

Two Revolutions

In 1991, two tourists hiking in the Oztal Alps on the Italy-Austria border discovered a frozen corpse. A number of bodies of dead climbers having been found in the mountains earlier that year, the find at first seemed tragic but unremarkable. Scientists who later examined the body, however, dated it as approximately 5,300 years old, among the oldest, if not the oldest, preserved humans ever found. “Otzi the Iceman,” as the man came to be known, was found with warm clothes, an axe, a quiver of arrows, a bird net, and—surprisingly—birch fungus, a medicinal mushroom. Many believe Otzi was using the mushroom, with its laxative and antibacterial properties, to battle the whipworm found in his colon.

Indeed, from long before the dawn of the modern age, humanity has used medicines and searched for new ones. Ayurveda in India and traditional Chinese medicine are both comprehensive systems thousands of years old, and their prescriptions remain under study to this day. The Greek physician Hippocrates knew in the 5th century B.C. that an extract from willow bark, the chemical forefather of modern aspirin, reduced pain and fever. Saffron was used as medicine through much of the ancient world, from Greece to Egypt to Persia to India; recent studies have shown it to in fact possess noteworthy properties. Even inoculation has long roots: over two thousand years ago, it was already known in Asia that infection with dried smallpox pustules provided protection against a severe episode of the disease. Throughout the centuries, though, many, or even most, medications in use were either useless or harmful (a problem we still, to a lesser extent, live with today). The reason for the experimentation through the ages was the same as ours today—to alleviate suffering and prolong life.

With the gradual formalization of the scientific method and acceptance of the idea that much disease was caused by microorganisms, the search for drugs started to become relatively more concerted. In 1796, Edward Jenner, motivated by the observation that milkmaids did not get smallpox, found that pus from cowpox provided immunity from smallpox more safely than inoculation. Over one hundred years later, Louis Pasteur produced vaccines against anthrax and rabies. Sulfonamides, or sulfa drugs, developed as antibacterials in Germany in the 1930s, helped both sides during World War II. After discovery and at least two rediscoveries of its antibiotic properties over the preceding decades, penicillin also saved many Allied lives during the war and was heralded as a magic bullet miracle drug. This was all still very limited however. The second half of the twentieth century saw the use of modern chemical techniques to synthesize a veritable explosion of new medicines, ranging from the polio vaccine to Prozac. No longer were people helpless in the face of heart disease or most infection or asthma. The success was enough to spur many predictions that the end of disease was imminent and an era of worldwide health was dawning.

Despite such optimistic predictions, many goals have of course proven far more elusive than expected. AIDS and many cancers are without cures despite billions of dollars of investment. Treatment of chronic ailments, such as blood pressure, arthritis, or

diabetes, is far from perfect. New illnesses like Mad Cow, SARS, and Avian flu threaten the global economy. And even infectious diseases once thought defeated are on the rise, boosted by growing resistance to decades-old antibiotics. At the same time, new lead molecules are appearing at decreasing rates despite increases in research and development investment.^{1,2} Our methods of developing drugs must evolve to greater efficiency, because disease certainly is not waiting.

As the drug revolution was taking hold in the mid-twentieth century, another revolution was picking up steam as well, this one in the way mankind could perform calculations and process information. For thousands of years, the abacus and paper had been state of the art in computational technology. Even in the first decades of 20th century—centuries after Wilhelm Schickard had built, in 1623, the first known mechanical calculator and Charles Babbage had first described, in 1835, a general purpose, programmable computer—the term “computer” was more a job title rather than the name of a machine. Then, innovation exploded forward, rapidly progressing from full room vacuum tube machines like ENIAC in 1940s, to mainframes with magnetic core memory in the 1950s, to microcomputers with integrated circuits in the 1970s, to the machines of today, leaving the slide rule far behind. Moore’s Law, stating that the number of transistors on an integrated circuit (correlated with speed) would double every 18 to 24 months, has held remarkably true. A notebook computer today has orders of magnitude more CPU power and memory than were on board the Apollo moon missions of the 1960s. Taking into account the advancement of networking capabilities to harness many processors together, the amount of progress is even more astounding.

The computation revolution, and the information revolution that sprung from it, progressed largely independently of the drug revolution for decades. In recent years, however, many researchers have applied computation to drug discovery. This still young and rapidly developing convergence will be the subject of our discussions. We will not discuss computational tools, like visualization software or literature databases, that are primarily in supportive roles, but rather methods that actively generate information. Certain methods we will describe, like QSAR, have now been long established, while several of the others, potentially more revolutionary, like free energy computation, are not yet integral parts of mainstream discovery.

How Drugs Work

Our focus will be on small molecule drugs. These mainly work by binding to a target in the body, either to a receptor in one of our own cells or to a foreign invader, like a harmful bacterium. A drug may either inhibit some activity (an antagonist) or spur it (an agonist). A few examples will help clarify the objectives of the methods presented later on.