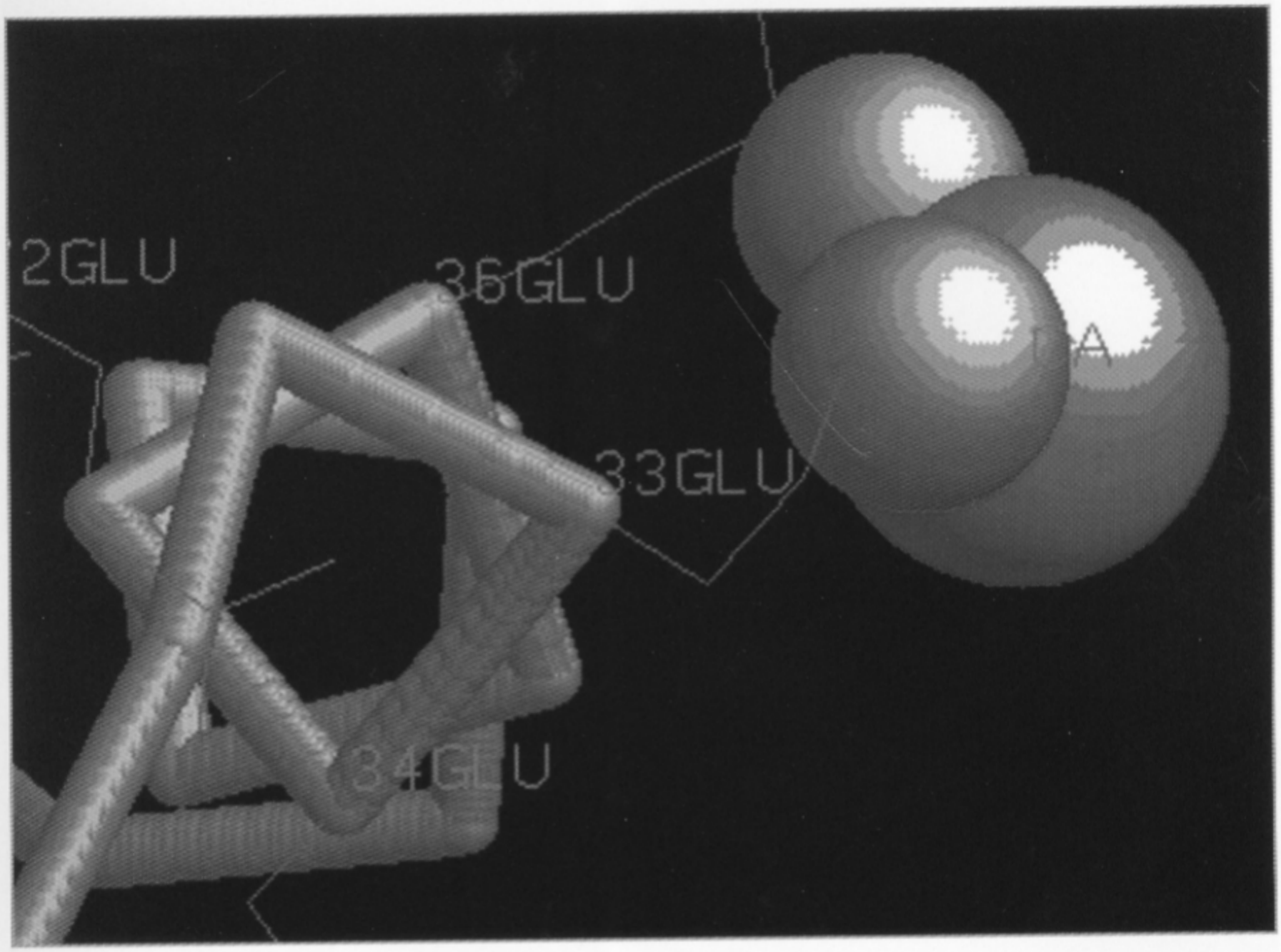
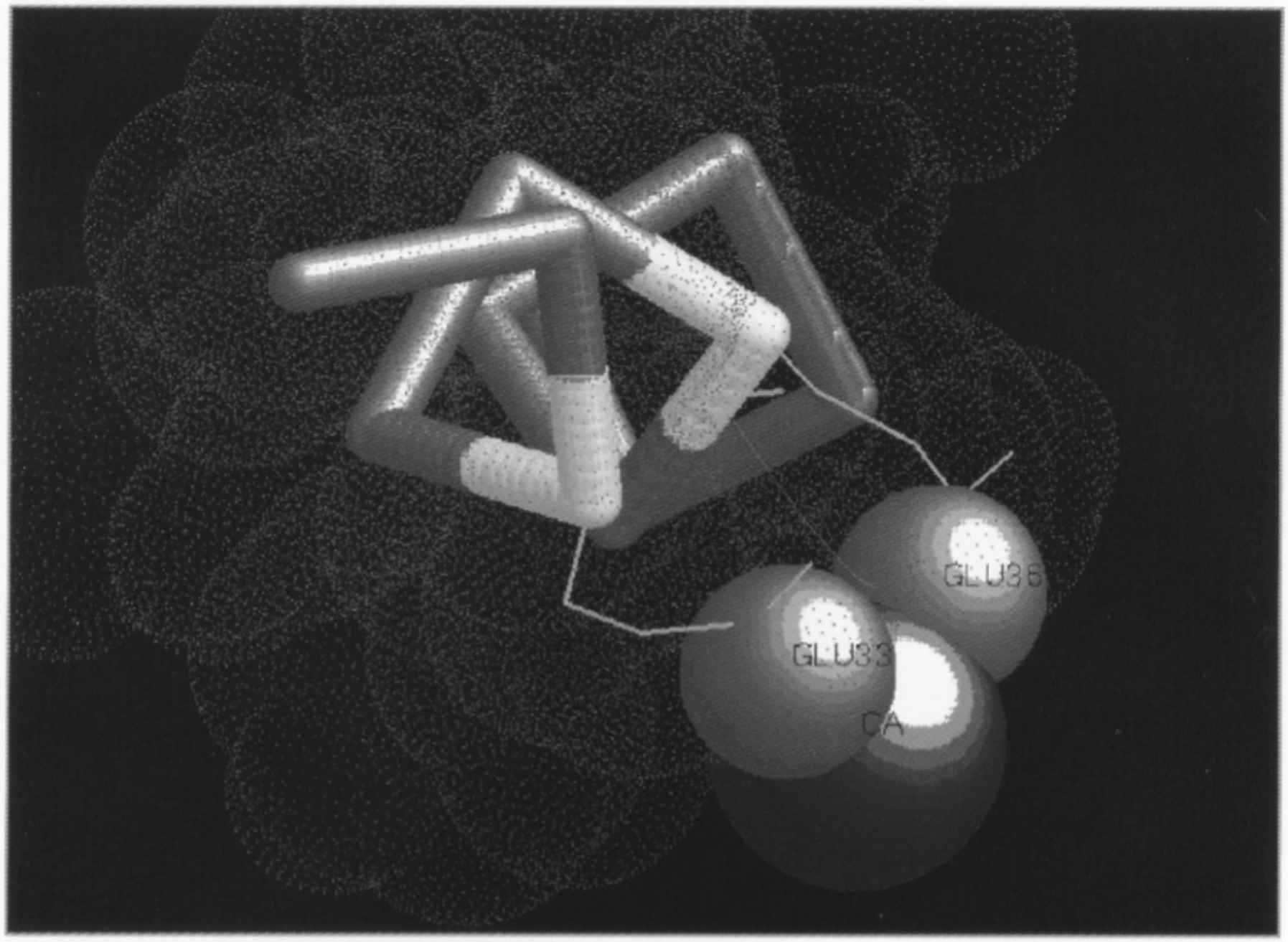
Introduction



Molecules of Life and Mutations has been written with the intention of providing insight into biomolecules, their materiality, their different sizes and complexities in shape and structure. The book is comprised of images that should make material the magnitude of the microscopic and teach us perhaps more than any other medium about the mechanisms and components of cellular systems that have been until now to most people theoretical. Pictures dynamically present the simplicity as well as the complexity of the shape, structure and function of the molecules of life as well as prove their interdependence. Seeing the concrete and 'real' structure of a molecule should explain to the reader its function in a cell or in an organism. It should become clear that no biomolecule by itself is effective, but becomes so only when it enters an interactive relationship with another specific molecule. This interaction requires a structural specificity, i.e. portions of the two molecules involved that match each other in form. The following pictures will show that these portions are not based on rough complementarity, but virtually on atomic precision.

For the most part, such interactions should not be long-lasting, but rather short and transient, i.e. it must be possible to discontinue an interaction after a short period of time. Noncovalent binding offers the best condition.

Random micro- and macromovements as well as vectorial transport processes of a molecule in the various compartments of a cell or an organism provide the opportunity for interaction. In this process, the probability of collision is determined by the concentration of one or both of the molecules that is ready to react. Noncovalent binding results from a collision of the two when they match in form at certain points. The basic pattern consists primarily of a small molecule (a ligand), which is not necessarily a protein, and a larger one, which is always a protein, that becomes activated by the former (also called an agonist). The latter can, by virtue of the inherent plasticity of most proteins, undergo a conformational change through binding of the agonist. The agonist activates (makes competent) the protein by inducing a specific conformational change that enables it to carry out its function, i.e. to interact with a further molecule, for example a membrane receptor with a signal transduction protein, or a transcription factor with a specific target gene.



The effect of an activated protein ceases on its own eventually because the condition of being functionally competent is, in itself, unstable due to the dissociation of the allosterically activating agonist from the activated target protein, which thus reverts once again to its initial inactive or resting conformation. This switching back and forth between two different conformational states is a characteristic property of certain proteins (switch proteins), but not a feature of the nonprotein ligands. Of course, these two states are only the extremes of a whole spectrum of many intermediate conformations. Nonprotein ligands have a rigid structure, as best demonstrated by the example of the smallest ligand, a single calcium atom, which will be detailed in the chapter 'Small Molecules'. It should be pointed out that peptides and proteins can also be ligands, and that ligands can induce both activation and inactivation of proteins.

This sequence of events and the temporal limitation of molecular interactions and their effects is the fundamental principle of cellular signaling, the communication between cells of an organism, and also of the cellular reception of signals from the outer world, such as light, nutrients (xenobiotica), toxins, microbes, or drugs, among others. Proteins are the most important mediators of signals. Specialized signal-receiving proteins are called receptors. Proteins are encoded by genes (DNA) and, in turn, as so-called transcription factors, they regulate gene expression. The importance of signaling is demonstrated by the fact that about 30% of the nearly 30,000 human genes code for signaling proteins. A multi-cellular organism is not viable and is inconceivable without communication, or signaling between its constituent cells.

Mutations in genes lead to diseases, often severe and even fatal, because mutated genes express functionally altered proteins. This is true of genes in general, and of genes encoding signaling proteins in particular. The exact nature of the functional disturbance cannot be read from the gene, but only from the structure of the protein involved, if this is known. Until a few years ago, however, the structure of most proteins was unknown.

Advances in molecular biology have permitted the production of large amounts of a specific protein (in recombinant form) and thus the production of protein crystals. X-ray diffraction analysis has made it possible to reconstruct a protein's structure with atomic detail in a three-dimensional form. The resolution of these techniques is below 2 Å, i.e. the same as the van der Waals' radius of sulfur, carbon, nitrogen and oxygen atoms. In the Brookhaven Protein Data Bank (PDB), the individual X, Y and Z coordinates of hydrogen, carbon, oxygen, nitrogen and all the other constituent atoms of approximately 10,000 proteins are so far deposited. These data have become generally accessible through the Internet, and can now, with the help of appropriate molecular modeling software, be manipulated, rotated, zoomed and visualized (in stereo!) on a personal computer.

If one knows the domain of a protein responsible for each function (e.g. the substrate-binding domain of an enzyme, the ligand-binding domain of a receptor, the DNA-binding domain of a transcription factor), or which of the multiple domains of a protein is afflicted by an abnormal conformation, it should be possible to directly deduce the biological consequence of the altered conformation. On one hand, mutations are productive and important for successful evolution and the creation of newer forms of life in the course of millions of years; yet, conversely, mutations can also be counter-productive in that they can cause diseases, and thus are of medical relevance.

The size of molecules covers a vast range, encompassing at one end of the spectrum tiny calcium atoms (with a molecular mass of 40), and at the other end large lipoproteins or chaperones (with a molecular mass above 1,000,000). It will become clear that where a protein is not large enough to form a specific structure, means will be employed, such as linking together smaller protein modules (domains) and even di- and multimerization of whole proteins. It will also become clear that the sizes of interacting molecules or portions thereof should be commensurate: A small ligand (e.g. a calcium atom or a steroid hormone) fits into the small ligand-binding pocket of a protein, while a larger ligand (e.g. a protein hormone, such as the human chorionic gonadotropin, hCG) fits only in a correspondingly larger groove, which can be formed only by a multimodular protein.

It has already been mentioned that fitting biomolecules requires atomic precision. Thus, it should be clear that even the smallest mutation, a so-called point mutation or change of a single base in a gene, can disturb this precision at the protein level. My primary concern was to make this obvious to the reader, in particular physicians, medical students and biologists. Moreover, pharmaceutical chemists can, through their knowledge of the 3-dimensional structure of a pocket in a macromolecule, construct artificial ligands (rational drug design), quasi-negative copies, with the ability to occupy this site and thus function as agonists or antagonists. Perhaps above all, every reader regardless of background and specific interest, may be captured and fascinated by the beauty of the structure and architecture of biomolecules, particularly proteins.