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Peer Review

Review of: "The Future of Longevity Medicine: Repairing the Parts or Preserving the Whole?Holmes' Carriage as a Metaphor for Two Fundamentally Different Models of Aging"

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The authors present a conceptual essay that contrasts two paradigms of biological aging, which they term "fragmented aging" and "coherent aging," using Oliver Wendell Holmes' image of a wonderful carriage as an organizing metaphor. Fragmented aging is characterized as progressive systemic decline driven by sequential failures of individual biological subsystems, sustained by continuous technological intervention, and taken to typify wealthy societies. Coherent aging is described as a state in which biological systems preserve long-term functional integration until a rapid terminal decline, and is offered as characteristic of traditional or rural populations, including so-called Blue Zones. The central thesis is that longevity medicine has focused disproportionately on repairing molecular damage while neglecting the mechanisms that maintain organism-level coordination over decades. The authors conclude by advocating a broader conceptual framework that integrates repair technologies with an understanding of the physical and biological principles underlying long-term systemic coherence.

In my opinion, the manuscript reads as an ambitious philosophical intervention rather than a scientifically rigorous commentary, and its evocative framing will likely attract readers interested in the conceptual foundations of geroscience. However, several weaknesses limit its persuasive force in its current form. The central dichotomy is more rhetorical than empirical; the notion of "systemic coherence" that anchors the entire argument is never operationalized; the engagement with existing literature is unusually thin for a piece that positions itself as a synthesis; and the tone occasionally slides from measured commentary into op-ed style rhetoric that undercuts the scientific claims.

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1. The distinction between "fragmented" and "coherent" aging is presented as if the two constituted mutually exclusive biological categories, whereas empirically they describe endpoints of a continuum along which the same population might sit at different ages and in different subsystems. The authors do not acknowledge that the "coherent aging" pattern they attribute to Blue Zones has become the subject of substantial demographic controversy, including Newman's analyses of registry errors and pension fraud that have raised serious doubts about the reliability of the underlying supercentenarian records. They also do not confront the well-documented fact that mean and healthy life expectancy are, on average, longer in high-income than in low-income settings, a pattern that sits uneasily with the claim that "rural or traditional populations sometimes achieve equal or even greater lifespan than far wealthier populations." Without engaging with these tensions, the paper risks romanticizing structural deprivation and reifying a comforting narrative that lacks solid empirical grounding.
2. In my view, the concept of "systemic coherence" is problematic. This term carries the entire argumentative weight of the paper and is never defined in operational, physiological, or measurable terms. Readers are told repeatedly that coherence should be preserved, monitored, and modulated, but they are not told what coherence is at the level of physiology, what its molecular substrates might be, how it would be measured longitudinally, or what would distinguish a coherent from an incoherent organism at a given chronological age. The recurrent citation of the same three references (Fedichev, Barabási, Alon) after every mention of the term is bibliographically unusual and suggests that a proper conceptual definition, drawing on network medicine, complex systems theory, or information theory, has been elided rather than elaborated. Without a working definition, the coherence concept remains rhetorical rather than analytical, and the paper's central hypothesis becomes difficult to falsify. The authors should provide, at minimum, a set of candidate operational measures (for example, physiological dysregulation indices, network-derived biological age estimators, entropy-based measures of physiological signals, or frailty-index-derived integration scores) and specify what pattern of longitudinal change would support or refute the hypothesis.
3. The manuscript raises deep questions about the biology of aging while citing only six references, three of which are used to prop up the coherence concept and one of which (Fries 1980) is invoked almost in passing. Several relevant intellectual traditions receive no acknowledgment. Kirkwood's disposable soma theory and the reliability theory of aging developed by Gavrilov and Gavrilova have long framed the trade-offs between damage repair and systemic stability that the authors treat as novel. Network theories of aging and disease (Barabási is cited but not integrated), the geroscience

hypothesis, and the recent work of Cohen, Rutenberg, Ferrucci, and others on physiological dysregulation and biological age acceleration are all directly relevant and absent. The hallmarks-of-aging framework (López-Otín et al.) is cited once but not engaged, despite the fact that several hallmarks (altered intercellular communication, disabled macroautophagy, stem cell exhaustion) already speak to loss of systemic coordination rather than to isolated molecular failure. The paper would be improved considerably by situating its argument within, rather than adjacent to, these bodies of work.

4. Beyond being unusually short, the reference list requires careful checking. The citation "Fedichev PO (2024). Longevity and Aging as a Systemic Process. Front Aging. 5:13245" should be verified against PubMed and the Frontiers in Aging index, because the volume and page numbering do not correspond to the standard format of that journal, and I was unable to locate a corresponding record (most likely the authors were victims of an AI hallucination). If the reference cannot be confirmed against a PMID or DOI, it should be replaced by a genuine primary source. The Barabási (2016) and Alon (2006) textbook citations, while legitimate works in themselves, are used here to support the specific claim of "systemic coherence" as a determinant of aging, which is not directly the subject of either book; more targeted primary references are needed. The Buettner (2008) reference to the popular Blue Zones book is inappropriate as the sole support for empirical claims about traditional populations; peer-reviewed demographic literature (Poulain, Herm, Robine, and colleagues) should be used instead, and Newman's critical demography should be cited as a necessary counterweight. In addition, a manuscript of this scope should probably cite between forty and sixty references, not six.
5. The passage arguing that reversing biological logic would require "tiny preassembled hearts, kidneys, brains, and livers to be mechanically integrated into a fetus" and that "a toy airplane placed inside a hangar would somehow 'grow' into a jetliner" is rhetorically vivid but scientifically weak. It sets up a straw man version of "engineering logic" against which biology is then contrasted, ignoring the fact that modern systems biology, tissue engineering, and complexity science have long faced the questions of emergence, hierarchical control, and self-organization. This section should be either removed or substantially rewritten to engage with the relevant literature rather than to caricature an unnamed opposing view.
6. The rhetorical device of imagining a wealthy individual choosing between paradigms, while accessible, does not sit comfortably in a scientific commentary. It shifts the register from analysis toward speculation about personal preferences and risks trivializing the underlying argument. This

section could be compressed or reframed as a substantive discussion of the difference between healthspan and lifespan as legitimate and distinguishable targets of intervention, which is the point actually being made.

7. The prose is generally clear, but its quality is compromised by the pervasive use of enumerated lists of the form "(i), (ii), (iii)..." embedded within otherwise continuous sentences. Whole paragraphs are broken into what read as bullet points wrapped loosely in prose, and the cumulative effect is fatiguing rather than clarifying. Many of these enumerations are entirely unnecessary; for example, the sequence "cardiovascular, metabolic, neurological, renal, immune, and musculoskeletal" would read far more naturally as an unornamented comma-separated series. Their overuse gives the piece a mechanical rhythm that is at odds with its philosophical ambitions. The manuscript also relies on stock phrases ("war against death," "escape velocity," "victory over aging") that would benefit from more measured formulations. Sweeping statements of the form "Modern medicine is extraordinarily successful at repairing individual failures" invite qualification. The repeated bracketing "[1][2][3]" after every occurrence of "systemic coherence" is bibliographically awkward and should be replaced either by a single integrated citation early in the text or by targeted references specific to each context. Finally, several sentences are burdened by cascading subordinate clauses and would benefit from being broken into two or reordered to place the topic first.
8. The manuscript would benefit from a clearer articulation of its thesis at the outset, including a working definition of "systemic coherence" and a statement of what evidence would confirm or refute the central hypothesis. A short section explicitly discussing measurement, for example, physiological dysregulation indices, frailty scores, and network-based biological age estimators, would ground the argument. A limitations paragraph acknowledging the demographic controversies surrounding Blue Zones, the trade-offs of forgoing biomedical interventions, and the risks of romanticizing structural deprivation would considerably strengthen the paper's credibility. At present, the argument moves from metaphor to conclusion without an intermediate step that a scientifically trained reader can evaluate.
9. The core observation that healthspan and lifespan can diverge, that morbidity can be compressed rather than prolonged, and that biomedical intervention often extends life without commensurate improvements in function, is well established in the geriatric and geroscience literature going back to Fries and continuing through contemporary work on the geroscience hypothesis. The manuscript's contribution lies chiefly in the Holmes-carriage framing and in the terminological emphasis on coherence. Whether this reframing constitutes a genuine conceptual advance, rather

than a re-branding of ideas already present in Fries, Kirkwood, Cohen, and the systems-biology literature, is not clear from the current draft. The authors should be explicit about what their framework predicts that existing frameworks do not, and what new empirical work it would motivate.

10. The paper's implicit valorization of populations that lack access to modern medicine as exemplars of "coherent aging" deserves careful reconsideration. Presented without qualification, this framing risks lending intellectual legitimacy to arguments against biomedical intervention and to fatalistic views of chronic disease management. The authors should make explicit that they are not advocating a withdrawal from repair-oriented medicine, but rather a complementary investment in coherence-preserving strategies. Otherwise, the essay may be read against its own likely intent.

Declarations

Potential competing interests: No potential competing interests to declare.