LESSONS FROM PSEUDOSCIENCE IN BIOLOGY

Troy A. Kervin
Division of Structural Biology, Nuffield Department of Medicine, University of Oxford, Oxford OX3 7BN, UK
troy.kervin@magd.ox.ac.uk

Madhur Mangalam
Department of Biomechanics, University of Nebraska at Omaha, Omaha, NE 68182, USA
mmangalam@unomaha.edu

November 17, 2025

ABSTRACT

We review three pseudoscientific frameworks that currently dominate their respective fields in biology but are now being phased out by each field's cognoscenti: the modified lipid raft theory in membrane biology, the oxidative stress as disease narrative in physiology, and the Free Energy Principle in brain sciences. Over time, each became increasingly vague, unbounded, and detached from reality. These frameworks have diverted resources, biased training, and created commercial ecosystems that exploit scientific terminology while evading empirical accountability. We observe that fields operating at higher spatial and organizational scales appear especially vulnerable to such pseudoscientific drift. The lipid raft theory remained confined to membrane biology; the oxidative stress as disease theory expanded across organ systems and disease domains; and the Free Energy Principle has been invoked to explain virtually every process in the universe. We suggest interventions that can displace these frameworks and prevent similar ones from emerging.

Keywords Pseudoscience · Lipid raft · Oxidative stress · Free Energy Principle · Theoretical overreach · Empirical constraint · Theory drift · Rhetorical portability · Falsifiability · Conceptual frameworks

1 Introduction

Pseudoscience occupies an ambiguous and uncomfortable space within scientific culture. It does not typically lack complexity or sophistication; many pseudoscientific frameworks are labyrinthine and include mathematical arguments. Nor does it lack eminent supporters; it is common for scientists in positions of institutional power to endorse pseudoscientific theories. These characteristics make pseudoscience all the more deceptive and challenging to dismantle. In recent years, biology has been particularly vulnerable to pseudoscience [1], as demonstrated by the rise of the modified lipid raft theory in membrane biology, the detoxification from oxidative stress narrative in physiology, and the Free Energy Principle in brain sciences. The trajectories of these three frameworks illustrate the counterproductive and expansive nature of pseudoscience and are examined here as case studies.

As challenges mounted, each of these pseudoscientific frameworks underwent conceptual drift, expanding their scope while relaxing validity criteria. This has made each framework impossible to discredit with scientific arguments alone. The lipid raft theory, initially a specific hypothesis about how a subset of proteins and lipids organize, now encompasses nearly any observed membrane region that is conformationally ordered. The oxidative-stress narrative, once testable through redox markers, now explains both disease and health. The Free Energy Principle, initially a formal model of neural inference, although with very questionable assumptions, now aspires to explain all living processes from thermodynamics to social behavior. In each case, the theory's boundary with metaphor erodes until criticism itself is reinterpreted as validation. This expansion superficially mimics what might be expected of a genuinely broad and important principle, yet lacks the corresponding empirical constraints.

Understanding this drift, alongside other pseudoscientific features embodied by these frameworks, is a matter of scientific hygiene. The consequences of allowing pseudoscience to take root within biology are profound: resources are misallocated, younger scientists learn to confuse persuasion with rigor, and the field's capacity for self-correction is quietly undermined. Without corrective measures, it is likely that many intelligent scientists who have not yet thought deeply about pseudoscience in their field will get swept up in it, especially since pseudo-theories often exploit a category of blunders that nearly all humans are susceptible to. Here, we aim to make the hidden standards of good science explicit, show how pseudoscience develops in practice, and offer practical solutions. Specifically, we (*i*) clarify what distinguishes science from pseudoscience; (*ii*) illustrate these distinctions with the three case studies; and (*iii*) recommend practical measures to uphold scientific rigor. The result: clearer guidance for students, better standards for journals, and a path toward theories that prove themselves through rigorous testing.

2 Demarcating science from pseudoscience

Many demarcation criteria have been proposed [2–11]. We will keep our central criterion broad: *pseudoscience* denotes a framework that appears scientific but can be identified as scientifically counterproductive through philosophical analysis alone, such as by recognizing logical fallacies or internally contradictory claims. It often manifests as conceptual sprawl and shifting definitions, as well as hypotheses labeled "testable" whose testability evaporates when confronted with data. These are not harmless quirks but systematic frictions that waste effort, spread confusion, and prevent accumulation of reliable knowledge.

As the below analysis shows, this expansion is often a symptom of trying to hide one or more underlying flaws, such as conceptual mistakes that ignore what was already known, or empirical failures that emerge when testing an initially scientific proposal. Pseudoscience thus often arises from dying science [7] and can be identified without new experiments. If experiments were required to recognize pseudoscience, this would imply uncertainty about its truth, suggesting the need for scientific inquiry.

Labeling a framework as pseudoscience will provoke resistance, especially when the framework has institutional backing and loyal practitioners. This pushback is inevitable but does not diminish the diagnostic value. In fact, clearly identifying pseudoscience becomes essential precisely because such frameworks exploit their superficial resemblance to science to claim authority they have not earned. Philosophical critique paired with promotion of disciplined alternatives, remains an effective strategy for confronting pseudoscience.

Diagnostics Two very useful diagnostics of pseudoscience are *ad hoc* modifications which contradict the original theory, and *motte–and–bailey* maneuvers [12]. While some have argued that the concept of *ad hoc* modifications is too poorly defined to be helpful [13], we believe it is appropriately used as a term for describing modifications (*i*) applied after-the-fact, in response to contradictory evidence, and (*ii*) nontrivially contradicting the original theory. Under this definition, *ad hoc* modifications are, in all cases, inferior to creating a new theory with the same content but a different label to disambiguate contradictory concepts. This fits within our demarcation that pseudoscience can be identified by philosophical analysis: it is confusing and undesirable to use the same name for two contradictory things, especially when one uplifts the other. Similarly, the *motte–and–bailey* fallacy is a deceptive switch-out: the *motte* is a modest, defensible claim few would dispute, while the *bailey* is a controversial claim that attracts attention, status, and resources. When challenged, proponents retreat to the motte; in promotional contexts, they expand to the bailey. Unlike *ad hoc* modifications, the motte and bailey need not be contradictory, but the fallacy still confounds two different claims. Both of these maneuvers allow scope to grow and constraint to shrink, lexical drift under pressure, and "wins" accrued by mere relabeling. The pattern is visible across our three cases (**Table 1**).

Case selection and method. We examine lipid rafts, the oxidative-stress narrative, and the Free Energy Principle because each has strongly influenced training, funding, and discussion within its field, shows a documented history of expanding its claims while loosening its standards, and has at least one rigorous alternative that permits direct comparison (the proteolipid code for membranes, redox systems biology for physiology, and standard control/Bayesian RL models for behavior and brains). In all three cases, vague language has invited commercialization, turning disputed ideas into marketable "innovations," research consortia, or AI platforms that trade clarity for financial appeal.

These frameworks also differ in instructive ways. Many membrane biologists embraced lipid rafts primarily due to the absence of an alternative; a gap only recently filled [14–16]. By contrast, the Free Energy Principle is one of hundreds of highly general, competing frameworks in brain science, yet it dominates this crowded landscape [17–21]. These cases represent opposite ends of a spectrum: lipid rafts filled a conceptual vacuum and persisted through inertia, while the Free Energy Principle proliferates through aggressive promotion in an already saturated field. The detoxification from oxidative stress narrative occupies somewhat of a middle ground, since its contender has been gradually revealed and

Table 1: Motte–bailey audit across the three case studies.

Framework	Motte (defensible core)	Bailey (expansive claim)
Lipid rafts	Ordered lipid–protein heterogeneity exists	Stable, sterol/sphingolipid L_o platforms preexist and *recruit* proteins
Oxidative stress	Excess/reactive species can damage macromolecules; redox enzymes buffer local chemistry.	"Oxidative stress" explains most disease/aging; generic antioxidants or "detox" regimes broadly prevent or reverse pathology across contexts.
FEP/Active inference	Variational free energy is a valid bound used in approximate Bayesian inference and control.	*All* living systems (cells, brains, societies) persist by minimizing (expected) free energy; Markov blankets carve nature at the joints; AGI should follow suit.

embraced through experimental nuance. In what follows, we highlight initial flaws, expansion of scope, and persistence features that allow comparisons to be made between these pseudosciences.

Box 1. A working guide to keeping theories scientific

Good theories buy scope with constraint. Before the figures multiply and the vocabulary begins to travel, pin words to measurements. Say what each central term *means in the lab*: which signal, which probe, which unit, which exclusion rule. If the noun drifts while the assay stays vague, you are bartering away precision for poetry.

Name the *bridge* if you plan to cross levels. A claim that runs from molecules to behavior must carry a map: variables, compartments, and timescales at each stop, plus the interventions that move them. Portability without a bridge is just relabeling.

Write down how you could be wrong, in advance, and resist the temptation to add escape hatches later. Failure conditions are the spine of a scientific theory. If a result lands outside a declared bound and the response is to widen the bound, the theory is learning how not to lose, not how to predict.

Do not win on parameter freedom. Put your account next to a strong alternative with a similar budget of states, priors, and knobs. Let both see the same data, and then ask for performance where neither model was tuned: out-of-sample, out-of-domain, or under a perturbation you held back on purpose.

Treat instruments as arguments. Use selective approaches, orthogonal readouts, and rescues. Avoid protocol-defined "success," single-probe stories, and metrics that integrate away the very compartment or timescale where your mechanism is supposed to live.

Watch your language after a null. Healthy theories narrow: definitions get tighter, claims retreat to where they still bite. Drift in the other direction—broader terms, softer edges, expanding umbrellas—is the signature of a program protecting itself rather than confronting the world.

Finally, when the stakes are high, share the pen. Write the protocol with your critics, post it, and let the outcome stand. Transparency and preregistration are not red tape; they are the simplest way to turn rhetoric into risk.

Use this box as a habit, not a hurdle. If most of these practices are in place before you see the data, you are doing science. If several are persistently absent while the scope of the claim keeps growing, you are courting pseudoscientific drift.

3 The lipid raft theory

> Like Hercules facing the Hydra, disproving one raft theory spawns two more; the only winning move is to torch the entire beast.

Having established our demarcation criteria, we begin with the lipid raft theory, which exemplifies how bold hypotheses can devolve into unfalsifiable rhetorical constructs. The lipid raft theory was proposed in the late 1990s to explain protein organization and trafficking within cholesterol-rich membranes such as the Golgi apparatus and plasma membrane [22]. Initially, it advanced a falsifiable claim: sphingolipids and cholesterol spontaneously cluster through direct molecular

interactions to form tightly packed regions that selectively recruit specific proteins. When high-resolution microscopy failed to detect such structures and biophysical measurements revealed no tendency for cholesterol and sphingolipids to spontaneously cluster under physiological conditions, the hypothesis should have been abandoned. Instead, it metastasized into a nebulous and unfalsifiable framework. "Rafts" eventually became the "most popular organelle for proteomic studies" [23], with the term applied promiscuously to virtually any membrane region exhibiting detectable lipid order or protein clustering. The lipid raft trajectory illustrates three diagnostic features of pseudoscience: an initial flaw of neglecting simpler alternatives, expansion of scope accompanied by proliferation of mutually contradictory variants, and persistence despite emergence of more empirically rigorous theoretical frameworks.

3.1 Initial flaw: Neglecting simpler alternatives

Although the original lipid raft theory was falsifiable, it violated Occam's razor. The hypothesis proposed a two-step process: (*i*) spontaneous assembly of tightly packed lipid platforms through lipid–lipid interactions, followed by (*ii*) selective recruitment of specific proteins into these preformed platforms [22, 24, 25]. A simpler mechanistic alternative was always available: proteins cluster directly without a prior platform, and any observed lipid ordering arises as a consequence of direct or indirect protein interactions. This alternative is more parsimonious because it requires neither assumption *i* nor *ii*, both of which face severe thermodynamic obstacles. For example, Assumption *i* requires lipid–lipid interactions to be sufficiently strong to form stable, tightly packed platforms; a claim that remains experimentally unsubstantiated under physiological conditions despite decades of investigation [26, 27]. Assumption *ii* posits that proteins can partition into these hypothetically dense platforms despite the substantial free energy barrier such lipid packing would impose on protein insertion and lateral diffusion. The direct protein clustering mechanism explains the same observations while avoiding both problematic assumptions. That said, the original hypothesis can be recognized for its boldness in proposing a specific, testable mechanism. We leave it to readers to decide whether the original lipid raft theory represents legitimate science that proved incorrect or constitutes a misstep comparable to N-rays and polywater.

3.2 Expansion: Many contradictory versions

Regardless of whether the original lipid raft theory possessed scientific merit, the subsequent proliferation of mutually contradictory modified versions has impeded scientific progress. Numerous modifications have been proposed: some purely semantic [28, 29], others making incremental adjustments [30, 31], a few building on the original framework [24, 25], and still others departing in entirely new directions [32, 33]. A central problem is that, while individual modifications might represent genuine theoretical advances, this possibility becomes indistinguishable within an archipelago of mutually incompatible theories sharing identical nomenclature [34]. The aggregate effect is an unfalsifiable framework that perpetuates conceptual confusion rather than resolving it [35, 36].

One influential modification reinterprets lipid rafts as liquid-ordered phases akin to those arising from equilibrium phase separation [37, 38]. This analogy is misleading: the model membrane systems demonstrating equilibrium phase separation, which are typically three-component lipid mixtures studied *in vitro*, only superficially resemble physiological membranes, which operate far from thermodynamic equilibrium and contain hundreds to thousands of distinct lipid and protein species with asymmetric transbilayer distributions [16]. Nevertheless, this comparison propagated the myth that cellular membranes spontaneously partition into coexisting liquid-ordered and liquid-disordered phases [39].

The raft concept has also been extended to organisms such as bacteria that lack cholesterol [33], where "rafts" in this context probably refers to protein clusters (although we cannot guarantee this). Thus, protein assemblies likely driven predominantly by direct protein-protein interactions [40, 41] are retrospectively relabeled as lipid raft phenomena. Some proponents have even claimed that the lipid raft theory is synonymous with membrane organization itself [35], exemplifying the motte–and–bailey fallacy while potentially expropriating credit from theories of membrane compartmentalization that predate raft proposals by decades [42]. Ultimately, attempting to rescue the lipid raft framework through cascading *ad hoc* modifications has proven inferior to developing new theories that abandon raft lexicon. This realization motivated the proteolipid code—a deliberately provocative proposal that gains falsifiability by rejecting both original and modified lipid raft theories [15, 16].

3.3 Persistence: Poor match against the proteolipid code

The decline of the lipid raft framework created space for a more empirically disciplined alternative. Michael Overduin and co-author T.A.K. introduced the proteolipid code to restore empirical constraint to membrane biology [43, 15]. The model uses as its foundational principle the concept of lipid fingerprints—unique lipid distributions that surround membrane proteins [44, 15]. The proteolipid code proposes that proteins cluster together with their lipid fingerprints without requiring preexisting lipid platforms, inverting the initial raft logic. These fingerprints constitute measurable

entities through lipidomics, site-directed mutagenesis of protein–lipid contact residues, and molecular dynamics simulations.

Crucially, the proteolipid code achieves falsifiability by explicitly contradicting not only the original lipid raft theory but also several other influential frameworks including the picket fence model [45], tiered mesoscale domain model [30], and the Shelby–Veatch phase separation model [16, 32, 46]. The architects of these competing theories and many of their collaborators have invested careers searching for lipid rafts and attempting to extrapolate equilibrium phase separation from simplified model systems to physiological membranes. The proteolipid code asserts these efforts were fundamentally misdirected, questions the validity of certain experimental methodologies [47], and redirects investigation toward more empirically tractable questions: resolving protein–lipid interactions through molecular dynamics and cryo-electron microscopy, for instance. Moreover, by establishing falsifiable mechanistic principles, it acts as a springboard for derivative hypotheses that inherit its empirical discipline [48, 49]. Although the proteolipid code currently remains broad in scope, it will progressively narrow through refinement and auxiliary theory development. Rather than rescuing an initially narrow claim through endless *ad hoc* modifications, it is more productive to begin with a broad yet meaningful framework that stimulates development of increasingly specific auxiliary theories.

4 The detoxification from oxidative stress narrative

> The dose makes the poison, but the narrative makes the cure—even when there is no disease to treat.

The detoxification from oxidative stress narrative is now primarily disseminated by supplement manufacturers and lifestyle media, while research biochemists increasingly regard it with skepticism, deploying the term "oxidative stress" only as residual professional jargon or communicative shorthand [50]. We therefore refrain from characterizing the entire oxidative stress research program as pseudoscience. Our critique is directed instead at the "perpetual disease" or "detoxification" narratives propagated in mainstream media—simplistic and alarmist framings that distort the underlying biology and are routinely exploited for commercial gain. The oxidative stress program originated as a testable biochemical hypothesis: reactive oxygen and nitrogen species (ROS/RNS) constitute harmful metabolic byproducts that can overwhelm enzymatic and small-molecule defenses, causing macromolecular damage [51–55]. This initial formulation usefully organized known biochemical components—enzymes (superoxide dismutase, catalase, peroxiredoxins, glutathione systems), damage markers (lipid peroxidation, protein carbonylation, oxidative DNA lesions), and pathological contexts (inflammation, toxicology, ischemia-reperfusion injury). However, the clinical term "detoxification" migrated from its legitimate meaning—hepatic biotransformation and renal clearance of xenobiotics—into lifestyle marketing, where generic antioxidants and cleanses promised to purge unspecified "toxins" through mechanisms never articulated. We highlight three diagnostic features: reliance on methodologically discredited assays, institutional pressure to maintain a simplified public narrative, and persistence despite systematic inability to accommodate empirical nuance.

4.1 Initial flaw: Unreliable methods

Standard laboratory methods for quantifying oxidative stress proved systematically unreliable [56], yet this foundational inadequacy remains ignored in detoxification marketing. TBARS and malondialdehyde assays substantially overestimate lipid peroxidation through artifactual oxidation during sample processing [57]. The fluorescent probe DCFH-DA reacts promiscuously with numerous cellular reductants and oxidants beyond its intended target hydrogen peroxide [58, 59]. Measurements of "protein carbonyls" increase artifactually from sample handling and provide no information about which proteins are modified or whether modifications are functionally consequential [60]. Most critically, measuring total glutathione redox ratios (GSH/GSSG) in tissue homogenates obliterated the essential question: *where* within the cell does oxidant signaling or damage occur—mitochondrial matrix versus cytoplasm versus peroxisomes—and at what temporal scale [61–63]?

These methodological inadequacies allowed researchers to detect "oxidative stress" in virtually any biological sample, whether or not oxidant chemistry played any causal role in the phenotype under investigation [64–67]. In contrast, genetically encoded fluorescent biosensors (HyPer, roGFP2-Orp1) [68–70] enabled spatiotemporally resolved measurements of hydrogen peroxide dynamics in living cells [71]. These methods revealed that hydrogen peroxide functions as a localized signaling molecule rather than a diffuse damaging agent, with brief subcellular bursts near plasma membranes proving essential for growth factor receptor signal transduction [72, 73] and immune cell activation [74].

These spatiotemporally resolved approaches demonstrated that oxidants are not uniformly deleterious but execute specific signaling functions within defined cellular compartments and kinetic windows.

4.2 Expansion: Incentive to perpetuate a simple story

The original oxidative stress predictions were systematically falsified by rigorous clinical testing. Antioxidants prevent health-promoting effects of physical exercise in humans [75, 76]. Large-scale randomized controlled trials of broad-spectrum antioxidant supplementation (vitamin E, β-carotene, selenium) failed to prevent cardiovascular disease, cancer, or all-cause mortality [77–80]. More disturbingly, in cohorts of smokers and asbestos-exposed workers, high-dose β-carotene supplementation significantly *increased* lung cancer incidence and mortality, directly contradicting the hypothesis that antioxidants are uniformly cytoprotective [81]. Mechanistic cell biology subsequently explained these failures: low, spatially restricted concentrations of hydrogen peroxide are biochemically *necessary* for normal signal transduction. Hydrogen peroxide transiently oxidizes specific regulatory cysteine thiols in protein tyrosine phosphatases, transcription factors, and metabolic enzymes, thereby controlling growth factor responses, innate immunity, and metabolic homeostasis. Indiscriminate antioxidant supplementation disrupts these tightly regulated oxidant-mediated signaling cascades [71–74]. Genetic disruption of specific NADPH oxidase isoforms (NOX1, NOX2, NOX4) produced tissue-specific and pathway-specific phenotypes rather than the broad health improvements promised by detoxification narratives [82].

Each negative result should have compelled the field to narrow its claims and refine its mechanistic models. Instead, the narrative expanded through *ad hoc* modifications: failed clinical trials became "problems of dosing or timing," harmful supplementation effects were relabeled "the antioxidant paradox," and new terminology—"oxidative eustress," "hormesis," "redox adaptation"—was introduced to explain away systematic disconfirmations [83]. This conceptual expansion was sustained by institutional pressure to maintain a simple, marketable story for public consumption and by commercial incentives that created self-reinforcing feedback loops preventing hypothesis abandonment among lay audiences [50]. The conceptual revisions that have deepened our understanding of cellular redox regulation appear *ad hoc* when viewed as patches to the original oxidative stress theory, yet they become coherent and scientifically justified when situated within the broader and more integrative framework of redox systems biology.

4.3 Persistence: Inability to accommodate nuance

A more empirically disciplined framework has emerged to supersede the oxidative stress narrative. In redox systems biology (sometimes termed the "redox code"), oxidants, enzymatic sources, thiol-based sinks, and protein targets are understood as components of interconnected biochemical networks governed by chemical identity, second-order rate constants, stoichiometric relationships, and subcellular compartmentation [84]. The analytical focus shifts from "oxidative stress" as an abstract physiological state to mechanistically specific questions: which oxidant species (hydrogen peroxide, peroxynitrite, hydroxyl radical), generated by which enzymatic source (NOX2, NOX4, mitochondrial complex I/III), acts upon which target cysteine residues (for instance, peroxiredoxin-mediated relay oxidation of protein tyrosine phosphatases or KEAP1 sensor cysteines), within which subcellular compartment and temporal window, and with what thiol-dependent repair capacity (thioredoxin versus glutaredoxin systems). Redox proteomics has systematically mapped regulated, reversible cysteine oxidations on specific protein sites, revealing targeted signaling networks rather than nonspecific oxidative damage [84].

Redox systems biology does not constitute a grand explanatory theory but rather provides a disciplined analytical framework accommodating mechanistically testable hypotheses that the oxidative stress narrative neglected. It therefore contrasts with the proteolipid code, which offers both a holistic perspective and falsifiable general mechanism [15]. Within this refined framework, the systematic failure of broad-spectrum antioxidant interventions becomes biochemically predictable: indiscriminate oxidant scavenging disrupts essential compartmentalized signaling while ignoring the kinetic constraints and spatial organization that govern redox control in living cells.

5 The Free Energy Principle

When a bound forgets its bounds...

The Free Energy Principle (FEP) originated as a mathematically correct identity: under variational inference, one can bound (and thereby minimize) surprise by minimizing a tractable quantity called variational free energy [17–21]. This identity is occasionally useful as a variational inference objective for approximate Bayesian filtering and control within restricted generative model classes, albeit requiring assumptions such as steady-state dynamics and ergodicity of

biological processes. The framework's transformation into pseudoscience began when this computational book-keeping device was elevated into an ontological principle—asserting that all organisms, brains, cells, and societies *exist because* they minimize (expected) free energy. As empirical challenges accumulated, theoretical scope expanded, definitions drifted, and the once-modest inference heuristic metastasized into a purported metaphysics of life itself [85–93]. This trajectory exemplifies pseudoscientific drift where questionable foundational assumptions constitute the initial flaw, systematic evasion of empirical constraint through conceptual flexibility drives expansion, and rebranding the framework as a "mere empirical method" while continuing to deploy it as explanatory ontology sustains persistence.

5.1 Initial flaw: Questionable assumptions

The FEP's rhetorical ascent depended on a foundational category error: conflating variational free energy (an information-theoretic bound used in approximate inference) with thermodynamic free energy (a physical state function governing spontaneous processes). Mathematical analogy hardened into conceptual identity; identity calcified into ontological necessity. In both popular exposition and ostensibly technical literature, these distinct meanings blur until the FEP is presented as explaining why single cells, organisms, neural circuits, whole brains, and even economies "minimize free energy" to persist [94, 95]. The operational meaning of "free energy minimization" transmutes across explanatory levels: biochemical reaction fluxes at the molecular scale [96, 97], prediction error dynamics at the neural level [98–100], and abstract "belief updating" or "policy selection" at cognitive and social scales [101, 102]. This semantic flexibility smuggles teleology beneath mathematical formalism: biological survival is redescribed as the inevitable consequence of minimizing surprise—a tautology that merely restates the observation that organisms that persist are those that have not yet failed to persist.

Markov blankets became another conceptual pillar of FEP's expansionist rhetoric: purportedly simple statistical constructs demarcating system from environment, sensory from active states, internal beliefs from external causes [103–105]. Yet the existence and uniqueness of such blankets in realistic, continuously coupled dynamical systems remain unproven. Multiple incompatible Markov blankets can be stipulated over identical processes, their mappings to biological boundaries are asserted rather than empirically determined, and their formal properties frequently fail to align with actual causal structure [85–93]. As the concept diffused through the literature, "Markov blanket" devolved from a mathematically specific construct into whatever boundary partition a theorist required to sustain narrative coherence. What initially promised operational rigor became instead mathematical scenery—decorative formalism permitting any system to be retrospectively classified as an FEP instantiation.

5.2 Expansion: Moving goalposts

The FEP's conceptual drift from inference identity to biological ontology could have been constrained by empirical accountability. Instead, every theoretical tension has been neutralized through auxiliary flexibility. Active inference models incorporate nearly unlimited degrees of freedom: choice of state-space dimensionality and discretization, hierarchical architectures, prior distributions and hyperprior parameterizations, policy repertoires, precision weighting schemes, noise covariance structures, and terminal cost specifications. When model predictions conflict with empirical observations, failures are rationalized through post-hoc appeals to "mis-specified priors," "suboptimal policies," "incorrect precision weighting," or "model class inadequacy." Because any observed behavior can be accommodated by adjusting unobserved prior beliefs and unmeasured cost functions, the framework becomes immune to empirical refutation—a perfect theory of everything, and therefore a useful theory of nothing. The literature systematically omits preregistered commitments specifying which parameters are theoretically fixed versus empirically fitted, or what patterns of evidence would constitute theoretical disconfirmation.

This mathematical plasticity has generated a parallel rhetorical economy. The FEP's vocabulary expands to absorb every empirical anomaly and assimilate every rival framework. Dopaminergic reward prediction errors—established through decades of single-unit electrophysiology and precisely characterized by temporal difference learning—are relabeled as "expected free energy minimization" [106–108]. Reinforcement learning's exploration bonuses become "epistemic value" [109]. Classical control theory's Kalman filtering is rebranded "active inference" [110]. The underlying mathematics remains identical, but the terminological transformation creates the illusion of theoretical unification. To critics, this constitutes systematic renaming of established results under new vocabulary; to proponents, it represents conceptual integration. Either interpretation reveals that the framework's conversion rate of genuine novelty into mathematical redundancy approaches unity.

5.3 Persistence: An empirical framework, but not a superior one

Confronted with sustained criticism, FEP proponents have conceded that the framework is unfalsifiable as a general principle [111], yet argue it retains value as an "empirical tool" or "modeling framework." This rhetorical retreat

proves strategically incomplete: the same proponents continue deploying FEP language to "explain" biological persistence, neural function, and social dynamics, contradicting their professed epistemological modesty. Phrases such as "organisms minimize expected surprise to persist" masquerade as mechanistic explanation while merely redescribing the explanandum in different vocabulary. Even evaluated charitably as a modeling approach rather than explanatory theory, the FEP carries substantial conceptual baggage that standard Bayesian methods avoid: reliance on Markov blanket uniqueness and biological realizability, conflation of information-theoretic with thermodynamic constructs, assumptions of ergodicity and nonequilibrium steady states, and teleological framing that obscures rather than clarifies causal structure [89–92]. Conventional Bayesian filtering, optimal control theory, and reinforcement learning algorithms achieve equivalent or superior empirical performance without invoking these problematic auxiliary assumptions, and can be straightforwardly applied in domains where FEP's foundational requirements are violated.

The FEP is rhetorically positioned as a fundamental law of biological organization—a "principle" in the sense of thermodynamics' laws or Hamilton's principle in classical mechanics. Yet this metaphysical promotion remains unjustified. Even granting that the variational inference identity holds mathematically under specified assumptions, this technical correctness does not constitute an explanatory advance. A formally valid tautology explaining everything in principle explains nothing in practice. The trajectory from useful mathematical technique to unfalsifiable ontology to retrospectively defended "modeling tool" exemplifies how theoretical frameworks, once insulated from empirical constraint, can persist indefinitely through rhetorical flexibility—accumulating citations, institutional support, and devoted practitioners while contributing negligibly to falsifiable understanding.

6 Pseudoscience for profit

Pseudoscience dying in the academic literature can reincarnate in the marketplace as slogans, startups, and investment pitches. Once a theory acquires the rhetorical aura of profundity and the vocabulary of universality, it becomes a marketing asset—rhetorical capital readily convertible into financial capital. Investors, startups, and even public research consortia increasingly treat theoretical ambiguity not as liability but as strategic advantage: it allows product narratives to promise everything while committing to nothing falsifiable. The same structural features that protect pseudoscientific theories from empirical refutation—elastic definitions, unverifiable claims, and grandiose unifying language—render them ideal for commercialization. Each framework examined here has spawned a characteristic variant of this pattern. The lipid raft theory inspired a multimillion-€ biotechnology consortium built on a nonexistent membrane structure. The oxidative stress narrative underwrites a multibillion-$ global "detox" industry peddling antioxidants and wellness products that violate basic redox chemistry. The Free Energy Principle has been rebranded as the intellectual foundation of corporate "agentic AI" platforms promising general intelligence while delivering no demonstrable product. What follows traces how these frameworks migrated from laboratory bench to investor pitch deck, revealing that pseudoscience constitutes not merely an epistemic failure but a viable business model.

6.1 The lipid raft economy: Built to float, not to hold water

For proponents of the original hypothesis, attraction to lipid rafts combined practical with theoretical motives. Defining and manipulating such platforms promised a toolkit for biotechnology and medicine. This ambition motivated *Rafts4Biotech*, an EU-funded consortium (H2020, CORDIS project ID 720776) operating from 2017–2021 with a reported budget of €6,733,580 on CORDIS [112] (and €7.5 million on the project website [113]), whose stated objective was generating "synthetic bacterial lipid rafts to optimize industrial processes." The project's public record reveals that actual investigation was only tenuously related to lipid rafts. Of 28 publications generated, not one explicitly references lipid rafts, and the lead investigator who pioneered the rafts-in-bacteria concept [33] appears as author on none of these outputs. Rather than advancing or testing any blueprint for membrane rafts, the consortium apparently reverted to generic synthetic biology and enzyme optimization—a sharp departure from the project's central premise that bacterial membrane organization could be engineered to control bioprocesses. The original "raft" framing likely served primarily as funding bait that helped secure H2020 support; once funded, the consortium redirected effort toward scientifically tractable deliverables. Despite this empirical abandonment, project outreach continued actively disseminating the lipid raft theory. Investigators produced instructional videos on isolating "bacterial lipid rafts" using detergent extraction [114]—a protocol considered debunked even among raft loyalists—and educational materials extending to a children's brochure [115], exemplifying how rhetorically vivid metaphors outpace any evidential substrate.

6.2 The oxidative stress industry: Reducing your bank balance

Few pseudoscientific frameworks have been monetized more successfully than the oxidative stress narrative, which has metastasized into a multibillion-dollar global industry selling supplements, beverages, cosmetics, and wearable devices

promising to "fight oxidative stress" and "detoxify" the body [116, 117]. This industry thrives precisely because the underlying framework is maximally elastic: any intervention failing to show benefit can be reclassified as incorrect dosage or timing, while any subjective improvement is interpreted as proof of restored redox homeostasis. Large-scale randomized controlled trials demonstrate that antioxidant supplementation neither prevents disease nor extends lifespan and instead might increase all-cause mortality [118, 119]. Moreover, widely deployed "oxidative stress" biomarkers such as plasma ascorbate cannot reflect the compartment-specific ascorbate concentrations and redox states that govern oxidant signaling in distinct subcellular locations [120]. Supplement manufacturers and wellness brands routinely invoke the vocabulary of redox biology and Nobel-affiliated enzymes to market formulations that would collapse under a single blinded trial or kinetic assay. A 2022 market analysis estimated the global antioxidant supplement market exceeds $5.6 billion annually with continued growth [116], despite repeated large-scale trials showing no consistent health benefit and, in some cohorts, increased morbidity among high-dose users. This pattern extends beyond oral supplements to consumer devices: "oxidative stress scanners" and "cellular rejuvenation lights" advertise quantification of redox potential using uncalibrated optical proxies wrapped in pseudo-biochemical terminology. Amplification is supplied by celebrity scientists turned media personalities and monetized podcast hosts who repackage redox jargon into lifestyle prescriptions, frequently paired with sponsorships, affiliate links, or promotional codes for antioxidant "stacks" and detox regimens, converting parasocial credibility into product demand [121, 122]. Even when financial disclosures are made, the format systematically rewards confident generalities over falsifiable specifics—a familiar asymmetry in nutrition communication that consistently overstates effect sizes [123]. Mainstream cosmetics exploit identical vocabulary, claiming to deliver "antioxidant defenses" at the level of mitochondria or DNA repair machinery. The result is an economy of perpetual motion: a theory incapable of empirical failure begets products incapable of consumer disappointment. The rhetoric of "detoxification" functions as an infinitely renewable marketing resource, transforming the absence of falsifiable metrics into a simulacrum of scientific legitimacy. Here, pseudoscience becomes a consumable lifestyle—its elastic chemistry underwriting a vast commercial ecosystem in which redox signaling operates less as a physiological process than as brand identity.

6.3 The Free Energy Principle and active inference: Free theory, premium pricing

A particularly illuminating example of unfalsifiable theory meeting financial opportunism is VERSES AI Inc. ("VERSES"), a publicly traded company that explicitly markets the Free Energy Principle and Active Inference as the foundation for "agentic software systems" and "general-purpose AI." VERSES claims these frameworks enable artificial intelligence to operate according to principles governing biological cognition, scaling from neurons to enterprises and entire economies. In practice, however, the company's public output consists almost entirely of press releases, patent announcements, and investor communications rather than verifiable products or reproducible demonstrations. VERSES recently issued a press release announcing a U.S. patent on "Method and system for specifying an active inference based agent using natural language" [124], and published an open letter to OpenAI asserting that its FEP-based approach to artificial general intelligence would "outperform deep learning with orders of magnitude less data and computation" [125]. The company website promotes a product called *Genius*™ [126], advertised as a cognitive engine that "learns like the human brain," yet as of this writing, no independent technical validation, benchmark performance data, or publicly reproducible implementation has been released. What persists instead is a pattern familiar from pseudoscientific drift: a self-sealing fusion of theoretical grandiosity and marketing opacity. The rhetoric of "unifying physics, biology, and AI" serves to attract capital and confer legitimacy while insulating the enterprise from empirical accountability, regulatory scrutiny, and falsifiable performance benchmarks. This synthesis of metaphysical ambition and speculative finance demonstrates that pseudoscience need not remain confined to academic discourse; when theories are structurally immune to failure yet rich in narrative appeal, they become not only intellectual liabilities but financial instruments—mechanisms for monetizing unfalsifiability itself, repackaged as innovation and marketed as inevitability.

7 Interventions

Welcome to the resistance. Readers who have made it this far understand how pseudoscience operates: through hypotheses that expand to absorb their initial failures and persist despite superior alternatives. Identifying the problem, however, proves easier than remedying it. Moreover, new pseudosciences will colonize the niches vacated by the old unless we address the underlying ecology that enables their proliferation. This section examines interventions we judge effective based on direct experience with pseudoscientific frameworks.

7.1 Understanding persistence

Not all pseudoscience stems from identical motives. Frameworks persist through naïveté, institutional incentive, or rhetorical opportunism, and distinguishing among these motives proves essential for designing effective countermeasures.

Viewed through this diagnostic lens, our three case studies occupy different positions along a spectrum of culpability. The lipid raft theory exemplifies persistence driven primarily by naïveté. Membrane biologists continued invoking "rafts" less from deliberate deception than from disciplinary inertia and absence of compelling alternatives [14]. The recent aversion to scientific debate among lipid raft investigators may reflect belated attempts by earlier proponents to distance themselves from an increasingly indefensible framework. We suspect that articulating the case for pseudoscience, as done here, will prove sufficient to accelerate abandonment of the theory. The oxidative stress narrative again occupies intermediate ground, with some practitioners deploying it as communicative shorthand [83] while others exploit it for commercial advantage. Here, both public education on redox biology and accountability for profiteers should be pursued. The Free Energy Principle exhibits the clearest markers of intellectual bad faith [89]. Its prominent advocates demonstrably understand the framework's impenetrable mathematics and immunity to disproof, yet persistently advertise it as an explanatory ontology spanning life, mind, and society. They routinely absorb substantive critiques through philosophical deflection and recast objections as confirmations of the framework's universality—a posture suggesting feigned omniscience. Given extensive recent pushback and the philosophical sophistication of many promoters, their continued advocacy likely reflects deliberate disregard for the theory's pseudoscientific character. As with the oxidative stress narrative, financial exploitation through entities like VERSES compounds the problem. In such cases, demanding accountability from loyalists must be prioritized.

7.2 Debating pseudoscience

Debates against pseudoscience typically follow one of two pathological patterns. In the first, loyalists refuse engagement with substantive critiques, thereby forestalling legitimization of rival theories by denying them a platform. As of 2024, this characterizes the lipid raft community's failure to address T.A.K.'s critiques through any channel, private or public [15]—a stance rendered especially egregious when those same proponents continue propagating the framework in research articles [127]. In the second, when direct exchange becomes unavoidable, the encounter is often choreographed not as mutual empirical adjudication but as rhetorical assimilation. This pattern defines engagement with the Free Energy Principle, which translates critics' arguments into house vocabulary, relabels anomalies as boundary cases already "anticipated," and archives objections within umbrella reviews and tutorials masquerading as theoretical maturation. The surface record suggests productive dialogue and emerging consensus, yet no concrete failure conditions have been conceded, no auxiliary freedoms retired, and no out-of-sample liabilities acknowledged. What can be done to combat these evasions? As our demarcation criteria establish, pseudoscience can be identified through characteristic philosophical failures and thus warrants rigorous philosophical analysis. This can be accomplished through comprehensive critiques—potentially leveraging humor to amplify attention. More fundamentally, scientific culture must adopt substantive engagement with criticism as a nonnegotiable professional standard rather than an optional courtesy.

7.3 Institutional pressure

Scientific institutions must cease passive complicity in disseminating pseudoscience and actively participate in its elimination. Currently, journals rarely require precommitted falsification criteria for theoretical papers purporting to explain observable phenomena. Since journal articles constitute the primary vector for pseudoscience transmission, implementing this editorial standard would substantially impede propagation. Funding agencies should develop competence in identifying proposals grounded in *ad hoc* redefinitions and motte–and–bailey maneuvers, prioritizing instead research employing well-defined, measurable constructs. Graduate training programs seldom venture beyond rudimentary methodological instruction into philosophy of science; consequently, scientists inherit disciplinary vocabularies whose empirical content they never learned to interrogate. Introducing trainees to the works of Popper [10, 11], Kuhn [5], Feyerabend [6], and Lakatos [7] would likely attenuate momentum behind naïve pseudoscience while potentially deterring deceit-driven variants that thrive on trainee indoctrination. Institutional passivity toward pseudoscience should be recognized as an acute professional failure demanding urgent correction.

8 Conclusions

> Science advances one funeral at a time—but only if the corpse is properly buried, not preserved in formaldehyde.

Researchers must be more vigilant about identifying and challenging pseudoscience. The cost of not doing so is severe. Pseudoscientific frameworks do not merely coexist with good science—they displace it. They colonize rhetorical

real estate in reviews and editorials, bias keyword ecosystems and search results, capture peer review in subdomains, and redirect funding, trainee effort, and instrument time toward questions that cannot resolve. Laboratories learn to optimize persuasion rather than prediction, junior scientists inherit citation rings in place of empirical comparators, and fields accumulate literatures that appear productive yet remain stubbornly noncumulative. When success is measured by portability of vocabulary rather than testability of predictions, resources flow toward theories that cannot fail, while falsifiable alternatives starve. The result is a silent reconfiguration of scientific incentives: what resembles progress in volume constitutes regress in epistemic value—more papers, fewer findings that survive independent replication [128–131].

This paper characterized pseudoscience, traced three instructive case studies, and proposed concrete remedies. Through lipid rafts, the oxidative stress detoxification narrative, and the Free Energy Principle, we demonstrated how initially flawed ideas metastasize into metaphors that survive through semantic flexibility rather than empirical constraint. We identified diagnostic patterns: *ad hoc* modifications that contradict foundational claims, motte–and–bailey rhetorical tactics, assertions without empirical commitment, and unfavorable comparison to more disciplined theoretical alternatives. These diagnostics translate directly into institutional remedies: distinguishing theoretical naïveté from calculated obfuscation, fostering adversarial collaboration and structured debate, and cultivating norms that reward frameworks capable of being wrong.

Avoiding pseudoscience requires first acknowledging that no one is immune to it. The cognitive and institutional pressures that sustain pseudoscientific frameworks—desire for explanatory scope, attachment to elegant theories, and motivated reasoning in defense of intellectual investments—are features of human inquiry itself. Recognizing this is not cynicism but realism: pseudoscience emerges not from malice but from the same creative impulses that drive scientific innovation. The safeguards we propose are therefore not external correctives but essential disciplines of thought.

Theorists should be prepared to abandon specific, testable conjectures when they fail, treating falsification as contribution rather than defeat. A cleanly refuted hypothesis advances science by clarifying what the world is *not*. Conversely, a theory repeatedly rescued through *ad hoc* adjustments ceases to be science at all. The community should celebrate intellectual honesty—the courage to retract and revise—as much as ingenuity. Broad theoretical frameworks, when pursued, must generate falsifiable predictions, employ independently measurable constructs, and make nontrivial claims relative to prior knowledge. Progress in science depends on this disciplined reciprocity between ambition and accountability: imagination tempered by constraint, boldness anchored in the willingness to be wrong. Only when these virtues coexist can theoretical innovation avoid the fate of pseudoscience and serve as a genuine engine of discovery.

Broad frameworks earn their keep when they make risky commitments with independently measurable constructs. The rest of us—authors included—should plan for being wrong in public and design our theories so the world can tell us so. That is the only durable antidote to pseudoscientific drift.

Competing interests

The authors declare no competing interests.

Data availability

Data sharing does not apply to this article as no new data were created or analyzed in this study.

Acknowledgments

We are grateful to Michalis Nikolaidis for his insightful comments and constructive suggestions, which helped to improve the clarity and precision of this manuscript.

Funding

This work was funded by a Clarendon Fund Scholarship in partnership with a Nuffield Department of Clinical Medicine Studentship and a Magdalen College Graduate Scholarship to Troy A. Kervin.

Author contributions statement

Troy A. Kervin: Conceptualization, Writing – Original draft, Writing – Review & Editing; **Madhur Mangalam:** Conceptualization, Writing – Original draft, Writing – Review & Editing, Visualization.

Declaration of generative artificial intelligence

Generative AI applications, including ChatGPT-5 (OpenAI, San Francisco, CA) and Claude Sonnet 4.5 (Anthropic, San Francisco, CA), were used during the brainstorming and editing phases of this manuscript to refine arguments, enhance clarity, improve structure, generate phrasing alternatives, organize ideas, and streamline language. The authors take full responsibility for all outputs.

References

[1] Pigliucci M. Nonsense on Stilts: How to Tell Science from Bunk. University of Chicago Press, Chicago, IL; 2010.

[2] Cartwright N. The Dappled World: A Study of the Boundaries of Science. Cambridge University Press, Cambridge, MA; 1999.

[3] Chalmers AF. The Scientist's Atom and the Philosopher's Stone: How Science Succeeded and Philosophy Failed to Gain Knowledge of Atoms. Springer, Dordrecht, Netherlands; 2009.

[4] Chalmers AF. What Is This Thing Called Science? Hackett Publishing, Indianapolis, IA; 2013.

[5] Kuhn TS. The Structure of Scientific Revolutions. University of Chicago Press, Chicago, IL; 1962.

[6] Feyerabend P. Against Method: Outline of an Anarchistic Theory of Knowledge. Verso Books, London, UK; 1975.

[7] Lakatos I. Falsification and the methodology of scientific research programmes. In: Lydia P, editor. Philosophy, Science, and History: A Guide and Reader. Routledge, New York; 2014. p. 89-94. https://doi.org/10.4324/9780203802458-7.

[8] Laudan L. Progress and Its Problems: Towards a Theory of Scientific Growth. University of California Press, Oakland, CA; 1978.

[9] Pigliucci M, Boudry M. Philosophy of Pseudoscience: Reconsidering the Demarcation Problem. University of Chicago Press, Chicago, IL; 2019.

[10] Popper K. The Logic of Scientific Discovery. Hutchinson, London, UK; 1934.

[11] Popper K. Conjectures and Refutations: The Growth of Scientific Knowledge. Highland, New York, NY; 1963.

[12] Shackel N. The vacuity of postmodernist methodology. Metaphilosophy. 2005;36(3):295-320. https://doi.org/10.1111/j.1467-9973.2005.00370.x.

[13] Hunt JC. On ad hoc hypotheses. Philosophy of Science. 2012;79(1):1-14. https://doi.org/10.1086/663238.

[14] Kenworthy AK. Have we become overly reliant on lipid rafts? Talking Point on the involvement of lipid rafts in T-cell activation. EMBO Reports. 2008;9(6):531-5. https://doi.org/10.1038/embor.2008.92.

[15] Kervin TA, Overduin M. Membranes are functionalized by a proteolipid code. BMC biology. 2024;22:46. https://doi.org/10.1186/s12915-024-01849-6.

[16] Kervin TA. No phases? No phase separation. Zenodo. 2025. https://doi.org/10.5281/zenodo.17201252.

[17] Friston KJ, Stephan KE. Free-energy and the brain. Synthese. 2007;159:417-58. https://doi.org/10.1007/s11229-007-9237-y.

[18] Friston K. The free-energy principle: A unified brain theory? Nature Reviews Neuroscience. 2010;11:127-38. https://doi.org/10.1038/nrn2787.

[19] Friston K. Life as we know it. Journal of the Royal Society Interface. 2013;10(86):20130475. https://doi.org/10.1098/rsif.2013.0475.

[20] Friston K, FitzGerald T, Rigoli F, Schwartenbeck P, Pezzulo G, et al. Active inference and learning. Neuroscience & Biobehavioral Reviews. 2016;68:862-79. https://doi.org/10.1016/j.neubiorev.2016.06.022.

[21] Parr T, Friston KJ. The anatomy of inference: Generative models and brain structure. Frontiers in Computational Neuroscience. 2018;12:90. https://doi.org/10.3389/fncom.2018.00090.

[22] Simons K, Ikonen E. Functional rafts in cell membranes. Nature. 1997;387:569-72. https://doi.org/10.1038/42408.

[23] Foster LJ. Lessons learned from lipid raft proteomics. Expert Review of Proteomics. 2008;5(4):541-3. https://doi.org/10.1586/14789450.5.4.541.

[24] Lorent JH, Diaz-Rohrer B, Lin X, Spring K, Gorfe AA, Levental KR, et al. Structural determinants and functional consequences of protein affinity for membrane rafts. Nature Communications. 2017;8:1219. https://doi.org/10.1038/s41467-017-01328-3.

[25] Simons K, Toomre D. Lipid rafts and signal transduction. Nature Reviews Molecular Cell Biology. 2000;1:31-9. https://doi.org/10.1038/35036052.

[26] Munro S. Lipid rafts: Elusive or illusive? Cell. 2003;115(4):377-88. https://doi.org/10.1016/s0092-8674(03)00882-1.

[27] Sezgin E, Levental I, Mayor S, Eggeling C. The mystery of membrane organization: Composition, regulation and roles of lipid rafts. Nature Reviews Molecular Cell Biology. 2017;18:361-74. https://doi.org/10.1038/nrm.2017.16.

[28] Pike LJ. Rafts defined: A report on the Keystone symposium on lipid rafts and cell function. Journal of Lipid Research. 2006;47(7):1597-8. https://doi.org/10.1194/jlr.e600002-jlr200.

[29] Kusumi A, Fujiwara TK, Tsunoyama TA, Kasai RS, Liu AA, Hirosawa KM, et al. Defining raft domains in the plasma membrane. Traffic. 2020;21(1):106-37. https://doi.org/10.1111/tra.12718.

[30] Kusumi A, Suzuki KG, Kasai RS, Ritchie K, Fujiwara TK. Hierarchical mesoscale domain organization of the plasma membrane. Trends in Biochemical Sciences. 2011;36(11):604-15. https://doi.org/10.1016/j.tibs.2011.08.001.

[31] Hancock JF. Lipid rafts: Contentious only from simplistic standpoints. Nature Reviews Molecular Cell Biology. 2006;7:456-62. https://doi.org/10.1038/nrm1925.

[32] Shelby SA, Castello-Serrano I, Wisser KC, Levental I, Veatch SL. Membrane phase separation drives responsive assembly of receptor signaling domains. Nature Chemical Biology. 2023;19:750-8. https://doi.org/10.1038/s41589-023-01268-8.

[33] López D, Kolter R. Functional microdomains in bacterial membranes. Genes & Development. 2010;24(17):1893-902. https://doi.org/10.1101/gad.1945010.

[34] Lichtenberg D, Goñi FM, Heerklotz H. Detergent-resistant membranes should not be identified with membrane rafts. Trends in Biochemical Sciences. 2005;30(8):430-6. https://doi.org/10.1016/j.tibs.2005.06.004.

[35] Levental I, Veatch SL. The continuing mystery of lipid rafts. Journal of Molecular Biology. 2016;428(24):4749-64. https://doi.org/10.1016/j.jmb.2016.08.022.

[36] Levental I, Levental KR, Heberle FA. Lipid rafts: Controversies resolved, mysteries remain. Trends in Cell Biology. 2020;30(5):341-53. https://doi.org/10.1016/j.tcb.2020.01.009.

[37] Brown D, London E. Functions of lipid rafts in biological membranes. Annual Review of Cell and Developmental Biology. 1998;14(1):111-36. https://doi.org/10.1146/annurev.cellbio.14.1.111.

[38] Risselada HJ, Marrink SJ. The molecular face of lipid rafts in model membranes. Proceedings of the National Academy of Sciences. 2008;105(45):17367-72. https://doi.org/10.1073/pnas.0807527105.

[39] Levental I. Lipid rafts come of age. Nature Reviews Molecular Cell Biology. 2020;21(8):420-0. Lipidraftscomeofage.

[40] Fu Z, MacKinnon R. Structure of the flotillin complex in a native membrane environment. Proceedings of the National Academy of Sciences. 2024;121(29):e2409334121. https://doi.org/10.1073/pnas.2409334121.

[41] Nichols B. Without a raft. Nature. 2005;436:638-9. https://doi.org/10.1038/436638a.

[42] Karnovsky MJ, Kleinfeld AM, Hoover RL, Klausner RD. The concept of lipid domains in membranes. Journal of Cell Biology. 1982;94(1):1-6. https://doi.org/10.1083/jcb.94.1.1.

[43] Kervin TA. A unifying membrane model. Zenodo. 2025.

[44] Corradi V, Mendez-Villuendas E, Ingólfsson HI, Gu RX, Siuda I, Melo MN, et al. Lipid–protein interactions are unique fingerprints for membrane proteins. ACS Central Science. 2018;4(6):709-17. https://doi.org/10.1021/acscentsci.8b00143.

[45] Ritchie K, Iino R, Fujiwara T, Murase K, Kusumi A. The fence and picket structure of the plasma membrane of live cells as revealed by single molecule techniques. Molecular Membrane Biology. 2003;20(1):13-8. https://doi.org/10.1080/0968768021000055698.

[46] Veatch SL, Rogers N, Decker A, Shelby SA. The plasma membrane as an adaptable fluid mosaic. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2023;1865(3):184114. https://doi.org/10.1016/j.bbamem.2022.184114.

[47] Veatch SL, Keller SL. A closer look at the canonical 'raft mixture' in model membrane studies. Biophysical Journal. 2003;84(1):725-6. https://doi.org/10.1016/S0006-3495(03)74891-7.

[48] Kervin TA. Lipid antagonists regulate protein clustering. Zenodo. 2025. https://doi.org/10.5281/zenodo.16893614.

[49] Overduin M, Bhat R, Dieudonné T, Zhang P, Kervin TA. Deciphering the language of mingling lipids and proteins. Current Opinion in Structural Biology. 2025;92:103061. https://doi.org/10.1016/j.sbi.2025.103061.

[50] Margaritelis NV, Nikolaidis MG. Science captured by storytelling: The oxidative stress narrative. Trends in Molecular Medicine. 2025. https://doi.org/10.1016/j.molmed.2025.09.004.

[51] Poljsak B, Šuput D, Milisav I. Achieving the balance between ROS and antioxidants: When to use the synthetic antioxidants. Oxidative Medicine and Cellular Longevity. 2013;2013(1):956792. https://doi.org/10.1155/2013/956792.

[52] Sies H. Oxidative stress: A concept in redox biology and medicine. Redox Biology. 2015;4:180-3. https://doi.org/10.1016/j.redox.2015.01.002.

[53] Sies H. Hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress: Oxidative eustress. Redox Biology. 2017;11:613-9. https://doi.org/10.1016/j.redox.2016.12.035.

[54] Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. Nature Reviews Molecular Cell Biology. 2020;21:363-83. https://doi.org/10.1038/s41580-020-0230-3.

[55] Sies H, Mailloux RJ, Jakob U. Fundamentals of redox regulation in biology. Nature Reviews Molecular Cell Biology. 2024;25:701-19. https://doi.org/10.1038/s41580-024-00730-2.

[56] Murphy MP, Bayir H, Belousov V, Chang CJ, Davies KJ, Davies MJ, et al. Guidelines for measuring reactive oxygen species and oxidative damage in cells and in vivo. Nature Metabolism. 2022;4:651-62. https://doi.org/10.1038/s42255-022-00591-z.

[57] Tsikas D. Assessment of lipid peroxidation by measuring malondialdehyde (MDA) and relatives in biological samples: Analytical and biological challenges. Analytical Biochemistry. 2017;524:13-30. https://doi.org/10.1016/j.ab.2016.10.021.

[58] Kalyanaraman B, Darley-Usmar V, Davies KJ, Dennery PA, Forman HJ, Grisham MB, et al. Measuring reactive oxygen and nitrogen species with fluorescent probes: Challenges and limitations. Free Radical Biology and Medicine. 2012;52(1):1-6. https://doi.org/10.1016/j.freeradbiomed.2011.09.030.

[59] Wardman P. Fluorescent and luminescent probes for measurement of oxidative and nitrosative species in cells and tissues: Progress, pitfalls, and prospects. Free Radical Biology and Medicine. 2007;43(7):995-1022. https://doi.org/10.1016/j.freeradbiomed.2007.06.026.

[60] Levine RL. Carbonyl modified proteins in cellular regulation, aging, and disease. Free Radical Biology and Medicine. 2002;32(9):790-6. https://doi.org/10.1016/S0891-5849(02)00765-7.

[61] Hu J, Dong L, Outten CE. The redox environment in the mitochondrial intermembrane space is maintained separately from the cytosol and matrix. Journal of Biological Chemistry. 2008;283(43):29126-34. https://doi.org/10.1074/jbc.M803028200.

[62] Morgan MJ, Liu Zg. Crosstalk of reactive oxygen species and NF-κB signaling. Cell Research. 2011;21:103-15. https://doi.org/10.1038/cr.2010.178.

[63] Schafer FQ, Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. Free Radical Biology and Medicine. 2001;30(11):1191-212. https://doi.org/10.1016/S0891-5849(01)00480-4.

[64] Halliwell B. The antioxidant paradox: Less paradoxical now? British Journal of Clinical Pharmacology. 2013;75(3):637-44. https://doi.org/10.1111/j.1365-2125.2012.04272.x.

[65] Halliwell B. Understanding mechanisms of antioxidant action in health and disease. Nature Reviews Molecular Cell Biology. 2024;25:13-33. https://doi.org/10.1038/s41580-023-00645-4.

[66] Nikolaidis MG, Margaritelis NV. Same redox evidence but different physiological "stories": The Rashomon effect in biology. Bioessays. 2018;40(9):1800041. https://doi.org/10.1002/bies.201800041.

[67] Nikolaidis MG, Margaritelis NV. Free radicals and antioxidants: Appealing to magic. Trends in Endocrinology & Metabolism. 2023;34(9):503-4. https://doi.org/10.1016/j.tem.2023.06.001.

[68] Belousov VV, Fradkov AF, Lukyanov KA, Staroverov DB, Shakhbazov KS, Terskikh AV, et al. Genetically encoded fluorescent indicator for intracellular hydrogen peroxide. Nature Methods. 2006;3:281-6. https://doi.org/10.1038/nmeth866.

[69] Gutscher M, Pauleau AL, Marty L, Brach T, Wabnitz GH, Samstag Y, et al. Real-time imaging of the intracellular glutathione redox potential. Nature Methods. 2008;5:553-9. https://doi.org/10.1038/nmeth.1212.

[70] Gutscher M, Sobotta MC, Wabnitz GH, Ballikaya S, Meyer AJ, Samstag Y, et al. Proximity-based protein thiol oxidation by H_2O_2-scavenging peroxidases. Journal of Biological Chemistry. 2009;284(46):31532-40. https://doi.org/10.1074/jbc.M109.059246.

[71] Mishina NM, Tyurin-Kuzmin PA, Markvicheva KN, Vorotnikov AV, Tkachuk VA, Laketa V, et al. Does cellular hydrogen peroxide diffuse or act locally? Antioxidants & Redox Signaling. 2011;14:1-7. https://doi.org/10.1089/ars.2010.3539.

[72] Bae YS, Kang SW, Seo MS, Baines IC, Tekle E, Chock PB, et al. Epidermal growth factor (EGF)-induced generation of hydrogen peroxide: Role in EGF receptor-mediated tyrosine phosphorylation. Journal of Biological Chemistry. 1997;272(1):217-21. https://doi.org/10.1074/jbc.272.1.217.

[73] Paulsen CE, Truong TH, Garcia FJ, Homann A, Gupta V, Leonard SE, et al. Peroxide-dependent sulfenylation of the EGFR catalytic site enhances kinase activity. Nature Chemical Biology. 2012;8:57-64. https://doi.org/10.1038/nchembio.736.

[74] Winterbourn CC, Hampton MB. Thiol chemistry and specificity in redox signaling. Free Radical Biology and Medicine. 2008;45(5):549-61. https://doi.org/10.1016/j.freeradbiomed.2008.05.004.

[75] Morrison D, Hughes J, Della Gatta PA, Mason S, Lamon S, Russell AP, et al. Vitamin C and E supplementation prevents some of the cellular adaptations to endurance-training in humans. Free Radical Biology and Medicine. 2015;89:852-62. https://doi.org/10.1016/j.freeradbiomed.2015.10.412.

[76] Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proceedings of the National Academy of Sciences. 2009;106(21):8665-70. https://doi.org/10.1073/pnas.0903485106.

[77] Forman HJ, Zhang H. Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nature Reviews Drug Discovery. 2021;20(9):689-709. https://doi.org/10.1038/s41573-021-00233-1.

[78] Hope and Hope-TOO Trial Investigators and others. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. JAMA. 2005;293(11):1338-47. https://doi.org/10.1001/jama.293.11.1338.

[79] Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. New England journal of medicine. 1996;334(18):1150-5. https://doi.org/10.1056/NEJM199605023341802.

[80] Miller III ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Annals of Internal Medicine. 2005;142(1):37-46. https://doi.org/10.7326/0003-4819-142-1-200501040-00110.

[81] Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. New England Journal of Medicine. 1994;330(15):1029-35. https://doi.org/10.1056/NEJM199404143301501.

[82] Lambeth JD, Kawahara T, Diebold B. Regulation of Nox and Duox enzymatic activity and expression. Free Radical Biology and Medicine. 2007;43(3):319-31. https://doi.org/10.1016/j.freeradbiomed.2007.03.028.

[83] Azzi A. Oxidative stress: What is it? Can it be measured? Where is it located? Can it be good or bad? Can it be prevented? Can it be cured? Antioxidants. 2022;11(8):1431. https://doi.org/10.3390/antiox11081431.

[84] Jones DP, Sies H. The redox code. Antioxidants & Redox Signaling. 2015;23(9):734-46. https://doi.org/10.1089/ars.2015.6247.

[85] Andrews M. The math is not the territory: Navigating the free energy principle. Biology & Philosophy. 2021;36:30. https://doi.org/10.1007/s10539-021-09807-0.

[86] Biehl M, Pollock FA, Kanai R. A technical critique of some parts of the free energy principle. Entropy. 2021;23(3):293. https://doi.org/10.3390/e23030293.

[87] Bruineberg J, Dołęga K, Dewhurst J, Baltieri M. The emperor's new Markov blankets. Behavioral and Brain Sciences. 2022;45:e183. https://doi.org/10.1017/S0140525X21002351.

[88] Colombo M, Wright C. First principles in the life sciences: The free-energy principle, organicism, and mechanism. Synthese. 2021;198:3463-88. https://doi.org/10.1007/s11229-018-01932-w.

[89] Mangalam M. The Emperor's new pseudo-theory: How the Free Energy Principle ransacked neuroscience. ResearchGate. 2025. https://www.researchgate.net/publication/390546288.

[90] Mangalam M. The illusion of internal models in biological movement. European Journal of Applied Physiology. 2025;125:3083-114. https://doi.org/10.1007/s00421-025-05963-3.

[91] Mangalam M. The myth of the Bayesian brain. European Journal of Applied Physiology. 2025;125:2643-77. https://doi.org/10.1007/s00421-025-05855-6.

[92] Mangalam M. The myth of optimality in human movement science. Neuroscience & Biobehavioral Reviews. 2025;178:106352. https://doi.org/10.1016/j.neubiorev.2025.106352.

[93] Raja V, Valluri D, Baggs E, Chemero A, Anderson ML. The Markov blanket trick: On the scope of the free energy principle and active inference. Physics of Life Reviews. 2021;39:49-72. https://doi.org/10.1016/j.plrev.2021.09.001.

[94] Badcock PB, Friston KJ, Ramstead MJ. The hierarchically mechanistic mind: A free-energy formulation of the human psyche. Physics of Life Reviews. 2019;31:104-21. https://doi.org/10.1016/j.plrev.2018.10.002.

[95] Ramstead MJD, Badcock PB, Friston KJ. Answering Schrödinger's question: A free-energy formulation. Physics of Life Reviews. 2018;24:1-16. https://doi.org/10.1016/j.neuron.2018.10.003.

[96] Karl F. A free energy principle for biological systems. Entropy. 2012;14(11):2100-21. https://doi.org/10.3390/e14112100.

[97] Friston K, Levin M, Sengupta B, Pezzulo G. Knowing one's place: A free-energy approach to pattern regulation. Journal of the Royal Society Interface. 2015;12(105):20141383. https://doi.org/10.1098/rsif.2014.1383.

[98] Friston K, Kiebel S. Predictive coding under the free-energy principle. Philosophical transactions of the Royal Society B: Biological sciences. 2009;364(1521):1211-21. https://doi.org/10.1098/rstb.2008.0300.

[99] Isomura T, Kotani K, Jimbo Y, Friston KJ. Experimental validation of the free-energy principle with in vitro neural networks. Nature Communications. 2023;14:4547. https://doi.org/10.1038/s41467-023-40141-z.

[100] Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ. Free energy, precision and learning: The role of cholinergic neuromodulation. Journal of Neuroscience. 2013;33(19):8227-36. https://doi.org/10.1523/JNEUROSCI.4255-12.2013.

[101] Ramstead MJ, Veissière SP, Kirmayer LJ. Cultural affordances: Scaffolding local worlds through shared intentionality and regimes of attention. Frontiers in Psychology. 2016;7:1090. https://doi.org/10.3389/fpsyg.2016.01090.

[102] Veissière SP, Constant A, Ramstead MJ, Friston KJ, Kirmayer LJ. Thinking through other minds: A variational approach to cognition and culture. Behavioral and Brain Sciences. 2020;43:e90. https://doi.org/10.1017/S0140525X19001213.

[103] Kirchhoff M, Parr T, Palacios E, Friston K, Kiverstein J. The Markov blankets of life: Autonomy, active inference and the free energy principle. Journal of the royal society interface. 2018;15(138):20170792. https://doi.org/10.1098/rsif.2017.0792.

[104] Parr T, Da Costa L, Friston K. Markov blankets, information geometry and stochastic thermodynamics. Philosophical Transactions of the Royal Society A. 2020;378(2164):20190159. https://doi.org/10.1098/rsta.2019.0159.

[105] Ramstead MJ, Hesp C, Tschantz A, Smith R, Constant A, Friston K. Neural and phenotypic representation under the free-energy principle. Neuroscience & Biobehavioral Reviews. 2021;120:109-22. https://doi.org/10.1016/j.neubiorev.2020.11.024.

[106] FitzGerald TH, Dolan RJ, Friston K. Dopamine, reward learning, and active inference. Frontiers in Computational Neuroscience. 2015;9:136. https://doi.org/10.3389/fncom.2015.00136.

[107] Friston KJ, Shiner T, FitzGerald T, Galea JM, Adams R, Brown H, et al. Dopamine, affordance and active inference. PLoS Computational Biology. 2012;8(1):e1002327. https://doi.org/10.1371/journal.pcbi.1002327.

[108] Friston K, Schwartenbeck P, FitzGerald T, Moutoussis M, Behrens T, Dolan RJ. The anatomy of choice: Dopamine and decision-making. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014;369(1655):20130481. https://doi.org/10.1098/rstb.2013.0481.

[109] Pezzulo G, Cartoni E, Rigoli F, Pio-Lopez L, Friston K. Active inference, epistemic value, and vicarious trial and error. Learning & Memory. 2016;23(7):322-38. https://doi.org/10.1101/lm.041780.116.

[110] Friston K, Samothrakis S, Montague R. Active inference and agency: Optimal control without cost functions. Biological Cybernetics. 2012;106(8):523-41. https://doi.org/10.1007/s00422-012-0512-8.

[111] Farias C. Karl Friston's Unfalsifiable Free Energy Principle; 2023. Accessed November 2025. https://www.youtube.com/watch?v=jZ1fsXQz7M4.

[112] Rafts4Biotech. Rafts4Biotech Project ID 720776; 2017. Accessed October 2025. https://cordis.europa.eu/project/id/720776.

[113] Rafts4Biotech. Rafts4Biotech Official Project Website; 2021. Accessed October 2025. https://rafts4biotech.eu.

[114] Rafts4Biotech. Rafts4Biotech: How to isolate bacterial lipid rafts; 2021. Accessed October 2025. https://www.youtube.com/watch?v=vE2AOxGF5no.

[115] Rafts4Biotech. Welcome to the Bacterial Park; 2021. Accessed October 2025. https://rafts4biotech.eu/welcome-to-the-bacterial-park/.

[116] Grand View Research. Antioxidant market size, share & trends analysis report, 2022–2030; 2022. Accessed October 2025. https://www.grandviewresearch.com/industry-analysis/antioxidants-market.

[117] Gunter J. The great detox delusion: Why 'cleanse' diets don't work and could be harmful; 2021. Accessed October 2025. *The Guardian*, https://www.theguardian.com/lifeandstyle/2021/jan/02/the-great-detox-delusion.

[118] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: Systematic review and meta-analysis. JAMA. 2007;297(8):842-57. https://doi.org/10.1001/jama.297.8.842.

[119] Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. Cochrane Database of Systematic Reviews. 2012. https://doi.org/10.1002/14651858.CD007176.pub2.

[120] Bánhegyi G, Benedetti A, Margittai É, Marcolongo P, Fulceri R, Németh CE, et al. Subcellular compartmentation of ascorbate and its variation in disease states. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2014;1843(9):1909-16. https://doi.org/10.1016/j.bbamcr.2014.05.016.

[121] Eisenberg MD, Avery RJ, Cantor JH. Vitamin panacea: Is advertising fueling demand for products with uncertain scientific benefit? Journal of Health Economics. 2017;55:30-44. https://doi.org/10.1016/j.jhealeco.2017.06.003.

[122] Federal Trade Commission. Guides concerning the use of endorsements and testimonials in advertising (16 CFR Part 255); 2023. Accessed October 2025. https://www.ftc.gov/business-guidance/advertising-and-marketing/endorsements.

[123] Ioannidis JP. The challenge of reforming nutritional epidemiologic research. JAMA. 2018;320(10):969-70. https://doi.org/10.1001/jama.2018.11025.

[124] VERSES AI Inc . VERSES receives patent for specifying an active inference-based agent using natural language; 2023. Accessed October 2025. https://finance.yahoo.com/news/verses-receives-patent-specifying-domain-124000640.html.

[125] VERSES AI Inc . VERSES identifies new path to AGI and extends invitation to OpenAI for collaboration via open letter; 2023. Accessed October 2025. https://www.globenewswire.com/news-release/2023/12/19/2798454/0/en/VERSES-Identifies-New-Path-to-AGI-and-Extends-Invitation-to-OpenAI-for-Collaboration-via-Open-Let
html.

[126] VERSES AI Inc . Genius™; 2023. Accessed October 2025. https://www.verses.ai/genius.

[127] Mukhamedova N, Fleetwood AJ, Huynh K, Xu Y, Van Buuren-Milne T, Faulkner A, et al. Targeting the ARF6-dependent recycling pathway to alter lipid rafts and reduce inflammation. Journal of Lipid Research. 2025:100900. https://doi.org/10.1016/j.jlr.2025.100900.

[128] Fanelli D. Do pressures to publish increase scientists' bias? An empirical support from US States Data. PloS One. 2010;5(4):e10271. https://doi.org/10.1371/journal.pone.0010271.

[129] Merton RK. The Matthew effect in science: The reward and communication systems of science are considered. Science. 1968;159(3810):56-63. https://doi.org/10.1126/science.159.3810.56.

[130] Nissen SB, Magidson T, Gross K, Bergstrom CT. Publication bias and the canonization of false facts. eLife. 2016;5:e21451. https://doi.org/10.7554/eLife.21451.

[131] Smaldino PE, McElreath R. The natural selection of bad science. Royal Society Open Science. 2016;3(9):160384. https://doi.org/10.1098/rsos.160384.