

Appetizer

Yes, I called this first section *Appetizer* because *Preface* or *Foreword* is just too boring. Many a preface consists of a laundry list of topics, which the author felt obliged to include, followed by acknowledgments in often cumbersome prose. And even if a preface actually contains true morsels of wisdom, readers don't expect as much and don't do what readers are supposed to do: read it. An appetizer, by contrast, is an artfully created tidbit to whet your appetite. Here it goes loosely with the theme of vignettes, that is, wine, vine leaves and stories that are short enough to fit on them. It is also more in line with the somewhat provocative chapter titles such as *I'd rather be fishin'*, but I will not launch into a laundry list. Mind you, esteemed reader, you are still with me, and I hope you will keep on reading until, as your mother might have said, you have earned the privilege to enjoy the *Dessert*. In the process, I hope to ease you into the fascinating field of systems biology as it attempts to decipher and understand the inner workings of life. As you will see, systems biology uses a lot of sophisticated techniques, all with their own jargon, so this is not exactly an easy topic to discuss. But there are so many exciting things going on in this young field, and in biology in general, that I am convinced you would be at a loss if you remained in the dark. You did not have the opportunity to experience the industrial revolution firsthand, and you may have missed the electronics revolution, so don't miss out on the biological revolution!

Allow me to back up a little and provide some context for the rise of systems biology. To some degree, we all have been systems biologists since our early days. We have marveled at ecological systems in our backyards and across the world, in deserts, on mountains, and in oceans, either with our own eyes and ears, or maybe through magazines and documentaries. We have watched with amazement how tiny ants carry heavy loads into their nests, apparently knowing that this is their assigned task in life and that other ants have their own roles and responsibilities for the greater good of the colony. Time and again we have been perplexed by the beauty of butterflies siphoning nectar from flowers, and

the intricacies of complicated food webs that have evolved over eons and have sustained and renewed themselves from one year to the next, in spite of – or maybe due to – their reliance on dozens of plant and animal species.

When we literally dig deeper and analyze a tablespoon of soil, we find not only plant roots and worms and insects, but also hundreds if not thousands of microbial species. They form complex and constantly adapting systems of their own, and without them plants and animals simply could not thrive. Similarly, our gut, our skin, our oral cavity are all home to thousands of microbial species, most of which are beneficial and indeed necessary for our health. But the complexity does not stop there. Each microbe, each plant or animal cell contains myriad genes, proteins, sugars, lipids and uncounted other molecules that play their specific roles for the organism's inner workings and are collectively essential to the well-being of the community of life.

The more we learn about these molecular systems, the more even hard-core scientists are in awe of the enormous complexity with which the components in these systems interact as self-organizing and controlling machines, reacting to signals from the outside and collaborating to mount appropriate and well-coordinated responses. These sub-microscopic systems are so robust and tolerant to all kinds of disturbances that we often take the living world around us for granted. Only if something goes wrong, if our well-being is compromised, whether the problem is a headache, an infection, or the onset of neurodegenerative disease, do we realize how intricate and vulnerable these systems are, and how processes, often entirely unknown to us before, can derail our existence when they fail. Intriguingly, the molecular systems in our cells involve thousands of different molecules and processes, yet they work together so smoothly, and usually adapt so effectively to altered conditions, that we don't even notice their normal function or their compensatory activities and internal rearrangements unless something is out of order.

Systems biology has declared that its goal is to elucidate and understand the functioning and regulation of biological systems under normal and disturbed conditions. That is a tall order, but then again, the potential of reaching, or even just approaching, the goal promises essentially unlimited rewards. Just imagine how well we could address cancer in a personalized manner if we really understood what had gone wrong. Try to fathom the possibilities of reliably steering

microorganisms or cells into making valuable medicines cheaply or into churning out lots of food products or energy without negative side effects.

The systems of life contain many different "moving parts," and it is therefore no surprise that their exploration requires a rich mix of diverse expertise. Clearly, one needs vast amounts of data, which immediately implies many types of biomedical investigation, but also the necessity of computer support for data handling and analysis. In addition, systems biology draws heavily from chemistry and physics. It needs sophisticated pure math to decode systems and formulate the laws that govern them, as well as applied math, on which all computer algorithms are based. Last but not least, the field could not possibly prosper without a constant stream of ingenious engineering feats that enable, automate, and miniaturize experimental explorations of ever finer biological details.

As a novel concoction of biology, chemistry, physics, math, computer science and engineering, systems biology is as yet a largely untested, but very promising, scientific endeavor. It has received quite a bit of buzz in recent years, to a point where it has become fashionable to sneak "systems biology" into the titles of articles or applications for research funding. Yet, outside the trenches, many laypeople and scientists alike only have a vague idea of how exactly systems biology intends to attack some of the biomedical grand challenges of our times, what one might realistically expect to be achievable, and what the current obstacles and limitations of systems biology are.

Several textbooks on systems biology have entered the market in recent years, but by the nature of the beast, these publications rely heavily on biological and mathematical jargon. This bridging between actual biological entities and the abstract language of mathematics is necessary to advance the field, and it can be very beautiful – to the expert. Unfortunately, it also triggers in some the all too familiar knot in the stomach that is often associated with everything mathematical. As a result, the curious and well-intended, yet unsuspecting, casual browser in a bookstore may be intrigued by the idea of trying to find out how life works but, opening any current systems biology book, finds so many unfamiliar or long-forgotten symbols and equations, and so much jargon of molecular biology, that the only way to save face seems to be a stroll to an aisle in the bookstore that offers something lighter, much lighter.

I started pondering the feasibility of a book on *Systems Biology without Equal ... Signs* many years ago. At first, it was difficult to envision doing the new field of systems biology justice without discussing computing and math, but I convinced myself that there is a big difference between making music or movies and sitting in the audience listening or watching. In fact, deep knowledge of all that's behind a literary play or a piece of art sometimes diminishes the visceral enjoyment that non-experts experience. Most of us do not have the opportunity, or are simply not fit enough, to climb Mount Kilimanjaro, and we will never feel the exhilaration of having made it to the top. Yet, we can vicariously enjoy the views through travelogs on television or in an IMAX theater. Borrowing from these analogies, I hope that you, the reader, will somewhat vicariously enjoy witnessing how we systems biologists are beginning to explore and decipher and understand the inner workings of life.

This book is certainly not an 8:00 a.m., hard-core text that is to be studied for an advanced college class. It is much too casual and non-technical for that. Rather, it is a curling-up-in-a-hammock-with-milk-and-cookies-in-a-summer-breeze read or maybe a deep-thoughts-about-the-secrets-of-life-at-midnight-with-scotch-and-candlelight treatise. It consists of vignettes, each of which is only a few pages long. These vignettes are presented in a loosely logical order, but they are all self-contained. My hope is that each vignette conveys a key thought that enlightens, provokes, interests, is maybe even fun to read, and leads to lasting thoughts that could easily float beyond biology and enter the philosophical realm of life.