Viral Shapeshifters

Strange Behaviors of HIV and Other Viruses

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To Keith, Volodya and James.

Without your help and support in the past, the research,
and thus this book, would not have been possible.

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Contents

Acknowledgments vi

Preface vii

1. Fighting Diseases with Computers and Disorder 1

2. A True Viral Shapeshifter: The HIV-1 8

3. The Smallpox Virus 23

4. Louis Pasteur and the Rabies Virus 34

5. The Poliovirus 40

6. A Tale of Two Little Viruses: The Coronaviruses 48

7. The 2014 Ebola Outbreak 63

8. A Family of Mostly Insect Hitchhikers 77

9. Herpes Simplex Viruses 89

10. Fighting Cancers and Infections 98

11. Epilogue 104

Appendix: Basic Biochemistry and Virology 109

General References on Biochemistry and Virology 112

Chapter References 113

Glossary 121

About the Author 127

Sample

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Preface

The story in this book is about a scientific adventure spanning over a decade of research that includes the building of a database of shell disorder with currently over 300 viruses. It also involves a discovery of specific odd behaviors of viruses, including some of the most dangerous ones. The behaviors pertain to the varying disorder observed at different shell levels. Most peculiar is the abnormal level of disorder found at the outer shell of HIV-1. I believe that this solves a mystery that has been plaguing the field of HIV vaccine research for more than 30 years. In actuality, the legendary Oswald Avery had unknowingly unveiled the answers to this mystery in a classic experiment in the 1920s, but its full implication was not realized until the publication of my scientific papers and now this book.

I have coined the phrase "viral shapeshifting" to explain the above-mentioned odd behaviors. The word "shapeshifter" originally arose in mythology, and later appeared also in the science fiction series Star Trek. It refers to creatures that change their shape to move among humans without detection. The analogy is striking. The true viral shapeshifter moves easily within the host body, with the immune system fumbling to keep it in control or to pinpoint its location. The HIV-1 is not the lone shapeshifter, even if it is the best known human virus as far as immune evasion is concerned.

The levels of disorder at different shells offer various evolutionary advantages to viruses. While the HIV, HSV-II (Herpes Simplex Virus II), and, to some extent, HCV (Hepatitis C Virus) show signs of being true viral shapeshifters in terms of shell disorder, other viruses could also show some signs of being shapeshifters, exhibiting various characteristics that could

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help them survive better in the host. However, being a viral shapeshifter apparently comes at a cost to the virus by lessening the chances of the survival of the virus in non-physiological environments.

While the true viral shapeshifter has a well-known history in causing carnage that involves death by the millions, there is a silver lining to our greater knowledge of how viral shapeshifting works to evade the immune system. Implications of this include applications to oncolysis, which involves using viruses to "attack" cancer cells, and viral chemotherapy of fungal and bacterial infections. The concept of viral shapeshifting suggests ways to evade the immune system to make the treatments more effective.

This book has been written in a way that is hopefully accessible to the lay person[1], while also being interesting to scientists. Each chapter after the first covers a different commonly known virus, or a family of viruses, that is often highly virulent. The chapters usually start with stories of human interactions with the virus, or relatives of the virus. Each virus has its story. Unless a critical part of the story would be missing without introducing them earlier, the physiology and shell disorder of the viruses are elaborated towards the end of each chapter. In this way, the lay reader can enjoy most of a chapter, and then attempt to comprehend its later part before moving to the next chapter. The summary at the end of each chapter highlights key takeaways.

References are indicated as, for example, (3), and collected at the end of the book.

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[1]An appendix and a glossary are at the end of this book.

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1.

Fighting Diseases with Computers and Disorder

The Rise of Modern Biology

In the last two centuries, there have been two revolutions that are of interest to us. The first was the rise in biochemistry and molecular biology. Modern biology came about with the work of Antoine van Leeuwenhoek, Robert Koch and Louis Pasteur (22, 34). Leeuwenhoek, a businessman who owned optical stores, was the first to discover bacteria using the microscope. He experimented with lenses to build optical instruments that were so powerful that they could be used to observe microscopic organisms. Of course, the microscopes then were only able to see bacteria and fungi, not the smaller viruses, unlike the powerful electron microscopes we have today. We will see images of some viruses arising from modern microscopy in later chapters.

Louis Pasteur, who is also known as the father of modern microbiology, developed vaccines for fowl cholera and rabies. A better understanding of modern biology came about when the chemistry of proteins was understood. While DNA and RNA are the blueprints for building the machinery that drive cells, proteins are the actual machines. Linus Pauling discovered a common helical structure, the alpha helix, among proteins. Breakthroughs in the field of physics, such as X-ray crystallography, were crucial for providing invaluable tools for experiments used to elucidate the structures of various proteins (35).

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Many of the functionalities of a protein can be traced to its structure. The structure of a protein is based on its amino-acid composition. Amino-acids, which are the building blocks of proteins, are linked in a chain. The discovery of DNA as the blueprint for the design of proteins in 1953 became a milestone for the birth of molecular biology. Since the amino-acid sequence of a protein can be inferred from the nucleotide sequence of the corresponding RNA or DNA, the information about the composition of a protein became more easily accessible as more efficient techniques became available for the rapid sequencing of DNA.

The Biology of Protein Intrinsic Disorder

Proteins have been observed to have various structures. The structures can take the form of loops, alpha helices or sheets. These structures, more specifically secondary structures, can be linked to the functionalities of the proteins (36). There are however puzzles that keep appearing in the structure-function paradigm. One such puzzle is the open secret that many proteins have never been successfully crystallized. If structures are related to the protein functions, how could there be such a thing as a structure-less protein or disordered proteins? The answer is: Protein disorder itself plays various roles for the proteins (18,19). “Protein intrinsic disorder” refers to the lack of structure in either parts of the protein or the entire protein. The protein disorder is sometimes referred to by other terms: “structure-less”, “unstructured”, “unfolded” or “flexible”.

One of the many roles that protein disorder plays is to recognize potential binding partners such as other proteins, sugars and DNA/RNA. The ability to recognize potential binding partners is an important aspect of biological processes. Based on experience, biochemists do have an idea of which proteins are easy to crystallize and which are not. With this knowledge, attempts to build disorder predictors were made as far back as in the 1990s. With the availability of advanced computing techniques and hardware, better tools have since been developed.

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Artificial Intelligence and Computer Technology

Another revolution that is important to this book is the computer revolution. We have come a long way since the first computer, ENIAC, was constructed by the US Army within the University of Pittsburgh campus in 1945. This computer was incredibly slow by today's standards and occupied a large area of around 2,000 square feet, which exceeds the size of many family houses. The IBM PC was first introduced in 1981, while Macintosh Apple went on sale in 1984. Along with the advances in hardware technology, there were also great strides in the art and science of software development. Among the areas most important to us are the techniques of artificial intelligence (AI) and database development. Various approaches in AI have been introduced (37). A predominant one involves the use of neural networks (NN), which basically attempt to mimic the brain by sending signals between nodes (points where signals meet). Neural networks have been used for pattern recognition, such as face and speech recognition. Facebook uses similar face recognition software to tag friends.

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Tools for Protein Intrinsic Disorder: Computer Science, Chemistry and Physics Meet Biology

The advances in modern biology and computer science provide us with endless opportunities that we have only begun to realize. One application that is of course of great importance is the application of computer technology to study protein intrinsic disorder. Given that crystallographers know which proteins can be crystallized and which are difficult, if not impossible, it became feasible to build a protein disorder predictor. The earliest predictor known was built by a group at the Washington State University (WSU), Pullman, under the leadership of Keith Dunker. It is referred to as the PONDR(r)-VLXT, and was built before 1998 (8, 9).

Initially, a simple model was built using the statistical technique, regression analysis, involving correlating the disorder prediction with the sequence of the protein. Based on biochemistry and observations, it has been known that hydrophobic (water repelling) residues tend to bring order, whereas hydrophilic (water attracting) ones do otherwise.

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That model was later replaced by a neural network. PONDR(r)-VLXT in its current form is a neural network that is trained on proteins that are known to be either ordered or disordered (Figure 1.1). Even as other disorder predictors became available as highly accurate tools for crystallographers who need to know which proteins are crystallizable, PONDR(r)-VLXT remains the most accurate predictor when used to study protein-protein interactions (10-12).

Figure 1.1 shows the steps involved in building a protein disorder database. Over a decade of research, the author has built a viral shell disorder database of over 300 viruses. The task is a multidisciplinary approach involving mathematics, statistics, computer science, biochemistry and biophysics.

Between graduate schools in chemistry and computer science respectively at the University of Idaho, I did a stint at the WSU Department of Biochemistry, where I became acquainted with Keith. The UI and the WSU campuses are across the state line just 8 miles apart. Keith later accepted a job offer to lead a newly formed center and I was offered a job to work under him at the Center for Computational Biology and Bioinformatics (CCBB) at the Indiana University School of Medicine, Indianapolis. During that time, I had the pleasure of meeting a Russian biophysicist, Vladimir Uversky, who had also been working on disorder since the 1990s and had then joined the same lab at Indianapolis in a supervisory position. Volodya (Vladimir) is now an Associate Professor at the Department of Molecular Medicine, University of South Florida.

It was at Keith's laboratory that I became familiarized with the disorder tools and had the opportunity to write computer programs to help further the applications. I am also grateful to James Foster, a computer science professor at the University of Idaho School of Biological Sciences for allowing me to complete my computer science degree while working at CCBB.

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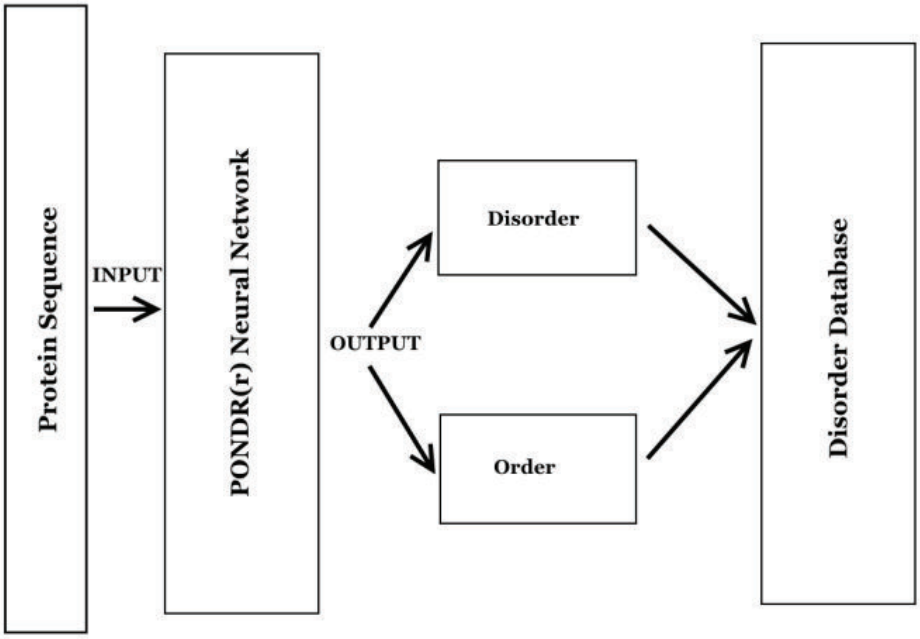

Figure 1.1: Steps involved in building a disorder database. PONDR(r) input is the amino-acid sequence of the protein of interest and the output will predict if each residue is ordered or disordered based on the training of the neural network with known ordered and disordered sequences respectively.

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Wearing Many Hats

Like many of my co-workers, my now ex-boss and I, it is not uncommon for researchers in the field of computational biology to come from non-traditional backgrounds. In fact, Keith and Volodya came from chemistry, physics and biophysics backgrounds.

As for me, the story is a little more complicated. As far back as when I was in grade school, I was fascinated by both the physical and biological sciences. I remember that I used to keep a journal with notes of all the famous biomedical scientists when I was in the 5th grade (or Primary 5 as it is known in Singapore). I also still recall with a mischievous smile a time when I lost interest in all my schoolwork in 8th grade (Secondary 2) because there was little that interested me. A certain Brother Godfrey, who was the disciplinary master at the Catholic high school, St. Joseph's Institution, that I attended, inspected my schoolbag one day only to find it immac-

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ulately clean and empty, apart from my sister's college chemistry textbook! Despite my obvious juvenile delinquencies, I was able to make it through high school and college.

But during my undergraduate years at St. Mary's College in California, I was discouraged from studying the sciences by my dad, who was a small business entrepreneur and wanted me to follow his footpath. Besides, I had no close relatives who were scientists and therefore I did not have a tangible role-model to follow, even though I had relatives who were physicians. I did however have an uncle who was an economist and who graduated from the London School of Economics; he became well-known as the architect and one of the founding fathers of modern Singapore. He was my dad's brother, Goh Keng Swee.

It was for those reasons that my first degree was in economics/math and that I then went on to study economics and MBA at the University of San Francisco and Santa Clara University, which are in the San Francisco Bay Area, just like St. Mary's College. Upon the completion of my MA and MBA, I came back to Singapore and worked in a warehouse as a computer system analyst, which was ideal to my background then. As it turned out, the skills that I acquired during my studies in quantitative and computational business economics came in handy later in my computational biology career, including the research that I describe in this book.

While working at the warehouse as a systems analyst in Singapore, I began to feel restless and wished that I had embarked on my boyhood dreams of becoming a scientist. I finally found an excuse to do so. When I had finished my undergraduate studies at St. Mary's College of California in the suburb of the San Francisco Bay Area, I was just one subject shy of getting another major, which would have been in mathematics with an emphasis in computer science, but at that time I was in a hurry to do graduate studies.

By the time I was working as a computer analyst in Singapore, my dad had long passed on and I had then thus the option of pursuing the sciences. Upon returning to St Mary's College to fulfill a boyhood dream, I decided to also add yet another major, chemistry/physics, to make the completion of a triple major. There are reasons that I chose those disciplines.

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I felt that it would be easier for me to make a transition to the biological sciences via physical science since it is closer to the mathematical science, which I was already familiar with. Also, by then I was already aware of the remarkable advances that chemistry and physics had made into biology.

Having finished my triple majors, I was offered a teaching assistantship for graduate school at the University of Idaho Department of Chemistry, where I studied bio-organic chemistry. I had also the opportunity later to grab another advanced degree, this time, in computer science with a concentration in bioinformatics. I am just an example of the varied, unusual and non-traditional backgrounds that many computational biologists and bioinformaticists come from.

Chapter Takeaways

- Modern biology, including computational biology, often involves the application of computer science, mathematics/statistics, chemistry and physics to the field of biology.
- PONDR(r)-VLXT is a neural network that predicts the disorder residues of proteins.
- A database of shell disorder from over 300 viruses has been collected using techniques and concepts from artificial intelligence, database development, physics and biochemistry.
- The building of the shell disorder database is an effort that spans over a decade.

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2.

Unveiling the Face of a True Viral Shapeshifter: The HIV-1

The Adventure Begins

Upon returning to Singapore after having worked as a computational biomedical researcher at the Indiana University School of Medicine, I decided to start a new line of research using a set of computational tools that I was still developing. One field that I was intrigued with was the area of virology, the study of viruses.

A virus survives by exploiting the protein machinery of its hosts and has to move, often quickly, among hosts and host cells. For this reason, like a traveling salesman, it must travel light, with as little baggage as possible. Therefore, the virion, the virus body, is generally made of a limited number of proteins and genetic material. There are usually just enough proteins to protect the virus from environmental damage, for it to anchor and enter the host, and for it to hijack the protein machinery of the host cell. We need to keep in mind, however, that I am saying this in the most general terms as viruses can vary greatly in size and complexity.

The compact nature of a virus allows for easier comparative study of the viral proteins across virus species. I figured then that any unique property of the proteins that I could uncover from such an exercise would likely be reflected in the specific behaviors of the viruses.

Being a computational biologist, I am heavily dependent on data from experimental laboratories throughout the world. The availability of viral protein structures that were elucidated by X-ray crystallography makes my work easier. Data on the

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HIV are in abundance due to the huge amount of resources spent during the last few decades because of the ongoing AIDS pandemic. Similarly, the influenza A virus has been studied quite extensively: There is always a fear that the virus could return as a pandemic, the way it did in 1918 (1) when over 40 million people died.

Shell Protein Disorder: HIV vs Other Viruses

In the first few years, I simply started collecting data on viral proteins from as many viral species as I could, and computationally grouped the proteins by protein type and virus species using a microbiology text (2) as my guide. A thing that attracted my attention was the shell proteins or coats of the viruses. Even though viruses come in various sizes, complexities and shapes, see Figure 2.1a (2-5), all viruses have layers of shells that are occupied by lipids and proteins. Even though they are called by various names, the "matrix", "capsid" and "nucleocapsid" usually refer to the outer, intermediate and innermost shells respectively as seen in Figure 2.1b. In the case of HIV and its retroviral cousins all three shells are present as seen in Figure 2.1c (6,7).

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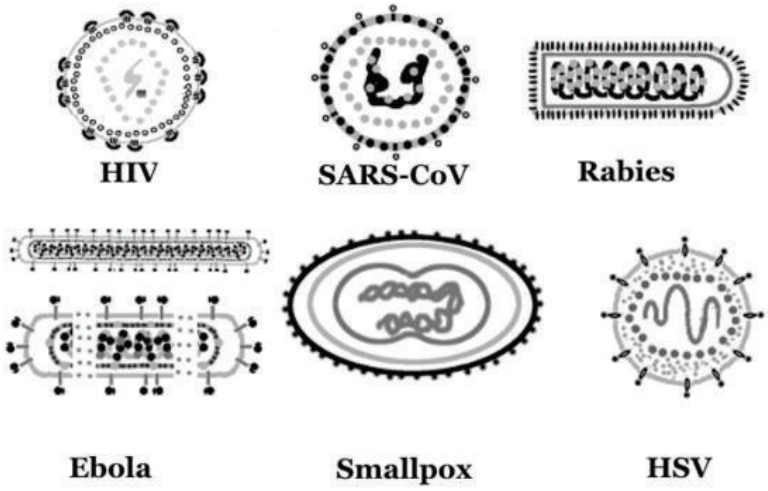

Figure 2.1a: Various shapes and structures of some viruses.

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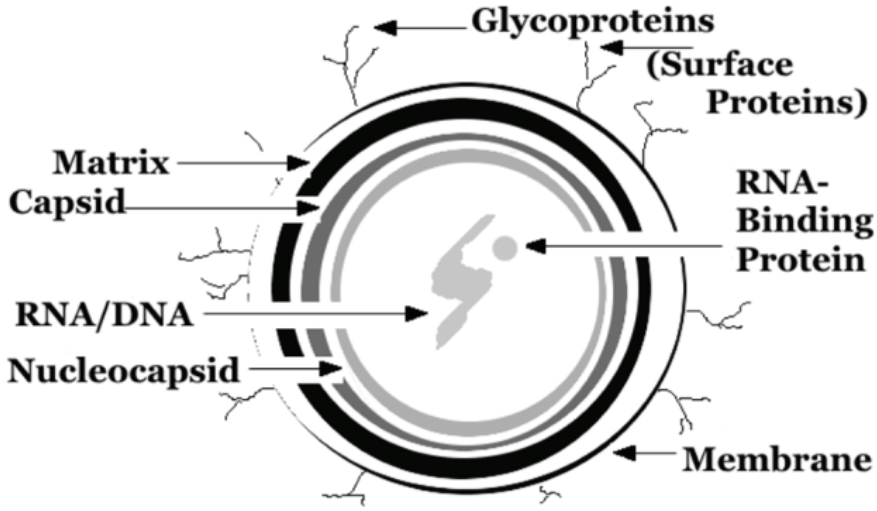

Figure 2.1b: General structure of a virus. Note: It is possible for a virus to be missing specific shell layers.

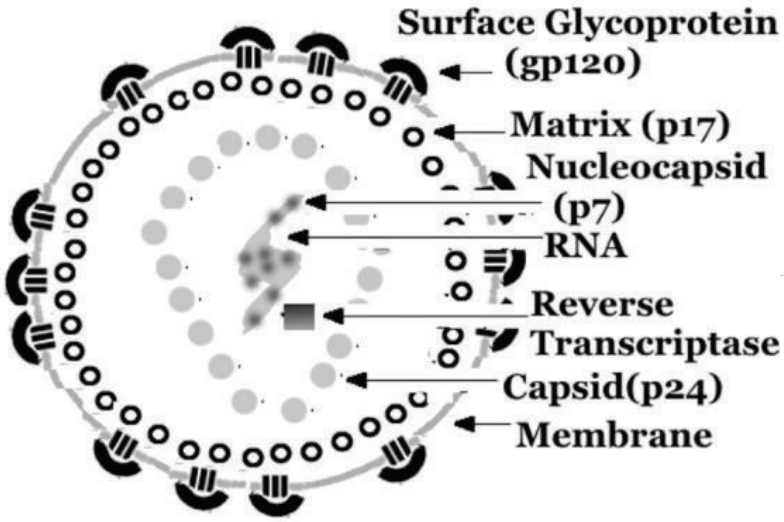

Figure 2.1c: Structure of HIV.

The most useful tool I found for my investigations was a computer program, PONDR(r)-VKXT, that uses artificial intelligence to predict the disordered portions of a protein chain. Traditionally, proteins, the machinery of life, were believed to be always structured, but with time, it became clear that many proteins are structure-less (disordered), and that feature serves various crucial functions. When the entire protein, or part of a protein, has no structure, the protein or part of the

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protein is labeled as “disordered”. PONDR(r)-VLXT, the earliest disorder predictor created, is highly effective in predicting protein-protein interactions, which can be responsible for the disorder-order transition (8-12). PONDR(r)-VLXT is trained to recognize the residues of a protein that are ordered (structured) or disordered (unstructured).

For my part, I built accessory tools that could be used in conjunction with PONDR(r)-VLXT to enable the automated feeding of input sequences of the amino-acids (i.e. the building blocks of the protein), and database storage that provides for further annotations of the proteins and disorder.

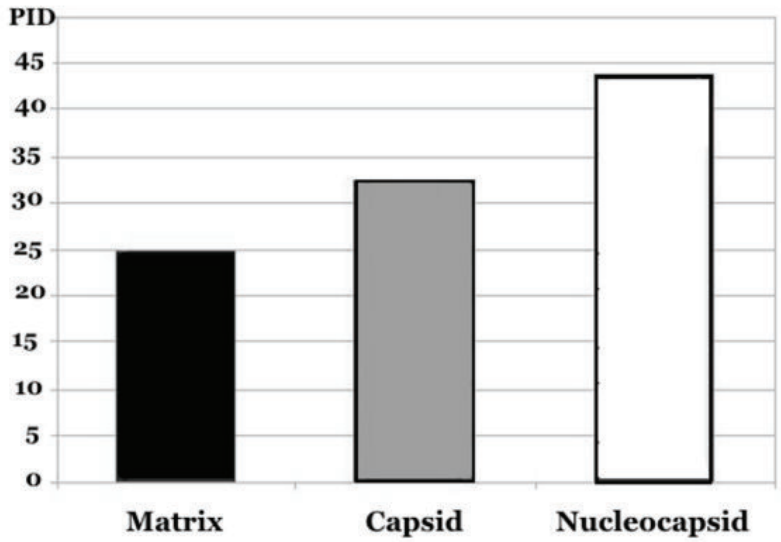

Figure 2.2: The mean PID (Percentage of Intrinsic Disorder) based on the 322 viruses found in my database. Not all viruses have all the three shell levels. The PID is defined as the total number of disordered residues divided by the total number of amino-acid residues (all proteins are sequences of amino-acid residues). For most viruses, the matrix (outer shell) is the most ordered, and the disorder increases as one moves to the inner shells.

As the protein disorder database was built, a general pattern of shell disorder began to emerge as seen in Figure 2.2: There is a stepwise increase in disorder as the shell level deepens. This basically means that viruses in general tend to have more rigid (harder) proteins on their outer shells. The immediate question is: Why? After some thought, I realized that the shells were playing an important role in protecting the virus

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from damage (4, 13-16). By providing a more rigid encasement at outer shells, the virus protects itself from physiological and non-physiological environments, which are often harsh. It is the same reason that crabs and lobsters have hard outer shells.

Then I started tabulating individual viruses and found that most viral shells abide by the rule of thumb as seen in Figure 2.2 with the outer shell being ordered, until I looked at the data for HIV-1. The shell disorder for HIV-1 (Human Immunodeficiency Virus, Type 1) looked odd, and it stuck out like a sore thumb. If you look at Figure 2.3, you will know what I mean: The pattern is opposite to that of Figure 2.2. Neither is there a relatively ordered (low PID ~ 25%) matrix protein in HIV-1. A mystery has then emerged. What is the source of this oddity? What are the implications?

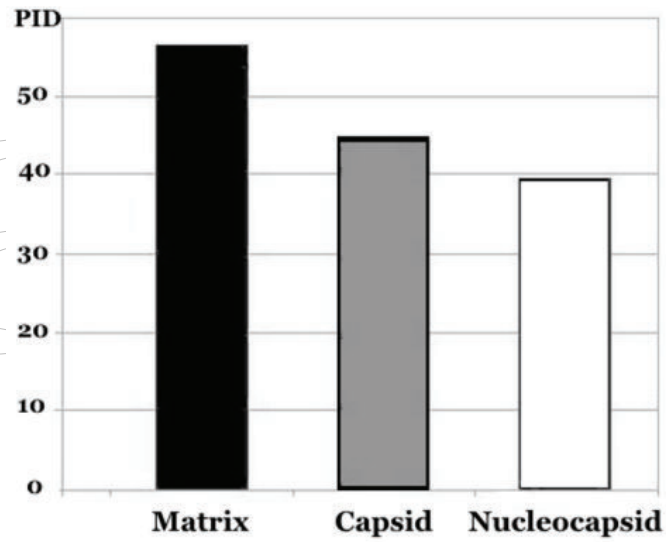

Figure 2.3: Protein shell disorder levels of the HIV-1. Notice the high average PID of the matrix protein, which is above 55% as compared to 25% for viruses in general in Figure 2.2.

We need to keep in mind that the 56% PID is only the mean and there are also HIV-1 strains that have matrix PIDs close to 70%. When a protein has 100% PID, it basically means that this protein is extremely disordered and will not have any structure whatsoever and will be virtually impossible to crystalize. Considering the 50-70% PID, it is quite remarkable for the outer shell to have such high levels of disorder, given that

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the outer shell has to play important roles in protecting the virion. Indeed, my database does show that very few viruses, if at all, have such a high disorder level at the outer shell.

We have seen that viruses in general tend to follow a disorder pattern that involves a stepwise decrease in disorder as the protein is located away from the core. As already mentioned above, a reason is that one of the functions of the proteins is to protect the virus from environmental damage that could arise from the physiological environment, and yet permit other functions that require it to be more disordered as it gets closer to the genetic material, i.e. DNA or RNA. The HIV data was simply out of whack with the general rule of the thumb for viruses in general. When I first noticed it, I went, "Huh? What the heck is going on with the HIV?"

But as time went on, and as I was able to get more data related to HIV and other viruses, it became clear that the HIV-1 is a shapeshifter, more specifically a true shapeshifter (15, 17): It is a shapeshifter, not just metaphorically, but in every sense of the word. The data are basically saying that the shells of the HIV are highly disordered, that is, in motion all the time when it is in fluid (18, 19). Physicists have named this kind of motion as Brownian motion, which was once studied by Einstein. There are also traces of similar behaviors in other viruses. The likelihood of finding such behavior in a particular virus, as it turns out, is highly dependent on the way the virus is transmitted. Being a shapeshifter allows a virus to evade the host's immune system more effectively and to increase its chances of survival.

I will argue in this book that the reason for the difficulty in finding effective vaccines against several viruses lies in this shapeshifting characteristic that is yet to be fully recognized by the scientific and medical communities even though the results have been published. There are only two other human viruses that I have thus far been able to find with shell disorder resembling that of the HIV, even if they are of lesser extremes. They are the HSV-2 (human herpes virus) and HCV (hepatitis C virus). There are however some differences in their shell disorder when compared to the HIV, but, like HIV, there is not yet any effective vaccine for those two viruses. We

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Chapter Takeaways

- The field of HIV vaccine research is still shrouded in mystery despite 30 years of effort.

- Most viruses tend to have an incremental increase in the disorder of their shells as one moves inward, with the outermost shell being most ordered to protect the virus from physiological and non-physiological damage. There is sufficient disorder at the inner most shells to carry out the replicative function.

- The HIV-1 has been observed to be strange and should be considered a true viral shapeshifter with its outer shell, the matrix, being highly disordered.

- By being a true viral shapeshifter, the HIV-1 is highly efficient in evading the host immune system.

- HIV-1 can afford to have a highly disordered matrix because it is transmitted mainly through sexual intercourse and intravenous drug abuse.

- EIAV, a close retroviral cousin of HIV, infects horses via a blood-sucking horsefly. Disorder analysis reveals ordered shell proteins at all levels, which explains the fact that effective EIAV vaccines are available, unlike the case for HIV.

- No effective vaccine has yet been found for HIV, HSV-2 or HCV, but it has been found for HIV's horse cousin, EIAV, which is usually not sexually transmitted.

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11.

Epilogue: Revisiting the Shapeshifters, with a Ghost from the 1920s

The term “viral shapeshifter” has been used in this book to describe disorder at any shell-level, with the HIV-1, HSV-2, and perhaps HCV, being the true shapeshifters as seen by the great disorder at their outer shells.

By contrast, there are viruses that have relatively hard shells at all levels[2]. These include the rabies virus and EIAV, HIV's horse cousin.

Then there are the shapeshifters that have hard outer shells but highly disordered inner shells. Many viruses fall into this third category. They include the Ebola virus, flaviviruses (e.g. dengue) and the coronaviruses (e.g. SARS-CoV and MERS-CoV). They are shapeshifters of a different sort and the more disordered their inner coats, the more pathogenic they tend to be. The way they evade the immune system resembles a Trojan horse. They do so by rapidly replicating themselves before the immune system can recognize or produce sufficient antibodies to eliminate them. This is in sharp contrast to the HIV-1, which evades the immune system by having a disordered outer shell, thereby preventing antibodies from binding to it strongly. It is however possible that the disordered HIV-1 matrix may also assist in helping rapid viral

[2]These viruses do show disorder at small segments of their shell proteins, but it is not comparable to the shapeshifters.

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Index

AIDS *14*
Avery, Oswald *105*
bacteriophage *101*
BEBOV *67*
cancer *99*
capsid *9*
CFR *29*
coronavirus *48*
cowpox *25*
Cox, Harold *43*
Crick, Francis 109
dengue *77*
d'Herelle, Felix *101*
disorder, protein *2*
Dunker, Keith *3*
Ebola *63*
EIAV *15*
Enders, John 42
enterovirus *41*
filovirus *64*
flavivirus 77
FMDV
Foot and Mouth Disease *42*
Gallo, Robert *14*
Goebel, Walther *106*
Hahn, Beatrice *16*
Hand, Foot and Mouth Disease *41*
HCV
hepatitis C virus *13*
herpes viruses *89*
HIV *8*
HTLV *14*
influenza virus *18*
Jenner, Edward 24
Koprowski, Hillary 43
mangabey *15*
MARV
Marburg virus *64*
matrix *9*
measles virus *49*
membrane *122*
monkeypox *29*
Montagnier, Luc *14*
neural networks *3*
nucleocapsid *9*
oncolysis *99*
Pasteur, Louis *34*
Pauling, Linus *111*
phage *123*
PID 11
Piot, Peter 63
poliovirus *40*

Sample

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PONDR(r)-VLXT *3*
Reed, Walter *78*
retrovirus.....*124*
Roosevelt, Franklin.....*42*
Sabin, Albert 42
Salk, Jonas 42
SARS.....*48*
SEBOV.....*67*
shapeshifting,viral .....*vii*
SIV *16*
smallpox *23*
TBEV *80*
TEBOV.....*67*
tegument *92*
Twort, Fredrick..... 101
vaccinia.....*25*
van Leeuwenhoek, Antoine *1*
variola.....*24*
variolation *24*
virotherapy.....*98*
Watson, James.....*109*
West Nile Virus *77*
yellow fever virus *77*
ZEBOV.....*67*
Zika virus.....*78*

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Viral Shapeshifters:
Strange Behaviors of HIV and Other Viruses

Gerard KM Goh

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