

Evolutionary Biology in Zürich, Switzerland

A Genomic Parasite

Mobile genetic elements are mostly deleterious. So why do they exist? Looking at the epidemiology of human disease through the eyes of an evolutionary ecologist can help us to understand.

If you look at Andreas Wagner's research topics, you will quickly see that his lab in Zurich tackles questions about genes, metabolic networks and even human-chimpanzee divergence. All of which have something in common: evolution. Wagner accepts that his interest in this topic goes back to his high school days. He then launched a career as a molecular biologist and, "as computation became more important to the field", he started to use mostly computational techniques to address his questions.

Simple insertion sequences

Transposable elements in genomes are one of the subjects that have caught his attention. The idea that genes can move around goes back sixty years and it was in the eighties when scientists started to suspect that these "jumping genes" could be harmful to their hosts. Now it is known that their effects are indeed, most of the time, deleterious. So why don't hosts get rid of them? There is more than one answer to this question, including the fact that from time to time these elements can be beneficial. But to deal with this problem, Wagner dug deep into evolutionary dynamics.

Wagner's first question was how long transposable elements generally stay in a genome? In order to answer this, he focussed on insertion sequences (ISs), which are one of the simplest types of mobile DNA. He and his team made genomic comparisons of the most important IS families in more than 350 completely sequenced bacterial genomes and looked at the divergence among them.

In 2006, he published the results of this analysis, which showed that IS within bacterial genomes present very low variation (*Mol. Biol. Evol.* 23(4): 723-33). This implies that these transposable elements actually stay in the same genome for

a rather short time, otherwise they would have greater opportunity for evolutionary divergence. So how can we explain the fact that, in general, these sequences were acquired only recently?

One possibility would be that they are quickly eliminated from the genome. But this idea contradicts experimental evidence that transposable elements, in general, tend to accumulate very rapidly once they enter a genome. The alternative explanation would be that the genomes harbouring insertion sequences for a long time tend to become extinct. But if they seem to be deleterious in the long run, why do they stay in the genome for some time and are not eliminated immediately? Of course, there might be a transitory selective advantage; however, Andreas Wagner has also been thinking about it from another perspective.

Borrowing an epidemiological model

While studying the mechanisms of bacterial transposable elements, Wagner started to think about their resemblance to epidemiological processes. Human diseases



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transposable elements: they can spread by horizontal gene transfer and can be inherited from the mother cell genome. "The disease agents harm the organism but before killing it, they spread to other organisms. Maybe it is useful to think of transposable elements, and IS in particular, as disease agents," suggests Wagner.

Horizontal gene transfer

Working under this analogy, his group started to design a model to understand the evolutionary dynamics of mobile DNA using epidemiological tools. Daniel Rankin, first author of the paper in which the results of this work were presented, did most of the modelling. He had previously worked in a behavioural ecology group and was gradually getting interested in questions to do with bacteria. Today, he is fascinated by the topic. "A lot of microbiologists are interested in the details but do not necessarily focus on an evolutionary ecology perspective," Rankin explains. He is particularly interested in the social evolution of microbes and was predominantly attracted by the roles of mobile DNA in prokaryotes.

Wagner, Rankin and Manuel Bichsel, another student in Wagner's group, started with a simple model inspired by human diseases (*J. Evol. Biol.* 23(11): 2422-31). They assumed a population of bacteria – the equivalent of a human population in epidemiological models – where two types of cells were to be found: those free of mobile elements (MEs) – healthy people – and cells carrying MEs in their genomes – humans infected with a particular disease agent.

The model uses the typical parameters used for ecology, including birth and death rates. But there were also two other param-



Photo: Nicolas Righetti, SIB

Andreas Wagner at the center of the umbrella association

are basically transmitted in two ways: horizontally via infection and vertically from parent to offspring. The same applies to

eters relevant to the questions asked here: the transmission rate of MEs, which can also be seen as the rate of Horizontal Gene Transfer (HGT); and the mortality rate induced by MEs. Sticking again to the analogy of epidemiological processes, we can compare HGT with the rate of disease transmission among humans and the mortality rate with the severity of the disease.

Horizontal gene transfer as the key

The Swiss team extended their first simple model into another one that, in addition, takes into account the number of MEs carried in the genome, which makes the cost of bearing one of these elements change, depending on the copies acquired. They even included a third complementary model, which resembles the metapopulation approach in ecology. In this case, instead of assuming a well-mixed population, space is modelled as patches inhabited by small sub-populations of bacteria.

The three related models resulted in similar outcomes. Rankin *et al.* found that, under certain conditions, MEs can indeed drive their host to extinction. One of the important factors involved is HGT. If there is no transmission or if it is too low, deleterious mobile DNA is not even able to persist. On the other hand, the cost (or mortality) caused by carrying these sorts of elements shouldn't be too high, because in that case MEs would never be able to invade the population. So a necessary condition for not being driven to extinction is that the mortality rate is smaller than the HGT rate. The same applies to humans: if people die because of the severity of the disease prior to transmitting it, the probability of spreading the disease agent is very low.

The challenge of time and space

The model gives a reasonable picture of the dynamics of transposable elements but some challenges remain. One of them is timescale. Human diseases typically spread over a much shorter timescale than that of evolution. Also, transposable elements spread more slowly than human diseases and, as Wagner suggests, "Their evolutionary dynamics plays out on a timescale that is an uncomfortable intermediate between laboratory timescales (<104 generations) and timescales at which molecular clocks measure time through nucleotide substi-

tutions (>107 generations)." Their model does not take into account these differences in time, nor the fact that the spreading of ISs within the genome is slower than the generation time of the organism. They are, however, interested in improving this, which could bring about interesting insights into the evolutionary dynamics of mobile DNA.

A second challenge is space. Analytical models, in general, assume well-mixed populations. But in this kind of phenomena, it is also important to have spatially explicit models. Over the next few months, Wagner and colleagues will also work to implement this. The main question is how much HGT is required in an explicit spatial structure to sustain transposable elements. The answer is still unknown but local dynamics, as observed in other models, could prevent the extinction of the population, as observed in analytical models.

Moreover, Wagner also considers an alternative explanation to the high similarities in IS within the genome, "The extinction of populations (as the outcome of the model) is a possibility but not a certainty." He is still unsure whether the transposable elements would really cause the extinction of the population or just the death of individual cells within the population – whether the cells that harbour ISs the longest would be wiped out first. That would also explain the short life of ISs. An issue Wagner and co. are about to clarify with further work.

Theory and practice

Wagner's group in Zurich has just entered its fifth year. He himself believes that there are only a few universities in the world that are able to offer the same kind of resources and intellectual environment. Wagner's funding comes, in part, from the university but he receives more than half from third parties, mainly the Swiss National Science Foundation.

Of course, mathematical modelling and computational approaches are the tools that Wagner's group will continue to use. Nevertheless, Andreas Wagner considers himself to be more of an evolutionary biologist than a pure theoretician. "In my view, this distinction between theoretical and experimental biology is somehow artificial. All that matters is that we ask real biological questions."

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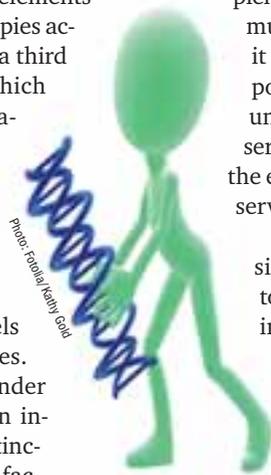


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Mobile DNA dynamics?