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Rethinking medical education through systems biology to address complexity

Laurent David^{1,2,3} ✉, Pierre-Antoine Gourraud^{1,4}, Guillaume Lamirault⁵ & Patricia Lemarchand⁵

While reductionism has advanced biology and medicine, it fosters a fragmented understanding of health, ill-suited to modern challenges like chronic and systemic diseases. Systems biology offers a new perspective, framing biological entities within interconnected networks. Using French medical education as an example, we argue that systems thinking should be foundational, not optional. Integrating systems biology early in medical education can better prepare future physicians for biomedical complexity and precision medicine.

Both biology and medicine are undergoing profound transformations¹. Advances in omics technologies, systems-level modeling, and precision medicine have revealed that diseases rarely confine themselves to single organs, that molecular pathways interact in complex and non-linear ways, and that patient outcomes depend as much on systemic factors as on localized lesions²⁻⁵. Yet, medical education remains largely rooted in 20th-century reductionist paradigm, presenting knowledge in discipline-specific silos and introducing systemic perspectives only late in training. Reductionism often leads to an overly mechanistic understanding of biology, prioritizing isolated molecular mechanisms over the interconnected systems that define health and disease. The epistemological challenge of symbolic substitution in medicine, where organs, cells, molecular pathways, or computational models replace the irreducible complexity of living organisms, highlights the limits of reductionist frameworks. As Georges Canguilhem argued, the normative and adaptive dimensions of life and care cannot be fully captured by static or fragmented models⁶. Using French medical training as a case study, we propose that embracing a systemic paradigm is essential for preparing physicians to address the biomedical complexity of 21st-century healthcare.

Revisiting the reductionist legacy in biology and medicine

The traditional model of organ-based medicine, which has dominated clinical practice for a century, shares deep conceptual roots with the reductionist paradigm in physics and biology^{7,8}. Both approaches follow a Cartesian logic of decomposition: to understand the whole, one must first isolate and analyze its constituent parts⁹. In medicine, this led to segment the human body into discrete functional units such as heart, lungs, liver, or kidneys, each governed by a specialized medical discipline. Similarly, in biology, reductionism has fostered the belief that biological phenomena can be explained by tracing them back to individual genes, proteins, or signaling pathways, each associated with a specific function¹⁰.

This organ-based logic has been remarkably effective, enabling highly specialized diagnostics and therapeutic interventions, supported by increasingly sophisticated tools in imaging, surgery, and pharmacology. In parallel, reductionist molecular biology has driven transformative discoveries as well as exponential growth of knowledge in genetics, cell biology, physiology, genetics, enzymology, and pathophysiology.

However, given the complexity of contemporary health challenges¹¹, both paradigms reveal their limitations. In medicine, the fragmentation inherent to organ-based approaches often preclude to adequately manage patients with multiple chronic conditions¹², functional disorders¹³, or syndromes that transcend anatomical boundaries, leading to partial treatments, delayed diagnoses, or failure to address underlying etiologies. In biology, the central dogma of molecular biology, “one gene, one protein, one function”, is at least incomplete (if not incorrect) to explain pleiotropy, gene-environment interactions, or epigenetic modifications^{14,15}.

These limitations are particularly evident in common chronic conditions, such as asthma and hypertension, where reductionist views have long obscured their systemic nature. Asthma, once considered a purely bronchial disorder, is now recognized as a heterogeneous disease involving systemic immune dysregulation, obesity, and microbiome alterations¹⁶ and thus multiple medical specialities. The identification of distinct inflammatory phenotypes (eosinophilic, neutrophilic, IgE-mediated) has led to the development of targeted biologics, calling for a personalized, system-level approach beyond bronchial mechanics. Hypertension, often reduced to a blood pressure threshold, is defined as a dysfunction of multiple regulatory systems, linked initially to renal, endocrine, neural, and vascular mechanisms, and now also to inflammation, immunity, microbiome, oxidative stress, and behavioral factors¹⁷. Its management extends far beyond pharmacological control of one target molecule, requiring synergistic pharmacological strategies, combined with lifestyle interventions, psychosocial evaluation and support, and continuous monitoring of comorbidities and

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Table 1 | From reductionist approaches to systemic paradigm: A comparative overview in medicine and biology

Dimension	Reductionism	Systemic paradigm
Medicine	Organ, specialty, localized symptom	Whole body, cross-system regulation, external factors
Biology	Gene → protein → function	Gene networks, cross-regulation, epigenetics
Strengths	Precision, control, targeted interventions	Holistic understanding, prevention, and personalization
Limitations	Fragmentation, oversimplification	Complexity, need for new conceptual frameworks

Adapted from ref. 9.

target-organ damages¹⁸. These examples illustrate how diseases traditionally defined by a single organ are, in fact, systemic disorders with localized manifestations.

Similar concerns apply to the field of therapeutics. Molecularly targeted therapies have revolutionized the treatment of several malignancies¹⁹. Designed to act on specific molecular alterations (e.g., oncogenic mutations, overexpressed receptors, or aberrant signaling pathways), these therapies embody the promise of precision medicine: offering treatments tailored to the patient tumor molecular profile. However, this therapeutic precision promoted a reductionist vision of diseases, that equates complex pathologies with discrete, targetable molecular entities. The conceptual elegance of the “one gene, one target, one drug” model, mirroring the earlier “one gene, one protein, one function” paradigm, provides clarity at the expense of obscuring the broader systemic context in which these molecular defects operate, including network-level interactions, compensatory mechanisms, and patient variability. Understanding this context is particularly critical in oncology, where tumors are not isolated entities defined solely by their genomic landscape; they exist within dynamic microenvironments shaped by immune interactions, metabolic flux, stromal remodeling, inflammation, and even psychosocial and circadian influences^{20–22}.

Moreover, this focused approach can lead to unexpected adverse effects, since many molecular targets are not entirely tumor-specific and systemic regulatory feedback loops may be significantly disrupted. Examples include inhibitors of angiogenesis (e.g., VEGF-targeting agents), which can cause hypertension, thrombosis, and impaired wound healing through both direct VEGF inhibition and off-target effects on other tyrosine kinases²³; immune checkpoint inhibitors, which can trigger immune-related adverse events in organs such as the gut, liver, skin, endocrine glands, or lungs due to widespread immune activation beyond the tumor site²⁴; and BRAF inhibitors in melanoma, which may paradoxically activate the MAPK pathway in normal cells, leading to secondary neoplasms²⁵.

A particularly illustrative case is imatinib, often celebrated as the first major success of rationally designed targeted therapy²⁶. Developed to inhibit the constitutively active tyrosine kinase produced by the BCR-ABL fusion protein in chronic myeloid leukemia, imatinib dramatically improved survival in patients with Philadelphia chromosome-positive disease. Yet the clinical reality is more nuanced. Some patients develop primary or secondary resistance due to kinase domain mutations, activation of alternative pathways, or host-related factors such as pharmacogenetic variation²⁷. Moreover, in addition to BCR-ABL, imatinib inhibits other tyrosine kinases, including c-KIT and PDGFRs, making it effective in unrelated malignancies such as gastrointestinal stromal tumors and in non-malignant disorders such as hypereosinophilic syndrome^{26,28,29}. What began as a highly selective drug revealed a broader, multi-targeted profile, demonstrating that even the most “targeted” therapies can act systemically. In some cases, these systemic effects may be beneficial, but in others, they give rise to unexpected toxicities such as fluid retention, hepatotoxicity, or myelosuppression, reflecting the complex, network-level interactions of the human organism³⁰.

These insights challenge the notion that a single molecular change can fully explain a disease or predict treatment response, urging the need to view the human body as a dynamic network of interacting physiological systems¹⁴. Although systems biology, for some authors³¹, is a notion that, in spite of its broad appeal, is still lacking a definition, it can be characterized as an integrative research strategy designed to tackle the complexity of biological systems and their behavior at all levels of organization (from molecules,

cells, and organs to organisms and ecosystems) in normal and perturbed conditions³². Systems biology is evolving to systems medicine as a new discipline that aims to offer new approaches for addressing the diagnosis and treatment of major human diseases uniquely, effectively, and with personalized precision³³. Systems medicine and systems biology integrate inter-organ communication, compensatory signaling, immune responses, individual variability, and broader social and environmental determinants, while examining interactions across molecular, cellular, tissue, and organismal scales^{34,35}. Advances in computational modeling, high-throughput omics, and artificial intelligence now enable predictive models that move beyond descriptive biology to uncover mechanisms underlying health and disease^{36,37}. Systems biology has transformed research in neuroscience, molecular biology, pharmacology, and translational medicine through data integration, modeling, and predictive analytics³⁸.

As shown in Table 1, reductionist approaches and systemic paradigm are complementary. While reductionism isolates variables for precise analysis, the systemic paradigm emphasizes interdependence, feedback mechanisms, and multiscale complexity. Importantly, embracing systems biology does not replace reductionist methods; rather, it integrates them into a broader framework that accounts for interactions within the environment sustaining the entire system³¹. This integrated view is crucial for the future of precision medicine, requiring more than molecular profiling to achieve a systems-level understanding of how individual variability shapes outcomes within complex pathophysiological networks^{32,39}.

From fragmented knowledge to integrated thinking: the case of French medical education

Medical education critically shapes how future physicians understand the human body, reason through clinical problems, and engage with biomedical complexity. Yet in many countries, including France, training remains rooted in 20th-century reductionist paradigms. While academically rigorous, it reinforces compartmentalized learning and organ-based reasoning. Introducing systems biology early in the curriculum could provide a crucial conceptual shift toward holistic care and systems thinking.

The first two years of medical school are highly selective and intensive, with limited basic science taught in fragmented, discipline-specific blocks. This structure emphasizes memorization over conceptual synthesis, leaving students with little sense of how molecular mechanisms connect to physiological and pathological processes. Furthermore, French medical education is strongly influenced by Claude Bernard’s “*méthode expérimentale*”, a hypothesis-driven approach that emphasizes the formulation of testable ideas, their evaluation through observable clinical signs or biological mechanisms, and the drawing of diagnostic conclusions⁴⁰. While invaluable for diagnosis, this linear, cause-effect model can leave students ill-prepared to interpret the multidimensional datasets central to modern research and precision medicine³¹.

The organization of medical curricula further reinforces this reductionist inclination. Teaching remains largely structured around organ-based disciplines. Beyond internal medicine, cross-disciplinary fields like geriatrics, general practice, mental health, or gender medicine, often remain peripheral. This siloed approach, which mirrors that of biological sciences, tends to fragment knowledge and may hinder the development of an integrated understanding of the human body. As a result, it can be challenging for students to understand the human body as a dynamic interconnected system and acquire a holistic view of the patient, which is essential for comprehensive and person-centered care.

Box 1 | Systems biology principles

Principle I: A biological functional process is multilevel

There is no one-to-one correspondence between genes or proteins and higher-level biological functions. Each function depends on many genes, while many genes play roles in multiple functions. A given cell function results from integration across multiple levels. The central (and simplistic) dogma (gene → mRNA → protein) is insufficient.

Example: Insulin production in pancreatic β cells exemplifies a multi-level biological process: gene transcription (nucleus) is followed by translation into preproinsulin (endoplasmic reticulum), then post-translational modifications (Golgi apparatus), including proteolytic cleavage and disulfide bond formation. Mature insulin is packaged into secretory vesicles for glucose-regulated exocytosis. This process integrates genetic, biochemical, and cellular mechanisms across specific subcellular compartments⁵⁵

Principle II: A biological function must be considered in a dynamic way

A function is not only based on the compound responsible for it (enzyme, kinase, protease, etc.), but also on its quantity, its activation (or inhibition), the presence of a cofactor, inhibitor, etc. The interpretation must take time into account. Observations are most often limited to one of the multiple states of the investigated protein or cell.

Example: Cyclin-dependent kinases (CDKs) are dynamically activated only when bound to their phase-specific cyclins, whose expression is tightly time-regulated during the cell cycle. Extending this principle, stem cells also display context-dependent functional plasticity: their differentiation potential is transiently restricted during active division but is then fully restored⁵⁶

Principle III: There is no privileged level of causality

Causes and consequences in biology are multifaceted: a given process can arise from multiple, sometimes opposing, factors and lead to a wide range of consequences. A key property of systems is the presence of feedback control across different levels of organization, meaning that no single level holds causal primacy.

Example: p53 function as both a promoter of cell survival and an inducer of cell death, depending on cellular context and stress signals. These functions are not hierarchically ordered but emerge as context-dependent outcomes, reflecting p53 integration of intracellular signals to balance survival and elimination⁵⁷

Principle IV: Transmission of information is multi-modal and multi-directional

The central dogma of molecular biology is that information flows from DNA to RNA, from RNA to proteins, which can then form protein networks, and so on up through the biological levels to that of the whole organism. This dogma is incomplete (if not incorrect). In reality, biological processes involve bidirectional signaling, with both positive and negative feedback loops operating across multiple levels.

Example: Regulation of p53 activity operates through a multilayered, systemic framework of feedback control, where multimodal signals, ranging from post-translational modifications to protein-protein interactions, converge and disseminate in bidirectional, non-linear pathways. This dynamic network integrates inputs from DNA damage, metabolic stress, and oncogenic cues, enabling p53 to act as context-specific response hubs that balance cellular adaptation and elimination⁵⁸

Principle V: Biological functions are never isolated: they only exist within interactions

Biological functions do not reside in isolated molecules or entities, but emerge from the networks of interactions among them. Diseases often result not merely from mutation in a single molecule but from the disruption of critical interactions.

Example: G protein signaling functions as a highly interactive molecular complex, where extracellular signals are transduced into intracellular

responses through multiple protein-protein interactions and second messenger cascades. In cholera, this system is systemically disrupted by cholera toxin, which locks a sub-unit of G proteins in an active state, leading to uncontrolled cAMP production and the collapse of ionic homeostasis⁵⁹

Principle VI: Biological function emerges from collective behavior

Biological functions rarely result from the action of a single molecule or cell in isolation. Instead, they emerge from the interactions among populations, whether of molecules, organelles, cells, or entire organisms. The overall outcome depends on factors such as abundance, spatial distribution, and interaction strength, which can introduce variability at the system level. Gaining predictive insight into such complex systems often requires simulations, network models, and mathematical analyses.

Example: Mitochondrial heteroplasmy exemplifies that biological function results from the sum of diverse, interacting units. Within a single cell, the dynamic competition and cooperation among mitochondrial DNA variants determine overall energy output, metabolic resilience, or disease susceptibility, much like how the behavior of a population shapes its ecological niche. This emergent functionality, dependent on the frequency, distribution, and interactions of mitochondrial DNAs rather than individual entity, highlights how system-level properties (e.g., cellular fitness) cannot be predicted from isolated parts alone⁶⁰

Principle VII: Biological function always have a stochastic dimension

Biological functions are subject to inherent randomness at the molecular and cellular level, arising from probabilistic events such as transcription, translation, or protein interactions. This stochasticity generates variability even among identical cells, contributing to robustness, adaptability, and phenotypic diversity. Recognizing and modeling these intrinsic fluctuations is essential for a complete understanding of biological systems.

Example: Cell differentiation illustrates that biological function is not deterministic but emerges from the interplay between genetic potential determinants and stochastic occurrences. This stochastic dimension ensures adaptability and diversity, allowing organisms to generate specialized cell types while maintaining the plasticity needed for development and repair. Tools like single-cell RNA sequencing now reveal how this “noise” is harnessed, rather than suppressed, to orchestrate complex tissues⁶¹

These principles were adapted from¹⁴ and from⁹ and reformulated in order to favor positive phrasing rather than contradicting the molecular view of biological function.

Activity 2: Cell fate as a pedagogical anchor

This activity is built as a course structured around cell fate, enabling students to integrate topics such as transcriptional regulation, development, stem cell plasticity, oncogenesis, and cellular signaling into a consistent, systems-level understanding. Cell fate describes the developmental paths a cell can follow, shaped by a complex interplay of external signals, transcription factors, and epigenetic mechanisms; it is therefore a powerful tool for teaching systems thinking.

The first example presents the fact that somatic cell reprogramming into induced pluripotent stem cells and oncogenic transformation begin with similar cellular states but diverge into distinct fates are a perfect illustration of the context dependency of cell fate. Comparing somatic cell reprogramming to tumorigenesis highlights shared molecular features, such as the rewiring of transcriptional networks and changes in cell identity, alongside key differences: reprogramming is a controlled process toward pluripotency, while tumorigenesis hijacks these pathways

aberrantly, causing loss of identity checkpoints and uncontrolled proliferation. Indeed, single-cell multiomics studies in murine models reveal that while plasticity (the ability to change fate) and identity (commitment to lineage) are regulated together in reprogramming, tumorigenesis involves deregulated plasticity without the safety “brakes” normal cells have^{48,49}. This uncoupling points to cancer risk but also offers opportunities to find strategies that separate beneficial plasticity from oncogenic transformation.

A complementary example involves forcing the differentiation of malignant cells into functional, non-proliferative ones. First established in acute promyelocytic leukemia with all-trans retinoic acid and arsenic trioxide⁵⁰, the approach is now applied to other malignancies such as acute myeloid leukemia⁵¹. These strategies show how modulating transcriptional and chromatin networks to restore normal cell fate can be more effective than indiscriminate cytotoxicity, reflecting a systems-level view of cell regulation and tissue homeostasis.

Activity 3: Promoting systems thinking as a catalyst for interdisciplinarity and precision medicine

This activity involves creating task forces to collaboratively rebuild teaching materials and classes into interactive, multidisciplinary courses grounded on systems thinking. Traditional clinical courses often focus on a single organ, causing content overlap and missed opportunities to address cross-system interactions. Systems biology’s integrative perspective aligns more closely with the foundational aim of (patho)physiology: understanding how organs and systems interact through regulation, feedback, and homeostasis. Explicitly connecting clinical

knowledge to systems biology helps students see them as complementary approaches.

Hypertension teaching provides a clear example. When addressed separately by different specialists, topics such as epidemiology, diagnosis, and initial workup are often repeated, while personalized approaches for specific populations and complex clinical contexts receive less attention. To address this, a multidisciplinary team created a coordinated course with a single introductory lecture followed by case-based sessions co-taught by multiple specialists. This streamlined structure reduced redundancy, clarified key concepts and learning objectives (detailed in supplementary data 2), and fostered genuine interdisciplinary dialogue.

We also developed a precision medicine course for medical students in their clinical training years (third to fifth year), in which clinicians and scientists collaboratively present common diseases and their clinical patterns within the frameworks of systems biology and precision medicine. The course examines how targeted therapeutic strategies, genomic profiling, and multi-omics analyses can be integrated into patient care, with attention to their broader systemic consequences. Systems biology provides the scientific basis for understanding complex biological networks. In turn, precision medicine translates these insights into clinical practice that sometimes need to be reductionist, for efficient diagnosis, prognosis, and therapy. Integrating both perspectives allows students to better shift between a molecular focus on targeted interventions and a systems-level view of disease and health policies, cultivating the integrative thinking required in contemporary medicine and policy making.

In this context, systems thinking offers a much-needed conceptual shift. It emphasizes the interdependence of biological, psychological, social, and environmental factors in health and disease, and encourages recognition of feedback loops, emergent properties, and the dynamic nature of complex systems. Although systems thinking is increasingly promoted by public health agencies (see for ref. 41), educators, and healthcare quality organizations, its implementation into the early years of medical school remains limited. Where present, courses are mostly restricted to global health or epidemiology courses^{42,43}.

Systems biology and systems thinking share conceptual foundations: both focus on integration across levels, networks, regulatory feedback, and emergent properties of complex systems. Introducing systems biology early in medical education offers far more than a technical or research-oriented perspective. It provides a conceptual framework that prepares students to think systemically, considering systems biology as a unifying paradigm for medical education⁴⁴. By learning how cells and molecules operate within dynamic, interconnected networks, students develop reasoning skills applicable across clinical care, public health, and health system domains.

Teaching cell biology through systems thinking

We illustrate this approach with an educational programme⁴⁵ that incorporates core principles of systems biology into medical training. Designed to demonstrate both feasibility and benefits, this programme consists of three activities spread across several years to promote progressive learning and reinforcement of systems biology concepts. The first, delivered at the very beginning of the first year, introduces foundational principles and establishes an epistemological framework for subsequent learning. The second, in the second year, provides a detailed example of systems biology in practice. The third, in the clinical phase, embeds systems thinking within organ-based teaching, linking basic science and clinical decision-making.

Activity 1: Introducing the principles of systems biology. This activity is built as an introductory class establishing systems biology as the foundational framework for teaching cell biology to first-year medical

reductionist teaching (e.g., one ligand, one receptor, one function) and only later introduce the complexity of networks, we present systems biology concepts from the outset. This early exposure positions molecular biology as a remarkable achievement of reductionist science that now requires extension into integrative, systems-level models³¹. The class begins by defining the concepts of system structure and organization, explores internal interactions within the system, expands to view the system as a whole, and finally examines its relationships with other systems⁴⁴. The class then builds on the presentation of the core *Principles of Systems Biology*, using seven principles inspired by Denis Noble in his influential essays, particularly his seminal 2006 article^{14,46}. These principles were originally conceived to counteract genetic determinism, a form of reductionism prevalent at the time. As Nobel laureate Sydney Brenner famously stated⁴⁷, and as Denis Noble emphasized: “The correct level of abstraction is the cell. The cell is the fundamental unit of structure, function, and organization.” Building on this perspective, we refer to the cell as the correct level of functional integration. In line with this, we have adapted several of these principles to the cellular scale and illustrated them with concrete examples drawn from the annual course in cell biology. This includes pathological processes and therapeutic strategies such as cancer or gene therapy for type 1 diabetes⁹ (see Box 1 and supplemental data 1 for further details and references). Recognizing that most 1st-year medical students have limited prior exposure to molecular and cellular biology, we adopted a pedagogical strategy aimed at making complex systems more accessible. Like Noble, we rely extensively on metaphors and analogies to build intuitive understanding¹⁴. For example, we compare the cell to a networked society, rather than a simple machine, in order to emphasize its dynamic, adaptive, and context-sensitive nature. This approach encourages students to move beyond static, linear representations and to appreciate the emergent properties and systemic interdependence that characterize living organisms. This conceptual grounding is then complemented in subsequent classes by classical content of cell biology (cell structures, molecular pathways), but with a deliberate emphasis on interconnections, regulatory feedback, and biological context.

Conclusion: preparing clinicians for complexity through systems thinking

Integrating systems biology from the outset represents a vital paradigm shift to prepare future clinicians for the complexity of modern medicine^{52,53}. Moving beyond the traditional reductionist, organ-based model, systems thinking offers a framework linking molecular, cellular, organismal, population and environmental levels, fostering a deep understanding of biological networks and their dynamic regulation⁵⁴. This approach aligns education with current scientific advances, strengthens interdisciplinary collaboration, and supports the principles of precision medicine. Embedding systems biology early and continuously within the curriculum can cultivate critical reasoning skills, cognitive flexibility, and an integrative mindset in medical students, enabling them to navigate multifaceted disease processes, interpret multidimensional data, and deliver personalized, context-aware patient care. Ultimately, embracing systems thinking is essential to train the next generation of physicians addressing the challenges of modern healthcare, where complexity and individual variability are the norm rather than the exception.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

L.D. drafted the original version, and was a major contributor in writing the manuscript. P.A.G. and G.L. were substantial contributors in writing and editing the manuscript. P.L. contributed to the conception and design of the manuscript, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Competing interests

L.D., G.L., and P.L. declare no conflicts of interest. PA Gourraud is the founder of Methodomics (2008) and its spin-off Big data Santé (2018- “Octopize” brand). He consults for major pharmaceutical companies, and start-ups, all of which are handled through academic pipelines (AstraZeneca, Amgen, Biogen, Boston Scientific, Cemka, Cook, Docaposte/Heva, Edimark, Ellipses, Elsevier, Grunenthal, Hemovis, Janssen, IAGE, Lek, Methodomics, Merck, Mérieux, Novartis, Octopize, Sanofi-Genzyme, Lifen, TunelInsight, Aspire UAE). PA Gourraud is a volunteer board member at AXA not-for-profit mutual insurance company (2021). He has no prescription activity with either drugs or devices. He receives no wages from these activities.

Additional information

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