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Never Grow Old? Maybe One Day.

In the fight against aging, restricting calorie consumption is among the few actually proven methods. The underlying mechanism is still unknown, yet calorie restriction has been shown to prolong lifespan in worms, yeast, flies, monkeys, and as per some recent studies, in humans too.

Keren Yizhak is a doctoral student in Prof. Eytan Ruppin's laboratory at Tel Aviv University's Blavatnik School of Computer Science. Together with her colleagues she developed a computer algorithm capable of predicting which genes can be ‘switched off’ to achieve an anti-aging effect identical to that in calorie restriction.

Scientists from Bar-Ilan University collaborated on this research, findings of which were reported in Nature Communications and could lead to the development of new drugs to treat aging.

Compared to most algorithms which try to find drug targets that kill cells to treat cancer or bacterial infections, the team’s innovative algorithm is unique in being the first to look for drug targets not to kill cells, but to transform them from a diseased state into a healthy one, as explained by Yizhak.

A leader in the growing field of genome-scale metabolic modeling or GSMMs, Prof. Ruppin's lab successfully uses mathematical equations and computers to create GSMMs that describe the metabolism, or life-sustaining, processes of living cells. The individual models serve as digital laboratories once built, enabling formerly labor-intensive tests to be conducted with the click of a mouse. Yizhak's algorithm, which she calls a "metabolic transformation algorithm," or MTA, can take information about any two metabolic states and predict the environmental or genetic changes required to go from one state to the other.

The measurement of the expression level of individual genes in a cell is called ‘gene expression’, and genes can be ‘turned off’ in different ways to prevent them from being expressed in the cell. Yizhak applied MTA to the genetics of aging in her study, and after using her custom-designed MTA to confirm previous laboratory findings, she applied it to predict genes that can be turned off to make the gene expression of old yeast look like that of young yeast.

Yeast is the most widely used genetic model because much of its DNA is preserved in humans. Researchers there found that turning off two of the genes, GRE3 and ADH2, in actual, non-digital yeast significantly extends the yeast's lifespan.

Yizhak expressed the team’s enthusiasm over the results, as about three percent of yeast's genes are expected to be lifespan-extending. Achieving a 10-fold increase over this expected frequency, as they did, was most encouraging since MTA showed that turning off the genes led to an increase in the yeast’s oxidative stress levels, thus potentially inducing a mild stress similar to that produced by calorie restriction.

The final test consisted of applying MTA to human metabolic information, where it was possible to identify a set of genes that can transform 40-70% of the differences between the old and young information from four different studies. Many of these genes are known to extend lifespan in yeast, worms, and mice, though there is currently no way to conduct result verification in humans.

Yizhak’s next project will investigate whether switching off the genes predicted by MTA leads to a prolongation of lifespan for genetically engineered mice. In future, gene-targeting drugs for humans could be developed, possibly enabling us to live longer.

Furthermore, the MTA method could be applied to finding drug targets for metabolism disorders such as obesity, neurodegenerative disorders, diabetes and cancer.

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