Osteoarthritis and Cartilage (1999) **7,** 81–94

1063–4584/99/010081+14 $12.00/0
Article No. joca.1998.0164, available online at http://www.idealibrary.com on IDEAL

Osteoarthritis and Cartilage
Journal of the OsteoArthritis Research Society International

Tensegrity and mechanoregulation: from skeleton to cytoskeleton

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Summary

Objective: To elucidate how mechanical stresses that are applied to the whole organism are transmitted to individual cells and transduced into a biochemical response.

Design: In this article, we describe fundamental design principles that are used to stabilize the musculoskeletal system at many different size scales and show that these design features are embodied in one particular form of architecture that is known as tensegrity.

Results: Tensegrity structures are characterized by use of continuous tension and local compression; architecture, prestress (internal stress prior to application of external force), and triangulation play the most critical roles in terms of determining their mechanical stability. In living organisms, use of a hierarchy of tensegrity networks both optimizes structural efficiency and provides a mechanism to mechanically couple the parts with the whole: mechanical stresses applied at the macroscale result in structural rearrangements at the cell and molecular level.

Conclusion: Due to use of tensegrity architecture, mechanical stress is concentrated and focused on signal transducing molecules that physically associate with cell surface molecules that anchor cells to extracellular matrix, such as integrins, and with load-bearing elements within the internal cytoskeleton and nucleus. Mechanochemical transduction may then proceed through local stress-dependent changes in molecular mechanics, thermodynamics, and kinetics within the cell. In this manner, the entire cellular response to stress may be orchestrated and tuned by altering the prestress in the cell, just as changing muscular tone can alter mechanical stability and structural coordination throughout the whole musculoskeletal system.

Key words: Tensegrity, Mechanotransduction, Cytoskeleton, Extracellular matrix, Integrins, Anatomy.

Introduction

Recent advances in molecular biology have focused our attention on the importance of molecular factors in tissue development. Yet, there are other regulatory signals, such as mechanical stresses, that are equally critical for control of tissue form and function. This is perhaps most evident in orthopedics where it is well known that muscle and bone actively remodel in response to changes in exercise or altered gravity as experienced in spaceflight [e.g., 1–6]. However, mechanoresponsiveness is actually a fundamental feature of all living tissues [7, 8]. Experiments with cultured cells confirm that mechanical stresses can directly alter many cellular processes, including signal transduction, gene expression, growth, differentiation, and survival [9–15]. Still, the mechanism by which mechanical stresses applied on the macroscale are transmitted to individual cells on the microscale and transduced into a biological response remains a mystery.

To understand this process of mechanoregulation, we must take into account that living organisms, such as man, are constructed from tiers of systems within a system within a system. A limb is composed of several organs (bone, muscle, blood vessels, nerves) that, in turn, are constructed from tissues (e.g., muscle fibers, vascular endothelium, connective tissue) which are composed of groups of living cells and their associated extracellular matrix (ECM). ECMs are macromolecular complexes composed of different collagens, glycoproteins, and proteoglycans that function as in-vivo scaffolds for cell anchorage [16]. Each cell contains intracellular organelles, a nucleus, lipid membranes, and a viscous cytosol permeating a filamentous cytoskeleton [17, 18]. Each of these subcellular components is, in turn, composed of aggregates of different molecules. In other words, living systems are neither homogeneous nor isotropic and therefore require the development of appropriate inhomogeneous and anisotropic engineering models to describe their behaviors. In

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tissues and cells, mechanical deformations must necessarily result in a coordinated structural rearrangement on many different size scales. Thus, the question of how the body senses and responds to mechanical stresses is not simply an issue of the material properties of its components, also it is a problem related to the architectural arrangement of its microstructure.

Engineering of the musculoskeletal system

Analysis of the mechanical functions of the human musculoskeletal system can help us understand the rationale for its design (see for example the papers by Allen *et al.*, and Setton *et al.*, in this special issue). This integrated framework provides a scaffold which supports the weight of our bodies, allows us to rapidly adjust to resist external forces, and permits us to move freely in our environment. Selective pressures demand that the construction of such a machine minimizes mass with sufficient flexibility, yet without compromising its structural integrity to handle unexpected forces: a light frame can move more quickly and explore a wider range of food sources with lower metabolic cost. The musculoskeletal system has evolved to address these demands through optimization of both material properties (how the individual support elements are designed) and architecture (how the different elements are oriented and connected together).

TENSION AND COMPRESSION

The problem of maximizing mechanical function while minimizing mass has been long studied in engineering. It has been established that a structure built with members of a given material will be of minimum weight when the members are either all in tension or all in compression (Maxwell's lemma) [19–21]. Unfortunately, a framework composed of either all tension or all compression elements can not withstand the complex and unexpected loading patterns experienced by man. The impact forces from running and jumping, tensile forces from hanging and climbing, and torques from picking up objects are just a few examples.

An alternative engineering approach is to create structures containing both tension and compression elements. If members of such a structure have a low aspect (length to width) ratio, they will exhibit similar strengths in tension as in compression, below the buckling load. In this case, the strength depends only on the cross-sectional area of the member for a given material. However, if these members are made progressively more slender to minimize the weight of the structure, the compression members will begin to yield before the tension members, as a result of buckling instability (i.e., bending). To maintain stability in the structure, tension members therefore can be made long and slender while compression elements must remain thick and bulky. As a result, systems that maximize tension elements and minimize those in compression use less mass to maintain structural form and hence, for biologic systems, minimize associated metabolic costs.

Examining the construction of the human body, we find that Nature has discovered the same solution to this optimization problem of maximizing strength per mass. The compression-resistant bones of the 'skeleton' are smaller subunits within a larger supporting framework, or 'musculoskeletal system', that is comprised of an interconnected network of bones, ligaments, tendons, muscles, and cartilage. Without the aid of surrounding tension-resisting muscles and tendons, bones would do little to support our upright forms, in its variety of positions. Through use of this sort of interconnected framework of tension and compression elements, we optimize structural efficiency without sacrificing the ability of the structure to withstand a variety of structural requirements such as torsion and bending as well as tension and compression demanded of our bodies.

ARCHITECTURE AND PRESTRESS

Importantly, the overall stability and range of motion of the hundreds of compression-resistant bones that comprise the human skeleton are actually strongly influenced by the architecture of our bodies. That is, their mechanical behavior depends on how the surrounding tensile muscles, tendons, and ligaments are joined and oriented in space (see paper by Allen *et al.*, in this special issue). For example, the freely sliding bones of the curved spinal column would easily fall to pieces without the stabilizing influence of the surrounding tensile guy wires (muscles and ligaments) that act to resist both the sliding of bones across one another, and the bending and twisting along the length of the spine. If the spine were simply a compression column, it would have to be much wider and hence, considerably heavier to bear the forces of gravity. The pelvis is similarly stabilized through multiple tension-dependent connections with interconnecting ligaments and muscles [22].

From engineering, we know that the stability of a structural network is determined by the material

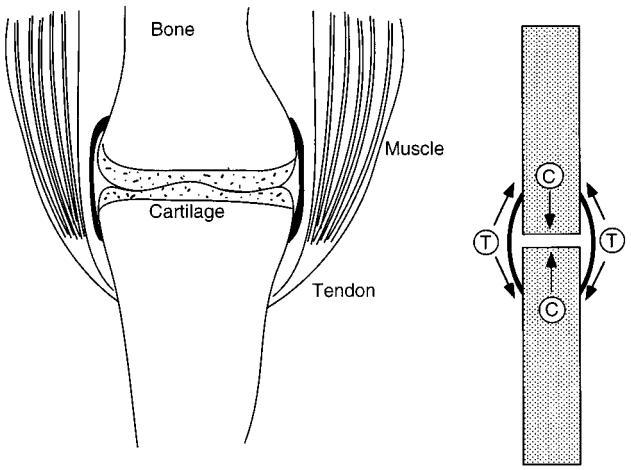

FIG. 1. Schematic diagram of a generic articular joint (left) and grossly simplified corresponding internal stresses in bone, cartilage, and ligaments (right). Acting external loads (relative to the material) are indicated as primarily compressive (C) or tensile (T).

properties of the building elements, their arrangment, and the 'play' (free movement) in the joints that interlink the different elements. To stabilize the critical joint regions, engineers often increase the amount of load-bearing materials in these regions. However, when weight is a consideration, engineers have developed 'prestress' structures such as reinforced concrete beams with pre-tensioned steel bars placed in regions where tensile loads are likely to occur in the concrete beam. This pre-compresses the concrete so as to overcome the tensile stress resulting from loads applied onto the concrete beam. This kind of optimization also occurs in biologic systems, to reduce the play in the system, ensuring immediate mechanical responsiveness (i.e., that movement of one element is immediately felt by all others) and reducing loads on the structures, and thus likelihood of fatigue of the materials comprising the joint. Indeed, Nature uses the same approach to obtain stability with minimum mass in the articular joint.

The stable position of the bones that articulate at any joint depends on the tensile forces of the muscles, tendons, and ligaments that bridge them. In the knee, for example, the cartilagenous regions at the end of apposing bones come into direct contact due to compression (Fig. 1). Most of this compression is not due to gravity, rather it is created by the surrounding ligaments and tendons that crosses the joint, and these are always under tension. The internal tension and/or pre-stress in this system stabilizes the joint: even when the bones are pulled away from each other (e.g., hanging upside down), the joint does not dislocate. In reality, there are multiple muscles, tendons, and ligaments that contribute to the structure of each joint and the number and position of these tensile elements (i.e., the architectural arrangement) play a critical role in defining the joint's potential strength, power, speed, and range of motion. To understand the critical importance of these internal tensions and/or pre-stress in this complex structure, one only needs to examine the case where tendons and ligaments loosen: this results in joint instability, increased wear on the articular cartilage, pain, and loss of function (see paper by Setton *et al.*, in this special issue).

Hierarchical organization in the musculoskeletal system

The large structural components that comprise the musculoskeleton, including bones, muscles, cartilage, ligaments and tendons, exhibit a broad spectrum of mechanical properties without using many different types of materials. This is made possible through use of a hierarchy of structural organization [23, 24]: different tissues and organs exhibit structures on several length scales such that the smaller building elements themselves exhibit specialized architecture. The existence of discrete networks within discrete networks in bones, cartilage, tendons and ligaments optimizes their structural efficiency (e.g., strength/mass) as well as energy absorption.

To visualize this structural hierarchy, let's return to the articular joint of the knee (Fig. 1). The upper bone (e.g., femur) functions as a single compression strut on the scale of the whole body since it bears a net compressive load. Long bones, such as this femur, have actually evolved a hollow center to increase their second moment of inertia and thereby, maintain their strength in bending and twisting, while minimizing mass. However, because of the bowed out shape of the femur and its vertical orientation when loaded, different regions of the same bone will experience very different mechanical loads on a smaller size scale (Fig. 2). Furthermore, the pattern of stress distributions is modified by the particular loading conditions that are experienced in the human body. This includes how the femur joins to bones above and below as well as the pattern of additional muscular insertion points. For example, muscles that pull the bone medially would function like tensile guy wires to resist buckling and thus, effectively decrease the level of tension and compression experienced in the lateral and medial walls of the femur, respectively (Fig. 2).

As a result of local variations in stress fields, the bony trabeculae that comprise the cancellous bone

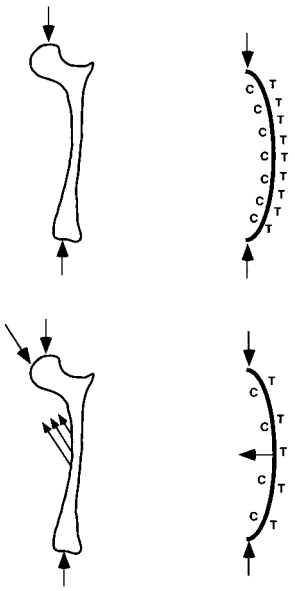

FIG. 2. Diagram showing the loading of a femur in standing position. The primary compressive forces generated by standing (top left) causes bending of the bone that results in local internal tension and compression (top right). With the stabilizing force of medial muscular tension on the bone shaft (bottom) the internal compression and tension felt by the medial and lateral aspects of the diaphysis are reduced.

in the medial and lateral regions of the femur primarily experience either pure compression or tension along their long axes, respectively [25]. These local stress patterns are clearly visualized in gross sections or radiographs of the human femur which demonstrate that the network of trabeculae bone is organized to approximate the principal stress directions (Fig. 3); note that these principal stress trajectories are derived from a linearly elastic, homogeneous, isotropic models for bone. This observation suggests that the living cells that continually remodel bone are able to sense changes in mechanical stresses in their local environment and that they respond by depositing new ECM where it is needed and removing it from where it is not. This process, which is known as 'Wolff's Law', results in deposition of bone ECM in specific patterns that correspond precisely to engineering lines of tension and compression characteristic for elastic structure of this size and shape with similar loading conditions (Fig. 3). Recent computer models of bone remodeling due to mechanical forces have been able to successfully simulate in-vivo descriptions of bone growth and development [26–29]. It is one of the most beautiful examples of the importance of cellular mechanotransduction for regulation of tissue morphogenesis.

The specialized microarchitecture of cancellous bone further optimizes its structural efficiency (strength/mass ratio). For instance, the total area of exposed bone is increased at joint surfaces so that there is less stress locally and thus, a porous trabecular network comprised of small bony struts can be utilized instead of a heavy, space-filling solid. Each of these short struts appears to be joined to lateral sideways struts which 'triangulate' at each joint (i.e., meet at vertices in such a way as to stabilize position of the joint in all three of the spatial axes with only tension or compression in the struts) and thereby stiffen each other against buckling. The use of this triangulated network serves to distribute the load on the articular surface and to transmit it distally into the sidewall of the shaft of the bone which is already thickened to resist bending (increased second moment of inertia about the neutral axis of bending). The open, porous quality of this triangulated trabecular network also enhances its compliance, allowing the energy of impact to distribute and dissipated throughout a larger volume of a more lossy material.

Architectural organization on yet a smaller size scale (the molecular level) also contributes significantly to the mechanical strength of biologic tissue [24]. In the bone, the matrix of each trabeculum consists of a composite material containing hydroxyapatite crystals embedded within a network of collagen fibrils [30]. The collagen augments the tensile strength of the bone, while the minerals contribute largely to its compressive stiffness and strength. In the living organism, the stress in the bone ECM is influenced by the shape of the entire bone, the pull of the surrounding muscles and tendons, and its loading conditions (Fig. 2). Contractile fibroblasts also likely prestress the collagen network during the process of tissue development and remodeling, before the surrounding ECM calcifies. This process of forming composites of distinct, specialized tensile and compressive materials as well as the use of prestress is well established in modern materials engineering, such as in the manufacturing of reinforced concrete or aeronautical carbon-fiberglass composites.

Pre-stress also plays an important role in determining the mechanics of cartilage, tendons, and ligaments [24]. In cartilage, the loose collagen network is stretched open and pre-stressed by the osmotic force of hydration of embedded proteoglycan molecules [15, 31, 32], however, the cellular components (chondrocytes) and their internal support elements (cytoskeleton, nucleus) may also bear some mechanical loads [33, 34 also see paper

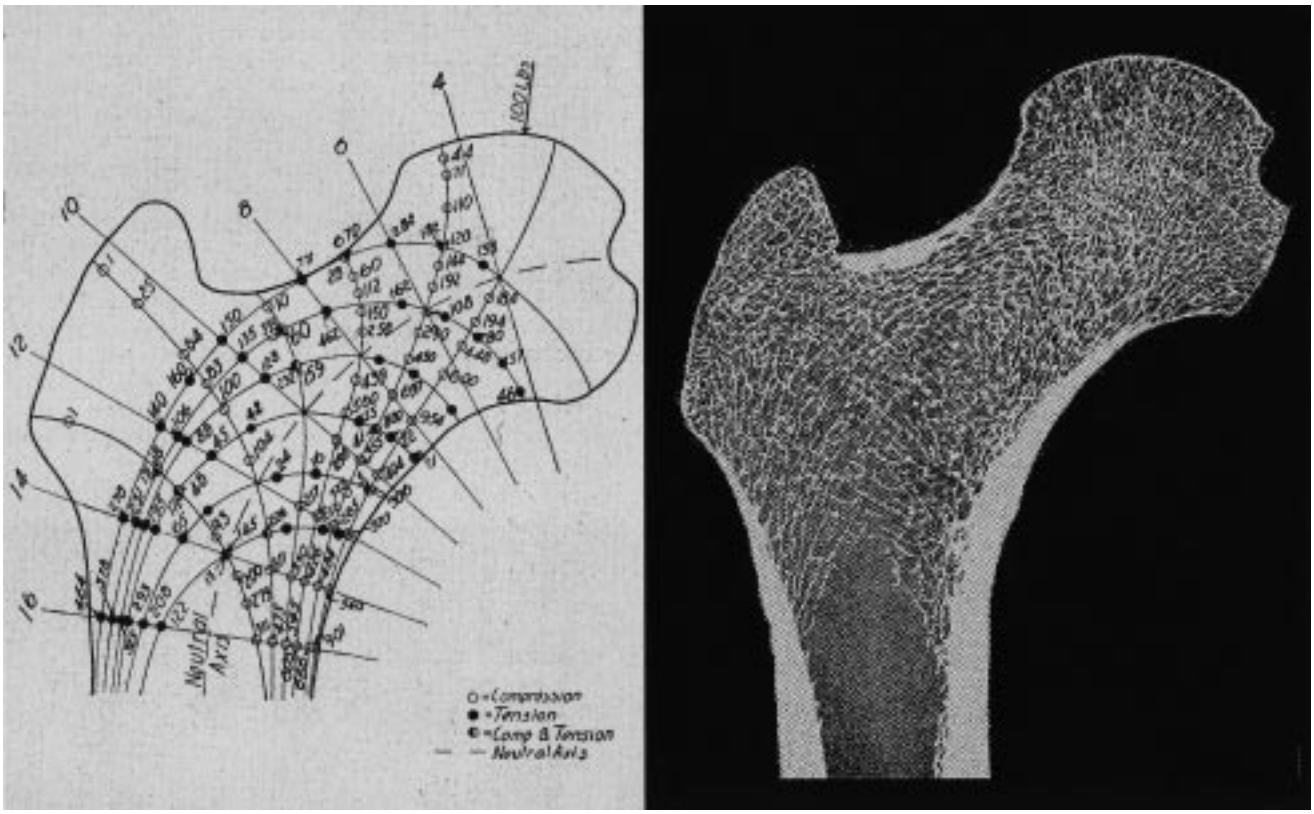

FIG. 3. Approximate principal axes of stress (predicted from a homogeneous, isotropic elastic model for the bone) shown as field lines in a loaded femural head (left) and the corresponding trabecular structure within it (right), indicating reasonable alignment of trabecular structures with stress field lines. Note that the lateral portion of the femur is primarily in tension while the medial aspect experiences pure compression. [Reproduced from Koch, 1917; ref. 25. Rights of the original copyright holder acknowledged.]

by Guilak in this special volume]. In soft tissues that are composed mostly of parallel collagen fibers and elastin [35, 36], such as ligaments and tendons, the pre-stress results from the active contraction of living cells (myofibroblasts) that are embedded within its ECM. The cell contractions pull the collagen into an undulating, buckled structure (Fig. 4) and keeps the ligament under tension at all times [37]. Like synthetic fabrics and foams, applying external forces causes the fibers within these networks to quickly adjust and align along the main axis of the applied tension field due to their flexibility and freedom of motion [38]. Hence, these soft tissues remodel and adjust their fiber orientations to optimize their load bearing capacity much like bone and cartilage, however, on a much faster time scale [24].

Mechanical engineering at the cellular level

Most conventional engineering models of living cells assume external forces are distributed evenly across the cell surface and consider the key load-bearing elements of the cell to be a homogeneous, isotropic viscous fluid cytosol or homogenous, isotropic viscoelastic solid cytoskeleton, and surrounding tensed membrane [15, 17, 18, 39–42]. In reality, we find that the cells within a living tissue, such as a tensed ligament (Fig. 4), are not evenly glued to their underlying ECM adhesive substrate, but instead, actually anchor themselves to ECM through spot weld-like attachments that are known as 'focal adhesions' [37, 43, 44]. These sites are where cells pull together or cluster multiple transmembrane receptors, known as 'integrins', that bind to specific ECM molecules on the outside of the cell and thereby mediate cell anchorage [7, 16]. Surrounding regions of the plasma membrane lack these receptors and do not mechanically connect to the ECM scaffold.

Importantly, all living cells are contractile: they generate tension within their internal cytoskeleton via an actomyosin filament sliding mechanism similar to that used in muscle [37, 45]. However, in non-muscle cells, these 'contractile microfilaments' are organized within a loose network rather than in a highly oriented contractile machinery. Furthermore, the tension that is

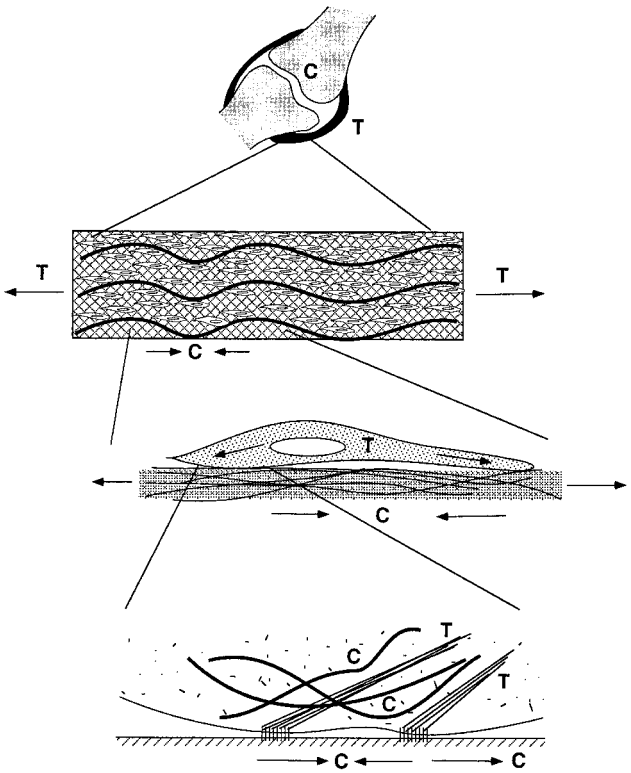

FIG. 4. Diagramatic views at progressively smaller size scales (from top to bottom) within the tensegrity structural hierarchy of a ligament from an articular joint. A pre-stressed balance of continuous tension (T) and compression (C) elements stabilize the physical structure of this living material at several size scales. Ligaments and bones (top), contractile cells and local regions of tensionally-stiffened ligament ECM (middle two views), and contractile microfilaments and microtubules (bottom) act as balanced tension and compression elements, respectively. Note that an element placed under tension (and stiffened) at one size scale (e.g., long collagen bundle) can act to resist local compression on a smaller size scale (e.g., between adjacent focal adhesions).

generated in these filaments is transmitted directly to the internal face of the focal adhesion anchoring sites because the ends of the largest bundles of contractile microfilaments ('stress fibers') insert on the cytoplasmic face of the clustered transmembrane integrin receptors [37, 43]. For this reason, living cells will contract flexible substrates (e.g., hydrated collagen gels, silicone rubber) and create compression wrinkles between these localized adhesions [37, 44–46]. Thus, it is the ability of the ECM to resist compression and the osmotic pressure within the local regions that span between these different focal adhesions (Fig. 4, bottom) that establishes the pre-stress necessary for maintenance of shape stability. Importantly, we have recently demonstrated that integrins provide a preferred path for mechanical stress transfer across the cell surface [48] and that cell growth and viability (apoptosis) can be controlled by varying the spacing between different focal adhesions and thereby modulating cell shape [49]. Cell shape (extension) also governs whether cells will grow or differentiate locally when stimulated by soluble mitogens [50, 51].

SHAPE STABILITY IN THE CYTOSKELETON

Due to the use of point-loading, cells have had to evolve a structural framework to transmit forces from one place to another inside their cytoplasm. This structure, known as the cell skeleton or 'cytoskeleton', is a highly interconnected three dimensional network composed of three major biopolymer systems, microfilaments, microtubules, and intermediate filaments along with their associated proteins:

- Microfilaments contain polymerized actin. They can appear alone or in association with myosin filaments. The latter structures represent the contractile microfilaments which generate tension that is continuously transmitted throughout the entire interconnected actin lattice and thus, the whole cell. When assembled *in vitro* from pure actin, microfilaments are highly flexible and exhibit a curved form. In living cells, on the other hand, actin filaments almost always exhibit a highly linear form, suggesting they are continuously under tension. Flexible actin filaments also can be laterally cross-linked to form highly stiffened bundles in certain locations in the cell. For example, stiff actin bundles push out against the surrounding tensed plasma membrane to form the filopodial extensions that appear at the leading edge of migrating cells [52].
- Microtubules are hollow tubular polymers composed of different tubulin monomer isotypes. Because this tube-like architecture increases the second moment of inertia, these biopolymers resist bending and twisting, maintaining an almost always highly linear form when studied *in vitro* [53]. However, microtubules commonly exhibit a highly curved or buckled morphology in living cells, suggesting that they may be experiencing local bending and/or axial compression, beyond their buckling instability load. This has been recently confirmed in living cells transfected with microtubule-associated proteins tagged with green fluorescent protein [54] and by mechanical measurements [55, 56].
- Intermediate filaments are composed of different protein monomers (e.g., vimentin, desmin, cytokeratin) depending on the specific cell type.

These filaments are highly flexible and ball-up into a condensed net of filaments *in vitro* [57] much like a spider web that has been cut free from its firm attachments. In contrast, intermediate filaments in living cells appear in a highly extended, but crenulated form, stretching from the border of the nucleus to discrete cell-cell and cell-ECM adhesion sites at the cell periphery. Intermediate filaments also laterally interconnect with the other cytoskeletal filament systems and thereby, function like guy wires which stabilize these elements against lateral buckling and strengthen the entire interconnected network [56].

CYTOSKELETAL MECHANICS

The cytoplasm is commonly viewed as a viscous or viscoelastic fluid [17, 18] that locally alters its stiffness as a result of changes in cytoskeletal polymerization. In fact, all cytoskeletal filaments are dynamic structures: individual molecular subunits can be added to or removed from the surface of cytoskeletal filament bundles. However, the reality is that living cells always retain most of their cytoskeletal filaments in a polymerized form whether the cell is round or spread [58]. Furthermore, mechanical continuity can be maintained in the cytoskeleton even when the local monomer on/off rate is high. For example, actin filaments that form the outer surface of larger stress-fiber bundles exhibit a rate of polymerization and depolymerization on the order of minutes, however, because a central core of filament bundle always remains intact they continuously transmit tension between the integrins and the ECM below over a period of many hours.

Quantitative analysis of the mechanical properties of the cytoplasm and nucleus have confirmed that structural interplay in the cytoskeleton is complex and that the behaviors of these different filament systems are not simply additive [56]. Actin microfilaments form a volume filling gel that can bear compression, but can not effectively resist external tension and they tear at high tensile strains. The intermediate filament network is itself poor at resisting lateral compression, yet it efficiently resists tension and hardens at high strains. However, when these two filament systems are combined in living cells, a fiber-reinforced composite material is formed that can provide both load-bearing functions with greater efficiency, just as many biologic tissues with hierarchical structural arrangements [24]. For cells, however, full mechanical responsiveness and structural stability requires the added presence of microtubules to locally resist the inward contraction of the surrounding tensile cytoskeleton and thereby, to impose a pre-stress in this interconnected molecular network. Cytoplasmic microfilaments and intermediate filaments also appear to act as tensile guy wires that anchor the nucleus in place, coordinate changes in cell and nuclear form, and provide the nucleus with its own mechanical stiffness [15, 33, 34, 56]. Importantly, altering the 'tone' in this network (e.g., using chemical activators or inhibitors of actomyosin filament sliding) results in immediate changes in the mechanical stiffness of the whole cell [59, 60]. It is also important to note that fully triangulated geodesic structures, including well-developed 'actin geodomes', have been observed within the cytoskeleton of living cells [61].

Recent studies have confirmed that living cells and nuclei are literally 'hard-wired' such that a mechanical tug on cell surface receptors can immediately change the organization of molecular assemblies in the cytoplasm and nucleus. When integrins were pulled by micromanipulating micropipettes bound to cell surface integrins (and the focal adhesion), cytoskeletal filaments reoriented, nuclei distorted, and nucleoli redistributed along the axis of the applied tension field in time periods much faster than those required for polymerization. Thus, while the cytoskeleton is surrounded by lipid membranes and penetrated by viscous cytosol, it is the discrete filamentous cytoskeleton that provides the main path for mechanical signal transfer through the cytoplasm. The efficiency of force transfer depends directly on the mechanical properties of the cytoskeleton which, in turn, are governed by various interactions between microfilaments, intermediate filaments, and microtubules acting in the cytoplasm [56].

Basic design principles

This brief overview of the musculoskeletal system as a whole, and the organization of its individual components reveal several fundamental design concepts:

MAXIMIZE TENSILE MATERIALS

The human 'skeleton' in reality is a composite of tension and compression elements, with the tensile materials dominating the system for the purpose of minimizing mass. This engineering design feature is shared by living cells, as well as almost all other biological networks and it is independent of size scale [16, 24]. Disproportionate use of heavier compression elements would put greater demands

on metabolism for their production, load support and movement. It is known from material science, combined use of materials specialized to resist either tension or compression also leads to creation of composite materials with mechanical properties superior to either component alone.

IMPORTANCE OF ARCHITECTURE

Due to the use of discrete networks, the material properties of any single element become much less important than how the different elements are joined and positioned in three dimensions. The stability, mobility, and strength of any tensile network, is therefore critically dependent on the architectural arrangement of its parts.

STABILITY THROUGH PRESTRESS AND TRIANGULATION

The existence of pre-stress within biological networks serves to optimize the stability of multicomponent systems at all size scales, while minimizing mass at the critical joints. Pre-stress also allows tissues to generate immediate reactionary forces to unexpected external loads and thus, to minimize the looseness within the system [62]. In situations in which pre-stress is not dominant, joints and members are stabilized geometrically, such as through use of triangulation (e.g., trabecular struts of cancellous bone). In general, triangulation is utilized where the greatest stiffness is required whereas prestress is used when greater flexibility is desired.

STRUCTURAL HIERARCHY

In all biological systems, structural efficiency is maximized through the use of hierarchical structures which themselves have structure on a smaller scale [24]. Use of multiple smaller networks that independently self-stabilize is also likely favored by environmental selection since the function of the whole is not necessarily compromised by the loss of a single part. A simple example: cutting one's Achilles tendon results in loss of the motion of the foot and lower leg, however, the other leg, arms, and upper body remain fully functional.

DYNAMIC REMODELING

For survival, even biological structures that are dominated by stiff elements must exhibit enough flexibility to remodel their architecture in response to new loading patterns (spine). This dynamic plasticity allows living organisms to continually adjust their structure as loading conditions change and to take on the most structurally efficient geometries at all size scales.

Tensegrity architecture

All of the basic design principles listed above are embodied in one architectural system that is known as 'tensegrity' [63–66]. Tensegrity structures are defined as systems that gain their load support function and mechanical stability from continuous tension and local compression (tensional integrity). This building approach is in direct contrast to most man-made structures which depend on compressional continuity for their stability (e.g., brick-upon-brick type constructions).

The tensegrity structures are constructed by interconnecting a set of isolated compression struts with a continuous series of tension wires that pull the struts up against the force of gravity and stabilize them in an open array (Fig. 5 top). These simple structures are the most striking examples of tensegrity and clearly visualize its basic mechanism of self-stabilization. However, structures do not have to contain isolated struts and wires to be defined as tensegrity structures. Rather, it is how a structure distributes stresses to establish a force balance and stabilize itself against shape distortion that defines tensegrity. Good examples are fully triangulated structures, such as the tetrahedron or a geodesic dome. These fully geodesic structures are tensegrity structures even though they are commonly composed entirely from stiff strut because, although each strut is stiff, it resists *either* tension or compression at a particular location depending on the loading conditions (Fig. 5 bottom). Compressional continuity (direct contact between all compression elements) is never required for the stability of these structures, regardless of the loading conditions.

Comparing the geodesic dome and a tensegrity 'stick and string' sculpture reveals that the joints in a tensegrity system can be stabilized in one of two ways: by imposing a pre-stress or through triangulation. In fully geodesic structures, such as a triangle, tetrahedron or dome, the tension and compression elements are not colinear (Fig. 5). Rather, each strut entering a joint is oriented so as to geometrically constrain the movement of the joint such that the struts collectively prevent the joint from moving in any direction, and hence, stabilize its position in space. In the minimalist sculptures, however, the tension elements map out geodesic lines (i.e., shortest distance paths between two points along a curved surface) and the stiffness of the entire structure depends on the

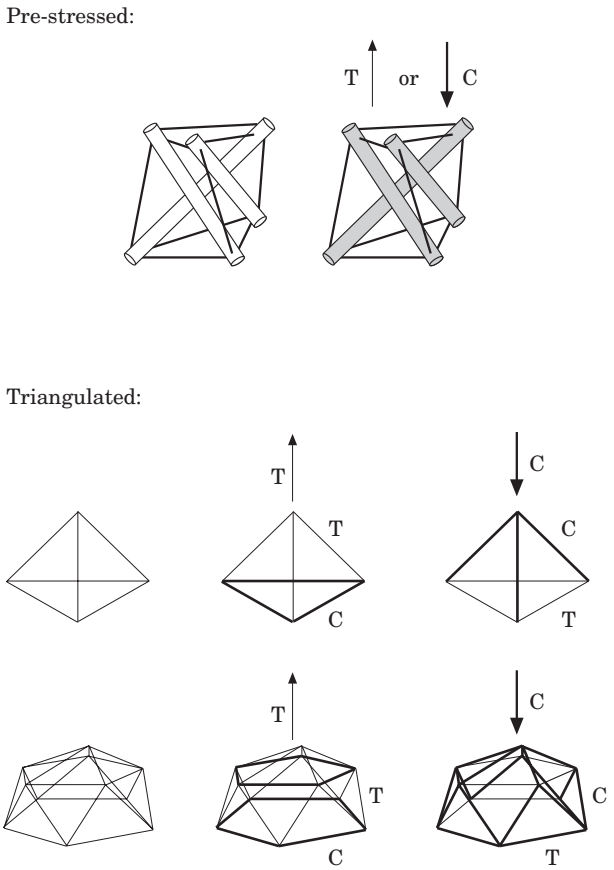

FIG. 5. Comparison of tensegrity structures that self-stabilize using either pre-stress (top) or triangulation of stiff elements (middle & bottom) to stabilize their joints. Structures are shown without and with application of external tension (up arrow) or compression (down arrow). Note that the same strut will bear either tension (T) or compression (C) depending on the direction of stress application, however, compressional continuity is never required for the stability of the structure.

level of pre-stress which is, in turn, determined by the placement of compression elements in this type of tensegrity system. As described above, increasing pre-stress results in decreased movement without resistance (i.e., decreased play), immediate mechanical responsiveness, proportional action at a distance. All of these features can be critical in biological systems and particularly in the musculoskeletal system (e.g., knee joint).

Tensegrity structures also optimize structural efficiency (strength to mass ratio) in a number of ways. First, they reduce the number of heavier compression elements by maximizing the use of tension materials and relying on continuous tension, rather than compression, for mechanical stability. This is particularly important as structures increase in size (e.g., this is how dinosaurs can be built using nearly the same musculoskeletal arrangement as man). Second, the use of networks composed of discrete elements, rather than a single continuum, permits design optimization (i.e., placement of materials where they are needed and removal from regions where they are not). In these networks, the same stress will be distributed to and resisted by many smaller elements, thereby optimizing the efficiency of the entire system. When structures are flexible, the individual support elements rotate and align in response to applied loads, rather than bending or fracturing locally. This is an effective means for long distance transfer of mechanical stresses (i.e., mechanical signal transfer) across the entire system. Another way in which structural efficiency can be increased is by building in a hierarchical manner [24]. Individual supporting members can themselves be tensegrity structures composed of discrete networks on a smaller size scale that are then interlinked and stabilized by continous tension. Finally, from a material engineering standpoint, the use of an architectural array with isolated tension and compression elements and built-in pre-stress affords the advantage of using specialized materials with properties optimized to most efficiently bear only tensile or compressive forces. Thus, tensegrity architecture incorporates many of the critical features that Nature has elected to use in the construction of living materials.

TENSEGRITY: IS IT NOVEL?

Like biological materials, tensegrity structures can resist tensile and compressive stresses that are equipollent to bending stresses using only tension and compression elements. Pre-stressed tensegrity systems also can be created that are highly flexible even when a subset of elements are relatively stiff. How can this work and is it really novel?

First, it is important to emphasize that all pre-stressed materials are not the same. For example, concrete can be pre-stressed by hardening the material around reinforcing steel rods that are held under tension. This tensile pre-stress compresses the surrounding concrete, and helps to stabilize the system by reducing play and by preventing the concrete (which is strong in compression but weak in tension) from experiencing tension, or by decreasing the magnitude of tensile stress that the concrete might experience. Although the rods are pre-stressed in tension and the concrete is under compression, this beam is not a tensegrity structure, however, because it lacks, by definition, triangulation: the tension and compression elements are colinear (Fig. 6).

Due to the use of triangulation and pre-stress, tensegrity structures display novel mechanical

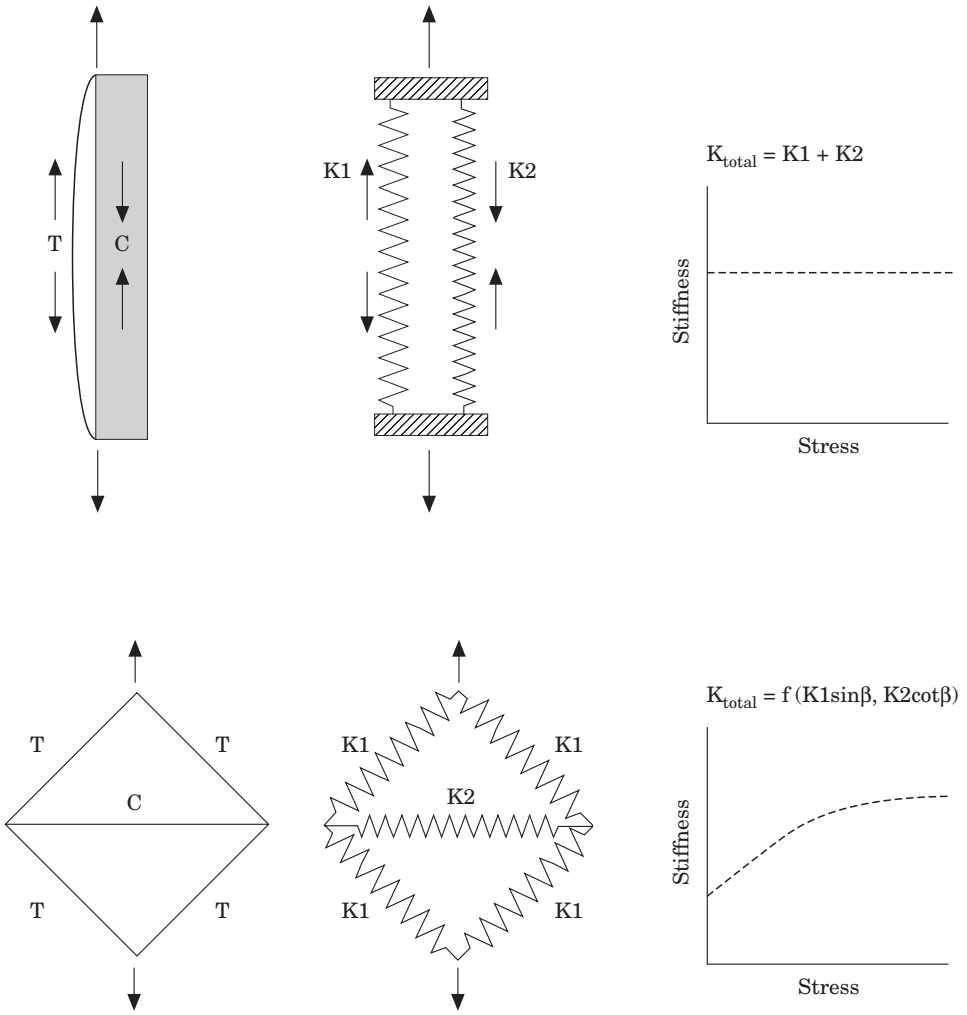

FIG. 6. Analysis of stiffness in a pre-stressed system of elements oriented in parallel (top) or placed in a triangulated geometry (bottom). A prediction of the qualitative behavior of the stiffness of the overall system with respect to its increased stress using springs to represent compression (C) and tension (T) elements is shown at the right.

behavior that is not exhibited by most man-made materials. For example, increasing the stress applied to reinforced concrete has no effect on the mechanical stiffness of the material since this configuration may essentially be represented as two springs with different constants oriented in parallel (Fig. 6). In contrast, increasing the stress applied to a two dimensional network of springs oriented to create a fully triangulated tensegrity array (i.e., which exhibits continuous tension and local compression when stressed) results in an increase in the stiffness of the entire network (Fig. 6). Interestingly, we have shown that both living cells and pre-stressed 3D tensegrity structures increase their mechanical stiffness in direct proportion as the level applied stress is raised over a wide range [48] and that this monotonic stiffening response may be mediated by global structural rearrangements throughout the network (Fig. 7). These types of flexible tensegrity structures also can predict many complex behaviors exhibited by living cells, including how cell shape varies when ECM mechanics is altered; how cell and nuclear form are coordinated when cells spread and move; how actin geodesics develop through stress-dependent restructuring of the continuous actomyosin filament lattice; as well as how chromosome movements are coordinated during mitosis [33, 34, 56, 65, 66].

Importantly, the monotonic stiffening response exhibited by living cells is also known to be a fundamental property of many living tissues, including muscle, cartilage, meniscus, ligaments and tendons. This effect is a direct manifestation of the fiber-reinforced composite structure of biologic tissues, and results from a fiber recruitment phenomenon as the material is stretched [1, 2, 24, 67, 68]. Over the past several decades, many investigators have used either a polynomial or an exponential stress-strain law to describe this stiffening

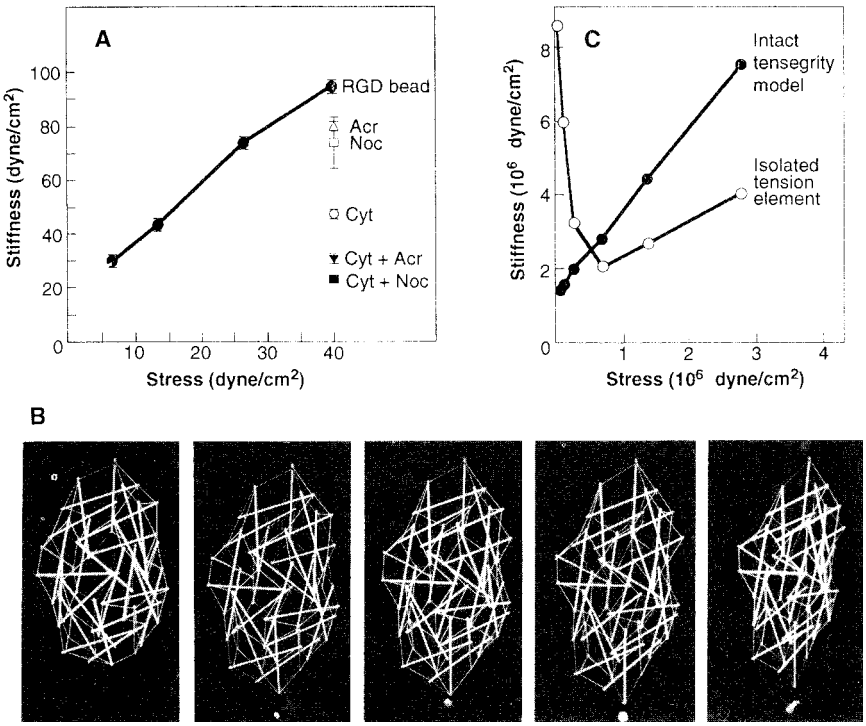

FIG. 7. Mechanical analysis of living cells and a 3D tensegrity model reveals that both exhibit monotonic stiffening behavior over a wide range of applied stress. (**A**) Stiffness of the cytoskeleton of living cells was defined as the ratio of stress to strain (in radians) at 1 min twisting using cell magnetometry (see ref. 48 for details). Noc, nocodazole (10 μg/ml); Acr, acrylamide (4 mM); Cyt, cytochalasin D (0.1 μg/ml). (**B**) A tensegrity cell model under different mechanical loads. This model consisted of a geodesic spherical array of wood dowels (0.3 × 15 cm) and thin elastic threads (0.06 × 6 cm). The model was suspended from above and loaded, from left to right, with 0, 20, 50, 100, or 200 g weights on a single strut at its lower end demonstrating that a local stress results in global structural rearrangements throughout the entire structure. (**C**) Stiffness of the stick and string tensegrity model was defined as the ratio of applied stress to strain (linear deformation of the entire structure). Similar measurements were carried out using an isolated tension element, that is, a single thin elastic thread of similar size to that found in the model. (Reproduced with permission from Wang *et al.*, 1993, ref. 48).

effect. Recently, we demonstrated that this particular linear stiffening behavior can be alternatively explained using a tensegrity-based approach [69, 70]. These studies revealed that pre-stress and architecture are the key features that the determine the structure's ability to regulate its shape. The pre-stress defines the initial stiffness of the system whereas the architecture determines how the structural stiffness changes during deformation.

Discussion

TENSEGRITY AND MECHANOCHEMICAL TRANSDUCTION

Our reason for adopting a micro-structural model of living organisms is to help us understand how living cells and tissues sense and respond to mechanical stresses. Through use of our tensegrity hierarchy model for living organisms, one can easily see how such structures respond to mechanical stresses applied at the macroscale by producing structural rearrangements at all size scales: micro as well as macro. The demonstration of discrete mechanical linkages between cells and their ECM via integrins also suggests how mechanical signals resulting from ECM deformation may be transferred across cell surface integrin receptors to distinct structures in the cell and nucleus, including ion channels, nuclear pores, nucleoli, chromosomes, and perhaps even individual genes, independently of ongoing chemical signaling mechanisms [14, 15, 33, 34]. In fact, recent studies have demonstrated that signal transduction pathways can be activated within milliseconds after cell surface integrins and associated cytoskeletal connections are mechanically stressed, but not when unanchored cell surface transmembrane receptors are similarly perturbed on the same cells [70]. This type of physical coupling between intracellular structures, cell surface receptors, and the ECM could serve to coordinate, complement, and constrain slower diffusion-based chemical signaling pathways and thus, explain

how mechanical distortion of ECM caused by gravity or other mechanical stresses can change cell shape, alter nuclear functions, and switch cells between different genetic programs [14, 75].

The question remains: how could these tensegrity-based structural rearrangements be transduced into a biochemical response? Several potential mechanisms can be envisioned. For example, recent work suggests that much of the cell's metabolic and signal transduction machinery effectively functions in a 'solid-state' [65]. The enzymes and substrates that mediate these pathways are physically immobilized on the insoluble molecular scaffolds that comprise the cytoskeleton and nuclear matrix (nucleoskeleton). In fact, many signal transducing molecules that are activated by cell binding to growth factors and ECM actually appear to be concentrated at the site of integrin binding, on the cytoskeletal backbone of the focal adhesion [72, 73]. Thus, mechanical signals may be integrated with other environmental signals and transduced into a biochemical response through stress-dependent changes in cytoskeletal scaffold geometry or mechanical deformation [15]. One potential mechanism, for example, for mechanochemical transduction is through stress-dependent cytoskeletal rearrangements that result in changes in proximity between different immobilized enzymes and substrates. If a protein kinase and its physiological substrate were both immobilized on the cytoskeleton and physically separated, then no phosphorylation would result. However, if mechanical deformation of the tissue, ECM, cytoskeletal composite resulted in structural rearrangements that brought these two molecules into direct apposition then phosphorylation might proceed causing a downstream signaling cascade to initiate.

Although this type of transduction may occur, the answer may be much more simple. For example, molecules that are incorporated within the insoluble scaffolds that bear mechanical loads will feel a pull exerted on the ECM whereas neighboring soluble molecules in the cytosol will not, unless viscous shear stress in the cytosol is large. If these molecular filaments physically deform (extend or compress) when the cell is distorted without breaking or depolymerizing, then at least a subset of the molecules that compose this filament must also deform. In other words, the transfer of focused mechanical energy to these molecules will alter their shape and hence, their electrochemical potential through mechanical distortion. Stress-induced changes in molecular mechanics (stiffness and conformation) can then produce direct mechanochemical transduction by altering thermodynamic (association and dissociation constants) or kinetic (molecular motion) parameters. Regulation of tubulin polymerization (microtubule formation) by mechanical stresses balanced between microtubules, contractile microfilaments, and ECM provides one example of a thermodynamic transduction mechanism [74]. Stress-dependent changes in the frequency of opening and closing 'stretch-sensitive' ion channels is an excellent example of the kinetic form of transduction [75].

One of the most important features of the use of the tensegrity paradigm is that it permits analysis of mechanotransduction within the structural complexity of living cells. Most work in this area commonly focuses on the effects of force on one particular transducing molecule or another. In reality, living cells sense multiple simultaneous inputs and yet are able to organize a single, concerted response. The tensegrity structure may be used to focus mechanical energy on critical transducing molecules and to 'tune' the entire cellular response to stress by mechanically coupling biologic structures at different size scales and in different locations within living cells, tissues, and organs. This tuning function may be accomplished by altering the pre-stress in the system (e.g., by varying cytoskeletal tension), remodeling architecture, or modifying the mechanics of individual structural components. Specificity results from local changes in material properties of the structural elements (e.g., stress will rapidly dissipate in highly viscous regions), and from how the different discrete elements are mechanically coupled (e.g., linkage of the cytoskeleton to the ECM by integrins and to the cytoskeleton of neighboring cells by cell–cell adhesion molecules, such as Cadherins). This architectural model of biologic organisms may help to explain one of the most fundamental properties of living creatures: how the parts and the whole function as a single integrated system.

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