Systems Medicine: physiological circuits and the dynamics of disease

Chapter 0

Introduction

Hi, I'm Uri Alon, a professor from the Weizmann Institute in Israel. In my PhD in physics I looked for patterns in turbulent flow; What I loved about physics were the moments of suddenly seeing within a complex system an angle where things looked simple.

Towards the end of my PhD I looked for subjects where the physics way of thinking might help to find new laws of nature. I didn't know much about biology - the only thing I knew about proteins was what I read on the back of a cereal box. Then a friend gave me a textbook on cell biology. It read like a thriller - here was matter that was alive! I fell in love with biology and resolved to see if there were laws to be found.

I wasn't alone. Luckily, Stanislas Leibler took me on as a postdoc, where I met other physicists who shared the vision of biological principles, Naama Barkai and Michael Elowitz. I was encouraged by biologists like Arnold Levine, Yosef Yarden and Benny Geiger. Before long I had my own group back in Israel.

In the first decade we focused on understanding the cell, with its networks of interacting proteins. At the time, around 2000, there was a massive amount of information on which protein interacts with whom, but it was hard to make sense of this information: the networks of interactions looked hopelessly complex. We discovered that they are simpler than they appear. The networks are made of a handful of recurring basic circuits which we named network motifs. These motifs show up again and again in different systems and in all organisms, and each has its own computational function. The basic circuits inside the cell are described in my book "An Introduction to Systems Biology".

Then, ten years ago, I saw a poster in the elevator in my building that changed everything. The poster announced a talk by Yuval Dor, saying that glucose makes the cells that control it, called beta cells, both grow and die. This seems like a paradox – why does glucose do two opposite things to the same cells? It reminded me of a paradox I had studied in bacteria, where enzymes do a reaction and also its reverse. I felt I could do something in an exciting field- human hormone circuits.

This was an opening to a new phase in my research career. I fell in love again, with human medicine and physiology, and how physics-style thinking can help make sense of our bodies in health and illness.
I'm excited to start this book with you, on systems medicine.
My wish is that some of you will feel the same way- that you can do something in this field- and join us.

Our topic is physiological circuits that describe how cells and organs communicate with each other. Rather than circuits inside a cell, we will discuss circuits between cells. This level of description is relevant to some of the most common and deadly diseases that plague humanity.

It's good to think about the goal of the book. **The goal is to start from basic principles or 'laws' and derive why physiology is built the way it is, why specific diseases happen and which new strategies might treat them.**

By the end you will be able to use simple and powerful mathematical models to describe physiological circuits. The models are powerful because they turn details into useful understanding and new ways to think about treating diseases. We will understand the fundamental causes of some of the most mysterious diseases: diabetes, autoimmune diseases and age-related diseases such as lung fibrosis and cancer.
Our trajectory begins with basic principles. From these we will derive the circuits and their fragility to disease. We will explore, in three parts, hormone circuits, immune circuits and aging and age-related disease. Our story culminates in a periodic table of diseases.

About math and biological terms
I write this book with a heterogeneous readership in mind. Your background might be biology, engineering, physics, math, computer science, medicine or other subjects, as an undergraduate, graduate student or researcher.
For some of you the following equation is familiar whereas others need brushing up:

$$\frac{dx}{dt} = -\alpha x$$

We will use this equation to describe the removal of cells, whose number is x. The rate of removal is α; You can think about this as the probability that a cell dies per unit time. Since cells are only removed in this equation, and not added, their number declines. In fact, x(t) declines exponentially with time, t, starting from the initial number of cells x(0), as given by the solution

$$x(t) = x(0)e^{-\alpha t}$$

You can check this solution by taking the derivative $\frac{dx}{dt}$, and since a derivative of an exponential $e^{-\alpha t}$ is -$\alpha e^{-\alpha t}$, you get our equation back, $\frac{dx}{dt} = -\alpha x$.
That's the level of the math in the book, ordinary differential equations that describe changes over time. You can skip the equations and still enjoy the book or go into them and learn ways of thinking about modeling.
Similarly, for some readers, biological terms like beta-cells and hormones are familiar; for others they are new. I'll assume no prior knowledge and use minimal jargon – biologists and physicians will see much fewer gene names than they are used to. I'll explain terms when needed. A hormone is a molecule secreted by one set of cells into the blood, where it flows in the circulation and affects cells in distant parts of the body; beta cells are the cells that secrete the hormone insulin.

I'd also like to say what this book is not. It is not a book on medical bioinformatics, the gathering and statistical interpretation of biomedical data. This field, sometimes also called systems medicine, is described in books listed at the end of this chapter. We will, however, use large medical datasets in this book to test our mechanistic models. This book is also not exhaustive, and I provide further reading below. The purpose of the book is to provide a way of thinking and the examples and exercises are chosen to clearly demonstrate principles.

Our first feedback loop

This book is also written to be fun. So let's jump right in! Here is our first feedback loop (Fig. 1). A person can be in a relaxed state of mind. The relaxed state is good for learning and memory.
In the relaxed state our body behaves in specific ways. For example, we take slow deep breaths. The wonderful thing is that we can decide to take a deep breath, and this increases the chances that we enter a relaxed state.
Because the relaxed state is good for learning, we will practice taking nice deep sighs of relief in this book from time to time. Let's practice now: you don't have to, but if you do, I promise you will enjoy it. Let's all together take a nice deep sigh of relief.

The next chapter gives a taste of our approach, and teaches basic concepts within a fascinating bit of physiology. So let's take a nice deep sigh of relief - here we go!

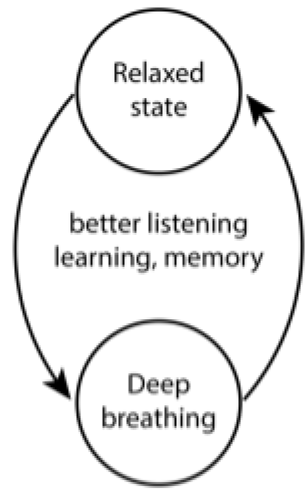

Figure 1. The relaxed state is better for listening, learning and remembering.

Background reading

This book combines several disciplines - Systems Biology, Evolutionary Medicine, Mathematical Physiology and Dynamical Systems. These are exemplified by the following books which are recommended reading if you want to go deeper.

Evolutionary Medicine, Medzhitov and Stearns (2015)

Dynamical Systems and Chaos, Strogatz (2nd Edition, 2015)

Mathematical Physiology, Keener and Sneyd (2008)

An introduction to Systems Biology, Alon (2nd edition, 2019)

A different approach to Systems Medicine focuses on statistical analysis of large datasets. It is described in the following books.

Wolkenhauer, Olaf. Systems Medicine: Integrative, Qualitative and Computational

Approaches. Academic Press, 2020.

Schmitz, Ulf, and Olaf Wolkenhauer, eds. Systems medicine. Springer, 2016.

Loscalzo, Joseph, ed. Network medicine. Harvard University Press, 2017.

Yan, Qing. Translational bioinformatics and systems biology methods for

personalized medicine. Academic Press, 2017.

Systems Medicine, Editors J.P.F. Bai and J. Hur (2022)