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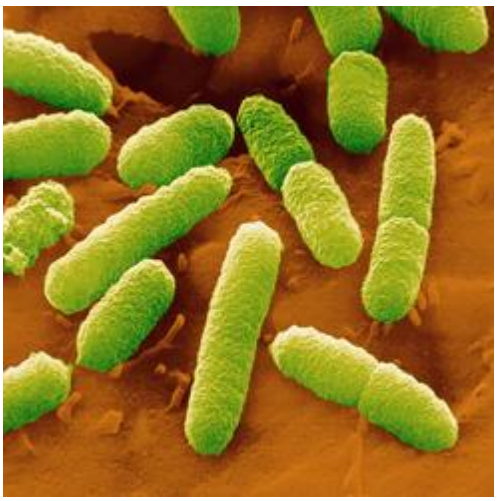
Chasing EHEC with the computer

Scientists in Saarbrücken provide free access to the enteric pathogen's genetic regulation data

Just a few genes make enterohaemorrhagic E. coli (EHEC) extremely dangerous to humans. If it were not for these genes, EHEC would hardly differ from harmless enteric bacteria. Bioinformatics scientists from the Saarbrücken Cluster of Excellence want to exploit this similarity to find starting points for effective drugs against the EHEC pathogen. In a very short time, the scientists have constructed EhecRegNet, a database and analysis platform that incorporates all known interactions between enteric E. coli genes. Using integrated simulations, genetic switches for the dangerous EHEC genes can be identified much faster and used medically. The virtual laboratory will thus help biomedical scientists and pharmacists all over the world to develop new drugs.



A few mutations in the genes is all it takes to turn the common enteric bacterium, Escherichia coli, into the dangerous enterohaemorrhagic E. coli (EHEC) strain.

All human beings carry roughly one to two kg of bacteria in their bodies. The most common enteric bacterium is *Escherichia coli*, which is also the best-studied microorganism on earth. "Its genetic composition has been documented in detail and we know of around 3,500 gene interactions, i.e., ca. 40% of the regulatory processes that go on in the bacterium," says Jan Baumbach, who heads a research group at the Cluster of Excellence for computer science at Saarland University. Together with his team at the Max Planck Institute for Computer Science in Saarbrücken, he quickly realised that the current rampant EHEC pathogen is closely related to normal intestinal bacteria. "We assume that no more than ten genes make the EHEC pathogen life-threatening. Some genes emerged a long time ago, over the course of evolution, but others were modified through an inter-bacterial exchange of plasmids. It is a kind of primitive sex that the bacteria use to transmit genetic information. This often leads to resistance to antibiotics", the bioinformatics scientist explains.

His research team has registered all the information concerning the harmless enteric bacteria's genome and interactions in a database, which also lists the genetic data of the dangerous EHEC pathogen. On the computer, the EhecRegNet system compares the genetic data of the EHEC bacteria with the data from harmless bacteria to track down genetic switches in EHEC. The goal is to use these switches to disable the genes which cause severe renal failure in some patients. "Genes can be switched on and off, much like a light bulb. But first you have to find the right switch. At the moment, you could say that we are throwing stones at the light bulb to put out the light. We still do not know where the switches are for EHEC, but we do know where they are located in evolutionarily related harmless bacteria. That is our starting point", says Baumbach. The computer simulations will allow scientists to locate the switches for dangerous

genes much faster than with expensive testing in biomedical laboratories.

Knowledge of around 80 to 90 per cent about interactions in normal enteric bacteria can be transferred to the EHEC pathogen by utilizing the computer simulations. This knowledge about harmless bacteria has been gathered by biologists and medical scientists over the last twenty years. "We cannot afford spending so much time with the EHEC bacteria, but we can take a short cut and use the available information about harmless bacteria and transfer knowledge about their genetic regulation to EHEC. It will save us time-consuming, expensive and even dangerous work in the laboratory", says Baumbach. Comparing the data on the computer is much faster. In this way, scientists hope to be able to find out which switches to flip in the genome in order to reduce EHEC's virulence.

Still, the scientist cautions against becoming too euphoric: "It may take years before a drug is actually approved for the market. However, it is possible that we will soon be able to pinpoint promising targets in experiments." The Saarbrücken-based scientists are therefore offering free access to their EhecRegNet web platform, in order to involve all biomedical scientists and pharmacists around the world in the search for drugs against the EHEC pathogen. "We envision a new generation of drugs which, in contrast to antibiotics, will not kill whole populations of bacteria. We want to use the genetic pathways in the bacteria to switch specific genes on and off", says Baumbach.

This could render the bacteria harmless or susceptible to the defence mechanisms of the immune system. "Perhaps this way we will be able to combat pathogens using their own genetic program in the future", Baumbach suggests. Less aggressive bacteria are often flushed out of the intestine with diarrhoea. The EHEC pathogens circumvent this natural mechanism with their strong adhesion to the intestinal wall.

Jan Baumbach's research group at the Saarbrücken Cluster of Excellence "Multimodal Computing and Interaction" at Saarland University has already constructed similar web platforms for corynebacteria which, among other things, trigger diphtheria, and for tuberculosis. With the help of complex computational methods, bioinformatics scientists use these platforms to compare harmless laboratory strains of bacteria with disease-causing bacteria. "Our computer simulations drastically reduce the number of necessary trials in animals and experiments in test tubes. This, in turn, cuts the time until medical scientists and pharmacists can develop drugs based on the genetic switches," Jan Baumbach adds.

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Get more information from us

Dr. Jan Baumbach
Saarland University Cluster of Excellence
Max Planck Institute for Informatics, Saarbrücken
Phone: +49 681 302-70880
Email: jbaumbac@mpi-inf.mpg.de

Address: http://www.mpg.de/4342889/EHEC_computer