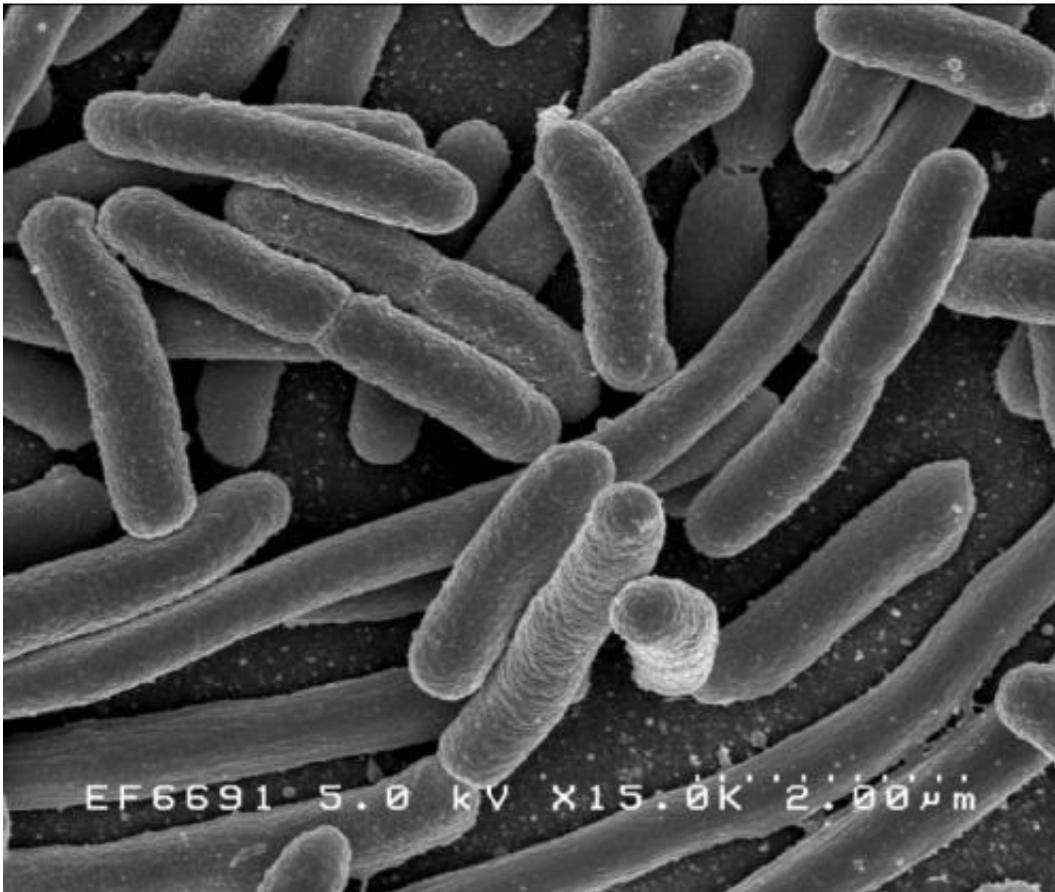


# Pausing evolution makes bioproduction of chemicals affordable and efficient

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Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

Bioproduction of chemicals using engineered microorganisms is routinely reported today, but only a few bioprocesses are functional in the large fermentation volumes that industry requires. For a longer

period, the lack of successful scale-up has been one of the most important challenges for engineers to solve, in order to replace oil-derived production with bio-based production of chemicals.

"One central issue is that bioproduction in large-scale fermenters is limited by toxicities and stresses that allow [evolution](#) to reduce or eliminate production of chemicals by engineered cells. This makes it expensive and challenging to commercialize bio-based production systems in particular when large amounts of chemicals are needed" says Morten Sommer, Professor and Scientific Director of the Bacterial Synthetic Biology section at the Novo Nordisk Foundation Center for Biosustainability, Technical University of Denmark.

A new study made by scientists from the Novo Nordisk Foundation Center for Biosustainability, just published in *PNAS*, suggests that cells can be engineered to overcome this evolutionary pressure and stably produce high levels of valuable chemicals.

The key is to rewire production cells to only grow when they contain high product concentration. Thus, the evolution can be circumvented and cells will be able to produce the biochemicals within an industrial time scale.

"When we rewire the production microorganism to slow down growth in case it loses production, we efficiently prevent it from performing evolution on the genes leading to production. This allows us to maintain productive cells even when the cells divide to fill up large fermentation tanks," says Peter Rugbjerg, Postdoc at the Novo Nordisk Foundation Center for Biosustainability.

Evolution is beneficial for the cell. However, what is good for the cell may not be good for a bio-based process in a fermentation tank. In a fermentation tank evolution can eliminate production—especially during

large-scale fermentations.

The underlying idea of the new study is to circumvent the evolution occurring in production cells by using a so-called molecular biosensor that senses the product, mevalonate, inside the production [cells](#). The biosensor has the ability to shut down growth if the production concentration declines below a certain point.

This concept is demonstrated by the scientists and can help in driving the development towards a more sustainable society. At this point, microorganisms do not naturally produce high amounts of valuable chemicals, which demands the use of many R&D resources, an expensive process that delays the launch of new bio-based processes.

"Engineered, high-level bioproduction of chemicals is not attractive for the cell that tends to grow slower and explore ways to evolve and stop production. This makes it difficult to bridge the gap between research conducted in lab shake flasks and industrial need for large cubic-meter quantities," says Peter Rugbjerg.

If the findings from the study are broadened out to more production cases, a major obstacle for investing in bio-based production is removed. The group at the Novo Nordisk Foundation Center for Biosustainability currently collaborates with biotech companies to investigate and solve the impact of the evolution in current fermentation tanks.

"The biotech industry clearly indicate that they see a great potential in solving this problem. This study can be a step towards more efficient and affordable large-scale biomanufacturing to the benefit of society," says Morten Sommer.

Since 2011, the Novo Nordisk Foundation Center for Biosustainability has been working on developing and perfecting foundational engineering

approaches for bio-manufacturing. This study is a splendid example of that.

**More information:** Peter Rugbjerg et al., "Synthetic addiction extends the productive life time of engineered Escherichia coli populations," *PNAS* (2018). [www.pnas.org/cgi/doi/10.1073/pnas.1718622115](http://www.pnas.org/cgi/doi/10.1073/pnas.1718622115)

Provided by Technical University of Denmark

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