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Biological Capital and Multicellular Synchronization

Capital Biológico y Sincronización Multicelular

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To the Editor of the Journal of the Paraguayan Society of Internal Medicine.

How is it possible that humanity has achieved unprecedented gains in food production, scientific knowledge, technological innovation, and life expectancy, while simultaneously experiencing an increasing prevalence of chronic diseases, frailty, functional decline, and biological vulnerability? This apparent paradox raises a fundamental question for contemporary medicine, have we become more successful at prolonging survival than at preserving the biological organization required to sustain healthy longevity? We propose that understanding this phenomenon may require moving beyond individual diseases and

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reconsidering a more fundamental biological process: the progressive erosion of biological capital driven by the loss of multicellular synchronization across increasingly long lifespans [1].

Modern medicine has achieved one of the most remarkable transformations in human history. Improvements in sanitation, food production, vaccination programs, healthcare systems, scientific knowledge, and technological innovation have dramatically increased human survival across the globe. Life expectancy has reached unprecedented levels in many populations, allowing millions of individuals to live decades longer than previous generations. Yet this extraordinary achievement has revealed a biological paradox. While longevity continues to increase, so do multimorbidity, frailty, disability, functional dependence, and chronic noncommunicable diseases. This observation raises a fundamental question: Are we merely extending survival, or are we preserving the biological mechanisms required to sustain healthy longevity? [1].

Traditionally, the epidemiological transition has been described as the progressive replacement of infectious diseases by cardiovascular, metabolic, renal, neurodegenerative, and neoplastic disorders. According to this framework, humanity moved from an era dominated by scarcity, infection, and premature mortality toward one characterized by chronic diseases associated with aging. Although this description remains useful, it may not fully explain the biological processes underlying contemporary patterns of disease. Increasing evidence suggests that we are witnessing something deeper than a shift in disease categories. We may be observing a transformation in the capacity of biological systems to preserve their functional organization over increasingly prolonged periods of survival [1].

Many chronic diseases traditionally considered distinct entities share remarkably similar pathophysiological trajectories. Visceral adiposity, chronic low-grade inflammation, insulin resistance, endothelial dysfunction, mitochondrial impairment, progressive skeletal muscle loss, and declining physiological resilience repeatedly emerge across obesity, type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, frailty, and pathological aging. These alterations rarely appear suddenly. Instead, they often develop silently over years or decades before reaching conventional diagnostic thresholds. Such observations suggest the existence of a common biological process that precedes overt disease and progressively increases vulnerability throughout the life course [2].

Within this context, we propose the concept of biological capital. Biological capital may be defined as the cumulative capacity of an organism to preserve its functional, adaptive, and regenerative organization throughout life. This capacity determines the ability to respond to internal and external stressors, restore physiological equilibrium after perturbations, and maintain functionality during aging, disease, and environmental challenges. Like other forms of capital, it can be accumulated, preserved, depleted, or

partially restored over time. Its magnitude influences an individual's future ability to tolerate physiological stress and recover from biological insults [1,2].

Recent advances in single-cell transcriptomics, systems biology, computational biology, and artificial intelligence have begun to reveal that biological capital cannot be understood solely as the sum of isolated physiological reserves. For decades, physiology viewed organs and tissues as relatively homogeneous structures. Biological measurements obtained from tissues represented average signals that concealed extensive cellular diversity. We now recognize that every organ is composed of highly heterogeneous cellular populations capable of activating distinct regulatory programs in response to changing environmental conditions [2].

Immune cells, endothelial cells, epithelial cells, neurons, muscle cells, and stromal populations do not necessarily respond uniformly to the same biological challenge. Even cells within the same tissue may adopt different functional states depending on their molecular context. This heterogeneity is not a biological defect; it is a fundamental property of living systems. Consequently, physiology can no longer be understood solely through the behavior of individual cells or organs. Instead, physiological function emerges from the coordinated interaction of billions of cells operating simultaneously within complex regulatory networks [2].

From this perspective, homeostasis may be reinterpreted as a state of multicellular synchronization. Multicellular synchronization refers to the capacity of diverse cellular populations to maintain compatible and coordinated regulatory programs that collectively sustain the functional integrity of the organism. Importantly, synchronization does not imply uniformity. Biological systems require specialization and diversity. Different cell types perform distinct functions, yet remain integrated through metabolic, immunological, endocrine, neural, mechanical, and bioenergetic communication networks that generate coherent adaptive responses [3,4].

Homeostasis therefore emerges not from static equilibrium but from dynamic coordination. The stability of living systems depends upon the continuous synchronization of multiple cellular programs operating across tissues and organs. Physiological adaptation, repair, regeneration, and resilience all require the preservation of this coordinated biological architecture. The organism functions effectively because its cellular components remain integrated within a shared regulatory framework despite constant environmental and internal fluctuations [3].

Disease may arise when this synchronization begins to deteriorate. Aging, chronic inflammation, metabolic stress, environmental exposures, and repeated physiological insults can progressively disrupt coordinated cellular behavior. Under these conditions, different cellular populations may follow divergent regulatory

trajectories. Some cells adopt persistent inflammatory phenotypes, others develop immunosuppressive states, some enter senescence, while others attempt compensatory repair mechanisms that fail to integrate effectively with the broader biological system. The consequence is not merely tissue damage. More fundamentally, it is the progressive loss of biological organization [2-4].

This perspective allows biological capital to be redefined with greater precision. Biological capital is not simply a collection of physiological reserves. Rather, it represents the organism's cumulative capacity to preserve the multicellular synchronization required to sustain adaptation, repair, functionality, and survival throughout life. In this framework, biological capital and multicellular synchronization are inseparable concepts. Multicellular synchronization represents the underlying biological mechanism, whereas biological capital represents its accumulated functional expression over time [3–5].

The greater the capacity to maintain synchronized interactions among cellular systems, the greater the biological capital available to confront future physiological challenges. Conversely, progressive deterioration of multicellular synchronization leads to erosion of biological capital, reducing resilience and increasing vulnerability. This relationship provides a unifying framework capable of integrating concepts that have traditionally been studied separately, including resilience, frailty, intrinsic capacity, functional aging, recovery after critical illness, and chronic disease progression [4,5].

Within this model, resilience may be understood as the capacity to restore multicellular synchronization following perturbation. Frailty reflects a progressive decline in this restorative capacity. Healthy aging corresponds to the long-term preservation of synchronized biological networks. Chronic disease represents varying degrees of synchronization failure. Each of these phenomena can be interpreted as different manifestations of a common biological continuum centered on the preservation or erosion of multicellular organization [5,6].

Sepsis provides a particularly illustrative example. Although the infectious agent may be eliminated successfully, many survivors develop persistent immune dysfunction, muscle weakness, neurocognitive impairment, and long-term physiological vulnerability [6,7]. From this perspective, sepsis can be viewed as an acute and systemic disruption of multicellular synchronization. Recovery depends not only on microbial clearance but also on the restoration of coordinated communication among immune, endothelial, metabolic, neurological, and musculoskeletal systems. Persistent dysfunction after sepsis may therefore reflect incomplete recovery of biological synchronization rather than unresolved infection alone [4,6].

Aging may be interpreted similarly. Different organs age at different rates because the cellular populations that compose them lose synchronization heterogeneously. Some systems

maintain adaptive capacity for decades, whereas others experience accelerated functional decline. Biological age may therefore reflect the degree of preserved multicellular synchronization more accurately than chronological age. Healthy longevity becomes less a function of time and more a reflection of the organism's ability to maintain coordinated biological organization across multiple physiological systems [4,5].

Obesity may also represent an early stage of synchronization loss. Long before diabetes, cardiovascular disease, or kidney dysfunction become clinically apparent, adipose tissue, skeletal muscle, the immune system, the liver, and the vascular endothelium begin exchanging increasingly discordant metabolic and inflammatory signals [6,7]. These alterations indicate a progressive decoupling of biological networks that previously functioned in a coordinated manner. Clinical disease emerges only after this loss of synchronization reaches sufficient magnitude to compromise physiological function [5,6] (figure 1).

Viewed through this lens, the modern epidemiological transition acquires an entirely new meaning. It is not merely the replacement of infectious diseases by chronic disorders. Rather, it represents a population-level manifestation of progressive biological desynchronization. Historically, human disease was dominated by conditions associated with scarcity of essential resources. Today, a growing proportion of disease appears to arise from the gradual erosion of biological capital driven by the inability to preserve multicellular synchronization over extended lifespans [6,7].

The conceptual sequence becomes clear: epidemiological transition leads to progressive erosion of multicellular synchronization; erosion of multicellular synchronization reduces biological capital; loss of biological capital increases vulnerability to disease, frailty, disability, and dependence. These are not independent phenomena but successive stages of a single biological process operating across the lifespan [4,6,7].

The central biomedical challenge of the twenty-first century may therefore not be simply extending life expectancy. Rather, it may be preserving the multicellular synchronization that sustains biological capital throughout increasingly long lives. If this hypothesis is correct, the future of medicine will depend not only on identifying isolated biomarkers or treating individual diseases, but also on understanding, measuring, and preserving the regulatory networks that maintain biological integration across cells, tissues, organs, and physiological systems [4,6,7].

Within this framework, biological capital emerges as the functional expression of multicellular synchronization, while the modern epidemiological transition becomes the population-scale consequence of its gradual erosion. Together, these concepts provide a unified biological narrative capable of integrating aging, resilience, frailty, chronic disease, and human longevity within a single systems-based model of health and disease [4,6,7].

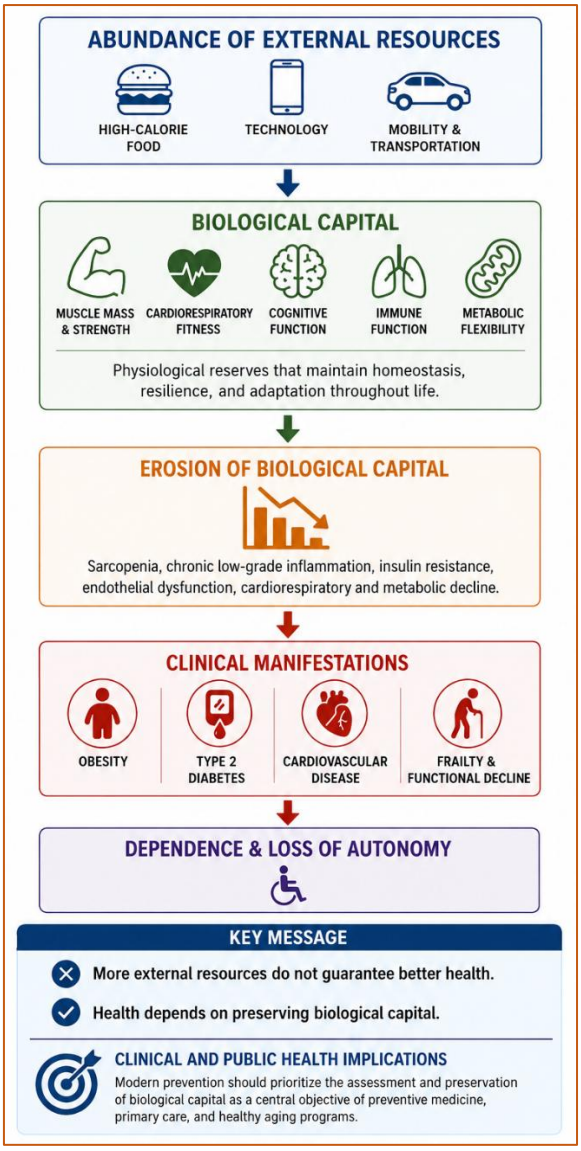

Figure 1. Conceptual framework of biological capital and the epidemiological transition.
The figure illustrates the proposed relationship between increasing availability of external resources and the progressive erosion of biological capital. Biological capital is conceptualized as the integrated reserve of physiological capacity, including skeletal muscle function, cardiorespiratory fitness, metabolic flexibility, immune competence, and neurocognitive integrity. Progressive deterioration of these reserves contributes to the development of chronic noncommunicable diseases, frailty, functional decline, and loss of autonomy. Source: Original figure developed by the authors based on references 1–5. Visual design assisted by generative artificial intelligence and subsequently reviewed, edited, and scientifically validated by the authors.

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Janeth Cecilia Gil Forero: Conceptualization of the manuscript, methodological design, development of the theoretical framework, scientific supervision, critical analysis of the evidence, interpretation of findings, intellectual review of the content, and approval of the final version.

Jhan Sebastian Saavedra-Torres: Literature search and analysis, integration of biomedical evidence, preparation of the original draft, development of the mechanistic narrative, clinical interpretation of findings, bibliographic review, manuscript editing, and approval of the final version.

All authors participated in the discussion of the concepts presented, critically reviewed the scientific content, approved the final version of the manuscript, and take responsibility for the integrity and accuracy of the information provided.

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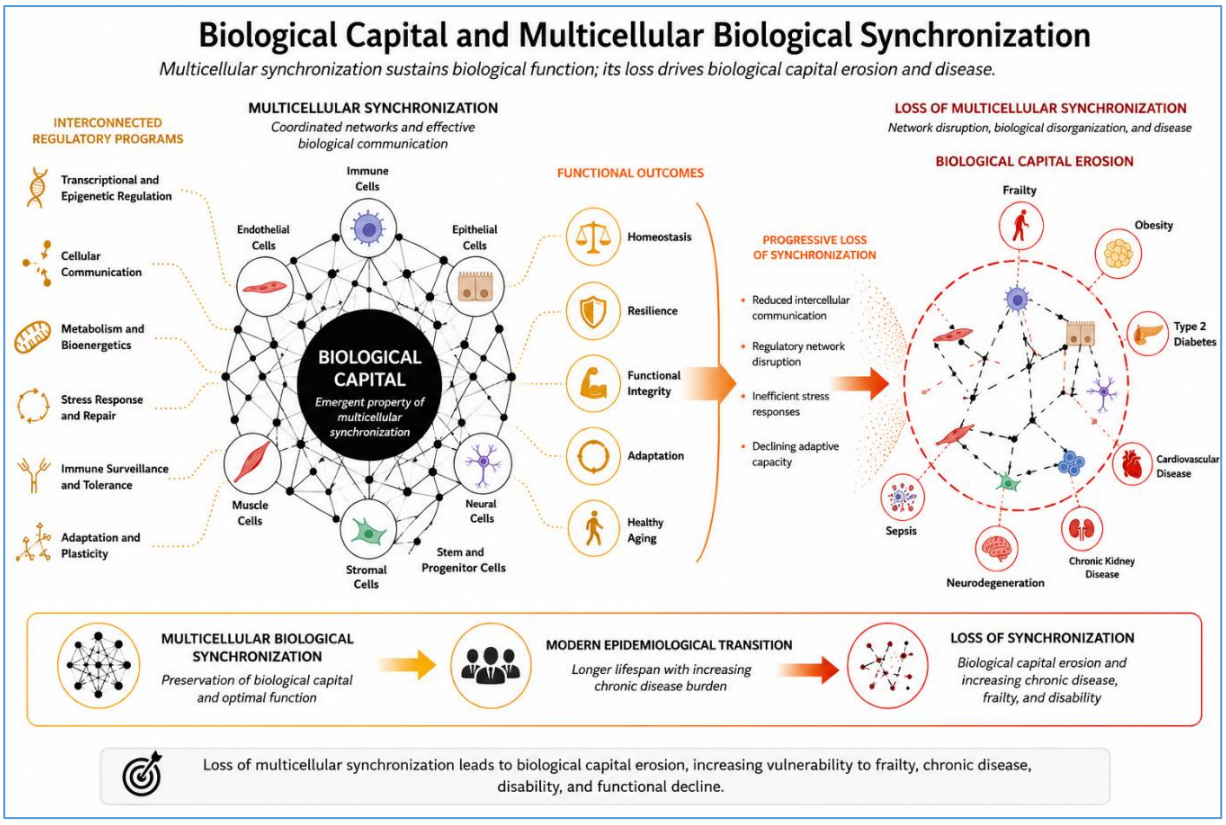

Figure 2. Original conceptual model proposed by the authors. The framework integrates concepts from biological capital, multicellular synchronization, resilience, frailty, and the modern epidemiological transition. The representation was inspired by cell-type-specific regulatory network reconstruction methodologies reported by Yao et al. (Nature Biotechnology, 2026) and developed as a systems-level biological hypothesis. Source: Original figure developed by the authors based on references 3–7. Visual design assisted by generative artificial intelligence and subsequently reviewed, edited, and scientifically validated by the authors.

REFERENCES

1. Basile AJ, Renner MW, Hidaka BH, Sweazea KL. An evolutionary mismatch narrative to improve lifestyle medicine: a patient education hypothesis. Evol Med Public Health [Internet]. 2021 [cited 2025 Dec 10];9(1): eoab010. Available from: https://academic.oup.com/emph/article/9/1/eoab010/6149126?login=false

2. Booth FW, Roberts ChK, Thyfault JP, Ruegsegger GN, Toedebusch RG. Role of inactivity in chronic diseases: evolutionary insight and pathophysiological mechanisms. Physiol Rev [Internet]. 2017 [cited 2025 Dec 10];97(4):1351-1402. Available from: https://journals.physiology.org/doi/full/10.1152/physrev.00019.2016

3. Fried LP, Cohen AA, Xue QL, Walston J, Bandeen-Roche K, Varadhan R. The physical frailty syndrome as a transition from homeostatic symphony to cacophony. Nat Aging [Internet]. 2021 [cited 2025 Dec 10];1(1):36-46. Available from: https://www.nature.com/articles/s43587-020-00017-z

4. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. J Gerontol A Biol Sci Med Sci [Internet]. 2016 [cited 2025 Dec 10];71(4):489-95. Available from: https://pubmed.ncbi.nlm.nih.gov/26718984/

5. Chhetri JK, Xue QL, Ma L, Chan P, Varadhan R. Intrinsic capacity as a determinant of physical resilience in older adults. J Nutr Health Aging [Internet]. 2021[cited 2025 Dec 10];25(8):1006-11. Available from: https://www.sciencedirect.com/science/article/pii/S1279770723007807

6. Yao L, Shah SR, Ozer A, Zhu Y, Pan X, Xiaet T, et al. High-resolution reconstruction of cell-type-specific transcriptional regulatory processes from bulk sequencing samples. Nat Biotechnol [Internet]. 2026 [cited 2026 Jul 15]. Available from: https://doi.org/10.1038/s41587-026-03218-w Subscription required

7. Saavedra Torres JS, Tamayo-Giraldo FJ, Bejarano-Zuleta A, Nati-Castillo HA, Quintero DA, Ospina-Mejía MJ, et al. Sepsis and post-sepsis syndrome: a multisystem challenge requiring comprehensive care and management—a review. Front. Med (Lausanne) [Internet]. 2025 [cited 2026 Feb 10]; 12:1560737. Available from: https://pubmed.ncbi.nlm.nih.gov/40265185/