The Hijacker's Guide to biological systems: Manipulation by self-defecting or foreign agents

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Contents

Abstract

Biological systems employ hierarchical regulatory networks to maintain structure and function at multiple scales, from molecules to whole organisms. This manuscript draws on evidence from various fields such as immunology, developmental biology, neuroscience and evolutionary ecology to examine how foreign agents (for instance, pathogens, parasites, trophoblasts) and self-defecting agents (such as cancer cells) override these networks and exploit the host's plasticity and regulatory flexibility, reshaping system morphology, function and behaviour. By breaching physical and informational barriers, mimicking host signals, and altering immune defences, intruders take advantage of multiscale information processing, propagating their influence across levels, from local bioelectric states to higher-order endocrine and neural circuits. Through these mechanisms, intruders disrupt homeostatic setpoints, creating periods of heightened plasticity that enable system reprogramming resulting in redirection of metabolic flows and overriding of neural, immune and endocrine signalling. These manipulation strategies rely on conserved mechanisms, transforming stable structures into flexible substrates for rearrangement, remodelling host tissues and creating niches that favour their survival. Understanding these routes of exploitation clarifies core biological principles of self-organisation and identity maintenance. Mapping how intruders induce plasticity and modify host form and function informs therapeutic strategies aimed at restoring normal tissue states, while also opening potential new paths for regenerative medicine and tissue engineering.

I. Introduction

Biological systems manipulation by internal or external agents occurs broadly in nature, appearing in immunology, host-pathogen interactions, microbiome studies, oncology, molecular biology, genetics and bioengineering, as well as in evolutionary ecology and animal behaviour. In biology, an 'agent' can be any entity – molecules, cells or organisms - capable of causing changes in a biological system. Here, we focus on living agents or organisms: bacteria, archaea, eukaryotes and, also, viruses which straddle the line between living and non-living entities, and the ways these systems hack each other's form and function. A key property of living matter is its dynamic, multiscale organisation, which consists of nested self-regulating systems that exhibit partial autonomy in addressing diverse functional challenges (Fields & Levin, 2022; Levin, 2023c; Davies & Levin, 2023), making them susceptible to manipulation by higher-level signals and information. Thus, the hacker metaphor (Rule, Tenenbaum & Piantadosi, 2020) is relevant here as these agents manipulate complex systems by subverting default control paths and outcomes. This manipulation occurs at all levels – from rewiring the molecular "hardware" to the high-level "social engineering" in cell collectives (McMillen & Levin, 2024; Levin, 2023a; Levin, 2022).

Living organisms sharing an environment interact in many ways, including parasitism, predation, symbiosis and social manipulation. The relationship between an agent and its environment is interdependent: the agent is influenced by its environment and, in turn, modifies it to achieve its goals. Gaining environmental control enhances survival, reproduction, resource availability, and defence. When multiple agents with differing goals share a habitat, taking control over the environment becomes advantageous. Here, we focus on scenarios wherein one agent (an intruder) invades and alters another agent's (the host) environment and exploits it for its own advantage. Mutualistic or obligate symbioses, where both parties depend on each other or suffer upon separation, are excluded. Instead, the focus is on cases where one agent advances its own interests at the expense of another's normal function or development.

Whilst an agent must extract resources and respond to environmental signals, it must also preserve its stability and identity as a separate entity. This is achieved through various mechanisms including barrier functions, homeostatic controls and regulatory networks. Understanding how intruders override these protective mechanisms provides insight into both basic biological principles and potential therapeutic strategies.

An intruder can either be a foreign agent or a self-defecting agent. Examples of foreign agents include heterologous transplants, pathogens, commensal and symbiotic organisms, or invasive species in the context of larger-scale ecosystems. A self-defecting agent - such as a cancer cell - is an intrinsic component of the host system that actively deviates from the cooperative regulatory networks essential for maintaining physiological, metabolic and anatomical homeostasis. In this context, 'self-defecting' denotes a departure from the integrated, collective behaviour that characterises healthy tissues (Nowak, 2006; Aktipis *et al.*, 2013). This paper examines manipulation from the cellular to the organismal scale, including certain aspects of social interactions at higher levels.

The study of biological manipulation offers a unique perspective on morphology and development, fields where common principles and mechanisms remain unclear. Unlike familiar passive materials which have been engineered for thousands of years, cells and tissues offer a multi-scale architecture of distributed, homeodynamic competencies (Bernheim-Groswasser *et al.*, 2018; Davies & Levin, 2023). We have previously highlighted advantages in prediction and

control that can be achieved by leveraging cell collectives' modularity: specific stimuli induce complex, coordinated downstream responses, such as the formation of entire organs (Lagasse & Levin, 2023; Levin, 2024a). Harnessing the problem-solving abilities of cellular materials in medicine and bioengineering requires an understanding of the signals that are meaningful to the host tissues, as well as the principles by which specific desired changes can be communicated through bioelectric, biochemical, and biomechanical interfaces. To drive progress in this field, we examine examples where active manipulation and exploitation of host form, function and behavioural plasticity alters the system's structure (morphology). Understanding how morphology, physiology, and behaviour are shaped not only enhances our comprehension of fundamental biological processes and disease pathology, but also holds significant implications for the development of therapeutic interventions, cellular reprogramming, tissue remodelling, regeneration, and the design of novel bioengineered constructs.

Here, we first describe how cells and tissues maintain coherent structure and function across multiple scales, highlighting the multi-level regulatory architecture that both confers stability and presents potential vulnerabilities. We then show how foreign or self-defecting agents exploit these weaknesses to reshape host form and function.

II. Hierarchical organisation in living systems

(1) Multilevel information processing

Biological systems exhibit a hierarchical organisation in which smaller units—molecules, organelles and individual cells - are nested within progressively larger structures such as tissues, organs and entire organisms (Fig. 1). Each level in this hierarchy has its own capacity for sensing, decision-making and self-maintenance, yet remains integrated with higher-order control systems (Fields & Levin, 2022). This multiscale arrangement enables distributed information processing that helps organisms adapt to complex, ever-changing environments.

The relationship between these nested agents is defined by three key principles: containment, communication, and control. Containment refers to the physical boundaries that define each agent - from plasma membranes in cells to tissue barriers in organs. These boundaries are not passive containers but active interfaces that regulate the flow of materials and information shaping how cells and tissues perceive and respond to internal or external signals. At the smallest scale, cellular membranes separate cytoplasm from the extracellular milieu, regulating ion gradients and selective transport. At higher levels, tissue barriers such as basement membranes and endothelial linings maintain compartmental integrity, while in the central nervous system, the blood–brain barrier protects the neural microenvironment by filtering substances and immune cells (Daneman & Prat, 2015).

Communication operates across a vast range of temporal and spatial scales. Rapid signalling via membrane potential changes or gap junctions synchronises local cellular states (Levin, 2021; Funk & Scholkmann, 2023). Conversely, hormones, growth factors, and cytokines function over longer distances and longer timescales, integrating cell and tissue behaviour into coherent organ-level or organism-level responses. Mechanical forces also transmit information: changes in extracellular matrix (ECM) stiffness or tension can trigger large-scale shifts in tissue architecture and cell fate (Vining & Mooney, 2017; Mammoto & Ingber, 2010; Mammoto, Mammoto & Ingber, 2013). Together, these signalling modalities create nested feedback loops that enable

complex responses, such as immune activation in distant tissues or synchronized developmental transitions.

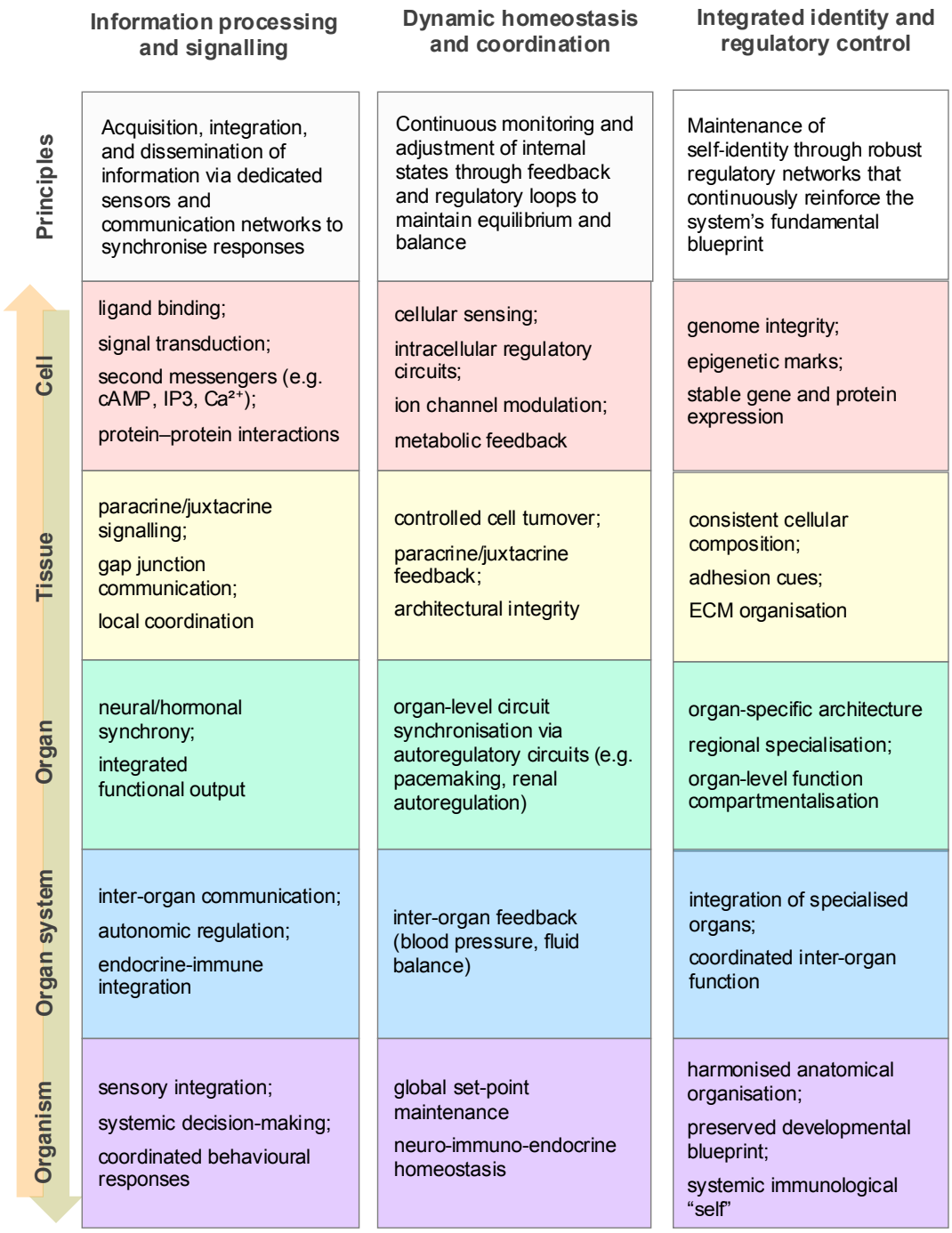

Fig. 1. Principles of hierarchical organisation in living systems operating uniformly across all scales.

Control mechanisms emerge at each level but are also integrated across levels. Cells modulate their metabolic states through pathways such as AMPK or mTOR, sensing nutrient availability and adjusting proliferation or autophagy accordingly (Kim *et al.*, 2011). Tissues organise division and differentiation via paracrine signalling, ECM composition and mechanical constraints,

balancing local cell requirements with higher-level objectives. At the level of entire organs or organ systems, more integrated control frameworks arise, often orchestrated by the nervous and endocrine systems, as seen in the regulation of body temperature, circadian rhythms or stress responses (Bass & Lazar, 2016). Importantly, these control layers exhibit reciprocal influence: local changes in cell behaviour can propagate systemically, while broad hormonal or neural signals drive shifts in cellular gene expression (Lafta *et al.*, 2024; Fields, 1996; Flavell & Greenberg, 2008).

Each level can influence and be influenced by those above and below, with higher levels shaping the constraints and options available to lower-level components, thereby aligning local processes with the systems' broader goals. Because chemical, bioelectrical and biomechanical signals propagate widely through tissues (McMillen *et al.*, 2021), local perturbations rarely remain confined to one area and can trigger larger-scale effects. For instance, local tissue injury triggers the release of danger-associated molecular patterns (DAMPs) that activate immune cells both locally and systemically (Kono & Rock, 2008). This inflammatory cascade, in turn, modifies neural and endocrine signalling, elevating stress hormones that feedback on immune function (Wilkinson & Brown, 2015). Simultaneously, energy demands at the cellular level change due to ongoing tissue repair, thereby influencing metabolic setpoints at the organ and organism levels (Hotamisligil, 2006). The propagation of effects across scales depends on the strength of coupling between levels and the presence of regulatory checkpoints. Strong coupling can facilitate rapid responses to threats but may also enable the spread of destructive influences. This multiscale, nested structure contributes to the resilience and adaptability of biological systems, as changes can be absorbed and managed at multiple levels. However, this same structure can be exploited by manipulating agents that have evolved to target specific vulnerabilities at different scales. Success at one scale can provide access to other scales, enabling systemic effects from initially localized perturbations. Many of the phenomena explored later - immune evasion, tumour-driven angiogenesis, parasite-induced behavioural changes - can be viewed as strategic manipulations that take advantage of the nested feedback loops supporting normal physiology.

Hence, understanding how biological information is processed across multiple organisational levels - how containment, communication and control interact to facilitate resilience or vulnerability – helps to examine how foreign or self-defecting agents hijack those same networks. This perspective helps clarify why disrupting a single checkpoint, barrier, or communication channel can allow intruders to exploit global processes, from metabolism to behaviour.

(2) Coordinated multimodal networks

Biological coherence refers to the coordinated behaviour of components that enables higher-order organisation, from individual cells to entire organisms (Kitano, 2004; Delvenne, Lambiotte & Rocha, 2015) (Fig. 1). This coordination depends on network motifs - such as negative feedback loops, feed-forward loops, and oscillatory circuits - that create robust yet adaptable regulatory systems (Alon, 2007).

Tissue level coherence arises from shared signalling pathways, cell–cell communication and mechanical integration. For example, in the intestinal epithelium, specialized cell types - enterocytes, goblet cells and enteroendocrine cells - coordinate nutrient absorption and barrier integrity through direct membrane contacts and paracrine interactions. This coordination spans multiple timescales, from transient calcium fluxes (milliseconds) to transcriptional changes (hours) and structural remodelling (days), integrated by molecular clock components that ensure

synchronised activity. Organ-level coherence emerges when tissues cooperate to fulfil a unified function. The heart exemplifies this principle: cardiac muscle, connective tissue, pacemaker cells and vascular endothelium form a synchronised, contractile system. Electrical impulses from the sinoatrial node spread through specialized conduction pathways, while the extracellular matrix aligns force transmission to ensure efficient pumping. At the organismal level, coherence manifests in integrated physiological responses. During exercise, the cardiovascular, respiratory and muscular systems adjust their activity in concert. The nervous system orchestrates acute alterations in heart rate and ventilation via neural reflexes, while endocrine signals such as catecholamines and glucocorticoids mediate longer-term adaptations. Inflammation, injury repair and other systemic processes rely on constant feedback between local cell populations and the central regulatory axes.

This multilevel coherence depends on communication systems which enables continuous monitoring and dynamic adjustment. Gap junctions coordinate local cell activity, whereas endocrine and neural signals integrate tissues and organs into organism-level feedback loops, with nanotubes, cytonemes and other mechanisms facilitating tissue-level communication (McMillen *et al.*, 2021; Yamashita, Inaba & Buszczak, 2018; Ariazi *et al.*, 2017). Coherent systems thus display resilience: if one component fails, others compensate to maintain overall function. In wound healing, local immune cells, fibroblasts and progenitor cells coordinate a regenerative response, while systemic signals maintain metabolic support. Importantly, intruders and self-defecting agents exploit these same networks. By mimicking host signals, disrupting hub nodes, or inserting new pathways, they co-opt the very processes that sustain system-wide coherence.

(3) Dynamic homeostasis and stability

Homeostasis - the maintenance of internal conditions within a viable range – is fundamental to physiology, ensuring reliable function despite environmental fluctuations (Modell *et al.*, 2015; Meizlish *et al.*, 2021; Medzhitov, 2021). Far from being static, homeostasis involves dynamic control of variables such as temperature, pH, osmotic pressure and metabolic energy stores. Multiple regulatory loops operate at every level, from intracellular buffers to organism-wide neuroendocrine axes, thereby conferring robustness and adaptability.

A straightforward way to conceptualise homeostatic loops is through a four-step framework: (i) detection of changes in key environmental or internal variables, (ii) processing the incoming information (e.g. thresholding, saliency detection, coarse-graining) relative to a stored setpoint, (iii) a response to minimize detected error (which can propagate non-locally as stress), and (iv) cycles of feedback. Although this sequence seems simple, it has considerable complexity of biological control, as multiple competing demands must be simultaneously weighed and integrated. Living systems rarely regulate a single parameter in isolation; rather, they constantly balance trade-offs, such as thermoregulation vs. fluid conservation, or immune surveillance vs. nutrient allocation. Prioritising and integrating these demands represents homeostatic adaptability.

Homeostasis involves various mechanisms that work together to maintain a stable internal environment within an organism: negative feedback (for instance, maintenance of blood glucose level or body temperature), positive feedback (for example, the blood clotting or immune cascades), feedforward/anticipatory mechanisms (increasing body fat in preparation for winter or glycogenolysis before exercise), oscillatory mechanisms (such as the circadian rhythm or

cardiac cycle), structural mechanisms (for instance, cell membrane, skin barrier, nephrons in the kidneys, alveoli in the lungs or structure of neurons). These mechanisms have distinct dynamic properties and function across various timescales, from rapid ion fluxes to slower metabolic shifts. Integrating these responses ensures robust yet flexible homeostatic control (Fig. 1).

Homeostasis maintains at different levels and by different levels. For instance, osmoregulation on the level of individual cells will involve cell membrane regulation (influx and efflux of materials) (Strange, 2004), contractile vacuoles (pushes the water out of the cell in some unicellular organisms) (Du *et al.*, 2008), osmoprotectants (small organic molecules which accumulate in cells and protect against osmotic stress) (Slama *et al.*, 2015), activation of signalling pathways and transcriptional factors (Zhou *et al.*, 2016; Choi *et al.*, 2019), expression of proteins (such as HSP-70 to maintain proper protein folding (Woo *et al.*, 2002)), adjustment of metabolic processes (for instance enzyme and structural proteins adaptation that remain stable and active at high salt concentrations in halophiles)(Edbeib, Wahab & Huyop, 2016; Gunde-Cimerman, Plemenitaš & Oren, 2018). Tissue-level osmotic homeostasis involves fluid exchange with capillaries and lymphatics, as seen in inflammation (Abdulkhaleq *et al.*, 2018). An example of osmoregulation on the organ level is brain's osmoregulatory independence, maintained by the blood-brain barrier (Abbott *et al.*, 2010). The illustration for the organ system and organismal levels is how the human body responds to dehydration. The organ systems contribute to osmoregulation in its own unique way, for instance: endocrine system activate renin-angiotensin-aldosterone system, antidiuretic hormone release, thirst stimulation; the renal system conserve water, integumentary system reduce sweat production, the nervous system triggers the sympathetic nervous system and motive the behaviours to seek out and consume water. At the organismal level, the regulation goas beyond the individual system responses and involve coordination of these systems to work together, for instance, the signals from the nervous and endocrine systems coordinating these responses to effectively mitigate the effects of dehydration.

Homeostatic regulation balances stability and adaptability. While stability is essential for optimal function, biological systems must retain sufficient flexibility to adapt to changing environmental demands. This balance is achieved through multiple mechanisms, including: 1) variable tolerance ranges that can be adjusted based on physiological state; 2) hierarchical control systems where local fluctuations are permitted within global constraints; 3) redundant regulatory pathways that provide backup mechanisms; 4) adaptive reset points that can shift in response to persistent changes.

Each biological component supports the functions of a higher-order unit. This hierarchical support structure allows for the multiscale organisation of biological systems, beginning from subcellular units and building up to cells, tissues, organ systems, and organisms. Homeostatic mechanisms act across this hierarchy to maintain stability and optimal functionality. The main challenge in studying and influencing homeostasis lies in its highly integrated and multi-dimensional nature, where numerous factors - cellular, genetic, epigenetic, biochemical, bioelectrical – operate in precise timing and coordination. If one mechanism fails, others compensate, preserving system stability. While essential for survival, compensatory mechanisms can mask underlying regulatory disruptions until critical thresholds are reached. Understanding these thresholds and the conditions under which compensatory mechanisms fail is crucial for both therapeutic intervention and understanding how manipulating agents can override host regulatory systems.

(4) Maintenance of identity

Biological systems maintain a coherent identity despite continual turnover of cells, molecules and structures (Fig. 1). This capacity operates at multiple organisational levels, making living agents active processes rather than entities that merely conserve specific components (Levin, 2024b; Solch, 2016). Recent studies have begun to characterise biological components not only by their metabolic and physical properties but also by their capacity to process and transmit information, positioning them as fundamentally informational (proto-cognitive) entities (Bongard & Levin, 2023; Kuchling *et al.*, 2020; Fields & Levin, 2020a; Fields & Levin, 2020b; Fields & Levin, 2019).

Cell maintains its identity – a unique combination of characteristics that distinguish one cell from another - through various cellular processes including gene expression patterns, the set of proteins produced and membrane integrity (Blazek, Paleo & Weisleder, 2015). The cell membrane not only segregate the intracellular from the extracellular environment, but also serves as an information processing interface that interprets mechanical, electrical and chemical cues, and therefore allow cell to be a separate agent. Cells allocate significant resources to maintain membrane potential (V_{mem}). V_{mem} is a form of stored energy for various functions. In multicellular organism, this bioelectric potential scales up to form a computational system that coordinates and integrates the activities of individual cells into larger, harmonised networks (Levin, 2023a). This bioelectric state serves as both an energetic resource and an information-carrying medium, enabling rapid cellular responses to environmental changes. Vmem is what creates cell's own controlled internal environment. The degree of cell autonomy or agency depends on to which extend the cell can control and change its Vmem. Beyond basic boundary maintenance, cells preserve their identity through multiple overlapping mechanism. For instance, DNA repair pathways maintain the integrity of the original DNA sequence (Chatterjee & Walker, 2017), while protein quality control pathways that recycle or refold damaged proteins.

Tissues develop a collective identity governed by the spatial arrangement of specialized cell types, the extracellular matrix (ECM) and local signalling networks. Cell–cell junctions reinforce tissue architecture, coherence, and synchronisation. For instance, epithelial tissues rely on tight junctions, adherens junctions and desmosomes to maintain polarity, structural integrity, selective transport and synchronised signal propagation. There are various mechanisms how tissue maintain self-identity and morphology, for instance by the regulatory mechanisms of cell polarity and adhesion molecules (Guzmán-Herrera & Mao, 2020) or tissue-specific transcription factors which associated with tissue environment (Sonawane *et al.*, 2017).

Organs derive identity from spatial organisation and functional integration of diverse cell populations into a functional whole. For instance, the liver's zonation requires precise architectural arrangement of hepatocytes, endothelial cells and immune cells (Kupffer cells) to optimise nutrient and oxygen gradients. Wnt/β-catenin and hedgehog signalling pathways maintain these zonation patterns and coordinate the organ's adaptive capacity (Matsumoto & Kikuchi, 2024). Organs maintain function and structure despite cell turnover.

At the organism scale, the interplay of neural, endocrine, and immune systems enables coordinated responses to environmental challenges and surveillance that preserves homeostasis through anomaly detection. The immune system, for example, distinguishes self from non-self through major histocompatibility complex (MHC) molecules, which present antigens to T cells. Cells lacking MHC or displaying foreign peptides are usually targeted for elimination. Nervous

system bioelectric integration and endocrine feedback loops support organismal coherence, ensuring that local perturbations are flagged or compensated across multiple tissues.

Higher organisational levels have broader perspective, capabilities and operational scope due to increased complexity and resource availability. Each ascending level of organisation not only coordinates lower-level functions but also acquires novel capabilities that emerge from this coordination (synergy). These emergent properties enable higher-level systems to pursue objectives and respond to challenges in ways that would be impossible for their individual components possibly conceive or achieve. This hierarchical organisation creates both opportunities and vulnerabilities for manipulation. Higher-level control systems can effectively coordinate responses across multiple tissues, but their complexity also provides multiple points for intervention by manipulating agents.

Biological systems preserve a coherent identity yet remain sufficiently flexible to respond to environmental challenges and ensure survival. Plasticity is short-term, reversible adjustments that allow agents to modify their function without losing core identity. This flexibility extends from subcellular processes, including DNA methylation and chromatin remodelling, to organismal strategies like thermotolerance and behavioural changes. Immune cells, for instance, can shift their phenotype in response to pathogens or tissue damage while retaining lineage markers. At the tissue level, bone undergoes mechanical remodelling, while the intestinal epithelium revises absorptive properties in response to dietary cues. Crucially, such shifts occur within defined limits safeguarding structural and functional integrity.

A clear example of machinery to maintain ‘self’ in relation to homeostasis and plasticity across multiple levels is immune surveillance. The immune system has a range of mechanisms which control the self-identity by countering external threats such as pathogens and internal disruptions like tumour formation. For instance, cells have evolved to recognise pathogen-associated molecular patterns (PAMPs) inside and outside the cell by pattern recognition receptors (PRRs), that allows cells to rapidly respond to infections, and alert neighbouring cells about the threat. Another very important mechanism of identify "self" versus "non-self" which is the feature of higher organisational level is the presentation of pieces of proteins from inside the cell to the exterior by MHC. If MHC presented proteins are foreign (e.g., viral or bacterial or cancer), they can be recognized and targeted by immune cells. If cell does not have MHC (a common feature in virally infected or tumour cells) or mismatch MHC (foreign cell), the cell will be also aimed by immune cells. Any cells which exhibit signs of stress (due to various reasons such as DNA damage, metabolic imbalance or mechanical damage) are also immune targets. Stressed cells express abnormal proteins, alter cell surface markers, and release or present "danger" signals - DAMPs. These signals can attract immune cells and highlight the stressed cell for inspection or elimination. The timely removal of stressed or damaged cells prevents the accumulation of malfunctioning cells which could potentially become neoplastic or disrupt tissue function and homeostasis.

The plasticity of the immune system is fundamental to its function and the brightest example of this plasticity is immunological memory. Although, the individual immune cells possess innate immune memory (trained immunity) (Netea *et al.*, 2016), the single cell or unstructured collection of the cells cannot develop the sophisticated immunological memory – the feature of the adaptive immune system, which enables faster, more effective responses to previously encountered pathogens. This kind of immunological memory is generated by the system and requires highly coordinated interactions among different cell types (such as antigen-presenting cells, T cells, and B cells) and structures (for instance, lymphoid organs). Therefore, the memory

about the past experiences persists in the system far beyond the lifespan of the original responding cells. Thus, the system uses learned behaviours and experiences provide by its parts for its own adaptation.

Self-identity is maintained through surveillance mechanisms that detect and respond to deviations from homeostatic setpoints. A compelling hypothesis suggests that certain self-reactive immune cells may perform interoceptive functions by monitoring tissue states through recognition of cell type- and state-specific antigens. These proposed 'Tx cells' would work alongside regulatory T cells to enable controlled tissue plasticity - promoting adaptive changes when needed while preventing excessive deviation from homeostatic baselines (Medzhitov & Iwasaki, 2024). This concept helps explain how tissues maintain their identity while retaining ability to adapt.

Plasticity enables not only homeostatic maintenance within normal physiological parameters but also more profound adaptations when survival is at stake. In response to severe challenges, organisms can temporarily override standard homeostatic mechanisms to establish new functional baselines - a process that manifests in immune responses, where acute inflammation directly counters threats, and in physiological adaptation, where persistent challenges lead to stable adjustments in homeostatic setpoints (Medzhitov, 2021). These adaptations beyond normal homeostatic boundaries can be either beneficial, as in altitude acclimatisation, or potentially harmful, as seen in chronic inflammatory conditions.

This hierarchical organisation of the system allows self-identity of its components via modular architecture. For instance, cells maintain their fundamental identity while exhibiting controlled plasticity in response to environmental signals. This modular architecture allows for both stability (through core identity modules) and adaptability (through functional-demand modules). Cell identity emerges through hierarchical transcriptional programs that integrate multiple regulatory inputs. The core identity is maintained through lineage-specific transcription factors that control fundamental cellular characteristics. This core program is supplemented by tissue-specific modules that adapt cell function to local environments, and demand-responsive modules that enable appropriate responses to specific challenges (Okabe & Medzhitov, 2016). For instance, tissue-resident macrophages maintain their core identity through PU.1-dependent transcription while adapting their function through tissue-specific transcriptional programs.

The persistence of identity, despite the continual turnover of cells, molecules and tissues, raises the philosophical “Ship of Theseus” paradox: can an entity remain itself if all its components are replaced over time? Biological systems resolve this by preserving organisational patterns and information flows**,** not simply by retaining identical hardware. Stem cell divisions, for instance, rebuild tissues in accordance with pre-existing spatial cues in the ECM, mechanical forces and bioelectric fields. Damaged or dying cells release “find-me” signals (ATP, nucleotides, HMGB1, CX3CL1) that recruit immune cells to clear debris and secrete factors guiding regeneration. This ensures that the architecture and function of the tissue - rather than its exact cellular membership - remain constant.

This principle of maintained identity through dynamic replacement is well illustrated in neural systems. Long-term memory persists despite continuous protein turnover, exemplified by the maintenance of synaptic strength. Key proteins like PKMζ, essential for memory maintenance, are constantly degraded and replaced. However, the memory's structural basis endures through persistent interactions between PKMζ and the scaffolding protein KIBRA, which anchor molecular processes supporting long-term potentiation at specific synapses (Tsokas *et al.*, 2024).

This creates a self-reinforcing system where the spatial pattern of synaptic connections is preserved even as their molecular components are renewed.

Despite their resilience, these systems of dynamic stability have thresholds beyond which identity fails. These critical transitions can occur when the rate of component loss exceeds replacement capacity, when regulatory networks are overwhelmed, or when spatial information becomes corrupted. For instance, severe tissue injury can disrupt the extracellular matrix scaffold and bioelectric patterns that guide proper regeneration, leading to scarring rather than true regeneration. Similarly, chronic inflammation can permanently alter tissue architecture through sustained disruption of normal replacement patterns. Cancer similarly crosses this boundary: gradual shifts in gene expression, metabolism and spatial organisation degrade a cell's original identity, creating a self-reinforcing microenvironment that resists reversion to normal states.

Recognising these limits is important for therapeutic strategies and understanding how manipulators push host systems past critical points. By establishing new stable equilibria, they lock hosts into altered identities that prevent a return to the original state.

(5) Modularity and top-down control

While whole organisms exhibit behavioural intelligence, living systems are composed of a hierarchical collection of dynamic agents that make context-sensitive decisions, learn from experience, allocate resources, and solve novel problems (Fig. 1). Though less apparent at the subcellular or tissue levels, these capacities are essential for adaptive functionality. Biological subsystems - ranging from molecular to organism-level networks - function within defined problem spaces to achieve adaptable homeostatic setpoints (the target conditions maintained by the regulatory circuits that sustain life) (McMillen & Levin, 2024). Evolution likely repurposed regulatory mechanisms for navigating diverse problem spaces - including metabolic, physiological, transcriptional, and anatomical domains – long before the specialised nervous system emerged to support advanced cognitive functions and information processing (McMillen & Levin, 2024; Levin, 2023c). In effect, all of these integrated systems - including the human body as a whole – can be regarded as a form of collective intelligence, sustained by informational and regulatory networks that synchronise the activities of individual components to achieve emergent outcomes even though no single component explicitly represents the overall objective (Levin, 2022; Levin, 2019).

A demonstration of adaptive self-organisation is the formation of a complex body during embryogenesis. In most species, this process is not simply the inexorable emergence of complexity from fixed biochemical rules, but rather an inherent capacity to achieve the species-specific target morphologies despite variable conditions. As reviewed in detail elsewhere (Levin, 2023b; Levin, 2023c), morphogenesis demonstrates remarkable targeted plasticity in its ability to reach consistent goal states despite radical variations in genome copy number, cell number, cell size, scrambled starting configurations, injury, chimeric recombination, and physiology - a phenomenon driven by the coordinated interplay of cellular regulatory networks (McMillen & Levin, 2024). For instance, animals that develop eyes on their tails instead of their heads can immediately adapt to visual input (Blackiston & Levin, 2013), bypassing the need for iterative rounds of mutation and selection to adjust to a novel sensory-motor configuration. Likewise, newts preserve their size and morphology by modulating cell number in response to the enlarged cells resulting from polyploidy, employing distinct molecular mechanisms to achieve consistent

anatomical outcomes despite differences in cellular composition (Fankhauser, 1945b; Fankhauser, 1945a).

Some evidence suggests that morphogenesis can be modulated by top-down signals from various sources, including parasites (Felt, 1940), neighbouring tissues (Gawne, McKenna & Levin, 2020) and bioengineering interventions (Davies & Levin, 2023). This susceptibility arises because morphogenesis is not a simple feed-forward process but is driven by a hierarchical network of information-processing agents that coordinate cellular and tissue behaviour toward defined outcomes (Levin, 2023a). Moreover, even subcellular networks adapt to overcome novel challenges (Biswas, Clawson & Levin, 2022; Biswas *et al.*, 2021; Stern *et al.*, 2007; Stolovicki *et al.*, 2006; Katzir *et al.*, 2012; Soen, Knafo & Elgart, 2015; Elgart, Snir & Soen, 2015; Csermely *et al.*, 2020).

This regulatory architecture provides modularity, evolvability, and robust adaptability in the face of novelty; however, it is vulnerable to co-option. Biomedical advances can be achieved by leveraging the inherent regulatory mechanisms of biological systems to develop interventions that reset homeostatic setpoints and refine perception, memory and informational boundaries (Lagasse & Levin, 2023; Levin, 2024a; Mathews *et al.*, 2023). However, these ideas remain predominantly conceptual, highlighting the need to develop simple quantitative models that capture the key mechanisms and provide testable predictions, thus turning these concepts into a solid empirical framework.

III. Mechanisms of biological hijacking

The manipulation of biological systems generally involves bypassing or overriding host regulatory safeguards while minimising detection. These strategies exploit core biological processes, blurring the boundaries between self and non-self, as well as between normal and aberrant functions. Manipulators often utilise existing regulatory networks and leverage cellular plasticity.

(1) Blueprint for host system subversion

To successfully manipulate a biological system, an intruder must execute a series of strategic actions that exploit the host's vulnerabilities and utilise its regulatory mechanisms. In this chapter, we outline the essential strategies for effective hijacking.

(a) Mimicry: imitating host systems

Mimicry involves producing or directly appropriating host or host-like molecules and structures to evade immune detection and integrate into host processes. Metastatic cancer cells, for example, adopt platelet-like signatures by incorporating platelet-derived glycoproteins, lipids and MHC class I molecules onto their surfaces (Martins Castanheira *et al.*, 2022; Schmied, Höglund & Meinke, 2021). This “platelet cloaking” deceives immune surveillance by obtaining a normal cell-like appearance, enhancing cancer cell survival and metastatic efficiency (Lim *et al.*, 2021; Spillane *et al.*, 2021). Rove beetles similarly acquire ant cuticular hydrocarbons through grooming, effectively adopting their chemical identity and enabling them to blend

seamlessly into ant colonies without rejection (Pires-Silva, Zilberman & Eloi, 2022). Pathogens often use molecular mimicry. Vaccinia virus encodes the A49 protein, which mimics the host's NF-κB inhibitor (Neidel *et al.*, 2019). By imitating the structure and function of a host protein that regulate inflammation, the virus suppresses the immune response, facilitating its survival and replication.

Manipulators typically employ multiple complementary mimicry strategies that work synergistically. Trophoblast cells in pregnancy represent perhaps the most successful example of integrated mimicry. The trophoblast, derived from the fertilised egg, is a biological anomaly - both 'self' and 'non-self' to the maternal organism due to its paternal antigens. This dual identity allows it to drastically manipulate maternal tissues without triggering rejection. Through endothelial and structural mimicry, the trophoblast transforms maternal spiral arteries to support the growing fetus. It integrates into the arterial walls, replacing endothelial cells and adopting an endothelial-like arrangement to remodel these vessels (Rai & Cross, 2014; Sung *et al.*, 2022). This structural mimicry allows the arteries to expand, accommodating increased blood flow - a process essential for placental development. At the molecular level, to ensure endothelial mimicry, trophoblast cells activate endothelial transcription factors, such as ERG, and produce proteins like VE-cadherin and PECAM-1, enabling them to function as part of the vascular system (Sung *et al.*, 2022; Rai & Cross, 2014).

(b) Direct interference: internal sabotage

Manipulators can actively disrupt host systems rather than mimicking them. This approach typically involves direct molecular interactions that block, modify, degrade or artificially activate key host signalling components.

The bacterial plant pathogen *Pseudomonas syringae* blocks immune receptors by injecting effector proteins into plant cells (Coburn, Sekirov & Finlay, 2007). Some of those effectors, such as effector AvrPto, directly bind to and inhibit PRRs (Zong *et al.*, 2008), preventing detection of bacterial PAMPs. Other effectors indirectly influence receptor expression; for instance, effector HopU1 blocks the interaction of their mRNAs with RNA-binding proteins associated with PRRs, thereby reducing their levels. Another effector HopZ3 adds acetyl groups to host proteins, contributing to immune evasion (Jeleńska *et al.*, 2021).

The human cytomegalovirus (HCMV) US28 protein acts as a constitutively active G protein-coupled receptor (GPCR) that can bind to a wide variety of chemokines and activate multiple signalling pathways (such as phospholipase C, NF-κB, and MAP kinase pathways) without the need for ligand binding (Vomaske, Nelson & Streblow, 2009; Daly, Smit & Plouffe, 2020). Furthermore, US28-mediated enhancement of HIF-1 leads to increased proliferation, angiogenesis and metabolic reprogramming (de Wit *et al.*, 2016). These HCMV US28 protein activities generate aberrant signals that dysregulate host cell behaviour, thus establishing a pro-viral environment (Daly *et al.*, 2020; Krishna, Miller & O'Connor, 2018).

Epigenetic reprogramming is another potent form of direct interference, inducing heritable changes in host gene expression. Cancer cells not only modify their own epigenetics but also reprogram surrounding cells. By secreting cytokines, growth factors and exosomes with regulatory microRNAs, they transform neighbouring stromal cells into cancer-associated fibroblasts (Paggetti *et al.*, 2015; Dong *et al.*, 2023) and suppress immune genes via TGF-β and IL-10 (Labani-Motlagh, Ashja-Mahdavi & Loskog, 2020; Tie *et al.*, 2022). Viruses similarly

exploit host epigenetic machinery - Epstein-Barr virus (EBV) proteins directly recruit DNA methyltransferases and histone-modifying enzymes to silence tumour suppressor genes while activating viral and pro-growth programs (Siouda *et al.*, 2014; Tempera & Lieberman, 2014; Saha *et al.*, 2015; Kaneda *et al.*, 2012). These epigenetic modifications create self-reinforcing regulatory states that persist even after the initial triggering signals diminish.

Signal molecule degradation provides another direct interference strategy. Many bacterial pathogens secrete enzymes that cleave antimicrobial factors (Hornef *et al.*, 2002). *Streptococcus pyogenes* produces streptococcal cysteine protease SpeB that cleaves multiple host proteins including chemokines and antimicrobial peptides, disrupting both immune signalling and direct antimicrobial defences (Barnett, Indraratna & Sanderson-Smith, 2022).

Physical barriers can also be undermined: *Plasmodium falciparum* restructure erythrocyte membranes to ease nutrient acquisition (Counihan *et al.*, 2017; Neveu & Lavazec, 2019), while some bacteria produce pore-forming toxins that breach tissues and also neutralise immune cells (Brito *et al.*, 2019). Self-defecting agents likewise engage in structural interference: cancer cells degrade the extracellular matrix via matrix metalloproteinases, facilitating invasion (Reunanen & Kähäri, 2000-2013).

As direct disruption often triggers detection, manipulators employ strategies targeting either specific pathways where detection can be minimised, or combining it with complementary tactics, including immunosuppression and mimicry.

(c) Homeostatic reset: overriding normal limits

Effective manipulation often hinges on overriding homeostatic circuits to lock in new setpoints. Homeostatic systems maintain physiological parameters within narrow ranges through layers of negative feedback loops (Modell *et al.*, 2015; Meizlish *et al.*, 2021). Extreme deviations beyond the homeostatic range - those that cannot be corrected by homeostatic circuits, including stress responses - trigger inflammation (Meizlish *et al.*, 2021; Kotas & Medzhitov, 2015), which serves as a physiological 'circuit breaker', temporarily suspending normal regulatory constraints. This inflammatory response drives major biological transitions by overriding homeostatic controls, allowing tissue remodelling and cellular reprogramming (Kulkarni *et al.*, 2016). Even processes that appear non-inflammatory, such as developmental transitions and apoptosis, rely on inflammatory signalling to initiate and coordinate systemic changes (Kolb *et al.*, 2017; Collins, Mitchell & Passegué, 2021; Newton *et al.*, 2024). This inflammation-mediated circuit breaking operates through multiple initiation pathways but aligns on shared inflammatory mechanisms to achieve system reset and restore to its functional state, which may not necessarily be the initial homeostatic range (Meizlish *et al.*, 2021). Instead, it can establish a new homeostatic range if the original is unachievable due to persistent changes or damage in the system, such as the continuous presence of a manipulator.

Successful manipulating agents exploit these normal physiological mechanisms. Whether triggered by the host's response to their presence or by existing tissue conditions, this inflammatory "window" of suspended homeostatic control allows manipulators to establish new set points that modify the host environment. For example, during early pregnancy, trophoblast cells invade the maternal decidua during implantation, initiating an inflammatory phase that is crucial for breaking the homeostatic circuit and overriding vascular homeostasis in maternal spiral arteries (Dekel *et al.*, 2014; Griffith *et al.*, 2017; Stadtmauer & Wagner, 2020). As this

process progresses, trophoblast cells transition to an immunomodulatory role by expressing anti-inflammatory mediators and immune checkpoint inhibitors such as PD-L1, ensuring immune tolerance (Vento-Tormo *et al.*, 2018). This inflammatory and immune-regulatory disruption enables radical vessel remodelling, transforming narrow muscular arteries into wide, non-contractile vessels that support placental development (Vento-Tormo *et al.*, 2018).

Multiple pathways can initiate inflammatory circuit breaking. For instance, membrane potential changes and ion fluxes activate the NLRP3 inflammasome complex (Yang *et al.*, 2019), while calcium waves through gap junctions can initiate inflammatory cascades across connected tissues (Fujii, Maekawa & Morita, 2017). Another example of inflammation initiation is metabolic stress: ATP depletion, altered nutrient availability, or oxidative stress trigger inflammatory responses through multiple mechanisms including inflammasome activation and stress kinase signalling (Zhong *et al.*, 2013). Mechanical disruption and tissue damage represent additional triggers, releasing damage-associated molecular patterns (DAMPs) that initiate inflammatory responses (Ma, Jiang & Zhou, 2024).

Cancer cells leverage inflammation as a circuit breaker to override normal tissue homeostasis. In the initial disruption phase, cancer cells trigger inflammatory responses through multiple mechanisms: oncogene activation, hypoxia, nutrient competition and mechanosensing (Abu, Rus Bakarurraini & Nasir, 2021). Inflammatory cascades involving NF-κB and STAT3 then establish altered metabolic and immune setpoints (e.g., via sustained IL-6, IL-1 and TNF-α release) (Wen *et al.*, 2022; Zhao *et al.*, 2021; Hänggi *et al.*, 2024). Tumours recruit regulatory immune cells and promotes tumour-associated macrophages, which adopt an M2-like phenotype that support tissue remodelling and maintain a supportive, immunosuppressive niche (Wen *et al.*, 2022; Turizo-Smith *et al.*, 2024), locking the host into a new, cancer-facilitating equilibrium.

Understanding how manipulators achieve homeostatic transitions is highly valuable for medical interventions and tissue engineering applications because offers two major capabilities. First, being able to re-write homeostatic setpoints would enable top-down control of complex system-level responses, allowing the use of low-complexity triggers rather than micromanaging every endpoint. Second, targeting these setpoints could potentially yield a "cure" – a stable reversion to a healthy state that persists long after the intervention has ceased (currently durable homeostatic shifts are rare, with few exceptions such as curative antimicrobials, certain surgical interventions or select gene therapies).

(2) Redirecting regulatory pathways

The evolutionary arms race between hosts and manipulators has driven the development of complex, redundant regulatory networks. Hosts develop overlapping control mechanisms to maintain stability, while manipulators acquire strategies to bypass these barriers. This co-evolution has shaped a wide range of biological control architectures, from redundant signalling pathways to advanced neural circuits. More broadly, the ability to differentiate self-initiated actions from external influences may have been crucial for the evolution of self-regulation and agency, especially in lineages that later developed complex nervous systems (Moccia *et al.*, 2024).

(a) Immune evasion and suppression

The immune system is often the first and most imposing obstacle for any manipulator because it distinguishes self from non-self and conducts both local and systemic defensive measures. Its centrality in maintaining organismal identity forces intruders to evolve methods that weaken immune vigilance or redirect it for their benefit.

Pattern recognition receptors (PRRs) form the first line of defence, monitoring both external and internal environments for signs of threat or damage. These include toll-like receptors (TLR) that detect pathogen-associated molecular patterns, NOD-like receptors that monitor intracellular spaces, and various danger signal receptors that identify tissue damage and cellular stress. *Mycobacterium tuberculosis* faces multiple pattern recognition receptors including TLR2, TLR4, and NOD2 that detect bacterial cell wall components and other conserved bacterial molecules (Kleinnijenhuis *et al.*, 2011). The bacterium overcomes these recognition systems by modifying its surface lipids, masking key molecular patterns, and actively interfering with receptor signalling pathways through secreted effector proteins that prevent proper immune detection (Jacobo-Delgado *et al.*, 2023; Day *et al.*, 2014; Blanc *et al.*, 2017; Drennan *et al.*, 2004).

Beyond innate recognition, the adaptive immune machinery presents increasingly advanced barriers that must be overcome. Trypanosomes undergo antigenic variation, constantly changing their surface coat glycoproteins to avoid antibody recognition (Glover *et al.*, 2013; Morrison, Marcello & McCulloch, 2009). Each switch creates a new surface identity, allowing the parasite population to persist despite host adaptive immune responses. Cancer cells exemplify more comprehensive immune reprogramming. Rather than being eliminated by tissue-resident macrophages, they convert these sentinels into tumour-associated macrophages (TAMs) through secretion of cytokines such as CSF-1 and CCL2 (Liu *et al.*, 2021; Mantovani *et al.*, 2022; DeNardo & Ruffell, 2019; Savage, 2024; Kuratani *et al.*, 2024). These macrophages adopt an M2-like phenotype that supports cancer progression, along with driving regulatory T cell induction. Meanwhile, cancer cells downregulate MHC class I expression (Cornel, Mimpen & Nierkens, 2020; Liu *et al.*, 2019), shed NKG2D ligands, and upregulate ‘don’t eat me’ signals such as CD47 (Lian *et al.*, 2019). They also release immunosuppressive factors including IL-10 and TGF-β, and induce metabolic remodelling to deplete nutrients in the tumour microenvironment (Labani-Motlagh *et al.*, 2020; Scott *et al.*, 2021; Lim, Rathmell & Rathmell, 2020). These steps form an immunosuppressive niche that supports further tumour growth, angiogenesis and metastasis.

During pregnancy, trophoblast cells demonstrate immune tolerance despite expressing paternal antigens that should trigger rejection (Moffett & Shreeve, 2023; Tirado-González *et al.*, 2013). Extravillous trophoblast - the cells that invade into the mother's tissues - evade immune detection by lacking HLA-A and HLA-B whilst expressing HLA-G, which suppresses T cells and modulates the function of natural killer (NK) and antigen-presenting cells towards a tolerogenic phenotype. The trophoblast expresses PDL1 and PDL2 to induce T cell exhaustion and suppression, whilst secreting immunosuppressive and anti-inflammatory factors such as prostaglandin E2, 2,3-dioxygenase (IDO), IL-10, and TGFβ (Carvajal *et al.*, 2021; Xu *et al.*, 2021; Moffett & Shreeve, 2023). Additionally, the trophoblast utilises domesticated viral elements, particularly syncytin proteins from endogenous retroviruses, which facilitate syncytiotrophoblast formation and provide immunosuppression (Mangeney *et al.*, 2007). These ancient viral sequences, now permanently integrated into mammalian genomes, serve as regulatory elements for placental development genes, demonstrating how viral machinery has been repurposed for tissue manipulation (Mi *et al.*, 2000; Imakawa *et al.*, 2022).

An extreme illustration of immune surveillance's importance is a case in which a tapeworm (*Hymenolepis nana*) developed malignant growths within a host with advanced AIDS (Muehlenbachs *et al.*, 2015). The severe CD4+ T cell depletion allowed the tapeworm cells to proliferate within host tissues, forming metastatic tumours. This case demonstrate that, in the absence of functional immune barriers, tumour cells from even phylogenetically distant organisms can proliferate and establish themselves within the host.

Manipulators bombard the immune system on multiple fronts: disguising themselves with host-like proteins, disabling antigen presentation, degrading pro-inflammatory mediators, secreting immunomodulatory signals, or hijacking checkpoint ligands that regulate immune cells, thereby dampening the very cascades meant to destroy them. By selectively disengaging these regulatory loops, intruders transform protective defences into permissive niches, ensuring their persistence despite a robust, multilayered immune architecture.

(b) Neural system manipulation: altering behaviour and physiological control

The neural system is a prime target for manipulation because it integrates multi-scale information to coordinate behaviour, physiology and organism-wide homeostasis. Its hierarchical structure, extending from synapses to complex circuits, enables intruders to exert broad control once they infiltrate critical neural hubs. An example of direct neural manipulation is the jewel wasp *Ampulex compressa*, which controls cockroaches, turning them into living food sources for its larvae. To do so the wasp must overcome the cockroach's central complex, a brain region controlling motor function and behaviour. The wasp injects venom containing GABA, β-alanine and taurine directly into the cockroach's central complex brain region, inducing temporary leg paralysis and facilitating guided locomotion (Haspel, Rosenberg & Libersat, 2003; Gal *et al.*, 2014). Dopamine release via D1-like receptors then triggers grooming behaviour followed by a hypokinetic state, ensuring the cockroach remains alive yet compliant until the wasp's larvae emerge (Nordio *et al.*, 2022; Gal & Libersat, 2010). Rather than evolving novel molecules, the wasp exploits standard neurotransmitters to hijack existing circuits.

Other manipulators create parallel regulatory systems. The parasitic barnacle *Sacculina carcini* persists for the host's lifespan by extending rootlets into a crab's ventral ganglia and other neural tissues. These rootlets modify their shape and structure to establish intimate contact with the host's nervous system, resulting a high degree of control, akin to a parallel regulatory system. The rootlets modulate host's neural signalling, causing reduced aggression, gonadal degeneration and care of Sacculina's external reproductive structures (Miroliubov *et al.*, 2020; Lianguzova *et al.*, 2023; Campos *et al.*, 2022). Although precise mechanisms are not fully described, serotonin-positive cells around the rootlets suggests that Sacculina may indirectly influence serotonin levels by changes in neurotransmitter receptor activity or the modulation of serotonin transport and release from nearby neurons (Miroliubov *et al.*, 2020; Lianguzova *et al.*, 2023).

A related but more complex example is the fungal pathogen *Ophiocordyceps unilateralis sensu lato*, which infiltrates various tissues of its host, carpenter ants, including muscles and haemolymph, and establishes an extensive network enabling mechanical control of ant movements (de Bekker & Das, 2022). Infected ants leave their colonies and climb vegetation at specific times conducive to fungal spore dispersal. Recent research suggests that this manipulation involves overriding the ant's normal circadian clock, with the host's daily rhythms disappearing during infection as the fungus imposes its timing for behavioural manipulation (de Bekker, Beckerson & Elya, 2021; Will *et al.*, 2020; Will, Attardo & de Bekker, 2023). The

manipulation involves replacing host muscle fibres, secreting molecules that affect dopaminergic, serotonergic and octopaminergic signalling, and expressing effector proteins (such as protein tyrosine phosphatases), that can potentially bind to ant proteins involved in circadian rhythm regulation (de Bekker & Das, 2022; Will *et al.*, 2023). The fungus appears to have its own light-responsive clock, synchronizing daily expression of key manipulation genes (de Bekker *et al.*, 2014).

Toxoplasma gondii has evolved a remarkable ability to manipulate its host's behaviour, potentially enhancing transmission success to its definitive feline host. This neurotropic parasite elevate dopamine in infected neural cells, which results in various behavioural alterations, including decreased aversion to cat odour, increased exploratory behaviour, and impaired prepulse inhibition response, which might affect the host's risk assessment and behaviour, particularly impaired fear memory and altered stress responses (Mahmoud, Fereig & Nishikawa, 2017; Mahmoud *et al.*, 2016; Ihara *et al.*, 2016). These changes potentially may increase the risk of predation by cats.

Breast and prostate cancers also manipulate neural systems to aid survival, particularly when metastasizing to bone. (Le *et al.*, 2022; Silverman *et al.*, 2021). They secrete neurotrophic factors such as nerve growth factor and brain-derived neurotrophic factor, prompting aberrant nerve sprouting that benefits tumour progression and their ability to spread. Additionally, metastatic cells upregulate receptors for neuropeptides such as substance P and calcitonin gene-related peptide, enabling them to respond to neural signals in ways that promote their survival and proliferation. In breast cancer specifically, tumour cells stimulate spontaneous calcium activity in sensory neurons, triggering substance P release, which then binds tachykinin receptors on tumour cells and drives metastasis (Padmanaban *et al.*, 2024).

Neural hijackers commonly exploit existing neurotransmitters, receptors or high-level circuit nodes to induce systemic shifts in host behaviour and physiology. By targeting these highly conserved mechanisms, they leverage the host's own molecular language to reprogram neural functions. Intruders often identify circuit 'super-nodes' (for example, brain regions integrating motor control or stress responses) whose manipulation yields broad downstream effects, inducing striking phenotypic outcomes through minimal genetic and biochemical modifications. Bridging neural signals with other systemic networks (immune, endocrine, metabolic), amplifying the scope of control. Additionally, there is evidence that some hijackers can sense and respond to neural electrical cues - for instance, herpes simplex virus type 1 senses neuronal hyperexcitability to time its reactivation when conditions in the cell (and perhaps the broader microenvironment) are favourable for productive infection (Cuddy *et al.*, 2020).

(c) Endocrine system: hijacking long-range signalling

The endocrine system is a prime target for biological manipulation due to its role in coordinating organism-wide responses and its capacity for long-range communication and regulation of development, metabolism, immune responses, reproduction and behaviour. Manipulators can produce hormone analogues, alter hormone production and reception, or hijack hormone-dependent developmental programmes.

Developmental hormone axes are particularly attractive targets because of profound influence on organismal physiology. Wolbachia infections in terrestrial isopods (woodlice) disrupt the androgenic gland hormone (AGH), which governs male sexual differentiation. By suppressing

AGH, Wolbachia feminises genetic males and skews the population's sex ratio, enhancing the bacterium's transmission through the maternal line (Herran *et al.*, 2021; Herran *et al.*, 2020).

Plant pathogens also exploit hormonal systems. *Pseudomonas syringae* synthesises coronatine, a mimic of the plant hormone jasmonic acid-isoleucine (JA-Ile), which binds jasmonate receptors with higher affinity than JA-Ile. By outcompeting the native hormone, coronatine compromises salicylic acid-dependent immune pathways essential for plant defence (Zheng *et al.*, 2012).

The trophoblast illustrates how endocrine manipulation achieves precise temporal control over host physiology. Embryo-derived syncytiotrophoblast cells secrete hormones - including human chorionic gonadotropin, placental growth hormone, human placental lactogen, and corticotropin-releasing hormone (CRH) - that reprogram maternal physiology (Malassiné, Frendo & Evain-Brion, 2003; Handwerger & Freemark, 2000). They override maternal metabolic regulation to increase fetal glucose availability, remodel cardiovascular function to enhance blood flow, and modify immune responses to prevent fetal rejection (Barbour *et al.*, 2007; Sanghavi & Rutherford, 2014; Arck & Hecher, 2013). The placenta also becomes a major source of estrogen and progesterone, elevating prolactin and oxytocin production (Grattan & Kokay, 2008). This fosters maternal care and moderates stress responses, effectively hijacking maternal behaviour to favour the fetus (Brunton & Russell, 2008). Placental CRH creates a positive feedback loop that differs from typical negative feedback in the maternal hypothalamic-pituitary-adrenal axis, leading to progressively rising hormone levels that help time labour onset (Smith, 2007). Although initiated locally, this manipulation achieves systemic effects through existing endocrine networks, demonstrating how hormone signalling coordinates physiological, metabolic, and behavioural changes across multiple organ systems.

The effectiveness of endocrine manipulation arises from several key principles: hormones amplify local signals into systemic responses, hormonal networks contain multiple reinforcing feedback loops that can be leveraged, and endocrine signalling integrates with other regulatory systems, including immune and neural networks.

(d) Metabolic system: redirecting resource allocation

The metabolic system is a target for manipulation owing to its central role in energy production, resource allocation and cellular homeostasis. There main tactics drive this manipulation: overriding nutrient sensing, reprogramming metabolic networks and establishing privileged resource access.

Nutrient-sensing override allows manipulators to maintain resource acquisition despite host regulatory signals that would normally restrict uptake. Cancer cells achieve this through constitutive mTOR signalling activation and suppression of AMPK-dependent metabolic checkpoints, enabling continued growth under nutrient-limited conditions (Magaway, Kim & Jacinto, 2019; Keerthana *et al.*, 2023). This override extends beyond individual cells; tumours establish restrictive microenvironments that deprive immune cells while channelling nutrients to themselves (Keerthana *et al.*, 2023).

Toxoplasma gondii reprograms host cell metabolism by altering oxidative states, mitochondrial function, and various metabolic pathways such as glycolysis, the Krebs cycle and arginine metabolism (Gallego-López *et al.*, 2023; Hargrave *et al.*, 2019). These metabolic changes support the parasite's growth and survival within diverse host cell environments.

Privileged resource access often develops through structural and functional modifications that allow manipulators to secure nutrients at the expense of over host tissues. The parasitic plant *Striga hermonthica* establishes vascular connections with host plants via a specialized organ called the haustorium, enabling direct access to host nutrients via alteration of multiple host plant hormones (abscisic and gibberellic acids) and the host's developmental programmes (Aoki *et al.*, 2022; Jamil *et al.*, 2024; Yap & Tsuchiya, 2023). Similarly, in human pregnancy, trophoblasts transform maternal spiral arteries into high-velocity, low-resistance vessels that facilitate sufficient blood flow into the placenta (Abbas *et al.*, 2020).

The metabolic manipulations typically operate in tandem with modifications of other regulatory networks such as developmental, immune and endocrine. By integrating metabolic changes with other regulatory networks, intruders maintain stable, long-term resource redirection without fatally disrupting essential host functions.

(e) Developmental reactivation: unmasking latent pathways

Many developmental pathways remain latent activation potential despite being tightly regulated after organogenesis. Manipulators exploit this developmental plasticity by either reactivating silenced embryonic programmes or hijacking active developmental pathways that control tissue maintenance and regeneration. By interfering with these fundamental mechanisms of tissue organisation and morphogenesis, intruders can coordinate complex cellular behaviours to remodel host tissues for their benefit.

Phytoplasmas illustrates how key developmental regulators can be harnessed. Their effector protein SAP54 interferes with floral development by forming a complex with MADS-box transcription factors and proteasomal shuttle factors, directing these essential developmental factors for degradation via the 26S proteasome (Teo, Zhou & Shen, 2019; Saavedra Núñez, González-Villanueva & Ramos, 2023; Kitazawa *et al.*, 2023). This disruption transforms normal floral development into leaf-like structures (phyllody), fundamentally altering organ identity and converting reproductive tissue into vegetative tissue that provides nutrients and space for phytoplasma proliferation.

The trophoblast exemplifies precise developmental reactivation during placentation. Trophoblast cells induce controlled changes in vascular smooth muscle cells of maternal spiral arteries, reactivating developmental programmes that enable radical vessel remodelling. This process involves coordinated activation of multiple pathways, including Notch signalling and vascular morphogenesis programmes, transforming narrow muscular arteries into dilated vessels optimised for placental perfusion (Cuman *et al.*, 2014; Perlman *et al.*, 2021; Zhang *et al.*, 2022).

Self-defecting agents frequently exploit developmental pathway reactivation. Cancer cells revive epithelial-mesenchymal transition (EMT) programmes through transcription factors like SNAIL and TWIST, acquiring invasive properties normally restricted to embryogenesis. This reactivation enables cells to break free from epithelial constraints while suppressing cellular senescence pathways (Mierke, 2019; Ko *et al.*, 2018). Similarly, many aggressive tumours reactivate neural crest-associated programmes, expressing molecules like NCAM, that facilitates cell-cell adhesion and migration (Amoureux *et al.*, 2010; Liu *et al.*, 2011).

Developmental manipulation usually involves coordinated activation of multiple pathways rather than single-gene effects. By harnessing these extensive regulatory networks, manipulators recapitulate aspects of embryonic development to remodel tissues. This capacity to reactivate developmental programmes with controlled tissue organisation suggests potential therapeutic strategies in regenerative medicine and anti-cancer interventions aimed at modulating cellular plasticity.

(f) Integration: multi-system attack

The evolutionary arms race between hosts and manipulators drives increasing complexity in biological control networks. As hosts evolve layered defences, manipulators must develop correspondingly integrated strategies to override these barriers. This recursive process has shaped both host regulatory architecture - from redundant signalling pathways to interwoven neural circuits - and manipulator attack strategies. Rather than targeting isolated pathways, manipulators coordinate interventions across immune, neural, endocrine, metabolic and developmental networks, overwhelming compensatory responses. The parasitic wasp *Cotesia congregata* exemplifies such multi-level manipulation in caterpillar *Manduca sexta* by injecting its eggs, venom, teratocytes and a symbiotic bracovirus (Cotesia congregata bracovirus, CcBV) into the caterpillar, thereby taking comprehensive control over its physiology:

1) The bracovirus is integrated into the wasp genome and amplified specifically in the wasp ovaries, where it is then packaged into viral particles and injected into the caterpillar (Louis *et al.*, 2013; Chevignon *et al.*, 2018; Bézier *et al.*, 2013). CcBV suppresses the host's immune response, allowing the wasp larvae to develop safely. Viral cystatins inhibit caterpillar proteases, diverting resources to the larvae and arresting caterpillar's pupation that would otherwise disrupt larval survival (Espagne *et al.*, 2005).
2) While the venom components are not detailed extensively, they synergise with CcBV to suppress both immune responses and host development (Moreau & Asgari, 2015).
3) Larvae feed on the caterpillar's haemolymph and, as they develop, they chew their way out of the caterpillar to spin cocoons on its surface. Emerging larvae secrete factors such as plasmatocyte spreading peptide (a cytokine) and spätzle (a Toll receptor ligand), which are involved in cytokine signalling and activation of the immune response. The cytokine storm induces sickness behaviour as well as a stress response, elevating neurohormonal mediators like octopamine (a vertebrate noradrenaline analogue). These changes trigger specific behavioural alterations in the host: the caterpillar ceases feeding and spontaneous movement, thereby preventing it from harming or consuming the wasp larvae (Adamo *et al.*, 2016; Miles & Booker, 2000). However, the caterpillar's defensive responses remain partially intact, enabling it to respond aggressively when disturbed. This behaviour protects the wasp cocoons from predators and is often referred to as "bodyguard manipulation."
4) Teratocytes are specialized cells that form a membrane around wasp eggs and are released into the host once the eggs hatch. These cells secrete various immunoregulatory factors and hormones that manipulate host development, modulate immune system, and alter metabolism. For instance, cysteine-rich proteins inhibit the synthesis of host storage proteins, thereby freeing up resources for the developing wasp larvae. Teratocytes also directly modify host nutrition by attaching to and digesting fat body tissue (Gao *et al.*, 2016; Nakamatsu & Tanaka, 2004).

This multi-component strategy achieves precise temporal control over host biology by exploiting the inherent connections between regulatory systems. The wasp effectively converts the caterpillar into a 'nursery' for its offspring through coordinated manipulation of immune, neuroendocrine, metabolic and developmental pathways.

Another example of integrated manipulation is plant gall formation induced by insects, which reveals remarkable morphogenetic competency in cells that normally produce the same pattern with high reliability. For instance, aphids transform plant tissues into highly organised structures that provide both shelter and nutrition. The gall-inducing process involves precise delivering effector molecules into individual plant cells via specialized mouthparts (stylets). This cell-by-cell manipulation accomplishes a targeted reprogramming of plant gene expression through the continuous release of effectors - proteins, phytohormones and signalling molecules - that modulate transcriptional and epigenetic regulatory networks (Holland *et al.*, 2023; Kutsukake, Uematsu & Fukatsu, 2019). Removal of the insect arrests gall development, that ongoing insect-host interactions are essential for gall formation:

1) Aphids deliver effectors that induce profound changes in plant cellular organisation. Plant cells near stylet injection sites undergo enhanced proliferation, involving periclinal divisions - a pattern not observed in normal leaf development (Korgaonkar *et al.*, 2021; Holland *et al.*, 2023). These changes involve reorganisation of subcellular structures and establishment of new developmental trajectories.
2) Aphids upregulate plant genes involved in nutrient transport and metabolism while suppressing photosynthetic pathways, thereby creating a privileged feeding site enriched in amino acid and sugars to sustain colony (Kutsukake *et al.*, 2019).
3) Aphids secrete diverse effector proteins that alter plant developmental programmes. One example is the BICYCLE protein family, which interferes with plant development and immune signalling, altering plant morphology to optimise it for aphid survival (Korgaonkar *et al.*, 2021; Holland *et al.*, 2023). Various BICYCLE proteins appear to target distinct aspects of plant biology and exhibit precise temporal regulation during gall formation. Different aphid species induce distinct gall morphologies, indicating precise control over plant development rather than random tissue overgrowth.
4) Gall formation requires sustained suppression of host defences. Aphids secrete effectors that interfere with plant immune signalling, preventing the activation of defence responses that normally restrict tissue transformation (Liu *et al.*, 2024; Gravino *et al.*, 2024).
5) The galls display remarkably specialized architectures that maintain a favourable microenvironment for aphid development. They contain nutritive tissues, modified vascular patterns and structural features that regulate internal environmental conditions (Kutsukake *et al.*, 2019; Korgaonkar *et al.*, 2021; Holland *et al.*, 2023). The consistent gall morphology seen within each aphid species, even across different plant hosts, demonstrates the precision of multi-system manipulation.

The precision with which manipulators align diverse host pathways reflects the same complex coordination that supports normal developmental transitions, from embryogenesis to metamorphosis.

(3) The recipe for hijackers: a unified model of hijacking principles

Throughout this paper, we have explored the strategies used by biological manipulators to hijack host systems. Below is a summary of the essential steps required to hijack a biological system (Fig. 2).

1. Breach and anchor. Intruders first bypass or weaken the host's physical and chemical barriers to enter into the system (Fig. 2A). Cellular invasion often involves exploiting existing receptor-mediated endocytosis pathways or directly modifying membrane

properties. For example, *Plasmodium falciparum* uses adhesins and proteases to breach the erythrocyte membrane, reorganising membrane lipids to establish a parasitophorous vacuole for intracellular survival (Mukherjee *et al.*, 2022; Triglia *et al.*, 2023; Geoghegan *et al.*, 2021). At tissue levels, manipulators degrade basement membranes and disrupt tight junctions, often by secreting matrix metalloproteinases or hijacking host cell migration machinery.

2. Disguise as self to evade detection and neutralise the host's defence to prevent elimination. Once inside, manipulators adopt molecular and structural characteristics that mimic the host's own components, camouflaging their identity to avoid triggering immune surveillance (Fig. 2B). For example, breast cancer cells can colonise bone tissue by activating osteomimetic transcription factors such as Runx2, adopting an osteoblast-like phenotype and integrating into the bone microenvironment (Barnes *et al.*, 2003; Tan *et al.*, 2016). Additionally, as extensively discussed in previous chapters, immunosuppression is a very important component of biological system hijacking. By blunting or misdirecting defensive host responses, intruders can maintain control with minimal opposition.

3. Shatter homeostatic controls. Biological systems rely on complex regulatory networks that coordinate processes across multiple scales. These networks incorporate numerous feedback loops, redundant pathways and hierarchical control structures that have evolved to maintain homeostasis and identity. Manipulating agents must overcome these robust control architectures to achieve their objectives. By pushing physiological parameters far beyond normal ranges, the host's homeostatic balance becomes disrupted (Fig. 2C), inducing inflammatory responses that temporarily suspend regulatory controls (Kotas & Medzhitov, 2015; Kulkarni *et al.*, 2016; Kolb *et al.*, 2017; Collins *et al.*, 2021; Newton *et al.*, 2024). This temporary suspension allows manipulators to reset setpoints, establishing new norms and permitting actions previously restricted - such as the reactivation of dormant developmental pathways or differentiation processes to remodel tissues and alter cellular functions. By exploiting the host's capacity for change (plasticity), intruders can induce transformations that favour their persistence.

4. Seize communication and reprogramming regulatory networks. Communication is central to biological systems - from molecular signals within cells and bioelectrical signals between cells to long-range hormonal signalling – communication coordinates cellular behaviours, tissue homeostasis and organismal level responses to environmental changes. Communication networks that emerged with increasing biological complexity lack the evolutionary-derived robustness of more ancient processes, as the new mechanisms accumulated less redundancy. In multicellular tissues, cells rely on collective resilience through shared stress responses, metabolic cooperation and coordinated defences. Once these communication networks are disrupted (Fig. 2D), individual cells become isolated from protective mechanisms, leaving them susceptible to further manipulation. Intruders employ three main strategies:
    - Block or disrupt existing signals by directly interfering with signal molecules, their receptors, or downstream pathways. Cancer cells, for example, alter gap junctions and surface adhesion molecules (Ugur *et al.*, 2022; Wilczyński *et al.*, 2024), thus, disrupting tissue architecture and cell-cell communication.
    - Produce mimics of host signalling molecules to generate false messages. For instance, the human cytomegalovirus protein US28 acts as a constitutively active G

protein-coupled receptor that generates aberrant signals under the facade of legitimate host signalling, dysregulating host cell behaviour (Krishna *et al.*, 2018).
- Establish new communication channels while isolating themselves from host control signals. By creating aberrant signalling environments, cancer cells coordinate tumour growth while remaining functionally detached from normal tissue regulation (Zhang *et al.*, 2016; Aramini *et al.*, 2022).

Rather than evolving entirely novel pathways, manipulators typically exploit the host's existing regulatory architecture, taking advantage of biological plasticity. Network reprogramming follows three main patterns:
- Pathway rewiring. Intruders modify protein–protein interactions, change spatiotemporal signalling dynamics or alter pathway crosstalk to redirect information flow. Many plant pathogens, including *Pseudomonas syringae*, secrete effectors that rewire host immune signalling networks by disrupting specific protein interactions or redirecting signals through alternative pathways (Toruño, Stergiopoulos & Coaker, 2016; Guo *et al.*, 2009).
- Control node hijacking. By targeting key regulatory hubs such as transcription factors or epigenetic regulators, manipulators induce broad changes in gene expression. Cancer cells, for example, exploit HIF-1α to synchronise metabolic reprogramming, angiogenesis and immune evasion (Infantino *et al.*, 2021; Corcoran & O'Neill, 2016; Sharma, Sinha & Shrivastava, 2022).
- Feedback loop modification. This involves introducing new feedback connections, dismantling existing loops or altering their dynamics. During placental development, trophoblast cells form new regulatory loops that sustain their invasive phenotype whilst preventing excessive invasion. These loops include positive feedback circuits that reinforce developmental programmes and negative feedback mechanisms that limit uncontrolled growth (Lu *et al.*, 2013; Knöfler & Pollheimer, 2013).

5. Engineer physical space. Intruders manipulate the physical organisation of host tissues to create niches that support their survival (Fig. 2E). This involves remodelling the extracellular matrix, modifying mechanical properties and reorganising tissue architecture. By degrading matrix components, manipulators gain access to essential nutrients and evade host defences. Changes in the physical properties of the tissue, such as stiffness or elasticity, can enhance invasive potential and promote survival in hostile environments. In pancreatic ductal adenocarcinoma, the abundant stromal components not only support tumour growth but also impede the delivery of chemotherapeutic drugs and shield cancer cells from immune surveillance (Perez, Kearney & Yeh, 2021; Thomas & Radhakrishnan, 2019; Bulle & Lim, 2020; Du *et al.*, 2023).

6. Establish long-term control. To maintain sustained manipulation, intruders implement changes that that remain even after initial triggers are gone (Fig. 2F). These changes often include epigenetic modifications that reprogram host gene expression to favour their persistence. Some manipulators integrate their genetic material directly into the host genome, creating a permanent blueprint for their continued replication, as seen with oncogenic viruses like human papillomavirus (HPV), whose viral oncogenes disrupt normal cellular function and promote malignancy (Warburton *et al.*, 2021; Lehoux, D'Abramo & Archambault, 2009). Others establish self-sustaining feedback loops that maintain manipulated states without further external input. By synchronizing diverse mechanisms and actions, intruders can persist undetected within the host system, revealing potential targets for future therapeutic interventions.

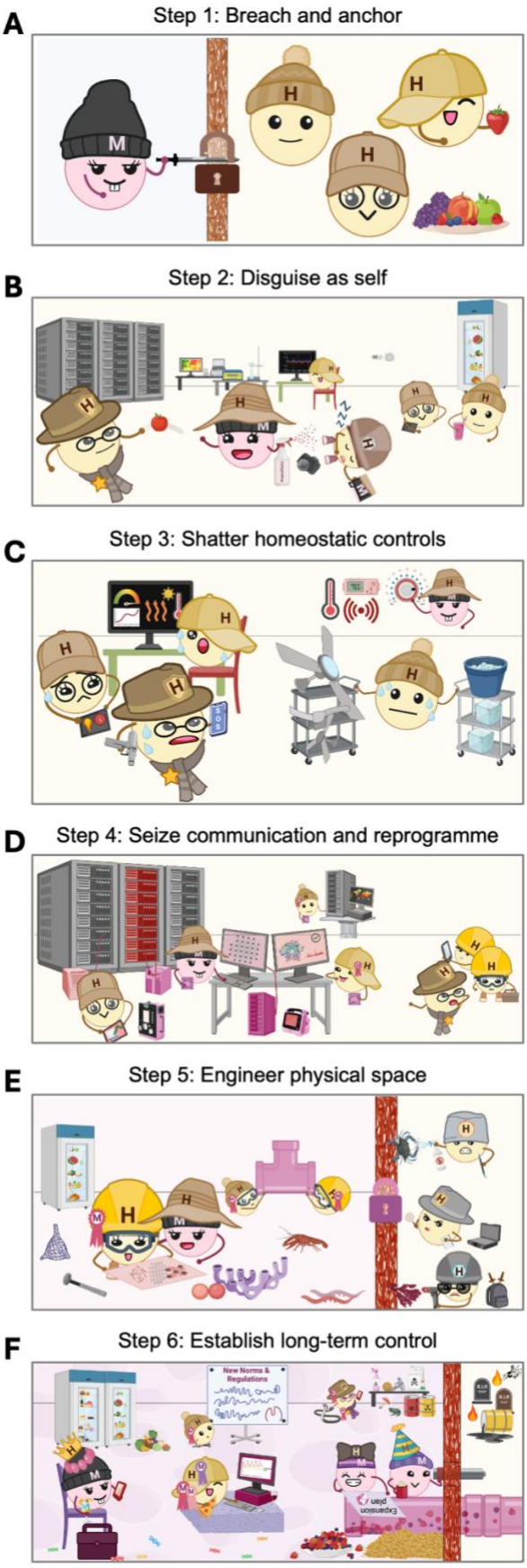

Fig. 2. The six-step recipe for successful biological manipulation. First (A), the manipulator (marked 'M') breaches and anchors itself within the host environment, bypassing or disrupting physical barriers. It then discards or conceals its 'M' identity (B), adopting host-like properties to evade immune surveillance. Once disguised, it shatters homeostatic controls (C), disabling the host's regulatory balance and inducing an inflamed, permissive state. Next, it seizes communication networks (D), rewiring or blocking signals to misdirect the host's collective defences. The manipulator then remodels tissue architecture (E), creating niches that favour its expansion and persistence. Finally (F), it consolidates long-term control by embedding itself within the host's regulatory fabric, ensuring that the altered state is maintained. Figure created with BioRender.

Biological manipulation synchronises diverse mechanisms and actions, enabling intruders to persist undetected within the host system. In the next chapter, we examine how leveraging or counteracting these same principles could guide new therapeutic strategies and engineered solutions inspired by nature's own methods of manipulation. Although this framework brings together many observed phenomena, it leaves open questions about which mechanisms are most critical and how they can be measured. Future studies should focus on these key aspects with controlled experiments to validate and refine our framework.

IV. Engineered interventions inspired by natural manipulation

Manipulators achieve lasting control over their hosts by reprogramming physiology, remodelling tissues and establishing new setpoints. Insights from these biological strategies can be used to develop interventions that steer diseased tissues toward healthier states through precise, context-dependent adjustments rather than simply suppressing pathology.

The first step requires breaking persistent pathological states that resist conventional treatments. Just as natural manipulators induce controlled disruption to increase host flexibility, engineered interventions must create defined windows of plasticity in target tissues. These transient windows enable reorganisation of existing regulatory networks, allowing emergence of new stable states that cannot be formed under ingrained maladaptive feedback loops. The aim of initial step is to induce conditions that loosen rigid regulatory feedback loops, creating a window during which cells and tissues become more receptive to subsequent guidance (Fig. 3). Moderate acute inflammation can prompt re-evaluation of setpoints without causing extensive damage. This approach mirrors controlled circuit-breaking observed during natural developmental transitions, where temporary suspension of homeostatic constraints enables profound tissue remodelling. Success depends on precise temporal and spatial control - disruption must be sufficient to enable subsequent therapeutic modification while remaining contained within defined tissue zones.

Once the pathological state is destabilised, the next challenge is steering the tissue towards desirable endpoints. The window of plasticity is brief, because once inflammation becomes chronic, it establishes a new rigid pathological homeostatic range. Successful reprogramming requires carefully timed signals that guide cells into the desired functional identity. Natural systems provide templates of sequential reorganisation: trophoblast cells remodel maternal vessels in a tightly regulated progression, parasites modulate host behaviour step by step and cancers gradually shift their microenvironment into a self-sustaining pathological niche. Thus, signals must be introduced in the proper order and intensity. This might be achieved by pairing sensing modules that detect local conditions with inducible genetic circuits or timed-release vehicles, thereby prompting tissues to adopt new phenotypes, regenerate structures or regain immunological balance (Xie & Fussenegger, 2018; Hun Jin & Weiss, 2019; Dang *et al.*, 2018). Manipulating the extracellular matrix, cell-cell communication pathways and metabolic resource flows consolidates these transitions, shifting the system away from disease and towards functional restoration. This is not limited to molecular signals. Modification of the extracellular matrix composition and tissue stiffness can shape cell fate, as well as electrical gradients or metabolic signals. Carefully engineered agents may leverage cells' innate capacity to respond to coordinated environmental changes.

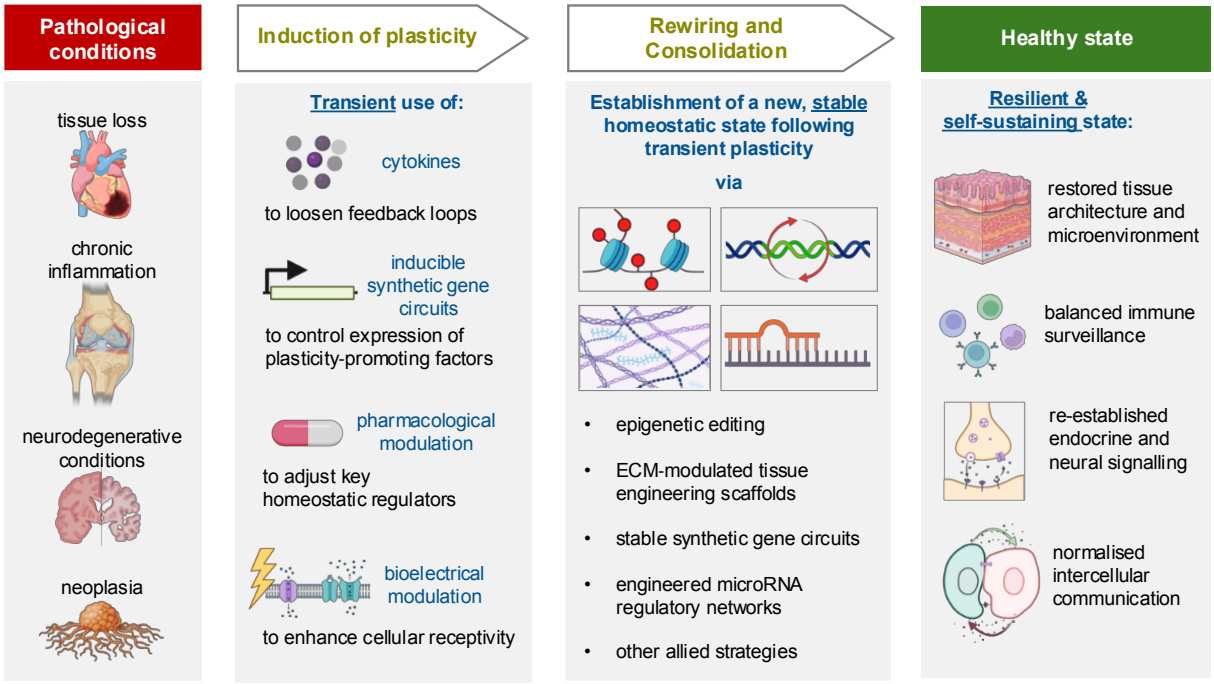

Fig. 3. Theoretical roadmap for engineered interventions, presenting a conceptual framework for re-establishing homeostasis via emerging technologies. These examples are illustrative potential strategies, rather than established clinical approaches. Figure created with BioRender.

The final step of an engineered intervention is to establish new regulatory baselines that persist after the initial triggers are withdrawn, enabling tissues to maintain improved structure or function under their own feedback loops (Fig. 3). By employing epigenetic modulation, adjusting long-range signalling or reconfiguring resource flows, it becomes possible to stabilise altered tissue identities and immune profiles. Achieving this stability depends on controlling both the local microenvironment and the broader systemic context. Strengthening a beneficial immune niche or ensuring that vascular patterns match healthy metabolic demands avoids the reliance on continuous external input. Over time, the host's own regulatory processes uphold the new steady states.

Modifying tissue structure, tuning metabolism, altering immune relationships or modulating neural inputs makes limited sense when pursued in isolation. In nature, successful manipulators coordinate interventions across multiple levels of organisation, harnessing innate plasticity to re-evaluate setpoints and establish new equilibria. These integrated tactics could guide new therapies - local inflammation could be induced to reset certain homeostatic parameters, reprogram cell identity through precisely timed morphogen pulses and re-establish vascular or neural patterns aligned with the intended outcome. As external signals are gradually withdrawn, the system settles into a stable new identity. Instead of constant management, the ultimate goal is a lasting internal reconfiguration that stands on its own.

Substantial research must concentrate on developing tools that enable interventions at each stage of biological system hijacking. Synthetic biology provides a growing toolkit to engineer responsive gene circuits that adapt to cellular states moving beyond uniform approaches. Advances in materials science offer dynamic scaffolds that adapt as tissues evolve. Whilst promising, these emerging fields require considerable scaling of efforts. It is essential to develop technologies that allow controlled spatial and temporal interventions, along with robust sensors to track cellular and tissue states in real time. Interventions must self-calibrate according to tissue

responses and/or changing conditions, adjusting signals and mechanical or biochemical properties based on evolving tissue contexts. Engineered cells must adjust their secretome in response to local cues. Furthermore, it is essential to develop tools that can edit chromatin states, DNA methylation profiles and histone marks in targeted cells, enabling stable shifts in gene expression without continuous intervention.

Identifying what to target and how to reprogram requires comprehensive data sets that capture the complexity of biological organisation. It is necessary to collect detailed spatial and temporal maps of gene expression, epigenetic profiles, electrical activity, proteomes, mechanical features and cell-cell signalling patterns across healthy and diseased tissues. Single-cell and spatial transcriptomics, advanced proteomics and metabolomics, and in vivo imaging will vital to document baseline states and how these states shift under stress or experimental manipulation. Machine learning and computational modelling can integrate these large data sets, identifying key regulatory constraints, point potential pathways for intervention and understand how alterations at one scale affect higher-level organisation. Developing predictive models that simulate tissues responses to controlled perturbations enables the design of interventions that achieve desired outcomes with minimal trial and error. These engineered interventions remain largely theoretical; developing mechanistic models and quantitative predictions is essential to harness these strategies and guide experimental validation.

V. Conclusions

(1) The hierarchical regulatory networks that maintain biological homeostasis contain intrinsic vulnerabilities; these weaknesses make systems susceptible to both self-defecting and foreign agents, which bypass established control mechanisms.

(2) Intruders exploit these vulnerabilities by hijacking conserved signalling pathways - through molecular mimicry, targeted interference and reprogramming of feedback loops - to override host defences and rewire host regulatory networks.

(3) The transient induction of plasticity is a critical step in hijacking; by perturbing homeostatic setpoints, manipulators establish a state in the host that becomes self-reinforcing and compromises normal function.

(4) Interactions among the immune, neural, endocrine and metabolic systems are central to both the disruption of host regulation and the reprogramming that follows.

(5) By clarifying the mechanisms underlying biological manipulation, this framework provides a blueprint for engineered interventions. Strategies that induce transient plasticity and rewire host regulatory networks to reset homeostatic setpoints may reverse pathological states, restore regenerative capacity and guide the development of integrated therapies that re-establish stable, self-sustaining tissue function.

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VII. Author contributions

E.V.S. and M.L. co-developed the idea, conducted the literature search, and co-led the writing. All authors contributed to revisions and approved the final manuscript.

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Figure legends

Fig. 1. Principles of hierarchical organisation in living systems operating uniformly across all scales.

Fig. 2. The six-step recipe for successful biological manipulation. First (A), the manipulator (marked 'M') breaches and anchors itself within the host environment, bypassing or disrupting physical barriers. It then discards or conceals its 'M' identity (B), adopting host-like properties to evade immune surveillance. Once disguised, it shatters homeostatic controls (C), disabling the host's regulatory balance and inducing an inflamed, permissive state. Next, it seizes communication networks (D), rewiring or blocking signals to misdirect the host's collective defences. The manipulator then remodels tissue architecture (E), creating niches that favour its expansion and persistence. Finally (F), it consolidates long-term control by embedding itself within the host's regulatory fabric, ensuring that the altered state is maintained. Figure created with BioRender.

Fig. 3. Theoretical roadmap for engineered interventions, presenting a conceptual framework for re-establishing homeostasis via emerging technologies. These examples are illustrative potential strategies, rather than established clinical approaches. Figure created with BioRender.