lymphoblast division is regulated by both cell size and age—that both a "sizer" and a "timer" are involved.

Numerous molecular mechanisms that might constitute cell sizers or timers have been proposed. Perhaps the best-informed ideas come from studies of yeasts, where the kinetics of cell growth and division and the molecules controlling them are relatively well understood. A bona fide sizer was recently proposed for *Schizosaccharomyces pombe*, a fission yeast that grows as a rod and divides at a constant length (*5*). In this case, a factor (Pom1) tethered at the cell ends was proposed to inhibit activators of division in the cell's center. As the cell elongates, it eventually passes a critical length at which Pom1's influence no longer reaches to the cell's center, triggering division. This is an attractive mechanism for a rod-shaped cell but seems unlikely to apply generally, especially for cells with different shapes. In the budding yeast *Saccharomyces cerevisiae*, and probably also in many mammalian cells, a growth or size threshold must be surpassed to initiate S phase of the cell cycle (when DNA replication occurs), and division into two daughter cells (mitosis, or M phase) follows automatically in a stereotyped sequence of events suggestive of a timer. In these cases, the various sizer and timer mechanisms proposed are potentially quite general.

One popular model invokes the rate of production of a limiting cell cycle activator as a critical parameter. This activator is envisioned to be produced at a constant rate per unit of cytoplasm and progressively concentrated in an organelle of fixed volume (e.g., the nucleus) or on target binding sites of fixed number (e.g., chromosomes). As the cell grows and the activator accumulates at its targets, it eventually reaches a threshold necessary to trigger cell cycle progression (normally, $G_1 \rightarrow S$ phase progression). With this arrangement, the sizer senses a metabolic index rather than size, and so a cell's size at division will be affected by its nutrient status and growth factor milieu, as well as the status of genes involved in cell growth and metabolism. Indeed, this is the rule from yeast to human cells (*6*).

There are many cell cycle activators that could fill the role of a limiting regulator in such a system. Likely candidates include the G_1 cyclins and cyclin-dependent kinases that promote S phase, origin-licensing factors (such as Cdc6 and Cdt1), and transcription factors that activate cell cycle genes (such as E2F). If the size-sensing cell cycle activator were stable and accumulated in one cell cycle phase (e.g., G_1) but was periodically degraded in another (e.g., S or at the $M \rightarrow G_1$ phase transition), as many of these factors are, then the sizing mechanism could also function effectively as a timer. Cell cycle suppressors might also act as size sensors if they were sequestered or degraded in a growing compartment, or as timers if their activity were periodically gated. Indeed, many of the core cell cycle regulators are able to affect cell size in dose dependency experiments, and so it has been expected for many years that some of these must function naturally as size sensors and timers. Precisely which factor fills this role in any particular biological context still needs to be determined, but given the marvelous diversity of cell types, stereotypical sizes, and proliferation styles found in nature, we are likely to find many different flavors of cell sizers and timers.

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MATERIALS SCIENCE

Oriented Assembly of Metamaterials

The creation of complex materials may be aided by advanced colloidal assembly methods involving anisotropically shaped particles.

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Regular assemblies of colloidal particles have many potential uses from self-assembled electronics to biosensors. Recent advances in particle self-assembly suggest that such assemblies may also provide a simple route to metamaterials at infrared and visible length scales. Such metamaterials may, for example, be used to create cloaking devices or light-based circuits based on manipulations of local optical electric fields rather than on the flow of electrons (*1*).

Metamaterials are periodically structured composites with unit cells smaller than the wavelength used to interrogate them (*2*). By tailoring the unit cells to create a wide range of responses, technologies that were once the realm of fantasy—from computing with light to invisibility cloaks and superlenses—become reality. Such materials are relatively easy to create for use at radio frequencies, where the subunits need only be a few millimeters in size. However, use at optical and infrared wavelengths requires the assembly of three-dimensional micrometer- and nanometer-scale structures. This task is extremely challenging, but recent studies of particle self-assembly point the way to metamaterials at relevant length scales.

Metamaterials contain inclusions deliberately embedded in host media. The size, shape, and electromagnetic properties of the inclusions, along with inclusion density, arrangement, and alignment, determine their effective properties in a given host. Negative index of refraction metamaterials have been demonstrated in the optical range, made by serial approaches based on lithography (*3*, *4*). If, instead, metamaterials were designed to incorporate anisotropic nanoparticles through self-assembly, cumbersome lithographic approaches could be avoided.

An extensive library of anisotropic microparticles and nanoparticles now exists (*5*), allowing inclusion size and shape to be readily selected. Particles can be synthesized from many different materials, which can be selected for their electromagnetic properties. However, incorporating the particles as inclusions in self-assembled metamaterials requires techniques for assembly with control over particle orientation and spatial arrangement in periodic structures.

Convective assembly is a promising technique for creating close-packed assemblies of particles. The method is easy, inexpensive, and amenable to creating relatively large, defect-free periodically ordered structures of spherical particles. New assembly methods are also being developed to promote oriented assembly of anisotropically shaped particles in close-packed structures and to control deposition of particles in prescribed spatial locations on substrates, with potential for creating non–close-packed structures. We review

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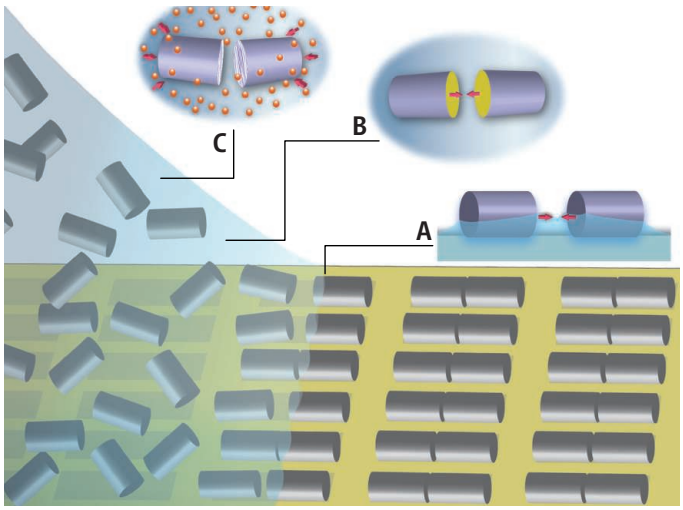
a few advances that are compatible with convective assembly, which enables mass production by continuous printing methods. The further development of these approaches is key to establishing robust methods for oriented assembly of metamaterials (*6*) (see the figure).

In convective assembly, a substrate is immersed in a colloidal suspension. The solvent forms a three-phase contact line where solvent, substrate, and vapor meet. As solvent evaporates, colloidal particles collect at the contact line. When particles protrude through the liquid-vapor interface, they create excess surface area and therefore excess surface energy. This energy diminishes as particles approach, creating capillary attraction that draws particles together to form an ordered structure (the nucleus). Continued evaporation collects particles near the nucleus, where they assemble into the growing colloidal crystal (*7*). Colloidal crystals are also grown from evaporating drops of suspensions in what is termed "drop-casting."



Metamaterial formed by convective assembly of anisotropic particles. Preferred locations can be lithographically defined or imposed by patterned evaporation. Oriented colloidal crystal nuclei could form by shape-dependent capillary interactions near the contact line (**A**). Oriented aggregation can be dictated by hydrophobic interactions created by selective surface functionalization (**B**) or by selective surface roughening to orient depletion attraction in bulk (**C**).

Ming *et al*. have recently used these techniques to make close-packed assemblies of anisotropic particles (nanorods, polyhedra, nanocubes, and bipyramids) into highly ordered structures in three dimensions (*8*). However, more systematic studies will be required to identify the conditions that promote such oriented assembly. To do so, two fundamental issues need to be addressed.

First, the particle orientation in colloidal crystal nuclei must be controlled. Solutions to this problem will likely use shape-dependent capillary interactions. Nuclei form near the contact line when particles protrude through the interface; particle shape and surface energy strongly influence the interfacial deformation fields and can be used to create orientation-dependent capillary interactions (see the figure). At free liquid-vapor interfaces, capillary interactions have been used to promote end-to-end or side-to-side assembly of elliptical microparticles (*9*). To promote formation of oriented nuclei in convective assembly, oriented capillary assembly of anisotropically shaped particles protruding through interfaces near contact lines should be studied (see the figure, panel A).

Second, means to dictate oriented assembly of particles in solution need to be developed. A recent numerical study predicts that elongated nanoparticles should readily form oriented liquid crystalline phases driven by the trade-off between translational and orientational entropy (*10*). In two recent experimental studies, particle orientation has been tuned by tailoring surface properties.

Rycenga *et al*. (*11*) tailored the surface energies of silver nanocubes by using self-assembled monolayers to render certain faces hydrophobic. When dispersed in an aqueous phase, the silver nanocubes form different structures depending on how many nanocube faces were functionalized. This approach could be used to orient any anisotropic particle (see the figure, panel B). Zhao and Mason (*12*) exploited depletion attraction and tailored surface roughness. In mixed suspensions of nanoscale and larger colloidal particles, the smaller particles are excluded from regions between the larger particles (see the figure, panel C). The resulting osmotic-pressure gradients push the larger particles together. Surface roughness increases this attraction by enhancing nanoparticle exclusion. Using these ideas, the authors assembled anisotropic particles with selected rough faces into highly ordered close-packed phases.

Methods have also been developed to deposit microscale and nanoscale particles in desired locations from evaporating suspensions to form non–close-packed structures. These will be useful for metamaterials with unit cells larger than the inclusion. For example, Aizenberg *et al*. have used lithographically defined attractive and repulsive regions on the substrate (*13*). When a drop of colloidal suspension evaporates on these surfaces, particles deposit on the attractive regions, and are drawn into ordered structures by capillary attraction. In another technique (*14*, *15*), particles near the contact line are swept into grooves cut into solid substrates as the contact line recedes. Within the grooves, the particles assemble into aggregates as solvent evaporates.

In these methods, spacing between the aggregates is defined by the spacing between the lithographically defined attractive regions or between the grooves on the substrate (see the figure). A particularly novel method reported by Harris *et al*. exploits the dependence of surface tension on temperature and evaporative cooling of the interface. By using a mask to pattern evaporation, patterned surface tension gradients were created. These gradients drove patterned flows within the drop. Particles were convected and deposited in patterns dictated by the flow (*16*).

These advances in colloidal science suggest that oriented assembly of anisotropic materials with three-dimensional control over particle position and orientation will soon be feasible. Such approaches present important opportunities in metamaterials design in the infrared and optical regimes. The challenge now is to move from hit-or-miss assemblies of academic interest to the creation of technologically relevant devices that combine particle and patterned assembly via large-scale processes.

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