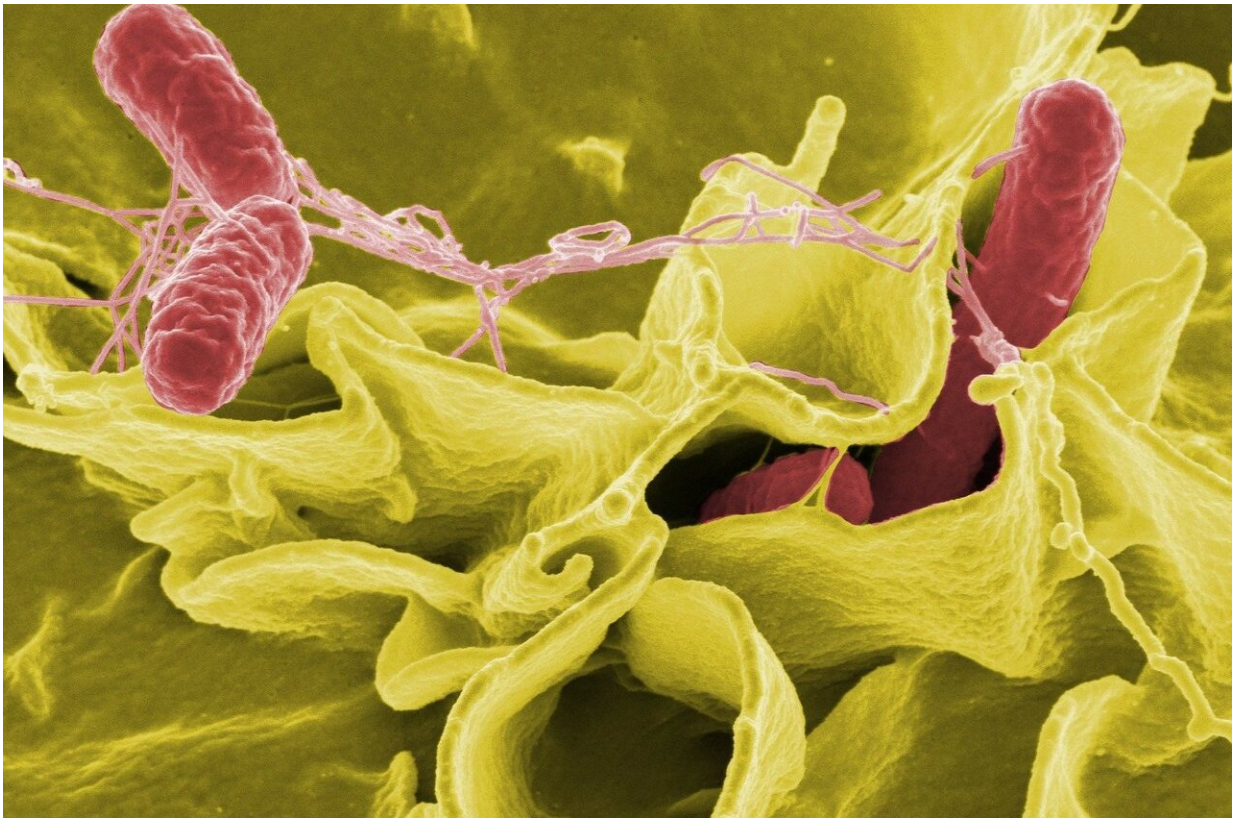
AI analysis of how bacteria attack could help predict infection outcomes

March 11 2021



Salmonella bacteria (red) cause up to a million deaths a year worldwide and there is a need for effective vaccines. New work from UC Davis shows how salmonella-specific T-cells can be stimulated to take up residence in the liver, ready to quickly fight off the infection. Credit: Rocky Mountain Laboratories, NIAID, NIH

Insights into how bacterial proteins work as a network to take control of our cells could help predict infection outcomes and develop new treatments.

Much like a hacker seizes control of a company's software to cause chaos, disease-causing bacteria, such as E. coli and Salmonella, use miniature molecular syringes to inject their own chaos-inducing agents (called effectors) into the cells that keep our guts healthy.

These effectors take control of our cells, overwhelming their defences and blocking key immune responses, allowing the infection to take hold.

Previously, studies have investigated single effectors. Now a team led by scientists at Imperial College London and The Institute of Cancer Research, London, and including researchers from the UK, Spain and Israel, has studied whole sets of effectors in different combinations.

The study, published today in *Science*, investigated data from experiments in mice infected with the mouse version of E. coli, called Citrobacter rodentium, which injects 31 effectors.

The results show how effectors work together as a network, allowing them to colonise their hosts even if some effectors are removed. The investigation also revealed how the host's immune system can bypass the obstacles the effectors create, triggering complementary immune responses.

The researchers suggest that knowing how the makeup of effector networks influences the ability of infections to take hold could help design interventions that disrupt their effects.

Study lead Professor Gad Frankel, from the Department of Life Sciences at Imperial, said: "The data represent a breakthrough in our

understanding of the mechanisms of bacterial infections and host responses. Our results show that the injected effectors are not working individually, but instead as a pack.

"We found there is an inherent strength and flexibility to the network, which ensures that if one or several components don't work, the infection can go on. Importantly, this work has also revealed that our cells have a built-in firewall, which means that we can deal with the hacker's corruptive networks and mount effective immune responses that can clear the infection."

Study co-lead Professor Jyoti Choudhary, from the Functional Proteomics Lab at The Institute of Cancer Research, London, said: "Our study shows that we can predict how a cell will respond when attacked by different combinations of bacterial effector proteins. The research will help us to better understand how cells, the immune system and bacteria interact, and we can apply this knowledge to diseases like cancer and inflammatory bowel disease where bacteria in the gut play an important role.

"We hope, through further study, to build on this knowledge and work out exactly how these effector proteins function, and how they work together to disrupt host cells. In future, this enhanced understanding could lead to the development of new treatments."

During their experiments, the team were able to remove different effectors when infecting mice with the pathogen, tracking how successful each infection was. This showed that the effector network produced by the pathogen could be reduced by up to 60 percent and still produce a successful infection.

The team collected data on more than 100 different synthetic combinations of the 31 effectors, which Professor Alfonso Rodríguez-

Patón and Elena Núñez-Berrueco at the Universidad Politécnica de Madrid used to build an artificial intelligence (AI) algorithm.

The AI model was able to predict the outcomes of infection with Citrobacter rodentium expressing different effector networks, which were tested with experiments in mice. As it is impossible to test in the lab all the possible networks that 31 effectors can form, employing an AI model is the only practical approach to studying biological systems of this complexity.

Co-first author Dr. David Ruano-Gallego from the Department of Life Sciences at Imperial, said: "The AI allows us to focus on creating the most relevant combinations of effectors and learn from them how bacteria are counteracted by our immune system. These combinations would not be obvious from our experimental results alone, opening up the possibility of using AI to predict infection outcomes."

Co-first author Dr. Julia Sánchez-Garrido, from the Department of Life Sciences at Imperial, added: "Our results also mean that in the future, using AI and synthetic biology, we should be able to work out which cell functions are essential during infection, enabling us to find ways to fight the infection not by killing the pathogen with antibiotics, but instead by changing and improving our natural defence responses to infection."

More information: "Type III secretion system effectors form robust and flexible intracellular virulence networks" *Science* (2021). science.sciencemag.org/cgi/doi … 1126/science.abc9531

Provided by Imperial College London