Leaking away essential resources actually helps cells grow

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Experts have been unable to explain why cells, from bacteria to humans, leak essential chemicals necessary for growth into their environment. New mathematical models reveal that leaking metabolites—substances involved in the chemical processes to sustain life with production of complex molecules and energy—may provide cells both selfish and selfless benefits.

Previously, biologists could only say that leaking is an inherent property of cell membranes caused by fundamental rules of chemistry.

"It is in the nature of membranes to leak, but if leaking is undesirable, why has evolution not stopped it? This question was never solved," said Professor Kunihiko Kaneko, a theoretical biology expert from the University of Tokyo Research Center for Complex Systems Biology.

The research team used calculations that can measure the changes of multiple factors over time, a process called dynamical-system modeling, in combination with computer simulations. By representing the cellular state as the concentrations of intracellular chemicals including nutrients, enzymes, and components to synthesize cellular body, the researchers considered the nonlinear processes for cell growth in which a cell takes in external nutrients and converts them to cellular body and energy through intracellular chemical reactions. All calculations assumed that the model cells were in a steady state of growth in which their internal metabolism and relative concentration of chemicals inside the cells were all stable.

The calculations were designed to identify what types of chemical synthesis pathways would become more efficient if some of their components leaked out to the environment. The mathematical models of chemical synthesis paths are simpler than the complex branching pathways in living cells, but allow researchers to look for fundamental patterns.

Researchers identified two such model chemical pathways with catalytic reactions that use enzymes to enhance the reaction rate, which they call the "flux control" and "growth-dilution" mechanisms. In both mechanisms, leaking one essential upstream chemical component of the pathway allows the end product to be produced more efficiently. Thus, leaking is something cells do to selfishly enhance their own growth.

"In theory, the flux control mechanism enhances the pathway for biomass synthesis by the leakage of an essential chemical in an alternative branching pathway, whereas the growth-dilution mechanism enhances the biomass synthesis by the leakage of the precursors of biomass (e.g., amino acids) essential for cell growth. These are a result of the balance between chemical reactions and concentration dilution associated with cellular volume growth," said Jumpei Yamagishi, a first-year graduate student who has worked in Kaneko's laboratory since his undergraduate years.

The models that the research team created so far only consider one type of cell at a time. However, leaking upstream components might become a problem for cells living only with identical types of cells leaking the same components.

"In many cases, if all cells are leaking the same molecule, their environment will become 'polluted.' But if multiple cell types live together, then they can leak one chemical and use a different chemical leaked by the others," said Kaneko.

This mutually beneficial exchange of leaked essential nutrients may be a selfless way to enhance the growth of the whole community of cells.

"Our work may partially answer why the natural environment is so different from artificial lab conditions where bacteria are grown in pure monocultures, but we will need additional models to be sure," said Yamagishi.

The researchers are planning to design more complex mathematical calculations to better simulate natural conditions where multiple types of cells coexist to see if that reveals other types of synthesis pathways that benefit from leaking.

More information: Jumpei F. Yamagishi et al. Advantage of Leakage of Essential Metabolites for Cells, *Physical Review Letters* (2020). DOI: 10.1103/PhysRevLett.124.048101

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