Concept Paper

Forms Dynamics in Human Pathology: A Gestalt-Inspired Perspective on In Silico Ecophysical Modelling

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Forms Dynamics in Human Pathology: A Gestalt-Inspired Perspective on In Silico Ecophysical Modelling

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Featured Application

Forms dynamics provides a physically grounded modelling framework that can be applied to the analysis of complex pathological systems characterized by nonlinear interactions and multi-scale dynamics. The approach may support the development of physics-informed digital twins of disease processes, enabling the integration of clinical observations, metabolic data and physiological measurements into mechanistic dynamical models. Potential applications include modelling disease progression, exploring therapeutic perturbations and improving the interpretability of computational tools used for clinical decision support.

Abstract

Understanding pathological processes remains challenging because clinical descriptions primarily rely on phenotypic observations, while the underlying dynamical mechanisms that generate and stabilize disease states often remain implicit. This article introduces forms dynamics as an applied physics framework aimed at interpreting pathology as the dynamical evolution of structured configurations sustained by continuous exchanges of energy, matter and information with the environment. The approach integrates concepts from non-equilibrium thermodynamics, complex systems modelling and Gestalt-inspired structural reasoning. Within this perspective, pathological systems are represented through physically meaningful variables and fluxes whose interactions can be expressed through coupled balance equations or equivalent graphical schematizations. Empirical data, including clinical observations, diagnostic measurements and network-based analyses of biological interactions, inform the identification of relevant variables and pathways. Model calibration constrains parameters using physiological ranges, characteristic timescales and observed trajectories, while validation relies on the consistency of the resulting dynamical regimes with clinical phenotypes and responses to perturbations. Within this framework, physiological conditions correspond to stable attractors in the system's dynamical landscape, whereas pathological states emerge from altered coupling between variables and fluxes, leading to alternative stable or metastable regimes. By providing a physically grounded representation of pathological dynamics, forms dynamics offers a unifying modelling strategy for complex diseases and may support translational research, physics-informed digital twins and more interpretable computational tools for clinical decision support.

Keywords: forms dynamics; ecophysical modelling; non-equilibrium thermodynamics; systems pathology; complex systems modelling; biophysical modelling

1. Applied Physics on the Phenomenon of Human Pathology

The investigation of human pathology has progressively moved beyond purely descriptive and reductionist paradigms toward integrative and computational frameworks. Advances in computational pathology, systems biology and artificial intelligence have enabled the analysis of

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large datasets and the identification of complex structural patterns associated with disease [1–3], fostering the adoption of omics approaches from bench to bedside.

Despite these achievements, a fundamental limitation persists. Many current models excel at describing correlations, structural features and alterations, yet struggle to explain how pathological states physically emerge, evolve and stabilize over time. Prevailing approaches demonstrate a remarkable ability to detect structural organization and heterogeneity, identifying diverse molecular or genetic architectures associated with similar pathological phenotypes. However, as increasingly recognized in complex disease biology, structural diversity does not necessarily translate into functional diversity. Distinct structural configurations may converge toward a limited number of functionally relevant regimes, governed by rate-limiting processes and interaction constraints that shape system-level behaviour. Therefore, models focused primarily on structural associations often lack the ability to discriminate between pathological states that are structurally different but dynamically and functionally equivalent, or conversely, states that appear structurally similar yet differ in their underlying dynamical stability and evolution. This limitation highlights the need for frameworks capable of explicitly linking structure to function through the dynamical laws governing pathological processes [4]. Structural representations, often expressed as networks or connectivity maps, are sometimes disconnected from explicit physical laws governing interactions, energy exchange and dissipation [5]. As a result, the link between structure, dynamics and measurable physical quantities remains weak or implicit.

From an applied physics perspective, pathology can be regarded as a dynamic phenomenon occurring in open biological systems operating out of thermodynamic equilibrium, in which disease emerges from disordered and evolving interactions rather than from isolated alterations. Pathological states arise through complex, time-dependent coupling among molecular, cellular and tissue-level processes, whose collective behaviour cannot be inferred by examining individual components in isolation. As emphasized in systems pathology, biological disease is characterized by complex interaction patterns, variable temporal evolution and context-dependent penetrance, reflecting the absence of a static notion of homeostasis and the predominance of non-linear, adaptive dynamics [6]. Consequently, pathology must be understood as the manifestation of evolving system-level configurations sustained by continuous energy and matter exchanges with the environment, being understood as descriptors of the pathological metabolism, rather than as a fixed structural condition [7,8]. In such systems, structure, function and stability emerge from underlying biophysical-chemical interactions constrained by energy balance, transport processes and non-linear feedbacks. Addressing pathology at this level requires an inter-disciplinary stance, since models need to be supported by biological knowledge and data, clinical evidence, physically grounded, mathematically expressible and suitable for in silico implementation.

2. Network Analysis and System Thinking in Pathology: Achievements and Open Limitations

Network-based approaches have profoundly influenced contemporary pathology. In fact, network representations are particularly effective in identifying disease-associated modules, hubs and signatures, supporting integrative views that move beyond isolated molecular descriptors [9]. By representing biological components as nodes and their relationships as links, network pathology provides a powerful and flexible language for describing the structural organization of pathological phenotypes and their coordination across multiple biological scales. In this context, a phenotype is defined as the set of observable characteristics associated with a pathological condition, encompassing molecular, cellular, tissue-level and functional manifestations that arise from underlying biological interactions. Network representations allow such phenotypes to be mapped as structured configurations emerging from interconnected components, rather than as isolated traits [10]. This formalism has proven particularly effective in capturing phenotypic heterogeneity, modular organization and shared structural signatures across diseases, enabling the comparison and classification of pathological states based on their relational architecture rather than single markers.

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In parallel, system thinking and its quantitative extensions have incorporated dynamic elements into pathological modelling. Disease evolution is described through interacting variables, feedback loops and resource constraints, often formalized via stock–flow representations or ecological analogies [11,12]. By introducing time dependence, such models capture regime shifts and long-term patterns characteristic of disease progression, providing insights beyond static descriptions [13]. A common feature of these frameworks is the use of energy-related quantities as organizing variables. Energy availability, metabolic constraints and resource allocation are increasingly recognized as drivers of pathological behaviour, particularly in cancer and infectious disease [14,15]. Disease is often interpreted as the outcome of altered balances between competing processes mediated by feedback mechanisms across scales.

Nevertheless, despite their sophistication, network and system thinking approaches largely retain a descriptive or organizational character. Network representations encode structural relationships inferred from data, while system-level models typically rely on schematic abstractions that organize variables without explicitly deriving them from physical and chemical interaction laws [16]. Consequently, pathological structure is often prescribed or parameterized, rather than emerging as a necessary outcome of underlying physical dynamics. Graphical representations further contribute to ambiguity. While diagrams of stocks, flows and feedbacks are intuitively informative, they might differ epistemologically from physically grounded schematizations used in applied physics, which correspond to abstractions of interaction laws convertible into mathematical formulations such as coupled differential equations or equivalent circuits [17,18].

Consequently, network pathology and quantitative system thinking delineate a continuum from structural representations toward increasingly dynamic descriptions of disease. However, while capturing essential organizational features, these approaches leave open a fundamental question: how pathological forms arise and evolve as physical configurations governed by explicit interaction laws. Addressing this question motivates the introduction of form dynamics.

3. Form Dynamics: From Gestalt Physical Foundations to Interaction-Based Modelling

Clinical reasoning and semeiotic evaluation are fundamentally oriented toward the identification and classification of phenotypes, that is, the set of observable signs, symptoms and measurable traits associated with a pathological condition [19,20]. Within evidence-based medicine, such phenotypic descriptions are formalized into clinical hypotheses and tested through statistical comparisons, ensuring robustness, feasibility and clinical relevance [21]. However, while this framework is essential for diagnosis and decision-making, it remains intrinsically phenomenological: it describes what is observed, but not how or under which dynamical conditions such phenotypes emerge, persist or change over time.

In complex diseases, distinct patients may exhibit heterogeneous structural or molecular alterations while converging toward similar clinical phenotypes, whereas apparently similar phenotypic presentations may correspond to markedly different disease trajectories and responses to intervention [22,23]. This well-recognized limitation reflects the fact that clinical phenotypes are manifestations of underlying system dynamics, rather than direct indicators of the interaction laws governing pathological processes. Thus, questions formulated solely in clinical or semeiotic terms are insufficient to capture the dynamical mechanisms that generate and stabilize pathological forms.

To address this gap, it becomes necessary to introduce hypotheses formulated at the level of biophysical interactions, specifying the variables, constraints and couplings that govern the evolution of the system. Such hypotheses do not replace clinical reasoning, but operate at a complementary level, providing mechanistic priors that link observable phenotypes to the underlying dynamics of energy, matter and information exchange [24]. It is within this conceptual space between phenotypic description and dynamical explanation that the notion of forms dynamics is introduced. The concept of form has deep roots in physics. Early forms theory (Gestalten, in German) emerged from the idea that coherent structures arise from interacting fields rather than from the aggregation of independent

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parts [25,26]. In its original physical framing, however, Gestalt (i.e.,: "forms" in English) were largely treated as archetypal configurations with intrinsic stability properties, discussed in relation to stationary or quasi-stationary regimes (i.e., a form as a stable organization maintained by consistent interaction constraints). However, a structure cannot be separated from the dynamics that generate and sustain it: forms cannot be interpreted as static structures, but as dynamic entities maintained by continuous interactions. This view resonates with modern non-linear physics and self-organization theory [27,28]. The conceptual step introduced here is to move from archetypal forms in stationary state to complex forms dynamics. In other words, forms dynamics treats archetypal forms as a generative vocabulary: basic interaction-driven structures can be combined, nested and coupled to represent the time evolution of complex organization, rather than being restricted to isolated archetypes or steady-state templates. With this respect, Table 1 shows some examples of potential relationship between dynamic archetypal forms and biological phenomena in normal and pathological physiological processes.

Forms dynamics shares with system dynamics the use of similar representation languages. However, the two approaches differ in their epistemological foundations. In system dynamics, variables and causal links are often defined at a phenomenological level. In contrast, forms dynamics constrains the model structure through physically meaningful variables associated with independent exchanges of energy, mass and information, and derives system behaviour from balance relations grounded in non-equilibrium thermodynamics. In this sense, forms dynamics represents a physically grounded extension of system-level modelling rather than a variant of classical system dynamics. This perspective implies that, in analogy with network motifs in systems biology, recurrent archetypal dynamical structures may exist in pathological systems in relation to biochemical and regulatory networks, acting as interaction patterns with characteristic dynamical behaviour which may combine to generate complex phenotypic dynamics.

Table 1. Some examples of potential relationship between dynamic archetypal forms and bio-logical phenomena in normal and pathological physiological processes.

Archetypal motif	Dynamical behaviour	Biological example
Positive feedback loop	Bistability / switch	Cell fate decisions
Negative feedback loop	Homeostasis / regulation	Metabolic regulation
Coupled oscillators	Periodic dynamics	Circadian rhythms
Resource competition	Trade-offs and metabolic reprogramming	Cancer metabolism

This is why, consistently with developments in complex-systems modelling, recurrent "archetypal structures" can be systematically identified and analysed also in combination, in order to explain model behaviour from structure and to guide intervention design. In the literature, causal/stock–flow representations are explicitly translatable into formal graph-theoretic objects (e.g., adjacency matrices), enabling algorithmic detection of archetypes and their interacting loop-combinations rather than heuristic, post-hoc storytelling [18]. This provides a direct methodological analogue for the present perspective. In fact, in pathology, recurrent interaction patterns could be treated as archetypal "forms", then used to construct higher-order pathological dynamics by coupling these forms across scales and times.

A complementary argument comes from nonequilibrium physics, where multi-layered archetypal symmetric motifs can generate qualitatively distinct dynamical regimes (e.g., multiple

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steady states, metastability, multi-timescale relaxation), and where the relevant signatures emerge specifically in the transient dynamics, not only in the final steady state [29,30]. This reinforces the epistemological point behind form dynamics: archetypal configurations are physically meaningful not merely as static templates, but as building blocks whose coupling reshapes the dynamical landscape (stability, relaxation times, regime shifts), which is exactly the level at which pathological evolution and therapeutic perturbations must be interpreted.

In pathology, form is often described through structural representations (i.e.,: the phenotype), that characterizes a sufficient persistence over time, that allows to identify a certain pathology over multiple observation timescales. From an applied physics standpoint, however, such structures represent transient configurations of an underlying dynamical process. In this perspective article, form dynamics is introduced as an applied physics framework that treats pathological form as a time-dependent outcome of measurable variables and their interactions, while explicitly extending the Gestalt notion of archetypal forms into a compositional modelling principle for complex pathological dynamics

Although modern clinical practice enables the measurement of a vast number of biological quantities, the dynamics of a pathological system, as phenomenological dynamic system, can be reduced to a more limited set of independent variables, which govern its dynamics [31]. From a physical standpoint, only variables associated with independent exchanges of energy, mass or information contribute to the system's effective degrees of freedom, whereas many clinically observable quantities represent correlated or dependent manifestations of the same underlying processes. Consequently, the inclusion of all measurable variables does not necessarily improve the description of system dynamics, but may introduce redundancy and obscure causal relationships. Therefore, the minimal set of variables is defined as the smallest set required to close the balance equations governing the system's interaction with its environment, yielding a low-dimensional yet physically complete representation of pathological dynamics.

Within this framework, variables act as state parameters, while interactions represent effective physical couplings rooted in physical-chemical processes such as reaction kinetics, transport phenomena and energy dissipation. Importantly, the identification of such variables does not occur independently of empirical observation. Clinical data, diagnostic measurements and statistically validated associations provide essential information on system structure, guiding the selection of experimentally accessible quantities that meaningfully capture the dominant interaction pathways. Network representations naturally integrate within this approach by organizing empirical relationships among measurable quantities into coherent structural patterns. Rather than constituting the dynamical model itself, networks delineate the relational architecture of the system under study, highlighting relevant components, couplings and scales. Thus, within form dynamics, these representations can be reinterpreted as instantaneous structural projections of an underlying interaction-based dynamical system. Nodes within the representation, also identified as stocks, correspond to experimentally measurable variables, while links encode effective physical couplings inferred from data. In this way, graphical schematizations acquire a precise epistemological role, analogous to abstractions used in physical modelling and readily convertible into mathematical formulations, such as coupled balance equations or equivalent circuit representations [32].

As previously remarked, within this perspective the formulation of a form dynamics model does not proceed independently of empirical evidence. Clinical observations, semeiotic patterns and statistically validated associations inform the initial biophysical hypothesis by constraining the admissible variables, interactions and scales to be considered. Then, the resulting model represents a hypothesis-driven yet data-informed description of pathological dynamics, whose solutions are not assumed a priori to be clinically meaningful. Rather, only those dynamical regimes that are consistent with observed phenotypes, disease trajectories and statistically supported clinical evidence are retained as physically and clinically admissible representations of pathology.

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4. Ecophysical Modelling of Human Pathology: Variables, Rates and Stability

Living systems are open systems maintained far from thermodynamic equilibrium through continuous exchanges of energy, mass and information with their environment [24,33]. Within non-equilibrium thermodynamics, such systems are described in terms of state variables (stocks) and rates (fluxes), whose coupling governs macroscopic organization [34]. This framework, originally established by Prigogine, has been further developed in physical models of dissipative and anti-dissipative systems, provides a rigorous physical basis for biological organization sustained by continuous dissipation and compensatory mechanisms. At its core, this description is fundamentally energetic. Living systems persist far from thermodynamic equilibrium by continuously transforming, storing and dissipating energy, and their observable structure is inseparable from the underlying energetic flows that sustain it. From this standpoint, energy constitutes the primary state variable of biological organization, while matter and information act as carriers and mediators of energetic exchange [35]. Metabolic reactions, transport processes, mechanical work and signal transduction can all be interpreted as specific modalities of energy conversion, storage and redistribution across scales. Therefore, biological variables such as molecular concentrations, electrochemical potentials or mechanical stresses acquire meaning not as isolated descriptors, but as energetically constrained components of an integrated dynamical system.

The central role of energy in pathological organization and evolution is strongly supported by metabolomics studies, which prove that disease states are characterized by coordinated, system-wide reprogramming of metabolic fluxes rather than by isolated molecular abnormalities [36]. Across a wide range of pathologies, metabolomic studies consistently reveal reproducible alterations in energy production pathways, substrate utilization, redox balance and dissipation mechanisms, giving rise to disease-specific metabolic signatures that correlate with phenotype, progression and response to therapy [37]. Importantly, metabolomics does not merely provide high-dimensional molecular data, but captures functional information on the rates and directions of metabolic processes, effectively probing the energetic state space of biological systems. Clinical applications such as metabolic imaging, isotope tracing and pathway-level biomarkers further show that disease-associated phenotypes are linked to quantitative and qualitative changes in energetic flux distributions, often preceding overt structural or symptomatic alterations [38,39].

Within this biothermodynamic perspective, pathological processes emerge when the energetic balance sustaining physiological organization is altered. Rather than being reducible to localized molecular defects, disease corresponds to a reconfiguration of energetic pathways, dissipation regimes and compensatory mechanisms, as empirically observed through metabolomic fingerprints. Changes in the coupling between energy storage, energy fluxes and dissipation give rise to new dynamical regimes, which may remain stable over clinically relevant timescales and manifest as persistent pathological forms. Form dynamics provides the physical interpretation of these observations by embedding them within a biothermodynamic model of interacting variables and fluxes, linking energetic constraints to the emergence, stability and transformation of pathological forms.

Therefore, within form dynamics, pathology is treated explicitly as an energetic phenomenon occurring in open systems operating far from equilibrium. The formulation of variables and fluxes is guided by energetic consistency: only quantities contributing to independent energetic exchanges define the effective degrees of freedom of the system. This naturally leads to low-dimensional yet physically complete models, in which structure, function and stability are unified through energy-based balance relations. Mathematical and computational techniques required to implement such models are well established in the literature of non-equilibrium and stochastic thermodynamics and biological physics [24]. Instead, the novelty lies in the systematic application of these principles to pathological forms, explicitly linking energetic organization to clinical observables and disease evolution. With this respect, Table 2 summarizes the relationship between the clinical domain aspect, its physical interpretation and its related model representation.

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State variables (i.e.,: stocks) represent accumulative quantities such as molecular concentrations, electrochemical potentials, densities, mechanical stresses or stored free energy, while rates (i.e.,: flows) describe rates of transport, transformation or dissipation of energy, matter or information. In living systems, structure is not preserved despite dissipation, but because dissipation is continuously compensated by external work, typically chemical work associated with metabolic exchange [40]. Therefore, pathological processes correspond to altered regimes of coupling between variables and fluxes, resulting in qualitative changes of system-level dynamics. Within this framework, system structure is not imposed a priori, but inferred from empirical observations. Network-based and pathway-oriented approaches play a crucial role at this stage by revealing patterns of functional organization among measured variables, integrating molecular interactions, regulatory processes and clinically observed phenotypes. By combining high-dimensional biological data with phenotypic information derived from clinical and semeiotic evaluation, these methods identify coherent structural modules and dominant pathways that characterize pathological states. In form dynamics, such structures are not interpreted as static graphs, but as empirical representations of the interaction architecture underlying the system. Network-derived pathways indicate which variables are dynamically coupled and therefore which fluxes must be explicitly accounted for in the biophysical model. In this sense, network analysis provides a data-driven means to delineate the structural backbone of the system, while the subsequent dynamical formulation translates this structure into a set of interacting variables and fluxes governed by physical balance relations. Thus, phenotypes, as observed clinically, acquire a precise role within the modelling framework. In fact, they constrain the admissible structural configurations inferred from network analysis and guide the selection of variables relevant for describing pathological dynamics. Structure and phenotype are jointly determined by data, while their temporal evolution and stability are addressed through the energetic and dynamical principles of form dynamics.

Table 2. Relationship between the clinical domain aspect, its physical interpretation and its re-lated model representation.

Clinical domain	Physical interpretation	Modelling representation
Clinical phenotype	Observable manifestation of system dynamics	Attractor or metastable dynamical regime
Biomarkers	Observable projections of underlying state variables	Dependent readouts of system dynamics
Disease progression	Temporal evolution of system configuration	Trajectories in phase space
Therapeutic intervention	External perturbation acting on system parameters	Parameter variation or forcing term
Disease transition	Loss of stability or regime shift	Bifurcation or attractor transition

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From this perspective, pathology is naturally framed as a problem of physical modelling. System dynamics can be expressed through sets of coupled balance equations (typically differential equations) describing the temporal evolution of state variables under the action of fluxes and external constraints. Rather than being purely hypothetical or purely phenomenological, these equations constitute an evidence-constrained descriptive representation whose adequacy becomes a biophysical research hypothesis: the model is accepted insofar as it reproduces observed phenotypes, characteristic timescales and responses to perturbations within physically admissible regimes. The choice of variables and fluxes is informed by empirical evidence (clinical measurements, diagnostic data and statistically validated associations), but constrained by physical consistency: only quantities associated with independent exchanges of energy, mass or information contribute to the effective degrees of freedom of the system. Many clinically observable variables therefore act as dependent readouts of the same underlying processes and do not increase the dimensionality of the dynamical description.

Model calibration plays a central role in this process. Parameters, such as reaction rates, transport coefficients, or dissipation terms, are constrained using experimental and clinical data, including baseline measurements, longitudinal observations and known physiological ranges. In pathological systems, calibration is inherently challenged by nonlinearity, partial observability and high dimensionality, as well as by the frequent lack of complete knowledge of initial and boundary conditions. Within this context, calibration does not aim at exhaustive parameter fitting or the identification of a single optimal solution. Rather, it seeks to restrict the model to regions of parameter space that are physically plausible, biologically meaningful and consistent with observed characteristic timescales and system-level behaviours. Thus, empirical data define admissible dynamical regimes instead of unique parameter sets, acknowledging that different microscopic configurations may produce similar macroscopic phenotypes. A variety of calibration strategies addressing these challenges has been developed and extensively discussed in the literature, including frequentist and Bayesian approaches, robust and conditional calibration schemes, identifiability and sensitivity analysis, and global optimization or metaheuristic methods for nonlinear dynamical systems [41]. These methodologies provide a mature computational foundation for parameter inference in complex biological models and are not reviewed here. Within form dynamics, calibration functions as a selection mechanism on the space of admissible models: it excludes parameter regimes incompatible with empirical evidence while preserving those capable of reproducing observed phenotypes, temporal evolution and responses to perturbations. This regime-oriented view of calibration is consistent with the objectives of form dynamics, which focuses on identifying and characterizing stable and metastable pathological forms rather than on reproducing isolated measurements.

The resulting dynamical system generally admits multiple mathematically admissible solutions. Within form dynamics, pathological structure is interpreted as an emergent property of these solutions. Stable physiological conditions correspond to attractors in phase space, whereas pathological states arise from loss of stability, bifurcations or the emergence of alternative attractors [42,43]. Then, model validation becomes a central and non-trivial issue. In the context of dynamical systems, validation does not coincide with goodness-of-fit, nor with the mere reproduction of the data used for calibration. Rather, it concerns the ability of a model to generate trajectories and system responses that are consistent with independent empirical observations, known physiological constraints and experimentally accessible perturbations.

Importantly, not all mathematically consistent solutions are considered biologically or clinically relevant. Within form dynamics, admissible pathological forms are selected by imposing constraints derived from empirical observation at multiple levels: consistency with measured variables and their temporal evolution, compatibility with observed phenotypes and disease trajectories, and coherence with clinical and statistical evidence across conditions [44,45]. Solutions that violate reachability constraints, generate unobserved states, or fail to reproduce known transitions under realistic perturbations are discarded as physically or biologically implausible. Then, validation is initially

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approached as a process of exclusion and refinement, rather than confirmation of a single optimal solution. This perspective aligns with established approaches in systems biology and mathematical physiology, where inverse problems are typically ill-posed and multiple parameterizations or trajectories may fit the same data. In such settings, ensembles of admissible models are retained, and their predictive performance is assessed under new conditions, perturbations or boundary constraints. Within form dynamics, validation acquires a specific dynamical meaning: a model is considered valid insofar as it captures the qualitative organization of the pathological system (its stable regimes, transition pathways and response to interventions), rather than reproducing isolated measurements. This emphasizes predictive coherence and mechanistic plausibility over parameter identifiability, providing a physically grounded criterion for selecting pathological forms that are both dynamically admissible and clinically meaningful.

Perturbations, including therapeutic interventions, can be modelled as parameter variations or external forcing acting on variables or fluxes, allowing quantitative assessment of system response and stability [13]. Thus, disease progression is interpreted as a dynamical transition driven by redistribution of energy, matter or information, often occurring through continuous deformation of the dynamical landscape rather than abrupt structural failure. Within this framework, early warning signals, tipping points and regime shifts naturally emerge as physically grounded indicators of pathological evolution.

In this sense, form dynamics does not replace clinical reasoning, semeiotics or statistical validation, but provides a unifying physical layer in which these elements acquire mechanistic meaning. Clinical data and network-based representations inform the identification of relevant variables and couplings, while the ecophysical model constrains their dynamical interpretation. Structure and dynamics are therefore treated as inseparable aspects of pathology, grounded in non-equilibrium physics and expressed through experimentally testable models.

5. Toward Forms Dynamics as a New Applied Research Field

Form dynamics is proposed here as a distinct research field within applied physics, conceived as a general modelling approach for complex systems whose organization and evolution arise from constrained interactions among physically meaningful variables. From this standpoint, form dynamics is not intrinsically biomedical: it represents a universal physical methodology for studying systems operating far from equilibrium, in which structure, function and stability emerge from the interplay of energy, matter and information flows. Its theoretical foundations are rooted in non-equilibrium thermodynamics and dynamical systems theory, and its scope extends, in principle, to any complex system characterized by interacting subsystems and multi-scale organization.

Within this general framework, forms are treated as dynamical entities rather than static configurations. Archetypal interaction patterns, whose characteristics are already assessed in the literature, constitute elementary physical forms, which can be combined, coupled and reorganized to describe the evolution of complex systems over time [46,47]. In this sense, form dynamics provides a modelling language capable of capturing how macroscopic organization arises, persists and transforms as a result of underlying interaction laws, without being restricted to a specific application domain.

Human pathology represents a particularly relevant and challenging application of this general methodology. When instantiated in the biomedical context, form dynamics provides a physically grounded framework for modelling disease as a dynamically evolving organization, rather than as a collection of correlated abnormalities. Pathological states are interpreted as metastable dynamical regimes of a biophysical system, while clinical phenotypes correspond to macroscopic manifestations of these regimes. Disease progression and therapeutic response are naturally described as transitions within a dynamical landscape shaped by energetic and interaction constraints.

In this setting, form dynamics does not replace existing biomedical approaches such as network analysis, system thinking or data-driven modelling. Instead, it integrates them within a physically consistent modelling framework, where structural information extracted from data constrains the

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interaction architecture, and empirical observations delimit admissible dynamical regimes. Clinical reasoning and evidence-based medicine remain essential for defining relevance, feasibility and validation, while form dynamics provides the physical model through which such evidence is interpreted dynamically.

As a result, form dynamics can function both as a research tool and as a supporting framework for clinical practice. In translational research, it enables the formulation and testing of biophysical hypotheses that link molecular, cellular and tissue-level observations to clinically observable phenotypes. In the clinical context, it supports the interpretation of disease trajectories and therapeutic interventions as controlled perturbations of a dynamical system, offering insight into stability, compensatory mechanisms and potential regime shifts.

More broadly, the form dynamics framework provides a foundation for physics-informed in silico representations of pathological systems, enabling the exploration of counterfactual scenarios beyond purely statistical extrapolation. Because models are constrained by physical principles and calibrated against empirical data, such representations retain interpretability and mechanistic coherence while supporting simulation-based reasoning.

In summary, form dynamics defines a general applied physics methodology for complex systems, whose application to human pathology illustrates its capacity to integrate modelling, empirical evidence and clinical interpretation within a unified physical description. In this sense, pathology does not define the limits of form dynamics, but rather constitutes a domain in which its methodological potential becomes both scientifically and societally significant.

6. Conclusions and Outlook

The perspective developed in this article proposes forms dynamics as a physically grounded framework for interpreting human pathology as the dynamical evolution of structured configurations sustained by continuous exchanges of energy, matter and information with the environment. By combining concepts from non-equilibrium thermodynamics, complex systems modelling and Gestalt-inspired structural reasoning, this approach reframes pathological states as emergent dynamical regimes rather than as static structural conditions.

A key question concerns the operationalization of this conceptual framework. In practice, forms dynamics can be implemented through a sequence of methodological steps that are already well established within biophysics and systems modelling. First, empirical data derived from clinical observations, diagnostic measurements and omics datasets can be used to identify candidate variables and interaction pathways, often through network-based analyses that reveal structural modules and dominant couplings. Second, these empirically inferred structures can be translated into physically meaningful dynamical representations by formulating variables and fluxes consistent with conservation laws and energetic constraints. The resulting models can be expressed either mathematically, through coupled balance equations, or graphically, using schematizations equivalent to interaction circuits that encode the same dynamical relations. Third, model calibration and validation procedures allow the identification of admissible dynamical regimes consistent with physiological ranges, observed trajectories and responses to perturbations. Within this workflow, pathological forms correspond to stable or metastable dynamical configurations emerging from the calibrated system.

From a research perspective, this framework offers a unifying methodological language for the study of complex pathological systems. By focusing on energetically consistent variables and interaction laws, form dynamics complements purely statistical or data-driven approaches with mechanistic interpretability. It allows heterogeneous datasets (clinical measurements, metabolic profiles, physiological signals and molecular data, etc.) to be integrated within a physically constrained modelling structure. Such integration may contribute to bridging the gap between high-dimensional biomedical data and explanatory models capable of capturing disease mechanisms across scales.

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In the biomedical domain, the potential applications of this approach are particularly relevant for translational research and clinical decision support. Dynamical models calibrated on patient-specific data could serve as the basis for physics-informed digital twins of pathological systems, enabling the exploration of counterfactual scenarios and the prediction of system responses to therapeutic perturbations. Within this perspective, treatments may be interpreted as controlled interventions that modify system parameters, alter flux distributions or shift the stability landscape of the pathological system. Such a representation may improve the understanding of treatment resistance, disease progression and regime shifts in complex disorders such as cancer, metabolic disease or chronic inflammatory conditions. In other words, the proposed framework would support the identification of archetypal dynamic structures, currently associated to metabolic pathways, that could be used to implement the classification of different pathologies, their diagnosis and the identification of poly-target therapeutic strategies, that are now being investigated in pharmaceutical research. Moreover, this approach would move beyond the purely phenomenological basis that still prevails in clinical practice, while allowing to implement in silico approaches, that would allow to implement digital medicine tools for the identification of disease progression patterns, supporting more effective diagnostic and therapeutic approaches.

Beyond scientific and clinical implications, the broader impacts of this perspective may extend to economic and societal domains. Mechanistically interpretable models of disease dynamics could enhance the efficiency of biomedical research by guiding hypothesis generation, prioritizing experimental targets and reducing reliance on purely empirical trial-and-error approaches. In clinical practice, improved predictive modelling of disease trajectories may contribute to more personalized therapeutic strategies, potentially reducing costs associated with ineffective treatments and late-stage interventions. From a societal perspective, such developments are directly aligned with the objectives of sustainable healthcare systems and with the broader framework of the United Nations Sustainable Development Goals, particularly SDG 3 (Good Health and Well-being). By improving the mechanistic understanding of disease processes and supporting earlier and more targeted interventions, physically grounded models of pathology may contribute to enhancing health outcomes, optimizing resource allocation and strengthening the resilience of healthcare systems. Moreover, the development of physically interpretable models of pathology may support the emergence of more transparent and explainable biomedical decision-support systems, reinforcing trust in computational tools used in healthcare and promoting responsible integration of modelling approaches into clinical practice.

More broadly, forms dynamics should be viewed not only as a biomedical modelling strategy but as a general methodological approach for the study of complex physical systems. By treating structured configurations as dynamical forms emerging from interacting variables and fluxes, the framework may be applicable across multiple domains of applied physics where complex organization arises far from equilibrium. Within the specific context of human pathology, however, its primary value lies in providing a physically consistent bridge between clinical observations, biological data and dynamical system modelling. Future research will be required to develop standardized workflows, datasets and computational tools that allow systematic implementation of form dynamics in biomedical contexts. Empirical validation across different classes of diseases will be essential to assess its practical utility and predictive capability. If successfully operationalized, this approach may contribute to establishing a new research direction at the intersection of applied physics, systems biology and clinical medicine, in which pathological processes are studied as evolving physical forms governed by identifiable interaction laws.

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References

1. Barabási, A.-L.; Oltvai, Z.N. Network Biology: Understanding the Cell's Functional Organization. *Nat Rev Genet* **2004**, *5*, 101–113, doi:10.1038/nrg1272.
2. Vidal, M.; Cusick, M.E.; Barabási, A.-L. Interactome Networks and Human Disease. *Cell* **2011**, *144*, 986–998, doi:10.1016/j.cell.2011.02.016.
3. Sporns, O. The Human Connectome: A Complex Network. *Annals of the New York Academy of Sciences* **2011**, *1224*, 109–125, doi:10.1111/j.1749-6632.2010.05888.x.
4. Chakravarti, A.; Turner, T.N. Revealing Rate-Limiting Steps in Complex Disease Biology: The Crucial Importance of Studying Rare, Extreme-Phenotype Families. *BioEssays* **2016**, *38*, 578–586, doi:10.1002/bies.201500203.
5. Barabási, A.-L.; Gulbahce, N.; Loscalzo, J. Network Medicine: A Network-Based Approach to Human Disease. *Nat Rev Genet* **2011**, *12*, 56–68, doi:10.1038/nrg2918.
6. Dietel, M.; Schäfer, R. Systems Pathology—or How to Solve the Complex Problem of Predictive Pathology. *Virchows Arch* **2008**, *453*, 309–312, doi:10.1007/s00428-008-0656-z.
7. Kitano, H. Systems Biology: A Brief Overview. *Science* **2002**, *295*, 1662–1664, doi:10.1126/science.1069492.
8. Vander Heiden, M.G.; DeBerardinis, R.J. Understanding the Intersections between Metabolism and Cancer Biology. *Cell* **2017**, *168*, 657–669, doi:10.1016/j.cell.2016.12.039.
9. Gustafsson, M.; Nestor, C.E.; Zhang, H.; Barabási, A.-L.; Baranzini, S.; Brunak, S.; Chung, K.F.; Federoff, H.J.; Gavin, A.-C.; Meehan, R.R.; et al. Modules, Networks and Systems Medicine for Understanding Disease and Aiding Diagnosis. *Genome Med* **2014**, *6*, 82, doi:10.1186/s13073-014-0082-6.
10. Ranea, J.A.G.; Perkins, J.; Chagoyen, M.; Díaz-Santiago, E.; Pazos, F. Network-Based Methods for Approaching Human Pathologies from a Phenotypic Point of View. *Genes* **2022**, *13*, 1081, doi:10.3390/genes13061081.
11. Conte, L.; Gonella, F.; Giansanti, A.; Kleidon, A.; Romano, A. Modeling Cell Populations Metabolism and Competition under Maximum Power Constraints. *PLoS Comput Biol* **2023**, *19*, e1011607, doi:10.1371/journal.pcbi.1011607.
12. Surra, F.; Conte, L.; Cavarzerani, E.; Rizzolio, F.; Romano, A.; Gonella, F. Towards a Disease Digital Twin: Howard T. Odum's Legacy for Cancer Biology and Medicine. *Ecological Modelling* **2025**, *510*, 111326, doi:10.1016/j.ecolmodel.2025.111326.
13. Romano, A.; Casazza, M.; Gonella, F. Addressing Non-Linear System Dynamics of Single-Strand RNA Virus–Host Interaction. *Front. Microbiol.* **2021**, *11*, 600254, doi:10.3389/fmicb.2020.600254.
14. Pavlova, N.N.; Thompson, C.B. The Emerging Hallmarks of Cancer Metabolism. *Cell Metabolism* **2016**, *23*, 27–47, doi:10.1016/j.cmet.2015.12.006.
15. Olive, A.J.; Sassetti, C.M. Metabolic Crosstalk between Host and Pathogen: Sensing, Adapting and Competing. *Nat Rev Microbiol* **2016**, *14*, 221–234, doi:10.1038/nrmicro.2016.12.
16. Lambiotte, R.; Rosvall, M.; Scholtes, I. From Networks to Optimal Higher-Order Models of Complex Systems. *Nat. Phys.* **2019**, *15*, 313–320, doi:10.1038/s41567-019-0459-y.
17. Brown, M.T. A Picture Is Worth a Thousand Words: Energy Systems Language and Simulation. *Ecological Modelling* **2004**, *178*, 83–100, doi:10.1016/j.ecolmodel.2003.12.008.
18. Schoenenberger, L.; Schmid, A.; Schwaninger, M. Towards the Algorithmic Detection of Archetypal Structures in System Dynamics. *System Dynamics Review* **2015**, *31*, 66–85, doi:10.1002/sdr.1526.
19. Robinson, P.N. Deep Phenotyping for Precision Medicine. *Hum. Mutat.* **2012**, *33*, 777–780, doi:10.1002/humu.22080.
20. Hunt, D.L.; Haynes, R.B.; Hanna, S.E.; Smith, K. Effects of Computer-Based Clinical Decision Support Systems on Physician Performance and Patient Outcomes: A Systematic Review. *JAMA* **1998**, *280*, 1339, doi:10.1001/jama.280.15.1339.
21. Binkheder, S.; Wu, H.-Y.; Quinney, S.K.; Zhang, S.; Zitu, Md.M.; Chiang, C.; Wang, L.; Jones, J.; Li, L. PhenoDEF: A Corpus for Annotating Sentences with Information of Phenotype Definitions in Biomedical Literature. *J Biomed Semant* **2022**, *13*, 17, doi:10.1186/s13326-022-00272-6.
22. Devi, G.; Scheltens, P. Heterogeneity of Alzheimer's Disease: Consequence for Drug Trials? *Alz Res Therapy* **2018**, *10*, 122, doi:10.1186/s13195-018-0455-y.

 doi:10.20944/preprints202603.0521.v1

23. Johansson, Å.; Andreassen, O.A.; Brunak, S.; Franks, P.W.; Hedman, H.; Loos, R.J.F.; Meder, B.; Melén, E.; Wheelock, C.E.; Jacobsson, B. Precision Medicine in Complex Diseases—Molecular Subgrouping for Improved Prediction and Treatment Stratification. *J Intern Med* **2023**, *294*, 378–396, doi:10.1111/joim.13640.
24. Cao, Y.; Liang, S. Stochastic Thermodynamics for Biological Functions. *Quant. Biol.* **2025**, *13*, e75, doi:10.1002/qub2.75.
25. von Ehrenfels, C. About Form Qualities. *Vierteljahrsschrift für wissenschaftliche Philosophie* **1890**, *13*, 249–292.
26. Köhler, W. Die stationären elektrischen Ströme. In *Die physischen Gestalten in Ruhe und im stationären Zustand*; Vieweg+Teubner Verlag: Wiesbaden, 1920; pp. 133–153 ISBN 978-3-663-00291-8.
27. Haken, H. *Synergetics: Introduction and Advanced Topics*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2004; ISBN 978-3-642-07405-9.
28. Cross, M.C.; Hohenberg, P.C. Pattern Formation Outside of Equilibrium. *Rev. Mod. Phys.* **1993**, *65*, 851–1112, doi:10.1103/RevModPhys.65.851.
29. De Domenico, M.; Granell, C.; Porter, M.A.; Arenas, A. The Physics of Spreading Processes in Multilayer Networks. *Nature Phys* **2016**, *12*, 901–906, doi:10.1038/nphys3865.
30. De Domenico, M. More Is Different in Real-World Multilayer Networks. *Nat. Phys.* **2023**, *19*, 1247–1262, doi:10.1038/s41567-023-02132-1.
31. Daniels, B.C.; Nemenman, I. Automated Adaptive Inference of Phenomenological Dynamical Models. *Nat Commun* **2015**, *6*, 8133, doi:10.1038/ncomms9133.
32. Odum, H.T.; Odum, E.C. *Modeling for All Scales: An Introduction to System Simulation*; Academic Press: San Diego, 2000; ISBN 978-0-12-524170-0.
33. Sertorio, L.; Tinetti, G. Available Energy for Life on a Planet, with or without Stellar Radiation. *Il Nuovo Cimento C* **2001**, *24*, 421–444.
34. Prigogine, I.; Nicolis, G. Self-Organisation in Nonequilibrium Systems: Towards A Dynamics of Complexity. In *Bifurcation Analysis*; Hazewinkel, M., Jurkovich, R., Paelinck, J.H.P., Eds.; Springer Netherlands: Dordrecht, 1985; pp. 3–12 ISBN 978-94-009-6241-5.
35. Sertorio, L.; Renda, E. *Orbits and life in the Universe*; Aracne: Roma, 2012; ISBN 978-88-548-5664-6.
36. *Metabolomics and System Biology in Human Health and Medicine*; Jones, O.A.H., Ed.; CABI PUBLISHING: S.l., 2019; ISBN 978-1-78639-542-9.
37. Johnson, C.H.; Ivanisevic, J.; Siuzdak, G. Metabolomics: Beyond Biomarkers and towards Mechanisms. *Nat Rev Mol Cell Biol* **2016**, *17*, 451–459, doi:10.1038/nrm.2016.25.
38. Buescher, J.M.; Antoniewicz, M.R.; Boros, L.G.; Burgess, S.C.; Brunengraber, H.; Clish, C.B.; DeBerardinis, R.J.; Feron, O.; Frezza, C.; Ghesquiere, B.; et al. A Roadmap for Interpreting 13C Metabolite Labeling Patterns from Cells. *Current Opinion in Biotechnology* **2015**, *34*, 189–201, doi:10.1016/j.copbio.2015.02.003.
39. Faubert, B.; Solmonson, A.; DeBerardinis, R.J. Metabolic Reprogramming and Cancer Progression. *Science* **2020**, *368*, eaaw5473, doi:10.1126/science.aaw5473.
40. Kondepudi, D.K.; De Bari, B.; Dixon, J.A. Dissipative Structures, Organisms and Evolution. *Entropy* **2020**, *22*, 1305, doi:10.3390/e22111305.
41. Villaverde, A.F.; Tsiantis, N.; Banga, J.R. Full Observability and Estimation of Unknown Inputs, States and Parameters of Nonlinear Biological Models. *J. R. Soc. Interface.* **2019**, *16*, 20190043, doi:10.1098/rsif.2019.0043.
42. Wang, J.; Zhang, K.; Xu, L.; Wang, E. Quantifying the Waddington Landscape and Biological Paths for Development and Differentiation. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 8257–8262, doi:10.1073/pnas.1017017108.
43. Scheffer, M.; Carpenter, S.R.; Dakos, V.; Van Nes, E.H. Generic Indicators of Ecological Resilience: Inferring the Chance of a Critical Transition. *Annu. Rev. Ecol. Evol. Syst.* **2015**, *46*, 145–167, doi:10.1146/annurev-ecolsys-112414-054242.
44. Chérel, G.; Cottineau, C.; Reuillon, R. Beyond Corroboration: Strengthening Model Validation by Looking for Unexpected Patterns. *PLoS ONE* **2015**, *10*, e0138212, doi:10.1371/journal.pone.0138212.
45. Darabi, N.; Hosseinichimeh, N. System Dynamics Modeling in Health and Medicine: A Systematic Literature Review. *Syst. Dyn. Rev.* **2020**, *36*, 29–73, doi:10.1002/sdr.1646.
46. Wolstenholme, E.F. Towards the Definition and Use of a Core Set of Archetypal Structures in System Dynamics. *System Dynamics Review* **2003**, *19*, 7–26, doi:10.1002/sdr.259.

 doi:10.20944/preprints202603.0521.v1

47. Sánchez, M.A. Exploring the Landscape of System Dynamics Archetypes: A Systematic Review. *Syst Res Behav Sci* **2025**, *42*, 1618–1632, doi:10.1002/sres.3066.