Where bacteria hide

Many of the bacteria in our bodies live in walled mini cities. That has some very important medical implications, biologist **Anders Hakansson** tells **Robyn Braun**

Inside our bodies, bacteria hide in enclosed communities called biofilms. What are they?
They are a way that bacteria aggregate, usually in pretty intricate architectural features. They are like little cities, with towers and water channels. Different bacteria form different kinds of biofilms, but they always produce some kind of matrix around themselves that acts as a protective coating. Many bacteria, including *Streptococcus pneumoniae*, which causes pneumonia, use dead cells to do this.

How do these little bacterial cities work?
In the biofilm, bacteria act a lot like an organism. Different bacteria and regions within the biofilm have different functions. Some retrieve nutrients or fix nitrogen, some might be good at taking up DNA from within the biofilm, and some even sacrifice themselves for the benefit of the community.

The bacteria also communicate with one another. They can sense oxygen levels in their environment, so depending on their location, some might increase their metabolism or, if there are few nutrients, stop metabolising. We think of bacteria as individuals, but in biofilm communities they're also altruistic.

Most of us think of bacteria as single cells – when did people first begin to understand these biofilm communities?
Traditionally, to study disease, people always grew bacteria in culture in the lab. They didn't look directly at snot, for example. When we grow bacteria in a broth or on a plate, they always grow as single cells.

By the 1990s, we understood that bacteria grow in biofilms, and that these are associated with disease and the spread of disease. But it wasn't until the past decade that the link became clearer – for example, in 2006 researchers showed that people with chronic sinusitis had *S. pneumoniae* biofilms in the tissue that lines their sinuses.

Do biofilms help us understand how bacteria can make us sick?
Biofilms can survive on surfaces for a long time and their spread is key to disease transmission. Biofilms are also where bacteria hide from our immune system, which is just what they want – to be spread among people and get carried around.

The development of antibiotic resistance through the transfer of DNA from one

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bacterium to another can also happen in the biofilm. Until recently, we studied the transfer of genetic traits from one organism to another in infection models based on single cells, not biofilms. But for the many *Streptococcus* species, DNA transfer is much more efficient during biofilm colonisation. With Michael Federle at the University of Illinois at Chicago, we have actually shown that for certain types of *Streptococcus*, DNA transfer only happens in a biofilm.

What else do we know about the way that biofilms work?
We know that most of the time bacteria within biofilms don't make us sick. It is when they leave that they cause problems.

In the biofilm, bacteria are safe from our immune system, they only leave when our bodies become unsafe for them. So, say you catch a virus like the flu and you get all these symptoms – the bacteria may react by leaving the biofilm to look for a safer environment. Or you may be exposed to new bacteria that come in and shake things up, making the biofilm bacteria disperse to look for somewhere else to go. In both cases, there must be some kind of active signal that causes them to be released. We can use biofilm technology to study these signals, and if we can understand them, then maybe we can control them.

You invented a way to grow biofilms that more closely mimic how they function in our bodies. What tools were there before?
Previous biofilm models were grown on plastic in the lab, which is useful for studying kinds that grow on things like catheters, but completely different from what you find in our bodies. To get bacteria that only live in the body to form biofims on plastic doesn't help us to learn more about how they act inside us. In order to get them to form biofilms on plastic, you have to remove the external shells that protect them from our immune systems. If you put a bacterium without a shell into a mouse, for example, it won't form a biofilm and the immune system throws it right out.

PROFILE
Anders Hakansson is a microbiologist and immunologist at the University at Buffalo, the State University of New York, where he investigates the bacteria that cause pneumonia. He has developed a way to grow bacterial biofilms that behave as they would if they were inside the human body

Photographed for New Scientist by Finn O'Hara

So how did you make a better model?
We were interested in an antimicrobial protein complex in human milk known as HAMLET, which causes tumour and bacterial cells, but not healthy cells, to die off. We knew we could kill bacteria with it. But we began to understand that the bacteria we were targeting made biofilms that made them more antibiotic-resistant. We needed a model system to test whether our protein could kill the bacteria in a biofilm.

So we made a surface out of the human epithelial cells that make mucus. We grew a biofilm on this that contained everything it would have had if it had been inside a person.

Did the milk protein cause bacteria to die in your realistic biofilms?
The HAMLET protein complex doesn't work terribly well against biofilms on its own, because they are very resistant to antibiotics. But we've noticed that HAMLET has a tendency to sensitise bacteria to antibiotics. So the combination of HAMLET and antibiotics can be effective.

What other kinds of antimicrobials or vaccines might destroy biofilms?
It depends on the type of bacteria and where they are in our bodies. There's a lot of work being done to figure out how to disperse the bacteria in biofilms, which makes them more susceptible to antibiotics.

That approach could cause problems though. More than half of biofilm bacteria don't cause disease while they are in the biofilm – they're not actually bad for us and in some cases they might even be good for us. Intestinal flora that make biofilms in our gut can help protect us from harmful bacteria, for instance. Getting rid of them would change the make-up of the microflora in our bodies, which can introduce its own problems. Adapting to these microbes has been a long evolutionary process. They sometimes make us sick, but we don't know if it might cause more trouble to have different bacteria there.

Are there other approaches that could destroy harmful biofilms?
There are materials in development that make it more difficult for bacteria to form biofilms in the first place. This would be ideal for things like catheters and tools in hospitals.

But we should bear in mind that we evolved with these microorganisms. Most of us need some exposure to bolster our immune systems. Beyond that, of course, the best strategy is to remember to wash your hands. ■