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Magnetic Levitation

Magnetic Levitation in Chemistry, Materials Science, and Biochemistry

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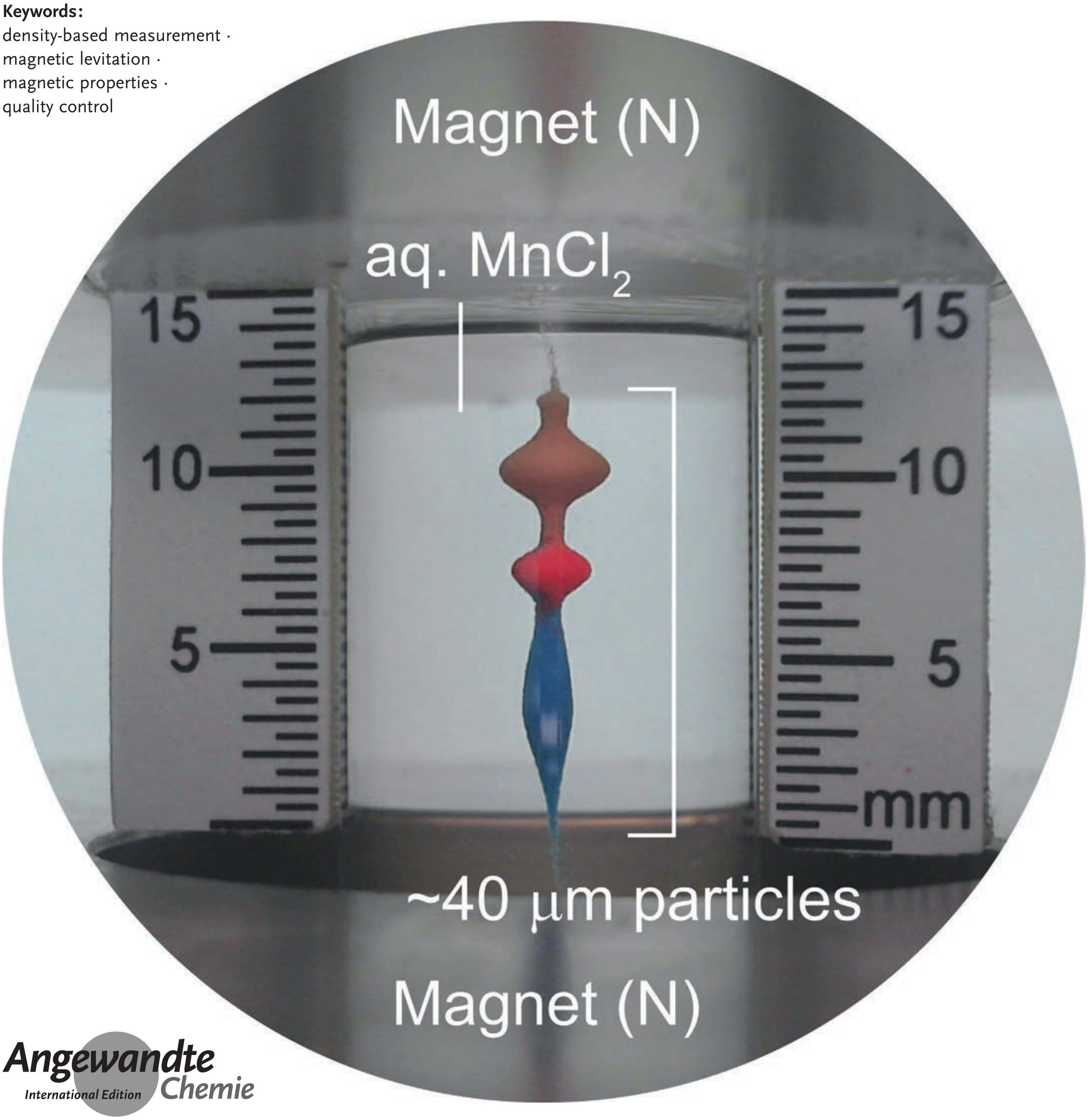

All matter has density. The recorded uses of density to characterize matter date back to as early as ca. 250 BC, when Archimedes was believed to have solved "The Puzzle of The King's Crown" using density.[1] Today, measurements of density are used to separate and characterize a range of materials (including cells and organisms), and their chemical and/or physical changes in time and space. This Review describes a density-based technique—magnetic levitation (which we call "MagLev" for simplicity)—developed and used to solve problems in the fields of chemistry, materials science, and biochemistry. MagLev has two principal characteristics—simplicity, and applicability to a wide range of materials—that make it useful for a number of applications (for example, characterization of materials, quality control of manufactured plastic parts, self-assembly of objects in 3D, separation of different types of biological cells, and bioanalyses). Its simplicity and breadth of applications also enable its use in low-resource settings (for example—in economically developing regions—in evaluating water/food quality, and in diagnosing disease).

From the Contents

MagLev is a physical technique that makes it possible to measure the density of an object (solid, liquid, gel, or heterogeneous mixture of materials) for characterization and separation of objects, particles, or materials. MagLev is also useful in manipulation of objects in 3D—without physical contact with the walls of a container—for self-assembly and other uses. To first order, its operation is independent of the shape of the object. The technique, as we describe it here, uses NdFeB permanent magnets to suspend objects in a paramagnetic liquid—typically a solution of Mn^{II} or Gd^{III} (or a chelate of these ions) in water (Figure 1). It measures a universal physical property of all matter—density—and is compatible with the majority of materials (virtually all organic, and many inorganic, and organometallic materials are diamagnetic). Table 2 lists the key characteristics of MagLev that enable it to solve a broad range of problems in chemistry, biochemistry, and materials sciences.

This Review summarizes the working principles of MagLev, the key components in a typical measurement using MagLev (including the rationale for their choices), and major demonstrations and applications of MagLev, in chemistry, biochemistry and materials science. It also discusses the limitations of current methods based on MagLev and outlines a roadmap to improve the performance of MagLev-based technologies, and to maximize their potential for future uses.

1. Introduction

1.1. Objective and Focus of the Review

This Review focuses on magnetic levitation (which we call "MagLev" as an abbreviation) of diamagnetic (and also weakly paramagnetic) objects suspended in paramagnetic media using permanent magnets (MagLev is also known as "Magneto–Archimedes Levitation" or "Diamagnetic Levitation").[2–5] MagLev (as we describe it here) is especially useful in separation of microparticulate powders of materials with different density, and in the determination of density. The Review discusses the uses of this type of MagLev in depth in two specific areas: (i) density-based analysis, separation, and 3D self-assembly of physical (nonbiological) and biological materials (including cells, composite materials, and powders), and (ii) contactless manipulation of levitated objects. It focuses on applications in the broad areas of chemistry, materials science, and biochemistry. We also refer readers to separate, excellent reviews by Turker and Arslan-Yildiz,[6] Gao and Zhang,[7] and Ozcivici and Tekin,[8] which summarize uses of MagLev in materials science and in biomedical applications, and are especially strong in the latter.

This Review excludes magnetic separations using attached or adsorbed superparamagnetic particles (Table 1). It also excludes techniques that carry out 3D cell culture at an air–liquid interface using cell-internalized magnetic nanoparticles and magnets (a distinct technique, sometimes also referred to as "magnetic levitation"),[9–12] levitating magnets (e.g., in ferrofluids),[13–15] large-scale industrial applications of magnetism (reduction of friction in high-speed trains, waste separations, mineral separations),[16–18] or in other kinds of levitation (e.g., acoustic levitation).[19] It does include some discussions of another method of determining density (aqueous multiphase polymer system, or AMPS), which has particular strengths in biochemistry.

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Table 1: Comparison of technical characteristics of MagLev and magnetic separation.

	MagLev (this Review)	Magnetic Separation (using superparamagnetic particles)
Function	Density-based analyses, separations, and manipulations[20–22]	Targeted separation[23–25]
Fluid medium	Paramagnetic	Diamagnetic
Target	Diamagnetic	Superparamagnetic
External label	Label-free or label mediated	Superparamagnetic particles with attached ligands
Affinity ligands	Not required	Yes (e.g., antibody)
Results of separation	Continuous	Discontinuous
Self-focusing	Along the axis of the field or at a field minimum	Magnetic field maximum
New effect	Stationary "effective" density gradient in a flowing liquid;[a] introduction of, or tuning of, forces by tilting, fluid flow, and other manipulations	Convenient affinity separations

[a] See Section 4.2.4 Separations of Materials Under Flow for more discussions.

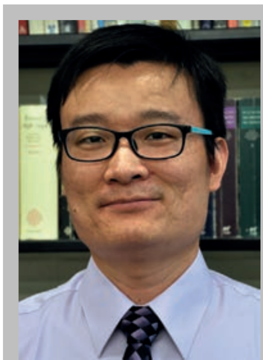
1.2. What is MagLev?

MagLev is a technique that suspends objects against the force of gravity using magnetic interactions, and separates them by density using a competition between gravitational and magnetic fields and field gradients. Historically, the term "magnetic levitation" has been used most commonly in two distinct areas of applications: (i) suspension and propulsion of vehicles, bearings, and flywheels with magnets,[26,27] and (ii) suspension of diamagnetic matter (including the exceptionally diamagnetic materials, graphite and bismuth[28]) in the magnetic field of a paramagnetic fluid or gas (especially liquid O_2), or in vacuum. This Review addresses only the latter type of magnetic levitation, in which the suspended object experiences a force—reflecting the relative magnitude of the interaction of the object and the suspending medium with the applied magnetic field—that is sufficiently large to overcome the effect of gravity, and thus, to levitate the object in the suspending medium.

There are four types of magnetism that are relevant to MagLev: diamagnetism, paramagnetism, ferromagnetism, and superparamagnetism. (See Section S1 for an overview of these four types of magnetism.) Figure 2 shows magnetic susceptibilities of a number of paramagnetic and diamagnetic materials relevant to the MagLev technique we describe here.

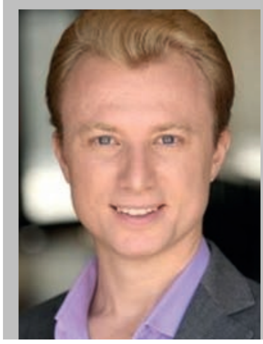
1.3. History and Prior Work

Examples of MagLev include levitation in vacuum,[28,29] air,[15,30–34] liquid[35] and pressurized[4,36,37] oxygen, in solutions of paramagnetic salts,[20,38–44] and in suspensions of ferromag-



Shencheng Ge received his B.S. degree from Fudan University (Shanghai, China) in 2005, and his PhD from the University of Minnesota, Twin-cities in 2011 (with Christy L. Haynes). He worked previously at the University of Chicago and California Institute of Technology (with Rustem F. Ismagilov), and is now working in the Whitesides Research Group at Harvard University. His research interests focus on biomedical analysis, microfluidics, bioanalytical chemistry, and materials science.

Katherine A. Mirica was born and raised in Ukraine. She received her B.S. in Chemistry in 2004 from Boston College, working in the laboratory of Prof. Lawrence T. Scott. In 2011, she earned her Ph.D. in Chemistry from Harvard University under the guidance of Prof. George M. Whitesides. During 2011–2015, she pursued an NIH postdoctoral fellowship in the laboratory of Prof. Timothy M. Swager at the Massachusetts Institute of Technology. Katherine began her independent scientific career as an Assistant Professor of Chemistry at Dartmouth College in July of 2015. Her current research interests revolve around multifunctional materials, electroanalysis, adhesion science, and self-assembly.



Alex Nemiroski received his BA degree from Cornell University in 2005 and his PhD from Harvard University in 2011. After completing a postdoctoral fellowship in the Whitesides Research Group at Harvard, he began his independent career at Illumina, Inc. (San Diego, CA). He is currently the head of Flowcell Development and Manufacturing at Omniome, Inc. (San Diego, CA).

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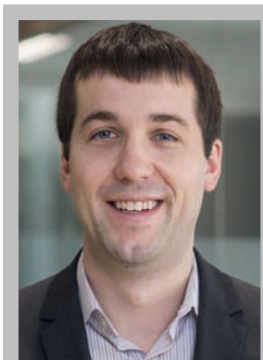
netic particles in a carrier fluid[45] using various sources of magnetic fields (e.g., permanent magnets, simple electromagnets, superconducting magnets). Here, we are concerned primarily with examples in which an object more dense than a paramagnetic suspending medium displaces this medium from a region of higher magnetic field to a region of lower magnetic field as it sinks under the influence of the gravitational field.

Initial demonstrations of MagLev were limited to the levitation of strongly diamagnetic materials, such as pyrolytic graphite and bismuth, using permanent magnets or electromagnets, in air or in vacuum. In 1939, Braunbek et al. demonstrated levitation of pyrolytic graphite and bismuth in air using an electromagnet generating fields of 2–3 T.[52] By the end of 1960s, the concept of levitating pyrolytic graphite with permanent magnets found a number of applications, including a frictionless rotor,[34] accelerometer,[53] a sensitive tiltmeter/seismometer (capable of measuring differences in tilt angles of $\sim 10^{-5}$ degrees, and detecting seismic activity),[33] and a sensitive pressure gauge (capable of measuring pressures of gas of 10^{-10} torr).[29] In the 1960s and 1970s, applications of MagLev extended to density-based analyses and separations of minerals, metals, and plastics suspended in paramagnetic fluids using permanent magnets and electromagnets.[38] The use of superconducting and resistive solenoid electromagnets in the 1990s and 2000 s expanded the range of materials that could be suspended against gravity to include wood, glass, gold, water, ethanol, living organisms, and many other samples.[4,15,30,31,35–37,50,54–60] The discovery of NdFeB magnets in 1982,[61,62] followed by their widespread commercial availability, enabled many of the most recent applications of MagLev highlighted in this Review by eliminating electromagnets, with their cost, weight, and complexity.[20,32,40–42,44,45]

A number of groups have recently contributed to the recent development in this field. In particular, the Demirci group has made innovative contributions to the separation, analysis, and assembly of biological cells (particularly single cell analysis).[63–70] Ghiran, Tasoglu, and colleagues have developed a range of new techniques (particularly in the combined use of MagLev and smartphones) and applications in medical analysis (cells and assays).[71–78] The Yildiz group has developed a method to carry out scaffold-free cell cultures.[6,79] Zhao and colleagues have made important advances in developing the technology base (particularly a single-ring MagLev system[80]) and applications in materials science (particularly for polymeric materials).[80–86] Zhang et al. have developed an innovative approach that integrates MagLev and centrifugation for dynamic control of density-based analysis.[7,87] The Martinez group has prototyped a serological assay for diagnosing disease in resource-limited settings.[88] Yu has applied Maglev to analyze cooking oils.[89] Grzybowski has developed potentially important methods to carry out magnetic tweezing and self-assembly of diamagnetic colloids in paramagnetic solutions.[90–92] The work of these groups is summarized in their papers and in separate reviews;[6,7,69,72,76,87–89,92] their work, and these summaries and analyses, are described and referenced in appropriate sections of this Review.



Jonathan Hennek completed his postdoc in the lab of George M. Whitesides at Harvard University where he applied his expertise in materials chemistry to problems in diagnostics and manufacturing. He received a Ph.D. in chemistry in 2012 from Northwestern University (under Tobin J. Marks) and a B.S. in chemistry from the University of Saint Thomas in 2008. He is currently at Indigo Ag where he leads an interdisciplinary team dedicated to the creation of systems across data, technology, and biology that drive radical change in agriculture.

Ashok A. Kumar received his BS degree from Stanford University in 2007 and his PhD from Harvard University in 2014. He began his independent career leading R&D at a point-of-care diagnostics company, Jana Care, and is now a Science Director in Systems Innovations at an agriculture technology company, Indigo Agriculture in Boston, MA. His research work focuses on sensors and diagnostics with an interest in applications related to human and environmental well-being.

George M. Whitesides received his AB degree from Harvard University in 1960, and his PhD from the California Institute of Technology in 1964 (with J. D. Roberts). He began his independent career at the Massachusetts Institute of Technology, and is now the Woodford L. and Ann A. Flowers University Professor at Harvard University. Among his current research interests are water, self-assembly, complexity and simplicity, origin of life, dissipative systems, affordable diagnostics, magnetochemistry, and soft robotics.

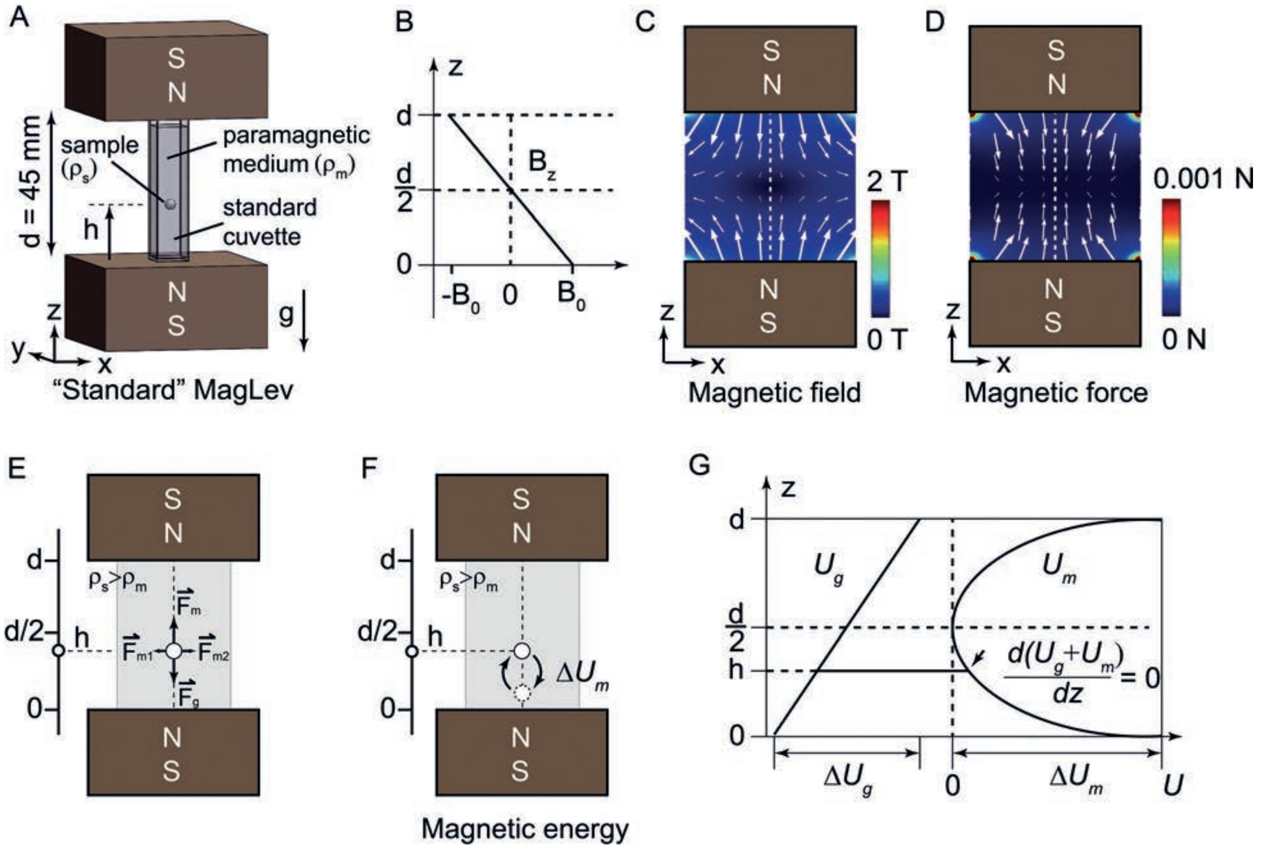


Figure 1. "Standard" MagLev system (A) The components of the "standard" magnetic system include two NdFeB permanent magnets, a paramagnetic medium (e.g., aqueous $MnCl_2$ solution), a sample container, and a ruler (to measure the position of the sample). The distance between the geometric center of the object and the top surface of the bottom magnet is most commonly defined as the levitation height h. (B) The "standard" MagLev system uses an approximately linear magnetic field along its central axis (also see vertical dotted line in C) to levitate objects. (C) The magnetic field between the two magnets (which effectively forms a "magnetic bottle" for diamagnetic particles). (D) The magnetic force $\vec{F}_m$ a 5-mm spherical glass bead experiences when it is suspended in a paramagnetic medium (1 M aqueous $MnCl_2$), and then placed in the magnetic field. The magnetic force is estimated using Eq. S6 and plotted as $2.3\log|\vec{F}_m|$ (in Newton). (E) An object (which, in this case, is more dense than the medium; that is $\rho_s > \rho_m$) reaches a stable levitation height h below the midpoint of the system when its effective gravitational force $\vec{F}_g$ (corrected for the effect of buoyancy) counterbalances the magnetic force $\vec{F}_m$ the object experiences along the central axis of the device. An object with a finite volume will also experience weaker magnetic forces ($\vec{F}_{m1}$ and $\vec{F}_{m2}$) perpendicular to the central axis, and they counterbalance one another. (F) A magnetic energy cost will be incurred when the object at equilibrium deviates from its stable levitation position toward the bottom magnet, and displaces an equal volume of the paramagnetic suspending medium (dotted circle) away from a region of higher magnetic field to a region of lower magnetic field. (G) Profiles of the gravitational energy U_g and the magnetic energy U_m of the system involving a diamagnetic object (in this case, $\rho_s > \rho_m$) suspended in a paramagnetic medium placed in the "standard" MagLev system. ΔU_g is the change in gravitational energy of the system (The zero-energy point is defined at infinity in distance), and ΔU_m is the change in magnetic energy of the system (The zero-energy point is located at the midpoint between the magnets).

1.4. Why is MagLev Useful?

Because all matter has density, and, with the exception of stable free radicals, essentially all organic matter is diamagnetic, MagLev is broadly applicable to analysis of many different types of materials in chemistry, biochemistry, and materials science. It is a relatively "information poor" technique, but almost universally applicable. It uses a single physical characteristic of matter—density—almost exclusively for its applications, and is insensitive to many other physical characteristics of the samples, such as the volume, mass, shape, viscosity, elasticity, and others; that is, it measures directly the density of a sample independently of its mass or volume (although density, of course, is the quotient of the two). It usually does not provide chemical or molecular information about the samples, such as chemical composition or structure. Sometimes molecular characteristics can be inferred indirectly (for example, through change in density on reactions). Its generality, however, makes it broadly applicable.

A version of MagLev developed in our laboratory is an inexpensive and uncomplicated methodology that can be adapted to a wide range of problems. The advantage of using a NdFeB magnet is that it does not require electrical power. NdFeB magnets combine a high field with a particularly large remanence (that is the magnetization they retain after any external applied magnetic field is removed; the remanence is up to ~1.5 T for the N52-grade permanent magnets), and thus, this type of magnet is resistant to demagnetization (the reduction or loss of magnetization of a material). This

Table 2: Key technical characteristics of MagLev using permanent magnets.

Characteristics	Description
Simplicity	It is *simple* in design and use. NdFeB permanent magnets do not require electricity to operate, are inexpensive, and are portable.
Maintenance	NdFeB magnets are commercially available, stable over time, and do not, in principle, need replacement beyond occasional calibration in the device.
Properties of suspending liquids	It uses, in general, common, non-toxic or environmentally friendly paramagnetic media (e.g., aqueous solutions of $MnCl_2$) to levitate objects. Some of the paramagnetic species (e.g., chelates of Gd^{III}) are both highly paramagnetic and biocompatible.
Compatibility with samples	It is compatible with different types of samples (e.g., organic, inorganic, polymeric, metallic (diamagnetic), and composite) and samples in different physical forms (e.g., gas, liquid, solid, gel, gum, paste, and heterogeneous mixture). It measures the density of a sample independently of its shape. It covers the entire range of densities observed in matter at ambient conditions—from a bubble of air (~0 g cm^{-3}) to the heaviest elements in the periodic table (osmium and iridium, ~23 g cm^{-3}). It is applicable to both small particles (as small as a bacterium, ~1 μm) and macroscopic objects (e.g., a plastic screw, ~a few cm).
Functionality	It is *functional* as a physical tool with which to measure densities of objects for analysis and separation, and to manipulate objects in 3D, without solid-solid contact, for self-assembly. It is also sensitive to differences in density within a single object.

property is critical for the MagLev systems we describe here, which typically use like-poles-facing configurations (e.g., Figure 1).

1.4.1. *Density is a Universal Property of Matter*

All forms of matter have finite mass and volume, and, therefore, have density. Because many chemical and physical processes are accompanied by changes in density, instruments that measure density have the potential to be broadly applicable as universal detectors of chemical composition (i.e., they respond to all analytes). A useful feature of density-based detectors is that they require straightforward (and often minimal) sample preparation to carry out measurements. Density can be homogeneous or heterogeneous in a sample, and its distribution in space (in samples having different shapes) may be a useful physical characteristic for application in which the heterogeneity in density is important (e.g., quality control of manufactured plastic parts).

1.4.2. *Uses of Density in Chemistry, Biochemistry, and Materials Science*

Historically, density measurements have been widely used to analyze and separate a variety of materials in chemistry, biochemistry, and materials science. Table 3 summarizes some of the uses of MagLev, specifically, for density-based analysis and separation. Density measurements can be used for both static and dynamic analyses of density, and by inference, of chemical composition in specific experiments. For instance, not only do the densities of polymers depend on their chemical composition, but also on the way in which the chains pack in space (i.e., crystalline or amorphous arrangements). The difference in density, therefore, can be used to analyze and separate many types of polymers, even of similar atomic compositions. For certain classes of polymers (e.g., polymers formed by polymerization of small monomers, such as acrylic esters or other vinyl monomers), the change in density associated with polymerization can be used to monitor the progress, and thus, kinetics, of the polymerizations.[110,111] The dynamic change in density over time can also be used to monitor other types of chemical and biochemical reactions, such as cycloaddition reactions (dimerization) of cyclopentadiene,[112] and chemical reactions (or binding) on a solid support (e.g., covalent attachments of low-molecular-weight organic molecules to 4-benzyloxybenzaldehyde polystyrene beads,[42] and binding of carbonic anhydrase to porous hydrogel particles presenting aryl sulfonamides—a class of inhibitors specific to carbonic anhydrase[106]). The density of minerals can also be used to assess their purity, and the difference in density provides the basis for mineral separations.[113] Differently sized carbon nanotubes, coated with structure-discriminating surfactants, show different densities, and thus provide a basis for simple separation.[114]

Density is also commonly used for the analysis and separation of biological samples. The density of urine correlates with dehydration and kidney function, while the density of blood correlates with its hematocrit.[115,116] The difference in densities of various biological particles (e.g., cells, organelles, bacteria, viruses, proteins, and nucleic acids) are used for fractionations (e.g., separation of viruses or bacteria from mammalian cells in a mixture).[94,117–120] Density can also be used to track the growth of cells during a cell cycle, and to analyze the pathophysiological changes associated with infections or genetic disorders.[121]

1.4.3. *Limitations of Conventional Methods in Characterizing Density*

The main classes of instruments used currently for measuring density include density gradient columns, pycnometers, hydrometers, hydrostatic weighing balances, vibrating tube density meters, suspended microchannel resonators, radioactive detectors, and refractometers.[122] Some of the disadvantages associated with these methods involve limited compatibility with different sample types, trade-offs between analytical sensitivity and dynamic range of density measurements, requirement for skilled technicians to operate the devices, and, sometimes, the necessity for expensive and/or

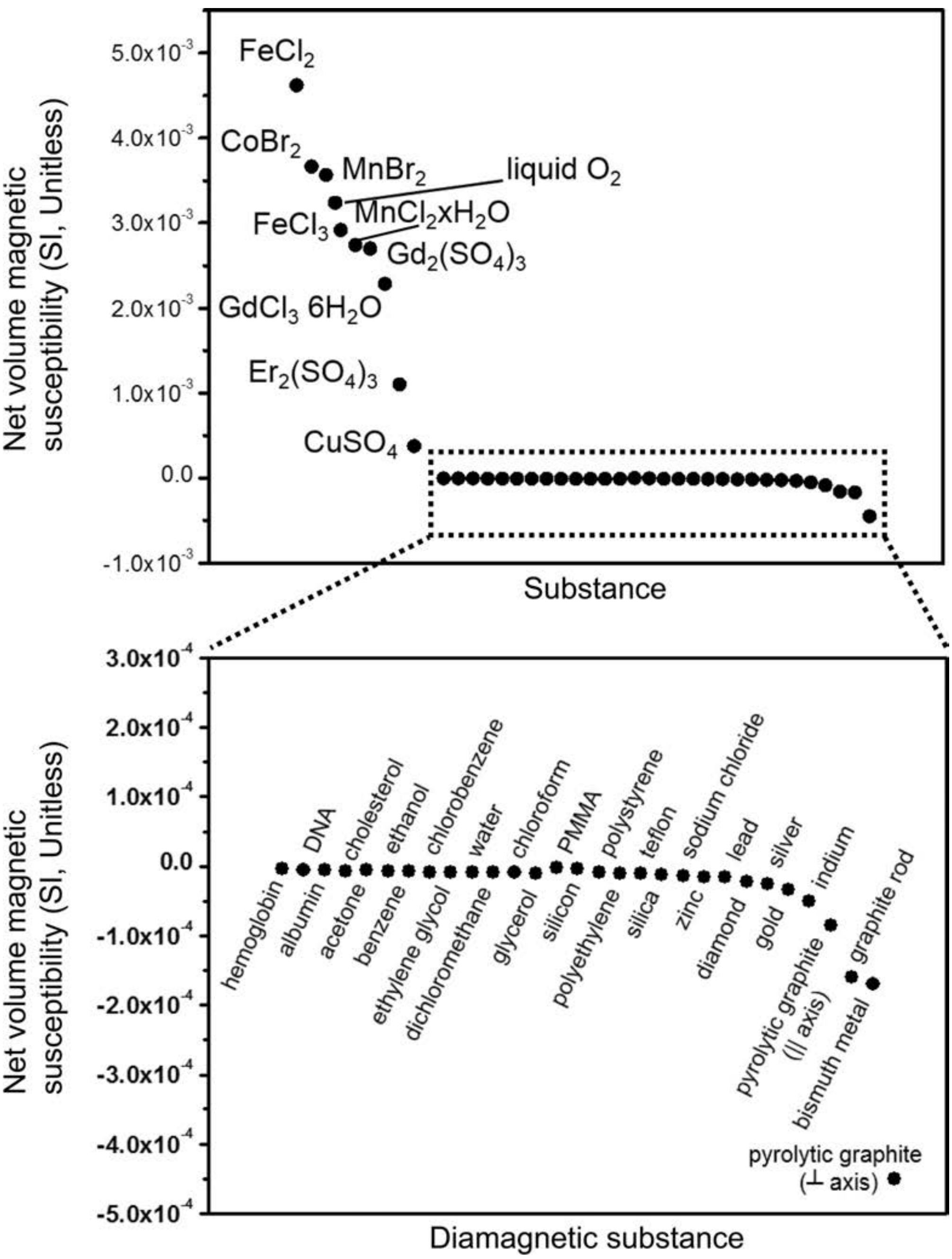


Figure 2. Volumetric magnetic susceptibilities of different types of materials. Those included in the dotted box are diamagnetic, and the rest are paramagnetic. Magnetic susceptibilities of pyrolytic graphite are anisotropic in directions perpendicular to (⊥ axis) and in parallel with (|| axis) the crystal lattice planes. The values are obtained from various sources.[15,36,46–51]

bulky equipment.[122] Table 4 summarizes different techniques—including MagLev—of measuring density and separating materials based on differences in density.

1.4.4. *Opportunities for MagLev as an Analytical Tool for Density-Based Analysis, Separation, and 3D Self-Assembly*

MagLev enables measurements of density, and monitoring of processes that involve changes in density. The method for measuring density based on MagLev is precise ($\sim\pm10^{-2}$ to 10^{-6} g cm^{-3}, depending on the experiment), applicable to a wide range of diamagnetic materials (including solids, liquids, pastes, gels, colloidal suspensions, and heterogeneous materials), easy to use, inexpensive, and portable. In addition, MagLev makes it possible to characterize and separate multiple objects with different densities simultaneously. This capability leads to applications of MagLev in density-based separations.[20,22,101,123,41,42,93,95–98,100] MagLev also provides a unique environment in which diamagnetic objects can be levitated and manipulated, without contacting the walls of the container, for 3D assembly. This capability, in conjunction with density-based levitation, opens unexplored domains of research, and enables new applications of MagLev in emerging areas such as advanced manufacturing, quality control, and 3D self-assembly of both hard and soft, fragile components.[21,135–139]

2. *How Does MagLev Work ? An Overview and Illustration of the "Standard" MagLev Technique*

This section focuses on the general *physical principles* of MagLev in the type we are developing (levitating diamagnetic objects in a paramagnetic medium using permanent magnets), and discusses the interplays between gravitational and magnetic forces and the associated experimental parameters that enable MagLev.

The form of MagLev system that we use most often—what we call in this Review the "standard" system (Figure 1)—uses two solid-state permanent magnets oriented with their like-poles facing (N/N or S/S give indistinguishable results). This configuration resembles the cusp trap or the anti-Helmholtz

Table 3: Examples of magnetic levitation and its uses for density-based analyses, separations, and manipulations.

Sample	Size	Density ($g\,cm^{-3}$)	Type of magnet	B(T)	Paramagnetic medium	Ref
Physical Samples (Nonbiological)						
Air bubble	mm	~0	NdFeB	0.4	$MnCl_2$ in water	[22,93]
Polymer particles (PMMA, PS, Nylon, etc.)	µm–mm	0.9–2.3	NdFeB	0.4	$MnCl_2$/$GdCl_3$ in water and alcohol	[20,42,44,74,86,93–95]
Organic liquids (e.g., chlorobenzene, 2-nitrotoluene, dichloromethane, 3-bromotoluene, and chloroform.)	µm–mm	1.107–1.492	NdFeB	0.4	$MnCl_2$/$GdCl_3$ in water	[20]
D_2O/H_2O	mm	1.00–1.10	NdFeB	0.4	Hydrophobic paramagnetic ionic liquid[a]	[96]
Polymorphs of crystals (e.g., sulfathiazole and *trans*-cinnamic acid), enantiomers (S-/RS-ibuprofen), cocrystals (e.g., carbamazepine/salicylic acid)	µm–mm	1.093–1.580	NdFeB	0.4	$MnCl_2$ in water	[97–99]
Drug microspheres from drug capsules	mm	1.3284	NdFeB	0.4	$GdCl_3$ in water	[95]
Powders containing illicit drugs (e.g., fentanyls)	µm–mm	1.10–1.58	NdFeB	0.4	$Gd(DPM)_3$TOPO[b] or $Gd(acac)_3$TOPO[c] in organic solvents	[100]
Forensic evidence: "glitter" and gunpowder	µm–mm	1.226–1.395	NdFeB	0.4	$MnCl_2$ in water	[101]
Water and Foods: vegetable oils, milk, cheese, peanut butter, grains	mm	0.9–1.4	NdFeB	0.4	$MnCl_2$/$GdCl_3$ in water; Gd-DTAD[d] in organic solvents	[41]
Si, Diamond, Al_2O_3, various minerals	mm	2.33–6.55	NdFeB	0.4	$MnCl_2$ in water	[93]
Al, brass, Hg, Sn, In, Cu, Ag, Pb, Au, Ir, Os	µm–mm	2.7–22.6	NdFeB	0.4	$MnCl_2$ in water	[93]
Graphite, Graphene, Bismuth	–	–	NdFeB	0.4	Air	[102–104]
Organic liquids (e.g., pentane, toluene, nitrobenzene, bromoethane, carbon tetrachloride)	mm	0.6–1.6	Electromagnet	1.9	$MnCl_2$ or $MnBr_2$ in water	[105]
KCl, Si, GaAs, Pb, Au	mm–cm	–	Super-conducting electromagnet	17	Liquid O_2	[35]
NaCl, KCl, water, glass	mm	–	Super-conducting electromagnet	12	Pressurized O_2 $MnCl_2$ in water	[50]
Biological samples						
Polymeric beads for enzyme–ligand binding	mm for beads	1.07–1.14	NdFeB	0.4	Gd-DTPA[e] in water	[106,107]
Polymeric beads for protein binding	mm for beads	~1.05	NdFeB	0.4	$MnCl_2$ in water	[108]
E. coli	µm	1.05–1.30	NdFeB	0.4	Gadobutrol[f] in water	[69]
Yeast	µm	1.06–1.20	NdFeB	0.4	Gadobutrol[f] in water	[69]
Erythrocyte	µm	1.09–1.12	NdFeB	0.4	Gadobutrol[f] in water	[67,69,70,73,76]

Table 3: (Continued)

Sample	Size	Density (g cm^{-3})	Type of magnet	B(T)	Paramagnetic medium	Ref
Leukocyte	μm	1.06–1.10	NdFeB	0.4	Gadobutrol[f] and Gd-BOPTA[g] in water	[67, 69, 70, 73]
Mammalian cell lines	μm	1.03–1.10	NdFeB	0.4	Gadobutrol[f] in water	[69]
Frog	cm	–	Super-conducting electromagnet	16	Air	[15]
Mouse	cm	–	Super-conducting electromagnet	17	Air	[109]
Frog embryo	mm	–	resistive solenoid electromagnet	13	Air	[57]
Protozoan	μm	–	resistive solenoid electromagnet	31	Gd-DTPA[e]	[49]

[a] Hydrophobic paramagnetic ionic liquid: [methyltrioctylammonium]$_3$[HoCl$_6$]. [b] Gd(DPM)$_3$TOPO: gadolinium(III) tris(dipivaloylmethanato) trioctylphosphine oxide. [c] Gd(acac)$_3$TOPO: gadolinium (III) acetylacetonate trioctylphosphine oxide. [d] Gd-DTAD: gadolinium (III) diethylenetriamine triacetic acid didecyldiacetamide. [e] Gd-DTPA: gadolinium (III) diethylenetriaminepentaacetic acid. [f] Gadobutrol: gadolinium (III) 2,2′,2″-(10-((2R,3S)-1,3,4-trihydroxybutan-2-yl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl) triacetate. [g] Gd-BOPTA: gadobenic acid.

configuration, which uses a pair of identical solenoid electromagnets aligned coaxially with like-poles facing, and has an inter-coil distance equal to the radius of the coil.[140,141] We position two indistinguishable NdFeB permanent magnets (typically L × W × H: 50 mm × 50 mm × 25 mm) coaxially (with faces aligned and parallel), and with like-poles facing at a separation of $d = 45$ mm. We then often align the central axis of the magnets to be parallel to the vector of gravity.

This configuration exploits three convenient features to levitate objects: (i) The use of two magnets expands the range of densities over which we can levitate object against gravity. The top magnet enables levitation of objects that float in the absence of the applied magnetic field (i.e., they are less dense than the surrounding paramagnetic medium), and the bottom magnet enables the levitation of objects that sink (i.e., they are more dense than the surrounding paramagnetic medium) in the absence of the magnetic field. (ii) Levitated diamagnetic objects automatically align along the central axis in the suspending medium ("axial focusing" due to the approximately axially symmetric magnetic field; see Section 3.6 for more discussion). This feature is convenient for density-based analyses, separations, and self-assembly. (iii) The distance between the magnets determines the gradient of the magnetic field, and thus, the magnetic force the object experiences in the suspending medium. The magnets can be positioned such that the magnetic field varies approximately linearly along the central line between the two magnets. This feature simplifies the procedures used to calibrate the system and to carry out density-based measurement.

Equation (1) describes the balance of physical forces acting on the object suspended in a paramagnetic medium in an applied linear magnetic field. Equation (2) describes the linear relationship between the density of the sample, ρ_s, and the levitation height, h, which we measure directly in an experiment.

$$\vec{F}_g + \vec{F}_m = (\rho_s - \rho_m)V\vec{g} + \frac{(\chi_s - \chi_m)}{\mu_0} V\left(\vec{B}\cdot\nabla\right)\vec{B} = 0 \quad (1)$$

$$\rho_s = \alpha h + \beta \quad (2)$$

In Equations (1) and (2), $\vec{F}_g$ is the buoyancy-corrected gravitational force acting on the suspended object.[20] $\vec{F}_m$ is the magnetic force the suspended diamagnetic object experiences as a result of the direct interaction of the magnetic field and the paramagnetic medium that surrounds it. ρ_s is the density of the object. ρ_m is the density of the paramagnetic medium. V is volume of the object. $\vec{g}$ is the acceleration due to gravity (where $|\vec{g}|$ is 9.80665 m s^{-2} on earth). χ_s is the magnetic susceptibility of the object. χ_m is the magnetic susceptibility of the paramagnetic medium. μ_0 is the magnetic permeability of free space. $\vec{B}$ is the magnetic field. h is the levitation height of the object. α and β are coefficients to describe the linear function between the density ρ_s and levitation height h of the object.

For most density-based applications, we use standards of known density to calibrate the system to determine the coefficients (α, β) and then calculate the density of the sample from its measured levitation height. (The Supporting Information to this article contains a much more thorough theoretical analysis, including both qualitative and quantitative description of MagLev. It also describes methods of

Table 4: Comparison of techniques for performing density-based analyses and separations.

Technique	Typical range ($g\,cm^{-3}$)	Typical sensitivity ($g\,cm^{-3}$)	Best for	Portability	Sample size	Advantages/disadvantages	Examples of applications	Ref
MagLev	0.8–3	1–10^{-3}	solids liquids pastes gels gums etc.	Yes	fL–mL	(+) inexpensive (+) easy to use (+) high precision (+) applicable to different physical forms (+) applicable to irregularly-shaped samples (+) requires small volume of sample (as low as ~fL) (−) not compatible with ferro- or ferrimagnetic materials	- Monitoring reactions - Analysis of foods, water, and fuel - Detecting binding interactions - Forensics - Separations of crystal polymorphs - Levitation of single cells	[20,41,42,44]
Floating bulb hydrometer	0.6–2	10^{-2}	liquids	Yes	> mL	(+) inexpensive (+) easy to use (−) limited precision (−) limited to liquids (−) requires large volume of sample	- Assess the quality of milk - Urinalysis	[122]
Refractometer	0.6–2	10^{-2}–10^{-4}	liquids	Yes	µL–mL	(+) easy to use (+) portable and laboratory options exist (−) measurement of density is indirect	- Test quality of wine or fermented beverages	[122]
Density gradient column	1–2	10^{-4}	solids liquids	No	pL–mL	(+) high precision (+) applicable to solids and liquids (+) applicable to irregularly-shaped samples (−) requires skilled user to set up and operate (−) changes over time	- Density measurements - Forensics	[124]
Pycnometer	0.6–23	10^{-3}–10^{-4}	solids liquids	No	µL–mL	(+) good precision (−) requires measurement of mass and volume (−) expensive (−) requires large sample volume	- Analysis of liquids and powders	[122]
Oscillating tube density meter	0.6–2	10^{-3}–10^{-5}	liquids	Yes	mL	(+) good accuracy (+) can be portable (−) expensive	- Analysis of liquids, and beverages	[122]
Suspended Micro-channel Resonator	1–2	10^{-4}	solids liquids	No	< pL	(+) excellent accuracy (+) small sample volume (−) expensive (−) limited to samples < pL (−) not applicable to heterogeneous samples	- Biomolecular detection - Measuring single-cell density - Monitoring growth of cells during cell cycle	[125–129]
Aqueous Multiphase Polymer Systems (AMPS)	1–1.5	10^{-3}	solids gels	Yes	µL–L	(+) AMPS is at equilibrium (+) AMPS has easily tunable steps in density (+) interfaces help concentrate and isolate species (−) sometimes requires a centrifuge for rapid operation (−) best for separations, not measurement of density	- Separation of plastics - Separation and isolation of cells	[118,130–132]

Table 4: (Continued)

Technique	Typical range ($g\,cm^{-3}$)	Typical sensitivity ($g\,cm^{-3}$)	Best for	Portability	Sample size	Advantages/disadvantages	Examples of applications	Ref
Density Gradient Centrifugation	1–2	10^{-3}	solids gels	No	mL–L	(+) best for small biological samples (e.g., organelles, viruses, proteins, and nanomaterials) (+) several biocompatible options for suspending media (e.g., solutions of Percoll, Nycodenz, Iodixanol, or sucrose) (−) expensive (−) requires a centrifuge	- Separations of organelles, viruses, proteins, nucleic acids, nanoparticles, carbon nanotubes	[133,134]

measuring densities using “absolute” (e.g., not based on empirical calibration) methods). In general, most practical measurements of density use Equation (2); Equation (1) is useful in understanding the method.

3. Operating Procedures and Experimental Design

This section describes a brief overview of the standard operating procedures used to perform MagLev experiments; systems involving different parameters (e.g., heterogeneous samples, non-linear fields, flowing liquids) are described later (Section 4). It also describes the essential components of the MagLev system and the rationale for choosing the combination of components most appropriate for a given experiment (i.e., experimental design).

3.1. Types of Samples

3.1.1. Simple solids

In practice, many measurements of density using MagLev are straightforward: (i) The simplest MagLev device comprises two permanent magnets in a fixed geometry. Straightforward procedures to calibrate the device (using density standards) can be carried out prior to performing a measurement.[20] (ii) The principal technical skill required for a user is the ability to read a ruler or caliper accurately to quantify the levitation height of a levitated object. (iii) The performance of the MagLev assay is a function of well-known physical parameters, and changes to most variables can be accommodated. (iv) The use of density standards removes user- and/or environment-dependent errors, and simplifies the method.

Logistically, a sample (e.g., a solid object) is placed in a container filled with a paramagnetic medium. A surfactant (e.g., Tween-20 or cetyltrimethylammonium bromide) may be included in the aqueous paramagnetic medium to help remove trapped or adhering air bubbles from the surface of the sample. Depending on the difference in density between the sample and the surrounding medium, the sample either sinks or floats without an applied magnetic field. The container is then placed in the magnetic field between the magnets. Provided that the values of χ and ρ for the sample and medium are appropriate for the range that can be examined in that magnetic field, the sample relocates from its initial position to a stable equilibrium position (“levitation height”) that is proportional to its density. A sample that floats on the liquid in the absence of the applied magnetic field levitates above the midpoint between the two magnets (closer to the top magnet); a sample that sinks in the liquid in the absence of the applied field levitates below the midpoint (closer to the bottom magnet).

3.1.2. Liquid, heterogeneous, or “sticky” samples

In cases where the samples are not simple solids (e.g., they are liquids, gases, gels, elastomers, gums, pastes, or heterogeneous materials), a modified procedure may be used to levitate the samples in the “standard” MagLev system. For instance, simple liquid samples can be injected into the sample container using common laboratory liquid handling tools (e.g., Pasteur transfer pipets, syringes, and pipettors) while keeping the container in the magnetic field between the magnets. This procedure reduces the time of physical contact between the sample and interfaces (e.g., the walls of the container, and the medium-air interface), which may lead to artifacts (e.g., temporary or permanent “pinning” of the liquid sample at the interfaces). For liquid samples having a small size (e.g., sub-mm droplets) and/or having a finite solubility in the paramagnetic medium, it may be useful to pre-saturate the medium with the same liquid prior to the density measurements to minimize sample loss (which may be different for heterogeneous systems, and lead to a change in the estimated density of the sample with time).

3.1.3. Samples not conveniently levitated

If stable levitation is not possible (that is, samples are too dense, or not dense enough, to be levitated conveniently.), several experimental strategies can be used to re-establish a regime appropriate to levitation. Three common approaches can be used to levitate these samples (see Section 3.5 for discussions in greater details): (i) increasing the magnetic susceptibility of the solution (e.g., by increasing the concentration of paramagnetic species in the medium, or using a paramagnetic species with a greater magnetic susceptibility, such as $GdCl_3$, $DyCl_3$ or $HoCl_3$, rather than $MnCl_2$.);[20,142] (ii) modifying the density of the paramagnetic medium using diamagnetic co-solutes (e.g., by adding $ZnCl_2$ or sucrose to the aqueous medium to increase the density of the suspending liquid and/or by switching to alternative solvents with suitable densities, such as alcohols (e.g., methanol[44]) instead of water if chemical compatibility permits, to decrease the density of the suspending liquid);[20,44] and (iii) reducing the influence of the gravitational force by tilting the MagLev device with respect to the vector of gravity to expand its dynamic range.[93] See Section 3.5 for more discussions.

3.2. Choice of Magnets

The experimentally accessible range of magnetic fields (Figure S1) spans a wide range of values with the magnetic field at the surface of the earth of $\sim 5\times10^{-5}$ T, the field of a typical refrigerator magnet at $\sim 10^{-4}$ T, the field at the surface of a typical NdFeB magnet of ~0.4 T, and the strongest stable fields of ~45 T generated by the combination of superconducting magnets with powerful electromagnets. How does one choose a magnet for a specific application of MagLev from such a wide range?

The choice of magnets for the MagLev procedures we have developed (with an emphasis of simplicity) is based on four requirements: (i) It must be able to generate enough force to achieve an equilibrium. (ii) It must generate a permanent magnetic field that does not diminish during the course of the experiment and the lifecycle of an apparatus. (iii) It must have a high coercivity H_c (a measure of the resistance of the magnet to demagnetization in an applied magnetic field; more specifically, the external field necessary to bring the magnetization of the material to zero), so that it does not become demagnetized easily. (iv) It must have a reasonable cost and be commercially available. It is preferable for the system not to require electrical power, to be compact and portable, and, importantly, to serve as a general platform with which to develop practical applications (including applications in the developing world, point-of-care settings, and/or on-site use, or in remote regions). Based on these criteria, NdFeB magnets are the best choice for many MagLev-based procedures, based on three characteristics: (i) They are capable of generating high magnetic fields on their surface because of their high remnant magnetic field B_r For instance, the strength of the magnetic field along the symmetric axes of single NdFeB permanent magnets (e.g., block and cylindrical magnets) can generate up to ~0.7 T with a typical remanence of ~1.5 T for the N52-grade NdFeB magnet.[143] This strength can be further increased by optimizing the geometry of the magnet (e.g., using a cone- or pyramid-shaped magnet).[144] (ii) They are highly resistant to demagnetization ($H_c\sim$ 900 kA m^{-1}) relative to other, commonly used permanent magnets (e.g., Alnico with $H_c\sim$150 kA m^{-1}), and thus, produce stable, permanent magnetic fields. (iii) They are relatively inexpensive, and commercially available (e.g., from K&J Magnetics, Inc. and Applied Magnets, Inc.) in many sizes and shapes (e.g., blocks, discs, cylinders, rings, spheres, and other more complex shapes, such as arcs and wedges).

3.3. Choice of Paramagnetic Media

The paramagnetic medium in MagLev has two roles: (i) It supplies the magnetic force (proportional to the difference in magnetic susceptibility between the medium and the sample) necessary to suspend a diamagnetic object against gravity. (ii) It supplies a buoyant force (proportional to the difference in density between the medium and the sample) to the objects that are suspended in the medium (e.g., aqueous solutions of $MnCl_2$). The relevant experimental parameters of the paramagnetic media that need to be considered in the context of MagLev are (i) magnetic susceptibility, (ii) density, (iii) inertness/compatibility with the sample (i.e., the medium should not dissolve or react with the sample), (iv) transparency in the visible region (to view the suspended samples clearly and measure height accurately), (v) cost and availability, and (vi) chemical toxicity, flammability, and vapor pressure (which should all be low; the last, to avoid changes in concentrations due to evaporation of the solvent of the paramagnetic salt during use).

This Review summarizes in the following sections (3.3.1–3.3.6) the paramagnetic media that are (i) easily accessible (that is, they can be easily obtained from commercial sources or be prepared using simple, non-specialized procedures), and (ii) compatible with the type of MagLev we are developing. Other less commonly used paramagnetic media (not reviewed in detail here) include pressurized oxygen gas and liquid oxygen;[4,15,35,45,50,145] these paramagnetic media are often used in conjunction with strong magnetic fields provided by electromagnets.

3.3.1. Aqueous Solutions of Simple Paramagnetic Salts

Aqueous solutions of simple paramagnetic salts (e.g., aqueous solutions of $MnCl_2$ or $GdCl_3$) are useful for levitating water-insoluble samples because they (i) have high magnetic susceptibilities, (ii) are chemically compatible with a variety of water-insoluble samples, (iii) are relatively inexpensive, non-toxic, and commercially available, and (iv) make transparent solutions that allow for straightforward visualization of the suspended samples. By using different paramagnetic salts (e.g., $MnBr_2$, $Mn(NO_3)_2$, $FeCl_2$, $CuSO_4$, $DyCl_3$, $HoCl_3$, and chelating agents), it is possible to adjust the density, magnetic susceptibility, and optical properties, of these solutions, and to have a measure of flexible control over the magnetic and gravitational forces.

3.3.2. Aqueous Solutions of Biocompatible Paramagnetic Chelates

Aqueous solutions of chelates of Mn^{II} and Gd^{III} (e.g., Mn·EDTA, manganese(II) ethylenediaminetetraacetic acid, and Gd·DTPA, gadolinium(III) diethylenetriaminepentaacetic acid), are useful options for biological applications (e.g., for protein and cellular assays), in which the biocompatibility of the paramagnetic media is critically important.[69,146] In particular, Gd^{III} chelates represent a large group of paramagnetic compounds that could be used for these applications,[147] and nine of them (Table 5), in fact, have been

Table 5: FDA-approved gadolinium-based contrast agents.[147–149]

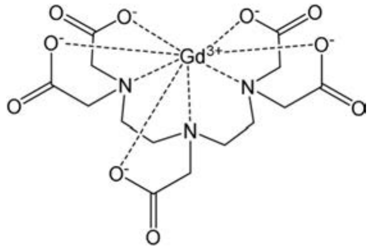
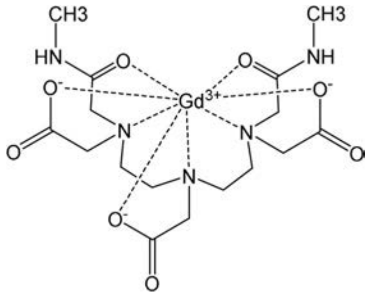
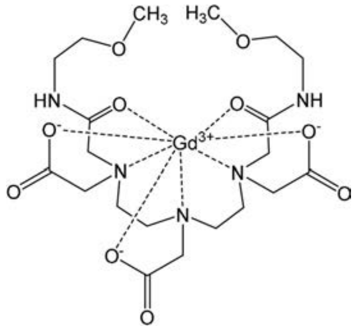
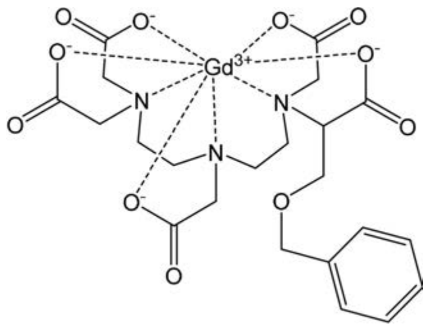
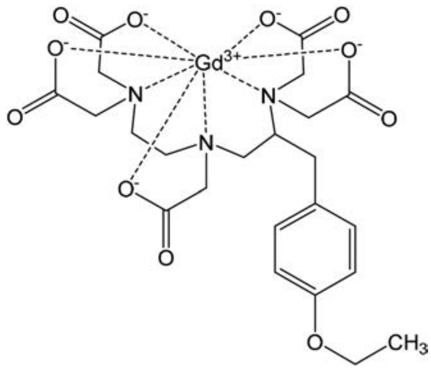
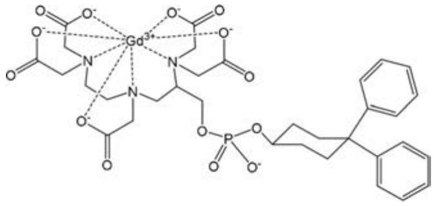
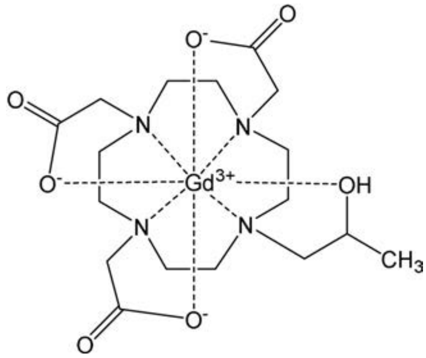
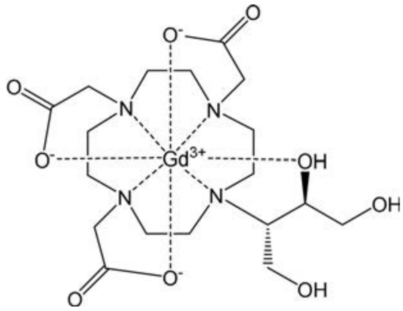
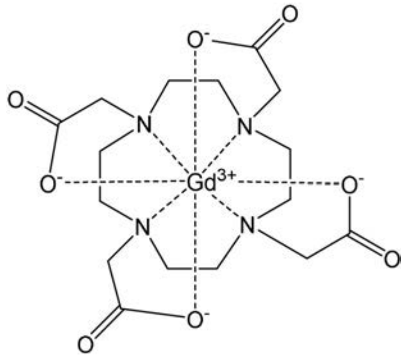
Trade name	Chemical names	Generic names	Chemical structures	Chelating ligand	Ionic property of the chelate
Magnevist	Gd-DTPA	gadopentetate dimeglumine		linear	ionic
Omniscan	Gd-DTPA-BMA	gadodiamide		linear	nonionic
OptiMARK	Gd-DTPA-BMEA	gadoversetamide		linear	nonionic
MultiHance	Gd-BOPTA	gadobenate dimeglumine		linear	ionic
Eovist/Primovist	Gd-EOB-DTPA	gadoxetate disodium		linear	ionic

Table 5: (Continued)

Trade name	Chemical names	Generic names	Chemical structures	Chelating ligand	Ionic property of the chelate
Ablavar/Vasovist	MS-325[147]	gadofosveset trisodium		linear	ionic
ProHance	Gd-HP-DO3A	gadoteridol		macrocyclic	nonionic
Gadavist	Gd-BT-DO3A	gadobutrol		macrocyclic	nonionic
Dotarem	Gd-DOTA	gadoterate meglumine		macrocyclic	ionic

approved by the U.S. Food and Drugs Administration for their in vivo uses as contrast enhancement agents in in vivo magnetic resonance imaging in humans.[148,149]

3.3.3. Non-Aqueous Solutions of Paramagnetic Species

Simple paramagnetic salts, $MnCl_2$ and $GdCl_3$, are also soluble in alcohols (e.g., methanol 0.792 $g\,cm^{-3}$ and ethanol 0.789 $g\,cm^{-3}$) and other polar solvents (e.g., N,N-dimethylformamide 0.948 $g\,cm^{-3}$).[20,44] These organic solvents are generally less dense than water, and thus are useful to levitate light samples, such as certain classes of polymers (e.g., polyethylene 0.93 $g\,cm^{-3}$ and polypropylene $\rho \sim$ 0.90 $g\,cm^{-3}$).[44] Hydrophobic paramagnetic compounds, such as hydrophobic Gd chelates (e.g., Gd·DTAD, gadolinium(III) diethylenetriamine triacetic acid didecyldiacetamide), are soluble in non-polar organic solvents (e.g., hexane 0.661 $g\,cm^{-3}$, toluene 0.865 $g\,cm^{-3}$, chloroform 1.489 $g\,cm^{-3}$, and tetrachloroethylene 1.622 $g\,cm^{-3}$), and thus can be used to levitate aqueous samples or samples that would dissolve in, or are sensitive to, water.[41]

3.3.4. Paramagnetic Ionic Liquids (PILs)

PILs are a class of paramagnetic liquids that can be used as paramagnetic media for MagLev.[96] PILs have several advantages over solutions of paramagnetic salts (in water or organic solvents), including (i) negligible vapor pressures, (ii) low melting points, and (iii) high thermal stabilities. In addition, their densities, magnetic susceptibilities, glass transition temperatures, melting points, thermal decomposition temperatures, viscosities, and hydrophobicity can be readily tuned by changing the cation-anion pair in the ionic liquids.[96] The low melting points and high thermal stabilities of PILs enable new analytical capabilities for density measurements. For example, 1-butyl-3-methylimidazolium tetrachloroferrate ([BMIM][$FeCl_4$]) is a liquid over a window in temperature from −88 °C to 280 °C, and allows, in principle, density measurements over this broad range.

More than a dozen PILs have been synthesized with nearly quantitative yield (100 %) using simple synthetic techniques (i.e., heating while stirring the reacting mixtures), and demonstrations (e.g., measuring the difference in density between whole milk and adulterated whole milk containing added melamine or water[96]) have established examples of uses as paramagnetic media for MagLev applications.[96]

3.3.5. Phase-Separated Paramagnetic Media

MagLev offers a linear gradient in density and can levitate objects having densities that vary continuously over a broad range (Table 3). Aqueous multiphase polymer systems (AMPSs)—a MagLev-compatible, but distinct, density-based technique that we developed for separations using distinct phases that form from mixtures of polymers, surfactants and/or salts—provide thermodynamically stable steps in density, and can separate objects by density with high resolutions (~± 0.001 g cm^{-3}).[130,150,151] Figure 3 A shows a five-phase AMPS that formed, upon centrifugation, from a mixture of five polymers dissolved in water: poly(ethylene glycol) (PEG), poly(2-ethyl-2-oxazoline (PEOZ), poly(vinyl alcohol) (PVA), Ficoll, and dextran; the five distinct phases (each containing primarily one polymer) self-assembled in a centrifugal field (or, more slowly, in the ambient gravitational field) to form stable, essentially molecularly-sharp interfaces. These interfaces, and also the additional two interfaces (one between the top phase and air and the other between the bottom phase and the bottom of the container), represent steps in density (and other properties), and are useful for density-based separations. AMPSs have four major characteristics that make them useful for density-based analyses and separations: (i) More than 300 AMPSs can be prepared from a small number (fewer than 40)[130] of polymers, salts, and surfactants; each AMPS can have two to six phases. (A two-phase system is commonly referred to as aqueous two-phase system, or ATPS.)[152] (ii) AMPSs, once formed, are thermodynamically stable; the interfaces are stable over time, and will reform spontaneously when they are disturbed or agitated. This characteristic makes these system particularly convenient for preparation, use, and storage. (iii) The steps in density can be very small ($\Delta\rho \sim 0.001$ g cm^{-3}), and can be adjusted using co-solutes (e.g., salts) or co-solvents (e.g., D_2O).[130] (iv) AMPSs can be made biocompatible. Figures 3 B and 3 C demonstrate the uses of AMPSs to separate reticulocytes from mature red blood cells,[118] and to separate less-dense red blood cells from more dense, healthy red blood cells for diagnosis of iron-deficiency anemia.[131] Table 6 summarizes uses of AMPS for both biological and nonbiological applications.

The *combination* of AMPS and MagLev—by dissolving paramagnetic species in an AMPS and placing the AMPS in an applied magnetic field—can provide a hybrid of step and linear gradients in density.[94] For each paramagnetic phase in an AMPS, the applied magnetic field creates an effective linear gradient in density in it, and the specific range of accessible density depends on the location of the phase in the applied magnetic field and also the concentration of the paramagnetic species. The applied magnetic field, therefore, effectively transforms simple steps in density of a paramagnetic AMPS (in the absence of an applied magnetic field, Figure 3 G) to a hybrid profile combining step and linear gradients in density. Since the range of densities accessible in each phase depends on their physical locations in the applied magnetic field, it is, therefore, particularly convenient to adjust the apparent densities of the phases—and by inference, the "density bins" at the interfaces—by repositioning the

Table 6: Density-based analysis and separation using aqueous multiphase polymer systems.

Sample	Size	Density (g cm^{-3})	No. of phases	Type of AMPS	Ref
Nonbiological samples					
Polymer beads (PS, Nylon, etc)	µm–mm		2–3	Ficoll/dextran Ficoll/PEOZ/Brij 35	[94,130,153]
Biological samples					
Erythrocytes (sickle cell disease)	µm	1.10–1.12	2 and 3	PEG/Ficoll, PEG/dextran/poly(vinyl alcohol)	[121]
Erythrocytes (Anemia)	µm	1.05–1.08	3	Ficoll/dextran/poly(vinyl alcohol)	[131]
Reticulocytes	µm	1.08	2	Ficoll/dextran	[118]
Bacteria	µm	1.03–1.10	2	PEG/Ficoll	[150]

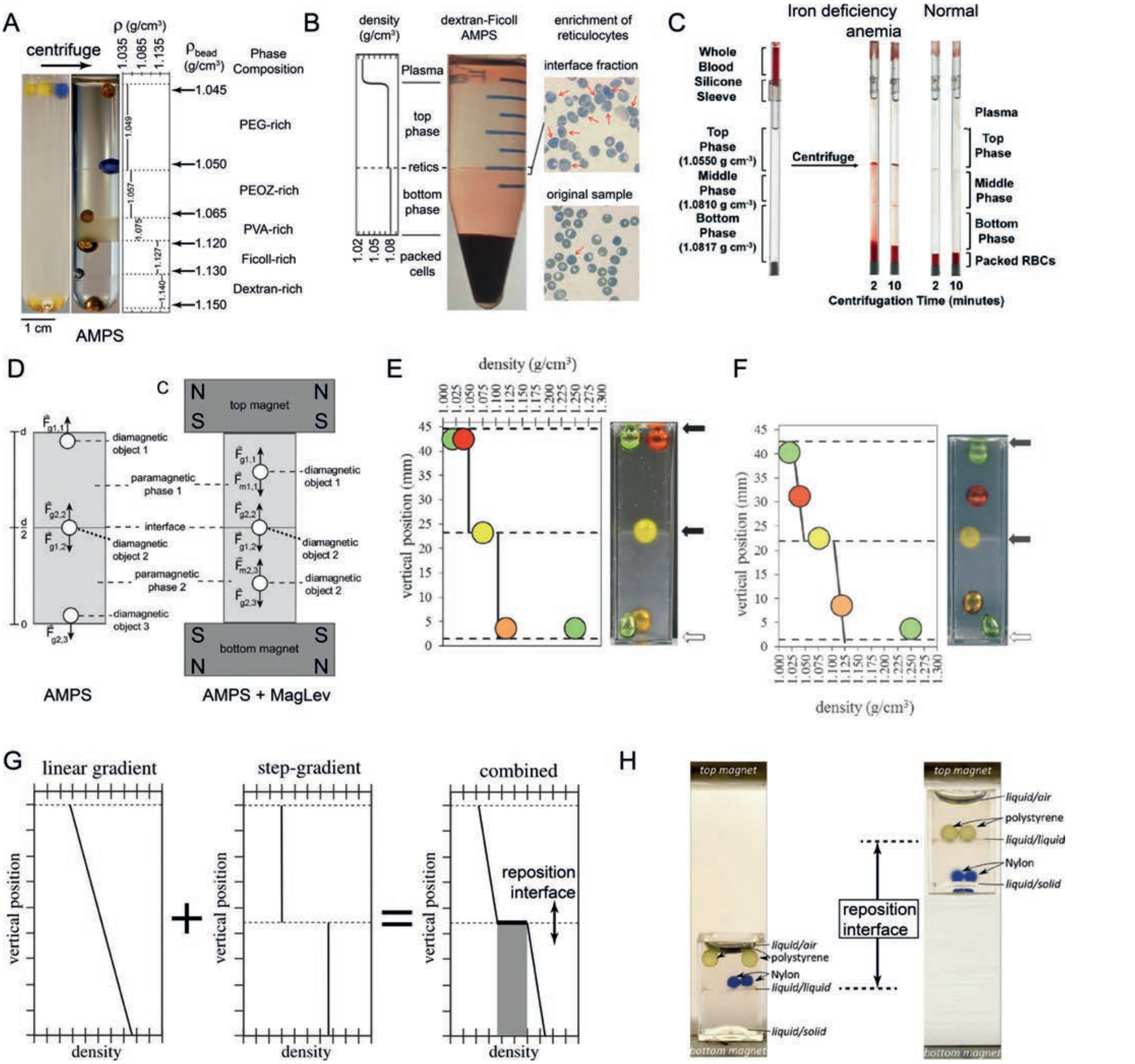


Figure 3. Aqueous multiphase systems and their combined use with MagLev (A) A five-phase AMPS forms upon centrifugation, and density standards (colored glass beads) indicate the densities at the interfaces. (B) A two-phase system separates enriched reticulocytes from the whole blood at the interface. (C) A three-phase AMPS separated less-dense red blood cells from a whole blood sample, and provided a simple tool to diagnose iron-deficiency anemia. (D–H) The combined use of AMPS and MagLev to produce hybrid gradients (both linear and step gradients) in apparent density. The interfaces between phases (e.g., liquid/solid) are indicated in (H). The container (the solid phase) in (H) is a cuvette made of PMMA. Sources: Images (A),[130] (B),[118] (C),[131] and (D–H).[94]

interfaces in the applied magnetic field, without having to adjust the chemical composition of the AMPS. Figure 3H demonstrates this capability of adjusting the effective step in density in a paramagnetic two-phase system by repositioning the interface relative to the bottom surface of the magnet.[94]

The combined use of AMPS and MagLev provides an operationally straightforward method to generate complex profiles of gradients in density—combining step and linear gradients—and, therefore, provides both a uniquely flexible capability to develop solutions to problems in density-based separations,[94] and a method of discovering new phenomena in MagLev.

3.3.6. Colloidal Systems: Ferrofluids

A ferrofluid is typically a colloidal system in which ~10-nm superparamagnetic particles (e.g., of magnetite) are suspended in a carrier fluid.[154] Ferrofluids are one of the suspending media used in the early applications of density-based separations of diamagnetic materials.[23,155] Although ferrofluids are optically opaque unless highly diluted, and have not been commonly used in the type of MagLev we are developing, they have useful characteristics to levitate diamagnetic samples (e.g., large magnetic susceptibility and commercial availability). They can be made biocompatible (one ferrofluid—based on superparamagnetic iron oxide nanoparticles—is used as a human therapeutic[156,157] and as a Gd-free contrast agent for MRI imaging[158]), and thus, can be useful to study biological samples.[159] The translucency or opacity of ferrofluids may not prevent localizing samples suspended in thin films or streams of even concentrated ferrofluid—for example, those found in microfluidic devices.[159–161]

3.4. Calibration, Measurement, and Error Analysis

3.4.1. The Shape of the Magnetic Field

We commonly use a linear magnetic field generated by two like-poles-facing permanent magnets to levitate an object in a paramagnetic medium. The linearity of the field enables simple calibration and measurement. Nonlinear magnetic fields, however, are also useful to carry out density-based analysis and separation (provided that the system is calibrated appropriately using density standards, or when only relative densities are important—as, for example, with separations). In addition to the magnetic field gradient along the axis between the magnets (which is commonly aligned with the vector of gravity), the magnetic field that surrounds this axis should have gradients that do not destabilize the levitation of the object—i.e., the magnetic force experienced by the levitated object in the plane perpendicularly to the central axis should focus the objects toward this axis.

3.4.2. Generating a Linear Field Gradient

The use of a linear magnetic field simplifies the operation of this method by establishing a linear relationship between the density of the sample and its levitation height in the MagLev systems. The generation of linear magnetic fields may require optimization of different parameters of the systems, including the number of magnets, and their geometries, aspect-ratios, and physical arrangements in space. We discuss below two MagLev systems we have developed: the "standard" and "axial" MagLev systems.

In the "standard" MagLev system (Figure 1), we adjusted (empirically) the distance of separation between the two co-axially aligned block magnets to achieve an approximately linear field gradient along the central axis between the two magnets.[20] In the "axial" MagLev system (See Section 3.6 for details),[22] the aspect ratio of the two co-axially aligned ring magnets, and the distance of separation between them, are optimized to generate an approximately linear magnetic field along its axis between the two ring magnets.

3.4.3. Calibration and Limits to Accuracy and Precision

There are, in general, two ways in which we measure unknown densities of samples using MagLev: (i) measurements of density by comparisons with calibrated standards (the "relative" approach), and (ii) direct measurements of density using known physical parameters of the components of the "standard" MagLev system (the "direct" approach). We briefly review the "relative" approach (which is the one we generally use), and detailed discussions for both approaches are given in Section S4 and also elsewhere.[20]

The simplest method to determine the unknown density of an object is to use the "relative" approach: it uses a set of calibration curves based on the levitation heights of density standards.[20] These calibration curves then facilitate the calculations of the unknown density of a sample. A feature of this approach is that it does not require detailed understanding of the physics of MagLev, or accurate knowledge of various experimental parameters (e.g., density and magnetic susceptibility of the medium, and the magnitude of the magnetic field).

Calibrated density beads ($\pm 0.0002\ g\,cm^{-3}$) can be purchased commercially, for example, from American Density Materials, Inc. (http://www.americandensitymaterials.com), and their physical sizes are typically in the range of 3–7 mm (too big for convenient use, but useful). Many common organic and inorganic substances (e.g., pure organic liquids, polymers, and crystals) have well-defined densities (which are sometimes available in the literature, or easily calculated from X-ray computed structures), and thus, can also be used as suitable density standards (Table S1).

Small (< mm), high-quality density standards can in fact be prepared using AMPSs[153] or MagLev;[22,153] polymeric microspheres (Figure 4) are commercially available (For example, they can be purchased from https://www.cospheric.com/). These commercial microspheres usually have a substantial spread in density (standard deviation in their density may span the range of ~0.001 to ~0.01 $g\,cm^{-3}$ even within one sample of the same material). A detailed, AMPS-based protocol (Figures 4 (A,B)) has been developed to fractionate microspheres, and thus, to prepare high-quality density standards (standard deviation from 0.0003 to 0.0008 $g\,cm^{-3}$).[153] MagLev can also be used to fractionate microspheres and prepare density standards with narrow distribution in density (Figure 4 C).[22]

For work requiring high precision, the system should be calibrated using density standards that are valid for the specified range of temperatures.[20,95] (The densities of most solids and liquids are a function of, inter alia, temperature.) Figure 5 B shows the calibration curves of the "standard" MagLev system using standard-density beads and aqueous solutions of $MnCl_2$ (with different concentrations) at room temperature. The concentrations of $MnCl_2$ under these conditions determine the sensitivity of the measurement (i.e. the slopes of the curves) in discriminating differences in density of the sample.[95] Relatively low concentrations of

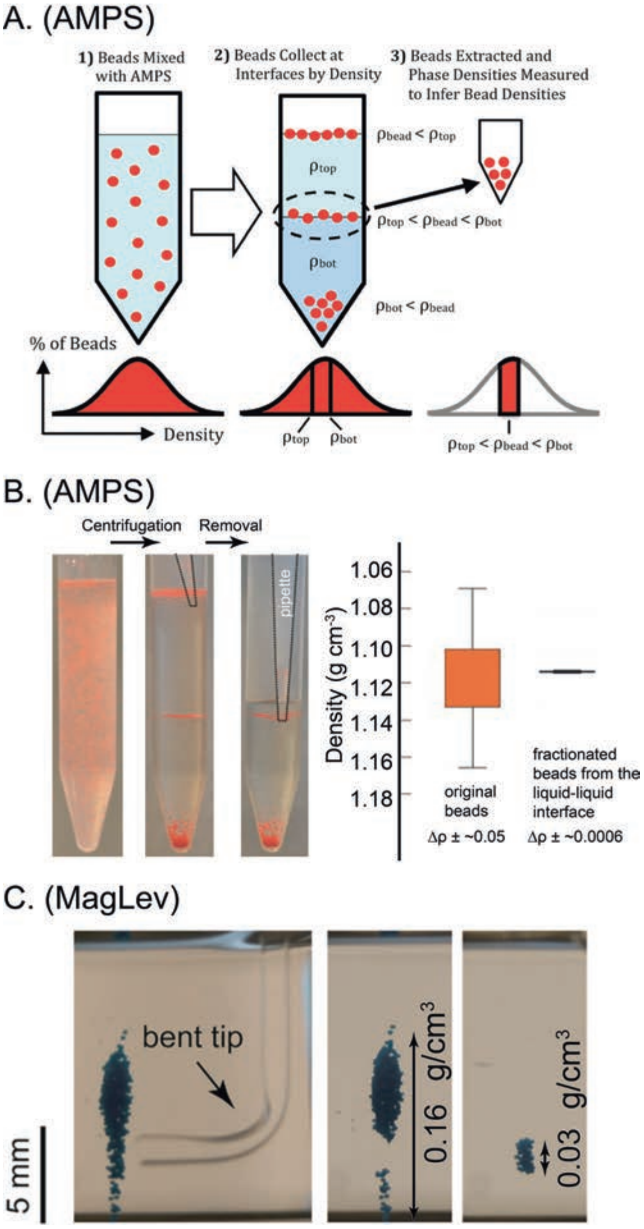


Figure 4. (A,B) An AMPS-based procedure to fractionate polymeric microspheres (commercially available) and prepare highly accurate density standards (standard deviation of distribution of density as low as 0.0003 $g\,cm^{-3}$ has been demonstrated.).[153] The densities of the aqueous phases can be measured sensitively using a calibrated U-tube densitometer.[153] (C) MagLev, as a distinct but complementary approach to AMPS-based procedures, could also be used to prepare high-quality density standards using commercially available microspheres. In this example, the "axial" MagLev was used to prepare density standards with narrower distribution in density ($\Delta\rho$ improved by ~5× in this case from $\Delta\rho$ ~0.16 $g\,cm^{-3}$ of the original microspheres to $\Delta\rho$~0.03 $g\,cm^{-3}$ of the fractionated microspheres). Sources: Images (A, B)[153] and (C).[22]

$MnCl_2$ (e.g., 0.1 M $MnCl_2$) enable high-sensitivity measurements to discriminate small differences in density ($\pm 10^{-4}$–10^{-3} $g\,cm^{-3}$); this MagLev system, however, has a limited dynamic range (1.00–1.10 $g\,cm^{-3}$). High concentrations of $MnCl_2$ enable a wider dynamic range (e.g., 1.00–1.56 $g\,cm^{-3}$ using 3 M $MnCl_2$); this MagLev system has a more limited sensitivity, and can only distinguish differences in density of $\pm 10^{-3}$ to $\pm 10^{-2}$ $g\,cm^{-3}$.

3.5. Sensitivity and Dynamic Range

Sensitivity and dynamic range are two important analytical characteristics of any system, and there is often a trade-off between them. One sometimes needs to optimize both characteristics of a MagLev system for a given application. For instance, broad dynamic range is important to analyze and separate samples having large differences in density (e.g., separating polymer particles from metal powders), while high sensitivity is critical to resolve subtle differences in density between levitated objects (e.g., biological cells, the level of crystallinity of an organic material, or the density of cross-linking in polymeric materials).[69,111,123]

We summarize five experimental strategies that have been developed to tune the sensitivities and dynamic ranges of MagLev systems,[20,87,93,95] and describe practical experimental guidelines in choosing MagLev systems for specific applications.

3.5.1. Adjusting the Chemical Composition of the Suspending Medium (Solvent, Solute, and Co-Solute)

The simplest way to tune the sensitivity and dynamic range of a MagLev system is to adjust the type and concentration of the paramagnetic medium. Using a paramagnetic species with a large magnetic susceptibility (e.g., $GdCl_3$, $DyCl_3$, or $HoCl_3$), and/or increasing its concentration, expands the dynamic range at the cost of decreased sensitivity; using a paramagnetic species with a relatively small magnetic susceptibility (e.g., $MnCl_2$, $FeCl_2$, or $CuSO_4$) and/or decreasing its concentration increases the sensitivity at the cost of a narrower dynamic range. Figure 5B shows an example of tuning sensitivity and dynamic range using an aqueous solution of $MnCl_2$ with different concentrations in the standard MagLev system. Under these experimental conditions, the maximum sensitivity is obtained using the lowest concentration of $MnCl_2$ (0.1 M); a difference in density can be resolved as small as ~1×10^{-4} $g\,cm^{-3}$. The largest dynamic range (from ~1.0 to ~1.6 $g\,cm^{-3}$) is obtained when using 3 M $MnCl_2$.[20]

The ability to tune the sensitivity and dynamic range of a MagLev system is limited by adjusting only the type and/or the concentration of the paramagnetic species in the medium—neither sensitivity nor dynamic range can be adjusted independently since they are coupled. The density of the medium, ρ_m, however, can be adjusted without changing the magnetic susceptibility of the medium, and, thus, the sensitivity of the MagLev system, by adding diamagnetic co-solutes in the medium, and/or by choosing an alternative solvent (e.g., D_2O or alcohol instead of H_2O). For example, Figure 5C shows that the sensitivities of these systems—characterized by the slopes of the calibration curves—remained unchanged when diamagnetic co-solutes, including NaCl and sucrose, were doped into the aqueous solution of $MnCl_2$ used in this experiment. The dynamic range, however, shifted toward the end of high densities. Less dense organic solvents, such as methanol (0.792 $g\,cm^{-3}$), ethanol (0.789 $g\,cm^{-3}$), and N,N-dimethylformamide (0.944 $g\,cm^{-3}$), can also be used to prepare paramagnetic media by dissolving paramagnetic transition metal salts, and thus, shift the dynamic range toward lower densities (between ~0.8 $g\,cm^{-3}$ and 1.0 $g\,cm^{-3}$), while maintaining the sensitivity of the system.[44] Table 7 summarizes the characteristics of

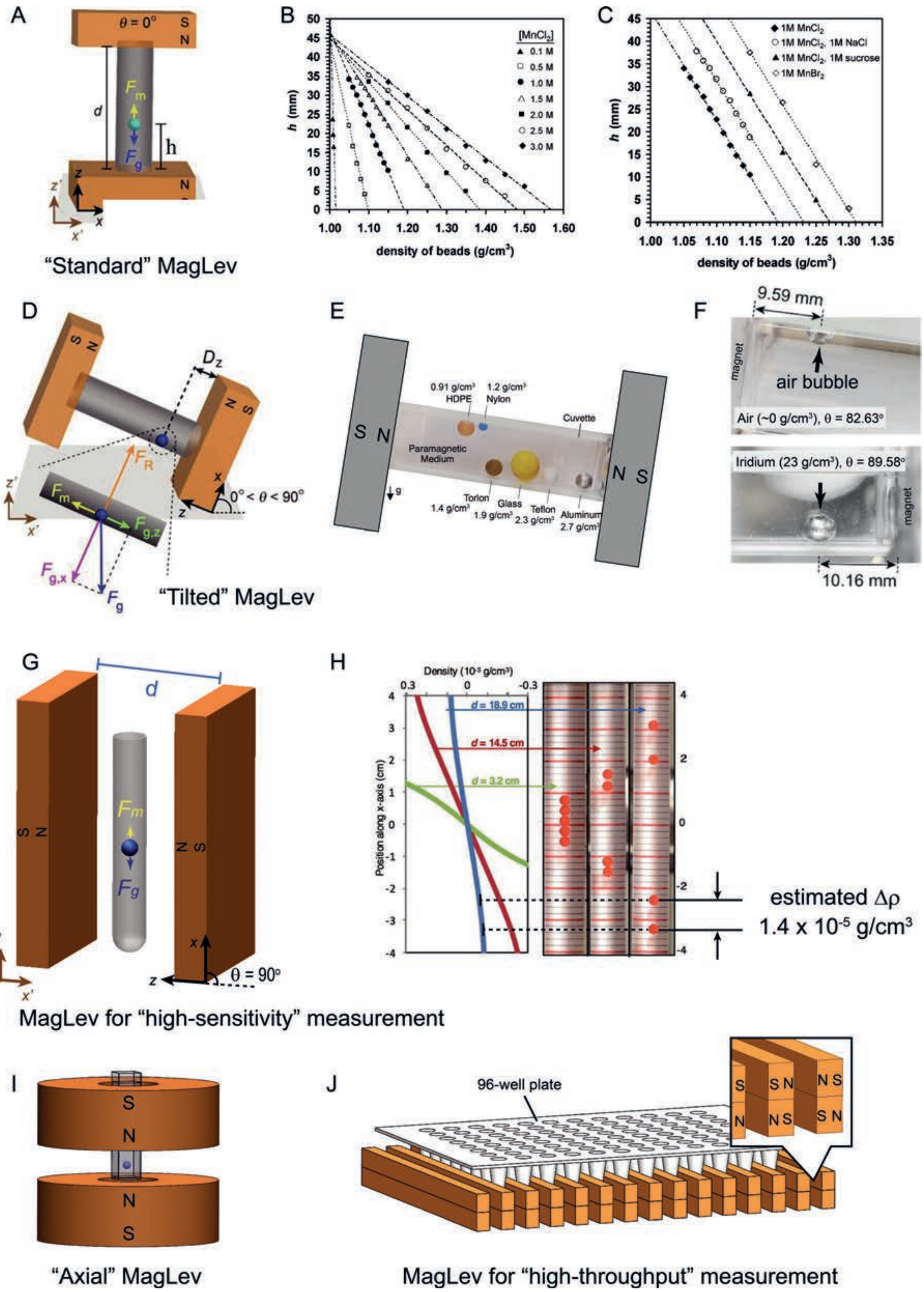


Figure 5. MagLev systems and Optimization of performance (A) The "standard" MagLev system. (B) The sensitivity (the slope of the curve) and dynamic range of the "standard" MagLev system can be tuned by adjusting the concentration of the paramagnetic salt $MnCl_2$. (C) The density of the paramagnetic medium can be adjusted independently without changing the magnetic susceptibility of the medium by adding diamagnetic co-solutes, or using a different type of salt containing the same paramagnetic species. (D) "Tilted MagLev" expands the dynamic range by tilting the "standard" MagLev system, and thus, effectively reducing the influence of the gravitational force along the central axis of the magnetic field, $F_{g,z}$, while maintaining the magnetic force along this axis, F_m. (E) Six beads made of different materials are simultaneously levitated using "tilted MagLev". (F) Levitation of a bubble of air and the heaviest metal (iridium) using "tilted MagLev". The levitation "height" of the bubble of air was measured from the surface of the top magnet, while the levitation height of the sample of iridium was measured from the surface of the bottom magnet. (G) MagLev optimized for high-sensitivity measurement. (H) Levitation of PMMA spheres in a high-sensitivity MagLev system (at $d = 18.9$ cm, the blue line in the left panel) resolved a difference in density as small as 1.4×10^{-5} g cm^{-3} (estimated based on the simulated profile of the magnetic fields in COMSOL) between two PMMA spheres. Red markings in the right panel correspond to 1-cm spacing (2 mm per division). In the second and third panels of the levitated spheres, the top sphere drifted out of the visible range as the sensitivity of the system increased, and thus only four spheres remained. (I) "Axial" MagLev uses two like-poles-facing ring magnets and enables operational simplicity by allowing access to the sample region from the top. (J) MagLev optimized for high-throughput measurements using stacked magnets and a 96-well plate. The device was calibrated using density standards (~200 μm polymeric microparticles) prepared in house.[123] Sources: Images (A–F);[20,93] (G, H);[95] (I);[22] and (J).[123]

commonly used additives, and their uses in density-based applications.

3.5.2. *Decreasing the Magnetic Field Strength and/or Gradient to Achieve High Sensitivity*

The standard MagLev system typically cannot resolve a difference in densities below ~10^{-4} g cm^{-3}. To improve the sensitivity of the standard MagLev system, the weak magnetic gradient parallel to the faces of the magnets (that is, the gradient perpendicular to the one exploited in the standard MagLev system) can be exploited and further engineered to improve the sensitivity for density measurement (by using elongated magnets and increasing their distance of separation, Figure 5G). The sensitivity of a given MagLev system, using a linear magnetic field gradient, scales inversely with the gradient squared (the $(2B_0/d)^2$ terms, Eq. S20), that is, every two-fold reduction in the magnitude of the gradient (unit: T m^{-1}) leads to a four-fold improvement in sensitivity (unit: m/(g cm^{-3})). Figure 5G shows the configuration of the MagLev device that has been optimized to carry out high-sensitivity density measurements. To "transform" the standard MagLev device to the high-sensitivity configuration, the standard MagLev system is first rotated 90° in the x'–z' plane (Figure 5A); the weak gradient of the magnetic field parallel to the faces of the magnets is then aligned with the vector of gravity in the laboratory frame of reference. In this rotated configuration (Figure 5G), the stronger gradient in the horizontal direction focuses the sample to the middle plane between the magnets (and thus, helps stabilize the samples in the system); the weak gradient along the central z'-axis separates the suspended samples according to their densities in the paramagnetic medium.

To increase the sensitivity further, two simple strategies can be implemented to reduce the magnitude of the gradient ($2B_0/d$) along the central z'-axis: (i) increase the distance of horizontal separation between the magnets to reduce the strength of the magnetic field along the central z'-axis between the magnets (the B_0 term); and (ii) elongate the magnets along the z'-axis to expand the physical range of the gradient (the d term). A difference in density as small as ~1.4×10^{-5} g cm^{-3} (Figure 5H) can be resolved experimentally between the bottom two orange PMMA spheres that were suspended in an aqueous solution of 1.886 M $MnCl_2$.[95] This MagLev system—one adjusted for optimized sensitivity—can separate particles differing in density by ~2.0×10^{-6} g cm^{-3}, which is an improvement of ~100× over the reported best sensitivity obtained for the standard MagLev system.[95]

In theory, the sensitivity of the MagLev system can be further improved by further reducing the gradients; there are, however, practical limits imposed by thermal fluctuations where the changes in density of the paramagnetic medium caused by thermal fluctuation become comparable to the difference in density between two levitated objects. To perform density measurements in very-high-sensitivity systems, additional experimental strategies, such as improved methods of thermal stabilization and development of high-precision density standards,[153] are required to exploit the technical capabilities of these systems fully.

3.5.3. *Increasing the Magnetic Field Strength and/or Gradient to Expand the Dynamic Range*

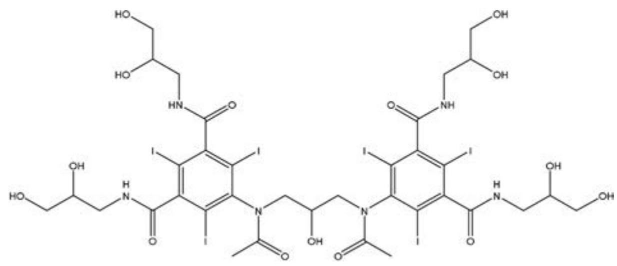
The standard MagLev system has a dynamic range of ~0.8–~3 g cm^{-3} even when we combined the uses of common aqueous paramagnetic media, and those less dense, non-aqueous media (e.g., alcohols).[20] It is, therefore, desirable to expand this range to measure samples having densities outside this window using strategies, such as adding light organic liquids and solids (e.g., toluene and n-alkanes), and dense metals (e.g., platinum and gold). Increasing the magnetic field strength and/or its gradient (Eq. S21) will lead to an improvement in dynamic range. We first summarize strategies to improve the strength of the magnetic field, and then discuss a simple approach to adjust the gradient of the magnetic field independently.

In the type of MagLev systems we describe, we use NdFeB permanent magnets, which often have field strength of ~0.4 T at the face of the magnet. Two related simple strategies to increase the strength of the magnetic field generated by permanent magnets include: (i) optimization of the shape of the magnets, and (ii) stacking magnets in space.[123] The specific type of magnets we use (i.e., NdFeB magnets) come commercially in different shapes (e.g., blocks, discs, and cylinders) from www.kjmagnetics.com, and the strength of the

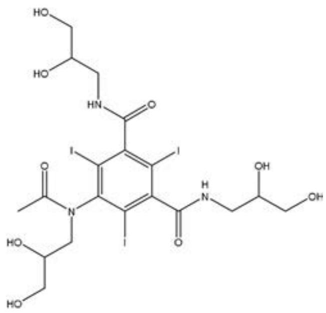
Table 7: Useful additives to aqueous paramagnetic suspending media for density-based applications using MagLev.

Type	Additive	Density ($g\,cm^{-3}$)	Applications
Solvents	H_2O and D_2O	H_2O (0.997 $g\,cm^{-3}$) D_2O (1.107 $g\,cm^{-3}$)	Majority of density-based applications
	Alcohols	methanol (0.792 $g\,cm^{-3}$) ethanol (0.789 $g\,cm^{-3}$)	Separations of plastics (e.g., polyethylene (0.93 $g\,cm^{-3}$) and polypropylene (~0.90 $g\,cm^{-3}$)) less dense than water[44]
	Other solvents	N,N-dimethylformamide (0.944 $g\,cm^{-3}$)	Monitoring kinetics of chemical reactions on solid supports[42,123]
Co-solutes	Simple salts	Examples include NaCl, Cs_2SO_4, CsCl ($\rho_{solution}$ up to 1.9 $g\,cm^{-3}$), and $ZnBr_2$	Adjustment of sensitivity and dynamic range of density measurements. Levitation of glass (2.4 $g\,cm^{-3}$), Teflon (2.2 $g\,cm^{-3}$), and heavy liquids, such as iodomethane (2.28 $g\,cm^{-3}$)[20]
	Sodium polytungstate	$\rho_{solution}$ up to 3.1 $g\,cm^{-3}$	Analysis and separation of minerals, diamond, gemstones, and manufactured metal/plastic parts[135]
	Low-molecular-weight organic materials	Examples include sucrose (1.587 $g\,cm^{-3}$), iodixanol,[a] iohexol,[b] and metrizamide ($\rho_{solution}$ up to 1.4 $g\,cm^{-3}$).[c]	Analysis and separation of biological samples (e.g., cells) (These additives do not change significantly the osmotic pressure of the suspending media, and are also compatible with AMPSs.[121,130])
	Polymers	Dextran, Ficoll, poly(vinyl alcohol), poly(ethylene glycol), and others (typical $\rho_{solution}$ ~1.0–1.1 $g\,cm^{-3}$).[130]	These polymers (as mixtures) can also form AMPSs.[121,130]
	Colloidal particles	Silica nanoparticles (Percoll, $\rho_{solution}$ up to 1.3 $g\,cm^{-3}$)	Analysis and separation of biological samples (e.g., cells) (This additive does not change significantly the osmotic pressure or viscosity of the suspending medium.)

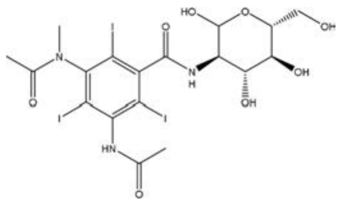
[a] iodixanol:



[b] iohexol:



[c] metrizamide:



magnetic field on the surfaces of these magnets depends on their specific shapes, and also their aspect ratios. The strength of the magnetic fields on the surfaces of single magnets with common shapes (e.g., cubes, blocks, and cylinders) can be calculated, and generally does not exceed a half of the remanence of the magnets along their principal axes.[143] The field strength on the surface of permanent magnets—particularly at sharp points—can reach as high as 2–3 T using geometry-optimized magnets, such as pyramid-shaped magnets (Figure S2).[144] Stacking magnets in space provides a complementary approach to increase the strength of the magnetic field that surrounds the magnets. An example is the Halbach array (Figure S2), in which permanent magnets are arranged in such a way that the magnetic field is augmented on one side of the array while the field cancels on the other side.[162]

Increasing the gradient of the magnetic field can in principle also improve the dynamic range.[22,69,123] The magnetic field around permanent magnets (single or stacked) is uniformly scalable:[163] that is, the spatial profile and strength of the magnetic field are maintained while the magnets scale in physical size. For example, the shape and strength of the magnetic fields around a cubical magnet remain the same while the physical size of the cube changes.[163] This property of permanent magnets offers a simple approach to adjust the gradient of the magnetic field conveniently. For example, scaling down the size of the "standard" MagLev system by 2× (that is, using smaller magnets with W×D×H = 25 mm × 25 mm × 13 mm, and an inter-magnet separation of 23 mm) increases the magnitude of the field gradient by 2× (the strength of the magnetic field remains unchanged), and thus, improves the dynamic range by 2×. The physical working distance of a MagLev system is effectively traded for an expanded dynamic range of accessible densities. This type of application is useful in working with small objects, such as cells and small organisms.

Two strategies[111]—scaling the MagLev device to smaller dimensions, and optimizing the aspect-ratio of the block magnets—expand the dynamic range, and allow the levitation of hydrophobic organic liquids having densities less than 1 $g\,cm^{-3}$ (e.g., toluene 0.865 $g\,cm^{-3}$, anisole 0.993 $g\,cm^{-3}$, and methyl methacrylate 0.936 $g\,cm^{-3}$) using aqueous solutions of $MnCl_2$.

MagLev, using a pair of like-poles-facing ring magnets with appropriate physical size and aspect ratios (inner diameter = 1 inch, outer diameter = 3 inch, thickness = 1 inch, distance of separation between the two magnets = 0.6 inch; Figure S3) allows the creation of a strong, linear magnetic field along the central axis between the two magnets (see Section 3.6 for more discussion), and enables the exploitation of the linear magnetic field (in combination with the use of a strongly paramagnetic medium, such as aqueous 3 M $DyCl_3$) to reach an expanded range. This range enabled the levitation of different types of samples (Figure S3E), ranging from a bubble of air (~0 $g\,cm^{-3}$) to a bead of zirconium silicate (~3.7 $g\,cm^{-3}$).[22]

While the MagLev systems we describe here use permanent magnets, magnets of other types, such as electromagnets and superconducting systems,[15,35,105] and also magnetic flux concentrators,[164,165] may be useful in further expanding the dynamic range.

3.5.4. Reducing the Influence of Gravity to Expand the Dynamic Range ("Tilted MagLev")

"Tilted MagLev" (Figure 5D) has been developed to expand the dynamic range to cover the entire range of densities observed in matter at ambient conditions from ~0 $g\,cm^{-3}$ (e.g., air, gases, and foams) to ~23 $g\,cm^{-3}$ (e.g., osmium and iridium, the most dense of all elements at room temperature).[93] The standard MagLev system is tilted with respect to the vector of gravity to decrease the influence of the gravitational force along the central axis of the MagLev system. Depending on the tilting angle θ, the fraction of the gravitational force acting on the object along the central axis of the magnets can change continuously from 1.0 ($\theta = 0°$, the standard system) to 0 ($\theta = 90°$, the central axis of the magnets becomes horizontal), while the magnetic force remains unchanged. For example, a dense object (e.g., a gold bead, 19 $g\,cm^{-3}$) would not levitate (it sinks) in the standard MagLev device using aqueous $MnCl_2$ solution (~1 $g\,cm^{-3}$) because the gravitational force acting on the object is greater than the magnetic force. Tilting the MagLev device allows the magnetic force to balance the reduced gravitational force along the central axis of the MagLev device, and thus, enables the "levitation" (perhaps better, "positioning") of the dense object along this axis.

In this tilted system, the sample almost always rests on or against the wall of the container (except a narrow range in density when the object has a density similar to the suspending liquid, and thus, would levitate in the suspending liquid without contacting the walls of the container); the wall provides a mechanical support that counterbalances the fraction of the gravitational forces perpendicular to the central-axis of the magnets. According to Eq. S21, the expanded range in density of the tilted MagLev system results from reducing the effect of the gravitational force (Figure 5D)—i.e., the effective g_z along the central axis of the magnets is only a fraction of g depending on the tilting angle θ (i.e., $g_z = g\cos(\theta)$).

Figure 5E shows the levitation of a number of objects made of different materials having densities ranging from 0.91 $g\,cm^{-3}$ (high-density polyethylene) to 2.7 $g\,cm^{-3}$ (aluminum, which is weakly paramagnetic[93]) in an aqueous solution of 3 M aqueous $MnCl_2$ using "tilted MagLev". By simply adjusting the tilting angle of the standard MagLev system, many spherical and non-spherical—plastics, glass, and various kinds of metals (including particles and powders)—samples can be levitated.[93] For certain types of samples that tend to stick to the wall of the sample container, such as gas bubbles, powders or flakes (e.g., aluminum, tin, copper, and gold), it was possible to minimize the effect of surface interactions (friction or adhesion) by mechanical agitation. Particularly when the samples are powders, it would be possible to accelerate the rate at which the samples reach the equilibrium positions by (i) increasing the viscosity of the suspending medium (e.g., by dissolving dextran in the aqueous paramagnetic medium) so that, when the sample container is rotated, the powered sample can be "picked up" by the viscous drag,[93] and (ii) rotating the container mechanically.[93]

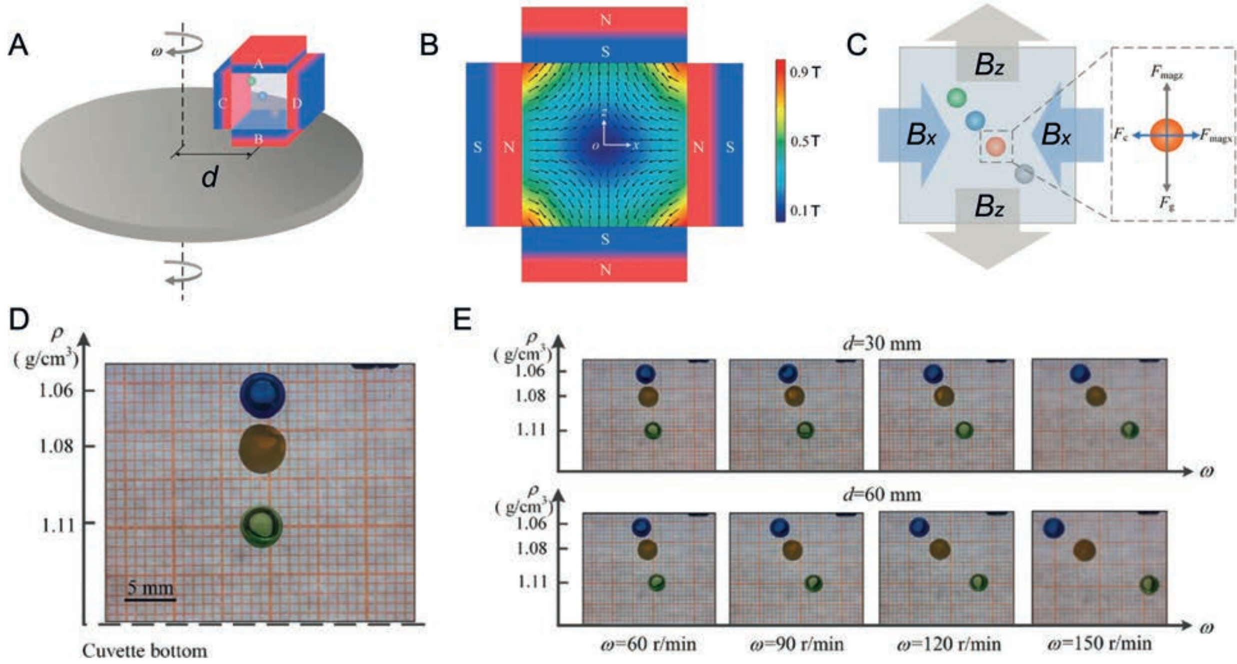


Figure 6. Rotational MagLev (A) A MagLev device consists of two pairs of like-poles-facing NdFeB magnets, and sits on a spinning disc (angular velocity ω, unit: s^{-1}) with an off-axis distance of d. Three beads levitate in a paramagnetic medium in the device while the entire device spins with the supporting disc. (B) The simulated spatial profile of the magnetic field in the cavity of the MagLev setup. (C) A bead reaches stable levitation when the magnetic force the bead experiences along the *z*-axis balances the gravitational force F_g (corrected for the effect of buoyancy), and the magnetic force the bead experiences along the *x*-axis balances the centrifugal force F_c. (D) Three glass beads with different densities levitate in an aqueous $MnCl_2$ solution in a static MagLev device. (E) Rotating the MagLev device about the axis of the supporting disc causes the beads to move radially with different responses to the rate of rotation. Source: Images (A–E).[87]

"Tilted MagLev" significantly expands the range of density accessible using the standard MagLev system, and enables measurements over the entire range of densities observed in matter at ambient conditions (~0 $g\,cm^{-3}$ to ~23 $g\,cm^{-3}$, Figure 5F).[93]

3.5.5. Using Centrifugation to Tune the Sensitivity and Dynamic Range Dynamically

Gao and Zhang developed a rotation-based MagLev system[87,166] (Figure 6) in which a MagLev device sits off-center on a spinning disk, and rotates about the central axis of the disk to impose a centrifugal force perpendicular to the vector of gravity on objects levitating in the suspending medium. This method allows flexible adjustment of the effective centrifugal acceleration at the position of the MagLev device (by controlling the distance of the MagLev system to the central axis of the disk and the speed of rotation), and, thus, enables a simple and flexible procedure to tune the sensitivity and dynamic range of the system dynamically by effectively adjusting the *g* values in eqs S20 and S21. The capability of adjusting the positions of the levitated objects dynamically without physical contact may be useful to carry out density-based analyses, separations, quality-control of plastic parts, and self-assemblies in 3D.

3.6. "Axial" MagLev

One somewhat inconvenient characteristic of the "standard" MagLev system is the particular configuration in which the sample container is physically sandwiched between two block magnets. The physical barrier present along the central axis of the MagLev system can make the addition of the materials (including the sample and the suspending medium) to, and their retrieval from, the sample container cumbersome. A configuration (which we call "axial" MagLev) in which two ring magnets are coaxially positioned and aligned with the vector of gravity (Figure S3) provides a useful alternative system.[22] Adjustment of the aspect ratio and distance of separation between the ring magnets enabled us to generate a linear magnetic field along the central axis between the magnets, and to carry out straightforward density-based analysis, separation, and manipulation. The regions close to the entrance surface of the holes through the magnets showed useful non-linear regions, as demonstrated in a separate study by Zhang and Zhao using a single-ring magnet.[80] The two-ring "axial" MagLev effectively forms a magnetic "bottle" between the magnets, and the strong radial field gradient (in a plane perpendicular to the central axis of the system) focuses suspended particles to the central axis, and thus, provides a useful self-focusing capability.

"Axial" MagLev has three attractive characteristics: (i) It enables simple procedures for physical sampling of the sample in the magnetic field between the magnets. (ii) It allows simple accesses, and the ability to view the levitated samples in the medium from vantages positioned 360° around the sample container, and from both the top and bottom of the system. (iii) It enables liquid to flow through the tubes while it is positioned in the magnetic field, and thus introduces fluid shear as another useful control parameter. The "axial" MagLev system is useful in levitating small drops of hydrophobic organic solvents, and in levitating (without contact with the wall of the tube containing the suspending medium) a variety of simple and composite materials (e.g., air (~0 $g\,cm^{-3}$), Teflon (~2.11 $g\,cm^{-3}$), aluminum (~2.68 $g\,cm^{-3}$), zirconium silicate (~3.70 $g\,cm^{-3}$), viscous polymer liquids (polydimethylsiloxane prepolymer, ~1.04 $g\,cm^{-3}$), sticky gels (Vaseline gel 0.87 $g\,cm^{-3}$), polymeric microparticles, and irregularly-shaped polymer samples saturated with hydrophobic solvents).[22]

3.7. High-Throughput Density Measurement

The throughput of density measurements using the standard MagLev system is low because the MagLev system is designed for a single sample container. A configuration of MagLev, which uses engineered magnetic fields provided by an array of NdFeB magnets,[123] makes it compatible with the 96-well plate, one of the most common liquid containers in the research laboratory. These plates are designed to handle an array of small (up to a few hundreds of microliters) aliquots of liquids for parallel screening (Figure 5J).

Long and thin magnets, inserted into the space between every column of tubes on the plate with magnets using the like-poles-facing configuration (i.e., N/N, S/S, N/N, …, and so on), organized the system so that every tube is physically sandwiched between a pair of like-poles facing magnets (Figure 5J). Optimization of the size and shape of the magnets generates an approximately linear field gradient for a distance about ~4 mm along the vertical axes of the tubes on the plate.[123] Stacking a second set of indistinguishable magnets below the first set increases the strength of the magnetic field in the gaps (to ~0.7 T), and also the magnitude of the magnetic field gradient, and thus, according to Eq. S21, expands the dynamic range. This increased field strength and gradient allowed the concentration of paramagnetic species required to levitate samples to be lower, a fact particularly important for biological samples.

Flatbed scanners are inexpensive and useful imaging devices to capture images of the entire 96-well plate. The integration of a flatbed scanner with the MagLev device requires an optical design to project the focused images of the levitated objects in the tubes to the flatbed of the scanner. We have used inexpensive mirrors (aluminum-coated Mylar film) angled at ~45° facing individual tubes and relay lenses (simple biconvex lenses)[123] positioned below the mirrors to accomplish this task. This integrated system makes it possible to carry out parallel, high-throughput density measurements with optical detection.[123]

Representative samples used to demonstrate the system include simple organic liquids and solids (e.g., 3-chlorotoluene and small crystals of cholesterol), glass particles, copper powder, and biological samples (human red blood cells).[123] It also allowed monitoring the kinetics of chemical reactions on solid supports (e.g., the coupling reactions of 2,5-diiodobenzoic acid with leucine-functionalized Wang resin), and determining the Arrhenius activation energy of this coupling reaction.[123]

Table 8: Guide to select MagLev techniques for density measurement.

		Standard[20]	Axial[22]	Tilted[93]	High-sensitivity[95]	High-throughput[123]
Sample	Type	Liquid, solid	Gas, liquid, solid	Gas, liquid, solid	Liquid, solid	Gas, liquid, solid
	Typical size of samples	mm	mm	mm	cm–mm	µm
Container	Common types	Cuvettes, vials	Cuvettes, vials, test tubes	Cuvettes, round vials	Test tubes, cylinders, bottles	Plastic 96-well plates
	Limitation	Height: < 45 mm	Width: < 25 mm	Height: < 45 mm	none	96-well plates
Paramagnetic medium	Common types	Aqueous solutions (e.g., solutions of $MnCl_2$)[20,22,93,95,123] Hydrophobic liquids[41,100] Ionic liquids[96]				
		AMPS	AMPS	–[a]	AMPS	AMPS
Measurement: typical ($g\,cm^{-3}$)	Range	0.8–3	0–4	0–23	0.8–3	0–9
	Sensitivity	10^{-2}–10^{-4}	10^{-2}–10^{-4}	1–10^{-2}	10^{-2}–10^{-6}	10^{-1}–10^{-4}
Operational simplicity in use		High	High	Medium	High	High

[a] It is operationally inconvenient to combine AMPS and tilted MagLev for density measurement as we normally use these methods.

Table 9: Summary of useful characteristics and potential applications of MagLev.

Uses	Parameter	Summary of Characteristics	Applications
Analysis	ρ	· Simple, inexpensive, rapid (s–min), no power consumption[20,22] · Measures a universal property (density) · Applicable to quantities in pL–mL scale in volume · Applicable to samples with different physical characteristics (simple solids, liquids, gases, viscous/sticky samples, pastes, gels, heterogeneous materials such as composites, soft matter such as hydrogel and cells) · Applicable to irregularly-shaped samples · Large dynamic range to cover the entire range of densities observed in matter at ambient conditions[93] · high sensitivity (up to $\pm 10^{-6}$ $g\,cm^{-3}$)[95] · high throughput (compatible with 96-well plates)[123]	· Soft materials (gels and cells)[69,73,106,107,123,167] · Foods and water (e.g., butter, cheese, milk, oil, grains such as rice and barley)[41] · Seeds · Illicit drugs (e.g., mixtures containing fentanyls)[95] · Forensics (glitter, gun powders)[101] · Glue, adhesive, and paint (acrylics etc.)[20,44,83] · Glass · Minerals[81] · Tire rubber · Fuels
Separation	ρ_A, ρ_B	· Separations based on density	· Density-based separation of common materials (e.g., polymers, metals, salts)[44,85,93,123,168] · Characterization and separation of crystals, including crystal polymorphs,[97] cocrystals,[99] enantiomers[98], and mixtures of microcrystals[95] · Density-based separation of biological particles[69,70,73,167]
3D Self-Assembly	$\rho_A+\rho_B$	· Contactless manipulations of components · Programmable magnetic fields · Compatible with a wide variety of materials (e.g., plastics and composites) in both regular and irregular shapes · Address components in parallel at the same time	· Positioning and alignment of components with optical function[138] · Self-assembly of multiple objects into well-ordered clusters[139] · Generation of multilayered, interlocking structures[138] · 3D Assembly of biological components (e.g., mammalian cells)[64,66]
Contactless manipulation	$\rho_A+\rho_B$	· Directs objects into specific regions for 3D assemblies · Controls position and orientation in 3D · Takes place in a fluid, without dry friction, stiction, contact adhesion, and static charging · Applicable to soft and fragile components · Occurs in an entirely closed container, if necessary	· Advanced manufacturing[21] · Complementary to automatic robotic systems
Quality control	$\frac{\partial\rho}{\partial z}$ or ρ	· Simple, inexpensive, rapid (s–min), no power consumption · Sensitive to the shape of manufactured parts · Sensitive to heterogeneity in density	· Quality control of injection-molded plastic parts[82,135,169] · Identification of counterfeit and defective parts[135]; qualification of manufacturing process.
Dynamic processes	$\frac{\partial\rho}{\partial t}$	· A label-free method to monitor progress of reactions and binding events · Characterization of kinetics of chemical reactions	· Characterization of kinetics of free-radical polymerization of low-molecular-weight monomers[111] · Monitoring of chemical reactions supported on a solid substrate (e.g. a polymeric bead)[42,123] · Carrying out density-linked assays for biological molecules (e.g., proteins)[88,106–108]

3.8. Practical Guidelines for the Users

Table 8 summarizes key characteristics of five major types of MagLev configurations, and provides a practical guide to select the appropriate configuration of MagLev and suitable type of sample containers for desired ranges and sensitivities of density measurements. Other configurations of Maglev devices are also possible.[69,80,81,83,84] Notable examples include the miniaturized version of the "standard" MagLev device developed by Durmus and Demirci for biological applications,[69] and the single-ring system developed by Zhang and Zhao for enhanced operational simplicity.[80]

4. Applications

This section describes representative applications enabled by MagLev, emphasizing two areas: (i) density-based analysis, separation, and assembly, and (ii) quality control and contactless manipulation. We also sketch problems to which MagLev could be applicable in resource-limited settings.

Table 9 summarizes important characteristics of MagLev and potential applications for density-based analysis, separation, self-assembly, and contactless manipulation.

4.1. Density Measurement of Materials

4.1.1. Simple Liquids and Solids

The densities of simple liquids and solids (in the form of liquid drops or solid particles, beads, or balls) in the size range of ~5 μm to ~5 mm in diameter (from ~0.1 pL–~0.1 mL in volume) can be readily determined using MagLev, with choices of the designs and dimensions described (Figure 7). Simple, non-spherical solid samples such as crystals, powders, rods, and flakes are also compatible with MagLev (Section 4.1.4).

A number of simple liquids (e.g., pure organic solvents) and solids (e.g., metal spheres and polymer beads made of a single component) have, in fact, well-defined densities, and are available commercially in high purity, and thus, can be used as density standards to calibrate MagLev systems (Table S1).

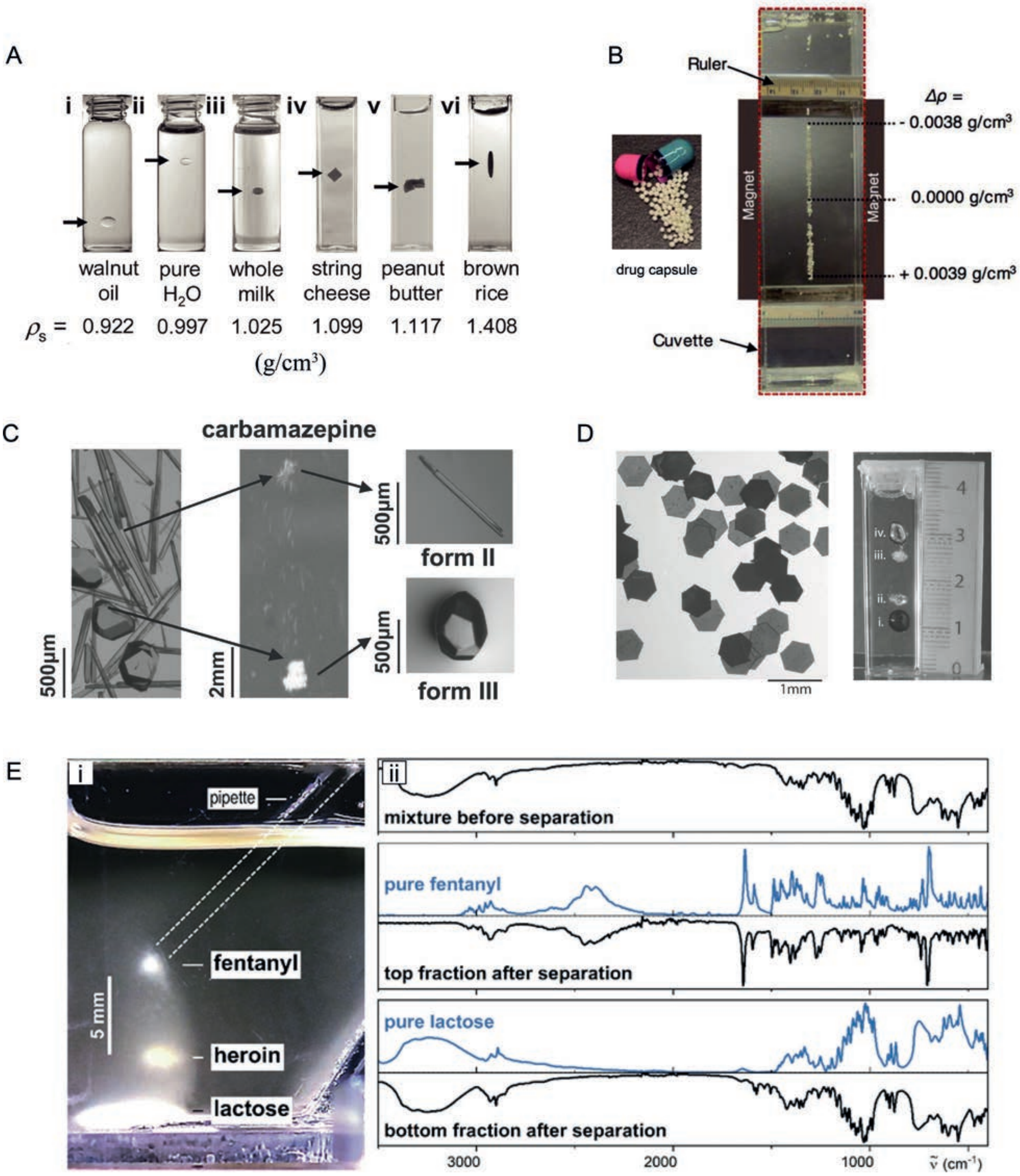


Figure 7. Density-based analyses and separations. (A) Density measurements of foods and water. Suspending media are the following: (i) 50 mм $GdCl_3$ in 62% methanol and 38% water (v/v); (ii) 50 mм gadolinium(III) diethylenetriamine triacetic acid didecyldiacetamide dissolved in 95:5 3-fluorotoluene/toluene (v/v); (iii) 40 mм gadolinium(III) diethylenetriamine triacetic acid didecyldiacetamide dissolved in 84:16 2-fluorotoluene/chlorobenzene (v/v); (iv, v) aqueous solutions of 1.0 м $MnCl_2$; and (vi) an aqueous solution of 0.475 м $GdCl_3$ and 4.5 м $CaCl_2$. (B) High-sensitivity density measurement of drug caplets. (C) Separation of polymorphs of crystals having different densities. Different forms of crystals of carbamazepine also show distinct morphologies (rod vs. polyhedral).[97] (D) Separation and analysis of forensic evidence, "glitter" particles.[101] Left: A mixture of two types of glitter particles with the same size and shape. Right: Separation of "glitter" particles into two populations (ii and iii) in an aqueous 3.0 м $MnCl_2$ solution in a MagLev device. Two density standard beads (i: 1.450 $g\,cm^{-3}$ and iv 1.350 $g\,cm^{-3}$) were also included. (E) Separation and spectroscopic analysis of a powdered mixture of illicit drugs. (i) The mixture comprised powdered fentanyl·HCl (1.3 wt%), heroin·HCl (2.6 wt%), and α-lactose (96.1 wt%). The compounds were separated as indicated by density into its constituents in a hydrophobic paramagnetic medium (gadolinium(III) tris(dipivaloylmethanato) trioctylphosphine oxide, $Gd(DPM)_3TOPO$, 450 mм, in a mixture of 23 vol% hexane and 77 vol% tetrachloroethylene) in an applied magnetic field provided by NdFeB solid-state magnets. The powdered mixture contained individual microcrystals in the range of 4–300 μm.[100] (ii) The extracted fractions of different powders were rinsed (with hexane), air-dried, and further characterized in their solid state using attenuated total reflectance-Fourier-transform infrared spectroscopy (FTIR-ART). Sources: Images (A),[41] (B),[95] (C),[97] (D),[101] and (E).[100]

4.1.2. *Gels, Viscous Liquids, Pastes, Gums and Other "Sticky" Materials*

"Soft matter"—including gels, viscous liquids, and gums—is often difficult to handle. It can be technically challenging to characterize objects composed of soft matter—especially if they are changing with time. (For example, a sample loses mass due to drying or evaporation of its volatile components, or changes its density as it polymerizes.) MagLev is a particularly useful technique to measure density of these types of samples because it often allows them to be suspended without contact with a solid surface. The magnitude of the physical forces (i.e., the gravitational and magnetic forces) that enable levitation of objects are on the order of micro-Newtons, and thus are "soft" forces, and compatible with small, fragile forms of "soft matter" that are otherwise difficult or impossible to handle (e.g., by a hard gripper in robotics). MagLev has been used to measure the densities of various types of soft and/or sticky samples, including emulsions (e.g., peanut butter 1.12 $g\,cm^{-3}$),[41] viscous liquids (e.g., uncured elastomers such as PDMS 1.03 $g\,cm^{-3}$),[111] hydrogels (e.g., PEG hydrogel 1.07 $g\,cm^{-3}$),[106] and others (e.g., cheese 1.10 $g\,cm^{-3}$).[41]

4.1.3 *Chemically Heterogeneous Materials*

Chemically heterogeneous materials encompass a broad range of common materials made of two or more constituent components, including alloys and many sorts of composite materials (e.g., concrete, reinforced plastics, metal and ceramic composites). MagLev can measure the densities of these materials. For example, for use in forensics, MagLev has been used to measure the densities of various types of "glitter" particles (sub-millimeter of the longest dimension, made of metals and plastics in a layered structure and used in cosmetics), and of gunpowder, as aids in characterizing forensic evidence available only in trace quantities.[101]

MagLev has also been used to measure the changes in density of composite materials in which liquid monomer or polymer was impregnated in a solid, porous matrix (e.g., carbon fibers), and then polymerized or cross-linked further (See also Section 4.5).[111] MagLev is also useful as a simple method with which materials scientists can measure swelling (the change in volume of a sample) of cross-linked polymers in solvents. It directly measures the density of the swollen polymer sample regardless of its volume, mass, or shape, and the measured densities can be converted to the swelling ratios.[22]

4.1.4. *Objects with Irregular Shapes or Low Symmetry*

Densities of samples with irregular shapes cannot be easily determined by weighing, and measuring dimensions. MagLev measures density directly (without determining independently the mass or volume of the object), and does so independently of the shape, or volume, of the object. The average density of the object correlates linearly with the levitation height, and thus, can be easily calculated so long as the centroid (the geometric center) of the sample can be determined.

Many samples for which MagLev has been used to determine densities are irregular in shape. Representative examples include molded plastic pieces (e.g., screws),[135] metal powders,[93] grains,[41] crystals,[97] and nonspherical cells (red blood cells and rod-shaped bacteria).[69,123] MagLev, thus, provides a particularly convenient method to measure the density of small, irregularly shaped objects.

4.1.5. *High and Low Densities*

MagLev has been used (using tilted MagLev or axial MagLev, see Section 3.5.4 for more discussion) to measure densities as low as that of an air bubble ($\rho \sim 0\,g\,cm^{-3}$) and as high as the most dense metal elements (osmium and iridium, $\rho \sim 23\,g\,cm^{-3}$) under ambient conditions (also using tilted MagLev).[93] At very high and low densities, it is more difficult to resolve small differences in density. The dynamic range and sensitivity of MagLev (as with most analytical techniques) are tightly coupled.[95] For high-sensitivity density measurement, the densities of the samples should match closely the density of the suspending paramagnetic medium. High-sensitivity density measurements are possible in the range of densities close to that of the easily used paramagnetic media, which spans approximately from $\rho \sim 0.8\,g\,cm^{-3}$ to $\rho \sim 3\,g\,cm^{-3}$ for common water- or alcohol-based suspending media. This range may be further expanded by using hydrophobic solvents (e.g., hexane (0.655 $g\,cm^{-3}$)) in combination with hydrophobic chelates.[41,100] Very high- or low-density paramagnetic liquids remain to be developed and validated.

4.1.6. Small (< 1 μm) Particles

Theoretical analyses and experimental studies establish the lower limit in size (~2 μm in radius) of particles the standard MagLev system can stably levitate (More discussion in Section 5.1). Particles that have radii below ~2 μm essentially remained as a diffuse cloud in the standard MagLev systems as a result of Brownian motion. Demirci and we[67,69,70,73,146] have used a millimeter-sized MagLev system to trap or levitate cells (such as bacteria and yeast cells). Stable levitation of single bacterial cells in an aqueous paramagnetic medium took an extended time period (hours).[69] Taken together, these observations indicate that it will be difficult to levitate small particles (< 1 μm) rapidly using simple MagLev systems under ambient conditions, unless the spacing between the magnets is small, or the magnetic field high (either change increases the magnitude of the magnetic field gradient.).

AMPSs that have been described in Section 3.3.5 using self-assembling phases made of polymers, surfactants, and/or salts, can be useful—as a complementary approach—to carry out density-based separations of small particles (e.g., bacteria, virus, and other non-biological particles, such as carbon nanotubes).[120,130] AMPSs have also been used to separate gold nanoparticles on the basis of their shape and size.[117]

4.2. Density-Based Separation and Manipulation of Materials

MagLev can effectively separate materials on the basis of their differences in density. This section outlines separations of four types of materials: polymers, powdered materials (both organic and inorganic materials), polymorphs of crystals, and crystals of enantiomers. We also sketch the uses of MagLev for 3D self-assembly.

4.2.1. Polymers

MagLev can separate polymeric solids and gels with different densities.[44,58,83–86,170–172] Typically separations of different kinds of polymeric materials (for example, polypropylene (0.90 $g\,cm^{-3}$), polyethylene (0.93 $g\,cm^{-3}$), and polystyrene (1.05 $g\,cm^{-3}$)) from a mixture into its constituent components can be carried out in a static paramagnetic medium.[44] This type of separation also applies to mixtures of polymer materials consisting of multiple subpopulations of small polymer particles with different densities.

4.2.2. Powdered Mixtures

The separation and characterization of constituents from powdered mixtures are challenging tasks (for example in materials characterization and forensic chemistry). A particular example in the management of public health is the need to separate and identify different types of fentanyls and other psychoactive compounds (e.g., heroin and cocaine) present in mixtures of powdered illicit drugs. MagLev separated different types of active compounds from diluents and adulterants (non-active constituents) present in mixtures of powdered illicit street drugs on the basis of the difference in density of these organic compounds in their solid states (Figure 7E).[100] MagLev has also been demonstrated to separate glass and copper particles from a powdered mixture.[123]

4.2.3. Polymorphs of Crystals

Crystallization of an organic compound can yield a mixture of crystalline solids with different crystal structures (i.e., polymorphs), which may have distinct densities for different forms.[97,173] Examples include minerals (e.g., $CaCO_3$),[174] proteins (e.g., lysozyme),[175] and small molecules (e.g., glycine).[176] The identifications of crystal polymorphs, and in some cases, the selection and retrieval of a specific form, can be important (e.g., for isolating seed crystals).[97]

The difference in density—albeit small: often $\Delta\rho < 0.01\,g\,cm^{-3}$—can sometimes be exploited for separations.[97] An example used four model compounds (5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, sulfathiazole, carbamazepine, and *trans*-cinnamic acid) with well-characterized crystal structures, and well-defined densities (which could be calculated independently from the X-ray diffraction data[97,177]) to validate the performance of separation using MagLev (Figure 7C).[97] In a related application, MagLev also provides a method to separate cocrystals.[99]

4.2.4. Enantiomeric and Racemic Crystals

Existing methodologies (e.g., HPLC and fractional crystallization) to enrich desired enantiomers from a racemic mixture are variable in their performance. MagLev provides an alternative approach, and successfully separated crystals of pure enantiomers and of racemic compounds.[98] We have used a mixture of *S-/RS*-ibuprofen crystals, as a model, to demonstrate the value of MagLev to improve the purity of *S*-ibuprofen, the desired enantiomer in the mixture of *R*- and *S*-enantiomers. (The *S*-enantiomer has a stronger anti-inflammatory activity than the *R*-enantiomer.[178])

4.2.5. Separations of Materials Under Flow

MagLev is compatible with fluidic flow in a microchannel system in an applied magnetic field, and thus, can be used for continuous separations of materials (Figure 8). In particular, the formation of a stable gradient in density in a flowing fluid provides a useful (and unique) capability to carry out separations in fluidic flows. Two specific spatial arrangements of fluidic flows and the magnetic field gradient are discussed here: (i) the fluidic flow is perpendicular to the magnetic field gradient, and (ii) the fluidic flow is parallel to the magnetic field gradient.

When the flow is perpendicular to the magnetic field gradient (Figure 8A), the viscous drag force $\vec{F}_v$ an object experiences (as a result of fluidic shear stress) in a flowing stream is orthogonal to the physical forces (gravitational force, buoyancy, and magnetic force) that drive the object to

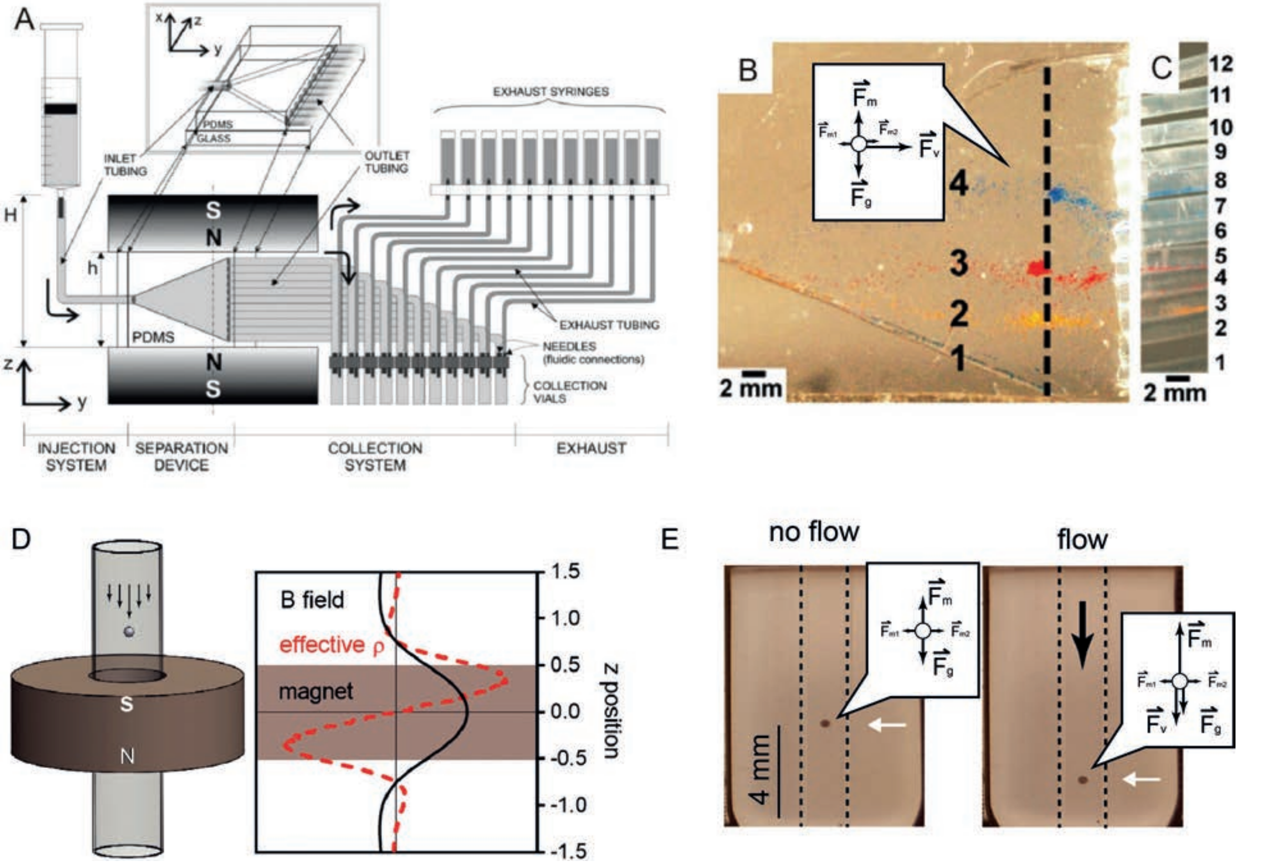


Figure 8. A stable gradient in "effective" density (based on magnetic levitation plus gravity) in a flowing liquid. (A) Fluidic flow is perpendicular to the magnetic field gradient. A suspension of beads (which were suspended in 250 mM $GdCl_3$) flowed into a V-shaped channel (fabricated in a PDMS-based microfluidic device); the beads separated into four fractions (labeled as 1 to 4) on the basis of their densities, and exited through the outlet tubing (C). (B) Each particle experiences a flow-induced viscous drag force $\vec{F}_v$, in addition to the gravitational force $\vec{F}_g$ (corrected for the effect of buoyancy), and magnetic forces ($\vec{F}_m$, $\vec{F}_{m1}$, $\vec{F}_{m2}$) as described in Figure 1 E. (D) Fluidic flow is aligned with the magnetic field gradient. The axial magnetic field of a ring-shaped NdFeB magnet (black line on the plot) produces a gradient in effective density in a paramagnetic liquid (dotted red line), and may allow its use for flow-based analyses and separations of materials. (E) A demonstration of stable levitation of a polymeric particle (~400 µm) in a flowing paramagnetic medium (aqueous 0.5 M $MnCl_2$ at a flow rate of 0.2 mL min^{-1}) in an applied magnetic field using "axial" MagLev. Dotted lines indicate the walls of a glass capillary. Source: Images (A, B).[44]

reach the stable levitation height in the direction orthogonal to the fluidic flow. The fluidic flows—particularly laminar flows—should affect the levitation height of the object in a flowing stream minimally, while carrying the objects across the applied magnetic field in a MagLev device. The same principle could be used to separate biological cells.[67,69,70,74,75]

A simple microfluidic device has been used to carry out continuous separations of polymeric particles in a flowing stream in an applied magnetic field (Figure 8 A). The device has a single inlet which leads to a gradually expanding, V-shaped chamber (which is used to direct the flow and to perform the separation within it). During operation, the V-shaped chamber was placed in the standard MagLev device, and aligned such that the plane of the chamber is in parallel with the vector of gravity; a mixture of polymeric particles (75–150 µm in diameter) in a flowing paramagnetic stream flowed into the device (driven by a syringe pump), and separated in the vertical direction—according to their densities—into different subpopulations. The separated particles were collected continuously by an array of vertically aligned tubes placed at the far-right end of V-shaped chamber.

When the fluidic flow is parallel to the magnetic field gradient (the vertical direction in Figure 8 D), the levitated object experiences a viscous drag force that is along the direction of the fluid flow. This additional force, thus, breaks the equilibrium the object would experience in a static fluid, and drags the object to a new position at which the strength of magnetic force increases to balance the viscous drag force (See illustration of physical forces at play in Figure 8 E). The object, therefore, reaches steady state (in position) in a flowing stream when the sum of the physical forces on it reach zero. To an approximation, the viscous drag force experienced by a small spherical object in a laminar flow is described by Equation (3):[20]

$$\vec{F}_v = -6\pi\eta R\vec{v} \quad (3)$$

In Equation (3), η ($kg\,m^{-1}s^{-1}$) is the dynamic viscosity of the flowing paramagnetic medium, R is the radius of the object, and v ($m\,s^{-1}$) is the velocity of the flowing fluid. The stable levitation height of the object in a flowing stream, therefore, reflects the physical characteristics of both the object (density and size), and also of the flowing medium that suspends the object (viscosity and velocity). When appropriately designed, MagLev systems and fluidic flows could be exploited to carry out separations that reflect both density and size/shape (e.g., drag) and non-magnetic characteristics of the flowing liquid (e.g., viscosity, velocity).

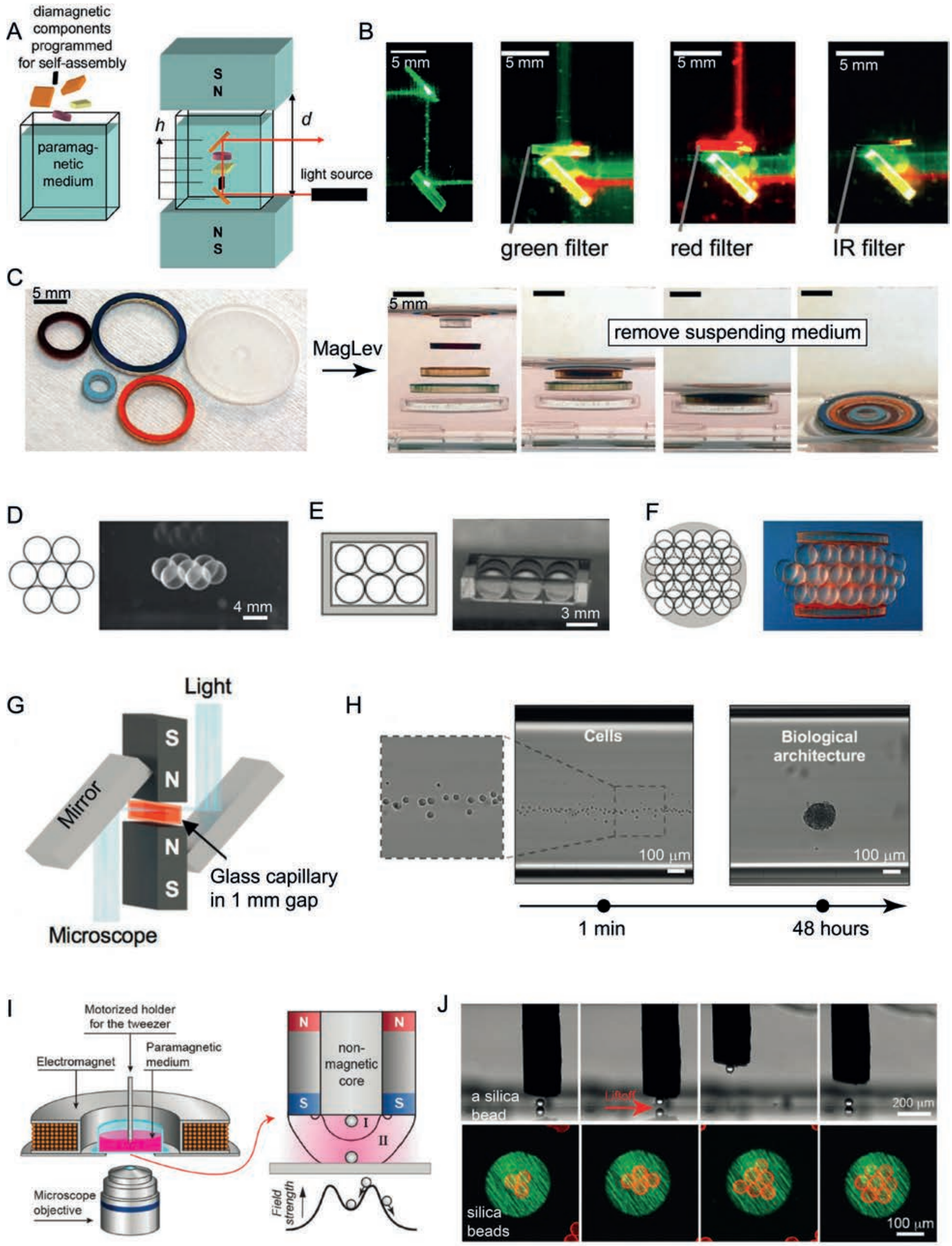


Figure 9. 3D Self-assembly without physical contact, directed using MagLev (A) Schematic suggesting the use of density to carry out 3D self-assembly in an aqueous environment (typically a $MnCl_2$ solution) using MagLev for desired functions. (B) The assembled components, as illustrated, steer a light beam to pass through a series of optical components (e.g., filters and mirrors). (C) Four plastic rings and a solid circular base were levitated and aligned concentrically in a paramagnetic medium; upon removal of the suspending medium, these components self-assembled into a co-planar structure supported on the circular base. (D) Self-assembly of mm-scale spheres using MagLev. (E and F) Templated self-assembly of mm-scale spheres using MagLev. (G) Self-assembly of mammalian cells (murine fibroblasts) in a biocompatible paramagnetic medium (an aqueous solution of Gadavist) using a glass capillary and two like-poles-facing permanent NdFeB magnets (length × width × height: 50 mm × 2 mm × 5 mm) positioned 1 mm apart. (H) The cells as described in (G) initially self-assembled into a line-like structure, and over 48 hours of culture, formed a spheroid in the MagLev device. (I and J) Use of a magnetic flux concentrator (a coaxial rod comprising a weakly magnetic core, e.g., tungsten, and a supermalloy cladding) and an electromagnet to carry out magnetic tweezing and self-assembly of diamagnetic particles (e.g., 50-μm silica beads) suspended in a refractive-index-matched paramagnetic medium ($Ho(NO_3)_3$ in a mixture of water and DMSO). Sources: Images (A–F);[138,139] (G, H);[64] and (I, J).[90]

4.2.6. 3D Self-Assembly

MagLev can be used to guide the self-assembly of diamagnetic objects without contacting solid surfaces (Figure 9). It is particularly attractive to self-assemble mm-scale objects (in principle, from ~10 μm to > 10 cm) that are otherwise inconvenient or difficult to handle (e.g., soft and/or fragile objects), because the gravitational and magnetic forces it experiences are comparable, for objects that fall in this range of sizes. MagLev has been used to direct 3D self-assembly[137,138] and templated self-assembly[137,139] of both spherical (e.g., plastic beads) and non-spherical, heterogeneous objects (e.g., blocks of composite materials). MagLev has also demonstrated potentially useful capabilities to self-assemble structures for practical applications (e.g., aligning optical components and steering optical beams).[138]

Grzybowski,[90–92] Demirci,[64–66,68] Arslan-Yildiz,[79] and others[45,179] have used similar approaches to carry out self-assembly of both biological (yeast cells, mammalian cells, and cell-encapsulated hydrogel particles) and nonbiological (polystyrene beads and cube-shaped silicon particles) samples.

4.3. Control of the Quality of Manufactured Parts

4.3.1. Understanding and Controlling Orientation of Levitated Objects

Orienting objects in 3D without physical contact can be useful in manufacturing[180–182] (e.g., inspecting parts for quality control, pre-positioning components for assembly, or sorting components). Handling soft, sticky, or easily-damaged structures, such as soft-robotic grippers made of gels, would also benefit from non-contact manipulation. MagLev enables objects to be oriented in 3D without physical contact by manipulating the magnetic field. The gradients of the magnetic field along all axes enable an object both to remain stably trapped, and to be oriented entirely by its shape and by the structure of the magnetic field. Objects can thus be manipulated in 3D by either rotating the MagLev device or by introducing a secondary external magnet or magnetic flux concentrator.

For objects with spatially homogeneous density and magnetic susceptibility, but non-spherical shape, the orientation in the "standard" Maglev system (or other systems using linear magnetic fields) depends exclusively on the aspect ratio of the object (Figures 10 A–C).[21] See Section S6 for a more detailed theoretical treatment and discussion. With this orientational trapping, it is possible to orient an arbitrary diamagnetic object with no physical contact using MagLev (Figures 10 D–G). In addition to orientation of rigid objects, it is similarly possible to manipulate soft, sticky, or deformable objects. Figure 10 H shows the manipulation of a hydrogel, a soft-gripper, and an armored droplet, using a secondary magnet to perturb the magnetic field. In each case, the objects orient to minimize the magnetic torque. Although this approach of perturbing the field with a secondary magnet is not as easily subject to analytical inspection as is the simple case of the MagLev system alone (due to strong non-linearities in the field), it nonetheless demonstrates the same principle: that the orientation of objects in a magnetic field can be controlled by either changing the shape of the objects, or changing the direction or distribution of the magnetic field.

4.3.2. Quality Control: Heterogeneity in Density in Injection-Molded Parts

Low-cost plastic components often have defects, including cracks, voids, embedded impurities, or regions of abnormal crystallinity, strength and (perhaps) density and magnetic susceptibility. In typical screens for defects, a representative part is tested either by destroying it (cross-sectioning) or by complex technique such as industrial computed tomography (ICT), ultrasonic testing, or infrared thermography. MagLev enables rapid, sensitive, non-destructive, quality control of plastic parts by measuring differences in levitation height and orientation of parts.[135,136]

Defects in otherwise homogeneous objects will result in a spatially inhomogeneous density and susceptibility at the position of the defect. Typically, the magnetic susceptibility of the object is negligible relative to the susceptibility of the suspending medium, so small variations in the susceptibility in the object are unlikely to have an appreciable effect on the orientation of the levitating object. By contrast, inhomogeneities in density *will* have a more significant effect. See Section S7 for a more detailed theoretical treatment and discussion correlating the levitation angle of an inhomogeneous, rectangular rod and its heterogeneity in density (Figures 11 (A,B)).

The density-dependence of levitation angle can be used to spot defective or damaged plastic parts. For example, Nylon parts change density when exposed to UV light or subjected

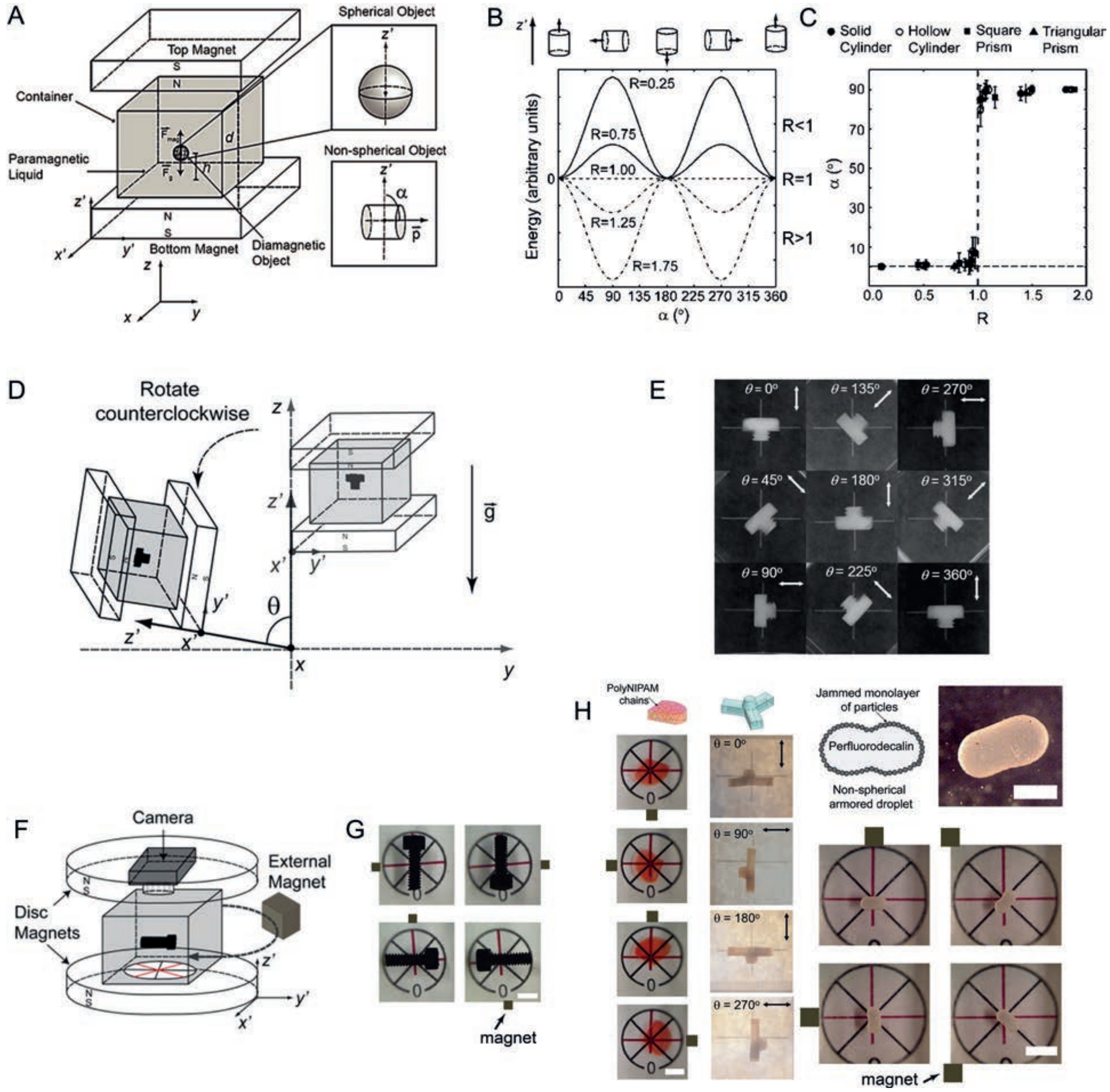


Figure 10. Understanding and controlling orientations of levitated objects in MagLev systems (A) A homogeneous spherical object levitates in a MagLev system without orientational preference, while a non-spherical object (we use a cylinder as an example) shows a preference. We define the angle of orientation, α, as the angle between the z'-axis of the MagLev system and a unit vector $\vec{p}$ of the levitated object. We also define a unit vector $\vec{p}$, which typically aligns with the long axis of the object. (B) The potential energy of a cylindrical object varies as a function of α. R is the ratio of the second moments of area of the object Eq. S24). For $R<1$, the minima in potential energy occur at 0° or 180°. For $R>1$, the minima in potential energy occur at 90° or 270°. When $R=1$, the curve shows a flat energy landscape, suggesting no preference of orientation of the levitated object. (C) Four types of objects having different shapes and different values of R yield overlapping curves, and show a sharp transition in α from 0° to 90° at $R=1$. (D) Schematic illustration of the control of the angle of orientation of a levitated screw by rotating the MagLev device about the x-axis of the laboratory frame of reference. θ is the angle between the central z'-axis of the MagLev device and the z-axis of the laboratory frame of reference. (E) A Nylon screw rotates with respect to the laboratory frame of reference (represented by the white cross in the background) by performing the procedure described in (D). (F) Schematic illustration of the control of orientation of a levitated object in the x'-y' plane using an external magnet. (G) Using an external magnet to control the orientation of a black, plastic screw. Scale bar: 5 mm. (H) Using an external magnet to control the orientations of soft, sticky, and easily deformable objects: a piece of hydrogel made of poly(N-isopropyl acrylamide), a soft gripper made of Ecoflex 0300, and an armored droplet (a Pickering emulsion: a liquid drop of perfluorodecalin covered by a layer of 10-μm-in-diameter polystyrene spheres). Scale bars: 5 mm for the hydrogel, 2 mm (upper right) and 5 mm (bottom right) for the armored droplet. Source: Images (A–H).[21]

to local thermal annealing (Figure 11 C). Real and fake parts can also be distinguished by a difference in levitation height of the parts in the MagLev system (Figure 11 D).

4.4. Quality Characterization of Water, Foods, and Others

MagLev can be used to characterize foods, based on density (Figure 7 A). As an example, MagLev characterized

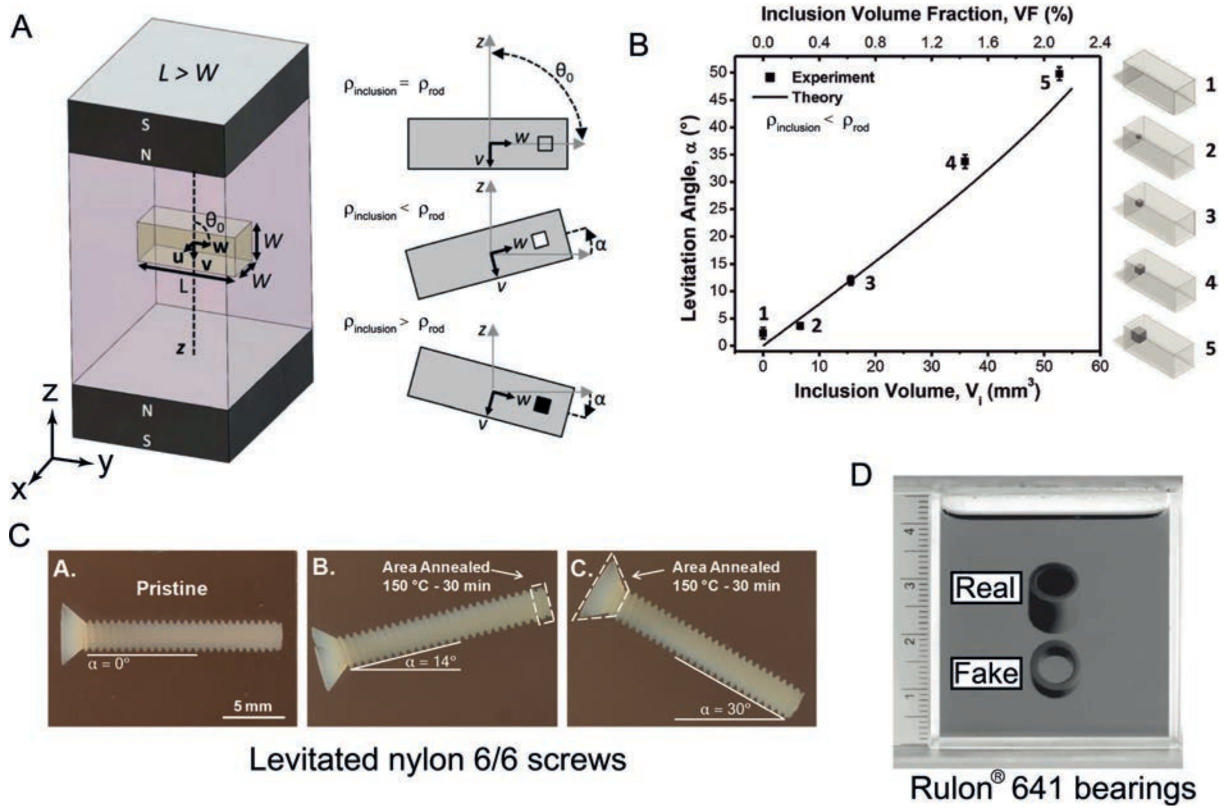


Figure 11. Examination of manufactured parts (A) Illustration of orientations of levitated 3D-printed polyacrylate rods containing inclusions having known densities. The angle θ_0 (0°, 90°, 180°, or 270°), defined by the *w*-axis of the rod and the *z*-axis of the MagLev device, is the equilibrium angle of the rod having a homogeneous density, which is determined by the aspect ratio of the rod alone. The angle α, defined by the *w*-axis the rod and the *y*-axis of the MagLev device, indicates the type of inclusion present in the rod. (B) Orientations of 3D-printed polyacrylate rods ($\rho = 1.184\ g\,cm^{-3}$) containing an inclusion ($\rho = 1.163\ g\,cm^{-3}$,less dense than the rod in this case) with increasing volumes at the same location. (C) Nylon 6/6 screws levitated at different angles of orientation due to local thermal treatments. The treatment caused a decrease in density in the treated regions, and led the screw to tilt in the MagLev device. (D) Detection of counterfeit Rulon® bearings. Rulon® is a class of branded polytetrafluoroethylene (PTFE) derivatives. In this case, a large difference in density was detected between the real and fake Rulon® parts. Source: Images (A–D).[135].

vegetable oils based on density, and also determined the densities of different grains (e.g., rice and barley).[41]

4.4.1. *Grains and Seeds*

Grains contain carbohydrates, protein, fat, and water; the ratio of these components in a grain determines its density. MagLev can, thus, be used in the analysis of grains (e.g., white rice 1.455 $g\,cm^{-3}$, brown rice 1.408 $g\,cm^{-3}$, whole grain kamut 1.354 $g\,cm^{-3}$, barley 1.371 $g\,cm^{-3}$, and millet 1.359 $g\,cm^{-3}$; Figure 7 A).[41]

4.4.2. *Fat Content in Milk and Butter*

Dairy products are often sold on the basis of nutritional content (e.g., fat and protein). Raw bovine milk—or milk from any mammal—can vary broadly in fat content, and, therefore, density, prior to processing. MagLev provides a method (using a hydrophobic organic liquid, such as 2-fluorotoluene, containing a hydrophobic paramagnetic species, such as gadolinium(III) diethylenetriamine triacetic acid didecyldiacetamide) of estimating the density of milk (reduced fat and whole milk).[41] Similarly, MagLev can be used to compare cheeses (e.g., "regular" 1.099 $g\,cm^{-3}$ and "low-fat" 1.131 $g\,cm^{-3}$ string cheese) based on fat content (Figure 7 A).[41]

4.4.3. *Water Salinity*

Water that contains even a low concentration of salt (concentration above 50–150 mM in NaCl) has limited uses, and is unsuitable for drinking or agriculture.[183] It is possible to estimate the salinity of water by measuring the density of aqueous solutions containing NaCl. Levitating aqueous solutions containing different concentrations of NaCl is possible in a paramagnetic medium composed of an immiscible organic solvent (e.g., 3-fluorotoluene) and a paramagnetic salt (e.g., gadolinium(III) diethylenetriamine triacetic acid didecyldiacetamide) that cannot partition into the aqueous drop that levitates in the paramagnetic medium.[41]

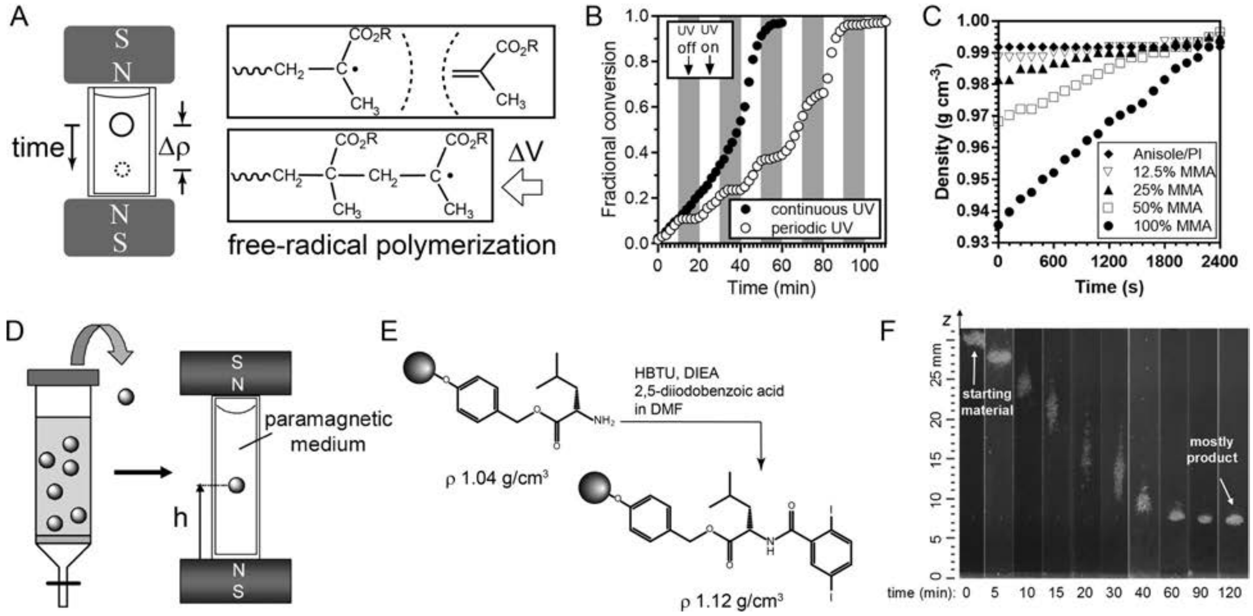


Figure 12. MagLev to monitor chemical reactions. (A) The increase in density (as a result of shrinkage of volume) associated with radical polymerization of low-molecular-weight methacrylate monomers can be used to characterize the kinetics of free-radical polymerization. (B) The progress of photopolymerization of the levitated drop can be controlled by continuous or periodic ultra-violet irradiation. The periodicity of the irradiation (each cycle consists of ten minutes of "UV on" and ten minutes of "UV off") is indicated by the shaded areas. The Trommsdorff effect (or simply the "gel" effect)[185] describing the accelerated rate of polymerization occurs between ~30–50 min under continuous ultra-violent irradiation (the black dots). (C) The rate of photopolymerization depends on the initial concentrations of the monomer methyl methacrylate (MMA, v%) present in the photopolymerizable mixture containing diluent anisole and photoinitiator (PI) 2,2-dimethoxy-2-phenylacetophenone. (D) MagLev monitors chemical reactions on solid supports. (E) Chemical derivatization of leucine-derivatized Wang polystyrene beads with 2,5-diiodobenzoic acid induces a change in density of the porous polymeric beads. (F) MagLev monitored the changes in density of the polymeric beads during the course of chemical derivatization. Sources: Images (A–C)[111] and (D–F).[42]

4.4.4. Applications in the Developing World

For applications in the developing world, at the point-of-care, or in general in resource-limited settings, it is useful for a technology to be inexpensive, simple, and robust. MagLev can be useful in these environments because the device used for analysis: (i) uses low-cost components, (ii) does not require power, (iii) uses permanent magnets that do not in principle need to be replaced or repaired, and (iv) has no moving parts. In addition, levitation heights—particularly when compared to an internal standard—are simple to measure and give an easily interpreted visual readout. Examples of uses include quality characterization of foods[41] and water.[41]

4.5. A Simple Technology for Chemistry
4.5.1. Reaction Mechanisms and Polymerization

Many chemical reactions occur with changes in density.[42,111,112,184] The use of density, thus, provides a simple, label-free method to monitor reactions and/or investigate reaction mechanisms. Historically, density-based approaches and techniques (such as those based on densitometers and dilatometers) have been important in characterizing reactions (especially mechanisms).[112,184] These density-based techniques, however, are largely limited to liquid samples, require large quantities of samples (~mL or greater), and/or are not easy to use.

MagLev can circumvent some of these difficulties. As an example, MagLev can be used to study free-radical polymerization of low-molecular-weight, hydrophobic monomers, such as methyl methacrylate (MMA), using aqueous $MnCl_2$ as the suspending medium (Figures 12 (A–C)).[111] The incorporation of low-molecular-weight monomers into polymer chains increases the density of the reacting mixture (cross-linking existing chains produces much smaller changes).[111] In particular, for photopolymerization, MagLev measured the density continuously of the levitated polymerizing drop as it transitioned from a liquid drop, to a viscous drop of liquid, and ultimately to a solid sphere (Figure 12 A). MagLev, therefore, could be used to monitor the conversion of the monomer MMA over its entire course of photopolymerization (from zero to nearly complete conversion, including the gel region).[111] The use of MagLev also enabled the monitoring of the kinetics of polymerization of MMA in the presence of an included solid (e.g., carbon and glass fibers)—a type of heterogeneous sample (a composite material) difficult to measure otherwise.[111]

MagLev makes it possible to monitor reactions and/or study reaction mechanisms for a broad range of sample types (e.g., especially simple liquids, viscous liquids, gels, and solids). MagLev is a particularly useful technique to study chemical reactions in "difficult" samples (e.g., opaque, composite materials, gels, samples that solidify).[111] MagLev can also be useful in studying chemical reactions that require extended observations, since levitation does not consume energy or occupy expensive instrumentation.

4.5.2. Organic Synthesis and Organic Reactions on Solid Supports

Solid-phase chemistry is widely applicable for the synthesis of peptides, oligonucleotides, libraries of small molecules, and capture reagents for affinity chromatography. There are, however, only a limited number of techniques capable of direct and rapid analyses of chemical reactions occurring on solid supports. MagLev provides a benchtop method for monitoring the progress of chemical reactions on solid supports and for distinguishing differences in the chemical composition of polymers.[42] Covalent modification of polymeric beads can alter the density of the beads. Incremental changes in the density of the beads, during reaction, thus correlate with the progress and kinetics of the reaction on the solid support. For example, MagLev monitored condensation reaction of leucine-derivatized Wang resin with 2,5-diiodobenzoic acid (as a model system), and successfully validated its use to monitor chemical reactions in time (Figure 12 D–F).[42]

4.6. Biochemistry and Biochemical Assays

4.6.1. Label-Free Biochemical Assays for Proteins and Ligands

Bioassays are ubiquitous in biology, and an important class measures the binding of proteins to molecules anchored on a solid support. The binding events are, generally, measured using labels, such as radioactive tags and fluorophores.[186–189] Label-free approaches, such as quartz microbalances[190] and surface-plasmon resonance,[191] are also important.

MagLev is being developed to perform bioassays.[106,192] A physical-organic approach has been used to investigate the physical processes by which this type of assays operate—a critical first step towards developing a practical technology.[106] Porous beads made of poly[acryloyl-bis(aminopropyl)polyethylene glycol] (PEGA) were selected as a suitable porous substrate to support the binding assay for three major reasons: (i) They have a density ($\rho = 1.07\ \mathrm{g\,cm^{-3}}$) different from that of protein (typically $\rho = 1.3$–$1.5\ \mathrm{g\,cm^{-3}}$);[106] the binding of protein onto the substrate, thus, generates a change in density that can be measured by MagLev. (ii) They are porous, and allow proteins to diffuse in and out of the matrix of the beads. (iii) They are resistant to non-specific binding of proteins. We used a well-characterized protein as model-carbonic anhydrase, with aryl sulfonamide ligands (Figure 13) immobilized on the porous beads[106]—to test the physical processes, including the kinetics of binding and the diffusion of proteins through the porous network in the resin. By measuring the concentration- and time-dependent changes in the levitation heights of the porous beads in solutions containing different concentrations of carbonic anhydrase, and by establishing an appropriate reaction-diffusion model, MagLev was useful to monitor the kinetics of binding, to determine the dissociation constants of the ligands (K_d), and to quantify the amount of protein bound to the porous substrate.[106] Multiplexed measurements can be implemented using dyed particles.

Time-dependent changes in density can, similarly, be used to determine the dissociation constants of ligands using a competitive format.[107] In this format, beads functionalized with a ligand are first incubated in a solution containing excess carbonic anhydrase, and then transferred to a solution containing no ligand or ligands with varied affinities. The rate at which the bound carbonic anhydrase dissociated from the beads depends on the types and concentrations of ligands present in the solution; the kinetics of dissociation—and thus dissociation constants—can be quantitatively measured and estimated using MagLev (Figure 13 C). The major advantage of performing the assays in the competitive format in comparison to the direct, non-competitive format is the shorter assay time (20–60 min vs. days).

A disadvantage of this system is the mass-transport limitation (of protein into and out of the beads) that makes this reaction slow. This limitation can, in principle, be circumvented using more porous beads.

4.6.2. Metal-Amplified Density Assays for Antigens and Antibodies

MagLev can also be used to measure binding events between proteins and ligands, and thus quantify proteins in a solution, using nonporous beads in a format we call "metal-amplified density assays" (MADAs) (Figure 13 E).[108] While the use of non-porous beads circumvents the problem of slow diffusion of proteins in the porous beads, the binding of proteins onto the surface of nonporous beads causes only a small overall change in density, which is not always convenient (or perhaps even possible) to detect directly using MagLev. Using signal amplification allows detection of the binding events by (i) labeling the biomolecules (e.g., protein, antibodies, antigens) with heavy, inert gold nanoparticles, and (ii) amplifying the changes in density further by using electroless deposition of gold or silver on these nanoparticles.

The MADA could be used to measure binding between antibody and antigen in a format analogous to ELISA (enzyme-linked immunosorbent assays), which we call density-linked immunosorbent assays, or "DeLISA" for short (Figure 13 F). A typical procedure includes (i) immobilization of an antigen on the surface of a bead, (ii) binding of an antibody from a sample (e.g., a blood sample) to the immobilized antigen, (iii) binding of a secondary antibody conjugated to gold nanoparticles to the immuno-complex on the bead, and (iv) electroless deposition of metal (silver or gold) to the gold nanoparticles on the bead to amplify the change in density associated with the binding events. DeLISA were demonstrated in two clinically relevant biological targets, neomycin in whole milk, and antibodies against Hepatitis C virus NS3 protein and syphilis *T. pallidum* p47 protein in human serum.[108]

4.6.3. *Density-linked Assays for Membrane-Bound and Soluble Antigens*

MagLev could be used to detect both membrane-bound and soluble antigens by (i) converting the binding events between antigens and antibodies to physical aggregation of cells and/or particles, and (ii) counting the number of aggregates following incubation of the particles in the sample, as described by Anderson and Ghiran (Figures 13 (G,H)).[72] In the assay, each type of particle (polystyrene beads or cells) has a distinct density, and presents only an antigen or antibody; the binding events between the antibody and antigen thus cause a physical aggregation of two types of particles, and the resulting change in density between the non-aggregated and aggregated particles allows the separations of these aggregated pairs or oligomers from non-aggregated particles, and thus, enables their enumeration for quantification in a MagLev device.

When the antigen is present on the surface of a cell, a bead bearing an antibody against the antigen binds to the cell and

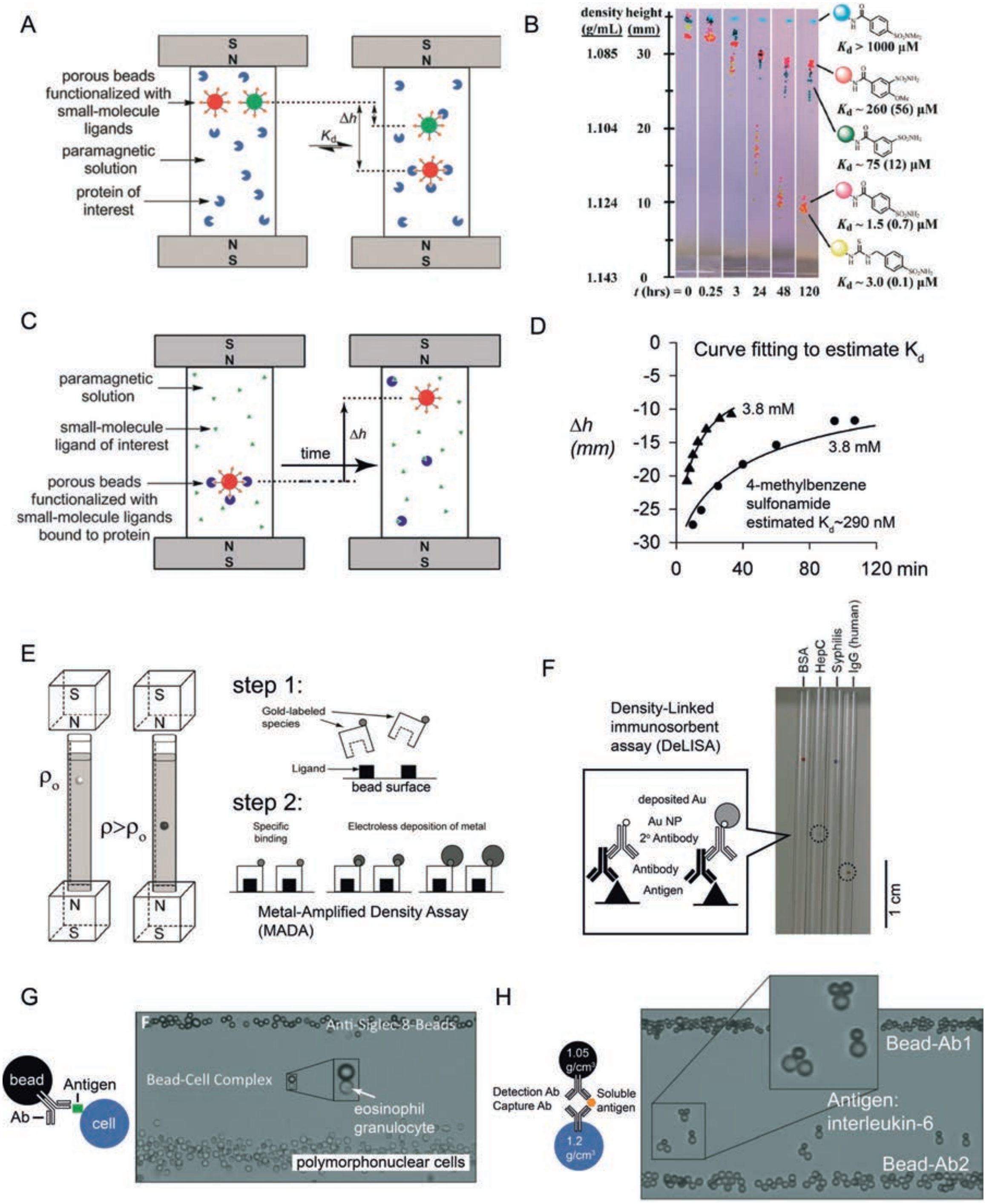


Figure 13. Detection of binding events using MagLev (A) Schematic illustration of characterization of kinetics of binding of a protein to ligands immobilized on porous beads. Multiplexed measurements are enabled by dyed beads. (B) Changes in levitation height over time of porous beads presenting aryl sulfonamides (one type of colored beads corresponds to one type of ligand) to which the enzyme carbonic anhydrase in the suspending medium binds. The kinetics of binding allows the estimation of dissociation constants of carbon anhydrase from these surface-supported ligands. Measured dissociation constants between the carbonic anhydrase and dissolved ligands in solutions are included in the parentheses. (C) Determination of dissociation constants using a competitive format. (D) The kinetics of dissociation of carbonic anhydrase from the beads allows the estimation of the dissociation constants by curve fitting, here using for an example, ligand 4-methylbenzene sulfonamide as ligand. (E) Schematic illustration of metal-amplified density assays using nonporous beads. (F) A demonstration of the use of a multiplexed metal-amplified density assay to measure antibodies present in a simulated serum sample. The serum sample was spiked with antibody against hepatitis C (HepC), but not antibody against syphilis. Bovine serum albumin was used as a negative control, and human IgG was used as a positive control. "Au NP" stands for gold nanoparticle. (G) Binding of the membrane-bound antigen Siglec-8 on eosinophil granulocytes, and an antibody against Siglec-8, immobilized on polymeric particles causes an aggregation of the cells and the particles. The difference in density of the aggregates from those of the cells or the particles enabled their separation in a MagLev device. (H) Binding of a soluble antigen (interleukin-6) to two antibodies immobilized on two types of polymeric beads (having different densities) causes an aggregation of the particles. The aggregates levitated at different heights in a MagLev device from non-aggregated particles, and a count of these aggregates can be used to quantify the concentration of the soluble antigen. Sources: Images (A–D);[106,107] (E,F);[108] and (G,H).[72]

forms an aggregate, which has a density different from both the bead and the cell, and thus, levitates at a different height from the non-aggregated bead or cell in a MagLev device.[72] The number of these aggregates correlated with—and thus, could be used to quantify—the abundance of the antigens of interest. This assay could sensitively detect a number of surface-bound antigens found in blood, including T-cell antigen CD3, eosinophil antigen Siglec-8, red blood cell antigens CD35 and RhD, and red blood cell-bound Epstein–Barr viral particles. For example, Figure 13G shows the sensitive detection of eosinophil granulocytes, a type of cells only making up 2–3% of all nucleated cells in normal blood, using anti-Siglec-8 antibody-coated beads.[72]

When the antigen is soluble (e.g., proteins in serum), a sandwich-type of aggregate forms from the bridging of two types of beads (each having a distinct density, e.g., 1.05 $g\,cm^{-3}$ and 1.2 $g\,cm^{-3}$) presenting antibodies against the same antigen (but against non-overlapping epitopes). The number of aggregates could be used to quantify the concentration of the antigen present in the solution (Figure 13H). This assay could detect interleukin-6 in the range of ~10–100 $pg\,mL^{-1}$ in the phosphate-buffered saline. While the concentration of interleukin-6 is low (~1.4 $pg\,mL^{-1}$) in healthy individuals, the reported range of concentrations (~10–100 $pg\,mL^{-1}$) is physiologically relevant for medical conditions, such as sepsis and myocardial infarction.[72]

4.7. Analyses, Separations, and Manipulations of Biological Particles

Uses of density to analyze and separate biological particles, including virus, bacteria, organelles, cells, and even whole organisms, is a common practice in biochemistry and biomedical studies. Blood cells, for example, can be routinely fractionated using a single step or multiple steps generated by one or more layers of biocompatible media (e.g. aqueous solutions of sugars, colloids, and polymers, including sucrose, Ficoll-Paque, Percoll, and Nycodenz) with density specifically tuned to separate certain groups of cells.[193–195] Certain diseases show characteristic changes in density for certain types of cells. In sickle-cell disease, for example, the small population of the erythrocytes that become sickled have higher densities than the normal erythrocytes. This characteristic change in density in sickled erythrocytes has been exploited to develop an AMPS-based technique to diagnose sickle cell disease; we validated its performance in resource-limited regions in Zambia.[121,132]

MagLev has two characteristics that make it compatible with analyses and separations of biological cells: (i) MagLev can stably levitate objects having a size of microns or above, and therefore, matches well with the range of sizes for biological cells (~μm to sub-millimeter); and (ii) biocompatible paramagnetic species, such as Gd chelates, are commercially available. For example, Gd·DTPA was used in our early study to manipulate living cells in space using a magnetic trap (Figure 14A),[146] and recently Gadavist has been used to levitate erythrocytes in a high-throughput format using 96-well plates.[123]

Demirci, Ghiran, Tasoglu, Arslan-Yildiz and co-workers have extended MagLev into density-based analyses and separations of single cells, including the development of a diagnostic prototype for diagnosis of sickle-cell diseases (Figure 14F).[69,70,73,74,77,78] Tables 10 summarizes the applications of MagLev for analysis, separation, and manipulation of cells (from bacteria and yeast cells to mammalian cells and whole organisms). See also excellent recent reviews by Arslan-Yildiz,[6] Zhang,[7] and Ozcivici and Tekin[8] on MagLev as an emerging tool in biotechnology for tissue engineering, disease diagnostics, and other applications.

5. Summary and Outlook: The Roadmap for the Future

MagLev—the type we are developing using permanent magnets and paramagnetic medium—has matured considerably in the last several decades, and found important applications in the areas of density-based analyses, including separations, magnetically directed 3D-assembly, quality control, and molecular- and cell-biological analysis. A robust technology base has been established for MagLev, which will open exciting new opportunities to solve problems in chemistry, biochemistry, biology, and materials science. In this section, we discuss the fundamental limitations of MagLev as it is now practiced, design principles to engineer

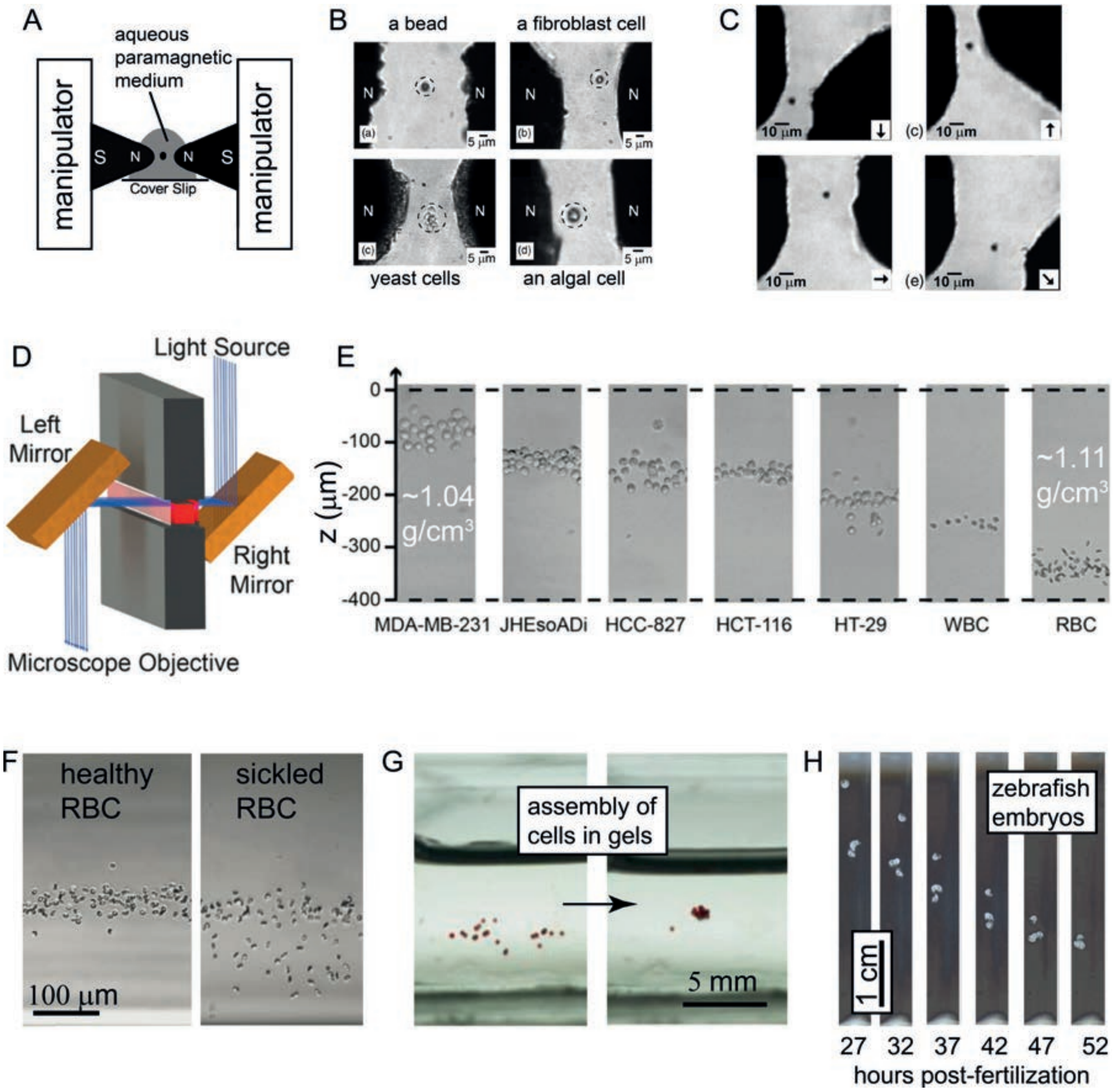


Figure 14. Analyses and manipulations of cells and organisms using MagLev (A–C) A magnetic trap using a pair of north-poles-facing permanent NdFeB magnets and an aqueous paramagnetic medium (containing Gd·DTPA at 40–50 mM) to "trap" and translate in 3D nonbiological and biological particles. Panel (C) shows the manipulations of a polystyrene bead by moving the magnet on the right, while maintaining the magnet on the left stationary. (D) A MagLev device using a pair of like-poles-facing NdFeB magnets (length × width × height: 50 mm × 2 mm × 5 mm, gap between the two magnets: 1 mm) and an aqueous paramagnetic medium (e.g., Gadavist) to levitate biological cells. (E) MagLev and density measurements of different types of mammalian cells in fetal bovine serum containing 30 mM Gadavist. MDA-MB-231, breast adenocarcinoma cells (estimated average density ~1.04 $g\,cm^{-3}$); JHesoAD1 esophageal adenocarcinoma cells; HCC827 nonsmall cell lung adenocarcinoma cells; HCT116 colorectal carcinoma cells; HT29 colorectal adenocarcinoma cells; WBC: white blood cells; RBC: red blood cells (estimated average density ~1.11 $g\,cm^{-3}$). (F) A subpopulation of red blood cells from a sickle cell disease patient became more dense than healthy red blood cells under the treatment of sodium metabisulfite (an reducing agent that reduces intracellular hemoglobin to induce the morphological changes in cell shapes). (G) Self-assembly of gel particles containing fibroblast cells in an aqueous solution of 50 mM Gd·DTPA. (H) Monitoring of changes in density during the embryonic development of zebrafish embryos suspended in an aqueous solution of 150 mM Gd·DTPA. Sources: Images (A–C);[146] (D, E);[69] (F);[70] (G);[65] and (H).[196]

the magnetic field (both the shape and strength), and unexplored opportunities to advance this methodology.

5.1. Fundamental Limits in the Size of the Levitated Object

MagLev cannot stably levitate objects below a limiting size in the standard MagLev system at ambient conditions. When developing the theoretical treatment of MagLev, we implicitly assumed that the two competing physical forces—the gravitational force and the magnetic force—dominate in the system (relative to physical forces originating from thermal motions of molecules in the suspending medium), and ultimately determine the position in space at which the object reaches stable levitation. This assumption is clearly invalid for an object as small as a low-molecular-weight single

Table 10: Analysis and manipulation of biological cells using MagLev.

Biological system	Suspending medium	ρ (g cm^{-3})	Description of applications
Bacteria			
Escherichia coli	Gadavist	1.1–1.3	Demonstrations of single-cell density measurements[69] Evaluation of antibiotic treatments[69]
Algae			
Chlamydomonas reinhardtii	Gd·DTPA	–	Magnetic trap[146]
Yeast			
Saccharomyces cerevisiae	Gd·DTPA Gadavist	–	Magnetic trap,[146] Demonstrations of single-cell density measurements,[69] Evaluation of drug treatments.[69]
Mammalian Cells			
Human erythrocytes	Gadavist Prohance	1.1–1.2	Demonstrations of density measurements,[69,123] Quantification of cell number,[67] Assessment of cellular aging,[70,73] Analysis of cells from anemic donors,[73] Diagnosis of sickle cell disease.[70,76]
Human leukocytes	Prohance	1.1	Assessment of cellular activation of polymorphonuclear leukocytes (e.g., caused by phagocytotic events of bacteria);[70] Diagnosis of sepsis by analyzing physical characteristics of levitated leukocytes (size, morphology, or magnetic susceptibility)[75]
Mouse bone marrow stem cells and osteoblasts	Gadavist	1.09	Demonstrations of single-cell density measurements and separations[197]
Mouse fibroblast (NIH-3T3)	Gd·DTPA	–	Magnetic trap,[146] Self-assembly of 3D living architecture.[64,79]
Sheep chondrocytes	Omniscan	–	Self-assembly to fabricate tissue spheroids[66]
Stem cell lines	Gadavist Magnevist Omniscan Dotarem Multihance		Self-assembly of 3D living architecture[198]
Cancerous cell lines	Gadavist	1.0–1.1	Demonstrations of single-cell density measurements and separations[69,79]
Cells in hydrogels	Gd·DTPA	–	Self-assembly of cell-containing hydrogels for tissue engineering[65]
Organisms			
Danio rerio (i.e. zebrafish)	Gd·DTPA	–	Monitoring of embryonic development[196]
Caenorhabditis elegans	Mn·EDTA	1.07	Evaluation of drug exposure using whole organisms[196]

molecule (where the thermal motions of the molecules dominate). See more work and discussions by Gryzbowski,[91] Eckert,[142,199] Fransaer[200,201] and co-workers on the impact of an applied magnetic field on the behavior of paramagnetic ions (e.g., rare-earth ions, such as Dy^{3+} and Gd^{3+}, and their clusters) in a solution. The limit in the size of an object that can achieve stable levitation can be estimated, assuming the total energy of the system ($\Delta U_g + \Delta U_m$) has to overcome the minimal thermal energy of the object [Eqs. (4)–(6)]. In practice, the total energy should exceed the minimal thermal energy by a significant factor to achieve stable levitation.

$$\Delta U_g + \Delta U_m > k_B T \tag{4}$$

$$(\rho_s - \rho_m)Vgd - \frac{1}{2}\frac{(\chi_s - \chi_m)V}{\mu_0}\vec{B}\cdot\vec{B} > k_B T \tag{5}$$

$$R > \left(\frac{k_B T}{\frac{4\pi}{3}\left((\rho_s - \rho_m)gd - \frac{1}{2}\frac{(\chi_s - \chi_m)}{\mu_0}B_0^2\right)}\right)^{\frac{1}{3}} \tag{6}$$

We used small polymer beads to evaluate this prediction in the standard MagLev system, and found a qualitative agreement between the experimental results and the theoretical prediction.[20] Beads below ~2 μm in radius could not be practically "focused" on the laboratory time scale to a specific levitation height using small NdFeB magnets, and thus, are close to the size limit of the standard MagLev system. Extending MagLev to smaller objects should be possible by maximizing the total energy used to trap the object at the levitation height, and/or minimizing the thermal energy. A few plausible improvements include: (i) using stronger magnets to improve the strength of the magnetic field and the intensity of the field gradient (the effectiveness of MagLev scales with magnetic field roughly as B^2), (ii) using smaller devices (to minimize the distance of travel for small objects and also to increase the magnetic field gradient), and (iii) operating at lower temperatures and higher viscosities with effects that would be most pronounced under cryogenic conditions.

5.2. Design Criteria in Engineering the Profile of Magnetic Field

MagLev exploits the interaction of an applied magnetic field and a paramagnetic medium to levitate (and manipulate) diamagnetic objects suspended in the medium; the profile of the magnetic field (including the shape and strength), therefore, is a critical component of the MagLev system in determining the performance.

We summarize three practical considerations in guiding the designs of MagLev systems using permanent NdFeB magnets. We do not discuss electromagnets in this Review; they may be a useful option to generate strong or shaped fields for certain applications, but are more complicated to operate than solid-state permanent magnets, and require a continuous source of power.

i) The maximum strength of a magnetic field on a surface of single permanent magnet with simple geometries (e.g., blocks, cubes, cylinders) is often limited to half of its remanence. For example, the limiting B_0 on the top face of an axially magnetized, N52-grade NdFeB cylinder magnet is ~0.7 T, which is half of its remanence, ~1.4 T.[143]

ii) The strength of the magnetic field on the surfaces of permanent magnets can be increased by design. Strategies exist to "sculpt" the shape of the magnetic field that surrounds the magnet(s): (a) optimizing the geometry of the magnet (e.g., using cone-shaped magnets), (b) arranging magnets in space in particular order (e.g., stacking), and (c) using magnetic flux concentrators (e.g., using sharp edges).[164]

iii) The spatial profile of the magnetic field can be uniformly scaled (the scale reduction law)[163]—that is, the shape and strength of a magnetic field are maintained when the magnets are uniformly scaled in physical size. This characteristic has important implications for designing MagLev systems. For example, one may independently adjust the magnetic field gradient without changing the strength or shape of the field by simply scaling down the MagLev system in physical size. Miniaturization of sizes, for example, of the MagLev systems would lead to steeper gradients of the magnetic fields, which, in turn, would reduce the time and concentrations of the paramagnetic species required to levitate objects. It, therefore, provides a useful strategy to levitate small biological particles (e.g., organelles and living cells).

Commercially available software (e.g., COMSOL Multiphysics and finite element method magnetics) can be used to visualize the magnetic fields that surround magnets (See Figure S4 for an example), and thus, to aid the design of MagLev systems.

5.3. New Device Designs and "Practical" Devices

The architecture of the MagLev systems we exploited thus far has focused on the simple like-poles-facing configuration in which we only use two indistinguishable magnets positioned coaxially to establish an approximately linear field. Exploring the design space in which magnets with varied numbers, sizes and/or shapes are arranged in space (and even manipulated in time), offers the flexibility in optimizing the characteristics of the magnetic fields—particularly the strength and gradient of the magnetic fields—and thus, tailoring systems for an optimized performance.

To develop MagLev further as a practical technology suitable for settings beyond temperature-controlled and well-equipped research laboratories, remaining efforts in engineering, optimization, and field-trials are required.[202] These efforts should preserve the useful characteristics of the technique—particularly its simplicity in design and use (including portability) and affordability in using this technology, while enhancing and/or developing complementary approaches to augment the desired capabilities required to solve a particular problem. For example, it is instructive to consider the "ASSURED" criteria (Affordable, Sensitive, Specific, User-friendly, Rapid/Robust, Equipment-free, and Delivered to those who need it, as outlined by the World Health Organization).[203]

5.4. What's Next?

MagLev as an analytical methodology is still in adolescence. The systems now being used are sufficiently developed technically to demonstrate many of the important features of static (equilibrium, or steady-state) systems, but still leave many important technical opportunities unexplored or undeveloped; for example, they have barely touched dynamic or dissipative systems. Perhaps as importantly, only a few of the possible areas of applications have been explored, and even of those, the best is yet to come.

There are a few important characteristics of MagLev that will guide its continuing development. Speaking broadly, (i) Increasing the strength of the magnetic field enables observation of a broader range of densities, and allows increased sensitivity. (ii) Increasing the magnitude of the gradient in magnetic field results in faster kinetics as the system moves toward equilibrium or steady state, and results in tighter distributions or clusters of magnetic particles with similar (but not identical) densities, (and also often in lower sensitivity). (iii) Balancing the density of the objects of primary interest, and the density of the paramagnetic medium, allows higher accuracy, and extends the range of densities that can be observed. (iv) Motion of small particles (< 1–10 μm) under the influence of thermal (Brownian) motion limits the localization of these particles—and thus the accuracy with which their density can be determined. (v) Decreasing the temperature both increases the magnetic susceptibility of the paramagnetic medium, and decreases the influence of thermal motion, but the effects are small and unlikely to be important except for specific applications that can be carried out at low temperatures (for example, in liquid O_2).

Table 11: Areas for future development of MagLev and related areas.

Magnetic Technology
Paramagnetic Media
Dynamic Systems
Detection and Sensing
Separations
Isolations
Applications:
- Biology and Biochemistry
- Chemistry and Materials Sciences
Combinations with Other Techniques

Table 11 lists areas in which it will be possible to develop new directions in either technology or applications. These areas are expanded in the following sections.

5.4.1. *Magnetic Technology*

Beyond the NdFeB permanent magnets that are commonly used for MagLev as described in this Review, electromagnets are also a useful source of magnetic fields to enable levitation and analysis of materials (based on density). In particular, low-cost, high-field superconducting electromagnets would revolutionize MagLev. Magnetic field engineering—such as optimizing the geometry of the magnets, stacking magnets, using flux concentrators (to focus spatially magnetic flux to localized regions), or modulating the strength and/or gradient of the magnetic field in time—would make it possible to engineer the magnetic field in space and time, and allow flexible design and control of the magnetic fields in various formats. For example, embedding micro-metal elements (flux concentrators) in microfluidic channels makes it possible to manipulate small entities in confined spaces using an externally applied magnetic field.[164]

5.4.2. *Paramagnetic Media*

The characteristics of the samples—both physical (solubility) and chemical (reactivity)—determine the most appropriate type of paramagnetic media in which to suspend and levitate them. In general, most paramagnetic media used in MagLev are based on H_2O (and/or D_2O) with dissolved paramagnetic species (e.g., metal ions). Non-aqueous media expand the useful capabilities of MagLev to levitate, analyze, and manipulate samples that are difficult to levitate otherwise. Stable paramagnetic chelates soluble in low-polarity organic liquids are also available.[100] A number of such media have been described both using organic liquids and paramagnetic ionic liquids,[41,96] but can be improved. A good system for working with fluorocarbon liquid would be especially useful. Yet others are evident. Liquid oxygen may be useful to levitate cryopreserved samples and non-living materials/structures, and to provide a medium for clean recovery of samples (upon evaporation of the medium). Fluorinated paramagnetic species dissolved in fluorinated solvents may enable the levitation of organic materials (e.g., organic solvents, such as DMSO, and polymers, such as polyethylene glycol) that may be soluble in, or sensitive to, both aqueous and hydrophobic suspending media.

Biological applications of MagLev require a set of more stringent criteria for the media for different types of cells-bacterial, yeast, eukaryotic cells—and organisms: toxicity, density, magnetic susceptibility, osmolality, viscosity, optical transparency, coefficient of partitioning between the media and suspended cells, vapor pressure, and cost. Gadolinium-based chelates have been useful to levitate biological particles. The cost of these chelates, however, is relatively high (particularly when a large volume of media is required, although they are—in principle—recyclable) and their biocompatibility has not yet been fully characterized (particularly over long time periods). Adapting AMPS-based methods to be a more integral part of MagLev systems has been demonstrated, but not extensively explored, and certainly has the potential to be useful.

Non-biological applications of MagLev will be expanded significantly by exploiting physical characteristics of many chemical systems, such as heteropolytungstates (highly soluble in water to yield unusually dense solutions), organic paramagnets, and magnetically responsive phases (liquid crystals).

5.4.3. *Dynamic Systems*

The broad areas of dynamic/dissipative systems—systems in which either the magnetic or gravitational forces acting on a particle vary with time, or in which other forces (for example shear) that rely on motion become important—have been barely touched on, and MagLev (when combined with microfluidics) offers a particularly simple, well-defined system to explore and study dynamic behaviors (in appropriately chosen media). Examples of other interactions that can be combined with MagLev include flow, centrifugation, electrophoretic and acoustic manipulations, and time-varying components of magnetic, gravitational, centrifugal, and other fields. The ability of MagLev, combined with a flowing paramagnetic liquid, to generate what is effectively a stationary density gradient in a flowing liquid is unique (Figure 8).

5.4.4. *Detection and Sensing*

Presently methods used for detection and sensing in MagLev are very primitive (primarily measuring the levitation height, h, of a levitating object). Future opportunities in these areas will exploit (i) flexibility of MagLev in repositioning of suspended objects, (ii) compatibility with "opaque" systems, (iii) synergistic interactions with other detection modalities, (iv) more accurate measurements of position (including in dynamic systems), and (v) measurement of objects with complex shapes.

5.4.5. Separations

MagLev will continue to evolve as a useful analytical technique for density-based separations, and the best application has yet come. In particular, the ability to separate fine-grained particulates (e.g., powdered mixtures)[100] will enable new applications in materials science, forensics, food processing, environmental monitoring, and other areas. It also is potentially useful with gels, drops of viscous liquids, objects with exceptionally diamagnetic components (graphene, carbon nanotubes, pyrolytic graphite, bismuth and some of its compounds).

5.4.6. Isolations

Selective removal of small samples of liquids containing suspended particles from a MagLev system—particularly from samples of small quantities/volumes—is not presently an entirely solved problem. New chemistries (e.g., gelation), engineering designs (flux concentrators), and fluidic flows will provide new capabilities to Maglev for separations and isolations.

5.4.7. Applications in Biology and Biochemistry

All cells have density. MagLev will find new applications for separation and isolation of cells of different types in the broad areas of studies of the microbiome, cellular life-cycle and death, and many others. Other unexplored opportunities may include antibiotic sensitivity, and response to environment, and use with higher organisms (e.g., worms, such as *C. elegans*).

Bioassays are another area in which MagLev will provides capabilities and solutions complementary to existing technologies (lateral flow immunoassays, surface plasmon resonance and others) and problems in different settings (label-free sensing, point-of-use/care applications, global health technologies). MagLev and much more complicated techniques, such as ultracentrifugation, are unique in sensing density. Important advances in this area will involve beads, labeled antibodies (density, fluorescence, catalytic activity), and multiplexed measurements.

5.4.8. Applications in Chemistry and Materials Science

Opportunities are numerous to analyze, separate, and manipulate different classes of materials in different physical forms. Possible applications include mixed particulates, forensics, food quality, liquids (kerosene and others) and solids (e.g., coal), drugs of abuse (fentanyl, heroin, cocaine, and others),[100] counterfeiting, part assurance, brand preservation, low temperature phenomena (that change either density or magnetic susceptibility), minerology, and environmental monitoring for particulates.

Graphite (and also graphene), and bismuth are exceptionally diamagnetic, and, in fact, graphite can be levitated in air using NdFeB permanent magnets.[102] These strongly diamagnetic materials, if included in a sample, can increase the contrast in magnetic susceptibility between the sample and suspending medium (including air), and thus, enable new ways to control the interaction of materials and applied magnetic fields.

5.4.9. Combinations with Other Techniques

The hybrid system combining MagLev and AMPS is uniquely flexible in generating complexed profiles of gradients in density (Figure 3D); it also makes it possible to tune dynamically the profiles of gradients by simply repositioning AMPS in the applied magnetic field—without the need to modify either the chemical or physical components of the systems (that is, MagLev or AMPS). The ability of AMPS—either using unmodified polymers, or after affinity modification—to combine affinity- and density-based separations is attractive.

Glossary

M	magnetization of a material ($\mathrm{A\,m^{-1}}$)
$\vec{H}$	external magnetic field ($\mathrm{A\,m^{-1}}$)
$\vec{B}$	magnetic field (T (= 10^4 gauss))
χ	magnetic susceptibility (unitless for volume susceptibility)
μ	magnetic permeability ($\mathrm{N\,A^{-2}}$)
$\vec{F}_m$	magnetic force (N)
$\vec{F}_g$	gravitational force (N)
R	radius of a spherical object (m)
V	volume ($\mathrm{m^3}$)
U	energy (J)
$\vec{g}$	acceleration due to gravity ($\mathrm{m\,s^{-2}}$)
ρ	density ($\mathrm{kg\,m^{-3}}$)
d	distance of separation between magnets (m)
h	levitation height (m)
η	viscosity ($\mathrm{kg\,m^{-1}\,s^{-1}}$)
ν	velocity of fluidic flow ($\mathrm{m\,s^{-1}}$)

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We have, for an internal purpose, tested a commercial MagLev device (Levitasbio, Inc.; www.levitasbio.com). Levitas licences technology in this area from Harvard University, from which the laboratory derives a small financial return. We are also involved with Soft Robotics Inc., which occasionally uses magnetic technologies unrelated to MagLev. We have, however, no significant conflict of interest from either of these activities in technology transfer.

Conflict of interest

The authors declare no conflict of interest.

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