



## Alexei Vagin (1944–2023)

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**Keywords:** obituaries; Alexei Vagin.



Alexei Vagin.

Doctor Alexei Vagin, who died on 25 March 2023, contributed greatly to the practice of X-ray crystallography for over 50 years. He organized the (sparse) computing services of the protein group at the Moscow Institute of Crystallography during the 1970s and 1980s, then after his move to Western Europe in 1994, made major software contributions for macromolecular structure solution, all now distributed through CCP4.

Alexei was born in 1944 in Perm, the most easterly city in Europe, located in the Urals near the natural borderline between Europe and Asia. His family had been evacuated there during the war, but they returned to Moscow for his education. For his degree he studied applied physics at the prestigious Moscow Engineering Physics Institute, specializing in mathematical techniques and computer programming. He started his scientific career in material science – his first publication in 1966 was concerned with the design of blast furnaces, but soon he became more interested in crystallographic method development and moved to the protein group of the Moscow Institute of Crystallography. He was part of the team that solved the structures of bacterial ribonuclease in 1977, catalase in 1979 and was the key player behind the computational part of the latter project where he applied non-crystallographic symmetry (NCS) for phase improvement. From then on, he was involved in almost all the protein structure analyses in the laboratory, developing and implementing many tools. Unfortunately, most of these developments were never written up as Alexei always considered this part of science too boring, a sentiment to which he was loyal for the most part of his life. His PhD thesis, awarded in 1982, described an improved and faster translation function for use in molecular replacement calculations. He organized the software into *BLANC*, a comprehensive package with almost all necessary programs and libraries for crystal-

lographic calculations, from experimental phasing to molecular replacement and map calculations. Considering that there was an embargo on computing resources for all of the Soviet Union, and those available to the institute were scarce, he had to come up with and implement clever algorithms that were both fast and used limited amount of RAM.

In 1990 the scientific scene in Moscow changed dramatically. Funding there became tighter and as the Iron Curtain dissolved it was possible for Russian scientists to move to laboratories in the West with better funding and equipment for science. Many laboratories worldwide benefitted greatly from this influx of well trained, motivated young people from the Moscow Institute (especially the York Structural Biology Laboratory!) but it meant Alexei was witnessing the decline of a great institute. In 1994 he joined the exodus, taking an EU-funded position in Brussels as a member of the team working on *CRITQUAL*. The Biotech contract he joined was entitled: 'Integrated procedures for recording and validating results of 3D structural studies of biological macromolecules'. It brought together in a complementary manner several established European laboratories working in the field of macromolecular 3D coordinate provision and analysis. The insights provided into each other's practices, working approaches and problems proved invaluable. This contract was a delight – all the participants were excited by the challenge and the six-monthly face-to-face meetings positively 'fizzed'. Atomic resolution structures solved in Hamburg revealed that some of the underlying assumptions about protein conformation derived from the existing databases developed in the EBI and Uppsala were sometimes too restrictive, and Alexei in Brussels was able to quickly recast the new insights into a well designed computer readable form to be used within the refinement program framework being developed in York. He found an elegant solution to the problem of describing 'LINKS' – between peptides, nucleic acids, and to covalently linked ligands. The restraint formats (mmCIF) he helped design are now accepted as standard.

In 1998 when the Brussels funding was exhausted, he moved to York and re-joined an active crystallographic laboratory, where he stayed until his retirement in 2010. This was a wonderfully productive period for him, and the community of structural biologists continue to benefit from his work. The program *SFCHECK* developed in Brussels to assess the quality of the agreement between model and experimental data was modified for inclusion in the *CCP4* suite. He contributed to further developments of *REFMAC*, advised laboratory members on programming problems, structure solution and partying. He was a highly sought-after tutor for training workshops, guaranteeing excellent teaching and good fun for all. But his life-long passion was for improving the methodology of molecular replacement. At one period when both Alexei and Jorge Navaza, the author of the *AMoRe* package, were working in York, it was tremendous fun to hear their on-going debates ranging from 'what are the best scoring functions?', to 'why my fast Fourier routine is faster than yours...'. In 1997 he published a description of a 'new'

package, *MOLREP*, in the *Journal of Applied Crystallography* before releasing it through *CCP4*. It was in fact partly a re-issue of much work he had done in Moscow, dating back to his 1982 PhD thesis, and partly described in the Russian journal, *Kristallografiya*.

*MOLREP* contained many innovative features that exploited information easily obtained from the experiment. For example, the package was able to analyse the model-free Patterson maps to consider non-crystallographic symmetry (NCS) and pseudo-translation if present. Once a search model was selected, *MOLREP* then analysed its shape and modified the search procedures to take this into account. In this package, Alexei introduced a translation function which considered all possible symmetry equivalents together. He also improved methods for searching for multiple copies and checked any solutions against the known NCS. Once a possible solution was found, the program checked whether it would pack, and positioned the symmetry copies to give optimal contacts for an assembly. One distinctive feature of Alexei's approach to software development was a user-centred perspective and he took pains to report results and data analyses with informative graphs and extensive text. *MOLREP* was an instant hit and is still widely used by crystallographers and electron microscopists. Searching the Protein Data Bank (PDB) for references to it yields the amazing score of 36 223 entries.

Once Alexei was reasonably satisfied with the software, he turned his attention to model selection. A search to match a new sequence against the many structures available in the PDB will often produce many closely related hits. Alexei designed a database, distributed first in the package *BALBES*, and later as *MorDa*. This weeded the hits to include only the best model, and then catalogued whether the model structure existed as an oligomer, whether it could be split into flexible domains, and then used this information to design an optimal search strategy.

Alexei will be remembered for his innovative science, and for his interest in and kindness to his many colleagues, both in Moscow and Europe. But of course, he was not just a scientist and the many friends who mourn him remember his humour, his generosity both at work and play, and his wide-ranging conversations. While still in Moscow, he was one of the very few laboratory members with a car, and he was the one who took his colleagues to the airport for their departure to join various crystallographic laboratories in Europe, USA and Australia. He had no children of his own but was very good with those of his friends – one of whom, a grown up artist now, designed the *MorDa* icon, a wise friendly cat face. He loved Russian culture and his Russian friends, but never Russian politics. He was rather a citizen of the world with a passion for French chanson and movies, and deeply in tune with British black humour which matched his own. He was also profoundly grateful to the NHS which cared for him until his last moments. But his real homeland was the international community of protein crystallography, and that is where he will be remembered with love and gratitude.