

# Preface

This textbook gives an introduction to numerical methods. They are key tools for the calculation of reaction schemes and for the development of functional models in life sciences. The most exciting of this is model development, but it probably cannot be taught in a book. It is surprisingly personal. I will illustrate some aspects together with an acknowledgment of the scientists who impressed me most.

*Multiple theoretical approaches:* I was fortunate to study physics at Bonn University at a time when Wolfgang Paul gave his main lectures on “Experimentalphysik”. The lectures themselves were spectacular, but the emphasis was laid on the variety of possible interpretations of the same experimental findings. For the topic of gravity, for example, Wolfgang Paul included geocentric astronomy and concluded that one cannot rule out angels carrying planets in retrograde loops around the earth, but that the assumption of gravity is so much simpler. For an experimental physicist the observation itself is the result. Theoretical models are only limited by the creativity of the analyst. All are valid when they can be verified experimentally.

*Courage and creativity:* Friedrich Cramer was my PhD supervisor at the Max-Planck Institute in Göttingen. He had published a structural model for tRNA based on a map of reactive groups. When I entered his group, this model just had been disproven, so that he was criticized for having published a preliminary model. Model building is part of a scientific discourse, and one sometimes needs courage to publish new ideas. Friedrich Cramer was a very creative, sometimes artistic, and sometimes philosophical personality. He has strongly influenced me and many other scientists in Göttingen.

*Additional low-affinity binding:* In the beginning of the 1980s, we had employed a newly synthesized fluorescent cholinergic agonist for molecular studies of cholinergic excitation. For a detailed pharmacological characterization of this drug Alfred Maelicke and I traveled to Göttingen, where we had convinced Bert Sakmann and Erwin Neher to perform a series of electrophysiological studies at different ligand concentrations. They confirmed that the ligand acted as a pure agonist at low concentrations, but cautioned that it changed channel open times and thereby acted as a local anesthetic at high concentrations on the same receptor. I as a

physicist who had calculated a model for cholinergic excitation found this particularly disturbing, but they had observed such concentration dependency before. It is well known that the physiological action of any compound depends on its dose, but before this moment of truth I had thought that different target proteins were responsible for the different interactions at different concentrations. Erwin Neher and Bert Sakmann were the first to perform functional studies on one single molecule. Independent of this, multiple interactions of ligands at the same target molecule may be quite common as discussed in Sect. 4.8. Unfortunately, additional low-affinity binding spoils the elegance of any mechanistic model. Additional sites are at odds with many published crystal structures and rigid docking programs used in drug design.

*Open-minded observations and scientific communication:* One cannot just sit down and write a new theory without experimental evidence. One cannot even plan for new functional models. Sometimes it just happens: One summer evening we were sitting in a beer garden when Jörg Striessnig, an Innsbruck pharmacologist, mentioned a discrepancy between a theoretical prediction and a common observation in the lab. He had observed that the addition of a second ligand to an existing ligand–receptor complex resulted in dissociation rate constants, which increased with the concentration of the second ligand. This observation corresponds to the German saying “viel hilft viel” (the more you take, the more it helps), and therefore “feels” all right, but, of course, it contradicts first-order dissociation kinetics. In the end, we calculated the observation with the assumption of overlapping sites as shown in Sect. 5.5. One really should talk science in relaxing environments.

*Quantitative plausibility check:* It is a good idea to present kinetic data to a critical audience before publication. Some questions can be as basic as: “When you have an equilibrium dissociation constant below nM, how can you have free protein?” The numerical values of rate constants imply scientific information which is evident to an experienced scientist. I have often admired Roger Goody for his overview.

*Different scientific approaches:* Scientists are individuals, who may have entirely different approaches to the same question. These differences can lead to individual animosities, but they also can lead to fruitful cooperation. Cooperation can be encouraged when the person in charge has a natural human understanding coupled to clear scientific goals. Herbert Waldmann is one scientist with such management qualities and I am happy to work in his department.

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