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EDITORIAL

Field-flow fractionation

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In the middle of the last century, Martin and Synge [1] had developed a technique for separating small molecules, such as amino acids, by column liquid chromatography. Their work evoked strong attention and resulted in a Nobel Prize in chemistry in 1952. The young thermodynamicist, *J Calvin Giddings*, who had taken a special interest in separations, was attracted by their concept, but could not refrain from brooding over the inability to use their packed column approach for the separation of larger species such as macromolecules and colloids.

Giddings was an eminent kayaker, at one point even president of the American White Water Association. Once during a trip to the Rocky Mountains, his pondering led to an inspired line of thinking. On a restless night, he clearly realized that items, like his kayak, that were transported by streaming water in laminar flow tended to move to the edge of the stream where they would progress at a stable but significantly reduced velocity compared to the average flow. The narrower the stream, the more stable the positioning along the edge. Why not introduce a particulate sample into a narrow flowing stream and apply a transverse field to force the suspended particles to the edge of this stream? A perpendicularly applied field, whose type and strength could be modulated at will would give an operator the ability to selectively transport the sample particles, or any other liquid borne items regardless of size into a flow regime where they would remain stably positioned. This line of thinking was clearly a lead up to a method for a liquid separation of samples of all kinds, varying from cells and virus particles to macromolecules and nanoparticles.

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Giddings first implemented his idea of "field-flow fractionation" (FFF) to polystyrene standards of different mass, dissolved in organic solvents and forced to flow through thin channels under the influence of a thermal gradient [2]. The polymeric molecules tended to concentrate at the cold wall of the channel, and this field-induced effect was stronger for larger molecular mass polymers.

Over the years, many fields, in addition to the thermal gradient [3–6], have proven useful to accomplish selective concentration near a wall in a thin channel under laminar flow, and today the hydrodynamic field, as used in "flow FFF", has by far outnumbered the other approaches in use as evidenced in this paper collection. To Giddings' delight and that of his many colleagues, it became evident that once the geometries of the FFF channels were known, existing fluid dynamic knowledge allowed a precise modeling of separation parameters of interest, such as retention, selectivity, zone broadening, etc., and enabled the determination of such sample characteristics as size or molecular weight, regardless of solvent. In today's analytical chemistry laboratory, there is an arsenal of detection principles available that, in combination with FFF channels of various types and operating with various fields and mobile phases, can solve a virtually limitless number of analytical problems, as discussed by several authors in this issue. It is important to stress that the ability to model the separation process, which was enormously important to Giddings, and has remained so to many FFF researchers, makes the FFF analysis far more than a mere separation. Indeed, it also allows a physical characterization of the sample.

Many areas of modern research involve particulates of different kinds, where the size and type are of fundamental importance. For example, environmental studies often require an understanding of waterborne particles [7] to enable the design of processes for capture; here, the FFF techniques have been an invaluable help. The impact of engineered nanoparticles on the environment and human health has given rise to the field of nanotoxicity wherein FFF plays a key role in facilitating nanoparticle characterization. FFF has also been instrumental in

isolating the uniform size or shape nanoparticle subpopulations for detailed investigative studies that correlate size/shape with important desired properties. Other examples are offered by the entire fields of proteomics and pharmaceutics that have grown enormously in the last decade. They are both built primarily around proteins, often of medical grade, i.e., macromolecules of precise composition and folding. Here purification is not enough, but one also needs to specify the state of aggregation of these macromolecules. This is extremely important to ascertain, since dimers and higher-order aggregates tend to give different immunological responses upon injection. Once purified, a sample's composition can in general be established by spectroscopic means, but how about the folding? The coefficient of friction is often a good measure of protein structure, and this characteristic falls out of the diffusivity that is a quantity directly yielded by the FFF retention, as reviewed by Wahlund in this issue.

In the field of pharmaceutics, one often has to consider pharmaca to be delivered by particulate carriers [8]. Nanoparticles of various kinds are used for this purpose, and for clinical use it is essential to be able to certify the size of the carrier particle as well as its monodispersity. A question that presents itself in the packaging of the pharmaceutical product is: How much of the active agent is present in each particle, and how many particles can reach the target tissue? These questions are typical for the many biomedical applications for which FFF is eminently suited to give an answer.

FFF has found a niche in the analysis of complex and high molecular weight synthetic and natural polymers [9]. The low shear degradation associated with separation in an open channel has enabled the analysis of polymers as large as 10^9 Da and studies that span a wide size and molecular weight range. Furthermore, composition-based separations have proven successful for complex materials such as terpolymers.

The present collection of papers illustrates some of the many uses the various FFF techniques in today's analytical laboratories.

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S. Kim R. Williams is a Professor of Chemistry and the Director of the Laboratory for Advanced Separations Technologies at the Colorado School of Mines. She began working with FFF as a postdoctoral fellow with the inventor of FFF, the late J. Calvin Giddings at the University of Utah, in 1987. She subsequently became the Assistant Director of the Field-Flow Fractionation Research Center and an Adjunct Assistant Professor at the University of Utah. In 1997, Kim joined the faculty of the Chemistry Department at the Colorado School of Mines and continued working actively with FFF. Research in the Williams group focuses on developing new capabilities for nanoparticle and macromolecular analyses using FFF and related methods. Kim has given invited lectures and taught FFF workshops worldwide. The application of newly developed FFF technologies are done through collaborations with scientists at universities, companies, and national laboratories. Kim recently co-edited a 2012 book with Karin Caldwell entitled *Field-Flow Fractionation in Biopolymer Analysis.*

Karin D. Caldwell, a biochemist by training, is an Emeritus Professor of Surface Biotechnology at Uppsala University, Sweden. She is also an Emeritus Professor of Bioengineering at the University of Utah in the USA. It was in Utah that she first came in contact with FFF during her postdoctoral work with Cal Giddings. The ability to sort cells, polymers and nanoparticles of various kinds has contributed to her career, as reflected in the just under 200 peer-reviewed publications emanating from her desk.