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

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The authors developed the AI-based hallmark generator and validated the gene set with computational approaches. Especially, causal emergence has attracted much attention in the field of complex sciences. It is very intriguing that the authors utilized the concept for building the hallmark gene set of age-related diseases.

I'd like to clarify the following two points.

- In figure 2, what are the values of the X-axis (Gene Association)?

If I understand correctly, the one scatter point in this plot represents a pathway or hallmark gene set, and each X-axis value can have the number of values equal to the number of included genes.

- In the methods section, the second paragraph of "Causal Emergence Analysis," is the age distribution of the healthy control group equal to that of the diseases group?

As it is widely known, also throughout this article, DNA methylation and aging have been strongly correlated with each other. If the age distribution of the healthy control is much younger than that of the diseases group, the calculated values are age-related associations rather than a gene-disease association index.

Although quantifying emergence is not a simple task and there has been discussion about how to calculate the phenomenon, the authors proposed the CE index and suggested that the index can explain the effect of age-related diseases. I think that this is one of the most exciting approaches in the big-data science era, and it is possible to build a de novo gene set based solely on the CE index. It will need more computing power, but using heuristic optimization approaches such as genetic algorithms can reduce the computational burden. Please try it if you are interested in.