Animal Foraging Meets Viruses

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Talk is one of the most important ingredients in creativity, in the bringing together disparate subjects to create a new synthesis. One of the many advantages of having Larry in the Department was that he was around for a chat, especially during morning tea time and lunchtime. The origin of the paper that we published together (Wang et al, 1996) grew out of these chats. I, DD, am acting as the narrator here since I played the least important role in the genesis of this paper.

In the early 1990s, the topic of evolution of virulence was popular. The major idea is that there is a trade-off between growth rate of the pathogen as expressed in virulence and transmission rate of the pathogen between individuals. If the virulence was too high, the infected individual was likely to die before the pathogen could be transmitted to another individual. While, if the virulence was too low, the rate of transfer would be so low that, even though the host survives, that transfer to another host is unlikely. Ing-Nang was interested in understanding the mechanistic causes of the assumptions used for formulating the transmission rate-virulence tradeoff hypothesis, and looked into literature on myxoma virus, where it had been shown that virulence is optimized to promote efficient transfer between rabbits (summarized in Richardson, 2001). Initially, when the rabbit was highly sensitive to the virus, virulence of the virus decreased. After the rabbits had been selected for increased resistance to the virus, higher virulence was selected in the virus. To understand this mechanistically, one has to understand the dynamics of virus accumulation inside an infected rabbit. Unfortunately, this information doesn't exist. However, there is information on how bacteriophages grow. The number of phage progeny within a cell accumulated relatively linearly. However, at the time of lysis, when the cell breaks open and releases the progeny phage, the burst size, or number of phage released, is usually much smaller than what an infected cell could produce, i.e., the resources to produce more phage had not yet been exhausted. As near as I remember, it was during one of these conversations that Larry suggested that animal foraging theory could be applied to virus behavior. The phage should lyse the cell early, before the resources were exhausted, if there are many other cells (patches) to infect, but should wait if the are few cells (patches) to infect. This triggered in Ing-Nang's memory. He had given an answer a few years back on the qualifying exam,

where in desperation, he had imagined what a virus would do, thinking of the virus as a little animals that foraged around for cells to infect. Thus the optimal burst size and lysis time for a virus was derived from equations isomorphic with animal foraging theory. Data from Ry Young's seminal review paper (Young, 1992) describing the lysis systems of various phages, supported the theory. We wrote the paper.

This paper starts with a very simple question: Why do phages lyse their hosts so much earlier than the time required for maximum burst size? The parallel is between each individual infected bacterial host and the patch for a foraging animal. As time goes on, more phage progeny will accumulate linearly inside the host. But by lysing the host, the released progeny can start many infections simultaneously and so increase faster. Just as a foraging animal should decide when it is best to stay in a patch and continue foraging or to move on to another fresh, unexploited patch, the phage should "decide" how long it is optimal to forage on the current host before lysing the host and infecting other hosts in the environment. That is, the optimal lysis time is a compromise between current, guaranteed linear increase and future, potential exponential increase. As a result, the density of the host in the environment should be the most important factor for a phage to decide when to lyse a host. By using the marginal value theorem from the animal foraging theory, we derived the condition and showed that (1) there should be an optimal lysis time under any host condition, and (2) a phage should evolve to a shorter optimal lysis time when it habitually encounters high host density or quality, and vice versa.

These predictions have been tested experimentally. For the first conclusion, a recent empirical study using isogenic strains of phage λ that only differ in lysis times showed that, under the laboratory condition, there exists an optimal lysis time (Wang, 2006). Furthermore, a recent result also shows that the optimal lysis time is shortened when the phage can "find" its host faster (Shao and Wang, unpublished result). Currently, there is an ongoing experiment to demonstrate that phage λ with suboptimal lysis times will evolve to an optimal lysis time given the experimental conditions.

The full impact of this paper has not yet been realized. The number of citations per year is rising. The approach of this paper is very different from the approach usually taken in the field of microbial experimental evolution. Instead of demonstrating an ecological or evolutionary principle, this paper simply tried to explain an observed phenomenon in microbiology, using a readily available conceptual framework from behavioral ecology. The approach is very similar to Larry's work on red tides: using principles in population biology to solve a specific and real problem. In the process, we found something interesting.

Ry Young was always puzzled by the saltatory nature of phage lysis (personal communication, I.-N. Wang). A typical lysis curve usually shows a steady increase of culture turbidity followed by a sudden and precipitous drop (Young, 1992). Before lysis, the bacterial culture seems normal, like nothing is happening. But a few minutes later, the culture clears, with most cells lysed. Under controlled conditions, a difference of a minute or two in lysis time can be easily and reproducibly differentiated. The abruptness of phage lysis was further demonstrated by an ingenious experiment using individually tethered *E. coli* cells (Gründling et al, 2001). The experiment showed that the membrane integrity (hence the physiology) of the infected host remained normal right before the scheduled lysis, even though large amount of holin protein (the phage protein that determines the lysis timing) has already been accumulated on the cell membrane (Chang et al, 1993). These observations make sense in the light of the hypothesis of optimal lysis timing. It can be reasonably argued that the selective pressure is such that not only is it important for a phage to release progeny into the environment at the opportune time, but also maximally exploit the current host up until the time of lysis. To do this, the phage should not disturb the cell physiology (via maintaining membrane integrity), allowing progeny production to proceed at the maximum allowable rate (Wang et al, 2000). Therefore, the pattern of seemingly normal host growth before lysis is shaped by natural selection. The model is specific to the system, but provides insights into how other transitions in state may be selected for.

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