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COMMUNICATION

Three-Dimensional Field-Flow Fractionation Using Helical Flow

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Field-flow fractionation (FFF) is a class of techniques in which a nonuniform (i.e., shear) flow is used to amplify differences in some physicochemical property (e.g., electrical mobility, sedimentation velocity, molecular or cellular diameter) by taking advantage of the fact that in a viscous flow the velocity at a motionless wall is zero, so that a species which tends to concentrate at the wall will be retarded relative to a species that is less concentrated at the wall. This class of techniques has been extensively developed since the original paper by Giddings (1). The reader is referred to recent reviews by Giddings (2, 3) for detailed discussions of the state of the art.

In this paper we present (in the same spirit as Giddings' original paper on FFF) a description of a class of FFF processes different from those discussed to date, which make use of the helical flow that can easily be achieved in the annular space between two concentric cylinders (by rotating one cylinder relative to the other and by simultaneously applying an axial pressure gradient). Unlike other multidimensional FFF techniques, these processes make use of the coupled action of two nonuniform (shearing) velocity components perpendicular to the "external" field in order to effect a separation in the direction of one of these components.

We consider the annular space between concentric circular cylinders of radii r_i and r_o, with $r_i/r_o \equiv \eta \leq 1$. The inner cylinder is held fixed, and the outer one rotates at a constant angular velocity $\Omega\mathbf{e}_\theta$. An axial pressure gradient $(dp/dz)\mathbf{e}_z$ drives a net flow through the annulus. Here, $\mathbf{e}_\theta$ and $\mathbf{e}_z$ are unit vectors in the azimuthal and axial directions, respectively.

For a constant-viscosity Newtonian fluid, the velocity field is given by

$$\mathbf{u} = u_\theta(r)\mathbf{e}_\theta + u_z(r)\mathbf{e}_z \tag{1}$$

where the azimuthal and axial components are

$$u_\theta(r) = \frac{\Omega(r - r_i^2/r)}{1 - \eta^2}, \qquad u_z(r) = \frac{-r_o^2 dp/dz}{4\mu}\left(1 - \frac{r^2}{r_o^2} - \frac{1 - \eta^2}{\ln \eta} \ln \frac{r}{r_o}\right) \tag{2a,b}$$

respectively, and μ is the absolute viscosity. The azimuthal velocity component varies monotonically from zero at the inner (nonrotating) cylinder to a maximum value of Ωr_o at the outer (rotating) cylinder. The axial velocity is zero at both cylinders, and attains a maximum at

$$r^* = \left[\frac{1 - \eta^2}{-2 \ln \eta}\right]^{1/2} r_o \tag{3}$$

In Eqs. (1) and (2) we have neglected the dependence of viscosity on temperature (as might be important in an electrophoretic, thermal diffusion, or thermophoretic separation) and composition. Variable viscosity effects will change the quantitative shapes of the velocity profiles (2a,b); since, however, as discussed below, it is the qualitative features of the axial and azimuthal velocity profiles that are responsible for the separation, we will neglect viscosity variation in this discussion. We have also neglected secondary flow that might be driven by buoyancy, electroosmotic, or electrohydrodynamic effects. Finally, we have assumed that this exact solution (Eqs. 1 and 2) of the Navier–Stokes equations is stable [cf. Joseph (4)], that the flow is fully developed axially, and that end effects are unimportant.

The class of separation processes will be discussed in terms of two solutes to be separated on the basis of a difference in radial migration rates under the action of an applied radial field (electrical, centripetal, thermal, etc.). The principle is generally extendible to separation of more components, or to viruses, other supramolecular assemblies, and cells. The present discussion considers deterministic trajectories of molecules of two species in the absence of diffusion, the effects of which are discussed below.

The mixture to be separated enters the annulus from a port (e.g., a porous membrane or frit) on the inner cylinder. The solutes will migrate toward the outer cylinder at different rates, depending on their respective electrophoretic mobilities, sedimentation coefficients, etc. We consider the trajectories of two molecules with different mobilities injected simultaneously at the same point on the inner cylinder. Since $u_z(r)$ initially increases as the molecules move away from the inner cylinder, and $u_\theta(r)$ increases monotonically with radius, the faster-migrating component will initially move ahead not only in the r-direction, but also in the z- and θ-directions. However, as each component's radial position passes r^*, its axial velocity decreases. Thus, some time after the faster-migrating species passes r^*, the axial velocity of the slower-migrating component exceeds that of the faster-migrating component, and remains so until the end of the separation. Furthermore, as the two components come closer to the outer cylinder, the difference in their azimuthal velocities increases monotonically, with that of the faster-migrating component being larger. Thus, as the outer cylinder is approached, the axial velocity of the faster-migrating component is less than that of the slower-migrating species. (The outlet, a constant-z exit plane, is located somewhere upstream of the point where the trajectory of the faster-migrating component would otherwise intersect the outer cylinder, so that neither species ever reaches the wall.) The result is that the faster-migrating species spends relatively more time near the outer cylinder, where the azimuthal velocity is highest. This causes the two components to emerge (at the exit plane) at different values of the azimuthal coordinate. Calculations (5) for β-lactoglobulins A and B, and racemic denopamine (one enantiomer of which is a potent cardiotonic agent) complexed with a stereoselective cyclodextrin, for which the relative mobility differences are 7 and 2%, respectively, show that (diffusionless) separations of 180° can be achieved with relatively modest angular rotation rates.

Such separations are clearly field-flow fractionation techniques according to the classification of Giddings (3). The flow is "integral" to the process, rather than "passive" (3), since in the absence of flow there is no azimuthal separation. Thus, this class of separations differs from continuous deflection electrophoresis and other processes in which flow simply aids in collection.

Put more generally, this class of separation schemes begins with the premise that a continuously operating separation process necessarily involves flow, and that in three dimensions:

1. One direction (in this case the radial, or r-direction) can be used as the force-induced "migration direction," in which direction a force acts differentially on two or more species (or types of particles).
2. A second direction (in this case the axial, or z-direction) can be used as the "elution direction," in which direction species are continuously washed out of the volume at a rate dependent on position along the "migration coordinate."

3. The third direction (in this case the azimuthal, or θ-direction) can be used as the "amplification direction," in which direction the flow field preferentially advects the faster-migrating species, allowing for azimuthal separation and collection at some downstream location in the elution direction.

It has been realized previously that a third direction (other than the elution and enrichment directions) can be used as a second "separation" direction (6) in FFF processes. What distinguishes the present class of processes from other multidimensional FFF and non-FFF techniques, including chromatographic (7–12), electrophoretic (13–18), shear-driven migration (19), and electrochromatographic (20) separations in rotating annuli, is that the present continuous approach uses flow in the elution (z-) and amplification (θ-) directions, respectively, to amplify the differential mobility in the radial (r-) direction into a large separation in the azimuthal direction.

The transport of each species ($k = 1, 2$) can be described by a conservation equation

$$\frac{\partial C_k}{\partial t} + \mathbf{u}\cdot\nabla C_k = -\nabla\cdot\mathbf{J}_k \tag{4}$$

where C_k is the concentration of the kth species, $\mathbf{u}$ is the fluid velocity, and $\mathbf{J}_k$ is the flux of the kth species. The flux consists of a diffusive contribution and a contribution from migration. If the solution is dilute, the flux can be approximated by

$$\mathbf{J}_k = -D_k\nabla C_k + \mu_k C_k f\mathbf{e}_r \tag{5}$$

where μ_k and D_k are the mobility and diffusivity, respectively, of the kth species, and f is the magnitude of the radial force responsible for migration.

The validity of the transport equation (4) may be limited by dilute solution approximations inherent in Eq. (5) [cf. Newman (21) for migration in an electric field], but is certainly useful for a first analysis.

Under steady conditions, Eqs. (1), (4), and (5) can be combined to give

$$\frac{u_\theta(r)}{r}\frac{\partial C_k}{\partial\theta} + u_z(r)\frac{\partial C_k}{\partial z} + \mu_k\frac{1}{r}\frac{\partial(rfC_k)}{\partial r} = D_k\left[\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial C_k}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2 C_k}{\partial\theta^2} + \frac{\partial^2 C_k}{\partial z^2}\right] \tag{6}$$

The first and second terms on the left-hand side of Eq. (6) represent the rates at which the kth species is advected in the azimuthal and axial directions, respectively, by the helical flow. We note that these rates depend on radial position. The third term represents the rate at which the *k*th species is transported toward the outer cylinder by migration. The terms on the right-hand side represent the rates of radial, azimuthal, and axial diffusion.

Since the separation takes place in the azimuthal direction, very long effective path lengths can be obtained in relatively small apparatuses by wrapping the trajectories around the inner cylinder many times, using a large ratio of the angular velocity to the axial velocity. Simple analysis shows that, on a diffusionless basis, the azimuthal separation increases linearly as this ratio increases, and monotonically as the field strength f approaches the limiting value f^* at which the trajectory of the faster-migrating species intersects the outer wall upstream of the exit plane. In real systems, however, one needs to account for diffusion.

Simple considerations show that diffusion will tend to increasingly degrade the separation as α increases and as f approaches f^*. In the diffusionless analysis, all molecules of a given species move along identical trajectories, and the concentration distributions at the exit plane consist of one point (ξ_k, θ_k) for each species. The effect of diffusion will be to smear each point out into a two-dimensional contour pattern in the exit plane. If diffusion is sufficiently weak, the patterns will be tightly distributed around the diffusionless points, the degree of overlap between the distributions for the two species will be small, and a nearly complete separation will be possible. As diffusive effects become more important, the two patterns will increasingly tend to overlap, thus degrading the separation.

The most obvious contributor to azimuthal broadening of the concentration distributions of the two species at the exit plane is the azimuthal diffusion term [second term on the right-hand side (RHS) of Eq. 6]. However, there are other contributing effects, which under some conditions will be considerably more important.

We recall the simple analysis of axial dispersion in laminar shear flows discussed by Taylor (22) and Aris (23). Taylor showed that in simple unidirectional shear flows (e.g., plane or circular Poiseuille flow, between parallel plates or in a circular pipe, respectively), two phenomena contribute to axial dispersion of a solute: axial diffusion (the last term on the RHS of Eq. 6), and differential axial advection, owing to the velocity gradient, of solute that has (radially) diffused into fluid elements different distances from the wall. This second effect is referred to as axial dispersion; in many cases of interest, it is more important than axial diffusion.

Similar considerations pertain in the present helical flow, in that radial diffusion (first term in the brackets on the RHS of Eq. 6) brings molecules of the *k*th species into fluid elements having different azimuthal velocities, leading to azimuthal dispersion that may exceed that due to the azimuthal diffusion term (penultimate term on the RHS of Eq. 6). As in the classical Taylor case, radial diffusion also leads to increased axial dispersion, which in the present case further leads to increased azimuthal dispersion, owing to the dispersion in residence times, and hence differential exposure to the azimuthal shear flow. Thus, for f just less than f^*, the faster-migrating species has a longer residence time in a region of high axial shear, possibly leading to significant axial (and hence azimuthal) dispersion. We refer to these two sources of broadening as "primary azimuthal dispersion," since they are direct consequences of radial and axial diffusion.

A final source of azimuthal broadening is a consequence of the classical Taylor axial dispersion that has its own origin in radial diffusion. Like axial diffusion, axial dispersion (owing to radial diffusion) also gives rise to azimuthal dispersion through a broadening of the residence time distribution. This contribution might properly be referred to as secondary azimuthal dispersion.

The preceding analysis and discussion neglects the effects of secondary flow (i.e., departures from the velocity field described by Eqs. 1 and 2) on the distributions of the two species. In most separations, secondary flow (or any unwanted flow, if the fluid is nominally motionless) is generally thought to indiscriminately mix fluid elements enriched in one species with fluid elements enriched in the others, thus degrading the separation. In the example considered, there are several possible sources of secondary flow. These include gravitationally-driven buoyant flow, associated with the existence of significant density variations (due to the nonuniform composition in any process, and possibly due to temperature variation, as in an electrophoretic or thermal diffusion separation) in the presence of gravitational acceleration, and centrifugally-driven buoyant flow, associated with the same source of density variation in the presence of the centrifugal acceleration accompanying fluid rotation.

If the separation is an electrophoretic one, in which application of a potential difference across a conducting fluid leads to passage of a current, this will lead to generation of heat, and hence temperature variations within the annulus. The temperature gradient will have at least a radial component and, depending on the spatial variation in electrical conductivity within the fluid, may also have axial and azimuthal components. Since the density depends on temperature, we will have a density gradient with at least a radial component. Since gravitationally-driven convection necessarily arises whenever $\nabla\rho$ isn't parallel to the gravitational acceleration $\mathbf{g}$ (24), and since there is no alignment of the cell for which $\mathbf{e}_r \times \mathbf{g} \neq \mathbf{0}$

everywhere, buoyancy-driven convection will necessarily occur if the separation is conducted at normal gravity.

In a centrifugal acceleration field (akin to a gravitational acceleration field), the only apparent source of secondary flow is the buoyant motion due to the presence of a density gradient (arising from the nonuniform distribution of the solutes).

Regardless of its source, gravitationally-driven motion can be largely eliminated by conducting the process in the microgravity environment of space. We also note that electromagnetically-driven and rigid-body rotation have been used by Kolin (14–16) and Hjertén (13), respectively, to achieve considerable inhibition of buoyancy-driven convection in an electrophoresis cell, and that shear-driven rotation in the present flow may have similar effects.

In conclusion, these separations constitute a new class of field-flow fractionation processes, potentially capable of large separations in relatively small geometries, using helical flow to wrap trajectories of species to be separated around a cylinder many times in an annular space. Actual performance will depend on the importance of both diffusion and the associated dispersion mechanisms, and of secondary flows superimposed upon the nominal helical flow.

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