Genetically engineered bacteria have learned to play tic-tac-toe

E. coli bacteria modified to act like electronic components called memristors can be set up to act as a simple neural network and trained to play noughts and crosses

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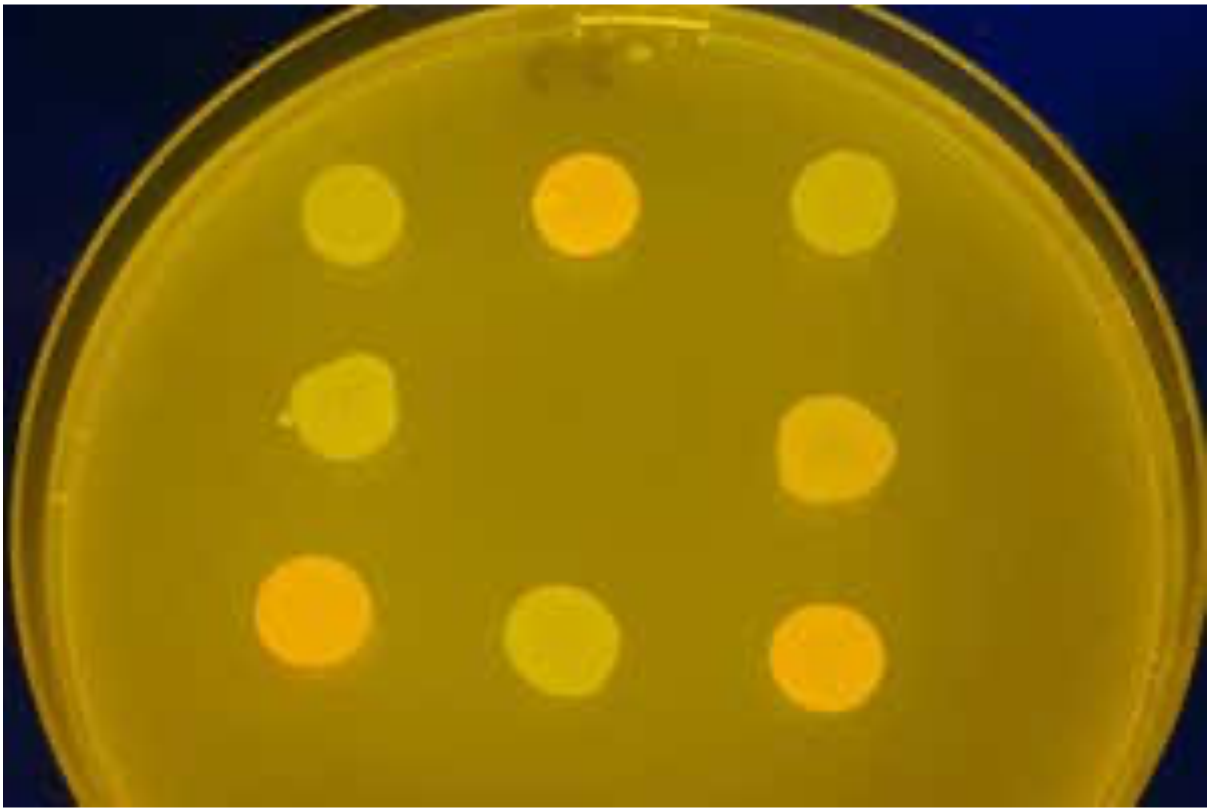

Wells of bacteria representing a tic-tac-toe grid
Alfonso Jaramillo/CSIC

For the first time, humans have played tic-tac-toe – also known as noughts and crosses – with bacteria. These were no ordinary bacteria, but *E. coli* extensively genetically modified and set up to act as a simple neural network, a form of artificial intelligence.

This approach could have all kinds of applications, from creating living materials capable of learning to making "smart" microbiomes, says Alfonso Jaramillo at the Spanish National Research Council.

He and his team started with an *E. coli* strain genetically modified to sense 12 different chemicals and respond by altering the activity of any genes the researchers chose. This strain, called Marionette, was created in 2019 by another group.

Jaramillo and his colleagues further modified the Marionette strain so that it had numerous copies of two bits of circular DNA, called plasmids, each coding for a different fluorescent protein: one red and one green.

The ratio of the number of these two plasmids – and hence the colour of the bacteria's fluorescence – isn't predetermined and can be altered by the 12 chemicals and by certain antibiotics. In the absence of any further input, this ratio remains constant and is thus a form of memory.

What's more, when the bacteria do get another input, the output – the colour resulting from the ratio of fluorescent proteins – depends on the previous ratio. This means that the bacteria behave in the same way as an electronic component called a memristor that is being used to create computer chips that mimic how the synapses in a brain work. Jaramillo calls these creations "memregulons".

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The team decided to teach these memregulons to play tic-tac-toe, as this is a benchmark often used to demonstrate new approaches in computing. The bacteria were grown in eight wells corresponding with the outer squares of a tic-tac-toe grid.

For simplicity's sake, the team assumed that the human player always starts and puts a cross in the centre square. The first bacterial nought is then placed on the square corresponding to the well with the reddest colour.

The human plays next and the bacteria are "told" of the move by one of the chemicals they can sense being added to each well – each chemical corresponds to one square. That changes the protein ratio in each well, indicating the next move. Each game takes several days as time is needed for the bacteria to respond.

"In the beginning, the bacteria play randomly," says Jaramillo. But they can be trained by "punishing" wells that play a wrong move with a dose of antibiotics.

After eight training games, the bacteria became expert players, says Jaramillo. The team simulated how the trained sets of bacteria play games, and these simulations show they could beat unskilled humans. But the researchers didn't play any further games after the training stage in which the bacteria lost every time, so *E. coli* have yet to actually beat humans at tic-tac-toe. "We did not bother to play those winning games," says Jaramillo.

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“[It] is a powerful demonstration of adapting a complex biological system to perform an entirely artificial task,” says Joanne Macdonald at the University of the Sunshine Coast in Australia. In 2006, Macdonald created a DNA-based computer that was unbeatable at tic-tac-toe.

“The tic-tac-toe game playing with bacteria is an excellent demonstration of their innovative work,” says Sangram Bagh at the Saha Institute of Nuclear Physics in India, who leads one of the two groups that have previously created bacteria-based artificial neural networks.

He isn’t convinced that Jaramillo and his team’s set-up meets the definition of an artificial neural network. “But still, it is a good strategy,” says Bagh.

Jaramillo says his system is a simple form of neural network known as a one-layer linear artificial neural network. His team is already creating more complex neural networks with the bacteria that can do tasks such as handwriting recognition, he says. “They can do very sophisticated things.”