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Peer Review

Review of: "AI-Generated Hallmarks of Aging and Cancer: A Computational Approach Using Causal Emergence and Dependency Networks"

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This is an interesting and ambitious manuscript that aims to formalize “AI-generated hallmarks” of aging, cancer, and related diseases using causal emergence analysis, pathway aggregation, and dependency networks. The topic is timely, and the authors clearly put substantial computational work into the study. That said, several methodological decisions are not sufficiently justified, and in a few places, the conclusions are presented more strongly than the data support. I believe the paper could become publishable, but a number of major revisions are needed before the framework can be properly evaluated.

Major Comments

1. The hallmark definitions rely on keyword-based pathway searches followed by selecting the “top 1000 recurrent genes.” It’s unclear why this threshold was chosen or whether alternative cutoffs materially affect the results. This step is central to the entire framework, so a more transparent rationale or some sensitivity analyses would help reassure readers that the hallmark signatures are not driven by construction artifacts.

2. The study combines whole-blood and saliva methylation data, as well as 450k and 850k platforms, with notable variation in sample size and age distribution. The manuscript does not clearly describe how batch effects or tissue-specific differences were handled. Given the downstream analyses (especially CE index comparisons and LASSO models), this is a major concern.

3. Defining causal emergence as the difference between macro-level association and the 95th percentile of single-gene associations feels somewhat ad hoc. Why the 95th percentile? Why should this difference

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quantify “causal emergence”? It may be helpful to provide mathematical motivation, discuss alternatives, or include simulation studies showing that the CE index behaves as expected under known conditions.

4. All LASSO models are trained and evaluated within the same cohort using repeated resampling. Without an external dataset or at least cross-dataset testing across diseases, it is difficult to evaluate generalizability. The claims about model parsimony are interesting, but the evidence remains exploratory.

5. The herb → chemical → predicted target workflow depends heavily on target prediction (STITCH), which carries considerable uncertainty. Some statements in the manuscript seem to imply mechanistic specificity that the data do not fully support. I recommend softening these interpretations.

6. The dependency networks are fitted using simple linear models on log–log plots. This is known to generate false positives. Methods such as the Clauset–Shalizi–Newman framework or likelihood-ratio testing would provide stronger support for the claim that the networks are genuinely scale-free.

Minor Comments

7. Several figures are visually dense, and some panels appear repetitive. Consolidating or restructuring a few of them may help readers follow the main message more easily.

8. Certain paragraphs—particularly in the Results section—are quite long and could be broken up to improve readability.

9. The Methods section should clarify how CpGs were selected, how methylation values were normalized, and whether any batch-correction procedures were applied.

10. Terms such as “super-regulators” or “macro-scale causal structure” should be used carefully and defined more precisely, as these may mean different things to readers from different backgrounds.

11. A language/consistency pass would help polish terminology and improve flow.

In summary, the manuscript tackles an appealing idea and contains several intriguing analyses. The concept of computationally derived hallmarks has potential, but the methodological foundation needs to be more transparent, and several interpretations should be moderated. With substantial revision and clearer justification of the modeling choices, the study could become suitable for publication.

Declarations

Potential competing interests: No potential competing interests to declare.