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Multiscale Information Processing in the Immune System

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Abstract: The immune system is a dynamic network that processes information across multiple biological scales, from molecular recognition of antigens to systemic coordination with the neuroimmune axis and microbiota. At the molecular level, pathways such as NF-κB and JAK-STAT regulate gene expression, integrating signals from pathogens and the organism itself while balancing activation through feedback loops. Cellular and tissue-level dynamics are exemplified by germinal centers, where B-cell hypermutation and clonal selection refine the humoral response, and by immunological synapses that regulate T-cell activation and fate. Systemically, the vagus nerve mediates neuroimmune interactions, while the microbiota co-evolves with the immune system, enhancing its plasticity and robustness. These processes embody antifragility, allowing the immune system to strengthen and expand its capabilities with each challenge. By understanding these multiscale processes, novel strategies emerge for precision medicine, including the modulation of the vagus nerve and microbiota, offering personalized approaches to treat infectious, autoimmune, and chronic diseases.

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1. Introduction

The immune system operates as a complex and dynamic network that integrates information from the molecular level to systemic coordination, continuously adapting to its ecological environment [1–4]. This ability to integrate signals, adjust them to their context, and generate adaptive responses is at the core of its functionality. However, the immune system does not merely resist disturbances; in many cases, it strengthens and evolves after each challenge, a quality that aligns with the concept of antifragility introduced by Nassim Nicholas Taleb [5]. Antifragility describes the ability of a system to not only survive but also thrive under conditions of uncertainty, stress, or disorder [6–8].

From this perspective, the immune system emerges as a model of biological antifragility [7,9]. Processes such as somatic hypermutation in B lymphocytes, clonal selection of T lymphocytes, and the consolidation of immunological memory illustrate how each encounter with a pathogen translates into an opportunity to refine future responses. By operating near a critical state—the point

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of greatest diversity with an optimal degree of order for information processing—the immune system maximizes its sensitivity to relevant stimuli while minimizing erratic responses to environmental noise. This balance is crucial for detecting minimal threats and amplifying them into effective responses, without compromising the stability of the organism [10–12].

Information processing in the immune system is not limited to molecular or cellular signals. It also integrates fundamental properties of information, such as entropy, redundancy, and non-locality [13,14]. Entropy, for example, manifests itself in the clonal diversity of lymphocytes, which maximizes the ability to recognize a wide range of antigens. Redundancy ensures the robustness of responses by allowing multiple pathways or mechanisms to compensate for failures or fluctuations [15]. On the other hand, non-locality allows local signals, such as those emitted at an infection site, to propagate and coordinate global responses through neuroimmune networks and chemokines [16,17].

Furthermore, the immune system is distinguished by its ability to integrate metabolic and epigenetic factors into its functional decisions. Metabolic reprogramming during immune activation not only satisfies immediate energy demands but also modulates the intensity and specialization of responses [18–20]. In parallel, epigenetic modifications act as "informational marks" that preserve the memory of previous encounters and recalibrate future responses, optimizing the plasticity and resilience of the system [21,22].

This article provides an integrated review of the principles of multiscale processing of immunological information, the properties that underpin its antifragility, and the key mechanisms that position it as a unique adaptive system. It also explores the clinical implications of these findings in the design of vaccines, immunotherapies, and personalized intervention strategies in infectious, autoimmune, and chronic diseases. Finally, it discusses future directions involving the development of computational models and the incorporation of systems biology tools to unravel the complexity and antifragile potential of the immune system.

2. Multiscale Processing of Immunological Information

The immune response is orchestrated through a complex integration of signals, processes, and feedback loops that operate at different levels of organization, from the molecular detection of antigens to systemic coordination. This section explores how each scale contributes to shaping a network of interactions critical for the antifragility of the immune system.

2.1. Molecular Scale

At the most fundamental level addressed here, immune cells possess pattern recognition receptors (PRRs) and antigen-specific receptors (BCR and TCR), responsible for discriminating signals from pathogens or the organism itself [23–26]. Their activation promotes structural changes that trigger signaling cascades (NF-κB, MAPK, JAK-STAT, etc.) [27–30] that regulate various biological processes such as metabolism and gene expression. For example, TCR activation promotes a metabolic shift towards aerobic glycolysis, increasing energy availability to sustain cell proliferation and cytokine production. In parallel, genes encoding key effector molecules are activated, adapting the response to the type and magnitude of the threat. However, immune cells do not respond to a single signal, but rather integrate information from costimulatory, inhibitory, and pattern recognition receptors (Figure 2). This integration ensures that responses are proportional to the context and prevents aberrant activations, as in cases of autoimmunity [31–34].

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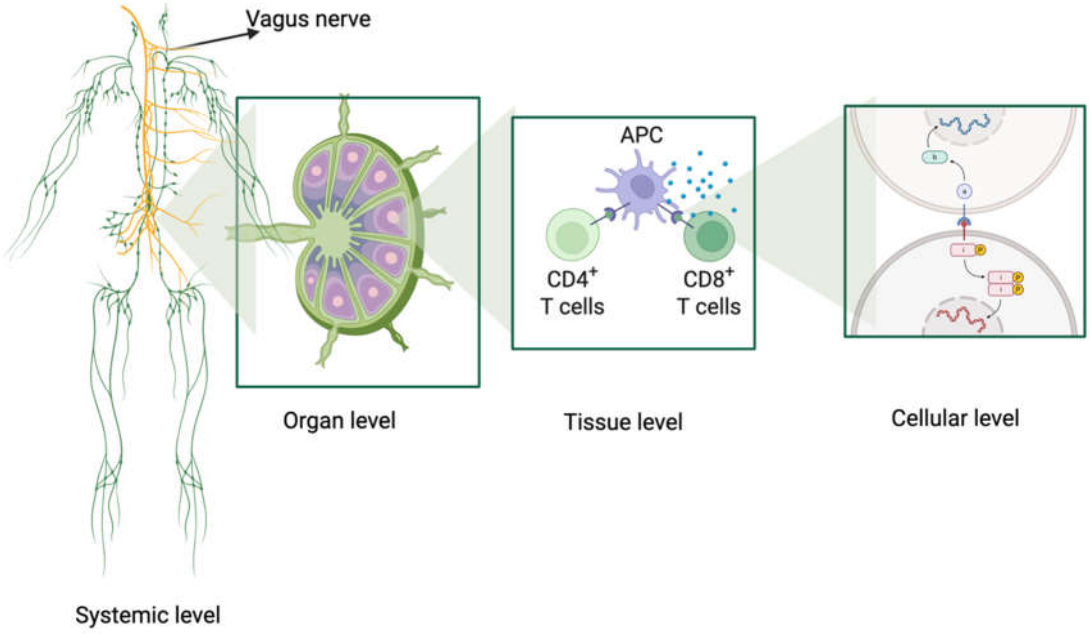

Figure 1. Graphical abstract illustrating the multiscale organization and information processing of the immune system. The figure highlights four interconnected levels: 1) **Systemic Level**: integration of the vagus nerve, showcasing the neuroimmune axis and its role in modulating immune responses; 2) **Organ Level**: representation of the lymph node structure as a hub for antigen processing, immune cell interaction, and coordination; 3) **Tissue Level**: detailed view of antigen-presenting cells (APCs) interacting with CD4+ and CD8+ T cells, emphasizing the role of cytokine signaling in cellular activation; 4) **Cellular Level**: intracellular processes including antigen recognition, signal transduction pathways (e.g., NF-κB, JAK-STAT), and gene expression. Created using BioRender, this figure encapsulates the dynamic, hierarchical organization of immune processes, linking systemic coordination to molecular specificity. Created in https://BioRender.com.

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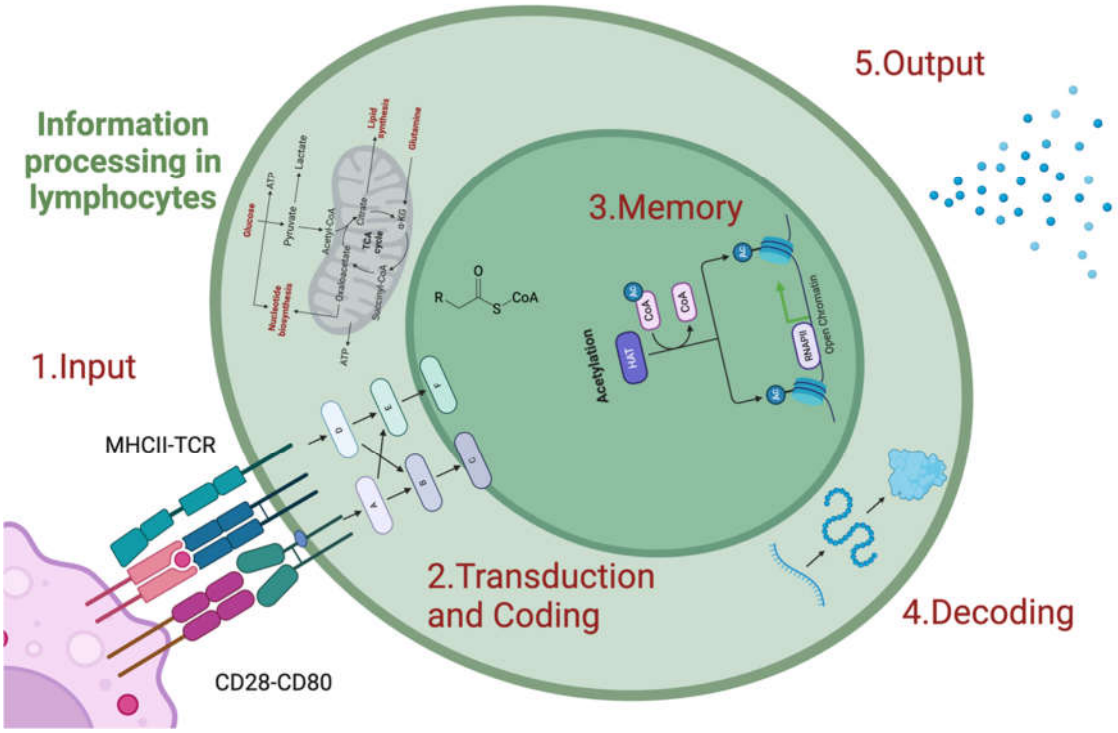

Figure 2. Schematic representation of information processing in a T cell, created using BioRender, illustrating five stages: 1) **Input**: antigen recognition mediated by the MHCII-TCR complex and costimulatory signals such as CD28-CD80, which initiate cellular activation and prime the immune response; 2) **Transduction and Coding**: signal integration through intracellular pathways, including NF-κB and JAK-STAT, that regulate metabolic reprogramming (e.g., glycolysis and lipid biosynthesis) and epigenetic modifications; 3) **Memory**: establishment of durable epigenetic marks and chromatin remodeling to encode functional and adaptive memory, enabling rapid responses to future challenges; 4) **Decoding**: gene expression and effector molecule synthesis, such as cytokines, that shape the immune response; 5) **Output**: secretion of cytokines and signaling molecules, amplifying and coordinating immune activity within the microenvironment. This figure integrates molecular, metabolic, and epigenetic processes into a multiscale framework, highlighting the adaptability and robustness of the immune system in response to external perturbations. Created in https://BioRender.com.

Positive and Negative Feedback

Feedback is a process in which the output of a system is used as input to modify or control the same system. In simple terms, it is the information that a system receives about its own performance or state, which it then uses to adjust and improve [35,36]. Positive feedback is a key mechanism that amplifies initial activation signals, ensuring a rapid and robust response to significant threats. A characteristic example is the overexpression of costimulatory molecules, such as CD80 and CD86, on antigen-presenting cells. These molecules interact with receptors such as CD28 on T lymphocytes, intensifying cellular activation, proliferation, and the production of pro-inflammatory cytokines such as IL-2 and TNF-α [37–39].

Activation of pathways such as NF-κB and MAPK generates positive feedback loops by inducing the expression of genes that encode more receptors or inflammatory mediators [40–43]. This amplifying effect is crucial during the initial phase of an immune response when the body needs to rapidly recruit a sufficient number of effector cells to contain infection or tissue damage [44–46].

Intracellular signaling cascades are also subject to control by negative feedback mechanisms that adjust their intensity and duration. In the JAK-STAT pathways, for example, SOCS (Suppressor of Cytokine Signaling) proteins are induced in response to pro-inflammatory cytokine signals. These proteins act by directly blocking cytokine receptors or inhibiting the enzymatic activities of JAK

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kinases, short-circuiting signal transmission and dampening the response [47–50]. Another example occurs in the NF-κB pathway, where the IκB protein acts as a key regulator. Following NF-κB activation and target gene transcription, IκB expression is induced. IκB re-enters the cytoplasm, binds to NF-κB, and sequesters it, inhibiting its nuclear activity and restoring a basal state in the cell [51–53].

In addition, soluble molecules such as anti-inflammatory cytokines (IL-10 and TGF-β) act as critical mediators by binding to their specific receptors on immune cells, triggering signaling pathways that repress the activation of pro-inflammatory transcription factors, such as NF-κB [54–56].

The effectiveness of negative feedback at the molecular level is not uniform but depends on the context and intensity of the stimuli received. For example, in an environment with a high density of antigens or damage signals, negative feedback may be delayed or adjusted to allow for a more prolonged response. However, when stimuli decrease, inhibitory pathways are rapidly activated, promoting the resolution of the immune response. [57,58]

This plasticity in molecular interactions and signaling cascades ensures that immune cells maintain a dynamic balance between activation and inhibition. In this way, the immune system not only responds efficiently to threats but also preserves the integrity of healthy tissue and prevents imbalances such as those observed in autoimmune or inflammatory diseases.

Information Encoding: Molecular Integration and Spatiotemporal Dynamics

Information encoding is the process of converting information from one form to another, usually using a set of rules or a code [59]. This conversion aims to facilitate the storage, transmission, or processing of information [60]. In the immune system, information encoding is based on the ability of cells to translate external signals into specific intracellular responses through an integrated set of molecular processes. These signals must not only be perceived with high fidelity but also integrated into a spatiotemporal framework that optimizes the response based on the biological context [61,62].

Information integration also depends on specific post-translational modifications, such as phosphorylation, ubiquitination, and acetylation of key proteins. These modifications allow signals to be amplified, diversified, or restricted as needed. For example, ubiquitination of components in the NF-κB pathway, such as IKKγ (NEMO), not only activates this pathway but also determines its duration and specificity. Similarly, phosphorylation of STATs in the JAK-STAT pathway modulates the activation of genes related to inflammation and immune regulation [63–66].

Adding to this complexity, immune proteins like PKR act as critical nodes in adaptive networks capable of processing and discriminating signals even in noisy environments. PKR's ability to distinguish between a viral decoy, such as K3, and a legitimate activator highlights the system's robustness and specificity. This process can be modeled as a decoding problem, where signal fidelity and the integration of multiple stimuli determine the outcome. This approach underscores the importance of coding and decoding patterns in optimizing immune responses at the molecular level [67].

Spatiotemporal Dynamics: Precision in the Response

The precision and timing of immune responses critically depend on a dynamic integration of spatial and temporal dimensions, as signal processing in the immune system is not static but highly adaptable. Both the location (space) and the time at which molecular events occur play a key role in defining the magnitude and specificity of the immune response [68,69]. For example, the subcellular localization of factors such as NF-κB or STAT3 directly influences their functionality. The nuclear translocation of NF-κB, triggered by pathogenic stimuli, occurs in temporal pulses, a mechanism that ensures sustained but carefully regulated activation of target genes, minimizing the risk of excessive responses or collateral damage.

From a spatiotemporal perspective, the structural and organizational properties of the plasma membrane play a crucial role [70–72]. The formation of lipid microdomains, such as lipid rafts, creates specialized platforms that facilitate the colocalization of receptors, adaptor molecules, and other signaling components. These microdomains not only improve the efficiency of signal transmission but also act as dynamic hubs that allow for the precise modulation of molecular interactions in real

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time. This spatiotemporal organization ensures that signals are amplified, integrated, or attenuated according to the specific needs of the biological environment, guaranteeing an effective and adaptive immune response while simultaneously preserving tissue homeostasis [73,74].

2.2. Cellular and Tissue Scale

The cellular and tissue level of the immune system is a fascinating example of how biological systems integrate signals, interaction, and adaptation. This level not only functions as a bridge between molecular and systemic responses but also reveals emergent properties that reinforce the adaptability, robustness, and antifragility of the system in the face of external challenges. The synergy between cells and microenvironments generates dynamic networks that give the immune system the ability to thrive in conditions of uncertainty [75–77].

Specialized Microenvironments: Centers of Learning and Humoral Robustness

Germinal centers, strategically located in the lymph nodes and spleen, are dynamic and highly organized environments that represent true centers of immunological learning [78,79]. In these structures, B lymphocytes undergo somatic hypermutation and clonal selection, generating antibodies that are increasingly fine-tuned against the present antigens. However, the role of germinal centers goes far beyond being simple sites of immunological activation: they function as true evolutionary factories where the interaction between cells and contextual signals drives the continuous optimization of the humoral response [80–82].

In the process of somatic hypermutation, B lymphocytes introduce point mutations in the genes that encode the variable region of antibodies, generating a wide clonal diversity. This phenomenon, mediated by the enzyme AID (activation-induced cytidine deaminase), is a unique example of accelerated evolution in real-time within the immune system. The generated diversity not only allows the identification of previously unknown antigens but also guarantees an effective response against pathogens that have mutated to evade immunological recognition. The ability of the system to dynamically evolve and adapt embodies an essential principle of antifragility: each challenge strengthens the system instead of weakening it [83–86].

After hypermutation, B lymphocytes compete within the germinal center microenvironment for survival signals. Follicular dendritic cells, by presenting antigens in the form of stable immune complexes, act as guides that allow the identification of clones with the highest affinity. Only those B lymphocytes that manage to interact effectively with follicular T lymphocytes, through key signals such as the CD40-CD40L interaction and stimulation by cytokines (IL-21 and IL-4), survive and differentiate. This selective process not only ensures the quality of the antibodies produced but also eliminates suboptimal clones, thus strengthening the overall efficacy of the humoral response [87–90].

Contextual signals within germinal centers are equally fundamental. Cytokines such as IL-4 and IL-21, produced by follicular T lymphocytes, regulate both the proliferation and specialization of B lymphocytes, influencing the class of antibody generated. These signals, combined with CD40-mediated interactions, constantly calibrate the balance between activation, survival, and memory, allowing the system to adjust its response precisely according to the body's needs [91,92].

Furthermore, germinal centers not only perfect the immediate response but also ensure a solid long-term immunological memory. The selected B lymphocytes can differentiate into antibody-producing plasma cells or memory cells, both essential to guarantee rapid and robust responses to future encounters with the same pathogen. This iterative process of mutation, selection, and differentiation turns germinal centers into true centers of adaptive learning, where each interaction contributes to the improvement of the immune system.

Immunological Synapses and Cellular Decisions: Non-linear Networks to Maximize Information

In the context of immunological synapses and cellular decisions, these platforms represent a key point of convergence where molecular biology, physics, and network theory intertwine to enable

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high-precision cell communication processes. Beyond being simple interfaces of physical contact between dendritic cells and T lymphocytes, immunological synapses are scenarios where chemical, mechanical, and biophysical signals are integrated to guide critical cellular decisions. This process is characterized by extreme sensitivity and an information processing capacity that not only determines cell fate—activation, anergy, or death—but also ensures that these decisions are made with minimal error, which is essential in a system that faces constant pathogenic challenges [93–95].

The amplification of signals received by T lymphocytes is mediated by non-linear dynamics, such as synergy in receptor activation, which allow small variations in the initial signals to trigger disproportionately large responses. This type of behavior is typical of complex systems operating in a regime close to criticality. This suggests that evolution has favored a biological design optimized to balance sensitivity and robustness, allowing the immune system to not only detect incipient threats but also process multiple signals efficiently [96–100].

Beyond the direct contact that defines immunological synapses, immune cells interact through an extended communication network that includes indirect mechanisms. Autocrine and paracrine signaling, for example, allows cells to not only regulate their own activity but also influence that of their neighbors by releasing molecules such as cytokines, which establish gradients that guide cell migration and activation. Likewise, extracellular vesicles, such as exosomes, act as specialized vehicles that transport proteins, lipids, and nucleic acids, facilitating the transfer of complex molecular information between distant cells. This mechanism not only ensures functional synchronization between different tissue compartments but also reinforces the ability of the immune system to operate in an integrated and coordinated manner [101–104].

Another critical component of this extended network is field effects or quorum sensing phenomena. In these processes, the accumulation of signaling molecules in the microenvironment generates collective responses that alter the individual behavior of cells, promoting patterns of synchronized action. This type of collective interaction is essential for processes such as the formation of immune microdomains in tissues and the regulation of inflammatory or tolerogenic responses [105–107]. This level of organization, both molecular and systemic, underscores the sophistication of the immune system as a non-linear network that maximizes information transfer to ensure survival [108–111].

Complementarily, the mitochondrial redistribution toward the immunological synapse can be viewed as a manifestation of evolutionary optimization processes in complex systems, where physical proximity to key points of cellular interaction not only enhances metabolic efficiency but also maximizes the precision of signal transmission. This phenomenon, occurring within a framework of positive feedback between Ca^{2+} uptake and the activation of intracellular signaling pathways, highlights the role of mitochondria not only as energy generators but also as dynamic integrators of biochemical and biophysical signals. Such integration, mediated by the system's emergent properties, ensures that cellular decisions are made robustly and in a coordinated manner, minimizing errors that could result in dysfunctional immune responses, such as inappropriate tolerance or hyperinflammation. Thus, the interplay between molecular biology, physics, and network theory in this context allows for a reinterpretation of mitochondria as critical nodes in a nonlinear cellular network optimized for the organism's survival and adaptability [112].

Emergent Properties at the Tissue Level: Self-Organizing Networks

Emergent properties at the tissue level in the immune system are a manifestation of the complex interaction between immune cells, soluble molecules, and surface signals, resulting in organized patterns that regulate both local and systemic dynamics. These self-organizing networks reflect the ability of the immune system to coordinate multiple cellular and molecular processes without relying exclusively on centralized supervision, taking advantage of physical and biological principles that maximize efficiency and minimize redundancies [113–115].

A example of these emergent properties is the formation of granulomas in chronic infections, such as those caused by Mycobacterium tuberculosis. In this context, immune cells such as

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macrophages, T lymphocytes, and dendritic cells converge in a specific microenvironment, where gradients of chemokines such as CXCL13 and CCL19 play a critical role in structural organization. These gradients act as chemical guides that direct the migration and positioning of cells, facilitating the containment of the pathogen within a central core surrounded by a protective ring of activated immune cells. This process not only reflects self-organization but also the ability of the immune system to create functional microenvironments adapted to the specific needs of the immune response [116–118].

Another prominent example is the development of fibrosis in tissues subjected to chronic inflammation or persistent damage. Here, the dynamic interaction between activated fibroblasts, macrophages, and lymphocytes regulates the deposition of extracellular matrix, promoting the structural repair of the tissue. However, this process can overflow, leading to an excessive accumulation of collagen and other matrix components, resulting in a loss of tissue functionality. This delicate balance between regeneration and pathology is an emergent characteristic of self-organizing networks acting at the tissue level [119–122].

The self-organization of these tissue networks is based on the ability of the immune system to establish dynamic gradients of signaling molecules, such as cytokines and chemokines, which regulate cell activation and migration in a spatiotemporal manner. This process ensures that cellular and molecular resources are concentrated in areas where they are most needed, thus optimizing the efficiency of the immune response. In addition, these networks exhibit fault tolerance properties, allowing the system to maintain its functionality even when some of its individual components are damaged or compromised. This robustness against perturbations guarantees the stability of the immune system in a dynamic and constantly changing environment [123–125].

From an evolutionary perspective, self-organizing networks at the tissue level represent a highly adaptive strategy, as they allow for a rapid and localized immune response without relying exclusively on centralized control. This not only minimizes metabolic costs but also ensures that the system can respond effectively to a wide variety of stimuli and challenges [126–128].

Temporal Dimension: Memory and Adaptive Plasticity

The temporal dimension of the immune system is a fundamental characteristic that reflects its capacity for adaptation through immunological memory and adaptive plasticity. These properties not only allow the system to remember and respond more efficiently to future challenges but also highlight its antifragility: a phenomenon by which stress, in appropriate doses, not only strengthens the system but prepares it to face even more adverse conditions. This principle can be understood through hormesis, where controlled exposures to stressors, such as vaccines or mild infections, act as an "optimal dose" that induces adaptive benefits. However, excessive stress or extremely virulent pathogens can overcome the system's adaptive capacity, generating damage or disease, which underlines the importance of carefully regulating this dynamic [129–131].

In the context of immunological memory, traditionally attributed to the adaptive system, memory T and B lymphocytes have proven to be fundamental for generating rapid and specific responses after a second exposure to the same pathogen. More recently, a "trained memory" has been recognized in the innate immune system, mediated by epigenetic changes such as DNA methylation and histone modifications [132–134]. These changes do not alter the genetic sequence, but they do reconfigure gene expression in cells such as macrophages and NK cells, providing a more robust and efficient response to future stimuli. This discovery not only expands our understanding of the immune system but also reveals a dynamic interaction between innate and adaptive memory, where the former can modulate and enhance the quality of the latter's responses [135–138].

Furthermore, immunological plasticity, defined as the system's ability to adjust in response to changing stimuli, is essential for its antifragility, although not sufficient on its own. It is in this interaction, where plasticity allows for change and antifragility ensures that stress results in functional improvements, that the immune system behaves as a complex adaptive system, exhibiting emergent properties that cannot be predicted solely from the study of its individual components.

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However, these properties have a dark side: both memory and plasticity can contribute to pathological states, such as "original antigenic sin," chronic inflammation, or autoimmunity, where the immune response is diverted towards inappropriate targets or exacerbated in an uncontrolled manner. This duality highlights the need to understand and carefully manage the temporal dimension of the immune system, not only to prevent dysfunctions but also to design innovative therapeutic interventions. From strategies that leverage trained memory to fight infections and tumors, to approaches that reprogram memory in autoimmune diseases, the possibilities are vast [139–142].

Connections with Network Theory: A Systemic Approach

Network theory provides a powerful conceptual framework for analyzing the emergent properties of this network, such as robustness, adaptability, and efficient coordination of immune responses. A key aspect of this network is the presence of hubs or concentrators, such as dendritic cells, which act as highly connected nodes essential for signal integration and coordination of immune responses. These hubs have the ability to gather information from various sources, such as antigens, damage signals, and chemokines, to activate T and B lymphocytes, thus ensuring a specific and effective response. Dysfunction or loss of these hubs can destabilize the network, underscoring their importance in maintaining the robustness of the system [143–145].

Another relevant principle is modularity, which describes the organization of the immune system into specialized functional subnetworks, such as germinal centers in secondary lymphoid organs or specific regions of inflammation in peripheral tissues. These subnetworks operate semi-independently, allowing for localized and precise responses to external stimuli without compromising the overall stability of the system. At the same time, connections between modules ensure signal integration to coordinate systemic responses when necessary. This modularity not only increases functional efficiency but also reinforces the resilience of the immune system by containing local disturbances and preventing their uncontrolled spread [146–149].

Finally, the immune system exhibits a small-world topology, characterized by short and efficient paths between nodes, allowing for rapid signal propagation and facilitating coordinated responses at the systemic level. This attribute is particularly critical during systemic infections or acute inflammation, where the rapid and efficient interaction between cytokines and chemokines connects specialized cells in peripheral tissues with lymphocytes in lymphoid organs. The redundancy of these connections also contributes to the robustness of the network, guaranteeing its functionality even in the face of random failures of some nodes [150–152].

2.3. Systemic and Neuroimmune Scale: A Dynamic, Adaptive Network with Deep Computational Processing

At this systemic scale, the immune system also emerges as a vastly complex distributed network that integrates and processes information from both organs and tissues, as well as neural circuits. Each interaction—whether between cells, metabolites, or neurotransmitters—acts as a "computational microprocess" capable of reconfiguring the immune response in real-time. This biological intelligence is sustained by a key principle called computational irreducibility, which indicates that it is not enough to reduce the system to simple equations or predictive "shortcuts": to know the total behavior (for example, when an inflammatory response ends or how it resolves) it is necessary to simulate or go through step-by-step the multiple interactions that occur in the network [153–155].

Within this framework, neuroimmunology takes on a preponderant role. The brainstem—traditionally considered the center of vital functions such as breathing and heart rate—is now revealed as a "volume controller" of inflammation throughout the body. Recent studies, driven by research on homeostasis and taste circuits, indicate that specific groups of neurons in the brainstem can detect and readjust inflammatory signals through the vagus nerve [156]. Instead of a simple back-and-forth between the brain and the immune system, this axis integrates circadian rhythms, stress, metabolic demands, and other external factors, ensuring homeostatic feedback that balances the elimination of pathogens without compromising the health of healthy tissues [157–159].

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A second axis of "computation" is provided by the microbiome. Intestinal bacteria and their metabolites (e.g., short-chain fatty acids) regulate the differentiation of T lymphocytes, activating or attenuating their inflammatory profile as needed. But the microbiota is not just a passive sensor: it evolves and co-designs strategies with the immune system, expanding its range of adaptive responses to changing environments. Its plasticity, coupled with dense humoral and neural communication (cytokines, chemokines, vagal pathways, etc.), provides the immune system with outstanding antifragility, that is, the ability to strengthen in the face of disturbances rather than just resist them [160–163].

Viewing the immune system as a complex and computationally distributed network offers new clinical perspectives. From interventions on the vagus nerve—capable of modulating inflammatory states in autoimmune, metabolic, or neurodegenerative diseases—to the targeted manipulation of the microbiota to fine-tune immunological tolerance, precision medicine ceases to be merely "suppressive" and advances towards the intelligent "reprogramming" of immunity. At the same time, the notion of computational irreducibility—also studied in models of biological evolution—warns that simple natural selection alone does not explain the emergent complexity of the system; the latter displays such great internal computing power that, without fully simulating it, it is impossible to predict exactly how the immune response will evolve in a specific scenario [164–166].

Ultimately, the brain, microbiome, and immune network form a high-performance integrating loop in which each cell, molecule, and neuron acts as a modifiable bit of information. This renewed vision positions the immune system not only as a defensive shield but as an evolutionary and computational engine that, in permanent dialogue with the environment, produces transcendental biological innovations. In this broad landscape, the brainstem, vagal pathways, and other central "controllers" constitute neural nodes of enormous influence, placing neuroimmunology at the core of modern medicine and redefining our scope for manipulating and optimizing the very evolution of human health [167–170].

Multiscale Integration of the Immune System and its Emergent Properties: Lung Cancer as a Case Study

Lung cancer is an archetypal example of how the emergent properties of the immune network can, in turn, be reconfigured by a complex pathology [171,172]. In this context, the tumor microenvironment stands as a co-evolutionary ecosystem that "disrupts" the defensive functions of the immune system and takes advantage of its plasticity. Tumor cells produce pro-inflammatory cytokines (IL-6, IL-10) and growth factors (TGF-β, VEGF) that transform the activity of macrophages (TAMs) and fibroblasts, promote angiogenesis, and stimulate extracellular matrix remodeling, creating a niche favorable for invasion and metastasis. In addition, the induction of hypoxia and the local release of adenosine allow for the inhibition of key functions of cytotoxic T lymphocytes and NK cells, facilitating tumor evasion [173–175].

Metabolic reprogramming is essential: tumor cells prioritize pathways such as aerobic glycolysis (Warburg effect) and intensive glutamine consumption, affecting nutrient availability for immune cells. This energy "monopoly," coupled with soluble factors and hypoxia, generates an immunosuppressive environment where dendritic cells have their maturation blocked and often fail to effectively activate T lymphocytes. This creates closed circuits of negative feedback in which chronic inflammation collaborates with tumor progression instead of stopping it [176–180].

The evolutionary dimension of lung cancer reflects the constant selective pressure exerted by both the metabolic environment and the immune response. Tumor subclones with mutations that facilitate evasion of surveillance (overexpression of PD-L1, loss of tumor antigens, secretion of anti-inflammatory cytokines) thrive in such a changing ecosystem, promoting intratumoral heterogeneity and resistance to therapies. The epithelial-mesenchymal transition (EMT) further expands the plasticity of cancer cells, reinforcing their invasive capacity and tolerance to hostile conditions [181–184].

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To address this complexity, both in health and disease, it is imperative to integrate mathematical and computational models that replicate multiscale dynamics. From cellular automata that simulate tumor progression and interaction with immune populations to complex network theory that identifies critical nodes ("hubs") where information transmission is concentrated. These approaches, nurtured by the massive collection of omics data (genomics, transcriptomics, metabolomics), allow for a more accurate approach to precision medicine. Bioinformatic analysis and experimental validation in vitro or in vivo close the feedback loop, facilitating the continuous generation of hypotheses and the refinement of therapeutic interventions.

Therefore, the flow and processing of information within immune circuits and the tumor microenvironment emerges as the true "guiding thread" of this complex multiscale dynamic. Every cell-to-cell interaction, every signal released into the environment, and every metabolic modification not only transmits data but also transforms it, generating new functional states and feedback loops that enhance—or block—immune responses. From the detection of molecular patterns by specific receptors, to the systemic orchestration of adaptive cellular populations and the modification of intracellular signaling pathways, information processing becomes the key axis that unifies the evolutionary aspect of cancer with the emergent properties of immunity. This approach, reinforced by mathematical models and computational simulations that replicate the dynamic nature of cellular communication, paves the way for therapeutic interventions designed to strategically interrupt or redirect these interaction networks; not merely targeting tumor cells, but reconfiguring the informational flows that sustain the disease's plasticity and resistance.

Conclusions

The immune system stands out as a multifaceted and antifragile network capable of not only resisting disturbances but also learning and strengthening with each experience. Far from being a mere defense mechanism, it acts as a biological engine of innovation whose functional boundaries expand with each challenge. Throughout these pages, the critical role of information processing at multiple scales—molecular, cellular, tissue, and systemic—has been highlighted as the foundation of its extraordinary adaptability and capacity for continuous evolution.

In the molecular dimension, receptors and signaling pathways operate as high-fidelity "biological microprocessors," whose balance between positive and negative feedback allows the system to operate near a critical regime. This "borderline" point maximizes sensitivity to relevant stimuli and enhances the ability to modulate the intensity and duration of the response, minimizing noise that could trigger self-destructive reactions.

Innovation is most clearly manifested at the cellular and tissue scale. Germinal centers emerge as genuine miniature evolutionary laboratories, where somatic hypermutation and clonal selection generate increasingly fine-tuned antibodies. Immunological synapses, on the other hand, illustrate how the convergence between network theory, biophysics, and molecular biology ensures high-precision cellular decisions in environments of high uncertainty. These processes constitute a complex mechanism whose final product is efficiency and systemic robustness.

At the systemic scale, interconnection with the nervous system and the microbiome enhances the plasticity and resilience of the immune system. Neuroimmunological regulation, mediated in part by the vagus nerve, adjusts inflammatory processes in real-time, while the gut microbiota functions as a co-evolutionary ally that co-designs strategies for recognition, tolerance, and immunological memory. This constant interaction underscores the distributed nature of immune processing, analogous to a biological intelligence in permanent reinvention.

The systemic vision rooted in network theory reveals highly connected hubs and modules—for example, dendritic cells or germinal centers—that orchestrate efficient responses even in highly complex scenarios. The "small-world" topology that characterizes these networks reinforces signal transmission and global coordination, inspiring clinical and engineering applications ranging from immunotherapy to the design of robust networks in other scientific and technological fields. The clinical and technological applications that are envisioned have the potential to mark a turning point

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in the conception and management of human health, with implications ranging from personalized medicine to the design of new architectures in artificial intelligence and complex networks.

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