Physical Models of Living Systems Prologue: A Breakthrough on HIV

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Los Alamos, 1994

Alan Perelson was frustrated. For some years, he, and many other researchers, had been staring at an enigmatic graph (Figure 0.1). Like any graph, it consisted of dry, unemotional squiggles. But like any graph, it also told a story.

What made HIV so dangerous was precisely the enigmatic feature of the graph: After a brief spike, the concentration of virus particles in the blood fell to a low, steady level. Thus, after a short, flu-like episode, the typical patient had no serious symptoms, but remained contagious, for up to ten years. Inevitably, however, the virus level eventually rose again, and the patient died.

In the early 1990s, many researchers believed that these facts implied that HIV was a slow virus, which remained in the body, nearly dormant, for years before rising sharply in number. But how could such a long latency period be possible? What was happening during those ten years? How could the patient’s immune system fight the virus effectively at first, and then ultimately succumb?

Perelson and others had suspected for some time that during the apparent latency period, HIV might not be slow or dormant at all. He made an analogy to a physical system: If we see a leaky container that nevertheless retains water at some steady level, we can conclude that there must be water flowing into it (Figure 0.2). But we can’t determine how fast water is flowing in. All we can say is that the rate of inflow equals the rate of

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**Figure 0.1:** [Sketch graph.] The time course of HIV infection, representing the progression of the disease as it was understood in the early 1990s. After a brief, sharp peak, the concentration of virus particles in the blood (viral load) settled down to a low, nearly steady level for up to ten years. During this period, the patient showed no symptoms. Ultimately, however, viral load increased and the symptoms of full AIDS appeared. [After Weiss, 1993.]
outflow. Both of those rates could be small—or both could be large. Applying this idea to HIV, Perelson realized that, during the long period of low blood concentration, the virus might actually be multiplying rapidly, but after the brief initial episode, it could be eliminated by the body just as rapidly.

A real leaky container has another simple property reminiscent of the HIV data: Because the outflow rate $Q_{\text{out}}(V)$ increases as the volume of the water (and hence its pressure at the exit point) goes up, the system can self-adjust to a steady state, no matter what inflow rate $Q_{\text{in}}$ we select. Similarly, different HIV-infected patients have quite different steady levels of virus concentration, but all maintain that steady level for long periods.

Perelson was head of the Theoretical Biology and Biophysics Group at Los Alamos National Laboratory. By 1994, he had already developed a number of elaborate mathematical models in an attempt to see if they could describe clinical reality. But his models were full of unknown parameters. The available data (Figure 0.1) didn't help very much. Without some better knowledge of the underlying cellular events giving rise to the aggregate behavior, how could he make progress?

**New York City, 1994**

David Ho was puzzled. As the head of the Aaron Diamond AIDS Research Center, he had the resources to conduct clinical trials. He also had access to the latest anti-HIV drugs and had begun tests with ritonavir, a “protease inhibitor” designed to stop the replication of the HIV virus.

Something strange was beginning to emerge from these trials: The effect of treatment with ritonavir seemed to be a very sudden drop in the patient’s total number of virus particles. This was a paradoxical result, because it was known that ritonavir by itself didn’t destroy existing virus particles, but simply stopped the creation of new ones. If HIV were really a slow virus, as many believed, wouldn’t it also stay around for a long time, even once its replication was stopped? What was going on?

Also, it had been known for some time that patients treated with antiviral drugs got much better, but only temporarily. After a few months, ritonavir and other such drugs
always lost their effectiveness. Some radically new viewpoint was needed.

Hilton Head Island, 1994
Perelson didn’t know about the new drugs; he just knew he needed quantitative data. At a conference on HIV, he heard a talk on a different topic by one of Ho’s colleagues, R. Koup. Intrigued, he later phoned to discuss Koup’s work. The conversation turned to the surprising results just starting to emerge with ritonavir. Koup said that the group was looking for a collaborator to help make sense of the strange data they had been getting. Was Perelson interested? He was.

Ho and his colleagues suspected that simply measuring viral populations before and after a month of treatment (the usual practice at the time) was not showing enough detail. The crucial measurement would be one that examined an asymptomatic patient, not one with full AIDS, and that monitored the blood virus concentration every day after administering the drug.

More clinical trials followed. Measurements from patient after patient told the same story (Figure 0.3): Shutting down the replication of virus particles brought a hundredfold drop in their population in 2–3 weeks.

Perelson and Ho were stunned. The rapid drop implied that the body was constantly clearing the virus at a tremendous rate; in the language of Figure 0.2, \( Q_{\text{out}} \) was huge. That could only mean that, without the drug, the production rate \( Q_{\text{in}} \) was also huge. Similar results were soon obtained with several other types of antiviral drugs. The virus wasn’t dormant at all; it was replicating like mad. We’ll see in Chapter 1 how analysis of the data yields a numerical value for \( Q_{\text{out}} \). Using this measurement, the researchers estimated that the typical asymptomatic patient’s body was actually making at least a billion new virus particles each day.\(^1\)

\(^1\)Later, more refined estimates showed that the average production rate was actually even larger than this initial lower bound.
As often happens, elsewhere another research group, led by George Shaw, independently pursued a similar program. This group, too, contained an “outsider” to AIDS research, a mathematician named Martin Nowak. Both groups published their findings simultaneously in *Nature*. The implications of this work were profound. Because the virus is replicating so rapidly, it can easily mutate to find a form resistant to any given drug. Indeed, as we’ll see later, the virus mutates often enough to generate every possible single-base mutation every few hours. Hence, every infected patient already has some resistant mutant viruses before the drug is even administered; in a couple of weeks, this strain takes over and the patient is sick again. The same observation also goes to the heart of HIV’s ability to evade total destruction by the body: It is constantly, furiously, playing cat-and-mouse with the patient’s immune system.

But what if we simultaneously administer two antiviral drugs? It’s not so easy for a virus to sample every possible pair of mutations, and harder still to get three or more. Thus, treatment with three drugs stops replication, because there is no preexisting triply-resistant subpopulation. And with no replication, there is no opportunity for further mutation. Indeed, subsequent work showed that “cocktails” of three different drugs, administered simultaneously, can halt the progression of HIV infection, apparently indefinitely. The patients taking these drugs still carry low levels of the virus; they have not been cured. But they are alive, thanks to the treatment.

The message
This book is about basic science. It’s not about AIDS, nor indeed is it directly about medicine at all. But the story just recounted has some important lessons. The two research groups mentioned above made significant progress against a terrible disease. They did this by following some general steps:

1. Assemble (or join) an interdisciplinary team to look at the problem with different sets of tools;
2. Apply simple physical metaphors (the leaky container of water) and the corresponding disciplines (dynamical systems theory, an area of physics) to make a hypothesis; and
3. Perform experiments specifically designed to give new, quantitative data to support or refute the hypothesis.

This strategy will continue to yield important results in the future.

The rest of the book will get a bit dry in places. There will be many abstract ideas. But abstract ideas do matter, when you understand them well enough to find their concrete applications. In fact, sometimes their abstractness just reflects the fact that they are so widely applicable: Good ideas can jump like wildfires from one field to another. Let’s get started.

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2 Actually the fact of mutation had already been established a few years earlier. Prior to the experiments described here, however, it was difficult to understand how mutation could lead to fast evolution.