of large compound libraries into biological targets are now commonplace in the pharmaceutical industry.[62] Computer-driven predictions of chemical and physical properties are also commonplace, as are homology models[63] designed to provide a better understanding of molecular interactions when X-ray crystal structures are not available. The ability to employ computer-aided design will continue to grow as computer science advances and additional structural details become available.

High Throughput Technology: Chemical Synthesis and Screening Science

While advances in animal models, X-ray crystallography, and molecular modeling had a substantial impact on the course of drug discovery, they did not address the two key bottlenecks in the process, chemical synthesis and screening science. In fact, for the majority of the twentieth century, these issues remained unresolved. Prior to the development of high throughput technologies, drugs were discovered primarily using endogenous ligands, natural products, or marketed drugs as starting points in an animal model. Chemical modifications to improve efficacy was followed by additional *in vivo* screening to chart a path forward.[64] By the 1980s, most pharmaceutical companies' compound collections consisted of only a few thousand compounds acquired through historical projects and screening programs remained primarily a manual process, heavily dependent on low throughput assays and animal models.[65] The situation changed, however, over the last two decades of the twentieth century with the creation of the fields of high throughput chemistry and high throughput screening. Although it is not clear when the concepts for each field were developed, there were significant technological hurdles to overcome in order to accomplish the end goal of increased efficiency in both chemical synthesis and biological screening.

In the case of high throughput chemistry, also referred to as combinatorial chemistry or parallel synthesis, the groundwork that provides the basis for much of the modern methods can be traced back to earlier synthetic efforts that were not originally geared towards increasing efficiency. The preparation of small, druglike compounds on polymer-based material, for example, was first reported by Robert B. Merrifield in 1963 when he described the synthesis of a short peptide sequence on a polystyrene resin (also known as solid phase peptide synthesis).[66] Shortly thereafter, Merrifield reported the preparation of the biologically active peptides bradykinin,[67] bovine insulin,[68] and deaminooxytocin,[69] thereby validating the approach. As interesting as these efforts may have been at the time, the utility of preparing compounds on solid support was met with some degree of skepticism, as indicated by Rappaport and Crowley's 1976 publication entitled "Solid Phase Organic Synthesis: Novelty or