

SYNTHETIC BIOLOGY

Differentiating bacteria

“ complex multicellular synthetic bacterial populations can arise from simple genetic circuits ”

Synthetic microorganisms hold great promise for a range of applications, from producing biofuels and drugs to detoxifying contaminants in the environment; however, synthetic microorganisms are relatively simple compared with multicellular organisms, limiting their potential in applications that require complex behaviours such as the compartmentalization of functions and spatiotemporal control. Multicellular organisms achieve their complexity through asymmetric cellular divisions and cellular differentiation. Now, two studies report synthetic genetic circuits for inducible asymmetric cell division that give rise to cellular differentiation in *Escherichia coli*.

In the first study, Molinari et al. engineered an asymmetric plasmid partitioning (APP) system that controls partitioning by sequestering

plasmids in a single position within the cell. During division, plasmids are retained by only one daughter cell, and the other cell is thus irreversibly differentiated from its sibling. The authors constructed a circuit based on the chromosome partitioning system (*par*) of *Caulobacter crescentus* for APP in *E. coli*. Two *par* elements (a centromere-like *parS* site and the *parS*-binding protein ParB) were cloned into ‘target’ and ‘regulatory’ plasmids, respectively. When expressed, ParB sequestered target plasmids into a single cluster, which was inherited by one daughter cell only. Importantly, cells underwent multiple rounds of APP.

Next, the authors used this system to physically separate genetically distinct cells by linking motility to the presence or absence of a target plasmid encoding

a repressor that downregulates *motA* (a gene required for motility). During APP in mutant *motA* cells, the target plasmid is lost, leading to *motA* expression and motility. Last, the authors produced cells with four distinct differentiated states by introducing a second APP circuit.

In a second study, Mushnikov et al. engineered fusions of *C. crescentus* PopZ (a cell pole organizing protein that is stably maintained at single cell poles over multiple generations) and a phosphodiesterase into *E. coli*, which degrades the signalling molecule cyclic di-GMP (c-di-GMP). In their system, expression of the PopZ fusion is induced through either the introduction of a small molecule or light, using optogenetics. When expressed, the PopZ fusion accumulated at single cell poles, which were asymmetrically inherited, resulting in two distinct cell types that have either high or low c-di-GMP levels. The differences in c-di-GMP levels were used to drive differential gene expression patterns in daughter cells, resulting in cells expressing different biosynthetic enzymes or motility phenotypes.

Together, these two studies show that complex multicellular synthetic bacterial populations can arise from simple genetic circuits, with potentially useful applications.

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Credit: Lara Crow/Springer Nature Limited



ORIGINAL ARTICLES Molinari, S. et al. A synthetic system for asymmetric cell division in *Escherichia coli*. *Nat. Chem. Biol.* **15**, 917–924 (2019) | Mushnikov, N. V. et al. Inducible asymmetric cell division and cell differentiation in a bacterium. *Nat. Chem. Biol.* **15**, 925–931 (2019)