

Soft biological materials and their impact on cell function†

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Most organs and biological tissues are soft viscoelastic materials with elastic moduli ranging from on the order of 100 Pa for the brain to 100 000 Pa for soft cartilage. Biocompatible synthetic materials already have many applications, but combining chemical compatibility with physiologically appropriate mechanical properties will increase their potential for use both as implants and as substrates for tissue engineering. Understanding and controlling mechanical properties, specifically softness, is important for appropriate physiological function in numerous contexts. The mechanical properties of the substrate on which, or within which, cells are placed can have as large an impact as chemical stimuli on cell morphology, differentiation, motility, and commitment to live or die.

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Introduction—importance of material mechanics in biology

The importance of mechanical properties in biology was recognized by early physiologists. A prominent text book from 50 years ago stated that “in any attempt to interpret the machinery of a living cell, it is essential to know something about the mechanical properties of the protoplasm in the cell that is being investigated.”¹ In the intervening decades the focus on molecular structures and signaling mechanisms has revealed many aspects of cell function and pathology, but the mechanical properties of individual cells, as well as multicellular tissues and organs, remain largely undefined.

Most research into tissue physiology and the underlying cellular processes has focused on the biochemical agents that determine tissue function, with the resulting mechanical properties considered a byproduct of the necessary biological functions. Concentrations, concentration gradients, and spatial orientations of an immense number of growth factors, extracellular matrix (ECM) molecules, steroids, hormones, and adhesion molecules are critical mediators of the interactions between cells and their environments. However, numerous dysfunctions and disease states can be viewed in part as a



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failure of the mechanical components of tissues. For example, emphysema, a chronic alveolar lung disease, is characterized by a loss of mechanical elasticity, induced by both biochemical changes to the extracellular matrix of the lung and forces produced during respiration.² Healthy lung tissue has been shown to have an elastic modulus in the range of 5–30 kPa when deformed at physiologically relevant rates,^{3–5} whereas tissues treated with proteases to mimic progression of alveolar disease showed a loss in mechanical rigidity of between 33% and 47%.⁵ Similarly, lung fibrosis is characterized as stiffening of the lung parenchyma, and is concomitant with an increase of ~50% in the mechanical resistivity of lung tissue.⁶

In addition to lung dysfunction, recent research suggests that the material properties of the ECM and cellular micro-environment may also be important in the progression of cancer in breast epithelial cells. A normal mammary gland has a stiffness of ~150 Pa, whereas tumors can be stiffer than 4000 Pa, a difference in stiffness easily probed by physical palpation, a common diagnostic for breast tumors. Mammary epithelial cells differ vastly in their morphology, growth rate, and invasiveness as a function of the compliance of their microenvironments in the same range of stiffness.⁷ Other diseases of tissue mechanical dysfunction include scleroderma, the stiffening of skin due to increased collagen deposition,⁸ and atherosclerosis, the hardening of arteries that leads to coronary vascular disease.⁹

Soft materials in tissue formation

Material properties also appear to be relevant to the normal development of tissue during embryogenesis and growth. For example, prenatal development of cartilage and bone is a function of locally applied stresses, with oscillatory normal stresses favoring formation of articular cartilage and shear stresses inducing growth and ossification.^{10,11} In addition to sensing externally applied forces, cells within developing

tissues sense their mechanical microenvironment and respond in ways that are cell type dependent. A recent demonstration of this effect is a study showing that the ability of endothelial cells to undergo tubulogenesis is a function of the precise material nature of their surroundings, whereby only soft substrates allowed proper tube formation that mimicked *in vivo* angiogenesis.¹²

Myoblasts, the developmental precursors of myotubes (striated, multinuclear muscle cells), differentiate into myotubes in a highly mechanosensitive way. Myoblasts grown on substrates with compliances comparable to mature muscle tissue (Young's modulus ~12 kPa) develop the actomyosin striations characteristic of proper muscle differentiation, whereas those grown on softer or stiffer substrates fail to develop normally.¹³ A similar sensitivity to tissue stiffness is seen with mammary epithelial cells that undergo normal morphogenesis to become hollow spherical structures resembling mammary glands when embedded in a compliant three-dimensional matrix of appropriate stiffness.⁷ However, when the compliance of that matrix is altered, this morphogenesis is disrupted, and the cells grow into aberrant, large clusters. The compliance of the matrix that best supports mammary cell morphogenesis matches the stiffness of mammary glands *in vivo*, supporting the notion that cells require appropriate mechanical signals, along with classical biochemical ones, for differentiation and development.^{7,14}

How soft are biological materials

The elastic moduli of soft mammalian tissues range from near 100 Pa for the softest organs such as the brain, to tens of thousands of Pascals in muscle tissues, and on the order of MPa in cartilage, as shown in Table 1.

However, since biological tissues are structurally complex and often anisotropic, rheological parameters are usually functions of time, the degree of deformation and the geometry

Table 1 A summary of elastic moduli of several different tissues. Experimental elastic moduli of a variety of tissues, including the animal of origin of the tissue, and the testing modality used to determine the modulus. When multiple stiffness values were available, the value at the lowest strain rate and lowest pre-strain was used to approximate the “resting stiffness” of the tissue

Tissue type	Animal	Testing method	Elastic modulus	Ref
Achilles' tendon	Rat	Tension	310 Mpa	15
Articular cartilage	Bovine	Compression	950 kPa	86
Skeletal muscle	Rat	Tension	100 kPa	87
Carotid artery	Mouse	Perfusion	90 kPa	88
Spinal cord	Human	Tension	89 kPa	89
Thyroid cancer ^a	Human	Compression	45 kPa	16
Spinal cord	Rat	Tension	27 kPa	90
Cardiac muscle	Mouse	Tension	20–150 kPa	91
Skeletal muscle	Mouse	AFM	12 kPa	13
Thyroid	Human	Compression	9 kPa	16
Lung	Guinea pig	Tension	5–6 kPa	5
Breast tumor	Human	Compression	4 kPa	7
Kidney	Swine	Rheology	2.5 kPa	92
Premalignant breast ^b	Human	Indentation	2.2 kPa	14
Fibrotic liver	Human	Compression	1.6 kPa	93
Liver	Human	Compression	640 Pa	93
Lymph containing metastases	Human	Vibrational resonance	330 Pa	17
Brain	Swine	Indentation	260–490 Pa	94
Lymph node	Human	Vibrational resonance	120 Pa	17
Mammary gland	Human	Compression	160 Pa	7
Fat	Human	Indentation	17 Pa	14

^a Thyroid papillary adenocarcinoma. ^b Mammary ductal carcinoma *in situ*.

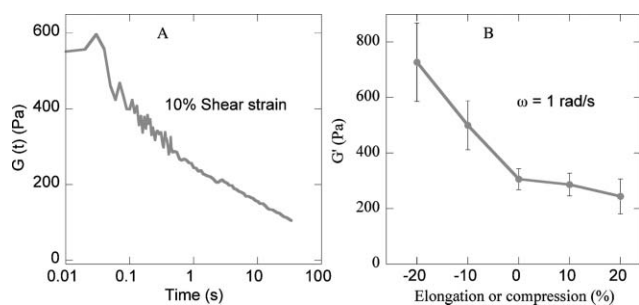


Fig. 1 Time and strain dependence of shear elastic modulus of rat brain. Rat brain tissue was stored in neurobasal media and tested within two hours of sacrifice in a humidified chamber. A. The shear modulus of a disk-shaped sample of intact rat brain was measured in a Rheometrics RFS-III rheometer as a function of time after rapid imposition of a 10% constant shear strain. B. The dynamic shear modulus at 1 rad s^{-1} and 2% maximal shear strain amplitude was measured at various constant compressional (negative) and elongational (positive) strain values in a direction orthogonal to the shear plane.

with which the deforming forces are applied. A typical example of tissue rheology is shown in Fig. 1A where the shear modulus of rat brain is measured as a function of time at a constant strain, and in Fig. 1B where the same sample is measured under compression or extensional strains at a constant oscillatory strain frequency.

As seen in Fig. 1A, the elastic resistance of brain to shear deformation decays rapidly with time, from magnitudes near 1000 Pa at very short times to near 100 Pa at 20 seconds. The short time stiffness value is relevant to the modeling of brain injury following rapid deformation by trauma, whereas the later, lower modulus is potentially more relevant to the contractile probing (*i.e.* stiffness sensing by active cytoskeletal contraction) done by cells within this tissue during development, wound healing, or maintenance of normal tissue. Applying compressional deformation significantly stiffens brain tissue when oscillatory shear strain is imposed, but elongational deformation has a very small and possibly softening effect (Fig. 1B).

Despite the inherent complexity of tissue stiffnesses, many different tissue types have been tested using a variety of experimental modalities, and comparisons of stiffness can be made from measurements at similar time-scales and strain magnitudes. The large range of stiffness values can be seen in Table 1, which shows that dense connective tissue (rat Achilles' tendon) is approximately 10 million times stiffer than more loosely packed adipose tissue (human fat).^{14,15} Despite large differences in stiffness between some tissues, most mammalian organs have elastic moduli between 100 and 10 000 Pa, values that are much softer than the stiffness of substrates typically used to study the behavior of cells derived from these tissues (typically plastic or glass which are on the order of GPa), suggesting that some prominent features such as stress fibers or a flattened morphology characteristic of cells on stiff substrates may be less prevalent in the cells' native environments.

Also included in this list are comparisons between healthy tissue and diseased tissue, whether that disease is a result of transformed native cells, cancerous metastases from other

tissues, or injury-induced fibrosis. These comparisons frequently reveal a distinct stiffening of diseased tissue compared to healthy tissue. For example, a papillary adenocarcinoma of a thyroid gland has an elastic modulus five times greater than normal tissue, as measured by compression.¹⁶ Similarly, lymph tissue containing metastases from other parts of the body is almost 3 times stiffer than healthy lymph nodes.¹⁷ The same observations of varying magnitudes can be made for the case of mammary tumors and fibrotic livers.^{7,14} Although an increase in elastic moduli of tissues is often a sign of disease and dysfunction, loss of mechanical stability and tissue softening can also signal pathological conditions, as in emphysema² or impairment of mechanical properties in spastic muscle.¹⁸

Networks of biological polymers

The rheology of soft biological materials depends on the assembly of long protein filaments into networks of different geometries. The specific geometries of these networks are determined by the chemical and mechanical properties of the filaments, as well as those of the crosslinks that hold the filaments together. Despite their chemical differences, the most abundant protein filaments of extracellular matrices and intracellular cytoskeletons have the common property of being semiflexible filaments crosslinked into open meshworks. Whereas some biopolymers such as elastin have elastic properties very similar to rubberlike materials,^{19,20} gels formed by stiffer filaments like fibrin, collagen, actin, and intermediate filaments have distinct rheological properties.^{21,22} For example, they are able to form elastic gels at very low volume fractions, less than 0.01% under optimal conditions, and become stiffer the more they are deformed, a property termed strain-stiffening, as shown in Fig. 2.

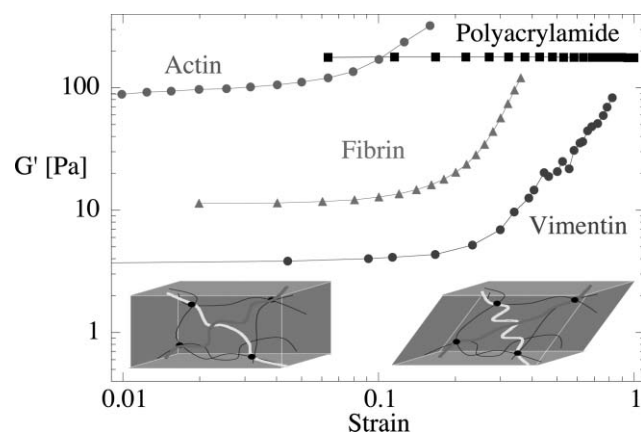


Fig. 2 Strain stiffening of cytoskeletal and extracellular matrix gels. Shear storage moduli of crosslinked actin, fibrin and vimentin intermediate filament networks measured by oscillatory deformation at 1 rad s^{-1} over a range of strain amplitudes in aqueous media at room temperature. The diagrams depict qualitatively that in open meshworks of semiflexible polymers under shear deformation, some filaments are stretched and some are compressed. The inherent non-linear force-extension relation of semiflexible filaments at finite strains produces a shear stiffening effect in these networks. Data and model derived from ref. 21

These mechanical properties likely contribute to the biological functions of cytoskeletal proteins in forming elastic networks with minimal protein production and networks with large mesh sizes that allow the passage of large macromolecular assemblies and some small organelles. The rheological properties of the networks formed *in vivo* are likely to differ in some respects from those formed *in vitro*. *In vivo*, the production of both filaments and networks is tightly regulated by numerous assembly-promoting and crosslinking factors^{23,24} that produce active networks with specified geometries far from equilibrium,^{25–28} and not yet capable of being produced from purified factors *in vitro*.

Models for tissue stiffness: are soft tissues gels, glasses, foams, colloids, or something unique to biology

In some cases, biological materials are structurally uniform or their mechanical properties are dominated by a single structure, and they can be reasonably interpreted by existing models for synthetic materials. For example, the mechanics of blood clots and some extracellular matrices are sufficiently dependent on the polymer networks that form them, *i.e.* fibrin^{29–32} and collagen,³³ respectively, that their rheology resembles that of gels of crosslinked polymers. Their relatively frequency-independent shear storage moduli and low mechanical loss, as well as the scaling of elastic moduli with polymer concentrations all resemble those of other semi-flexible polymer networks. The relatively large elastic moduli for low volume fractions and the strain-stiffening behavior distinguish these biomaterials from hydrogels of flexible polymers, but they are relatively well modeled by theories for semiflexible chains.²¹

Some materials, such as muscle fibers, are complex but contain well-oriented fibers. Close agreement of macroscopic tissue force–elongation curves with single molecule measurements has been reported in which the restoring force of the tissue appears to derive from a large number of well-defined molecules working in series and in parallel.³⁴ Elastin, the major component of several extracellular matrices is well modeled by entropic elasticity²⁰ modulated by hydrophobic interactions between polymer chains,^{19,35} and is among the best characterized of all soft biological solids.^{2,3,6,36–38}

In contrast, most biological materials, including single cells, are not well defined by a single synthetic analog. In part, this results from their structural complexity and the fact that many are under internal tension,^{39–44} are constantly remodeling, or are subject to apparently random, but non-thermal, fluctuations that are rarely, if ever, found in synthetic materials.⁴⁵ Many recent studies have reported that cells and some purified systems mimicking the cytoskeleton have frequency-dependent elastic moduli that follow a power law with a small fractional exponent, often near 0.1 to 0.2 over several orders of magnitude in frequency.^{41,42,46–53} This behavior is inconsistent with polymer models containing a small number of relaxation times, or a finite longest relaxation time, but rather implies a continuum of relaxation times consistent with the rheology of immobilized colloids or soft glasses. The evidence in favor of power law rheology of single cells and other soft tissues is

increasingly documented, although the precise molecular nature of this behavior remains unexplained. A related finding from microscopic measurements of the fluctuations of particles within the cytoplasm shows that while these motions appear random, they are much too large to be accounted for by thermal fluctuations. Instead, these motions seem to result from random jostling of the cytoskeleton, membranes and other structures that are in contact with motor proteins that produce mechanical motions of various kinds using the energy of ATP hydrolysis to do work.⁴⁵ In many cases, the resulting motions are unidirectional for long distances and easily distinguished from Brownian motion, but in other cases single steps in random directions could produce the apparently random but active movements within the cell, with a resulting spectrum of relaxation times that could contribute to the power law behavior of the overall rheology. On the other hand, some features of single cell rheology, such as strain-stiffening³⁹ and the effects of internal stress, are consistent with the importance of a continuous elastic network of filaments within the cell. Whether the cell appears to behave as a glass, a gel, or something else may depend on the magnitude of the deformation and the time over which the response is observed.

On a larger scale, whole tissue mechanics are also often difficult to relate to a simple mechanical model. For example, even though the brain is rich in cytoskeletal elements, especially neuronal intermediate filaments which exhibit dramatic strain-stiffening,^{21,54} the intact brain or spinal cord has a highly distinct rheology. In contrast to purified cytoskeletal networks, brain tissue does not strain-stiffen, and has a relatively high mechanical loss.⁵⁵ In a sense, this result is not surprising because despite being rich in cytoskeletal elements, the brain lacks extracellular matrix networks that tie the cellular elements together, leading to a case where the lipid-dominated cell–cell contacts within the tissue produce interfaces that may make foams or colloids more realistic models than polymer gels.

In summary, very few biological tissues are simple enough to approximate by any specific rheological model. As a result, most rheological studies have been phenomenological, with either a finite number of elastic and viscous elements coupled in series or parallel to mimic the rheological behavior, or else scaling exponents and limiting values to define how they may be fit by glass-like models.⁴⁶ These phenomenological models have been essential in many bioengineering contexts to develop protective or therapeutic strategies. However developing mechanical models by which the properties of specific molecular structures, motor-derived forces, and cell–cell or cell–matrix interactions account for tissue mechanics remains an area of active investigation.

Cellular response to material properties

A seminal set of experiments conducted on fibroblasts (connective tissue cells) grown on protein-laminated polyacrylamide gels showed that the spread area, traction force, speed of migration and size and dynamics of adhesion sites are regulated by the mechanical rigidity of the cell substrata.^{56,57} Further experiments with fibroblasts were able to elucidate these effects and refine the molecular mechanisms involved in

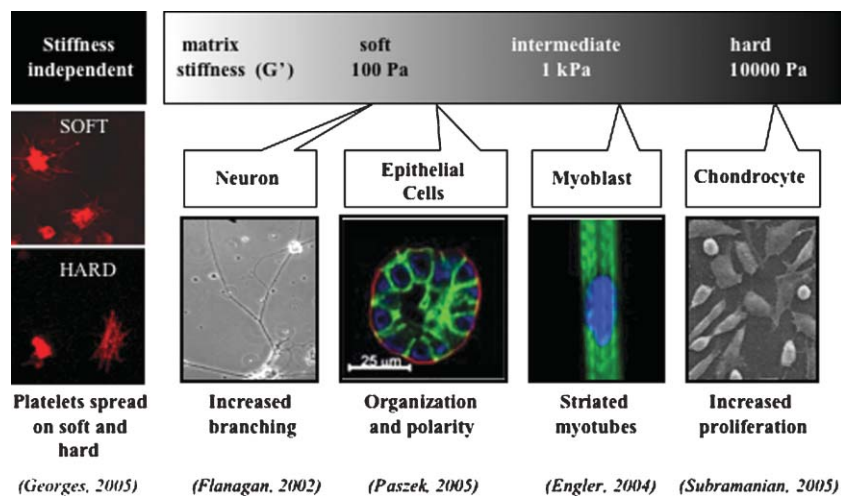


Fig. 3 Effects of substrate stiffness on cell morphology. Cell types grown on flexible polyacrylamide gel substrates display *in vivo*-like morphological and functional properties on compliance similar to that of the particular tissue from which they are derived. Platelets, which circulate through the blood and are normally nonadherent, do not respond to substrate mechanics.⁵⁹ Neurons, mammary epithelial cells, and other epithelial cells isolated from soft tissue thrive on soft materials (shear modulus (G') \approx 100 Pa).^{7,69,95} Myoblasts of the muscle display actomyosin striations only on intermediate compliance substrates ($G' \approx$ 4 kPa).^{13,96,97} Chondrocytes exhibit increased growth and proliferation markers on hard gels with compliance similar to hard cartilage ($G' \approx$ 10 kPa).^{98,99}

the response of fibroblasts to substrates of varying stiffnesses, as reviewed in ref. 58–61.

Numerous other cell types have been found to be mechano-responsive, with the nature and magnitude of that response being highly cell type-dependent in a way that echoes the tissues from which those cells are derived.^{13,59,62,63} A few examples of the stiffness ranges to which different cell types respond and the characteristic morphologies they take on substrates with rigidity similar to those of the native tissue are shown in Fig. 3. A larger and rapidly increasing list of cells documented to be sensitive to matrix rigidity is shown in Table 2.

As these examples show, material rigidity affects cell migration, overall morphology, the structure of the cytoskeleton, expression of specific genes, as well as the lineage of stem cell differentiation. As more research into the relationship between matrix rigidity or compliance and cell fate is conducted, the importance of mechanical properties on the biological function of cells and tissues is likely to be confirmed.

Isolating mechanical from structural differences in networks

Changes in matrix stiffness require at least some degree of change to the matrix structure, and changes in cell morphology or function might be due to chemical differences resulting from the altered structure and not just to differences in stiffness. To address this possibility, several studies have shown that one important parameter, the density of adhesion sites on the surface of polyacrylamide gels, does not depend on the stiffness of the gel.^{63–65} Differences in mesh size, resulting from changing the polymer concentration, for example, might also change the rate at which solutes diffuse to the basal surface of the cell. One study compared gels of similar stiffness formed from either high polyacrylamide concentration and low crosslinker or lower total polyacrylamide and higher crosslinker concentration and found no difference in cell morphology on gels of these different formulations but similar stiffness.⁶² Furthermore when two entirely different matrices,

Table 2 Comparison of cell responses to hydrogels with variable stiffness

Cell type	Adhesive ligand	Unique response to mechanical properties of matrix	Reference
Aortic smooth muscle cell	Collagen	Minimal spreading on gels with moduli less than 5 kPa, spreading saturates around 15 kPa	64
Neuron	Matrigel	Increased branching and neurite extension on softer gels ($G' \approx$ 230 Pa)	69,70
Hepatocyte	Matrigel	Increased aggregation and differentiation markers on $G' >$ 150 Pa gels	100
Hepatic stellate cell	Matrigel	Return from reactive to quiescent phenotype on $G' <$ 100 Pa materials	101
Mammary epithelial cell	Matrigel	Polarized mammary gland duct morphogenesis on $G' <$ 200 Pa	7
Transformed NIH-3T3 fibroblast	Collagen	Transformation causes loss of response to mechanical stimuli	102
Astrocyte	Laminin	Increased spread area and process extension on $G' >$ 500 Pa	63
Chondrocyte	Chitosan	Increased growth and proliferation on $G' >$ 10 kPa	99
Alveolar macrophage	Collagen	Increase in cell stiffness and area on $G' >$ 10 kPa without F-actin stress fiber formation	103
Neutrophil	Fibronectin	Cell spread area is independent of matrix mechanics	62
Myoblast	Collagen	Striated myotube formation on gels $G' \approx$ 12 kPa	13
Platelet	Collagen	Process extension and adhesion are independent of matrix mechanics	104
Human blood outgrowth endothelial cell	Collagen	Branched multi-cellular <i>in vivo</i> -like structures in $G' \approx$ 6 kPa collagen gels	105

protein-laminated polyacrylamide and fibrin, were compared, mixed cultures of neurons and astrocytes exhibited a similar dependence on the elastic moduli of the gels.⁶³ The increasing number of reports of the significant effects of stiffness on specific cell types using a variety of different matrices provide data that increasingly implicate matrix stiffness, as opposed to some accompanying chemical effect, as a primary determinant of cell structure.

Soft materials in biological research

The material properties of hydrogels produced from synthetic materials and some natural biopolymers approximate those of biological tissues, and are therefore appropriate as substrates to mimic the natural mechanical environment for cell studies. One of the more common materials used for cell research, polyacrylamide hydrogels, has stiffnesses that range from hundreds to tens of thousands of Pascals, as a function of polymer and crosslinker concentrations. Natural biopolymer gels are also amenable for cell research, with stiffnesses ranging from 10 Pa to thousands of Pascals, depending on protein concentration. While these polymer gels only cover the lower range of biorelevant stiffnesses, other synthetic materials, such as poly-HEMA copolymer gels, can attain stiffness close to 1 MPa.⁶⁶

The ability to synthesize materials that approximate the mechanical nature of biological tissue, as well as the recent interest in cell mechanics and the effects of substrate elasticity on cell structure and function, have motivated studies of many different materials for applications in wound healing and tissue engineering. For example, poly(2-hydroxyethyl methacrylate-co-methyl methacrylate),⁶⁷ poly-[N-(2-hydroxypropyl)-methacrylamide],⁶⁸ protein-laminated polyacrylamide,^{63,69} agarose,⁷⁰ alginate,⁷¹ and collagen⁷² hydrogels have all been tested as guides for neuronal growth. Current studies suggest that derivatives of the natural biopolymers fibrin and collagen are most efficient at supporting neurite outgrowth in culture,^{63,73} and selected advantages of natural and synthetic soft polymers can be combined in composite matrices that might have many applications in medicine and biotechnology.^{74,75} A particularly interesting aspect of stiff biopolymer fibers like fibrin and collagen is that they can be aligned in magnetic fields to produce oriented networks that have the potential for guiding cell migration and extension.⁷⁶ Additionally, many of the naturally-derived matrices cited above can be chemically and mechanically altered after cells have been embedded as an *in vitro* model of tissue remodeling. Examples include glycation⁷⁷ and enzyme-induced⁷⁸ stiffening of collagen matrices, improved mechanical properties of tissue-engineered blood vessels by addition of retinoic and ascorbic acid,⁷⁹ as well as remodeling of collagen constructs by mechanical stresses.⁸⁰

In addition to the examples cited above, many other novel materials based on synthetic hydrogels such as polyethylene glycol,⁸¹ polyacrylate derivatives, poly(2-hydroxyethyl methacrylate),⁸² and polyelectrolyte multilayers^{83,84} are being designed for use in many different cellular systems. The synthetic hydrogels can be made alone or in combination with natural biopolymers such as polysaccharides, glycosaminoglycans, and protein polymers. In parallel research, novel

chemistries to link signaling or adhesion molecules to the matrix or to produce, for example, photoactivatable or photodegradable crosslinks within the matrix,⁸⁵ offer the possibility of production and manipulation of both the chemical and the mechanical properties of materials. These new soft materials can be used to mimic more closely the native tissues in which most cells live.

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