior paradigms.

Hierarchical modularity is introduced here as an organizational abstraction that structures the circulation of generative processes (energy-dependent) across spatial, temporal, and historical scales. Rather than defining levels where properties would reside, this organization enables the emergence of functions—such as sensitivity, cognition, and regulation—as distributed, system-level phenomena.

Addressing this organizational question requires a shift from properties to abstraction, motivating the introduction of hierarchical modularity as a conceptual scaffold. Hierarchical modularity facilitates the coordination, coupling, and propagation of processes across various scales, thereby allowing sensitivity and cognition to manifest as distributed, system-level properties.

Figure 2 schematizes this hierarchical modular organization and its role in the emergence of functions.

This organization allows processes to be coordinated, intertwined and transmitted across phylogenetic, ontogenetic, and contextual time scales, enabling structures and functions to emerge dynamically in space and time from generative processes rather than being predefined.

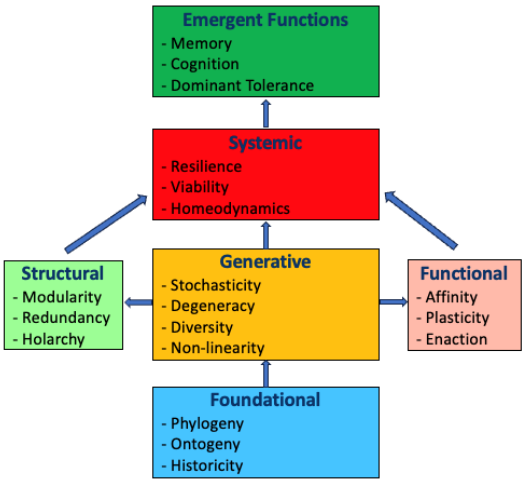

Fig.2: Hierarchical modularity for emergence of functions- Hierarchical modularity spans multiple scales and dimensions, from foundational to generative, and systemic levels up to emergent functions as memory and tolerance when considering the immune systems

The structural properties are organized through modular, redundant, holarchy couplings that enable functional attributes such as affinity, plasticity, and enaction and support systemic characteristics including resilience, viability, and homeo-dynamics. This multilevel organization provides the structural dynamic basis for the emergence of functions such as memory, cognition, and dominant tolerance in living systems.

In this framework, sensitivity is not attributed to isolated components but arises from the coordinated integration of generative processes within a hierarchical modular organization.

Crucially, this hierarchical modularity provides living systems with the capacity of sensitivity and reactivity to absorb, propagate, and reconfigure responses to environmental distortions across time, whether during development, aging, or sustained ecological perturbations, without losing overall coherence nor historicity of living systems.

The multi-level organization of properties and hierarchical modularity emphasizes the model capacity to integrate degenerative distortion, stochasticity, diversity up to emergent functions. Moreover, these generative capacities play a central role in transforming noise and distortions into structured sensitivity, memory, and regulation, rather than suppressing variability.

The immune system provides a concrete biological realization of this multi-level auto-organization, where sensitivity, memory, and adaptive coherence emerge from the continuous dynamic management of internal and environmental distortions across the lifespan.

The immune system indeed serves as a model of evolution (during phylogenesis) and individual adaptivity (during ontogenesis) in living systems. It exemplifies how somatic stochastic diversification, degeneracy, and variability enable the emergence of supra-clonal networks of distributed lymphocytes that regulate identity and integrity in poly-genomic organisms [31, 32, 38]. The immune system's capacity for distributed sensing, memory, and adaptation provides a foundation for understanding the emergence of cognition and resilience in complex living systems.

3. The Immune System as a Model of Living Co-Organization

The immune system provides a paradigmatic example of how living systems achieve sensitivity, adaptability, and coherence through distributed, dynamic networks in poly-genomic organisms. Far from being a simple collection of reactive clones, immune organization displays degeneracy, multiscale coupling, and self-organization, giving rise to emergent system-level properties such as memory, and context-dependent discrimination allowing for tolerance or inflammation /rejection. These properties arise from the collective dynamics of interacting components and cannot be attributed to any single cell or molecule in isolation. For this reason, the immune system constitutes a privileged biological model for exploring how living systems maintain identity and integrity of the host, while remaining sensitive to environmental distortions across phylogenetic and ontogenetic timescales [25, 31, 32, 38].

3.1. Cognitive Features and Idiotypic Networks

One of the most distinctive properties of the immune system is its capacity to display cognitive-like behaviors: As questioned in 1989 [54] *"cognitive properties of immune systems - learning, discrimination, memory - these can only emerge as features of an organized system"* : the immune system learns and maintains an internal reference of self, acquires experience-dependent states, memorizes and modulates responses— ignorance, tolerance or activation up to repair or destruction, according to the context. The experimental grounding of this idea can be traced back to Jerne's idiotypic network theory, which proposed that immune regulation emerges from a constant internal dialogue among antibodies, even in the absence of external antigenic stimulation [25].

Instead of stimulating immune response in adult mice, the immune system organization was then observed in mice during the early ontogeny and before microbial colonization at birth, then before clonal selection and even clonal deletion by "external" antigens. This provides key insight into the self-organization of the immune system related to spontaneous internal activities and autoreactivities of early lymphocytes (the secretion of natural polyreactive IgM being dependent on early fetal B-1 cells). Rather than being pathological, this early auto-reactivity

sustains a spontaneously active internal network state, forming a dense web of degenerated, sensitive low-affinity interactions throughout the organism [54]. This core network constituting the CIS [30, 55] form a supra-clonal regulatory network that calibrates sensitivity, establishes dominant tolerance [38, 56], and provides an internal reference of self in perinatal life, against which later antigen-driven responses are interpreted. The post birth, the PIS processes external signals, but its responses remain constrained by the internal context established by the CIS [55]. The distinction between the CIS and the PIS further emphasizes the distributed nature of immune cognition, not only across tissues but also across complex times.

According to these concepts memory and tolerance therefore arise not solely from clonal lymphocyte persistence, but from changes in the global configuration of the immune networks.

The *in vivo* experimental foundations of these emergent properties are developed in **Section 4**.

3.2. Sources of Variability and Innovation: From Germline Invariance to Somatic Diversity

At the molecular level, immune sensitivity is grounded by a multiplicity of stochastic generative processes that operate during ontogeny at various levels. The discovery of V(D)J gene recombination by Tonegawa recognized with the Nobel Prize [57] revealed how random rearrangements of germline gene segments, mediated by RAG enzymes and reinforced by junctional diversification (including N-nucleotide additions), and protein chain combinations. Thus such four "somatic diversifiers" [57] allow the adaptive immune system to generate a vast repertoire of Variable Region Molecules capable of detecting unforeseen perturbations, thereby enabling the emergence of novel detectors beyond phylogenetically inherited recognition.

The functional diversity of the available repertoire of T cell clones present in an individual at any given time (approximately 2 million in the spleen of mice [58]) is significantly lower than the theoretical somatic repertoire (approximately 10^{61} in humans [59]). However, the generation of this clonal diversity along with the efficient clonal renewal and selection of lymphocytes in young mammals [4] are sufficient to facilitate degeneracy and cross-reactivity [60]. This adaptation addresses the limitation imposed by the approximately 20,000 genes available in humans and mice for encoding new receptors, thereby facilitating the exploration of a diverse range of molecular affinities. These somatic processes establish the biological basis for innovation and exploratory sensitivity beyond phylogenetically inherited recognition.

From an evolutionary perspective [17, 18], the adaptive immune system evolution exemplifies how immune sensitivity is rooted in germline inheritance at the molecular level. Additionally, it involves somatic clonal stochastic generative processes, which are reintroduced during individual development and include a Lamarckian transmission of the maternal repertoires network reflecting her history, through maternal IgG inheritance [61]. This process is stabilized by clonal selection and transmission, resulting in detector diversity that enables distortion-sensitive recognition throughout phylo-ontogenesis.

Figure 3 provides a synthetic representation of the phylo-ontogenetic continuum of immune organization, linking germline-encoded invariants to the progressive ontogenetic diversification of detection repertoires. It situates early invariant specificity and stochastic somatic diversification and sensitivity within a unified temporal framework, highlighting how successive developmental waves, quantitative constraints, and holobiont integration condition the emergence of supra-clonal, system-level immune properties. This representation supports the generic properties discussed in Sections 3.3 and 3.4 by making explicit the multiscale origins of multiplicity of detection.

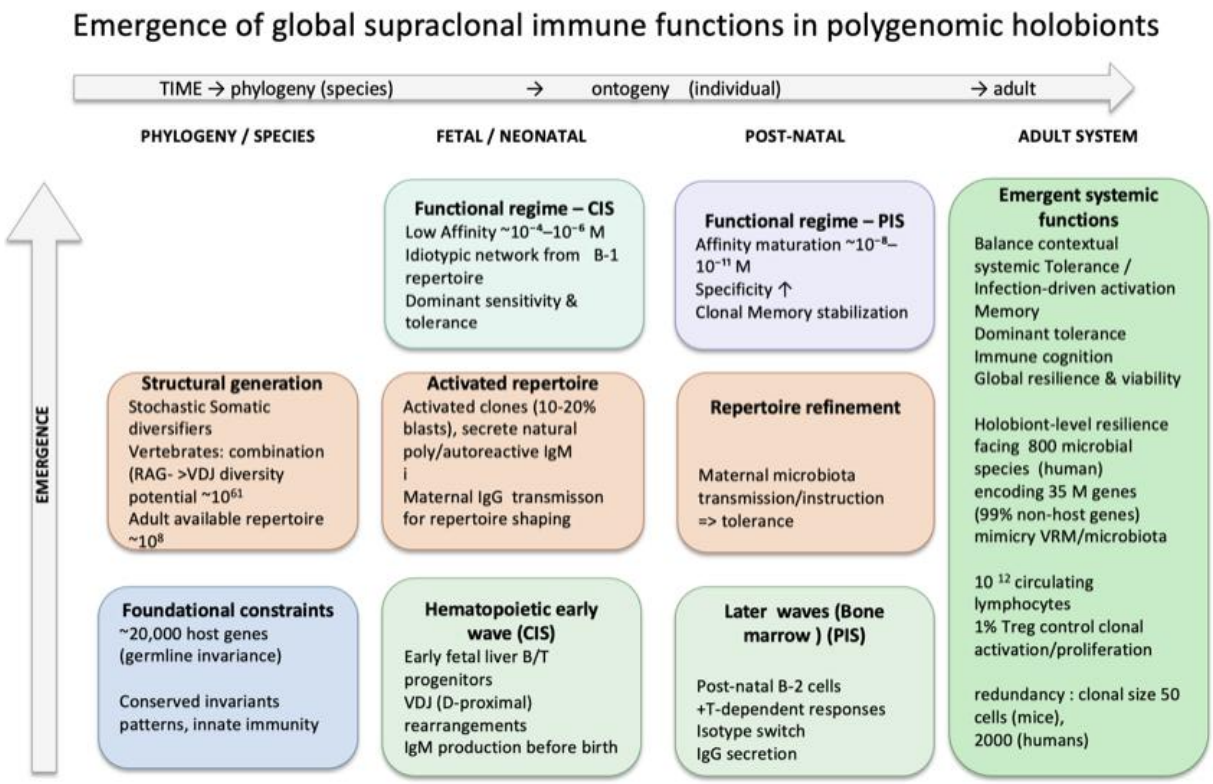

Fig. 3. Phylo-ontogenetic emergence of supraclonal immune functions in polygenomic holobionts. Schematic synthesis of how global immune functions emerge bottom-up from germline constraints, developmental cellular waves, and repertoire organization across phylogenetic and ontogenetic time. The figure emphasizes regimes, scales, and transitions rather than molecular detail, illustrating how successive stages condition distinct modes of immune operation that culminate in supra-clonal properties at the system level.

Reading guide: bottom → top indicates emergence; left → right indicates time. Repertoire sizes refer to the human adult state.

3.3. Four Core Generative Properties: From Immune Processes to Generic Living Systems

Referring to Fig. 2, four fundamental properties of the immune system can be identified:

Stochasticity provides the generative substrate of sensitivity by introducing variability of events and exploratory potential of somatic receptors as revealed by Tonegawa [57] in the immunoglobulins.

Degeneracy [53] provides robustness and flexibility because many distinct clones or molecules can compensate for each other. Multiple T cell receptors (of different sequence) might recognize the same peptide–MHC epitope; conversely, one T cell clone can have cross-reactivity to several epitopes [60]. If one pathway is blocked, another can fill in (e.g., parallel cytokine pathways can induce immune activation). Degeneracy is a hallmark of immune regulation and has been recognized as a general principle of biological networks contributing to resilience and evolvability [62].

Diversity expands the functional repertoire and spreads risk. In immunity, diversity is evident in the huge array of lymphocyte specificities and in the variety of cell types (T cell subsets, B cell classes, innate cells, etc.) and the wave of hematopoietic cells that generate them during the individual development. Diversity also refers to genetic polymorphisms in populations and to microbial diversity in holobionts, which can train and prepare the immune system for a wider range of inputs. Ecological studies and systems theory have long noted that higher diversity can confer stability (up to a point) by enabling adaptive responses to perturbations [63].

Emergence is the appearance of qualitatively new properties or behaviors at the system level. Foundational work on far-from-equilibrium thermodynamics and nonlinear network dynamics illustrated how oscillations, chaotic cycles, and multi-stability can spontaneously emerge in systems with nonlinear interactions [63, 64]. In the immune system emergence arise from the interactions of components *in vivo* helped by idiotypic interactions during the early ontogeny, completed by formation of supra-clonal immunological memory and dominant tolerance with

multi-stable behaviors with distinct regimes (resting, inflammatory, tolerant), with transitions driven by collective and network shifts rather than single components.

Table 3 summarizes these core properties, their systemic roles, and their relevance to emergence.

Table 3: Core properties of living systems and their systemic roles.

Property	*Systemic Role*	*Biological Example*	*Relevance to Emergence*
Stochasticity	Generates variability and novelty; enables exploration of possibilities.	Random gene recombination in lymphocytes; gene expression noise in development.	Produces a repertoire for future self-organization and selection; enables rare responses (e.g., preparedness for new pathogens).
Degeneracy	Provides robustness and flexibility; multiple ways to achieve function.	Different immune receptors/convergent pathways achieving similar target recognition; neuronal synapse redundancy.	Robustness: system tolerates loss or mutation of components; innovation: overlap can allow new functions to evolve as supra-clonal functions and memory.
Diversity	Enhances adaptability and resilience; broadens functional range.	Polymorphic MHC genes; diverse microbiome species; Stochastic diversity of clonal immunoreceptors.	Resilience: more components can handle environmental changes; specialization: allows tailored responses and division of labor.
Emergence	Produces novel system-level order and functions from interactions.	Immune memory and tolerance from Ig-like and lymphocyte networks.	Novel functions: (e.g., memory, consciousness) not possible in parts; system self-regulates via emergent patterns (attractors, oscillations).

3.4 From Invariance to Exploration: Multiplicity of Detection and Distributed Immune Sensing

Why do living systems exhibit such extreme degeneracy and diversity and (overlapping functions), instead of one optimal solution for each task? The answer lies in the interplay of variation and selection across different time scales. As **Edelman** noted, degeneracy is an inherent outcome of complex systems selected for performance rather than a single rigid configuration—multiple distinct solutions co-exist for the same challenge, and structurally different components can perform similar or overlapping functions [53]. This view is echoed in theoretical biology: Ehresmann & Vanbremeersch's "multiplicity principle" posits that multiple realizations of similar functions are essential for complex learning networks [65]. Rosen's relational biology argues that what matters are the relations among components, not the specific parts—different components can fulfill the same role, yielding degeneracy in implementation [66]. Edgar Morin's concept of eco-organization similarly suggests that organisms co-evolve with unpredictable environments by developing interwoven, redundant pathways that confer resilience [3]. In sum, degeneracy is a fundamental feature of complex adaptive systems, enhancing robustness and capacity to evolve.

In the high vertebrate immune systems, the principles of multiplicity, degeneracy, diversity, and emergence are concretely embodied as a dynamic interplay between phylogenetically inherited invariants and ontogenetically generated exploratory stochastic diversity, allowing the use of a multiplicity of criteria to balance performances and their potential optimality [15].

This architecture illustrates how invariance and innovation are coupled through phylo-ontogenesis, underpinning sensitivity, intra/inter-cellular communication, memory and tolerance favoring resilience in vertebrate holobionts.

Immunological sensitivity should therefore not be understood as a static property, but rather as an evolving trajectory, progressively shaped by differentiation and the coexistence of diverse detection regimes. As illustrated in **Figure 4**, this diversity emerges from the ongoing interaction between conserved, germline-encoded molecules and somatically diversified, exploratory sensors, thereby enabling organisms to flexibly discriminate under uncertainty and communicate.

The developmental layering of immune contexts and repertoires dynamics—particularly early-life regimes and their impact on tolerance and distributed memory—will be examined in detail in **Section 4**.

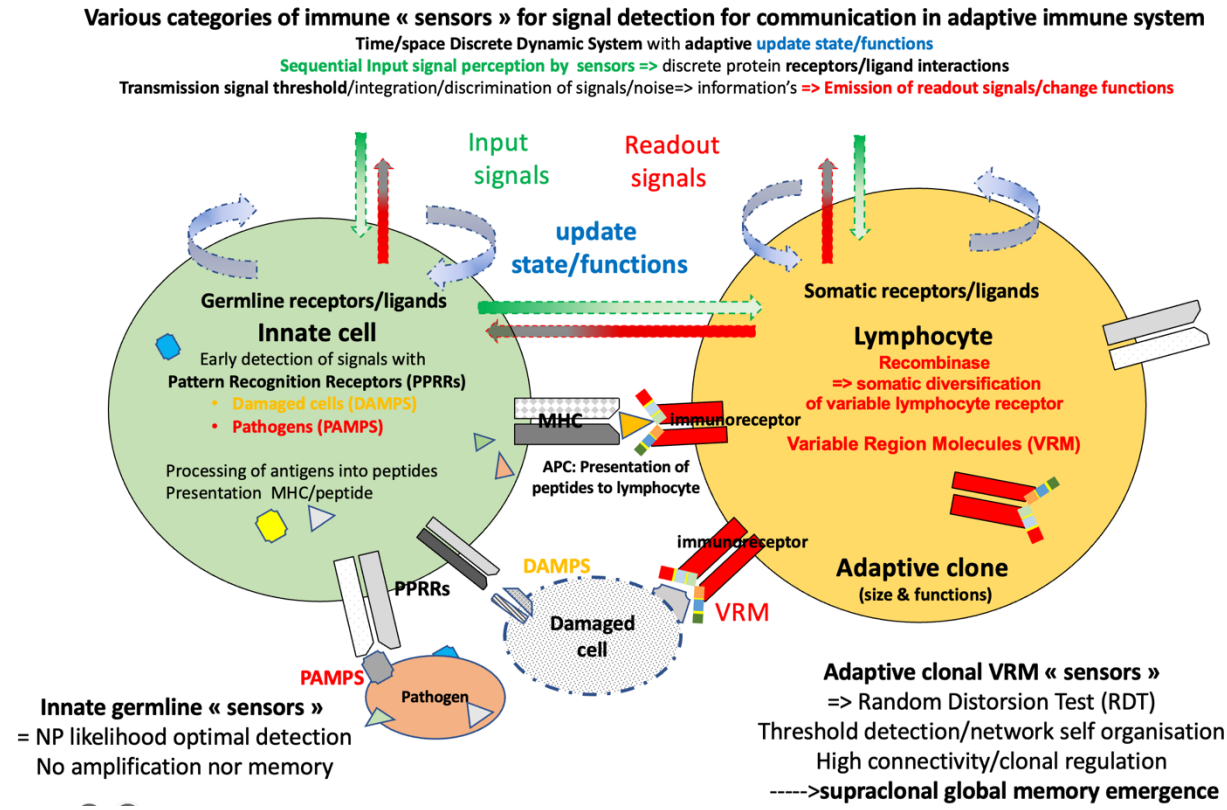

Fig. 4: **Multiplicity of Immune Detection Regimes: Communication Between Germline-Invariant Molecules (NP-like) and Somatically Diversified Sensors (RDT-like)**

The immune system relies on the coexistence and interaction of multiple receptor–ligand detection regimes. (Left): Phylogenetically conserved, germline-encoded molecules ensure the interaction between receptors and ligands that propagate signals and intracellular information's. Pattern Recognition Receptors, (PRRs) recognize highly conserved "Damaged Molecular Patterns "(DAMPs), "Pathogen Molecular Patterns" (PAMPs) with high affinity to capture these cells. The MHC polymorphic molecules are involved in peptide presentation to T cells initiating the contextual communication between the Antigen Presenting Cell (APC) and the T lymphocytes. These receptors or ligands provide invariant or recurrent molecular motifs and function as low-dimensional, expectation-driven detectors (NP-like regime). (Right): Concurrently, the ontogenetic expression of the RAG recombinase in lymphocytes facilitates somatic V(D)J gene stochastic recombination, generating clonally distributed Variable Region Molecules (VRM), which allow lymphocytes to explore a vast array of molecular affinities and support individualized, distortion-sensitive detection (RDT-like regime).

Finally, this framework aligns with the distinction between organizational closure and structural openness: immune identity is maintained by closure of the network of processes that constitute the system, while the system remains continuously open to matter, energy, and environmental perturbations. This open yet self-referential organization is precisely what a multiplicity of coupled RDT-type (random distortion functions) and NP-type (invariant likelihood selected) detectors enables: the immune system can preserve internal coherence (tolerance and distributed memory) while incorporating and regulating novel inputs, including those arising in poly-genomic holobionts, without relying on a rigid dualism of self versus non-self.

4. Experimental Evidence In Vivo: Emergence of Degeneracy, Randomness, and Immune Functions

A broad range of experimental evidence—much of it from our own studies—shows that critical immune cognitive functions such as self-tolerance and memory maintenance are emergent properties that only fully manifest at the level of the whole organism *in vivo*. These functions rely on distributed population dynamics, on tissue-dependent organization, and on history-dependent processes of inference, and they often cannot be recapitulated *in vitro*, where the spatio-temporal constraints, historicity, long-range interactions and systemic feedback of the living immune system and context are disrupted.

4.1. Early B cell waves, natural IgM, and idiotypic network dynamics (B-centered CIS core)

Addressing Jerne's question of what precedes clonal selection in immunity [23], early B-cell waves provide a concrete entry point of how the systems self-organize and lead to emergent functions.

The foundations of the first B cell wave producing the natural IgM/B-1 cell involved in the initiation of this idiotypic were established from spontaneous immune activities observed in unmanipulated mice [54]. B-1 cells, enriched in the peritoneal cavity, spontaneously produce polyreactive IgM antibodies from fetal and neonatal life, including in germ-free conditions, thereby coupling early self-reactivity with broad protection against pathogens and providing a low-stringency inferential "screening" regime compatible with later adaptive specialization [54, 55]. At the network level, natural IgM repertoires engage in idiotype–anti-idiotype interactions and support a functional idiotypic network among natural antibodies, consistent with complex, metastable configurations that reorganize under perturbation while preserving coherence [27, 54]. Indeed, *in vivo* perturbation experiments show that a single injection of antibody idiotype can propagate cascades of anti-idiotypic interactions for long periods, stabilizing through network feedbacks [27].

Importantly, these early B-1 cell populations originate during fetal life, from hematopoietic waves arising in the yolk sac, placenta, and fetal liver, before the establishment of definitive bone marrow hematopoiesis. These fetal-derived B-1 cells seed peripheral compartments, including the peritoneal cavity, and persist long-term through self-renewal, providing a stable source of natural IgM early in life. In contrast, conventional B-2 cells emerge predominantly from bone marrow–derived lymphopoiesis around the perinatal period and progressively dominate adaptive, antigen-driven responses requiring T cell help. This temporal layering of B cell ontogeny establishes distinct detection regimes and functional roles, with early B-1–derived repertoires contributing to a tolerant, self-referential network core, upon which later B-2–mediated adaptive clonal amplification/death is constrained and regulated.

We also showed that the dynamic of B-cell persistence, renewal and expansion are strongly shaped by the host tissue environment and the developmental context: transferred B-cell populations display distinct kinetics according to organ localization (including peritoneal cavity versus spleen), route of transfer, and the age or state of the recipient [33, 34]. This environmental dependence is coupled to repertoire-level selection: clonal persistence is determined by variable region–dependent selection, and VH family representation evolves with time in the host, consistent with context-dependent shaping of the B-1/natural IgM repertoire using VH gene close to D regions [35, 55, 67]}.

The origin and reconstitution potential of CD5+ B cells and natural IgM-secreting cells further supports that natural IgM secretion can be reconstituted from different cellular sources under appropriate conditions, again emphasizing population-level constraints and differentiation trajectories rather than fixed cellular attributes [36].

Collectively, these B-1/natural IgM observations support the view that early immune organization constructs internal reference states—i.e., a first form of "memory of self"—through distributed inferential processes embedded in population dynamics.

A layered ("wave-based") view of B cell development and natural antibody biology, spanning fetal to adult stages and extending to proposed human B-1 counterparts, has consolidated these observations and reinforces the relevance of early B-1/natural IgM dynamics for both tolerance and early protection [68-72].

Thus, *in vivo* observations in mice, but also clinical treatments in humans, with the intravenous administration of immunoglobulin pools from normal donors delivering anti-idiotype against autoantibodies favor network regulation of autoimmune responses [73]. Thus, the presence of an initial core and supra-clonal network of B cells able to establish emergent functions was established. Furthermore, the Lamarckian transmission of "internal" images of antigens naturally occurs from mother to fetus through the transfer of IgG [61], showing that constraints also exist to set up the emergence and activation of the neonatal repertoire that can learn from the immunological history of the mother.

Then, we questioned the dominant immunological tolerance [37] and the memory [10, 74] establishing through T cell selection.

4.2. Thymus as central organ for the learning of T-cell confronted to ectopic tissue antigens and idiotypic presentation

In parallel with early B-cell driven organization, the thymus shapes the T-cell repertoire through central tolerance, but it does not eliminate all self-reactive T cells. Some autoreactive T cells generated during early waves of thymic colonization resist deletion and instead become part of self-regulatory circuits [75]. Thymic epithelial cells contribute to this process by presenting a broad array of self and tissue-restricted antigens through ectopic expression programs, in part AIRE-dependent, enabling developing T cells to learn these ligands as internal references within temporally constrained "windows" of education [37, 76-78].

Failures of this thymic educational context can be sufficient to bias repertoire selection toward pathology: abnormal selection on NOD thymic epithelium induces autoimmune manifestations in otherwise non-autoimmune recipients, showing that altered thymic inference trajectories can establish autoimmunity independently of peripheral target context [79].

4.3. Central/Peripheral Immune Systems and dominant peripheral "infectious" tolerance targeting RTEs

In the "third generation" immune network perspective, the Central Immune System (CIS) and the Peripheral Immune System (PIS) characterize immune systems (compartments/organizations), not isolated immune responses: the CIS corresponds to an early self-referential, supra-clonal organization integrating self antigens into ongoing regulatory dynamics, whereas the PIS corresponds to later antigen-driven clonal expansion and effector differentiation under CIS constraints [30-32, 80]. In this view, tolerance is not a passive absence of response but a dominant, actively maintained network property, i.e., a maintained "memory of self" embedded in regulation.

Peripheral maintenance and transmission of tolerance provide direct *in vivo* evidence for this dominance. Thymic epithelium–induced tolerance is mediated by regulatory T cells and can be transmitted to non-tolerant T cells [81], and crucially the peripheral education process targets Recent Thymic Emigrants (RTEs) rather than long-resident mature T cells, under antigen-specific and local conditions [78]. This "infectious tolerance" thus corresponds to a distributed inference process in peripheral tissues, allowing tolerance to spread while preserving global immune competence.

In addition, dominant peripheral tolerance to several tissue types (skin, heart, pancreatic islets) can be induced by transiently perturbing the balance between effector and regulatory T cells through selective depletion of proliferating T cells. This approach preferentially removes dividing effector populations while largely sparing regulatory populations, thereby shifting the global network configuration toward tolerance without generalized continuous immunosuppression [82-84].

4.4. Emergent memory and systemic integration: in vivo perturbation and in silico convergence

Similar principles apply to immunological memory. Robust immune memory—which ensures faster and stronger responses upon re-exposure to a pathogen or allogeneic challenge—depends on the dynamic maintenance of a structured network of interacting lymphocytes. By disrupting that network *in vivo* we abolished a previously established memory response leading to immunological amnesia even if some "memory" phenotype cells remain present [10]. This indicates that memory is not an intrinsic property of isolated cells but a supra-clonal, system-level inference state emerging from population dynamics and sustained interactions.

In silico immune network models converge with these observations by reproducing memory, tolerance, or autoimmunity as collective properties of interacting repertoires and feedback structures rather than localized attributes [30, 85-88]. This convergence supports the interpretation of immune memory as a history-dependent global configuration of the network, whose stability can be lost under specific perturbations despite persistence of phenotypic markers.

4.5. Plasticity Over the Lifespan

The immune system remains plastic throughout life: the balance between tolerance and reactivity can adjust to new conditions, though early self-referential organization provides stability. As animals age, changes in the immune network can gradually erode immune function and network topology; in older mice, reorganization of gene co-expression networks and a narrowing of receptor diversity are observed [89], concomitant with alteration of proliferative capacities and their regulation [90]. This suggests that the aging immune network drifts toward a less regulated state under chronic constraints and altered turnover.

Importantly, however, tolerance-oriented configurations can be re-established by interventions that perturb population dynamics in a controlled and transient manner. In particular, the transient depletion of dividing T lymphocytes induces the emergence of regulatory T cells favoring the dominant tolerance to allografts, consistent with the idea that tolerance and memory are maintained as system-level properties through dynamic reconfiguration rather than fixed cellular states [84].

As a summary of this section, **Figure 1** (Sensitive Living Systems interactions Complexity in Holobionts) recalls how inferences and communication occur in complex living systems through coupled temporalities, leading to adaptation to distortions.

The Fig. 5: Environmental and Ontogenetic Influences on Immune Network Formation illustrates the contribution to the formation of the Central Immune System (CIS), highlighting the early emergence of a multi-reactive B-1 cell and T cell network and its role in establishing systemic tolerance and distributed immune memory.

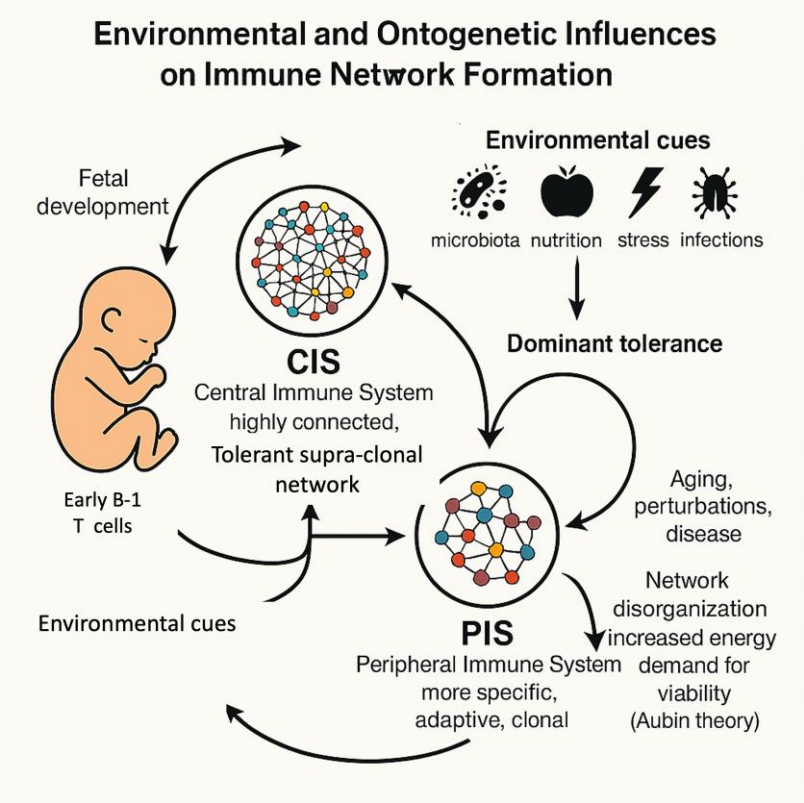

Fig. 5: Environmental and Ontogenetic Influences on Immune Network Formation: This schematic illustrates how immune network formation is shaped during fetal and neonatal development through early Central Immune System (CIS) auto-organization, thymic education. The CIS emerges early in ontogeny from the first waves of hematopoietic cells in fetal life, as a highly connected, multi-reactive degenerated B-1 cell (IgM) and early T cell network that supports systemic tolerance and distributed immune memory that can transmit such functions to later waves. Thymic selection and regulatory T cell differentiation further stabilize this organization. From birth, environmental cues such as microbiota, nutrition, stress, and aging drive clonal selection/expansion of specific clones in Peripheral Immune System (PIS). This integrative view emphasizes that immune tolerance and adaptation arise from coupled processes operating across ontogenetic, cellular/molecular Ig network, and environmental constraints, and provides a natural entry point for qualitative multilevel modeling approaches.

Taken together, these *in vivo* and *in silico* observations show that tolerance and memory are supra-clonal properties of a self-organized, degenerate network and not mere byproducts of antigen-driven clonal expansion. They also clarify why classical modeling approaches that decompose immune systems into isolated components, static interactions, or single-scale dynamics struggle to account for emergence, multiscale coupling, history dependence, and distortion-sensitive inference—issues addressed in the following sections.

4.6 Degenerate Detection, Function Regimes and Trajectories of Immune Sensitivity

Building on the experimental observations described above, immune functions across development and throughout life relies on a spatio-temporal balance between partially degenerate structures and functions that support distinct regimes of sensitivity and specificity. Rather than operating through a single mode of recognition at only one scale, the immune systems combine multiple detection and functional regimes that coexist, overlap, and are progressively tuned along ontogenetic and experiential trajectories.

Phylogenetically conserved innate sensors implement a likelihood baseline detection regime (modelled later by NP-type). Shaped by long-term evolutionary selection, these sensors encoded by germline genes are tuned to recurrent molecular patterns and enable immediate responses by innate immune cells, such as Antigen-Presenting Cells. While highly efficient for detecting stereotyped signals, this regime is intrinsically limited in its ability to identify distortions in noisy environments or unexpected highly reproductive variants and mutants, as frequently encountered during rapid viral evolution.

In parallel, somatically diversified receptors generated in B and T lymphocytes implement an exploratory detection regime through the stochastic, degenerated, cross-reactive and clonal exploration and adaptation (modelled by RDT-type). By sampling a vast affinity space, these receptors enable the detection of deviations or distortions that extend beyond the inherited germline baseline.

For example, in the thymus [4], various interactions resulting from both the structural clonal receptor diversity but also the contextual antigen encounter on various APC's as epithelial cells or hematopoietic cells drive the functional cell dynamics of lymphocytes to orient their status according to the flux of contextual events: each cell is educated during a 3-4 weeks residence in the thymus allowing to the somatic stochastic immunoreceptor diversification and clonal identity related to the structural amino acid sequence of the variable regions that cognate the antigenic epitopes. Then, the thymus act as a functional filter that control the multiple somatic generation of diversity processes [57] to generates structural and functional diversity learning and memorizing self-context to induce dominant tolerance. Thus, non-productive gene rearrangement of receptors results in death by neglect of many lymphocytes, while the external signals of lymphocytes displaying excessive self-affinity induce the clonal deletion (apoptosis) leading more than 90% of lymphocyte produced in the thymus to death. The context-dependent bifurcation of

lymphocytes with intermediate affinities, shaped by contextual antigen exposure, and orient their functions: the thymic epithelial ectopic antigen presentation inducing regulatory T-cell differentiation in a small fraction of T cells, (about 5%) the other being oriented to effector functions of surveillance. Thus, the fluxes and sequences of interactions can trigger various signals and information transmission that influence the production, renewal, death or survival, activation, proliferation, differentiation, oriented migration and export of thymocytes to peripheral lymphoid tissues that is also perturbed through aging [4, 7, 89-91]. Together, these processes progressively stabilize a multi-scale detection and function architecture across life.

Critically, these NP-type and RDT-type regimes should not be understood as a fixed dichotomy between innate and adaptive recognition. Instead, they define a developmental and historical trajectory, in which immune sensitivity emerges from the coupling of detection and functional modes, lymphocytes expressing both, operating at different temporo-spatial and organizational scales. The immune system thus continuously adjusts its sensitivity to events and context, through the interaction of conserved likelihood-based detectors and exploratory, experience-dependent distortion detectors and functions.

Now we outline the current limits encountered with classical modeling approaches and how the abstraction of various detection mode could open new ways for the abstraction and modeling of the sensitivity in living systems.

5. Limitations of Classical Modeling Approaches

The multiplicity and coupling of detection regimes described above—ranging from phylogenetically stabilized likelihood-based baselines to exploratory, experience-dependent distortion detection—pose fundamental challenges for classical modeling approaches. While systems biology and computational modeling have yielded major insights, most conventional formalisms remain ill-equipped to capture the sensitivity, historical dynamics, and emergent organization that characterize living systems, as exemplified by the immune system. In this section, we examine why these approaches struggle to account for emergence, multi-scale integration, and context-dependent adaptation.

5.1. Reductionism and Linearity

Classical models such as deterministic ordinary differential equations (ODEs), which implicitly assume a single, homogeneous detection regime, require aggregation of individuals into average concentrations, assuming smooth, continuous changes. This makes it difficult to represent nonlinear threshold events or the combinatorial diversity of receptors explicitly. Important behaviors like bi-stability or critical phase transitions in immunity (e.g., the sudden lymphocyte clonal expansion when a pathogen is detected) may be "averaged out" in such models. Similarly, agent-based models, while more fine-grained, often still treat agents as following pre-set rules, rather than genuinely sensing and adapting to signals in an open-ended way.

ODE models have been valuable for understanding average behaviors and achieving a first-order approximation of dynamics (e.g., viral infection kinetics, or homeostatic population turnover) [4, 92]. They capture continuous feedback loops (like a rise in antigen leads to a rise in effector cells which then lower antigen), and can reproduce phenomena like oscillations or steady states. However, ODE models are inherently deterministic and population-based, often presupposing homogeneity and neglecting the individual variability and stochasticity that characterize actual immune systems. They encounter difficulties in capturing rare events, emergent behaviors, and the influence of local microenvironments—factors that are crucial for understanding immune memory, tolerance, and resilience. Additionally, the stochastic disorganizations and oligoclonal expansions that occur during aging remain beyond the scope of these models [4, 6, 90].

5.2. Stochastic Rare Events

Many immune events (e.g., the initial recognition of a rare antigen by exactly one B cell, or a random somatic mutation that creates a high-affinity receptor) are inherently stochastic and rare. Yet these improbable events can dictate the future course of the system (a successful recognition can trigger a cascade of responses). Standard dynamical systems theory does not easily incorporate such noise-driven events—stochastic differential equation models exist, but they become intractable with high dimensionality and can miss discrete jumps.

5.3. Multiscale Integration

The behaviors of living systems arise from interactions occurring at various scales, including molecules, cells, organs, organisms, and ecosystems, as well as across diverse temporal frameworks, ranging from milliseconds to years, encompassing phases of individual development but also evolutionary processes and the millennia of co-evolution. Classical models typically focus on one or two scales at a time—e.g., molecular signaling or population dynamics—failing to capture cross-scale feedback. For instance, an ODE might simulate cell population changes over days, but cannot incorporate how evolutionary selection over millennia shaped those cells' properties along historical trajectories. Likewise, a model might simulate one infection, but not how prenatal factors (maternal antibodies) set initial conditions.

5.4. Object-Based vs. Perception-Based

Perhaps most critically, many classical modeling approaches—including differential-equation frameworks and agent-based or UML-inspired models—represent biological components as *objects*

endowed with predefined states and rule-based interactions. In such formulations, interactions are encoded as fixed reaction terms, transition rules, or decision trees, and detection or response is inferred indirectly from object states.

When modeling living systems, an object-centered representation proves inadequate, as these systems operate based on perception and sensitivity rather than fixed rules. In the immune system, for instance, responses are governed by the coexistence of multiple families of receptors with distinct origins and functional regimes: phylogenetically stabilized, germline-encoded receptors optimized for recurrent patterns, and ontogenetically generated, somatically diversified receptors arising through stochastic processes and selection. Capturing how these heterogeneous detectors are generated, selected, stabilized, or extinguished across different temporal regimes—and how they collectively shape tolerance, memory, and adaptation—is difficult when interactions are primarily expressed as object-to-object rules or averaged reaction terms.

As a result, perception, conditional reactivity, and adaptive decision-making must be reconstructed a posteriori from object dynamics, rather than being treated as first-class modeling variables. This limitation motivates approaches that explicitly model detection and response in terms of graded sensitivity, affinity, and context-dependent thresholds, rather than solely through predefined object interactions [12-15]. This limitation persists even when moving from equation-based models to agent-based representations, as discussed below.

5.5. Agent-Based and Visual Modeling Approaches

To address some of these limitations at the level of object interactions, researchers have turned to agent-based models (ABMs) and state-transition diagrams [93, 94], which simulate the behavior of individual cells and their interactions and emerging functions within complex environments. ABMs offer greater granularity and flexibility, allowing for the simulation of heterogeneous cell populations. However local interactions and feedback loops across various levels of organization, spatial and temporal dynamics, and emergent phenomena are more difficult to simulate. These models are often computationally intensive and require detailed knowledge of agent behaviors and rules. Integrating ABMs across biological scales—from molecules to organisms to ecosystems—remains a significant challenge. Results can be sensitive to those rules, making it tricky to validate or generalize conclusions.

Moreover, ABMs produce a lot of "raw" outcome data (the simulated histories of thousands of agents), from which it can be hard to extract general principles or to intuitively understand what parameters are most important.

5.6. Holistic and Multi-Scale Theoretical Models

Recognizing these issues, some researchers have proposed more holistic frameworks that focus on high-level organization and information flow rather than simulating individual molecules. Notable examples include Parisi's idiotypic network model [88], Ulanowicz's "Third Window" [1, 95], and the Ehresmann & Simeonov HMES and WLIMES [21], which model emergent memory, multi-scale regulation, and adaptive communication. These models also align with Morin's complexity theory and auto eco-organization [3], Kourilsky's normative self-model [96], Cohen's immunological homunculus and recent developments considering fittedness and autoencoding [97], as well as Root-Bernstein's work on ecosystems co-evolution and cross talk [98]. Semiotic approaches of the immune system, implying the signification, interpretation of context, were studied by interdisciplinary researchers [99, 100].

However, these approaches often remain at a qualitative or metaphorical level. They provide vocabularies to discuss complexity (e.g., "the immune system functions like a language" or "like a neural network"), and sometimes qualitative predictions (e.g., degeneracy is expected to correlate with robustness [53]), but they do not easily translate into concrete computational models that one can use to simulate or predict specific outcomes. For instance, knowing that the immune system can be thought of as a "semantic web" (in Jerne's terms) is enlightening, but if one wants to predict how that web changes after a vaccine, one still faces a gap in formalism. In short, purely holistic models often lack a way to incorporate quantitative data (like omics measurements) or to yield testable simulations. They may also omit the role of energetic constraints entirely—something fundamental to any real biological process.

These limitations become particularly apparent when considering poly-genomic holobionts, where immune, microbial, and environmental processes interact across multiple temporal and organizational scales, as illustrated in **Figure 6.**

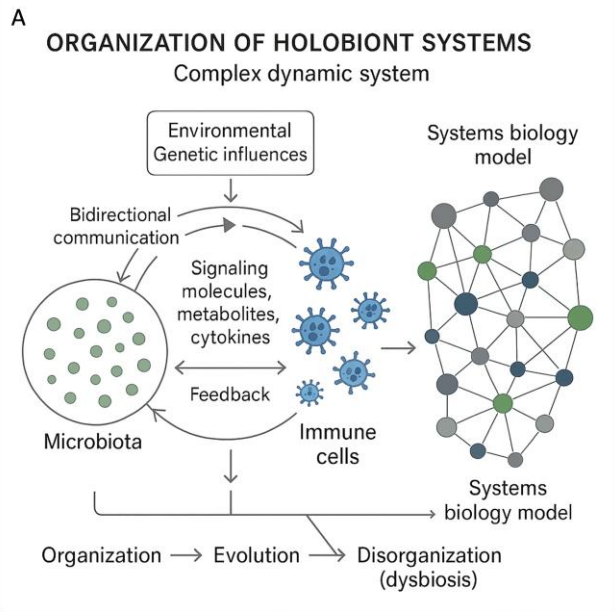

Fig.6A: Organization of holobiont systems
Depicts the influences of random events and the multi-directional communication that establish through times between the immune system and microbiota with mimicry, and the challenge to provide system biology models across times/spaces.

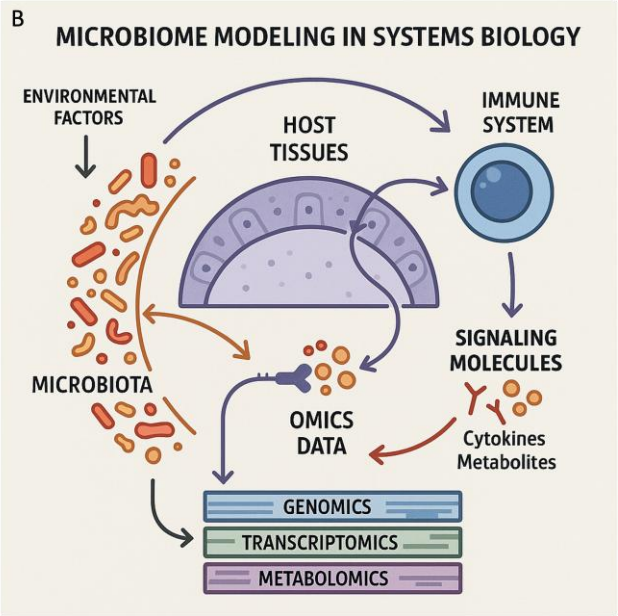

Fig.6B: Immune system & Microbiome modeling in systems biology. The generation of Omics data because of multiparameter analysis questions their integration through multiscale and how to infer and reconstruct the system dynamics between the different ecosystems of the holobiont.

5.7. The Need for a New Generic Paradigm

Together, these limitations highlight the need for a generic modeling paradigm capable of accounting for emergence, multiscale organization, and historical dynamics in living systems, without reducing them to predefined objects, fixed rules, or averaged equations. Such a paradigm must be able to accommodate heterogeneous components, stochastic generation and selection processes, and the coexistence of multiple temporal regimes shaping system organization over development and evolution.

This motivates the introduction of a generic conceptual framework that abstracts living systems as sensitive, adaptive organizations structured by sensitive variable interactions across scales and time. A central difficulty is to model how living systems infer meaningful distortions amid stochastic fluctuations and noise, and how detector repertoires with different origins (germline-stabilized vs somatically diversified) are generated, selected, and tuned over time. This motivates a generic framework that treats distortion-sensitivity and affinity/energy-based evaluation as primary modeling variables.

6. The Generic Sensor–Actuator Framework: GenSA and GENSA

Living systems are embedded in disorder and stochasticity, yet they continuously infer which fluctuations correspond to meaningful distortions rather than background variability. In the immune system, this process does not reduce to binary distinctions (such as self/non-self or innate/adaptive) but emerges from intertwined detector repertoires forming a continuum—from phylogenetically stabilized germline constraints to ontogenetically generated somatic diversification—coupled by network feedback, eco-auto-organization, selection, and stabilization across time. The key modeling challenge is therefore to treat distortion sensitivity and affinity- and energy-based evaluation as primary drivers of detection and reconfiguration, rather than encoding responses as predefined object-based rules. This conceptual–formal articulation is synthesized in **Figure 7**.

Within this context, GenSA is introduced as a conceptual framework describing sensitive living systems as multiscale, historically constituted organizations structured by energy- and affinity-based interactions. This framework supports representations ranging from qualitative biological descriptions to formal mathematical implementations. GENSA is introduced as one possible formalization of selected GenSA principles, designed to support probabilistic inference and state reconfiguration in a generic and scale-independent manner.

Developed to overcome the limitations of reductionist and deterministic models, the

GenSA/GENSA framework models living systems as adaptive holarchies coping with uncertainty across phylo-ontogenesis, enabling the emergence of tolerance, memory, and resilience. **Table 4** summarizes its main dimensions.

Table 4:Generic Sensor-Actuator Framework

Dimension	Core elements of the GenSA framework
Modeling focus	Sensitive and reactive living subjects interacting through energy- and affinity-based processes
Organizational structure	Holarchic, multiscale organization (from molecules to organisms and ecosystems)
Biological grounding	Immune system as a model: CIS/PIS organization, receptor diversity, tolerance and memory
Generative properties	Stochastic generation, degeneracy, diversity, and selection
Dynamics	Context-dependent reconfiguration driven by interactions and perturbations
Memory and identity	Emergent, distributed memory and dominant tolerance
Temporal organization	Intertwined developmental, decision-based, and evolutionary temporalities
Scope of application	Holobionts, immune ecosystems, and living communication systems

6.1. Living Systems as Sensitive Holons Across Phylo-Ontogenetic Time

Within the *GenSA* conceptual framework, the understanding of living systems shifts from entities conceived as isolated objects to the flows of energy and affinity that dynamically couple living subjects. Rather than describing fixed components and predefined interactions, *GenSA* characterizes how sensitive and reactive units continuously evaluate, transmit, and transform perturbations through graded, affinity-based processes.

In this perspective, what is considered is not the entity itself, but the relational flux—the energetic and informational coupling—between subjects embedded in their environment. These affinity-based fluxes are inherently probabilistic, context-dependent, and history-dependent, and they evolve through recursive integration of signals and feedback. System organization, memory, and adaptation thus emerge from the reconfiguration of interactions, rather than from the manipulation of static objects.

GenSA conceptualizes living systems as sensitive holons, simultaneously autonomous and integrated, capable of sensing perturbations, interpreting them in context, and [12, 15, 101]. This holonic organization provides a generic description of how local sensitivity and global coherence coexist within living systems.

Crucially, *GenSA* embeds holons within complex, intertwined temporalities. Fast sensor–actuator dynamics operate at the scale of molecular or cellular interactions, while slower ontogenetic processes modulate responsiveness and internal organization, and phylogenetic constraints define inherited invariants. Memory, tolerance, and robustness thus emerge from the interaction between short-term distortions and long-term selection, rather than from predefined rules or centralized control. This phylo-ontogenetic embedding is central to understanding how living systems maintain coherence while remaining adaptable across changing environments.

6.2. From Biological Strategies to Statistical Inference Criteria

The immune system relies on intertwined detection strategies spanning a continuum from phylogenetically stabilized germline biases to ontogenetically generated somatic exploration. This biological organization directly inspired the inference architecture underlying the *GenSA* framework.

Innate immunity, optimized for the rapid recognition of recurrent and evolutionarily conserved patterns, corresponds to a likelihood-based detection regime for expected signals. In statistical terms, this regime can be formalized by a Neyman–Pearson (NP) criterion, which maximizes sensitivity to known patterns under a controlled false-positive rate. In contrast, adaptive immunity remains largely quiescent until encountering sufficiently novel or unexpected perturbations. This behavior corresponds to distortion- or anomaly-oriented detection, formalized by Random Distortion Testing (RDT), which emphasizes specificity to deviations, close to discontinuity theory [102], rather than to expected signals. The immune system's "conserved plus diversified" solution is thus naturally reflected in a combined NP/RDT inference architecture, formalized in the GENSA framework.

From an inference perspective, the two detection regimes differ markedly in their robustness to noise, interference, and signal mimicry, as highlighted for immune systems [15]. NP-like detection is optimal when the expected signal model is accurate and the signal-to-noise ratio is high, a situation typical of conserved, high-affinity interactions. However, this regime is vulnerable when unexpected perturbations resemble known patterns, potentially leading to false positives under structured noise. By contrast, RDT does not rely on an explicit signal model and instead detects significant deviations from a reference state, making it intrinsically more robust to background noise, unmodeled variability, and interference. The coexistence of NP-like and RDT-like strategies in immune systems thus reflects a biologically grounded solution for balancing efficiency, exploration, and robustness in uncertain environments.

Biologically, antigen-binding affinity provides a natural bridge between immune recognition and statistical inference. Broad, low-affinity interactions—such as those mediated by natural IgM antibodies—support wide coverage and low detection thresholds, enabling early screening of antigenic space with high sensitivity and degeneracy. In contrast, high-affinity interactions—such as affinity-matured IgG responses—correspond to sharply tuned detectors focused on known targets, favoring specificity. In *GenSA*, this continuum corresponds to adjustable decision thresholds that regulate the balance between sensitivity and specificity. Additionally, the concept of degeneracy in immune responses, where multiple receptors or pathways can compensate for each other, justifies the implementation of redundant inference functions operating concurrently, thereby enhancing robustness and fault tolerance.

Beyond NP-like and RDT-like strategies, immune systems rely on a multiplicity of detection regimes distributed across cell types and organizational levels. This multiplicity provides complementary "viewpoints" on the same perturbation, analogous to zooming on distortions at different spatial, molecular, and temporal resolutions. Phagocytes and B-1 cells capture whole objects, antibodies neutralize complex structures, while T cells sample peptide-level representations through MHC-restricted presentation. Such distributed perspectives increase detection coverage while reducing blind spots, without requiring centralized control.

This multiplicity of viewpoints echoes classical cybernetic principles, including Ashby's Law of Requisite Variety, whereby system robustness emerges from diversity of responses rather than from optimization of a single detector. Within the GenSA framework, this organization complements NP-like and RDT-like inference by distributing sensitivity and specificity across scales and contexts, thereby enhancing robustness to noise, interference, and unanticipated distortions.

6.3. Random Distortion: From Generative Variability to Statistical Distance

Building on the inferential architecture introduced in the previous section and synthesized in Figure 7, random distortion should be understood as a generic principle of sensitive living systems, extending beyond detection alone.

In this framework, random distortion refers to a generative source of variability and exploration in living systems, while detection and update functions govern how such distortions are locally evaluated and integrated into the system's ongoing organization.

In living systems, random distortions play a generative and creative role by introducing variability, exploration, and open-endedness into system trajectories. Stochastic processes driving receptor diversification, fluctuating activation thresholds, developmental plasticity, and idiotypic interactions all rely on random distortions to produce novel configurations and to blur rigid boundaries between functional states.

From this perspective, random distortion contributes to the capacity of living systems to explore their space of possibilities under uncertainty, rather than merely to classify inputs. By continuously perturbing internal states, random distortions prevent premature stabilization and enable adaptive reorganization across phylogenetic, developmental, and ecological timescales.

Within the GenSA/GENSA framework, Random Distortion Testing (RDT) represents a formalizable projection of this broader principle, focusing on how deviations between incoming signals and internal reference states can be evaluated under noise and uncertainty. RDT does not exhaust the role of random distortion in living systems but provides a probabilistic framework for modeling how systems assess the significance of perturbations relative to their current organization.

From a biological perspective, this evaluative process is closely related to affinity-based interactions, such as ligand–receptor binding, which operate through graded attraction and repulsion under energetic constraints. These interactions are inherently probabilistic, context-dependent, and history-dependent, motivating a distance-based formalization rather than Boolean matching.

Within GENSA, deviations can be quantified using norm-based distance measures that compare incoming signals to internal reference distributions. Affinity functions express degrees of compatibility, while statistical distances, such as the Mahalanobis distance, evaluate deviations relative to the variance and correlation structure of the reference ensemble. This approach acknowledges that variability itself carries functional meaning in biological systems.

Activation is therefore governed by fuzzy, context-dependent thresholds rather than fixed cutoffs. Weak deviations are absorbed as background fluctuations, strong deviations trigger responses, and intermediate deviations can induce adaptive tuning of internal parameters. In this way, RDT provides a formal counterpart to biological phenomena such as tolerance, graded activation, and affinity maturation, while preserving openness to novelty and generativity.

6.4. GENSA as a Meta-Model for Multiscale Integration

GENSA is not designed to replace existing modeling approaches, but to act as a unifying formal meta-layer for sensitive living systems. Rather than prescribing specific biological implementations, it provides a generic language for representing detection, evaluation, degeneracy, and state reconfiguration across scales.

Within this perspective, diverse modeling approaches—including ordinary differential equations, agent-based models, and graphical state-diagram representations—can be embedded as modules within GENSA, provided that their dynamics can be interpreted probabilistically through state transitions. Integrative hierarchical meta-models, such as

WLIMES and HMES [21], are therefore naturally compatible with the GENSA framework.

By operating at this meta-level, GENSA preserves biological meaning while enabling formal integration of heterogeneous models. It provides a coherent bridge between multiscale biological organization and formal representations, without reducing living dynamics to object-based rules or fixed functional architectures.

6.5 Key features of the GENSA framework

This integration perspective is consistent with previous efforts using graphical state diagrams to bridge immunologists, theoreticians, and programmers [91, 94, 103].

The *GenSA*/GENSA framework combines architectural, functional, and inferential components that together support multiscale modeling of sensitive living systems:

- **Holon-based architecture:** Each holon (mathematically abstracted as a GENSA) is a unit that is both autonomous and cooperative, modeled as a sensor-actuator/sensory-automata with internal memory and adaptive thresholds.
- **Sensors and retroactivity:** A GENSA infers or measures its environment (input events, signals, and noise), integrates changes, and acts on the environment in return—capturing biological feedback.
- **Update and readout functions:** These represent energy (as affinity in ligand-receptor binding) and the emission of signals or effects, impacting the environment or other holons.
- **Memory from memoryless units:** While basic automata is memoryless, memory emerges at the network level, through structured interaction and invariant transformations.
- **Random Distortion Testing: RDT** ensures robustness and adaptivity in signal processing. It models how a GENSA can interpret distorted inputs even among noise or in a different context and still respond meaningfully. It provides a formal tool for evaluating deviations under uncertainty, complementing likelihood-based inference without collapsing system behavior into binary decision rules.
- **Multiscale composition** : Networks of GENSA form holarchies that can themselves be abstracted as higher-level GENSA, enabling scalable modeling from molecular interactions to organisms and ecosystems, including immune networks, organs, receptors, sensors, etc.

Mathematical constructs and biological correspondence:

- **Affinity function:** Measures the “closeness” or compatibility between the input and the reference (memory or expected state).
- **Norm-based affinity:** Affinity can be quantified using vector norms; a smaller norm indicates higher affinity (stronger binding, more likely recognition).
- **Mahalanobis distance:** Used for discriminative signal analysis, measuring deviation from expected signal distribution to distinguish stimuli.
- **Fuzzy threshold:** Activation occurs when affinity exceeds a context-dependent threshold, not a fixed value.
- **Degeneracy:** Multiple structurally distinct states can yield similar functional outputs.

Taken together, these features define a generic formal architecture that remains continuous with the biological organization of sensitive living systems, preparing the integrative perspective developed below.

6.6. GenSA and the Immune System: Two Faces of the Same Framework

Section 6 culminates in the articulation of a single generic framework expressed through two complementary and inseparable faces. On the one hand, the GenSA framework provides a conceptual and biologically grounded description of sensitive living systems as historically constituted sensor–actuator organizations. On the other hand, its formal counterpart expresses this same organization in terms of probabilistic, energy-sensitive state transitions and multiscale propagation of signals. As synthesized in Figure 7, these two descriptions preserve continuity between biological meaning and formal abstraction rather than opposing them.

Within this unified perspective, living systems are understood as continuously evaluating perturbations, regulating their engagement with the environment, and reorganizing their internal states under uncertainty. Crucially, internal reconfiguration implies that memory is not stored as a separate entity, but emerges from the succession of states generated by repeated evaluations. Through this process, locally evaluated distortions progressively shape a global contextual memory and the system’s historicity, which in turn conditions subsequent multiparametric evaluations and adaptive trajectories across scales.

In this framework, the immune system is not approached as a special case but as a paradigmatic instantiation of how sensitive living systems integrate variability, degeneracy, and historical constraints to maintain coherence. More generally, this perspective provides a basis for understanding and potentially simulating the emergence of cognition, tolerance, and identity in complex systems such as immune networks and holobionts, whose present behaviour cannot be dissociated from developmental, ecological, and evolutionary history.

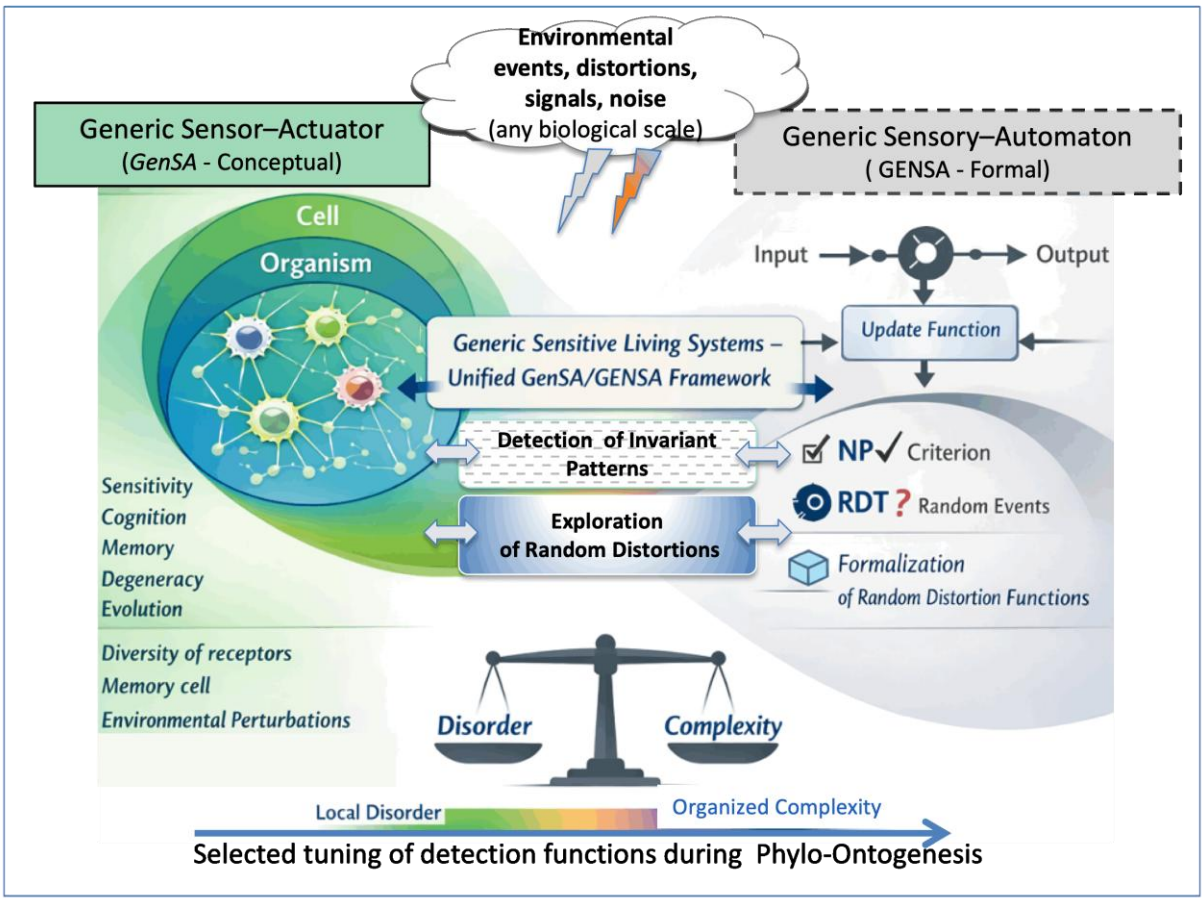

Fig. 7. Unified GenSA/GENSA framework for sensitive living systems. The figure summarizes the two complementary and inseparable faces of a single generic framework. GenSA (left) provides a conceptual description of sensitive living systems as historically constituted sensor–actuator organizations confronted with multiscale environmental perturbations. GENSA (right) presents the corresponding formal description in terms of generic sensory automata, expressing evaluation, state updates, and exploration under uncertainty. Bidirectional arrows emphasize continuity rather than translation between conceptual and formal levels. Across both descriptions, disorder is not eliminated but progressively shaped into organized complexity through phylo-ontogenetic tuning of detection functions.

While the formal component is not yet a fully operational computational tool, its conceptual and mathematical advances define a unifying formal layer capable of integrating and extending existing modeling approaches. By explicitly incorporating historicity, sensitivity, and energy-constrained adaptation, the GenSA framework opens new directions for interdisciplinary modeling efforts bridging biology, systems theory, and artificial intelligence, positioning living systems not merely as adaptive systems, but as historically constituted organizations whose resilience and viability emerge from their trajectories rather than from static structures.

7. Discussion and Interdisciplinary Perspectives

7.1. Innovations of the GenSA Framework

GenSA introduces a set of complementary innovations that operate at epistemological, theoretical, and formal levels.

At an epistemological level, GenSA departs from object-based and rule-driven models by treating living systems as sensitive and historically constituted subjects rather than as passive entities governed by predefined mechanisms [12, 15].

At a theoretical level, GenSA identifies random distortion as a core organizing principle of living systems. Random distortion is not limited to detection but supports the generation of diversity, adaptive tuning, and exploratory dynamics, allowing systems to relate current situations to their own history through non-Boolean, context-dependent evaluation.

At a formal level, these principles are expressed through a probabilistic, energy-sensitive sensory–actuator architecture. State transitions are conditioned

by internal context and prior states, allowing memory and learning to emerge from the succession of state reconfigurations in a network, rather than from explicit storage.

7.2. Integration of Phylo-Ontogenesis with Statistical Inference

GenSA's unification of phylogenetic inheritance (innate biases) with ontogenetic learning (adaptive exploration) is a key innovation. Traditional models seldom merge evolutionary timescales with real-time inference; GenSA does so by design. This holistic integration means our framework inherently accounts for both deeply conserved responses and individual-specific adaptations, fulfilling the multi-temporal complexity that living systems exhibit.

This allows for the modeling of how living systems detect, memorize, and adapt to environmental signals across time and scales, from molecular to ecosystem levels [1, 2]. The explicit modeling of onto-phylogenetic continuity is uncommon in immunology and cognitive science, making GenSA a novel approach for capturing the co-evolution of structure and function.

7.3. Random Distortion Function or Test as a Core process

In the GenSA framework, random distortion is a generic principle of living systems and must not be reduced to detection alone. Living systems continuously generate, propagate, and exploit random distortions as part of their normal functioning, supporting diversity, exploratory dynamics, and adaptive reorganization across scales.

Random Distortion Testing (RDT) represents one formal and operational instantiation of this broader principle, specifically oriented toward decision making under uncertainty. As a probabilistic and non-Boolean statistical test, RDT allows systems to evaluate whether observed variations exceed tolerated fluctuations. This formalization captures situations in which a system must explicitly assess deviation, but it does not exhaust the broader role of random distortion in living organization.

In biological systems, random distortion plays a creative and generative role, for instance through stochastic processes that produce variable region repertoires and diversify affinities, as demonstrated by V(D)J recombination mediated by RAG enzymes following Tonegawa's discovery. Such processes endow immune systems with broad reactivity and degeneracy, enabling exploration of novel configurations before any selective stabilization occurs.

By contrast with Boolean classifiers, RDT accommodates fuzziness, redundancy, and probabilistic inference, reflecting the behavior of biological sensors and immune receptors. This allows GenSA to account for how living systems distinguish meaningful perturbations from background variability, maintain viable dynamics, and adapt to changing environments through internal creativity and network-level reconfiguration [15, 53].

``

7.4. From Feedback Control to Sensitive Regulation

As discussed earlier (Section 2.3), Ashby's cybernetic framework provided an early formalization of regulation through feedback and requisite variety [43]. However, like other models summarized in **Table 1**, such approaches remain limited to control-oriented regulation and do not account for key biological properties, including historical organization, emergent memory, and the detection of novel perturbations.

Living systems—particularly poly-genomic organisms and ecosystems—do not merely stabilize predefined variables, but continuously **detect, interpret, and integrate distortions** arising from internal diversity and environmental coupling. The GenSA framework addresses these limitations by combining **multiple detection principles**, **degenerate and probabilistic recognition** (via a multiplicity of RDT to NP detector evolution and state transitions), and **emergent memory encoded at the network level**, allowing regulation to arise from dynamic interactions rather than fixed set-points.

In this perspective, feedback is not a control logic but a consequence of sensitive organization: tolerance, resilience, and long-term viability emerge from the capacity of living systems to regulate meaningful distortions across scales and time, rather than from equilibrium maintenance alone.

7.5. GenSA as a Meta-Model

GenSA is designed as a meta-framework capable of non-Boolean and non-Bayesian statistical inferences based on structures and function distortions, also able to integrate previous modeling approaches, such as ODEs, agent-based models, and holonic/holarchic frameworks. This enables the unification of diverse modeling strategies under a single, probabilistic, and energy-based formalism. GenSA's architecture supports the integration of multi-scale data and evolutionary processes, providing a platform for interdisciplinary research that bridges biology, systems theory, and artificial intelligence.

7.6. Semiotics, Signification, and Temporal Complexity

Within the GenSA perspective, fluctuating thresholds and blurred boundaries between interacting systems are not treated as modeling limitations but as intrinsic features of living organization. They reflect the fact that living systems continuously interpret perturbations in context, rather than reacting to fixed inputs or crossing rigid decision boundaries.

This reinforces the semiotic dimension of GenSA, according to which signals do not carry meaning intrinsically but acquire significance through their interpretation relative to the system's internal state and history [26, 100]. Meaning therefore depends not only on the presence of a signal, but on when, where, and under which systemic conditions it is encountered.

This interpretative process unfolds across intertwined temporal regimes. Immediate perception and local dynamics operate within Chronos, while context-dependent decision windows correspond to

Kairos. Longer-term persistence of memory, identity, and organizational coherence unfolds within Aion, embedding individual events within enduring system trajectories.

In immune systems, this temporal integration is exemplified by the fact that identical molecular interactions may result in tolerance or inflammation depending on developmental stage, physiological state, prior history, and local contextual cues provided by antigen-presenting cells, including cytokine-mediated signaling. By supporting such multi-temporal interpretation, GenSA provides a framework for modeling how meaning, memory, and adaptive regulation emerge from dynamic interactions rather than from static representations.

7.7. Computational Scalability and Future Directions

While GenSA's mathematical foundation is established, its computational implementation raises significant challenges, particularly for systems exhibiting high degeneracy and dynamically evolving topologies. Future work will focus on the development of scalable algorithms and on the integration of multi-omics data from previous model to enable the simulation of complex biological networks, cell population dynamics in aging processes, and resilience [4, 7, 89, 91].

The mathematical formalization of these principles is developed in detail in the companion paper (Pastor et al., 2026).

7.8. Communication Across Living Systems and Socio-Ecological Implications

A central aspect of immune function in holobiont organisms lies in the mimicry-based and co-evolutionary interplay between immune systems and microbiota, as emphasized by Root-Bernstein and Tauber [104]. Rather than responding to isolated signals, immune systems interpret distributed patterns of signals whose meaning depends on their succession, frequency, and contextual embedding over time.

In holobionts, continuous fluctuations and perturbations generate persistent "live traces" that shape immune and microbial repertoires across the lifespan [105]. These traces are not residual noise but contribute to a historical encoding of interactions, modulating how subsequent signals are perceived and interpreted. Communication thus relies not only on molecular specificity but also on temporal organization, whereby repeated or sustained cues progressively acquire meaning.

At broader ecological and socio-ecological scales, the "One Health" concept highlights that system resilience depends on the capacity to detect distortions, propagate alerts, and coordinate responses across interconnected biological, ecological, and social networks [106]. Such coordination emerges from distributed communication processes rather than centralized control.

Long-term exposure to environmental or social stressors further illustrates the cumulative effect of historical perturbations, from altered gene co-expression networks to reduced immune repertoire diversity and impaired signal transmission [89, 105]. As described in viability theory, maintaining coherence under these conditions requires increasing energetic investment, and system failure can occur when viability thresholds are exceeded [107].

By explicitly integrating contextual, temporal, and energetic dimensions of communication, the GenSA framework provides a basis for modeling how living systems preserve relative stability without exhausting their resources. It offers a unified approach for exploring how disturbances propagate across holarchies, how resilience emerges from distributed interpretation of signals, and how breakdowns may arise under accelerating environmental or societal pressures.

8. Conclusion and Perspectives

This article proposes a reconceptualization of living systems as sensitive, historically constituted organizations and introduces the Generic Sensor–Actuator (GenSA) framework as a unified perspective for modeling their complexity. Using the immune system and the holobiont as paradigmatic instantiations, we show how living systems achieve resilience, coherence, and adaptability through the dynamic balance between disorder and organized complexity.

A central contribution of this work is the identification of sensitivity, degeneracy, and historicity as core organizing principles of living systems. Controlled disorder—expressed through stochastic diversity, random distortion, and variability—is not a limitation but a prerequisite for contextual interpretation, adaptive tuning, and learning [108]. Conversely, organized complexity—supported by network structure, functional redundancy, and multiscale integration—preserves system identity and viability. Resilience emerges from the interplay between these two poles, positioning living systems at the edge between rigidity and chaos.

By combining probabilistic, energy-sensitive inference with historically constrained state reconfiguration, the GenSA/GENSA framework provides a generic way to model how memory, tolerance, cognition, and identity emerge from trajectories rather than from predefined structures. Beyond the NP/RDT duality, the framework formalizes the necessity of multiple concurrent inference functions, reflecting the functional degeneracy observed in biological systems and strengthening robustness and fault tolerance in fluctuating environments [15].

While GenSA is not yet a fully operational computational tool, its formalization as a meta-framework allows the integration of heterogeneous modeling approaches—including ordinary differential equations, agent-based models, and holarchic architectures—without subsuming their specificity. This position enables continuity between biological organization and mathematical abstraction, making the framework applicable beyond immunology to ecology, cognitive science, aging, disease dynamics, and artificial systems.

More broadly, GenSA offers a basis for modeling communication, coordination, and resilience in complex systems across biological, ecological, and socio-ecological scales. By explicitly incorporating context, temporal organization, and energetic constraints, it provides a coherent perspective on how living systems preserve viability while remaining open to adaptation and transformation.

In summary, GenSA represents not a single model but a shift in perspective: from static, object-based descriptions toward historically constituted, sensitive organizations whose dynamics and resilience emerge from their trajectories. This framework opens new directions for interdisciplinary research bridging biology, systems theory, and artificial intelligence, and for the development of future computational implementations grounded in the principles of living organization.

Author contributions

VTV developed the biological and conceptual model
DP developed the mathematical model

Appendix

Glossary

Term / Concept	Academic Definition
Affinity	The strength of molecular binding, such as antigen-antibody interactions, reflecting recognition specificity.
Agent-Based Model (ABM)	A computational modeling approach simulating the behavior and interactions of individual agents.
Aion, Kairos, Chronos	Temporal dimensions: Aion (evolutionary time), Kairos (critical event time), Chronos (developmental time).
Antibody (Immunoglobulin)	A Y-shaped protein that binds specific antigens to neutralize or opsonize them.
Antigen	A molecule recognized as foreign by the immune system, triggering a response.
Attractor States	Stable configurations or patterns in immune networks or dynamical systems.
Auto-organization	The process by which living systems self-organize through internal interactions and feedback.
B Cell	A lymphocyte that produces antibodies and mediates humoral immunity.
Central Immune System (CIS)	The core, self-referential immune network formed during early development, maintaining tolerance and identity.
Chemokines	A subset of cytokines that direct cell migration.
Clonal Selection	The process by which lymphocytes with specific receptors are activated and proliferate.
Complement System	A protein cascade that enhances phagocytosis, inflammation, and cell lysis.
Dendritic Cell	An antigen-presenting cell that bridges innate and adaptive immunity by activating lymphocytes.
Degeneracy	The ability of different components to perform the same function (functional redundancy).
Degenerate Inference Functions	Redundant statistical detectors in GenSA, enhancing fault tolerance and flexibility.
Germline	Genetic elements inherited and conserved across generations, providing baseline immune functions.
Holarchy	A hierarchical organization of holons across multiple levels.
Holobiont	A host organism together with its symbiotic microbiota, considered as a single evolutionary and ecological unit.
Holon	An entity that is both a whole in itself and a part of a larger system; holarchy is a hierarchy of holons.
Homeo-dynamics	The dynamic maintenance of system stability and resilience in biological systems.
Idiotypic Network	A self-referential network of antibodies and receptors regulating immune homeostasis and self-recognition.
Inflammation	A local immune response to infection or injury, marked by redness, heat, swelling, and pain.
Interferons (IFNs)	Cytokines that interfere with viral replication and activate immune cells.
Interleukins (ILs)	Cytokines that mediate communication between leukocytes.
Mahalanobis Distance	A statistical measure of deviation from an expected distribution, used for discriminative signal analysis.
Macrophage	A phagocytic cell that engulfs pathogens and presents antigens to initiate immune responses.
Major Histocompatibility Complex (MHC)	Molecules that present antigens to T cells (MHC I to $CD8^+$, MHC II to $CD4^+$).
Memory Cell	A long-lived lymphocyte that responds rapidly upon re-exposure to antigen.
Memory Imprint / Holographic Memory	Distributed memory encoded in the configuration of immune networks or biological systems.
Natural Killer (NK) Cell	A lymphocyte that destroys virus-infected and tumor cells without prior sensitization.
Neutrophil	A first-responder phagocyte that eliminates pathogens via degranulation and formation of NETs.
Neyman–Pearson (NP) criterion	A statistical decision strategy maximizing sensitivity for detecting a known pattern, while controlling the false-positive rate.

Term / Concept	Academic Definition
Noise	Random fluctuations or variability in biological systems, contributing to stochasticity and adaptation.
Omics	High-throughput biological data domains, such as genomics, proteomics, transcriptomics, etc.
One Health	An integrated approach to health considering interactions between humans, animals, and ecosystems.
Ordinary Differential Equations (ODEs)	Mathematical equations describing the continuous change of system variables over time.
Pattern Recognition Receptors (PRRs)	Receptors (e.g., TLRs) that detect pathogen-associated molecular patterns (PAMPs).
Peripheral Immune System (PIS)	The immune system components that interact with external antigens and environmental cues.
Phylo-ontogenesis	The integration of evolutionary (phylogenetic) and developmental (ontogenetic) processes in living systems.
Random Distortion Function	A mathematical function in GenSA for detecting significant changes or perturbations in system states.
Random Distortion Testing (RDT)	A statistical anomaly-detection strategy prioritizing specificity, triggering a response only for significant deviations.
Regulatory T Cell (Treg)	A subset of T cells that suppress immune responses to maintain self-tolerance.
Sensitivity/Specificity	Sensitivity: ability to detect true signals; specificity: ability to ignore noise or self.
Somatic diversification	The process generating diversity in immune receptors (e.g., V(D)J recombination), as opposed to germline invariance.
T Cell	A lymphocyte mediating cellular immunity, including cytotoxic ($CD8^+$) and helper ($CD4^+$) subsets.
Viability Theory / Kernel of Viability	Theoretical framework describing a system's capacity to remain viable under constraints.
Variable Region Molecules (VRM)	Immune receptors (such as antibodies and T-cell receptors) whose variable regions are generated through somatic recombination, enabling recognition of a vast diversity of antigens.

The GENeric Sensory-Automaton (GENSA) Model: A Digestible Overview for Biologists and Philosophers

Why GENSA? Context and Key References

The **GENSA (GENeric Sensory-Automaton)** model was developed to address the limitations of classical mathematical models (such as ODEs and agent-based models) in capturing the adaptive, event-driven, and decision-making nature of complex biological systems, especially the immune system [5, 12, 15]. GENSA formalizes the capacity of living systems to detect, interpret, and respond to environmental changes, integrating memory of the current state and probabilistic decision-making (NP/RDT) [15].
For mathematical details, see the companion paper:
Pastor, D., Fernandez, J., Thomas-Vaslin, V. The Generic Sensory Automaton (GENSA) for modeling affinity-based dynamics and interactions in biology

A.1. Motivation and Context – In the main text, we introduced the notion of modeling sensitive living systems as ***Generic Sensor-Actuator (GenSA)*** and the formalization through the **GENeric Sensory-Automaton** (GENSA). This is illustrated in the schematic

This Appendix provides a concise, accessible overview of the **GENSA** mathematical formalism for readers with a biological background. The goal is to bridge the gap between biological concepts (as discussed in the paper) and their implementation in a mathematical/computational model that can be used for simulations and data-fitting. We describe the structure of the GENSA (automaton), the role of statistical inference criteria (NP and RDT), and how multiple such automata can be organized in a **holarchy** to model complex systems. No advanced mathematical knowledge is required; we emphasize concepts and operational principles with minimal formal notation.
A.2. The GENSA simulate a Sensitive Holon – At its core, such automaton represents an **elementary holon** (an autonomous component of a living system) as a simple discrete dynamical system with inputs and outputs. In practical terms, one can think of a **GENSA** as a **state machine** (like a UML state diagram [94, 103], with the following components:

- **States:** The internal condition of the holon. For example, a cell might have states like "quiescent" vs "active," or an immune cell might be in "naive," "activated," or "memory" state. States can be binary or multi-valued.
- **Inputs (Signals):** External or internal stimuli that the holon perceives. These correspond to the **events or cues** in the environment of the holon. For an immune cell, inputs could be the presence of a particular antigen or cytokine; for a holobiont, inputs could be signals from the microbiota or stress signals from the environment. Each input can have an associated intensity or "energy." In GenSA, we treat input intensity abstractly as a quantitative value – this could be a concentration, binding affinity, or any measure of signal strength.
- **Sensor Function (Update Criterion):** This is a key feature of GENSA. Upon receiving an input, the automaton uses a **detection rule** to decide whether and how to change its state. We formalize this rule using statistical criteria that balance sensitivity and specificity. Two primary families of update functions are used:
  - *Neyman–Pearson (NP) update function:* optimized to maximize the chance of detecting a specific expected signal (high sensitivity) at a controlled false alarm rate. It's as if the automaton has a preset "template" for a known signal and will switch state if that signal is present, even faintly, while trying not to react to noise. NP criteria are analogous to a very alert guard dog – quick to signal if the known cue appears, but it might be tricked by something similar if not carefully tuned. Formally, NP corresponds to a threshold on likelihood ratios: the automaton changes state if the input's "match" to an expected pattern exceeds a threshold, without directly accounting for all possible unusual inputs.
  - *Random Distortion Testing (RDT) update function:* designed to guarantee a high specificity by only responding to inputs that deviate significantly from the norm (i.e., large "distortions"). This is like an anomaly detector with a high threshold – the automaton mostly ignores common fluctuations and noise, and only when an input is extreme or very surprising does it trigger a state change. In practice, an RDT criterion might look at the input intensity (or a statistical distance of the input from what's usual) and only update the state if that intensity is beyond a certain high quantile. It's analogous to how a lymphocyte requires a strong activation signal (antigen + co-stimulation) to initiate a response, thereby avoiding activation by minor random stimuli.
-

- **State Transition:** If the sensor function's condition is met (e.g., NP detects its target or RDT flags an anomaly), the automaton transitions to a new state. For instance, a quiescent cell might enter an "active" state. If no criterion is met, the automaton may remain in its current state. Importantly, GenSA allows for **multiple criteria to be checked simultaneously** (see *Degenerate Detection* below); the first criterion that meets its condition can trigger the transition, or potentially transitions could be multi-step. The model is flexible: we can configure an automaton to require one or several concurrent signals to change state, much like some biological cells need multiple triggers.
- **Outputs (Actuator Function):** After a state transition (or when in a certain state), the automaton produces an output or action. In a biological sense, this could be the secretion of a molecule, a change in gene expression, or any action that affects other holons. In the model, we define a **readout function** that generates an output signal based on the automaton's new state. For example, if the automaton enters an "active" state, it might output a signal (like "emit cytokine X") which becomes an input to neighboring automata in the network. This is how communication is represented: one holon's state change leads to signals that other holons can detect.

In summary, a GenSA automaton can be specified by a set (States, Inputs, Update Functions, Outputs). It is **memoryless** in the basic formulation (the next state depends only on the current state and current input, not on past history, akin to a Markov process). However, memory effects can be built in by expanding the state space (e.g., having a "memory" state) or by networks of automata (see below). Biologists can visualize this as a flowchart: *sense signal -> update internal state -> produce output*.

A.3. Degenerate Detection and Multiple Criteria – A single automaton can incorporate more than one detection criterion to mirror the biological degeneracy of sensing. In practice, this means we allow **multiple sensor/update functions in parallel** within one holon model. For example, an immune cell might have:

- An NP-type detector tuned to a known pathogen-associated molecular pattern (as LPS receptor expressed by B cells), **and**
- An RDT-type detector looking for any unusually strong signal, (as Ig on B cell membrane).

The automaton would then evaluate both when an input arrives. If either criterion is satisfied, it may change state (or potentially a combination of criteria could be required, depending on model configuration). By having redundant detectors, the model mimics the immune system's overlapping safeguards: even if one sensor fails (or one pathway is fooled by a pathogen's evasion), another can catch the signal. From a modeling perspective, this increases the **reliability** of the automaton's behavior in noisy environments, at the cost of a bit more complexity. The 2022 work by Pastor et al. demonstrated theoretically that using a *multiplicity of statistical models* (multiple NP and RDT-like functions with different parameter settings) can recreate the kind of fault-tolerant performance we observe in systems like immunity.

For modelers: this degeneracy means you might implement an automaton with several transition rules. Note we previously implemented parallel state diagram transition for agents involved in various tasks [91, 94, 109] as thymocytes during their thymic education. In UML state diagrams, for instance, a single state could have multiple outgoing transitions each labeled with different guard conditions (one for NP, one for RDT, etc.) leading to the same next state. Each guard represents one detection criterion. The system will proceed along whichever transition's condition is met first. If multiple trigger at once, the model refinement might give one priority or consider simultaneous outcomes (depending on how you want to simulate it).

A.4. Energy Sensitivity and Affinity Thresholds – GENSA is described as an "energy-sensitive" model. In practical terms, the "energy" of an input can be thought of as how strongly that input can push the automaton to change state. In immunology, this maps to **affinity** or avidity of interactions – e.g., how tightly an antigen binds to a receptor, or how many receptors are engaged. NP and RDT criteria both involve thresholds that can be related to energy:

- The NP threshold might be set to detect relatively low-energy signals if they match the expected pattern (analogous to detecting a weak but specific binding).
- The RDT threshold is generally high-energy: only an input that crosses a high energy or "surprise" threshold causes a reaction (analogous to requiring a high-avidity binding or a strong signal with co-factors).

By tuning these thresholds, we can model different sensitivity settings. For instance, a tolerant state might correspond to raising the RDT threshold (requiring an even stronger disturbance to react), whereas an alerted state might temporarily lower thresholds (making the holon more reactive). Advanced implementations of GENSA could allow thresholds to adjust dynamically, emulating phenomena like priming or activation-induced

sensitivity changes.

A.5. Networks of Holons and Holarchies – A single GENSA (automaton) represents one holon (e.g., a cell). To model complex systems, we connect many automata into a **network**. Outputs from one become inputs to others, creating feedback loops and feed-forward pathways. This network-of-automata approach lets us simulate, for example, an immune network or a host-microbiome ecosystem. The structure can be organized in layers (a *holarchy*): for example, molecules as automata at the lowest level, cells at the next, organs or host as another, and ecosystem as another. Each level's components communicate within and across levels. Because each automaton follows the same basic rules (sense–update–act), this approach naturally embodies the *fractal-like, self-similar communication processes* discussed in the paper. A lower-level automaton (molecule) might output a signal that changes a cell's state; a cell's output might influence the whole organism's state, etc. In simulations, one could instantiate thousands of GENSA units to represent, say, a repertoire of lymphocytes, and observe emergent properties like network tolerance or synchronized activation waves.

A.6. Implementing and Fitting the Model – For those interested in using GENSA in practice: one can implement these automata in various computational frameworks. UML statecharts can be a starting point for design, laying out states and transitions clearly. Implementations could then be done in agent-based modeling environments or even custom code (Python, NetLogo, C++ simulations, etc.). The parameters to fit from experimental data would include:

- Transition thresholds (how sensitive each criterion is, analogous to binding affinity distributions or signaling thresholds measured experimentally).
- The number and types of detectors each automaton has (e.g., does a particular cell type use an NP-only rule or both NP and RDT?).
- Initial states and connectivity (how many automata, in what initial state, and how they are wired together – which could be informed by known biology, such as network motifs in immunology).

By adjusting these parameters, one can simulate scenarios and compare outcomes to real data (e.g., cell proliferation, kinetics of an immune response, or stability of a lymphocyte repertoire). The **companion paper by Pastor et al. (2026)** provides the detailed mathematical formulation of the GENSA update functions and examples of how multiple criteria improve detection performance. Biologists can refer to that work for the theoretical proofs and to this overview for practical intuition. As a next step, we plan to publish example model implementations (in UML and code) to serve as templates for researchers aiming to apply GENSA to their specific system.

Comparison with Classical Models

Aspect	*Classical ODE Models*	*GENSA (Sensor Automaton)*
Representation	Continuous, global variables	Discrete states, agents with memory
Time Treatment	Continuous	Discrete, perception-action cycles
Nonlinearity	Complex to model	Intrinsic via thresholds and decisions
Rare Events	Difficult to integrate	Naturally included (noise, thresholds)
Biological Link	Population-level, less intuitive	Cell/holon-level, matches biological logic

The Sensor-Actuator Cycle of the GENSA Holon

Unlike a simple regulator, each holon (cell, organ, organism) in GENSA:

- **Observes** its environment (signals, noise, context)
- **Compares** the perceived state to its internal memory
- **Decides** (via an activation function) if a change is significant
- **Updates** its state and transmits a response (action, signal, memory).

Summary Table: GENSA Components and Biological Analogues

GENSA Element	*Mathematical Definition*	*Biological Analogy (e.g., lymphocyte)*
Internal State (S)	State vector	Activation, differentiation, memory
External State (Sext)	Input vector	Antigen/cytokine levels, microenvironment
Observation (Xobs)	Sext + internal noise	Signal perceived (antigen seen by TCR, noise)
Dissimilarity (δ)	Distance S vs Xobs	Surprise, deviation from expected context
Activation (act)	Threshold function on δ	Response decision (probability, intensity)
Update (fupdt)	S_{t+1} = f(S, Xobs, act)	State change (activation, proliferation)
Output (frdout)	Output function	Observable action (cytokine, killing, etc.)

NP-GENSA / RDT-GENSA Complementarity

- **NP-GENSA:** Optimized for detecting a specific pattern (innate, invariant receptors, low noise, with high specificity) [15].
- **RDT-GENSA:** Robust detection of any significant change (adaptive, diversity, high noise, high sensitivity) [15].
- **Complementarity:** These strategies coexist in immunity (innate/adaptive), ensuring robustness and resilience [12].

A.7 Critical Perspective and Accessibility

The companion mathematics paper provides rigorous proofs and formal definitions, but its technical density may challenge non-mathematicians. For biologists and philosophers, the key is to focus on the **intuitive cycle**: sensing, evaluating, deciding, and acting, with explicit thresholds and noise. GENSA is flexible and can be adapted to various biological systems, from immune cells to ecological populations.

Summary Table: GenSA's Innovations and Future Prospects

Dimension	*GenSA Innovation*	*Future Direction*
System Identity	Subject-centered, memory-based holons	Integration with omics and AI
Adaptation	Probabilistic, context-sensitive inference	Scalable computational models
Memory and Cognition	Emergent from network dynamics and RDT	Modeling aging, disease, resilience
Integration	Meta-framework for multi-scale modeling	Unified platform for interdisciplinary research
Semiotics & Temporality	Contextual meaning, multi-temporal modeling	Application to cognition and communication

In all these cases, GENSA's advantage is that it can incorporate the **wealth of multi-scale data** accumulated over decades. The rules (NP, RDT thresholds, state transition probabilities) can be calibrated with experimental data: for example, flow cytometry or sequencing data can set the initial state distributions and detector frequencies, and longitudinal patient data can validate the model's predictive accuracy. By refactoring earlier models under GENSA, we gain a unified platform where **heterogeneous data (molecular, cellular, clinical)** feed into the same formal structure. This opens the door to simulations that are both biologically faithful and predictive. In summary, GENSA automata provide a mathematically grounded yet flexible way to model immune dynamics, improving upon previous models by combining their strengths (clear state logic, population fitting, network feedback) and addressing their gaps (lack of stochasticity, difficulty integrating diverse data). The result is a framework capable of capturing how an immune system – as a sensitive, adaptive ensemble – maintains stability while responding to the unpredictable challenges of its environment.

References

1. R. E. Ulanowicz, A third window-natural life beyond Newton and Darwin (2009),
2. S. A. Kauffman, A. Roli, A third transition in science? Interface Focus **13** (2023).https://doi.org/10.1098/rsfs.2022.0063
3. E. Morin, complex thinking for a complex world about reductionism, disjunction and systemism. systems journal **2** (2014),
4. V. Thomas-Vaslin, H. K. Altes, R. J. de Boer, D. Klatzmann, Comprehensive assessment and mathematical modeling of T cell population dynamics and homeostasis. J Immunol **180** (2008).https://doi.org/10.4049/jimmunol.180.4.2240
5. V. Thomas-Vaslin, A. Six, B. Bellier, D. Klatzmann, "Lymphocyte Dynamics and Repertoires, Biological Methods" in Encyclopedia of Systems Biology, W. Dubitzky, O. Wolkenhauer, K.-H. Cho, H. Yokota, Eds. (Springer New York, 2013), 10.1007/978-1-4419-9863-7_95 chap. Chapter 95.https://doi.org/10.1007/978-1-4419-9863-7_95
6. V. Thomas-Vaslin, A. Six, B. Bellier, D. Klatzmann, "Lymphocyte Dynamics and Repertoires, Modeling" in Encyclopedia of Systems Biology, W. Dubitzky, O. Wolkenhauer, K.-H. Cho, H. Yokota, Eds. (Springer New York, New York, NY, 2013), 10.1007/978-1-4419-9863-7_96 chap. Chapter 96.https://doi.org/10.1007/978-1-4419-9863-7_96
7. J. Vibert, V. Thomas-Vaslin, Modelling T cell proliferation: Dynamics heterogeneity depending on cell differentiation, age, and genetic background. PLoS Comput Biol **13** (2017).https://doi.org/10.1371/journal.pcbi.1005417
8. C. Lavelle et al., From molecules to organisms: towards multiscale integrated models of biological systems. Theoretical Biology Insights **1** (2008), http://www.la-press.com/from-molecules-to-organisms-towards-multiscale-integrated-models-of-bi-article-a1056
9. V. Thomas-Vaslin, "Understanding and Modeling the Complexity of the Immune System" in First Complex Systems Digital Campus World E-Conference 2015, P. Bourgine, P. Collet, P. Parrend, Eds. (Springer International Publishing, Cham, 2017), 10.1007/978-3-319-45901-1_29 chap. Chapter 29.https://doi.org/10.1007/978-3-319-45901-1_29

10. B. Bellier, V. Thomas-Vaslin, M. F. Saron, D. Klatzmann, Turning immunological memory into amnesia by depletion of dividing T cells. Proc Natl Acad Sci U S A **100** (2003).https://doi.org/10.1073/pnas.1936194100
11. V. Thomas-Vaslin, "Multi-scale complexity of the immune system : Evolution, from chaos to fractals" in Le vivant critique et chaotique, A. S. Nicolas Glade, Ed. (2015), https://hal.archives-ouvertes.fr/hal-01298282
12. V. Thomas-Vaslin, Individuation and the Organization in Complex Living Ecosystem: Recursive Integration and Self-assertion by Holon-Lymphocytes. Acta Biotheor **68** (2020).https://doi.org/10.1007/s10441-019-09364-w
13. D. Pastor, Q.-T. Nguyen, Random Distortion Testing and Optimality of Thresholding Tests. IEEE Transactions on Signal processing **61** (2013),
14. D. Pastor, F. X. Socheleau, Random distortion testing with linear measurements. Signal processing **145** (2018),
15. D. Pastor, E. Beurier, V. Thomas-Vaslin, A multiplicity of statistical models for modeling the degeneracy of living communicating holons. EPJ Web of Conferences **263** (2022).https://doi.org/10.1051/epjconf/202226301006
16. L. D. Pasquier, Germline and somatic diversification of immune recognition elements in Metazoa. Immunol Lett **104** (2006).https://doi.org/10.1016/j.imlet.2005.11.022
17. V. Muller, R. J. de Boer, S. Bonhoeffer, E. Szathmary, An evolutionary perspective on the systems of adaptive immunity. Biol Rev Camb Philos Soc **93** (2018).https://doi.org/10.1111/brv.12355
18. Y. Zhang et al., Transposon molecular domestication and the evolution of the RAG recombinase. Nature **569** (2019).https://doi.org/10.1038/s41586-019-1093-7
19. R. E. Nisbett, T. Masuda, Culture and point of view. Proc Natl Acad Sci U S A **100** (2003).https://doi.org/10.1073/pnas.1934527100
20. M. E. Varnum, I. Grossmann, S. Kitayama, R. E. Nisbett, The Origin of Cultural Differences in Cognition: Evidence for the Social Orientation Hypothesis. Curr Dir Psychol Sci **19** (2010).https://doi.org/10.1177/0963721409359301
21. P. L. Simeonov, A. C. Ehresmann, Some resonances between Eastern thought and Integral Biomathics in the framework of the WLIMES formalism for modeling living systems. Progress in biophysics and molecular biology **131** (2017).https://doi.org/10.1016/j.pbiomolbio.2017.05.014
22. M. F. Burnet, A modification of Jerne's theory of antibody production using the concept of clonal selection. Aust. J. Sci. **20** (1957),
23. N. K. Jerne, "What precedes clonal selection ?" in Ciba Foundation Symposium 5 : Ontogeny of acquired immunity, R. Porter, J. Knight, Eds. (Elsevier, Amsterdam, 1972), 10.1002/9780470719886.https://doi.org/10.1002/9780470719886
24. N. K. Jerne, Towards a network theory of the immune system. Ann Immunol (Paris) **125C** (1974), https://www.ncbi.nlm.nih.gov/pubmed/4142565
25. N. K. Jerne, Idiotypic networks and other preconceived ideas. Immunol Rev **79** (1984).https://doi.org/10.1111/j.1600-065x.1984.tb00484.x
26. N. K. Jerne, The generative grammar of the immune system. Science **229** (1985),
27. I. Lundkvist, A. Coutinho, F. Varela, D. Holmberg, Evidence for a functional idiotypic network among natural antibodies in normal mice. Proc Natl Acad Sci U S A **86** (1989).https://doi.org/10.1073/pnas.86.13.5074
28. N. Vaz, The Specificity of Immunologic Observations. Constructivist Foundations **6** (2011),
29. J. Stewart, The primordial VRM system and the evolution of vertebrate immunity (R.G.Landes, Georgetown, Texas, 1994),
30. J. Carneiro, A. Coutinho, J. Faro, J. Stewart, A model of the immune network with B-T cell co-operation. I--Prototypical structures and dynamics. J Theor Biol **182** (1996).https://doi.org/10.1006/jtbi.1996.0192
31. J. E. Stewart, The direction of evolution: the rise of cooperative organization. Biosystems **123** (2014).https://doi.org/10.1016/j.biosystems.2014.05.006
32. A. Coutinho, The Le Douarin phenomenon: a shift in the paradigm of developmental self-tolerance. Int J Dev Biol **49** (2005).https://doi.org/10.1387/ijdb.041965ac
33. V. Thomas-Vaslin, A. A. Freitas, Lymphocyte population kinetics during the development of the immune system. B cell persistence and life-span can be determined by the host environment. International immunology **1** (1989), https://doi.org/10.1093/intimm/1.3.237
34. V. Thomas-Vaslin, A. A. Feitas, Population kinetics of peritoneal LPS-reactive B lymphocytes. Int Immunol **2** (1990).https://doi.org/10.1093/intimm/2.1.73
35. V. Thomas-Vaslin, L. Andrade, A. Freitas, A. Coutinho, Clonal persistence of B lymphocytes in normal mice is determined by variable region-dependent selection. Eur J Immunol **21** (1991),
36. V. Thomas-Vaslin, A. Coutinho, F. Huetz, Origin of CD5+ B cells and natural IgM-secreting cells: reconstitution potential of adult bone marrow, spleen and peritoneal cells. Eur J Immunol **22** (1992).https://doi.org/10.1002/eji.1830220520
37. N. Le Douarin et al., Evidence for a Thymus-Dependent Form of Tolerance that is Not Based on Elimination or Anergy of Reactive T cells. Immunological reviews **149** (1996),
38. V. Thomas-Vaslin, A complex immunological idiotypic network for maintenance of tolerance. Front Immunol **5** (2014).https://doi.org/10.3389/fimmu.2014.00369
39. F. G. Varela, H. R. Maturana, R. Uribe, Autopoiesis: the organization of living systems, its characterization and a model. Currents in modern biology **5** (1974).https://doi.org/10.1016/0303-2647(74)90031-8
40. F. Capra, The Hidden Connections (HarperCollins, London, 2002),
41. F. E. Yates, Order and complexity in dynamical systems: Homeodynamics as a generalized mechanics for biology. Mathematical and Computer Modelling **19** (1994).https://doi.org/10.1016/0895-7177(94)90189-9
42. H. R. Maturana, What is it to see? Arch Biol Med Exp **16** (1983), https://www.ncbi.nlm.nih.gov/pubmed/6680992
43. W. R. Ashby, An Introduction to Cybernetics (Chapman & Hall, London, 1956),
44. J. Stewart, A. Coutinho, The affirmation of self: a new perspective on the immune system. Artif Life **10** (2004).https://doi.org/10.1162/1064546041255593
45. E. Schrödinger, What is life? (Cambridge University press, 1944),
46. K. Friston, The free-energy principle: a unified brain theory? Nat Rev Neurosci **11** (2010).https://doi.org/10.1038/nrn2787
47. R. Noble, N. D., <23 Noble physiology evolutionary biology.pdf>. Biological Journal of the Linnean Society **139** (2022),

48. P. Lyon, The cognitive cell: bacterial behavior reconsidered. Front Microbiol **6** (2015).https://doi.org/10.3389/fmicb.2015.00264
49. K. J. Friston, W. Wiese, J. A. Hobson, Sentience and the Origins of Consciousness: From Cartesian Duality to Markovian Monism. Entropy (Basel) **22** (2020).https://doi.org/10.3390/e22050516
50. F. Baluska, A. S. Reber, W. B. Miller, Jr., Cellular sentience as the primary source of biological order and evolution. Biosystems **218** (2022).https://doi.org/10.1016/j.biosystems.2022.104694
51. A. S. Reber, F. Baluska, Cognition in some surprising places. Biochem Biophys Res Commun **564** (2021).https://doi.org/10.1016/j.bbrc.2020.08.115
52. F. Baluska, W. B. Miller, P. Slijepcevic, A. S. Reber, Sensing, feeling and sentience in unicellular organisms and living cells. Biosystems **247** (2025).https://doi.org/10.1016/j.biosystems.2024.105374
53. G. M. Edelman, J. A. Gally, Degeneracy and complexity in biological systems. Proc Natl Acad Sci U S A **98** (2001).https://doi.org/10.1073/pnas.231499798
54. A. Freitas et al., B cell activities in normal unmanipulated mice. Contrib Microbiol Immunol **11** (1989), https://www.ncbi.nlm.nih.gov/pubmed/2684508
55. A. Coutinho, Germ-line selection ensures embryonic autoreactivity and a positive discrimination of self mediated by supraclonal mechanisms. Semin Immunol **12** (2000).https://doi.org/10.1006/smim.2000.0233
56. R. Schulz, B. Werner, U. Behn, Self-tolerance in a minimal model of the idiotypic network. Front Immunol **5** (2014).https://doi.org/10.3389/fimmu.2014.00086
57. S. Tonegawa, Somatic generation of antibody diversity. Nature **302** (1983).https://doi.org/10.1038/302575a0
58. A. Casrouge et al., Size estimate of the alpha beta TCR repertoire of naive mouse splenocytes. J Immunol **164** (2000).https://doi.org/10.4049/jimmunol.164.11.5782
59. T. Mora, A. M. Walczak, Quantifying lymphocyte receptor diversity. 10.1101/046870(2016).https://doi.org/10.1101/046870
60. D. Mason, A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol Today **19** (1998).https://doi.org/10.1016/s0167-5699(98)01299-7
61. H. Lemke, A. Coutinho, H. Lange, Lamarckian inheritance by somatically acquired maternal IgG phenotypes. Trends Immunol **25** (2004).https://doi.org/10.1016/j.it.2004.02.007
62. Q. Leng, Z. Bentwich, Beyond self and nonself: fuzzy recognition of the immune system. Scand J Immunol **56** (2002).https://doi.org/10.1046/j.1365-3083.2002.01105.x
63. S. Kauffman, The Origins of Order: Self Organization and Selection in Evolution (Oxford University Press, N.Y., 1993),
64. I. Prigogine, Life and physics. New perspectives. Cell biophysics **9** (1986).https://doi.org/10.1007/BF02797383
65. A. C. Ehresmann, J. Gomez-Ramirez, Conciliating neuroscience and phenomenology via category theory. Progress in biophysics and molecular biology **119** (2015).https://doi.org/10.1016/j.pbiomolbio.2015.07.004
66. R. Rosen, On the dynamical realization of (M,R)-systems. Bull Math Biol **35** (1973).https://doi.org/10.1007/BF02558788
67. L. Andrade et al., Biased VH gene expression in murine CD5 B cells results from age-dependent cellular selection. Eur J Immunol **21** (1991).https://doi.org/10.1002/eji.1830210908
68. N. Baumgarth, The double life of a B-1 cell: self-reactivity selects for protective effector functions. Nat Rev Immunol **11** (2011).https://doi.org/10.1038/nri2901
69. E. Montecino-Rodriguez, K. Dorshkind, B-1 B cell development in the fetus and adult. Immunity **36** (2012).https://doi.org/10.1016/j.immuni.2011.11.017
70. A. M. Vale, C. B. Cavazzoni, A. Nobrega, H. W. Schroeder, Jr., The Global Self-Reactivity Profile of the Natural Antibody Repertoire Is Largely Independent of Germline DH Sequence. Front Immunol **7** (2016).https://doi.org/10.3389/fimmu.2016.00296
71. F. L. Smith et al., B-1 plasma cells require non-cognate CD4 T cell help to generate a unique repertoire of natural IgM. J Exp Med **220** (2023).https://doi.org/10.1084/jem.20220195
72. M. S. Mattos, S. Vandendriessche, A. Waisman, P. E. Marques, The immunology of B-1 cells: from development to aging. Immun Ageing **21** (2024).https://doi.org/10.1186/s12979-024-00455-y
73. F. Rossi, G. Dietrich, M. D. Kazatchkine, Anti-idiotypes against autoantibodies in normal immunoglobulins : evidence for network regulation of human autoimmune response. Immunol. Rev. **110** (1989),
74. A. Coutinho, Will the idiotypic network help to solve natural tolerance? Trends Immunol **24** (2003).https://doi.org/10.1016/s1471-4906(02)00035-2
75. V. Thomas-Vaslin, J. Salaun, M. Coltey, P. Vaigot, R. Fucs, Kinetics and repertoire selection of T cells derived from the early waves of fetal thymus colonization after thymus grafting in allogeneic nude recipients. Scand J Immunol **45** (1997).https://doi.org/10.1046/j.1365-3083.1997.d01-424.x
76. Y. Modigliani et al., Regulatory T cells in thymic epithelium-induced tolerance. I. Suppression of mature peripheral non-tolerant T cells. Eur J Immunol **25** (1995).https://doi.org/10.1002/eji.1830250924
77. Y. Modigliani et al., Lymphocytes selected in allogeneic thymic epithelium mediate dominant tolerance toward tissue grafts of the thymic epithelium haplotype. Proc Natl Acad Sci U S A **92** (1995).https://doi.org/10.1073/pnas.92.16.7555
78. Y. Modigliani et al., Establishment of tissue-specific tolerance is driven by regulatory T cells selected by thymic epithelium. European Journal of Immunology **26** (1996),
79. V. Thomas-Vaslin et al., Abnormal T cell selection on nod thymic epithelium is sufficient to induce autoimmune manifestations in C57BL/6 athymic nude mice. Proc Natl Acad Sci U S A **94** (1997),
80. J. Stewart, J. Carneiro, "The Central and the Peripheral Immune Systems: What is the Relationship" in Artificial Immune Systems and Their Applications, D. Dasgupta, Ed. (Springer Berlin Heidelberg, Berlin, Heidelberg, 1999), 10.1007/978-3-642-59901-9_3 chap. Chapter 3.https://doi.org/10.1007/978-3-642-59901-9_3
81. V. Thomas-Vaslin, M. Coltey, J. Salaun, On the mechanisms of thymic epithelium induced tolerance. C R Acad Sci III **319** (1996), https://www.ncbi.nlm.nih.gov/pubmed/8763739
82. V. Thomas-Vaslin et al., Prolonged allograft survival through conditional and specific ablation of alloreactive T cells expressing a suicide gene [see comments]. Transplantation **69** (2000),

83. E. Braunberger et al., T-Cell suicide gene therapy for organ transplantation: induction of long-lasting tolerance to allogeneic heart without generalized immunosuppression. Mol Ther **2** (2000),
84. S. Giraud et al., Transient depletion of dividing T lymphocytes in mice induces the emergence of regulatory T cells and dominant tolerance to islet allografts. Am J Transplant **8** (2008).https://doi.org/10.1111/j.1600-6143.2008.02195.x
85. G. Weisbuch, R. J. De Boer, A. S. Perelson, Localized memories in idiotypic networks. J Theor Biol **146** (1990).https://doi.org/10.1016/s0022-5193(05)80374-1
86. H. Bersini, "Revisiting idiotypic immune networks" in Advances in Artificial Life. (Springer, 2003),
87. F. Varela, A. Coutinho, B. Dupire, N. Vaz, "Cognitive networks: immune, neural and otherwise" in In Theoretical Immunology, A. S. Perelson, Ed. (Addison-Wesley Publ. Co., Inc., Redwood City, 1988),
88. G. Parisi, A simple model for the immune network. Proc Natl Acad Sci U S A **87** (1990).https://doi.org/10.1073/pnas.87.1.429
89. M. L. Mair, N. Tchitchek, T. M. Witten, V. Thomas-Vaslin, Network topology and evolution of the gene co-expression of T-cells during immuno-senescence. BioRxiv https://doi.org/10.1101/2021.09.01.458500 (2021).https://doi.org/https://doi.org/10.1101/2021.09.01.458500
90. V. Thomas-Vaslin et al., "Immunodepression & Immunosuppression during aging" in Immunosuppression, M. B. Portela, Ed. (InTech open acces publisher, Brazil, 2012), http://www.intechopen.com/books/immunosuppression-role-in-health-and-diseases/immunodepression-immunosuppression-during-aging-
91. V. Thomas-Vaslin, A. Six, J. G. Ganascia, H. Bersini, Dynamical and Mechanistic Reconstructive Approaches of T Lymphocyte Dynamics: Using Visual Modeling Languages to Bridge the Gap between Immunologists, Theoreticians, and Programmers. Front Immunol **4** (2013).https://doi.org/10.3389/fimmu.2013.00300
92. A. S. Perelson, G. Weisbuch, Immunology for physicists. Rev. Mod. Phys. **69** (1997),
93. S. Efroni, D. Harel, I. R. Cohen, Emergent Dynamics of Thymocyte Development and Lineage Determination. PLoS Computational Biology **preprint** (2005).https://doi.org/10.1371/journal.pcbi.0030013.eor
94. H. Bersini, D. Klatzmann, A. Six, V. Thomas-Vaslin, State-transition diagrams for biologists. PLoS One **7** (2012).https://doi.org/10.1371/journal.pone.0041165
95. R. E. Ulanowicz, Socio-Ecological Networks: A Lens That Focuses Beyond Physics. Frontiers in Ecology and Evolution **9** (2021).https://doi.org/10.3389/fevo.2021.643122
96. P. Kourilsky, The natural defense system and the normative self model. F1000Res **5** (2016).https://doi.org/10.12688/f1000research.8518.1
97. I. R. Cohen, A. Marron, Evolution is driven by natural autoencoding: reframing species, interaction codes, cooperation and sexual reproduction. Proc Biol Sci **290** (2023).https://doi.org/10.1098/rspb.2022.2409
98. R. Root-Bernstein, A General Theory of Autoimmune Disease Causation: Integrating Innate and Adaptive Immunity, Altered Antigen Processing, Sex and Genetic Predispositions, and Microbiome Effects . Preprints.org DOI: 10.20944/preprints201906.0028.v1. (2019).https://doi.org/ DOI: 10.20944/preprints201906.0028.v1.
99. E. E. Sercarz, F. Celada, N. A. Mitchison, T. Tada, The Semiotics of Cellular Communication in the Immune System (Springer, 1988), 10.1007/978-3-642-73145-7https://doi.org/10.1007/978-3-642-73145-7
100. U. Eco, "On Semiotics and Immunology" in The Semiotics of Cellular Communication in the Immune System, E. E. Sercarz, F. Celada, N. A. Mitchison, T. Tada, Eds. (Springer Berlin Heidelberg, Berlin, Heidelberg, 1988), 10.1007/978-3-642-73145-7_1 chap. Chapter 1.https://doi.org/10.1007/978-3-642-73145-7_1
101. A. Koestler, Beyond Reductionism- Proceedings of the Alpbach Symposium 1968-Holons and Holarchy of Arthur Koestler. (Arthur Koestler and J. R. Smythies, 1968), http://www.panarchy.org/koestler/holon.1969.html
102. T. Pradeu, S. Jaeger, E. Vivier, The speed of change: towards a discontinuity theory of immunity? Nat Rev Immunol **13** (2013).https://doi.org/10.1038/nri3521
103. C. H. McEwan, H. Bersini, D. Klatzmann, V. Thomas-Vaslin, A. Six (2011) Refitting Harel statecharts for systemic mathematical models in computational immunology. in 10th International Conference on Artificial Immune Systems (ICARIS), eds G. N. a. T. Pietro Lió, Stibor (Cambridge), https://link.springer.com/chapter/10.1007/978-3-642-22371-6_4
104. R. Root-Bernstein, Autoimmunity and the microbiome: T-cell receptor mimicry of "self" and microbial antigens mediates self tolerance in holobionts: The concepts of "holoimmunity" (TcR-mediated tolerance for the holobiont) and "holoautoimmunity" (loss of tolerance for the holobiont) are introduced. Bioessays **38** (2016).https://doi.org/10.1002/bies.201600083
105. V. Thomas-Vaslin, " Le rôle des traces dans le système immunitaire : des anticorps au corps" in Des traces du corps au corps-trace, L'Homme-trace, Ed. (CNRS éditions, Paris, 2017), vol. 4, http://www.cnrseditions.fr/sociologie-ethnologie-anthropologie/7489-l-homme-trace.html
106. V. Thomas-Vaslin, A. Douillet (2021) Poster "EcoSysTerm" Communication des systèmes vivants : Cartographie de la littérature en lien avec les perturbations environnementales multi-niveaux. (ARTEX Journée Arts et Sciences -Institut des Systèmes Complexes de Paris Ile-de-France, Oct 2021, Paris, France. 2021.).https://doi.org/hal-03527987
107. J. P. Aubin, A. Bayen, P. Saint-Pierre, Viability theory new directions. S. S. B. Media, Ed. (Springer, ed. 2d edition, 2011),
108. D. Noble, The role of stochasticity in biological communication processes. Progress in biophysics and molecular biology **162** (2021).https://doi.org/10.1016/j.pbiomolbio.2020.09.008
109. C. McEwan, H. Bersini, D. Klatzmann, V. Thomas-Vaslin, A. Six, A computational technique to scale mathematical models towards complex heterogeneous systems (Luniver press, 2011), https://books.google.fr/books?hl=fr&lr=&id=M6swBFhZNCYC&oi=fnd&pg=PA31&ots=ZQCAYUzCw4&sig=9mTs1EdhLqJaO-Ty_LmFhBQskPg#v=onepage&q&f=false