

Cellular and Molecular Magnetic Separation

Introduction

Separation processes, or more broadly, the controlled movement of cells and molecules, is fundamental to bioprocesses. Means of separating are not infinite: size differentiations (i.e. filtration), density differences (i.e. centrifugation), electrical charge (either intrinsic or applied), solubility difference (i.e. distillation, “salting out”, and extraction), weak molecular forces (i.e. Van der Waals, hydrogen bonding), and magnetics.

Historically, magnetic separations were probably the least developed in biotechnological systems. This changed with low-cost, extremely powerful permanent magnets and the commercial availability of paramagnetic particles.

Fundamentally, a magnetic force is quantified by the following relationship:

$$\vec{F}_{mag} = MV\nabla\vec{B}_o \quad (1)$$

where F_{mag} is the magnetic force, M is the magnetization of the entity to be separated, V is the volume of the entity, and B_o is the applied magnetic field. Depending on the intended use, Equation 1 can be written in variety of forms, which assists in the analysis and design of the separation system. For example, Equation 1 can be written in a form in which the magnetically induced velocity, u_m , of the entity to be separated is related to a number of fundamental variables:

$$u_m = \frac{\Delta\chi D_p^2}{18\eta} \left(\frac{1}{2\mu_o} \frac{dB_o^2}{dx} \right) = m S_m \quad (2)$$

where $\Delta\chi$ is the difference in the magnetic susceptibility of the entity to be separated and the suspending buffer, m is the magnetophoretic mobility of the entity of interest, and S_m is referred to as the magnetic energy gradient. Inspection of Equation 2 indicates that four primary variables are adjustable: $\Delta\chi$, the diameter of the particle to be separated, D_p ; the magnitude of the magnetic field, B_o ; and the gradient of the magnetic field, dB_o/dx . A recent publication, partially supported by the NSEC, continues to test this relationship by exploring these four variables (Jin et al. submitted).

Recent advances

Research, partially supported by the NSEC, is focused on continuing to push the limits (both theoretically and experimentally) of each of the four variables listed above to determine the feasibility of developing a platform technology that can exploit magnetic forces to achieve practical, inexpensive movement/separation/detection of molecules on a submicron scale.

Theoretical range of values of S_m .

As indicated by Equation 2, the driving force for a magnetic separation is the value of S_m . Currently, one of the most practical ways to create a high, well-defined value of S_m is through the use of a Quadrupole field (Williams et al. 1999). Figure 1 presents the value of S_m as a function of the radius and a practical range of maximum magnetic fields that can be created with permanent magnets. In addition, a current system as well as a system under construction are presented.

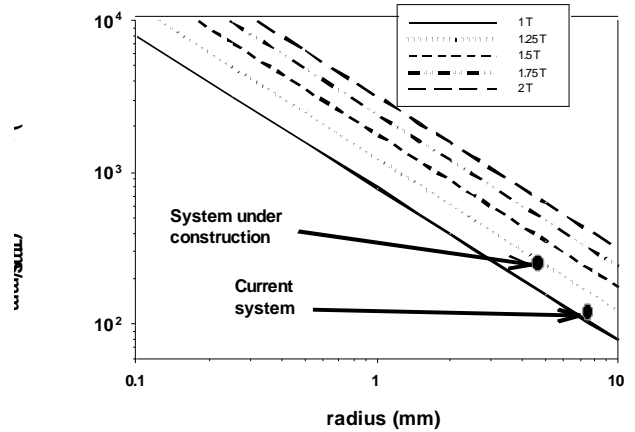


Figure 1. S_m as a function of radius in a Quadrupole magnet for different values of B_o .

Feasibility of separating individual proteins by magnetic nanoparticles

Simplifying assumptions including particle and field uniformity, Stokes flow, and classical diffusion, allow estimates of the relative distance a particle moves as a result of magnetic forces and thermal effects. Once particle trajectories are created, the separation potential may be quantified by chromatographic resolution,

$$R_s = \frac{\Delta x}{2(\sigma_1^x + \sigma_2^x)} \quad (3)$$

where x is the particle translation and σ^x is its standard deviation along the axis. Subscripts refer to the label and separand.

With this simple mode, we estimate the feasibility of separating any two uniform populations from a given starting point. Figure 3 plots the distribution (due to diffusion) of the magnetically induced, perpendicular displacement of the magnetic nanoparticle for different values of S_m . This displacement is shown as a function of time. The values of S_m are consistent with what is currently achievable, as shown in Figure 1.

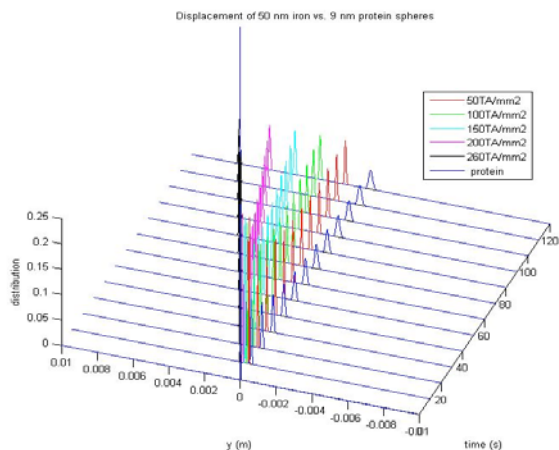


Figure 2. Displacement (y-axis) of magnetic particle as a function of time (s) for various values of S_m values (different colored peaks)

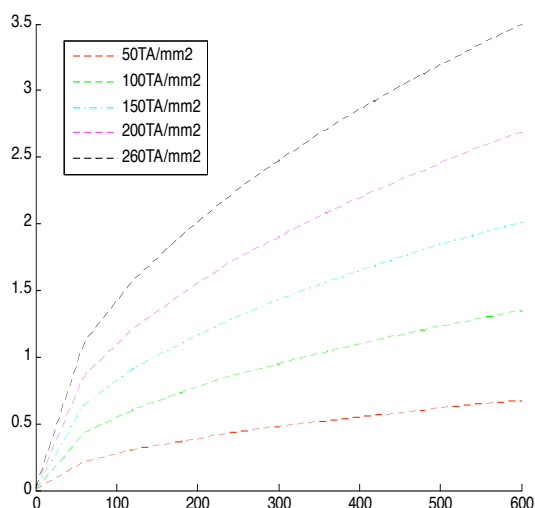


Figure 3. Resolving power (Equ 5).

Conclusion of model

Figures 1 through 3 indicate that it is theoretically possible to develop a molecular, magnetic cell separation system. Figures 2 and 3, and Equation 2 indicate that the greatest potential to improve performance (increase the value of R_s) is to significantly increase the value of S_m . Also, while the value of the magnetic susceptibility of a nanoparticle is determined by the composition of the material, the synthesis of a uniform magnetic nanoparticle in which the surface properties can be highly controlled can still be significantly improved.

Current and future research.

Current and future research can be classified into four areas: 1) Development of inexpensive magnet systems that create higher values of S_m than currently available; 2) Development of improved magnetic nanoparticles; 3)

Development of micro-/nanofluidics to fit within new magnet systems, and 4) Demonstration of molecular, magnetic separations.

Development of inexpensive magnet systems

Figure 5 is a diagram of a new magnet design, for which a patent has been submitted, which cost less than 1/10 of the current system. It has the potential to increase S_m 10 to 100 higher than current system.

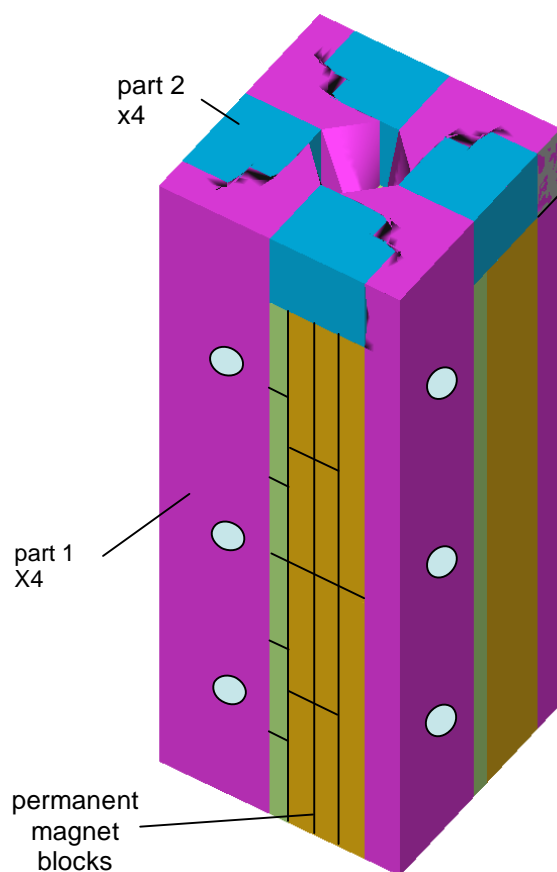


Figure 5. New Magnet design.

Publications

1. Jin, X., Zhao, Y., Moore, L., Williams, S., Zborowski, M., Chalmers, J.J. Detection of type of microparticle magnetization (paramagnetic v. ferromagnetic) by using variable field Cell Tracking Velocimetry. Submitted to *The Analyst*.
2. Williams, P.S., Zborowski, M., Chalmers, J.J. Flow Rate for the Quadrupole Magnetic Cell Sorter. *Analytical Chemistry* 71:3799-3807, 1999.