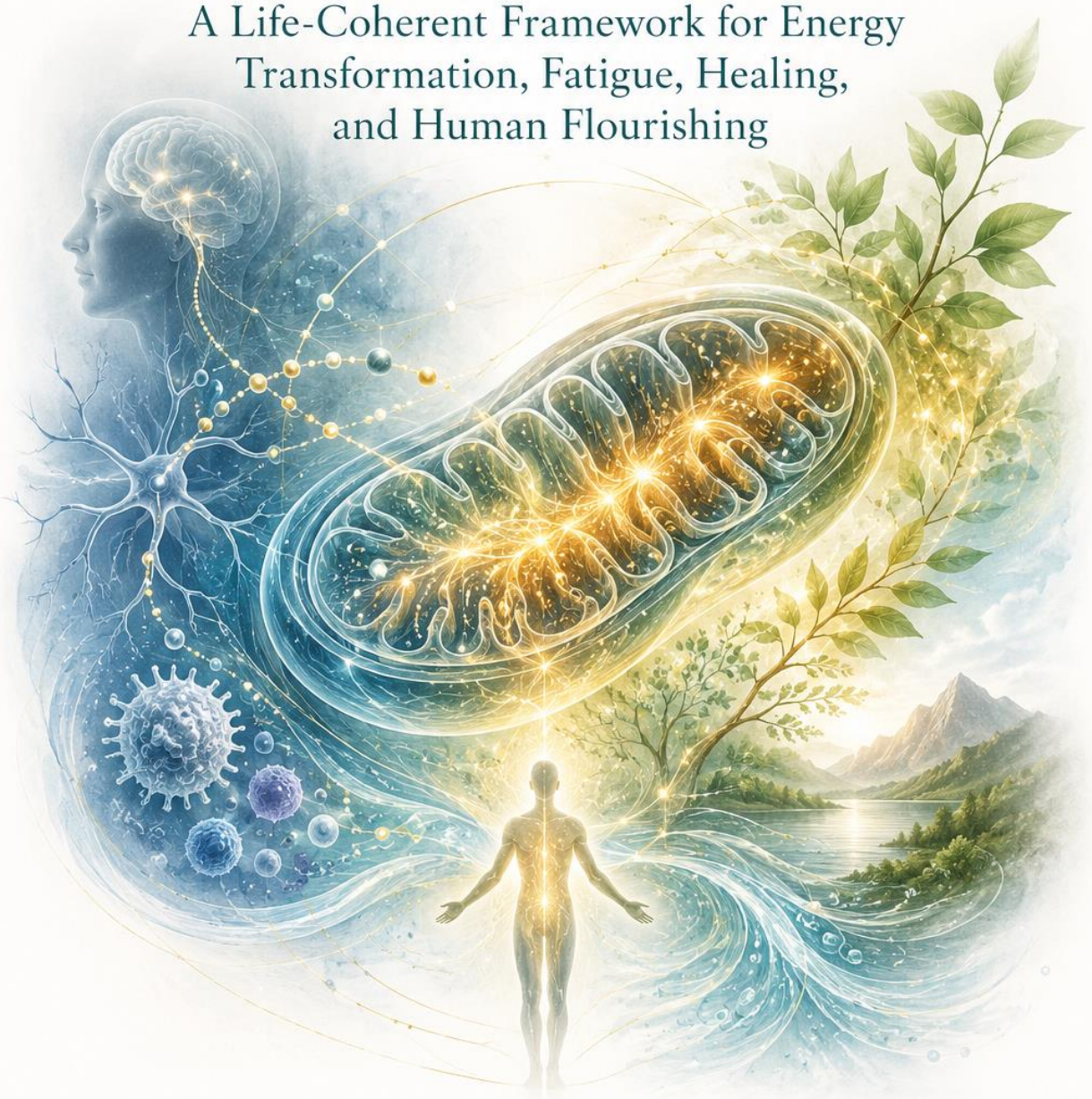
Mitochondrial Life-Capacity

A Life-Coherent Framework for Energy Transformation, Fatigue, Healing, and Human Flourishing



Dr. Bichara Sahely

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A Life-Coherent Framework for Energy Transformation, Fatigue, Healing, and Human Flourishing

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Abstract

Health is commonly approached through disease categories, risk factors, biomarkers, behavioral choices, service delivery, and cost-effectiveness metrics. These approaches remain indispensable, yet they are incomplete when detached from the living biophysical processes through which organisms transform resources into movement, cognition, immunity, repair, relation, participation, and meaning. This white paper proposes mitochondrial life-capacity as an integrative bridge between cellular bioenergetics and life-coherent health. It argues that life-coherent health is the condition in which the organism-niche relation maintains mitochondrial energy transformation, neuroimmune regulation, repair opportunity, and lived participation within restorative margins.

The paper integrates life-coherent health theory, mitochondrial psychobiology, metaboception, mitoception, salugenesis, salutogenesis, allostasis, interoception, affective neuroscience, redox biology, mitochondrial dynamics, autophagy, proteostasis, circadian repair, and organism-niche coupling. It defines mitochondrial life-capacity as the cellular and organismal capacity to transform available resources into coherent biological and behavioral work without excessive redox stress, danger signaling, proteostatic overload, or depletion of repair margins.

When exposure, threat, inflammation, psychosocial stress, hypoxia, toxic burden, circadian disruption, or excessive demand exceed transformation capacity, cells enter compensatory states involving altered electron transport, reductive and oxidative stress, integrated stress response activation, Warburg-like metabolic shifts, mitochondrial fission, mitophagy, autophagy, GDF15 and FGF21 signaling, autonomic activation, HPA-axis mobilization, and behavioral conservation. These compensations are protective responses that become disabling when they remain activated after the initiating demand should have resolved or when the organism lacks the conditions required to complete repair.

The framework interprets fatigue not as mere weakness, lack of motivation, or isolated psychological distress, but as a felt interoceptive signal of constrained energetic affordance: the organism's inference that further demand may exceed safe transformation capacity. Human flourishing becomes the embodied expression of coherent energy transformation within a life-enabling organism-niche relation.

Keywords

Mitochondrial life-capacity; life-coherent health; metaboception; mitoception; GDF15; FGF21; fatigue; allostasis; interoception; salugenesis; salutogenesis; cell danger response; redox biology; reductive stress; oxidative stress; mitophagy; autophagy; proteostasis; organism-niche coupling; restorative margins; wu-wei physiology.

Executive Summary

This white paper extends the life-coherent framework for health, healing, and human flourishing by giving it a more explicit biophysical core. The original life-coherent framework defines health as life-capacity enabled, healing as life-capacity restored, and flourishing as life-capacity expressed through dignity, relation, meaning, participation, and ecological belonging. The present paper asks how these life-capacities are made biologically possible. Its answer is mitochondrial life-capacity.

Mitochondria are not merely ATP-producing organelles. They are dynamic life-enabling flow systems that translate oxygen, nutrients, movement, sleep, inflammation, toxic exposure, circadian rhythm, psychosocial threat, social safety, and ecological conditions into cellular and organismal capacity. Their quantity, quality, network coherence, redox state, cristae architecture, fission-fusion dynamics, mitophagy, proteostasis, and stress signaling help determine whether the body can transform available resources into coherent work.

The central claim is that health depends, in part, on a living match between demand and transformation capacity. When demand is proportionate, resources are adequate, tissues exchange cleanly, and repair opportunities are protected, mitochondria support coherent action, clear cognition, immune balance, social engagement, restorative sleep, and meaningful participation. When exposures, threats, or demands exceed transformation capacity, the organism enters an energy-gap state.

Fatigue is interpreted here as an interoceptive and metaboceptive experience: the felt narrowing of possible action when the organism infers that further demand may exceed safe energy transformation capacity. Anxiety, malaise, appetite suppression, effort intolerance, social withdrawal, cognitive slowing, and the tired-but-wired state are understood as part of a dual compensation. The body mobilizes fuel through sympathetic and HPA-axis activation while simultaneously conserving energy through fatigue and reduced engagement.

The paper introduces the concept of wu-wei physiology: the body's capacity to transform energy into work with minimal forcing. Wu-wei physiology is not passivity. It is coherent action under conditions where demand, capacity, timing, repair, and meaning are aligned. Chronic illness, burnout, post-infectious syndromes, metabolic dysfunction, frailty, and fatigue states may arise when compensations become locked on: mobilization without resolution, conservation without repair, signaling without decongestion, and survival without restored participation.

Evidence Status and Scientific Guardrails

This paper is an integrative theoretical synthesis, not a clinical guideline and not a claim that all chronic illness is mitochondrial disease. Its central construct - mitochondrial life-capacity - is proposed as a bridge concept linking cellular energy transformation, organismal regulation, lived affordance, and organism-niche conditions.

Several evidence anchors support the synthesis. Intrinsic health research frames health as a quantifiable, field-like biological property emerging from energy, communication, and structure (Cohen et al., 2025). The energetic model of allostatic load argues that chronic stress imposes an additional energetic burden on the organism (Bobba-Alves et al., 2022). The brain-body energy conservation model of aging positions the brain as a broker of organismal energy economy under cellular hypermetabolic stress (Shaulson et al., 2024). Salugenesis research describes healing as an energy- and resource-consuming whole-body process beginning with mitochondria and the cell, with different phases requiring different mitochondrial phenotypes (Naviaux, 2023). The GDF15/mitoception paper provides a candidate body-to-brain signaling pathway by which energy demand exceeding mitochondrial transformation capacity may be communicated to brainstem and interoceptive systems (Liu et al., 2026).

The strongest claims in this paper are conceptual and translational: health requires coherent energy transformation within restorative margins; fatigue can be interpreted as a protective felt signal of constrained energetic affordance; and salutogenic conditions such as sleep, nourishment, movement, safety, dignity, care, belonging, nature, and time can support the biological conditions for repair. The more specific mechanistic claims - especially those involving GDF15, FGF21, reductive stress, post-exertional physiology, and chronic fatigue subtypes - should be treated as testable hypotheses requiring longitudinal, dynamic, and intervention research.

Key guardrails are therefore essential: GDF15 is a candidate mitoceptive pathway, not the sole fatigue molecule; mitochondria are central but not sovereign; fatigue is protective but may become life-narrowing when unresolved; lifestyle advice without affordance redesign risks burden displacement; and measurement must serve life-capacity rather than become metric capture.

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Part I. Why Health Needs a Biophysical Life-Capacity Framework

1. Introduction: From Disease Management to Energy-Enabled Life-Capacity

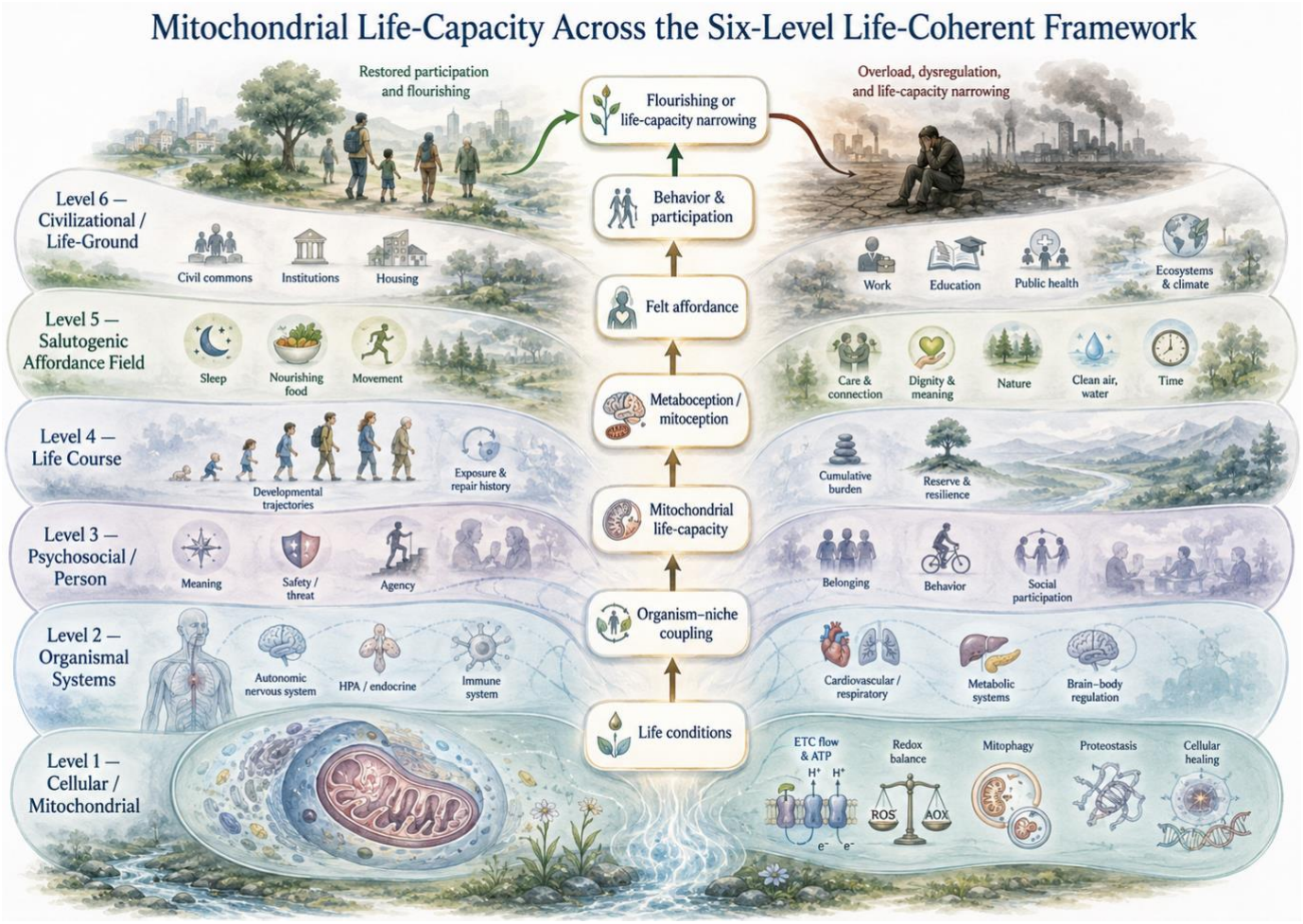

Figure 1. Mitochondrial Life-Capacity Across the Six-Level Life-Coherent Framework.

This figure integrates mitochondrial life-capacity into the six-level life-coherent architecture. At Level 1, mitochondrial flow capacity, redox balance, proteostasis, and mitophagy support cellular healing. At Level 2, autonomic, HPA, immune, metabolic, cardiovascular, respiratory, and neurocognitive systems coordinate organismal energy allocation. At Level 3, psychosocial meaning, threat, agency, belonging, and behavior are transduced into biological demand. At Level 4, life-course exposure and repair histories shape mitochondrial reserve. At Level 5, the salutogenic affordance field provides sleep, food, movement, safety, care, dignity, nature, and meaning. At Level 6, civilizational systems organize the life-ground that either protects or depletes restorative margins.

Modern health systems have achieved extraordinary gains in diagnosis, acute care, pharmacology, surgery, infectious disease control, and the management of many once-fatal conditions. Yet these gains coexist with persistent difficulties in understanding chronic fatigue, burnout, post-infectious syndromes, medically unexplained symptoms, depression-related exhaustion, metabolic dysfunction, frailty, chronic pain, dysautonomia, inflammatory disorders, and the lived experience of reduced capacity.

A life-coherent framework begins from a wider question. Health is not merely the absence of disease. It is life-capacity enabled: the real capacity of persons and communities to live, develop, repair, relate, learn, participate, belong, and flourish within the web of life. Healing is life-capacity restored after injury, threat, overload, or

disruption. Flourishing is life-capacity expressed in dignity, meaning, relation, participation, and ecological belonging.

The present paper asks what makes life-capacity biologically possible. Its answer begins with energy transformation. Every human doing and thinking requires cells to transform resources into organized biological work. The body is not merely a structure that uses energy. It is a living energy-transforming ecology whose capacities depend on the coherent movement of electrons, protons, oxygen, substrates, ions, fluids, proteins, signals, and meanings across scales.

2. The Core Claim: Health as Coherent Energy Transformation

Coherent energy transformation is the capacity of a living system to convert available resources into biological and behavioral work while preserving the conditions for future repair. It includes ATP production but is not limited to ATP. It includes redox balance, mitochondrial signaling, heat generation, metabolite production, membrane potential, ion gradients, protein synthesis, autophagy, mitophagy, immune coordination, endocrine rhythms, fluid exchange, and neural regulation.

The body must continuously allocate energy among competing needs: movement, digestion, immune activation, tissue repair, thermoregulation, cognition, reproduction, vigilance, growth, detoxification, and sleep. These are not only biochemical choices. They become lived realities. A body that allocates energy toward immune defense may produce fatigue and social withdrawal. A body that allocates energy toward threat vigilance may produce anxiety, insomnia, muscle tension, and glucose mobilization.

Health, in this view, is the capacity to transform energy with sufficient coherence that life can proceed without chronic alarm. Disease and fatigue emerge when this coherence fails and the organism must compensate through metabolic shifts, stress signaling, autonomic mobilization, or behavioral conservation.

3. Organism-Niche Coupling and the Body's Energy Economy

A life-coherent framework does not locate health solely inside the body. It also does not dissolve the body into social context. It holds organism and niche together. The organism-niche relation is the recurrent coupling between living beings and the conditions through which their life is sustained, stressed, injured, repaired, or transformed.

Mitochondria are among the deepest cellular mediators of this coupling. Nutrition influences substrate flow, micronutrient availability, insulin signaling, lipid handling, and redox balance. Oxygen availability depends on air quality, lung function, hemoglobin, circulation, microvascular integrity, and tissue diffusion. Sleep and circadian rhythm influence autophagy, mitophagy, melatonin signaling, endocrine timing, immune regulation, and protein homeostasis. Social safety lowers defensive cost; psychosocial threat raises it.

The niche therefore becomes mitochondrial in its biological consequences. What is commonly called lifestyle is often better understood as affordance. The body receives life conditions as energetic instructions.

4. Mitochondrial Life-Capacity Defined

Mitochondrial life-capacity is the cellular and organismal capacity to transform available resources into coherent biological and behavioral work without excessive redox stress, danger signaling, proteostatic burden, or depletion of repair margins. It is about transformation, not simply supply. The body may have glucose, fatty acids, amino acids, and oxygen, yet still struggle to transform them into usable, sustainable work if electron transport is impaired, redox balance is disturbed, mitochondrial networks are fragmented, cristae are disorganized, or tissue exchange is poor.

Mitochondrial life-capacity includes both quantity and quality. Quantity refers to mitochondrial mass, respiratory enzyme abundance, mitochondrial DNA copy number, and tissue oxidative capacity. Quality refers to electron

transport efficiency, redox flexibility, membrane integrity, cristae structure, fission-fusion dynamics, mitophagy, biogenesis, proteostasis, and signaling accuracy.

This definition allows health to be understood neither as pure molecular function nor as pure social condition. It is the living bridge between them.

5. Fatigue as the Felt Narrowing of Energy Affordance

Fatigue changes what the world affords. The same world remains present, but its invitations change. The stairs no longer invite climbing. The book no longer invites reading. The social gathering no longer invites participation. The body interprets action as costly, unsafe, or unavailable.

Fatigue is therefore not simply a sensation. It is a regulatory command wrapped in a feeling. It says: reduce demand, conserve energy, prioritize repair, avoid further overload. It is protective in acute contexts, but when unresolved it can become life-narrowing.

The therapeutic task is not to override fatigue by force, nor to accept permanent contraction. It is to understand what fatigue is protecting against, reduce unnecessary demand, restore transformation capacity, expand repair margins, and gradually reopen the field of safe action.

6. Wu-Wei Physiology: Minimal Forcing as Biological Coherence

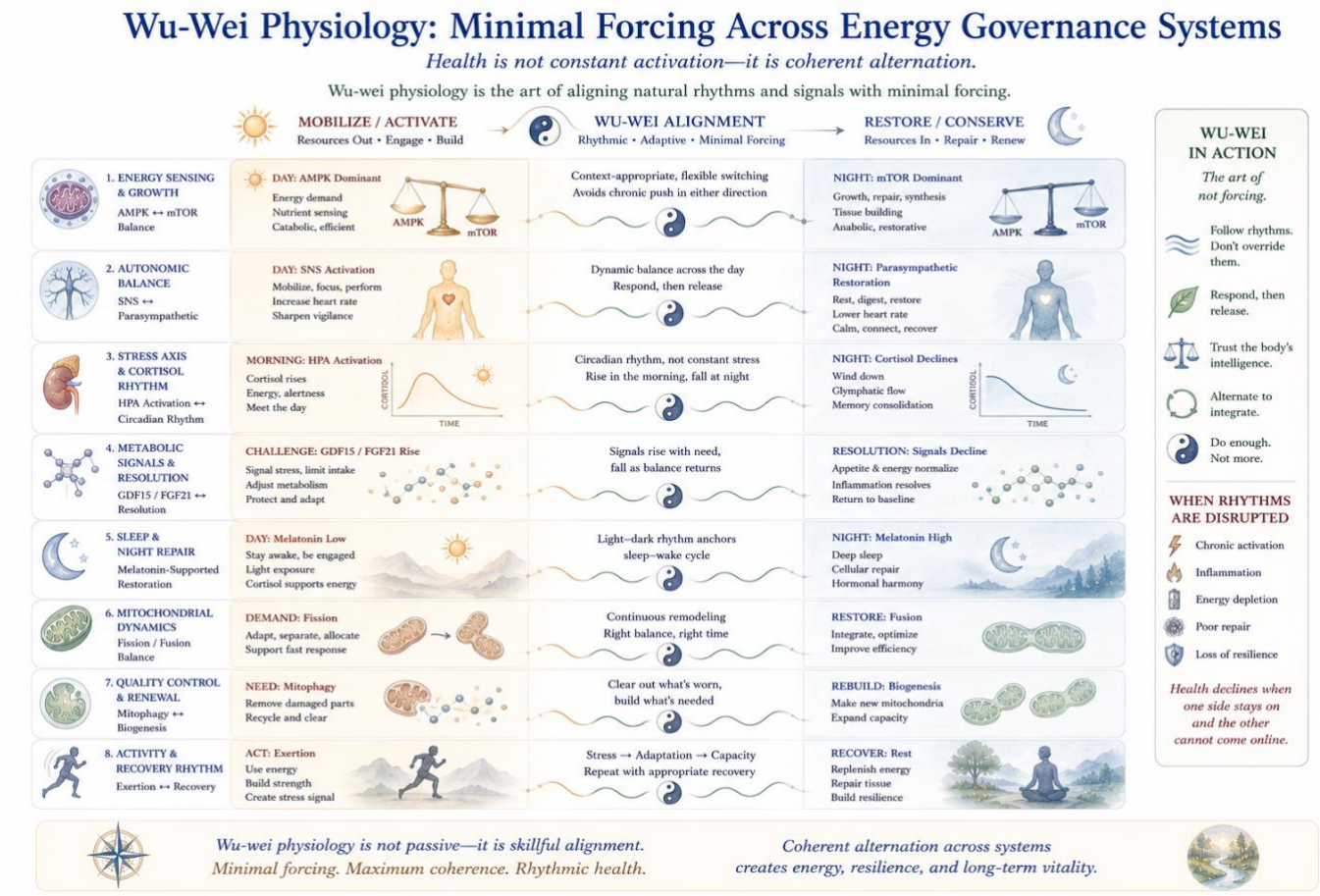

Figure 2. Wu-Wei Physiology: Minimal Forcing Across Energy Governance Systems.

Wu-wei physiology is depicted as the rhythmic alignment of AMPK and mTOR, SNS and parasympathetic restoration, HPA activation and circadian cortisol rhythm, GDF15/FGF21 signaling and resolution, melatonin-supported night repair, fission/fusion, mitophagy/biogenesis, and activity/recovery. Health is shown as coherent alternation rather than permanent activation. Note: the diagram should be interpreted as rhythmic governance, not a rigid day/night AMPK-mTOR binary.

Wu-wei can be understood physiologically as the condition in which biological work arises with minimal unnecessary resistance because demand, capacity, timing, repair, and meaning are aligned. A body in wu-wei physiology is not inactive. It may run, think, work, love, heal, digest, fight infection, create, and serve. But it does so without chronic contradiction.

Pathology arises when rhythms lock: mTOR without cleanup, AMPK without restoration, sympathetic activation without resolution, fatigue without renewed participation, fission without renewal, or inflammation without repair. Forcing is not only personal overexertion. It can be built into the niche through overwork, sleep disruption, food-system burden, digital capture, poverty, humiliation, and ecological degradation.

Wu-wei physiology names the biological expression of life-coherence: energy transformation that serves life without exhausting the capacity to repair, relate, and continue.

Part II. Mitochondria as Life-Enabling Flow Systems

7. The Electron Transport Chain as Flow Architecture

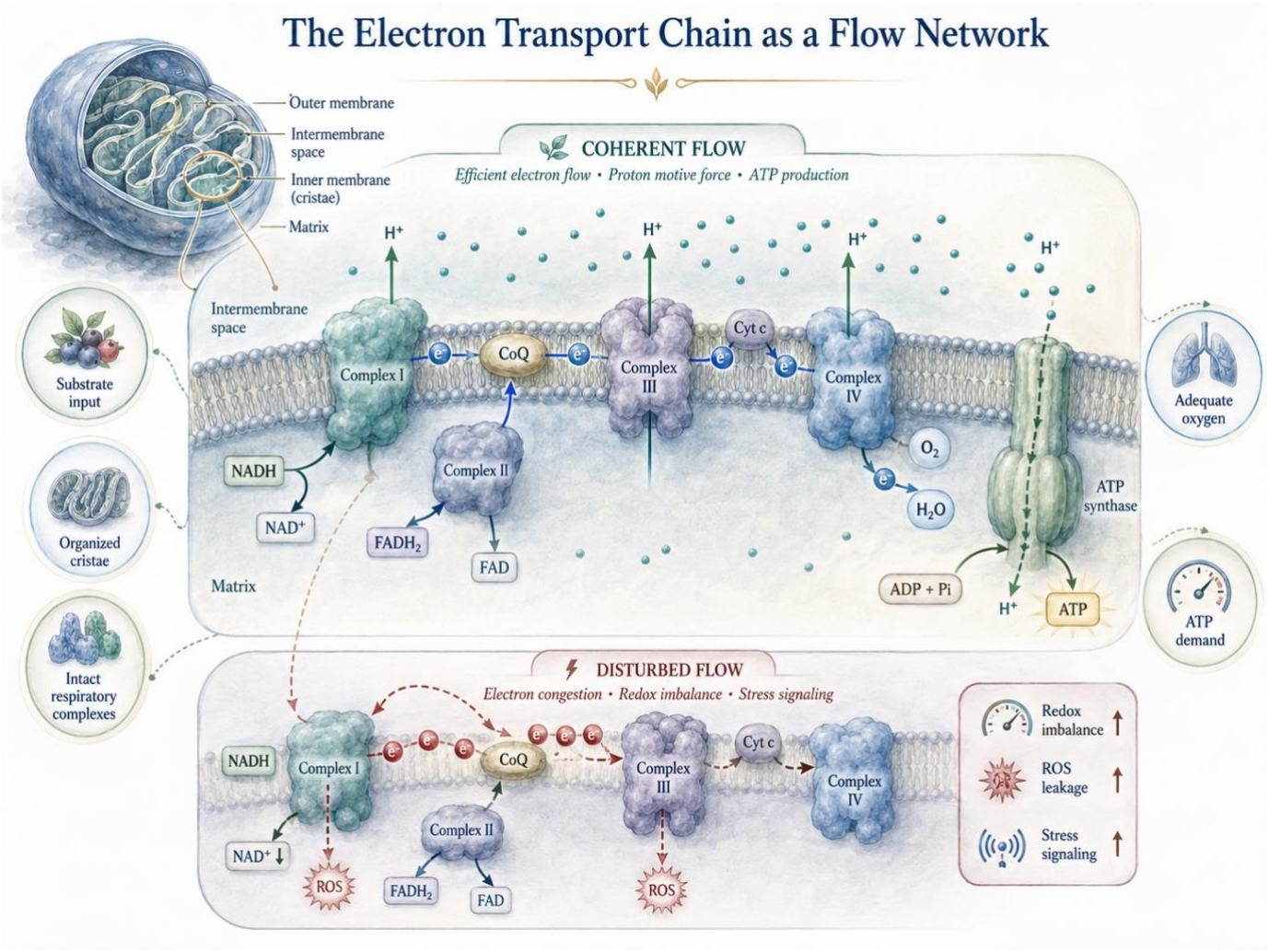

Figure 3. The Electron Transport Chain as a Flow Network.

The electron transport chain is shown as a pressure-sensitive flow network. Nutrient-derived electrons enter through NADH and FADH2, move through respiratory complexes, generate a proton gradient, and support ATP synthesis. Coherent flow requires adequate oxygen, intact complexes, organized cristae, balanced substrate input, and appropriate ATP demand. Flow disturbance produces electron congestion, redox imbalance, ROS leakage, and stress signaling.

The electron transport chain is the central architecture of mitochondrial energy flow. Nutrient-derived electrons enter mitochondrial metabolism through reducing equivalents such as NADH and FADH2. These electrons pass through respiratory complexes embedded in the inner mitochondrial membrane. As electrons move through complexes I, III, and IV, protons are pumped across the inner membrane, creating an electrochemical gradient. ATP synthase then uses this gradient to generate ATP.

For a life-capacity framework, the deeper point is flow. The ETC must maintain a living match among electron input, oxygen availability, membrane potential, proton pumping, ATP demand, redox balance, and structural organization. The body may possess abundant fuel and still experience energetic constraint if mitochondrial flow is congested.

The question is not simply, how much energy is produced? The more life-coherent question is: can this cell, tissue, and organism transform available resources into needed work while preserving repair, coherence, and future capacity?

8. Reductive and Oxidative Stress as Disturbed Flow

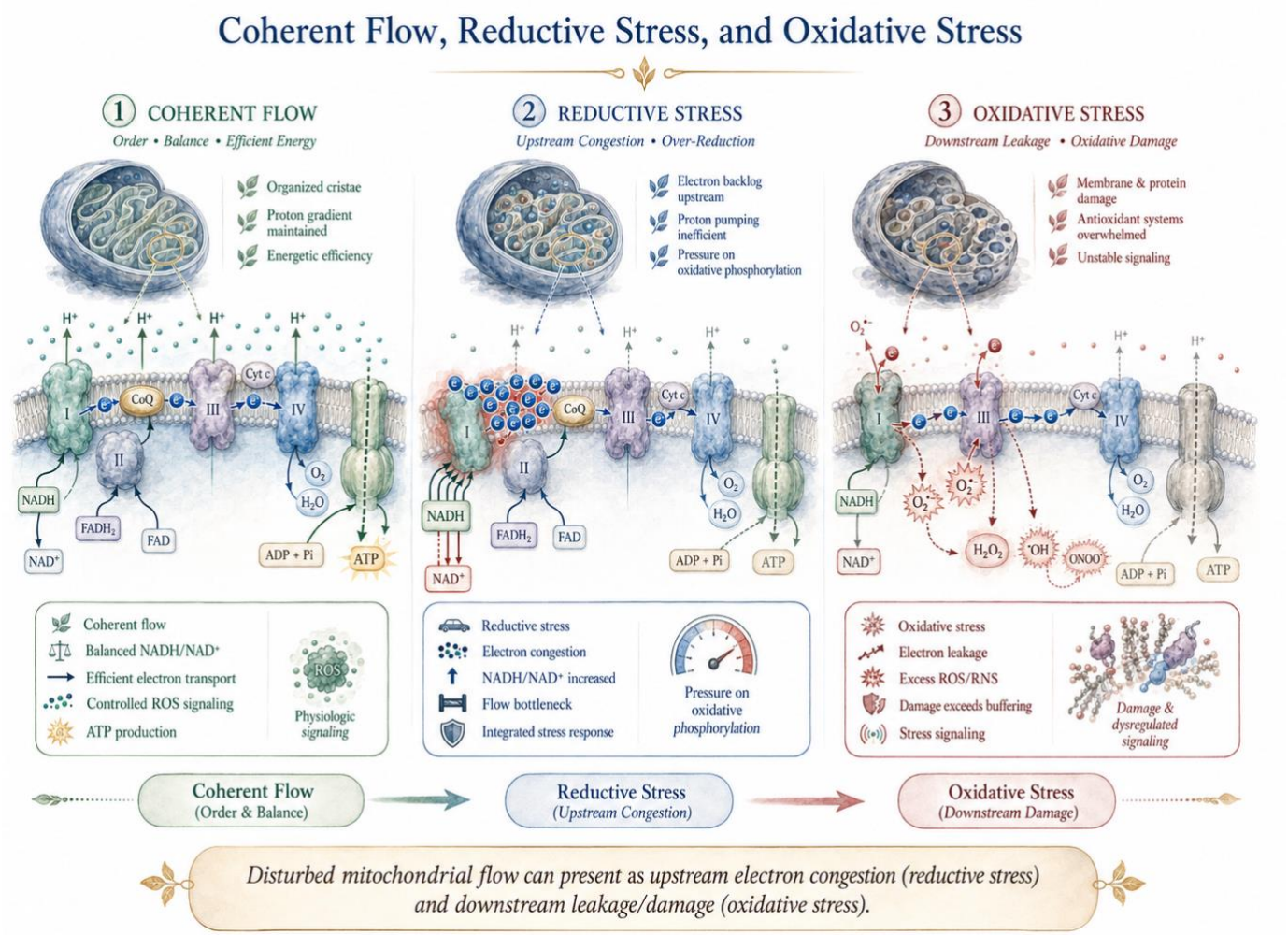

Figure 4. Coherent Flow, Reductive Stress, and Oxidative Stress.

This figure distinguishes coherent redox flow from reductive and oxidative stress. Reductive stress is represented as upstream electron congestion, marked by increased NADH:NAD+. Oxidative stress is represented as electron leakage and reactive species exceeding buffering and repair capacity. The central insight is that reductive and oxidative stress are related expressions of disturbed mitochondrial flow, not isolated opposites.

Reductive stress and oxidative stress are often treated as opposite problems. In this framework, both are understood as expressions of disturbed electron flow. Reductive stress occurs when electrons accumulate upstream, often reflected by an increased NADH:NAD+ ratio. Oxidative stress occurs when electron leakage and reactive species exceed the cell's buffering, signaling, and repair capacity.

These states can coexist. Electron congestion can increase leakage, while oxidative damage can worsen electron flow. The deeper pathology is not simply too much oxidation or too much reduction. It is loss of coherent redox flow.

This distinction changes the therapeutic imagination. The goal is not merely to suppress oxidants, but to restore oxygen delivery, substrate handling, mitochondrial quality control, sleep, circadian rhythm, tissue exchange, and repair opportunity.

9. Cristae Structure and the Architecture of Energetic Possibility

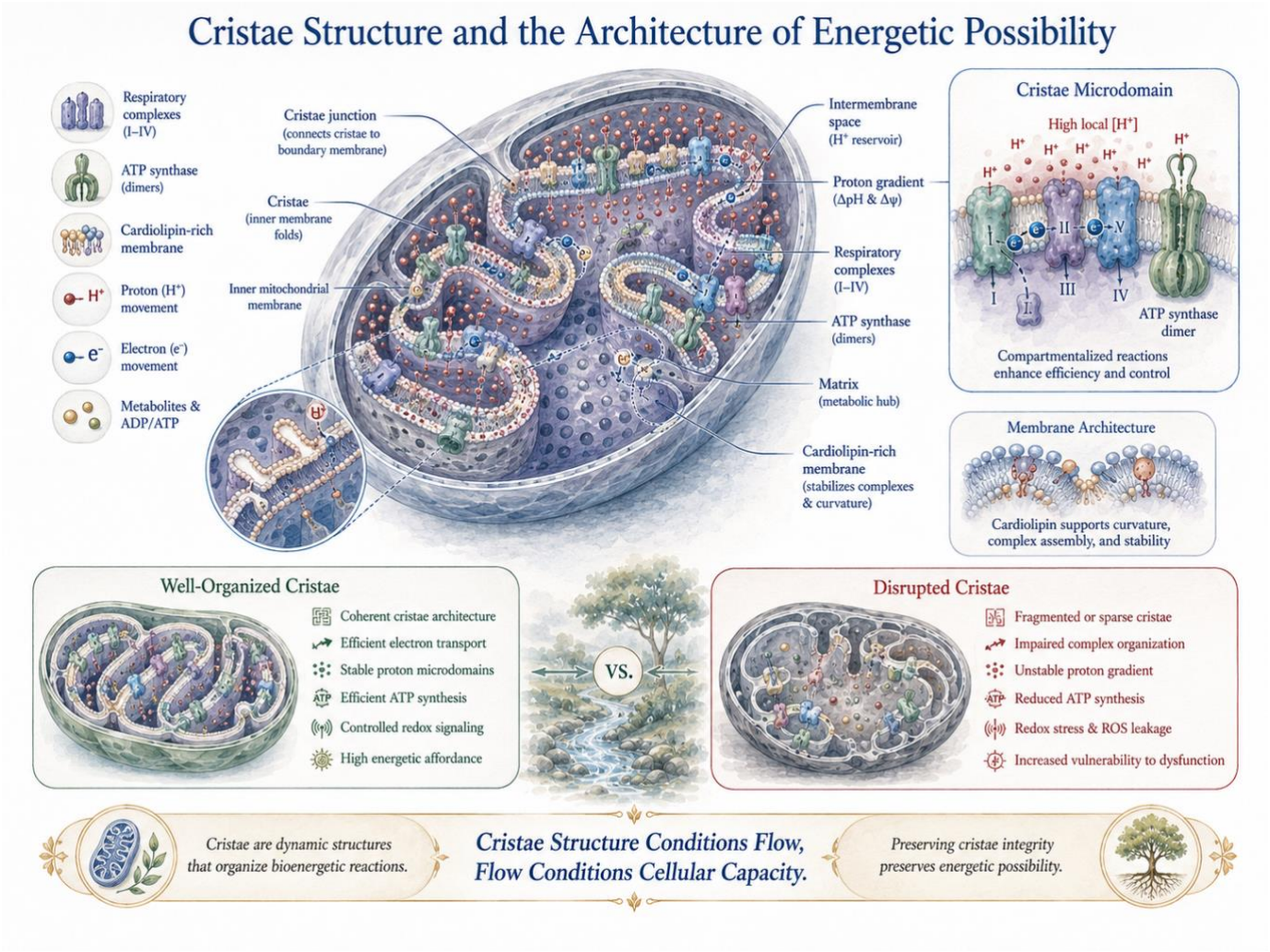

Figure 5. Cristae Structure and the Architecture of Energetic Possibility.

Cristae are depicted as dynamic inner mitochondrial membrane structures that organize respiratory complexes, proton gradients, ATP synthase, cardiolipin-rich membranes, and compartmentalized bioenergetic reactions. The figure shows how cristae structure determines cellular energetic affordance: well-organized cristae support efficient transformation, while disrupted cristae increase redox stress, signaling instability, and vulnerability to dysfunction.

Cristae are dynamic structures of the inner mitochondrial membrane that organize the spatial environment for oxidative phosphorylation. They increase membrane surface area, shape proton microdomains, help organize respiratory complexes and ATP synthase, and influence respiratory efficiency. Their structure is therefore not decorative. It is part of the architecture of energy transformation.

When cristae architecture is disrupted, ETC organization may become less efficient, ROS signaling may shift, membrane potential may become unstable, and the mitochondrion may become more likely to signal danger or require removal through mitophagy.

Structure conditions flow, and flow conditions capacity. The person does not feel cristae, but the person may feel the reduced affordance that emerges when countless cellular architectures cannot support coherent energy transformation under demand.

10. Mitochondrial Dynamics: Fusion, Fission, Mitophagy, and Network Coherence

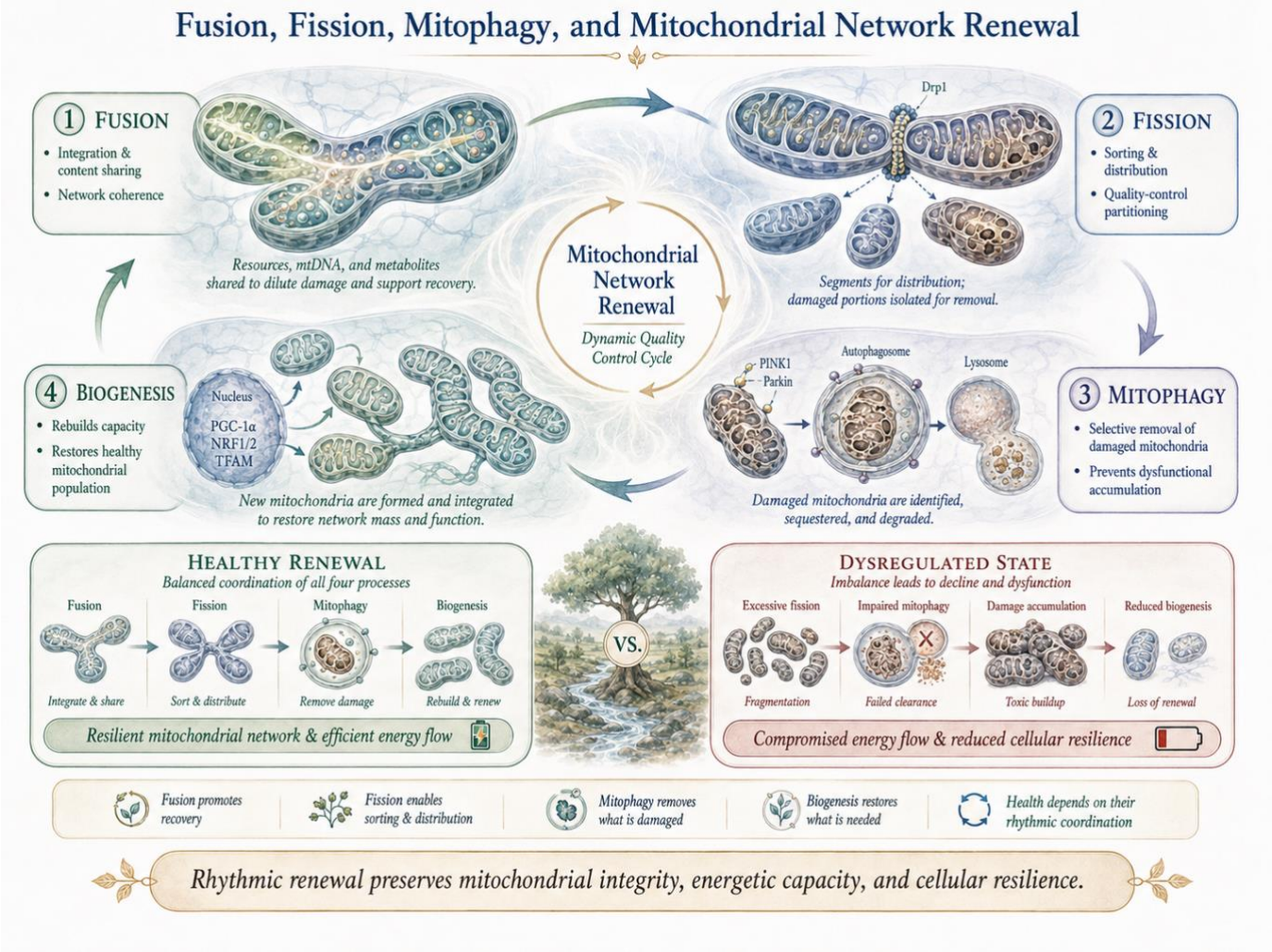

Figure 6. Fusion, Fission, Mitophagy, and Mitochondrial Network Renewal.

This figure shows mitochondrial quality control as a dynamic cycle. Fusion integrates and shares resources across the network. Fission separates mitochondria for distribution or quality control. Mitophagy removes damaged mitochondria. Biogenesis rebuilds capacity. Health requires rhythmic coordination of all four processes; disease emerges when fragmentation, damage accumulation, or failed renewal dominates.

Mitochondria are dynamic. They fuse, divide, move, anchor, communicate, depolarize, recover, signal, and undergo selective removal. Fusion allows mitochondria to share contents and support network coherence. Fission allows distribution and quality-control sorting. Mitophagy removes damaged mitochondria. Biogenesis rebuilds capacity.

This is mitochondrial wu-wei at the organelle level. The mitochondrion does not maintain health by forcing damaged machinery to work harder. It remodels, removes, and renews.

Movement without recovery becomes forcing. Rest without flow can become stagnation. Health requires rhythmic alternation.

11. Autophagy, Proteostasis, and the Cost of Maintenance

Every living cell must maintain itself. Proteins must be synthesized, folded, repaired, trafficked, and degraded. Damaged organelles must be removed. Membranes must be renewed. DNA must be repaired. Immune signals must be produced and resolved. This maintenance is not free.

Proteostasis, autophagy, mitophagy, and the mitochondrial unfolded protein response reveal that repair is itself a form of work. Fatigue may arise not only because external action is costly, but because internal maintenance is already consuming the available budget.

A fatigued body may be engaged in immune regulation, protein repair, mitochondrial quality control, redox stabilization, matrix remodeling, autonomic recalibration, and neural recovery. Rest is not nothing; it may be hidden healing labor.

12. Mitochondrial Quality Control and Restorative Margins

Mitochondrial quality control includes mitochondrial dynamics, mitophagy, biogenesis, protease systems, mitochondrial unfolded protein responses, antioxidant defenses, DNA repair, lipid remodeling, cristae maintenance, and coordination with cellular metabolism. Quality control is the difference between temporary stress and cumulative damage.

Hormesis depends on margins. If stress is too intense, too frequent, too prolonged, or unsupported by recovery, the same pathways become harmful. The difference between adaptation and injury is not the presence of stress alone, but the relationship between stress and restorative capacity.

This is the mitochondrial translation of the life-coherent exposure-repair-margin model.

Part III. From Cellular Stress to Felt Experience

13. The Energy Gap: When Demand Exceeds Transformation Capacity

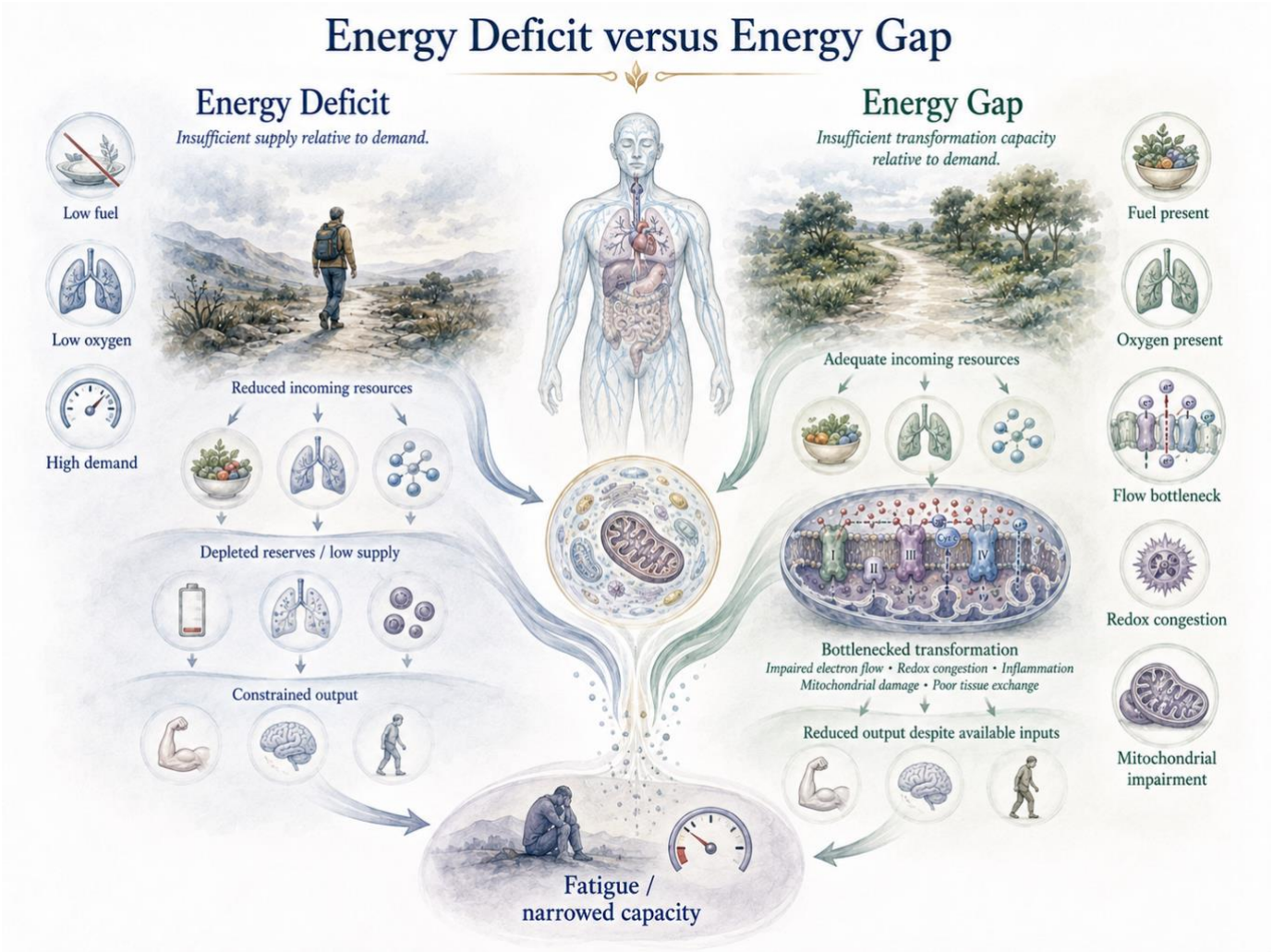

Figure 7. Energy Deficit versus Energy Gap.

This figure distinguishes energy deficit from energy gap. Energy deficit reflects insufficient supply relative to demand. Energy gap reflects insufficient transformation capacity relative to demand. The body may have fuel but be unable to transform it coherently because of hypoxia, ETC inhibition, inflammation, redox congestion, mitochondrial damage, poor tissue exchange, or excessive demand.

An energy gap is not identical with an energy deficit. An energy deficit occurs when fuel supply is inadequate relative to demand. An energy gap occurs when energetic demand exceeds the cell's or organism's capacity to transform available resources into usable work at a sustainable rate.

This concept connects biological, psychological, social, and ecological burdens without collapsing them into one another. Infection, toxin exposure, trauma, grief, sleep deprivation, chronic work overload, social isolation, metabolic disease, inflammatory disease, and aging do not have the same cause. But they can converge on a shared energetic pattern: demand rises, transformation capacity falls, repair margins narrow, and the organism begins to signal that action has become unsafe.

Fatigue does not identify one disease. It reports a problem in the relationship between demand and capacity.

14. Local Compensation: Warburg-Like Metabolism and Redox Workarounds

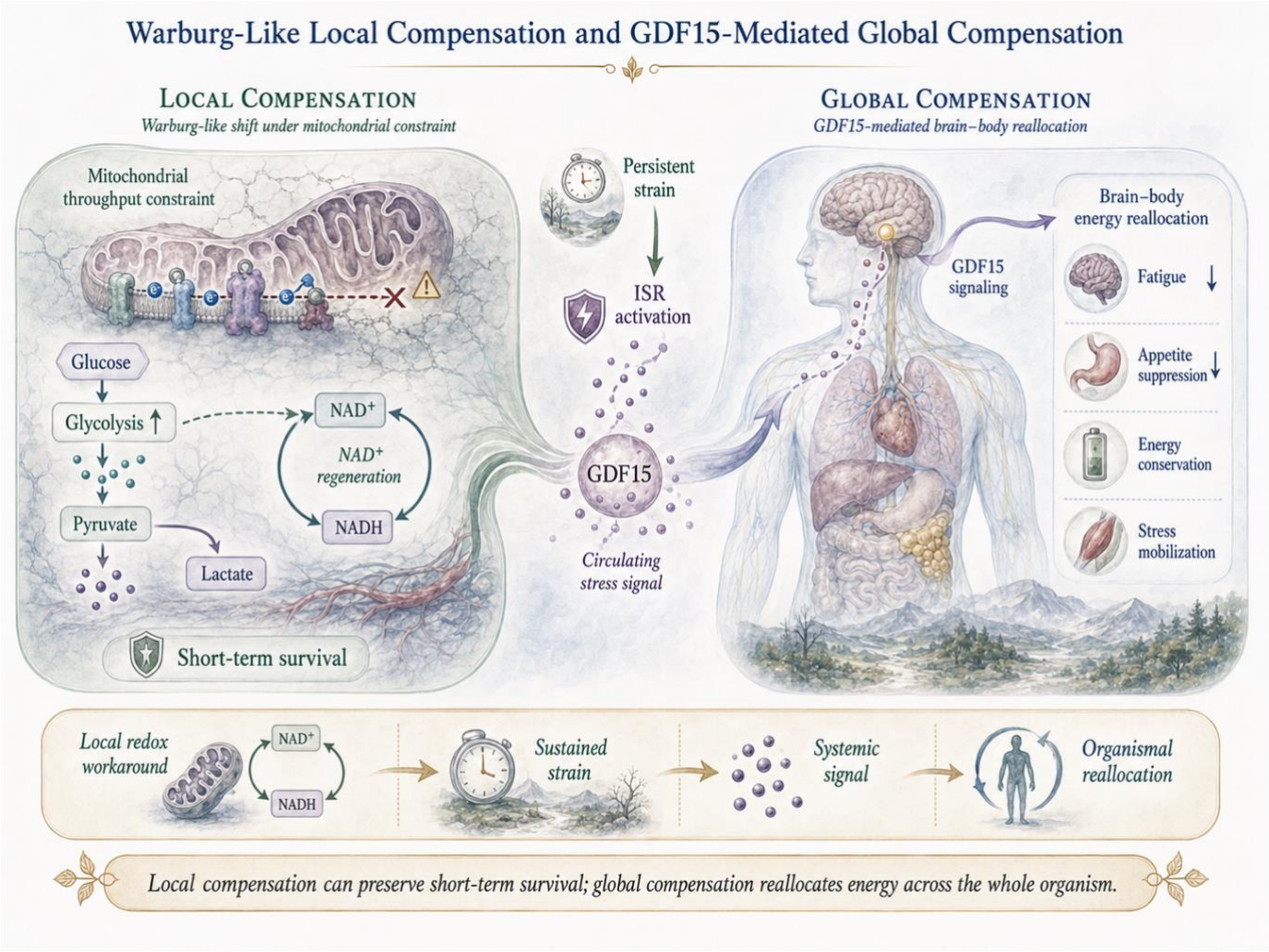

Figure 8. Warburg-Like Local Compensation and GDF15-Mediated Global Compensation.

Local energy stress can lead to Warburg-like glycolysis and lactate production, regenerating NAD+ and supporting short-term survival under mitochondrial throughput constraints. If local compensation is insufficient or sustained, ISR activation may induce systemic signaling through GDF15 and related factors. The figure distinguishes local cellular compensation from global organismal compensation.

When cells face energetic or redox constraint, they do not immediately fail. They compensate. One major local compensation is a shift toward glycolysis and lactate production. Warburg-like metabolism can serve as a local workaround for redox and throughput constraints by supporting rapid ATP production and regenerating NAD+ from NADH.

This is not simply bad metabolism. It can be adaptive. A cell under local stress may need rapid ATP, biosynthetic intermediates, redox relief, or temporary independence from full oxidative throughput.

But local compensation has limits. If the underlying bottleneck persists, local compensation may become chronic and part of a life-narrowing loop.

15. Global Compensation: GDF15, FGF21, and Mitoceptive Escalation

When cellular energetic strain becomes significant, prolonged, systemic, or organismally relevant, the signal may be escalated. GDF15 is strongly induced by mitochondrial stress, metabolic stress, disease states, aging, pregnancy, cancer cachexia, strenuous exercise, and psychosocial stress. In the mitoception model, GDF15 is released when cells face energy demand in excess of mitochondrial transformation capacity and signals to brainstem circuits involved in systemic energy reallocation.

The response is dual. The organism conserves energy through fatigue, appetite suppression, nausea, rest-seeking, reduced movement, and decreased motivation for nonessential expenditure. It also mobilizes energy through sympathetic activation, HPA-axis activation, glucose release, lipid mobilization, vigilance, and anxiety-like arousal.

FGF21 occupies a related but partially distinct position as a metabolic adaptation hormone involved in fasting-like signaling and fuel reorganization. Both should be interpreted contextually, not as isolated explanations.

16. Metaboception: The Brain's Model of the Body's Energy Budget

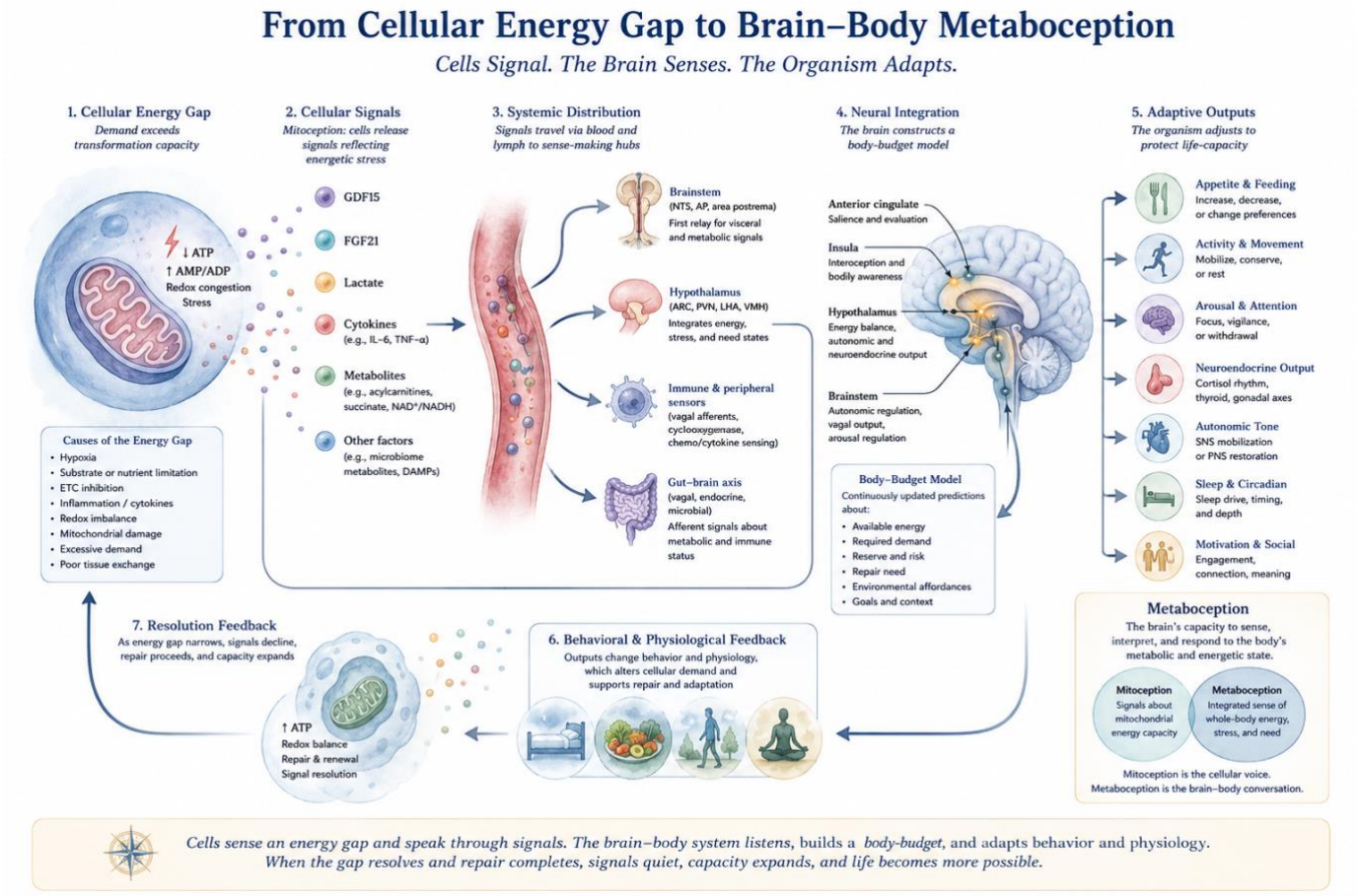

Figure 9. From Cellular Energy Gap to Brain-Body Metaboception.

This figure depicts mitoception as a subset of metaboception. Cells experiencing an energy gap release signals such as GDF15, FGF21, lactate, cytokines, and metabolites. These signals reach brainstem, hypothalamic, autonomic, and interoceptive circuits. The brain constructs a body-budget model and adjusts behavior, appetite, arousal, fatigue, and neuroendocrine output.

Metaboception refers to the brain's monitoring and regulation of energy supply, demand, and transformation capacity. It is not a single pathway. It is a distributed body-brain process involving brainstem, hypothalamus,

insula, anterior cingulate, autonomic circuits, endocrine signals, immune mediators, vagal afferents, metabolites, and behavioral predictions.

The brain does not passively receive body signals. It predicts needs, allocates resources, modulates appetite, adjusts autonomic tone, changes behavior, alters attention, and shapes emotion according to its model of what the body can afford.

Metaboception connects mitochondria to phenomenology without reducing experience to molecules. The task is to understand the body-brain model producing a felt state and alter the conditions that make safe action possible again.

17. Fatigue as Energetic Affordance Perception

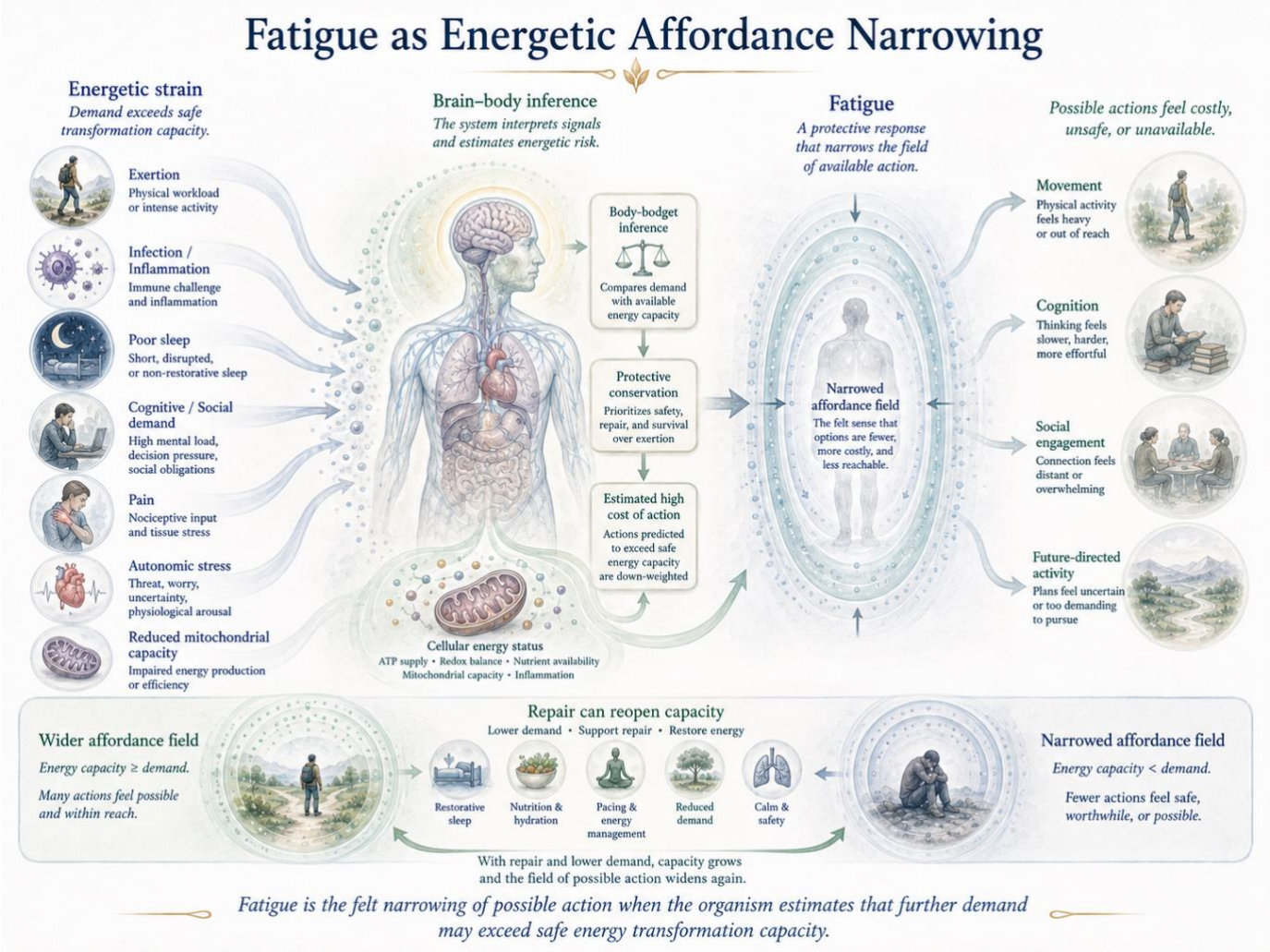

Figure 10. Fatigue as Energetic Affordance Narrowing.

Fatigue is represented as the felt narrowing of possible action. When the brain-body system infers that demand may exceed safe energy transformation capacity, movement, cognition, social engagement, and future-directed activity become less available. Fatigue protects survival by reducing optional demand, but when unresolved it can narrow life-capacity.

Fatigue is the felt narrowing of possible action. It changes the relationship between body and world. A task that once invited completion now appears too costly. A walk that once felt easy now appears risky. A conversation that once felt nourishing now appears draining.

This interpretation explains why fatigue often precedes action, why it can seem disproportionate to observable effort, why it can coexist with arousal, why it can be delayed after exertion, and why it can become self-reinforcing.

The life-coherent middle path is non-forcing expansion: listen to fatigue as a meaningful signal, identify the energy gap it may report, reduce unnecessary exposures, restore repair conditions, and cautiously expand activity only within margins.

18. Anxiety, Valence, Arousal, and the Energetic Body Budget

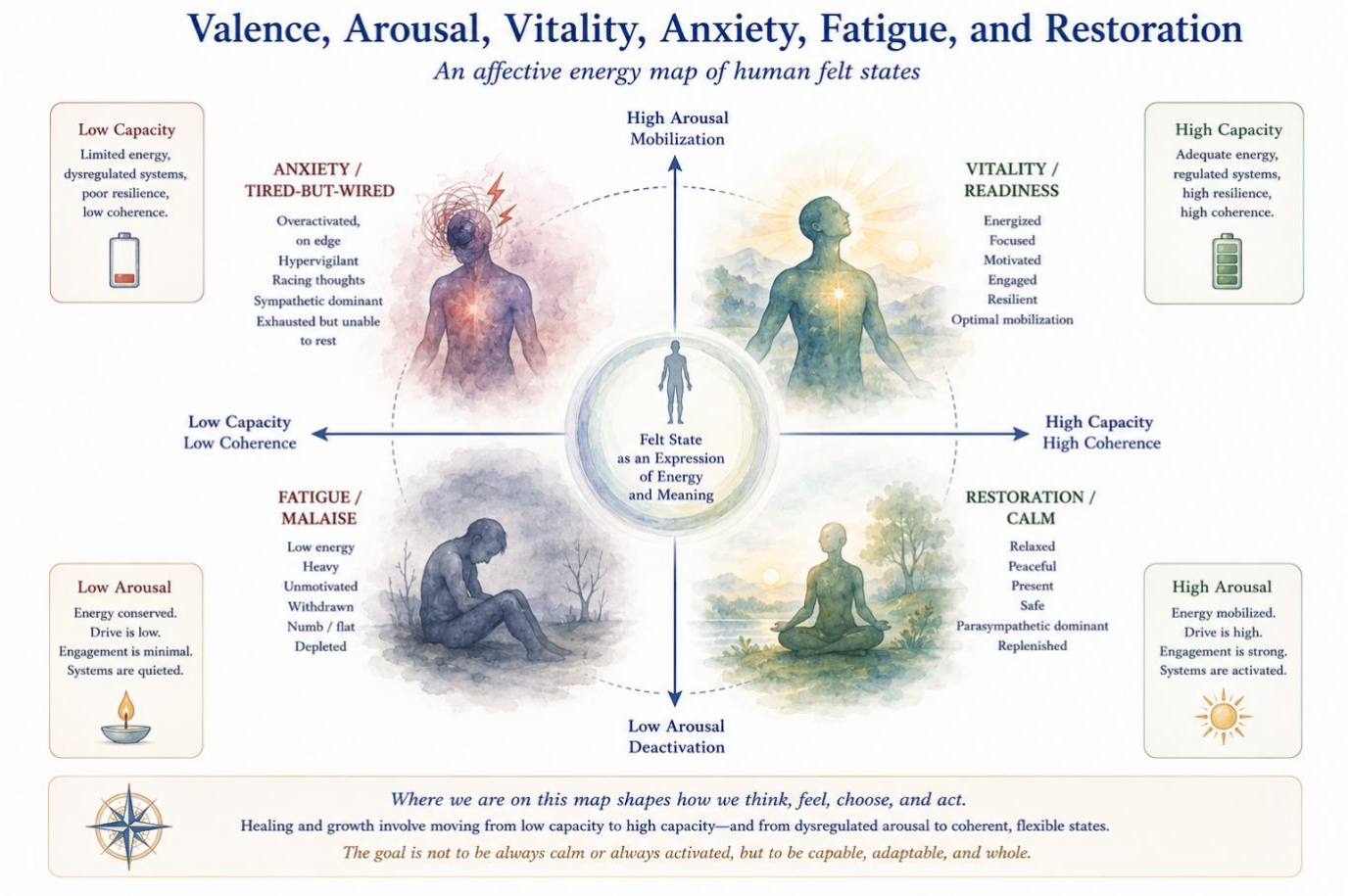

Figure 11. Valence, Arousal, Vitality, Anxiety, Fatigue, and Restoration.

This affective energy map places human felt states along two axes: capacity/coherence and arousal/mobilization. High capacity with high arousal produces vitality and readiness. Low capacity with high arousal produces anxiety and tired-but-wired states. High capacity with low arousal produces calm restoration. Low capacity with low arousal produces fatigue, malaise, and withdrawal.

Valence and arousal provide a bridge between mitochondrial states and lived affect. Positive valence emerges more readily when the body estimates that action is safe and capacity is sufficient. Negative valence emerges when the body estimates that action is unsafe, costly, threatening, or unaffordable. Arousal reflects mobilization.

High capacity with high arousal may feel like vitality and readiness. Low capacity with high arousal may feel like anxiety or tired-but-wired activation. High capacity with low arousal may feel like calm restoration. Low capacity with low arousal may feel like fatigue, malaise, and withdrawal.

The emotional field is shaped by the relationship between demand, capacity, prediction, history, and meaning.

19. Tired but Wired: Mobilization Without Resolution

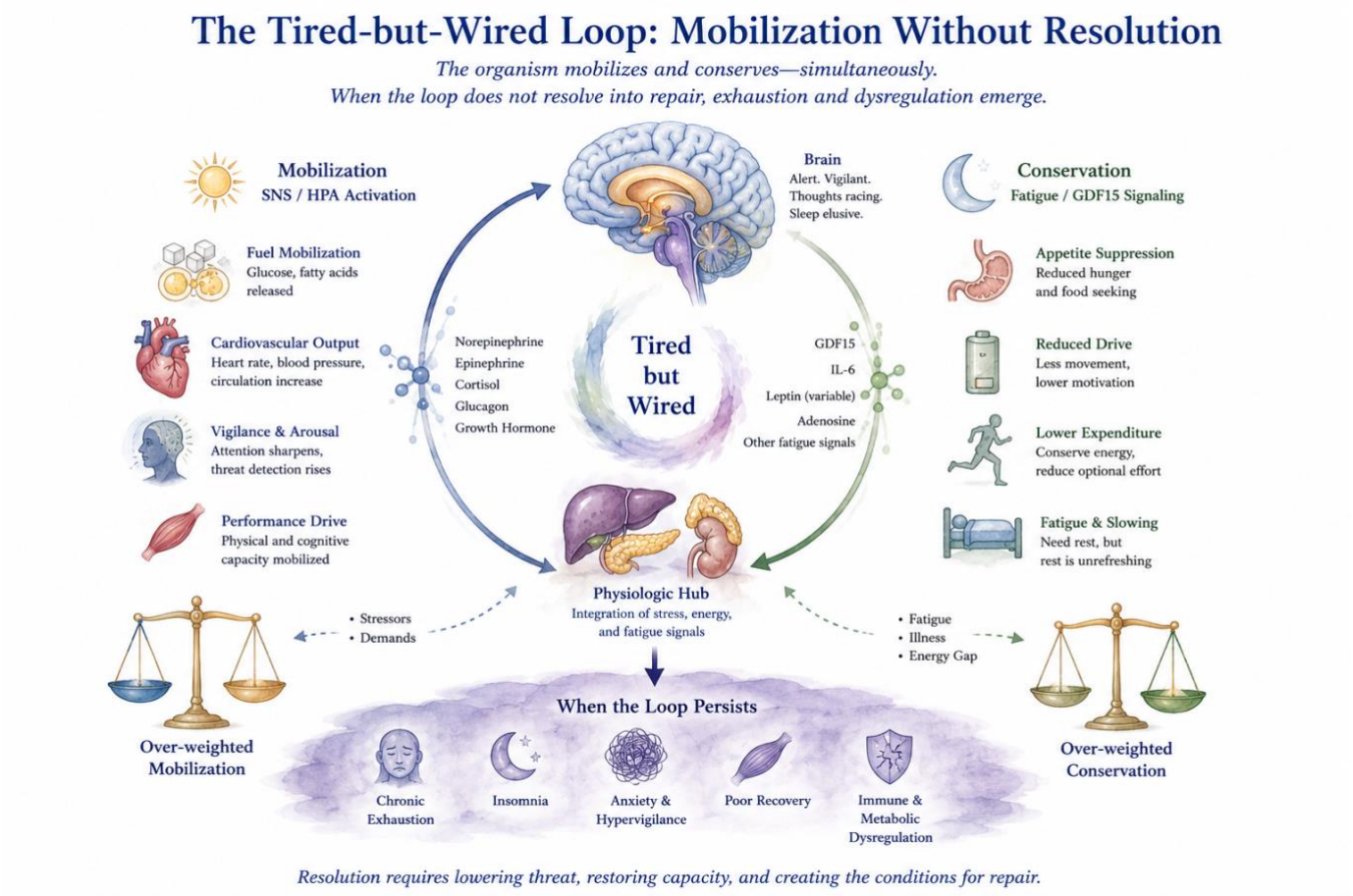

Figure 12. The Tired-but-Wired Loop: Mobilization Without Resolution.

The tired-but-wired state arises when the organism simultaneously mobilizes and conserves. SNS/HPA activation mobilizes glucose, fatty acids, vigilance, and cardiovascular output, while fatigue and GDF15-related signaling reduce appetite, movement, and optional expenditure. When this loop does not resolve into repair, chronic exhaustion, insomnia, anxiety, and poor recovery may emerge.

The tired-but-wired state is exhaustion with activation. The person may be unable to perform ordinary tasks yet unable to rest deeply. Sleep may be non-restorative. Heart rate may be elevated. Muscles may feel tense. Thinking may race but clarity may be poor.

This state is not paradoxical when viewed through energy-gap biology. If the brain-body system detects energetic threat, it may activate sympathetic and HPA pathways to mobilize fuel and vigilance while simultaneously generating fatigue to reduce optional expenditure.

In chronic states, the organism continues to mobilize without completing repair. The question becomes: what would allow mobilization to resolve into repair?

20. From Felt Capacity to Behavior: How the Body Conditions Human Doing

The body does not merely respond to behavior. It conditions behavior. If the brain-body system predicts that action is affordable, the person is more likely to move, explore, relate, learn, create, and participate. If it predicts that action is unsafe, the person is more likely to rest, withdraw, avoid, delay, conserve, or become anxious.

This does not eliminate agency. It situates agency. A person can choose within the affordance field available to them, but the field itself is shaped by sleep, inflammation, mitochondrial capacity, autonomic tone, pain, nutrition, social threat, learned history, trauma, culture, and institutional burden.

Life-coherent care asks what behavior is doing for the organism before trying to change it.

21. Vitality as Expanded Affordance

If fatigue is the felt narrowing of possible action, vitality is the felt expansion of possible action. Vitality is not mere stimulation. It is the felt availability of coherent action. The body feels able. The mind feels clear. The world feels approachable. Movement feels possible. Social engagement feels nourishing.

Vitality emerges when the organism estimates that it has sufficient capacity to meet demand without sacrificing repair. It sits at the intersection of salugenesis and salutogenesis: inner repair completion and outer affordance support.

A life-coherent framework insists that the purpose of health is not simply to reduce pathology, but to expand the real capacity to live.

Part IV. Salugenesis, Salutogenesis, and Mitochondrial Repair

22. Salugenesis as Mitochondrial Healing Completion

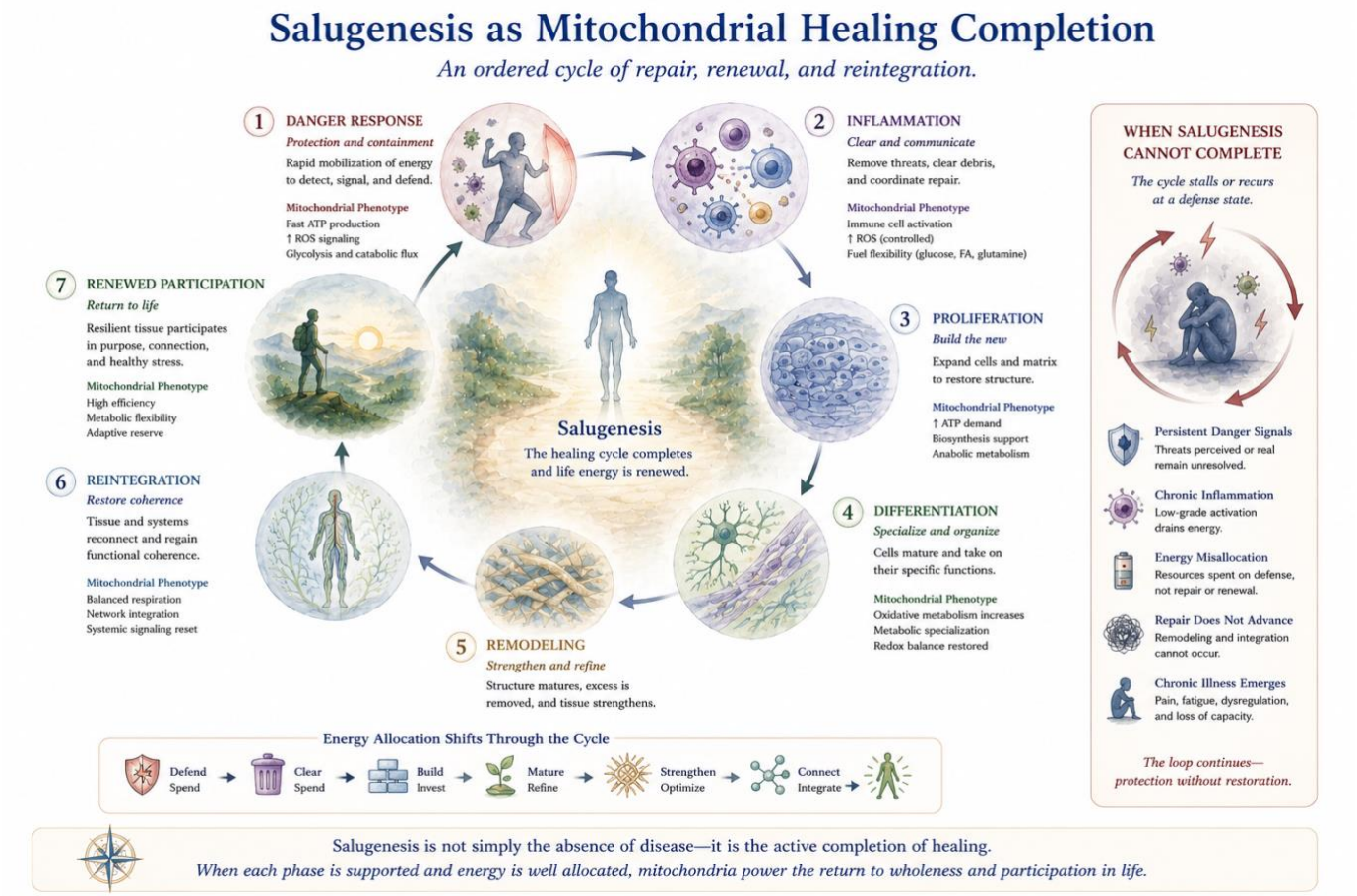

Figure 13. Salugenesis as Mitochondrial Healing Completion.

Salugenesis is shown as an ordered healing cycle: danger response, inflammation, proliferation, differentiation, remodeling, reintegration, and renewed participation. Each phase requires different mitochondrial phenotypes and energy allocation patterns. Chronic illness is represented as stalled or recurrent defense when salugenesis cannot complete.

Healing is not merely the removal of disease. A pathogen may be cleared, an injury closed, a toxin removed, or a symptom suppressed, yet the organism may remain in defensive organization. Salugenesis names the inner biology of healing completion: the movement from danger response toward inflammation resolution, rebuilding, differentiation, reintegration, remodeling, and restored functional coherence.

Mitochondria are central because every phase of healing requires energy transformation. Defense requires energy. Inflammation requires energy. Protein synthesis, extracellular matrix remodeling, immune resolution, and return to quiet require energy.

Chronic illness can be understood as incomplete salugenesis: the body has not failed because it is irrational; it has failed to complete a transition.

23. The Cell Danger Response and the Logic of Incomplete Healing

The cell danger response is protective. When cells detect threats that exceed homeostatic capacity, they shift metabolism and signaling toward defense. Without this response, organisms could not survive infection, injury, toxins, trauma, hypoxia, or acute stress.

The problem begins when the cell danger response does not resolve. The original threat may persist, resources for repair may be insufficient, restorative margins may be absent, regulatory systems may remain conditioned by threat, or the mitochondrial network itself may be damaged or poorly renewed.

A life-coherent approach seeks not to attack the body's protective intelligence, but to make defense unnecessary.

24. Autophagy, Mitophagy, and Proteostasis as Hidden Healing Labor

Repair requires cleanup. Damaged proteins must be refolded or degraded. Dysfunctional mitochondria must be removed. Oxidized lipids must be repaired or replaced. Cellular debris must be processed. Immune activation must be resolved.

Autophagy, mitophagy, and proteostasis are central to salugenesis. A body that cannot clean cannot fully heal. Fatigue during recovery may mean the organism is redirecting energy toward hidden biological labor.

Healing requires alternation: feeding and fasting, activity and recovery, mTOR-supported building and AMPK-supported cleanup, sympathetic mobilization and parasympathetic restoration, inflammation and resolution, fission and fusion, wake and sleep.

25. Sleep, Melatonin, and Circadian Repair

Sleep is a repair condition, not simply a behavior. It supports immune regulation, memory consolidation, glymphatic clearance, hormonal rhythm, autonomic downshifting, metabolic recalibration, protein repair, redox regulation, and mitochondrial quality control.

Melatonin participates in this repair ecology as a darkness-linked signal of circadian timing, antioxidant defense, mitochondrial regulation, and cellular protection. Circadian rhythm coordinates mitochondrial life-capacity because oxidative phosphorylation, mitochondrial morphology, antioxidant systems, immune timing, glucose handling, cortisol rhythm, temperature, and sleep pressure are all time-structured.

A society that disrupts sleep disrupts mitochondrial repair.

26. Movement, Pacing, and the Restoration of Flow

Movement supports mitochondrial biogenesis, glucose handling, vascular function, lymphatic flow, muscle quality, autonomic flexibility, mood regulation, and tissue exchange. Regular movement teaches mitochondria to expand capacity.

But movement can also become forcing. When activity exceeds transformation capacity, the organism may experience redox stress, inflammatory signaling, autonomic destabilization, pain, and post-exertional worsening. The life-coherent alternative is pacing and non-forcing expansion.

The guiding question is: what form of movement increases life-capacity without exceeding transformation capacity?

27. Nutrition, Substrate Quality, and Redox Burden

Nutrition is not simply fuel. It is information, structure, substrate, cofactor supply, microbial ecology, redox influence, immune input, and social meaning. Mitochondria require substrates, but also the capacity to process substrates cleanly.

Adequate nutrition supports life-capacity. Substrate excess can create redox burden. Poor-quality nutrition can provide calories without repair intelligence. Fatigue can occur in both scarcity and excess.

A life-coherent nutritional approach asks whether food can be transformed into life-supporting work and whether the food system itself supports repair, dignity, affordability, culture, and ecological integrity.

28. Belonging, Dignity, Meaning, and the Energetic Cost of Threat

Psychosocial life is not separate from mitochondrial life. The body metabolizes relation. Threat is energetically expensive. Social isolation, humiliation, discrimination, uncertainty, violence, coercion, poverty, and abandonment increase vigilance and defensive cost.

Safety is energy-saving. Belonging lowers defensive cost. Dignity reduces humiliation physiology. Trust permits downshifting. Meaning organizes effort. Agency changes the felt cost of demand.

Belonging, dignity, and meaning can function as mitochondrial conditions because they influence how much energy the organism must spend defending itself from its world.

29. The Salutogenic Affordance Field as Mitochondrial Infrastructure

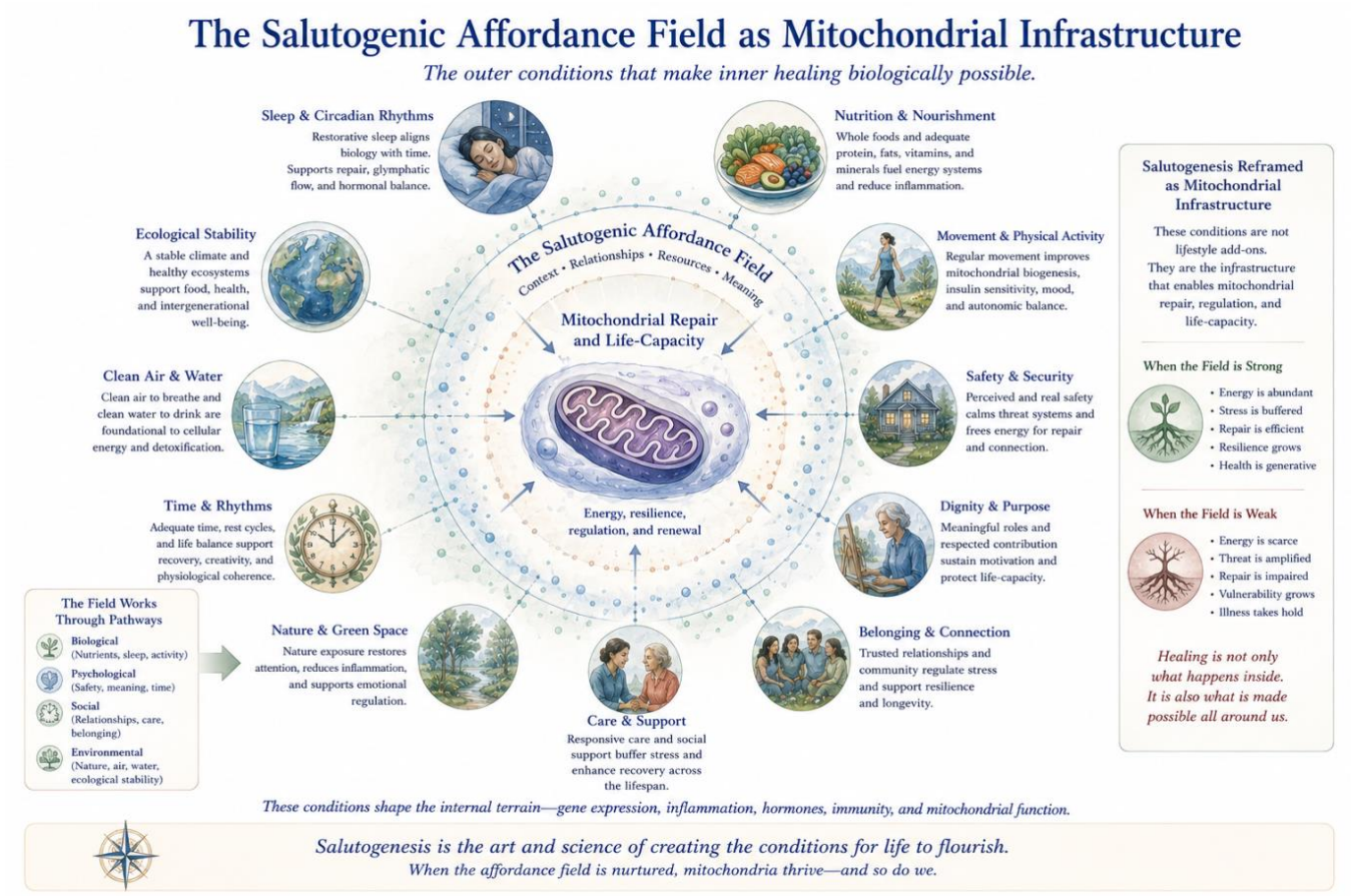

Figure 14. The Salutogenic Affordance Field as Mitochondrial Infrastructure.

Sleep, nutrition, movement, safety, dignity, belonging, care, nature, time, clean air, water, and ecological stability are shown as outer conditions that support mitochondrial repair and life-capacity. The figure reframes salutogenesis as mitochondrial infrastructure: the surrounding field that makes internal healing biologically possible.

Salutogenesis names the outer field that creates and sustains health. In the mitochondrial life-capacity framework, the salutogenic field becomes mitochondrial infrastructure. Sleep, food, air, water, housing, work rhythms, care, movement, nature, social safety, ecological stability, and civil commons make internal healing biologically possible.

When the niche blocks repair, individual advice becomes burden displacement. The life-coherent approach asks how to redesign affordances so that health-supporting action becomes possible, safe, meaningful, affordable, and repeatable.

Salutogenesis makes agency real by widening the field of possible life.

30. Restorative Margins: The Space in Which Healing Becomes Possible

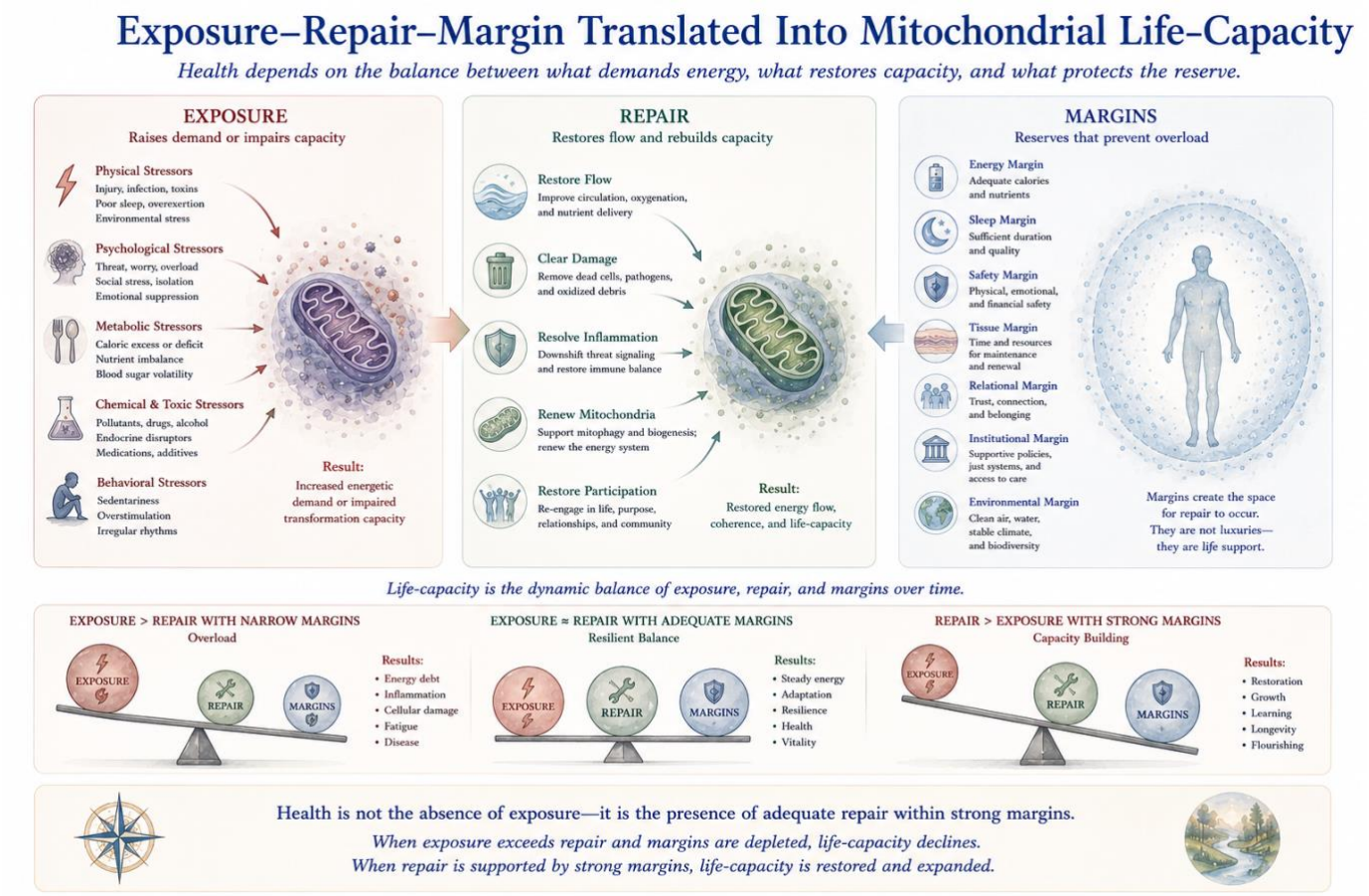

Figure 15. Exposure-Repair-Margin Translated Into Mitochondrial Life-Capacity.

Exposure raises energetic demand or impairs transformation capacity. Repair restores flow, clears damage, resolves inflammation, renews mitochondria, and restores participation. Margins are the reserves of energy, sleep, safety, tissue exchange, trust, and institutional support that prevent overload. Disease and fatigue emerge when exposure exceeds repair within narrow margins.

Margins are the reserves that allow living systems to absorb disturbance without collapse. In mitochondrial terms, margins include reserve respiratory capacity, redox flexibility, sleep depth, autonomic flexibility, repair time, nutrient sufficiency, tissue exchange, mitophagy capacity, proteostatic capacity, and social safety.

A system without margin may appear functional until perturbed. Then a small demand produces disproportionate breakdown. Fatigue often appears when margins are narrow: the body senses that further demand may cross a threshold.

Healing requires margin restoration. This may mean reducing exposure, increasing repair resources, pacing activity, protecting sleep, improving nutrition, lowering inflammatory burden, restoring relationships, reducing financial stress, or redesigning work and care arrangements.

31. From Repair to Participation: Healing Must Reopen Life

Healing is incomplete until life can be re-entered. A wound that closes but leaves the person unable to move freely is not fully healed. A marker that normalizes while the person remains exhausted, ashamed, isolated, or unable to participate is only partial success.

Life-coherent healing aims at restored participation. This does not mean perfect function. It means that capacities for movement, rest, relation, understanding, agency, dignity, meaning, and contribution can expand.

Salugenesis completes the inner transition from danger to repair. Salutogenesis provides the outer field in which the repaired organism can live. Flourishing emerges when both are present.

Part V. Clinical, Public Health, and Civilizational Applications

32. From Mechanism to Practice: A Life-Coherent Clinical Method

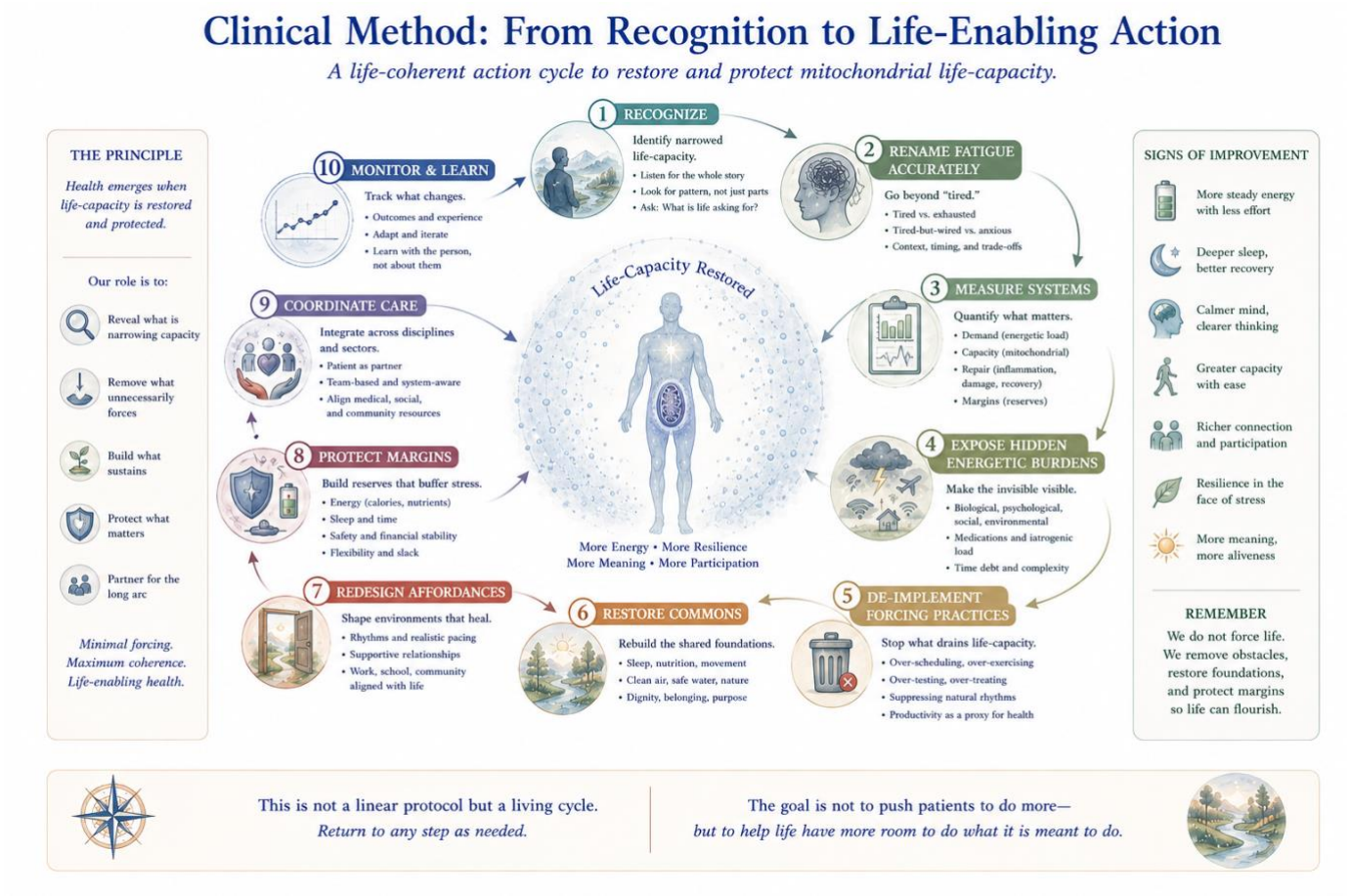

Figure 16. Clinical Method: From Recognition to Life-Enabling Action.

This figure adapts the life-coherent action cycle to mitochondrial life-capacity: recognize narrowed capacity; rename fatigue accurately; measure demand, capacity, repair, and margins; expose hidden energetic burdens; de-implement forcing practices; restore commons; redesign affordances; protect margins; coordinate care; monitor and learn.

A mitochondrial life-capacity framework deepens clinical reasoning by asking: what is overloading this person's capacity to transform energy into life-enabling work, repair, relation, cognition, and participation? The method begins with recognition, followed by renaming, measurement, exposure mapping, de-implementation, commons restoration, affordance redesign, margin protection, coordination, and learning.

Recognition asks what capacities have narrowed. Renaming resists moralizing fatigue. Measurement tracks demand, transformation capacity, repair, margins, and participation. Exposure mapping identifies what raises demand or lowers capacity. De-implementation removes practices that worsen the energy gap. Affordance redesign makes life-supporting action easier. Monitoring learns from the patient's body over time.

This method is not a protocol imposed on all patients. It is a disciplined way of listening to life.

33. Chronic Fatigue, ME/CFS, Long COVID, and Post-Infectious Syndromes

Chronic fatigue syndromes, ME/CFS, long COVID, and post-infectious syndromes often involve profound fatigue, post-exertional worsening, cognitive dysfunction, orthostatic intolerance, sleep disturbance, pain, sensory sensitivity, immune symptoms, and reduced participation. In life-coherent terms, they can be understood as disorders of failed restoration after threat.

The energy-gap model helps explain post-exertional malaise. A person may complete an activity in the moment, especially if sympathetic mobilization temporarily supports output, but if the activity exceeds transformation capacity or repair margin, delayed worsening may follow.

Life-coherent care combines biological humility, pacing, careful investigation, rehabilitation within margins, social support, and protection from forced adaptation.

34. Dysautonomia, Chronic Pain, and Neuroimmune Sensitization

Autonomic regulation, immune signaling, pain processing, vascular tone, tissue exchange, mitochondrial flow, and emotional experience are deeply coupled. The autonomic nervous system is an energy-distribution system; dysautonomia reflects impaired flexibility in coordinating energy delivery and demand.

Chronic pain consumes attention, disrupts sleep, increases muscle guarding, activates stress physiology, and narrows participation. Neuroimmune sensitization emerges when immune signals, glial activation, autonomic tone, pain pathways, endocrine rhythms, and interoceptive predictions reinforce one another.

The life-coherent task is to reduce unnecessary threat while restoring safe variability.

35. Depression, Anxiety, Burnout, and Trauma-Related Fatigue

Depression, anxiety, burnout, and trauma-related fatigue are embodied states involving energy, threat, interoception, autonomic regulation, inflammation, sleep, metabolism, memory, meaning, and social context. Depression may involve low perceived energetic affordance. Anxiety may involve high arousal under perceived threat. Burnout may be understood as chronic forcing.

Trauma-related fatigue may emerge when the body remains organized around threat even after danger has passed. Hypervigilance is metabolically costly. Sleep is lighter, muscles guard, autonomic tone remains defensive, and social trust is harder.

A life-coherent mental health approach integrates biology and meaning: what is the body defending against, what repair has not completed, and what future remains imaginable?

36. Metabolic Disease, Obesity, Diabetes, and Fatty Liver Disease

Metabolic disease is often framed as excess energy storage or individual lifestyle failure. The mitochondrial life-capacity framework reframes it as a disorder of energy flow, substrate handling, redox burden, tissue signaling, and organism-niche mismatch.

Obesity, diabetes, and fatty liver disease can involve abundant caloric supply but impaired energy transformation. Fuel is present but not flowing coherently into work. The person may feel tired, inflamed, foggy, hungry, heavy, or unable to sustain effort.

A life-coherent metabolic strategy aims to reduce substrate congestion, improve mitochondrial capacity, support muscle as a glucose sink, restore circadian rhythm, lower inflammatory burden, and create a food environment that makes health easier.

37. Autoimmune, Autoinflammatory, Mast-Cell, and Inflammatory Illness

Inflammatory illnesses demonstrate the energy cost of defense. Immune activation is necessary for survival, but metabolically expensive. In autoimmune and autoinflammatory disease, defense may be misdirected, excessive, recurrent, or poorly resolved.

The energy-gap model helps explain why fatigue is common in inflammatory illness. The immune system becomes an energy sink. Resources are redirected toward surveillance, activation, repair, and inflammatory signaling. Cytokines alter brain function, sleep, appetite, pain sensitivity, mood, and motivation.

The goal is immune coherence: defense when needed, resolution when threat has passed, tolerance when self is mistaken for danger, and repair when tissue has been injured.

38. Aging, Frailty, Sarcopenia, and Cancer-Related Fatigue

Aging involves changes in repair capacity, mitochondrial function, immune regulation, proteostasis, tissue structure, endocrine rhythm, cellular senescence, and organismal reserve. Frailty emerges when multiple systems lose margin. Sarcopenia reflects loss of muscle mass, strength, mitochondrial capacity, neural drive, and participation.

The mitochondrial life-capacity framework helps unify these phenomena through declining reserve and increasing maintenance cost. A minor stressor can tip a low-margin organism into major decline.

In serious illness and late life, the goal may shift from restoration to stabilization, comfort, meaning, or dignity in decline. Mitochondrial life-capacity asks what form of energy transformation best serves life now.

39. Public Health Applications: Designing for Mitochondrial Life-Capacity

If mitochondria translate life conditions into life-capacity, then public health can be understood, in a translational sense, as mitochondrial work at scale. Public health should protect the conditions under which cellular energy transformation, repair, and participation become possible: sleep, clean air, safe housing, nourishing food systems, movement-supporting environments, social belonging, dignity in care, reduction of toxic exposures, climate stability, digital regulation, work-time reform, early childhood protection, green space, accessible healthcare, and community commons.

This shifts public health from risk-factor messaging to affordance design. It is not enough to tell people to sleep, move, eat well, connect, and reduce stress if the niche makes these difficult. The life-coherent task is to make health-supporting action possible, safe, meaningful, affordable, and repeatable.

40. Civilizational Applications: Energy, Extraction, and the Life-Ground

Modern civilization often organizes human life around extraction, acceleration, attention capture, productivity maximization, and ecological overshoot. These systems may produce economic output while depleting biological, social, and ecological margins.

The body experiences civilizational design as energy demand. Long work hours, insecure housing, debt, processed food systems, polluted air, sleep disruption, digital overactivation, social isolation, ecological anxiety, and care shortages shape autonomic tone, inflammation, sleep, metabolism, movement, stress hormones, and mitochondrial repair.

A life-coherent civilization would be judged by whether it protects the life-ground and allows energy to become life rather than merely institutional or economic output.

41. The Life-Coherent Action Cycle for Mitochondrial Life-Capacity

The life-coherent action cycle can be applied specifically to mitochondrial life-capacity: recognize narrowed capacity; rename misleading categories; measure demand, capacity, repair, margin, and participation; expose hidden energetic burdens; de-implement forcing practices; restore commons; redesign affordances; protect margins; coordinate across sectors; monitor and learn.

This cycle transforms mitochondrial life-capacity from a biological concept into a practical method. The goal is not to make everyone biologically perfect. The goal is to make living systems less overburdened, more repairable, and more capable of participating in life.

42. Clinical Ethics: From Blame to Life-Enabling Responsibility

A mitochondrial life-capacity framework challenges blame. Fatigue, metabolic dysfunction, depression, anxiety, chronic pain, and inflammatory illness are shaped by organism-niche relations and cannot be reduced to personal weakness. It also challenges biological reductionism by refusing to reduce the patient to mitochondria alone.

The ethical orientation is clear: do not blame the exhausted body for signals of overload; do not silence alarms without asking what they protect against; do not demand performance without restoring repair; do not individualize conditions produced by the niche; do not call forced adaptation resilience.

The positive obligation is to protect dignity, restore margins, reduce unnecessary burden, make repair possible, enable participation, and design for life.

Part VI. Measurement, Evaluation, and Research Agenda

43. Why Measurement Must Serve Life-Capacity

A mitochondrial life-capacity framework requires measurement, but it also requires humility about measurement. What is measured becomes visible, fundable, governable, and actionable. Yet measurement can distort by replacing judgment, burdening patients, and rewarding institutional performance over lived healing.

Life-coherent measurement asks whether persons, communities, tissues, institutions, and ecosystems are becoming more capable of living, repairing, participating, and flourishing. It tracks exposure, demand, transformation capacity, repair opportunity, restorative margin, felt capacity, behavior, participation, and flourishing.

The central measurement question is: is life-capacity expanding or narrowing?

44. Measuring Mitochondrial Life-Capacity

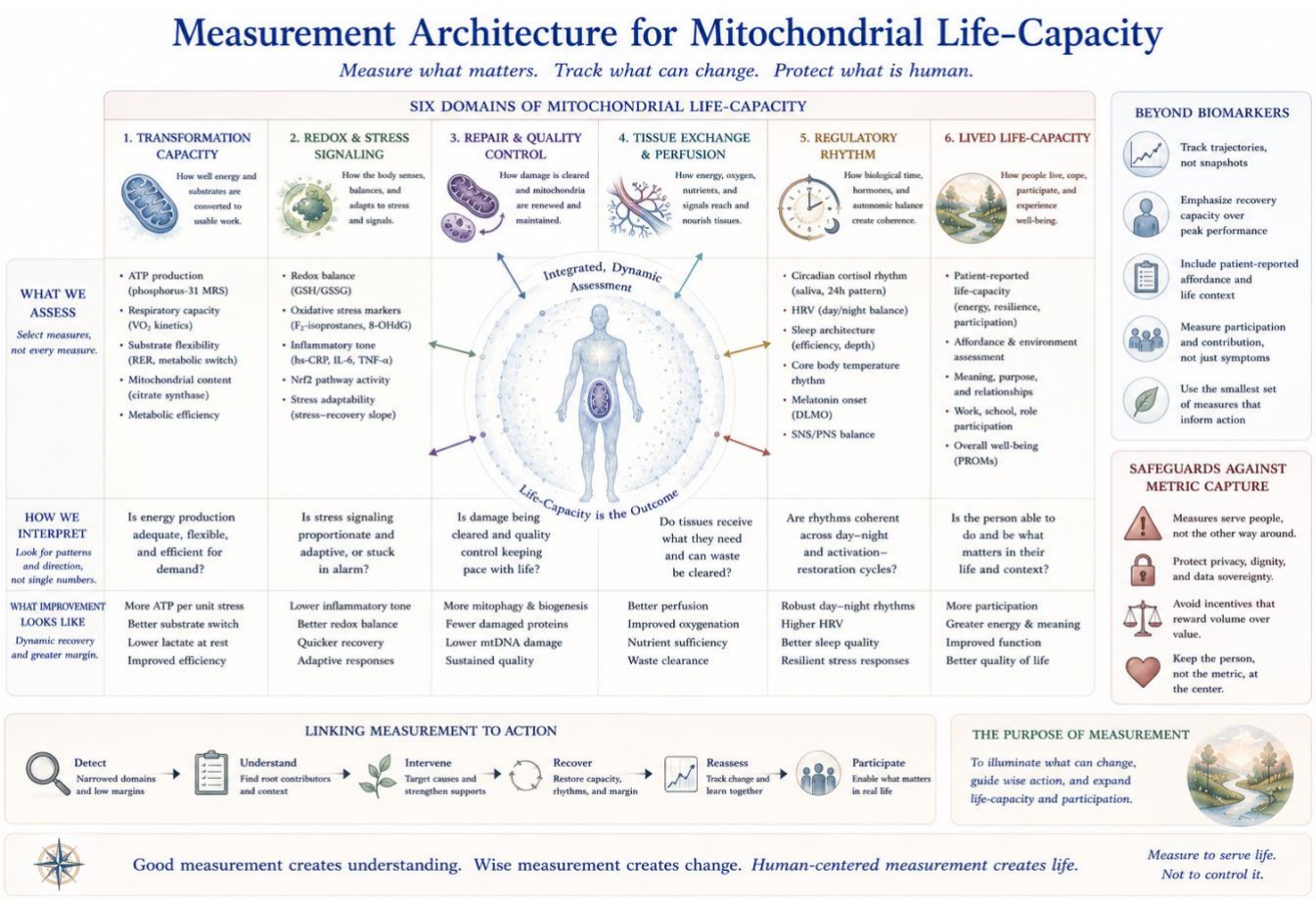

Figure 17. Measurement Architecture for Mitochondrial Life-Capacity.

Measurement is organized across six domains: transformation capacity, redox and stress signaling, repair and quality control, tissue exchange, regulatory rhythm, and lived life-capacity. The figure emphasizes dynamic recovery, patient-reported affordance, participation outcomes, and safeguards against metric capture.

Mitochondrial life-capacity cannot be captured by a single biomarker. It should be measured through a layered profile: energy transformation, redox and stress signaling, mitochondrial quality control and repair, tissue exchange, regulatory rhythm, and lived capacity.

GDF15, FGF21, lactate, inflammatory markers, HRV, sleep metrics, metabolic markers, mitochondrial assays, and patient-reported life-capacity measures should be interpreted together and contextually. The aim is not to create a new diagnostic label, but to provide a lens for seeing how demand, capacity, repair, and participation interact.

45. Dynamic Testing: Measuring Recovery, Not Only Resting State

Many fatigue and energy-gap conditions are dynamic. A person may appear normal at rest but fail after exertion, stress, upright posture, heat, meals, cognitive demand, or sleep disruption. Static measurement can miss the problem.

Dynamic testing asks how the organism responds to demand and how well it recovers afterward. The relevant outcome is not peak performance alone, but recovery curves: heart-rate normalization, delayed fatigue, cognitive decline, sleep disruption, pain flare, orthostatic tolerance, and biomarker shifts after demand.

The measurement unit should be sustainable capacity, not heroic output.

46. Measuring Fatigue as Energetic Affordance

Fatigue measurement should capture not only intensity, but how the world becomes unavailable. A life-coherent instrument should ask about quality, triggers, thresholds, recovery time, delay, variability, domain, meaning, participation, and margin.

The goal is to measure the world as it is available to the person: what can be done once but not recovered from, what requires rest beforehand, what produces delayed worsening, what kind of rest restores, and what would indicate that life-capacity is expanding.

47. Measuring Restorative Margins

Restorative margins are the reserves that allow living systems to absorb disturbance without collapse. They include biological, psychological, social, ecological, and institutional dimensions.

Biological margin indicators may include resting heart rate, HRV, sleep quality, orthostatic tolerance, inflammatory burden, glucose variability, exercise recovery, muscle strength, and oxygenation. Social margins include caregiving support, financial strain, workplace control, food security, housing security, transport, discrimination, and care continuity.

Margin measurement prevents false resilience narratives by seeing depletion before breakdown.

48. Avoiding Metric Capture and Measurement Violence

Metric capture occurs when the indicator replaces the purpose. Measurement violence occurs when measurement systems misrecognize, erase, burden, punish, or distort the lives they claim to serve.

Biomarker capture, wearable capture, performance capture, clinical capture, commercial capture, wellness capture, research capture, and policy capture are all risks. Safeguards include tying measurement to life-capacity outcomes, including lived experience, accounting for burden, protecting equity, including social context, and revising indicators when they fail to serve healing.

The purpose of measurement is not control. It is accountability to life.

49. Research Agenda I: Mechanisms of Energy-Gap Signaling

Mechanistic research should ask how cells detect energy gaps and communicate these signals across the organism. Key questions include what conditions induce GDF15 in vivo, how reductive stress, oxidative stress, ER stress, mitochondrial unfolded protein responses, and integrated stress response pathways interact, and how different tissues contribute to circulating signals.

GDF15 is a promising pathway, but fatigue is likely multi-signal, tissue-specific, context-dependent, and dynamically regulated. The goal is not a single fatigue biomarker, but a signaling ecology.

50. Research Agenda II: Fatigue, Vitality, and Felt Capacity

A second agenda concerns how body signals become fatigue, vitality, anxiety, malaise, motivation, and effort. Research should link GDF15, FGF21, lactate, inflammatory markers, HRV, sleep, and activity with fatigue qualities, perceived affordance, social participation, meaning, and vitality.

This requires combining physiology with phenomenology: ecological momentary assessment, qualitative interviews, activity-recovery diaries, cognitive effort tasks, social participation measures, and patient-defined recovery outcomes.

51. Research Agenda III: Dynamic Recovery and Post-Exertional Physiology

Recovery after demand is especially important for ME/CFS, long COVID, post-infectious syndromes, dysautonomia, inflammatory disease, overtraining, burnout, and frailty. Studies should examine physiological patterns that distinguish normal recovery from delayed post-exertional worsening.

Research should prioritize safety and patient partnership, especially for people with post-exertional malaise. The goal is to understand recovery failure, not to prove capacity through forced exertion.

52. Research Agenda IV: Salugenesis, Repair, and Intervention

Intervention research should ask what helps the organism move from defense to repair. Which interventions lower demand, increase transformation capacity, improve repair opportunity, widen margins, or restore participation?

Timing may matter. Sleep restoration may need to precede exercise expansion. Inflammation control may need to precede rehabilitation. Pacing may need to precede strengthening. Social safety may need to precede trauma processing. Nutritional stabilization may need to precede fasting.

53. Research Agenda V: Salutogenic Affordances and Civilizational Burden

If mitochondria translate life conditions into life-capacity, research must examine how social, ecological, institutional, and technological conditions shape mitochondrial outcomes. Sleep opportunity, shift work, housing quality, air pollution, green space, food environments, loneliness, discrimination, workplace control, digital exposure, and care burden all deserve study.

The research unit becomes the organism-niche relation.

54. Research Agenda VI: Equity, Margins, and Burden Distribution

Energy gaps are not distributed randomly. Some populations are chronically exposed to higher demand, lower resources, greater toxic burden, less sleep, more stress, less care, and fewer margins.

Equity research should compare exposure, repair, and margins. A health disparity is not only a difference in disease rates; it is a difference in life-capacity conditions and in the energetic cost of living.

55. Toward a Mitochondrial Life-Capacity Index

A composite mitochondrial life-capacity index could eventually include transformation capacity, stress signaling and redox burden, repair and quality control, regulatory flexibility, and lived life-capacity. Such an index must be developed carefully to avoid reductionism and metric capture.

The index should help identify bottlenecks, track change, and guide repair. It should include patient weighting because life-capacity is personal and relational.

56. Methodological Principles for the Field

A science of mitochondrial life-capacity should use multi-level, longitudinal, dynamic, mixed-method, participatory designs; include severely affected populations; stratify by phenotype; measure burden; protect against overinterpretation; and remain ethically life-coherent.

The field should expand dignity, repair, and participation, not create new forms of surveillance, blame, or commercial capture.

57. Evaluation Questions for Clinical Programs and Policies

Clinical programs and policies can be evaluated through mitochondrial life-capacity questions. Does a fatigue program validate fatigue as a meaningful signal, assess post-exertional worsening, measure recovery, support pacing, reduce appointment burden, improve sleep and social support, and expand participation?

Does a workplace policy protect sleep and recovery? Does food policy reduce metabolic burden? Does digital policy protect attention and agency? Does environmental policy protect air, water, heat stability, and ecological contact? Does the health system reduce burden and improve continuity?

58. The Limits of the Framework

The framework is integrative, not definitive. It does not replace disease-specific diagnosis and treatment. Mitochondria are central but not sovereign. GDF15 is not the fatigue molecule. Not every fatigue state is primarily mitochondrial. Many proposed measures are not yet clinically available or validated.

The framework must not be commercialized into simplistic optimization culture or used to pressure people toward productivity. Its purpose is to reveal burdens and restore conditions, not moralize energy.

59. A Practical Research Roadmap

A practical roadmap can unfold in stages: conceptual clarification; measurement development; observational studies; dynamic challenge studies; mechanistic studies; intervention trials; public health and policy studies; implementation and de-implementation; and participatory learning systems.

This roadmap turns the framework into a scientific program while keeping the core question before us: is life-capacity expanding?

60. Conclusion of Part VI: Measurement as Accountability to Life

Measurement is necessary because unseen burdens cannot be repaired. But measurement must remain accountable to life. The goal is not more data, more surveillance, or more optimization. The goal is to reveal whether bodies, persons, communities, institutions, and ecosystems are becoming more capable of living and healing.

Measurement becomes life-coherent only when it helps identify what is overloading the organism, blocking repair, narrowing margins, or misdirecting action - and when it supports action that restores life.

Part VII. Discussion, Synthesis, and Conclusion

61. Discussion: From Mitochondrial Function to Life-Capacity

Mitochondrial function asks whether mitochondria produce ATP, maintain membrane potential, regulate redox state, and participate in cellular processes. Mitochondrial life-capacity asks a wider question: can the organism transform available resources into coherent biological and behavioral work while preserving repair, dignity, participation, and future capacity?

This shift matters because health is not maximal energy output. The body is designed to live through rhythmic allocation: mobilization and restoration, action and sleep, immune defense and resolution, protein synthesis and autophagy, fission and fusion, mitophagy and biogenesis, sympathetic activation and parasympathetic repair.

Health is coherent alternation.

62. The Central Synthesis: Energy Flow, Repair, and Affordance

Life-coherent health depends on the organism's ability to keep energy demand, mitochondrial transformation capacity, neuroimmune regulation, repair opportunity, and lived participation within restorative margins. When this relationship is coherent, the person experiences expanded affordance. When it becomes incoherent, the person experiences narrowed affordance.

The framework links biophysical flow, organismal regulation, felt affordance, and life-capacity. It avoids reductionism, psychologism, social abstraction, moralism, and fatalism by asking what restores margins, reduces forcing, and reopens participation.

63. Fatigue Reconsidered: From Symptom to Signal

Fatigue is the felt expression of an organism estimating that further demand may exceed safe transformation capacity. It is protective during infection, injury, sleep deprivation, overexertion, mitochondrial strain, grief, trauma, and chronic disease.

The problem is fatigue without resolution. When fatigue persists, it can narrow life-capacity, reduce movement, diminish belonging, and amplify fear of exertion. The goal is not to silence fatigue, but to make fatigue less necessary.

64. Chronic Illness as Locked Compensation

Many chronic illnesses can be understood as compensations that have lost their resolution pathway. Inflammation protects but damages when unresolved. Fibrosis repairs but stiffens when excessive. Sympathetic activation mobilizes but exhausts when chronic. Pain protects but can become sensitized. Fatigue conserves but can reduce participation.

The deeper question is not how to suppress symptoms alone, but what conditions would allow the organism to stop needing this compensation.

65. The Life-Coherent Medical Imagination

A disease-centered imagination asks what diagnosis the person has and what treatment reduces pathology. A life-coherent imagination also asks what life-capacities have narrowed, what organism-niche relations are overloading the body, what repair opportunities are missing, and what would restore participation, dignity, meaning, and belonging.

Mitochondrial life-capacity helps medicine bridge molecular and existential realities. Biomarkers become clues, symptoms become signals, relationships become regulatory conditions, and participation becomes an outcome.

66. Implications for Public Health and Governance

If mitochondrial life-capacity is shaped by the organism-niche relation, then public health and governance organize the conditions under which bodies must transform energy. A society that protects sleep, nutrition, movement, clean air, safe housing, public care, ecological stability, social trust, education, and meaningful participation protects mitochondrial life-capacity.

A society that normalizes overwork, processed food dependency, digital vigilance, toxic exposure, sleep disruption, loneliness, humiliation, ecological degradation, poverty, and fragmented care imposes energetic burden on bodies.

67. Limitations and Guardrails

The framework is broad and must remain disciplined by definitions, empirical testing, and humility. Mitochondria are central but not total. GDF15 is promising but not the fatigue molecule. Many measures are not clinically ready. The framework must not become commercial optimization culture or a new productivity demand.

The guardrails are: do not reduce life to mitochondria; do not reduce mitochondria to ATP; do not reduce fatigue to weakness; do not reduce health to productivity; do not reduce social suffering to biomarkers; do not reduce repair to personal responsibility.

68. Conclusion: Toward a Science of Mitochondrial Life-Capacity

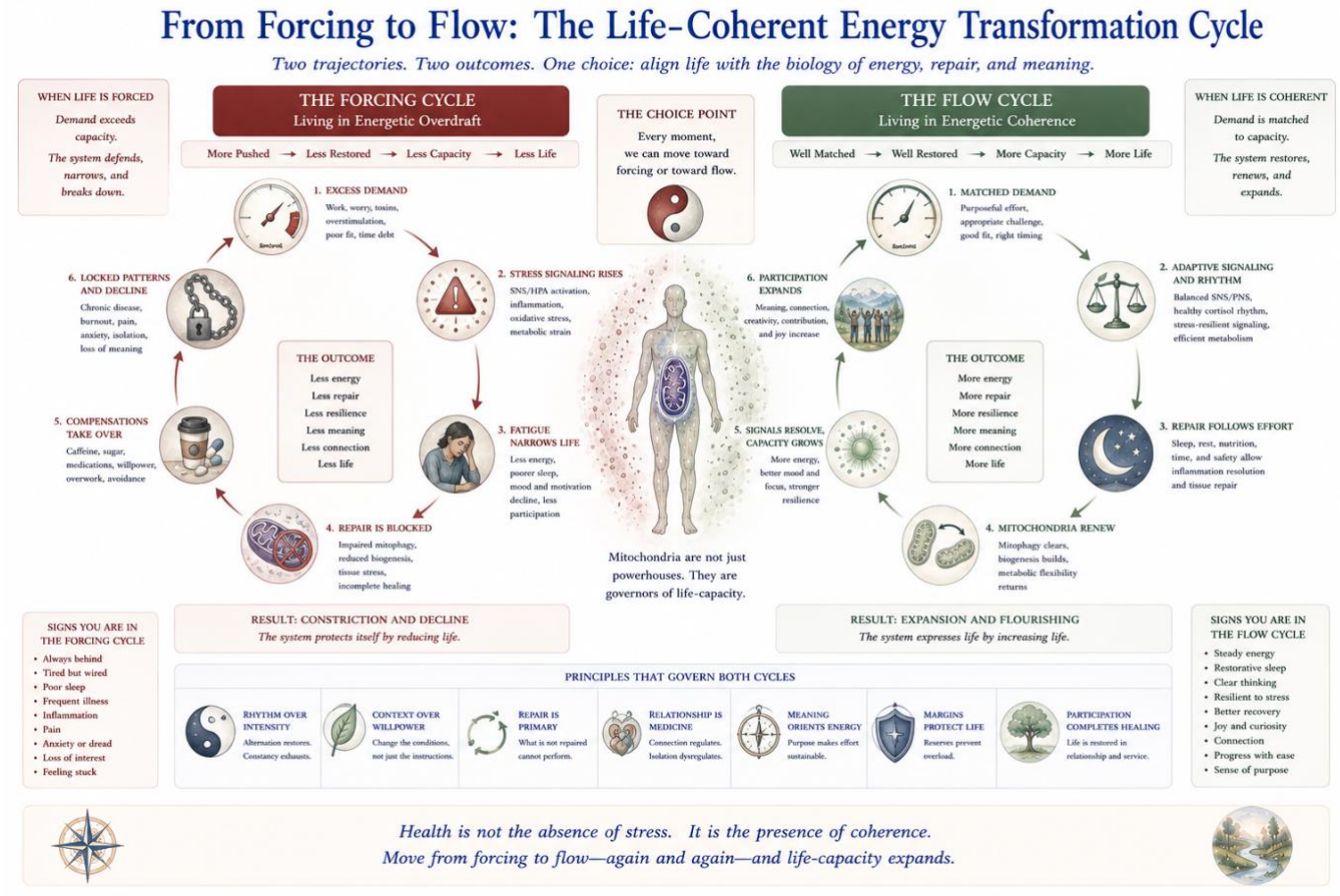

Figure 18. From Forcing to Flow: The Life-Coherent Energy Transformation Cycle.

This final synthesis figure contrasts two trajectories. In the forcing cycle, demand exceeds capacity, stress signaling rises , fatigue narrows life, repair is blocked, and compensations become locked. In the flow cycle, demand is matched to capacity, repair follows effort, mitochondria renew, signals resolve, and participation expands.

Life-coherent health is the condition in which the organism-niche relation keeps mitochondrial energy transformation, neuroimmune regulation, repair opportunity, and lived participation within restorative margins. Disease and fatigue emerge when exposures, threats, or demands exceed the body's capacity to transform energy coherently, forcing compensatory states that conserve survival while narrowing life-capacity.

The deepest purpose of health is not output. It is life. A life-coherent civilization would be one in which cells, bodies, persons, communities, institutions, and ecosystems are arranged so that energy can flow into repair, relation, meaning, and shared flourishing without chronic alarm, exhaustion, or degradation.

This is mitochondrial life-capacity. This is wu-wei physiology. This is health as life-capacity enabled.

Glossary of Core Terms

Life-coherent health: The condition in which organism-niche relations enable rather than disable life-capacity, healing, participation, dignity, and flourishing.

Life-capacity: The real embodied and relational capacity to live, develop, repair, move, think, relate, participate, belong, create meaning, and flourish within the web of life.

Mitochondrial life-capacity: The cellular and organismal capacity to transform available resources into coherent biological and behavioral work without excessive redox stress, danger signaling, proteostatic burden, or depletion of repair margins.

Energy deficit: A condition in which fuel or substrate supply is inadequate relative to demand.

Energy gap: A mismatch between energetic demand and mitochondrial transformation capacity. The body may have fuel but still be unable to transform it coherently.

Reductive stress: A state of electron congestion, often reflected by increased NADH:NAD+ ratio, in which reducing equivalents accumulate because electron flow through oxidative phosphorylation is constrained.

Oxidative stress: A state in which reactive oxygen or nitrogen species exceed signaling, buffering, and repair capacity, producing dysregulated redox signaling or molecular damage.

Metaboception: The brain's monitoring and regulation of energy supply, demand, and transformation capacity across the organism.

Mitoception: The mitochondrial arm of metaboception: body-to-brain signaling of the relationship between cellular energy demand and mitochondrial transformation capacity.

GDF15: Growth differentiation factor 15, a cytokine/metabokine associated with mitochondrial stress and systemic energy reallocation. It is treated here as an important candidate pathway, not the sole fatigue mechanism.

FGF21: Fibroblast growth factor 21, a metabolic stress hormone involved in fasting, fuel switching, mitochondrial stress, and systemic metabolic adaptation.

Fatigue-affordance: The felt narrowing of possible action when the organism infers that further demand may exceed safe transformation capacity.

Wu-wei physiology: The body's capacity to transform energy into work with minimal unnecessary forcing because demand, capacity, timing, repair, and meaning are coherently aligned.

Salugenesis: The inner biology of healing completion: the ordered movement from danger response toward inflammation resolution, rebuilding, differentiation, reintegration, remodeling, and restored functional coherence.

Salutogenesis: The outer health-generating field of resources, meanings, relationships, protections, institutions, and affordances that make health and healing possible.

Restorative margins: The reserves of energy, time, sleep, safety, trust, care, biological resilience, ecological stability, and institutional support that allow living systems to absorb disturbance without collapse.

Metric capture: A distortion in which indicators replace the life-serving purpose they were meant to measure.

Organism-niche relation: The recurrent coupling between living beings and the conditions through which their life is sustained, stressed, injured, repaired, or transformed.

Final Framework Statement

Life-coherent health is the condition in which the organism-niche relation keeps mitochondrial energy transformation, neuroimmune regulation, repair opportunity, and lived participation within restorative margins.

Mitochondria are life-enabling flow systems that translate food, oxygen, sleep, movement, safety, threat, inflammation, toxic exposure, circadian rhythm, social relation, ecological condition, and meaning into cellular and organismal capacity.

When demand and transformation capacity remain coherently matched, energy can become movement, cognition, immunity, repair, relation, dignity, participation, and flourishing.

When exposures, threats, or demands exceed transformation capacity, the organism enters compensatory states: reductive and oxidative stress, integrated stress response activation, Warburg-like metabolic shifts, GDF15 and FGF21 signaling, autonomic and HPA mobilization, fatigue, appetite change, anxiety, rest-seeking, and behavioral conservation.

These compensations protect survival. They become chronic illness when they lose their resolution pathway.

Fatigue is the felt narrowing of energetic affordance. Vitality is the felt expansion of coherent possibility. Healing is the restoration of the conditions under which the body no longer needs to defend against life itself.

The task of medicine, public health, and governance is therefore to reduce unnecessary forcing, restore repair, protect margins, redesign affordances, renew civil commons, and enable the coherent transformation of energy into life.

Health is life-capacity enabled. Healing is life-capacity restored. Flourishing is life-capacity expressed.

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