

Throw of a dice dictates a bug's life

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For an *E. coli* bacterium, 300 is its lucky number. That's about how many protein molecules it takes to make a life-changing shift in its diet preference, according to new research.

But this shift happens entirely by chance, says [Sunney Xie](#), a biochemist at Harvard University. "You don't know when it's going to occur. It's a random event."

While this may sound more like chaos theory and quantum mechanics than biology, it is how all living cells operate at the molecular level, from drug-resistant tuberculosis to stem cells, he says.

In *Escherichia coli's* case, Xie studied a simple trait: the ability to digest lactose sugar.

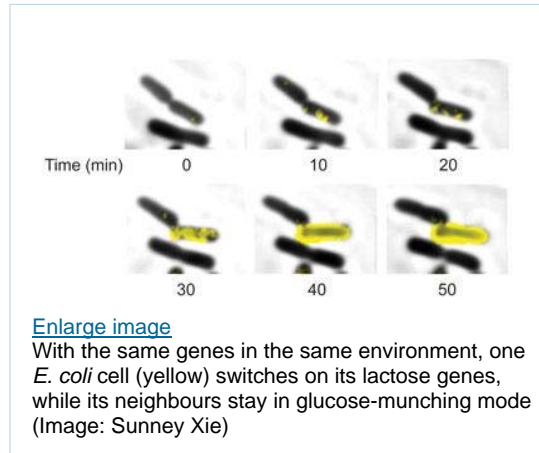
E. coli normally prefer to dine on a sugar called glucose. To conserve energy, bacteria shut down the genes that control lactose consumption when glucose is around. This is achieved with the help of a "repressor protein" that sits on the lactose genes.

However, when glucose runs out and lactose is available, evolution has come up with an ingenious solution to bring the lactose-digesting genes out of slumber.

Tipping point

A protein called permease sits in the cell's membrane and imports stray lactose molecules into the cell. These sugars latch onto the repressor protein, stopping its repressive activity, and allowing the lactose genes to switch back on.

This ensemble – called the *lac* operon – then



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produces more permease proteins that let in even more lactose, sending *E. coli* down a one-way street to lactose digestion.

Outlining this behaviour earned two scientists a Nobel prize in 1965. "The *lac* operon is like the hydrogen atom of molecular biology, it's the first system that describes gene regulation," Xie says.

His team sought to understand what happens at the tipping point between repressing and activating these genes under low levels of lactose in genetically identical bacteria.

"A single cell has to make a decision whether it wants to be induced or not," he says. "How is this life-changing decision made?"

To answer that question, Xie and colleagues Paul Choi and Long Cai, used a technology pioneered in their lab to count permease molecules tethered to a fluorescent marker protein.

They found that when a cell hit a critical threshold of about 300 permease proteins, the *lac* operon switched on in a burst of activity and the cell gained the ability to break down the sugar. With fewer molecules, a cell remains stuck in neutral.

Double grip

However, this flurry of activity is all controlled by the repressor protein, which grabs onto the *lac* operon at two different places.

Losing grip of one of these points allows for little bursts of lactose gene expression – enough to get a taste of the outside world – but cell division prevents cells from reaching 300 in this way.

The repressor protein must completely let go for a cell to reach the magic number, Xie says. And this happens by chance.

The random event allows the expression of more permease molecules, which means more lactose gets into the cell, and so the lactose genes are active for longer. Eventually a point is reached where the cell is switched to lactose digestion.

"It's a beautiful paper," says [Michael Elowitz](#), a molecular biologist at Caltech in Pasadena. "Trying to understand the behaviour of cells in terms of the behaviour of the individual molecules within them is one of the most fundamental goals of biology."

The bizarre behaviour of single proteins could explain why one tuberculosis-causing bacterium is antibiotic resistant, while another bacterium with an identical genome falls prey to drugs, Xie says.

Even our own cells depend on life-changing fluke events involving single molecules. While vastly more complicated than an *E. coli* bacterium, embryonic stem cells capable of turning into any kind of tissue probably make this decision with a small cast of molecules.

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