Obituary

Carl-Ivar Brändén (1934–2004)

When Max Perutz and John Kendrew solved the structures of the oxygen-delivering proteins haemoglobin and myoglobin in the 1950s, the time was clearly ripe for more extensive studies of the molecular structures of biological systems. Thus it was that, in 1962, the UK Medical Research Council opened the splendid Laboratory of Molecular Biology (LMB) just south of Cambridge. Carl-Ivar Brändén, a mathematics and chemistry student from Uppsala, Sweden, was one of the first postdoctoral students at the new laboratory, from 1962 to 1963. His PhD work in Uppsala had dealt with the crystallography of inorganic metallic salts, but his experience at the LMB became decisive in shaping his future career, in which he used structural studies to elucidate protein function. Brändén died on 28 April 2004, just two weeks short of his seventieth birthday.

Calle, as he preferred to be called, was born in 1934 in a tiny village in Lapland. He spent his first six years at school under the supervision of his father, who was the local teacher. The village was poor; with nine months of winter, the climate was even worse. His determination to get away made him study hard, and he was subsequently awarded a state fellowship for university studies in Uppsala, where he also gained his PhD. He retained a lifelong interest in nature, however, and loved to pick mushrooms and cloudberries.

In his university years, Brändén began by studying mathematics and physics, but quickly dropped the physics, opting for chemistry instead. With this background, he was ideally placed to contribute to the computational refinement of the X-ray structures of inorganic molecules during his PhD with chemist Ingvar Lindqvist. Crystallographic refinement is used to make a rough atomic model fit the data better. At the time, there was a dearth of computer programs capable of dealing with X-ray diffraction data — a fact that prompted Brändén to write his first program for the early Swedish electronic computer, BESK, using the method of least squares. The program was used for more than ten years by the entire Scandinavian crystallographic community.

A course in biochemistry stirred Brändén to switch allegiances once again, as he became keen to apply his knowledge of computing and crystallography to biological molecules. He obtained a year's placement at the LMB, where, together with one of us (K.C.H.), he engaged in writing a

From mathematics and chemistry to computing and structural biology

computer program for refining the structure of myoglobin. This protein has 1,500 atoms, and no one had ever attempted to refine a system that big before. The method involved treating each peptide group as a planar unit, to reduce the number of parameters. In those days, one cycle of refinement required 16 hours of computing time, at a cost of £3,000 (US$5,500). Although the method worked, the cost was prohibitive, and the structure of myoglobin was not refined for another 20 years.

When he returned to Sweden in 1963, Brändén was appointed an associate professor at the Swedish University of Agricultural Sciences in Uppsala. There, his first problem was to solve the structure of the alcohol dehydrogenase enzyme, which is involved in decomposing alcohol. Funding was scarce, and the first crystals were made in the kitchen refrigerator. Eventually, however, Brändén and his colleagues were able to postulate a detailed mechanism of action, based on the structures of several complexes in different conformations. Through pioneering studies of allosteric effects and the binding of coenzymes and substrates to enzymes, his interest in integrating structure with function and molecular biology continued into the 1980s.

When the Swedish Research Council awarded him a full professorship in molecular biology at the University of Agricultural Sciences in 1970, Brändén was ready to take on a new challenge. He decided to tackle the structure of Rubisco, the enzyme that catalyses the initial fixation of carbon dioxide during photosynthesis in green plants. Despite some initial opposition — Rubisco, being a large, multi-subunit protein complex, was thought to be too difficult a subject for crystallography — Brändén and his group finally published the structure in 1986. The structure represented a turning point in the study of this enzyme. Not only did it provide the first detailed picture of Rubisco's active site, it also revealed the so-called fold of the large subunit of the Rubisco molecules found in all plants, aiding their interpretation.

Around this time, Brändén realized that protein structures would become an ever more important tool in the molecular life sciences. So in 1987 he and John Tooze, who ran the European Molecular Biology Organization, began writing a textbook to introduce biologists to the concepts of structure determination. The result was *Introduction to Protein Structure*, published in 1991. With its superb pictures and accessible text, the book quickly acquired a strong following among graduate students and newcomers to the field.

Brändén also had a marked impact on science policy in Sweden. He became one of the scientific advisers to the Swedish government, for instance, and served nine years on the Nobel Committee for Chemistry. Many international appointments followed, culminating with the directorship of research in life sciences at the European Synchrotron Radiation Facility in Grenoble, France, from 1992 to 1997. While there, Brändén was responsible for building up experimental facilities for chemistry, biology and medicine. He realized that this facility provided a prime opportunity for extending the frontiers of structural biology, by facilitating the determination of the structures of large molecular complexes, and enabling the dynamics of biochemical reactions to be studied in the microsecond time range by time-resolved crystallography.

Throughout his life, Calle continued to share his views on molecular biology and structure, as well as on producing a creative research environment. With his open-door policy, he also inspired and supported many young scientists and students. Calle was not only generous but also knowledgeable, determined and full of humour — characteristics that can perhaps be put down to his tough childhood years. Despite spending his final 18 months under treatment for lung cancer, from which he died, he remained optimistic and quite satisfied with the richness of his personal and professional life.

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