[Frontiers in Bioscience 4649-4656, May 1, 2008]

Cytoskeletal thermal ratchets and cytoskeletal tensegrity: determinants of brain asymmetry and symmetry?

John Gardiner, Jan Marc, Robyn Overall

The School of Biological Sciences, The University of Sydney, Camperdown 2006, Australia

TABLE OF CONTENTS

1. ABSTRACT

Evolution can be viewed as a dynamic process that leads to increased complexity. This process appears to be driven by the interplay between a breaking of symmetry in biological organisms that leads to increased differentiation and complexity on one hand, and the intrinsic tendency of physical systems to maintain symmetry on the other. Thus thermal ratchets act to break symmetry, suggesting they may have played an important role is the evolution of complexity, while physical systems, including biological ones, have a tendency to maintain symmetry. We propose that, in the brain, development is driven by a combination of asymmetry-creating properties of cytoskeletal thermal ratchets and by the symmetry-maintaining properties of cytoskeletal tensegrity architecture.

2. INTRODUCTION

Traditional Darwinian evolution has struggled to explain the apparent increase in complexity of biological organisms that has occurred over geological time. Lamarck saw evolution as a process of increasing complexity and "perfection". Thermal ratchets act to do work using only the energy present in Brownian motion. A variety of proteins have been shown to act as thermal ratchets, including the cytoskeletal elements microtubules and actin filaments. The presence of thermal ratchets in living organisms allows the development of complex processes and organisation not driven purely by chance or natural selection.

The evolution of complexity has been traditionally seen as largely due to co-evolution of different

organisms. However, at least during the very early stages of evolution when living organisms "progressed" from non-biological beginnings, this factor would not have been in play. Indeed, thermal ratchets can only operate if there is a loss of symmetry, such as that seen with cytoskeletal elements, and the attachment of motor proteins and substantially long-time correlations, such as that seen with the finding of molecules under biochemical conditions (1). The action of these thermal ratchets will then further reduce a system's symmetry and thus provide a feedback loop engendering further biological complexity.

There is experimental evidence that the polymerization of cytoskeletal elements, a process that requires a thermal ratchet mechanism, results in decreased symmetry. When a bead is coated with molecules that promote actin polymerization, initially it is surrounded by a symmetrical cloud of actin filaments. This symmetry is then broken spontaneously, after which the bead undergoes directional motion (2). Such behavior is only possible in molecules that have a significant "off-rate", such as actin and microtubules (3). If the off-rate is small, symmetry-breaking cannot occur because the filaments are constantly growing and thus maintain symmetry about the bead, causing the bead to undergo a random walk with step-size smaller than the size of the actin subunit. If the off-rate is too high, the filaments will depolymerise and the bead will undergo a random walk dependent on the diffusion coefficient of the bead. Interestingly, polymerizing microtubules can activate F-actin assembly in neuronal growth cones (4), suggesting that the asymmetry introduced into the system by the polymerizing microtubules is sufficient to cause actin polymerization.

Alexander (5) suggested a way in which such a loss of symmetry can lead to ordered structures. His suggestion is that if a system loses one level of symmetry, it will act to try to conserve remaining levels of symmetry. This can lead to differentiation that conserves as much of the previous symmetry as possible. Thus thermal ratchets, which act to decrease the symmetry of biological systems, will also act to create differentiation. This again suggests that such Brownian ratchets may have played a key role in the generation of biological diversity both through doing work without energy inputs and through the disruption of Brownian symmetries.

3. THERMAL RATCHETS AND BRAIN ASYMMETRY

3.1. Microtubules, actin and asymmetry

Microtubules are also required for the specification of asymmetry in various systems. Zebrafish blastomeres require substances transported along microtubules from the vegetal hemisphere into the yolk cell for correct axis formation, and the initial asymmetry is dependent on an array of parallel microtubules (6). RNA encoding Vg1 (vegetal 1) protein, which is required for the initiation of the left-right axis (7), is localized by its association with microtubules in Xenopus oocytes (8), again showing a key role for microtubules in the development of asymmetry.

However, it appears that actin plays a more fundamental role in the determination of asymmetry in early development. There is an unambiguous chiral polarization in maternally-derived actin in Xenopus laevis embryos and disruption of this chirality with anti-actin drugs leads to randomization of left-right orientation of tadpole heart and gut (9). A role for actin is also seen in the development of left-right body handedness in gastropods, with actin-depolymerization neutralizing handedness (10). Myosins also appear to be important in actin-dependent asymmetry since handedness of the gut and testes is reversed in a Drosophila myosin mutant (11).

The breaking of symmetry by actin and myosin at the rear of keratocytes prior to cell movement also suggests that the actin thermal ratchet plays a key role in this cellular process (12). What occurs may be similar to the movement of a bead by actin polymerization driven by thermal-ratchet (2).

3.2. Breaking of symmetry accompanies increased complexity in evolution

The breaking of symmetry necessarily accompanies increased complexity in biological systems. This process may be driven by thermal ratchets. Symmetry-breaking and the evolution of development has been reviewed by Palmer (13). Asymmetry has apparently arisen as often through non-genetic factors as through mutation, supporting our theory that thermal ratchets may underlie the process. In addition there have been declining instances of asymmetry-reversal over geological time, suggesting that increased complexity canalizes evolution. This again agrees with a model whereby organisms over time show reduction in symmetry and an increase in complexity driven by thermal ratchets.

3.3. Actin in neuronal growth

Both actin filaments and microtubules are required for correct axon and dendrite growth in neurons. Similarly, addition of a microtubule-depolymerising drug slightly affects dendritic growth and completely abolishes axonal growth. Addition of an actin-depolymerising drug causes a curly morphology in axons. This suggests that actin acts to antagonise the asymmetry introduced into axon growth by polymerising microtubules (14). The direction of turning of the growth cone in developing neurons also depends on both microtubules and actin. Selective stabilisation of microtubules causes the growth cone to turn towards the stabilised microtubules (15) while microtubule destabilisation causes a turning away. This again suggests that the asymmetry introduced into neuronal growth by polymerising or depolymerising cytoskeletal elements is crucial for the development of neuronal topology.

Interestingly actin also undergoes some strain-stiffening since this seems to be a property of filamentous proteins arranged in an open cross linked mesh (16). Actin filaments also undergo buckling, again suggesting that they may play a role in counteracting compression forces in a cell (17). The force generated by polymerising actin filaments has been found to be 0.4-1.6 pN for a moderate length of actin filament (~10μm), rising up to 10 pN for

much shorter actin filaments (17). This is of the same order as the force needed to extract a membrane tether from growth cones which is about 8 pN (18). Therefore the force generated by actin polymerisation may, in itself, be sufficient to promote growth cone-extension.

It appears that actin may have two distinct roles in neuronal growth. Actin forms two structures at the growing tip of the growth cone ŕ€ filopodia and lamellipodia, which have different functions. Filopodia contain actin filaments with their growing tips oriented towards the cell surface (19), while lamellipodia have an actin meshwork (20) that plays a role in regulating tension necessary for growth cone movement (21). Interestingly, in Aplysia growth cone, actin polymerises at the leading edge and depolymerises in peripheral regions, enabling these subunits to add onto the growing ends of actin filaments (22). This may also be necessary to keep the length of actin filaments involved in growth cone extension relatively short, so that they can exert sufficient force to overcome membrane tension.

3.4. Limiting thermal ratchet-dependent growth

Since both microtubules and actin will polymerise under conditions of tension, the question arises how does a cell stop this polymerization from getting out of hand? It appears that for microtubules in axons and dendrites this is done by controlling the amount of tubulin available for polymerization. The protein superior cervical ganglia, neural specific 10 protein (SCG10) sequesters tubulin subunits, thus reducing the amount of free tubulin available for polymerization in growing neurons. In turn C-Jun N-terminal kinase (JNK) phosphorylates SCG10, thus reducing its tubulin sequestering potential in developing neurons (23). This control of tubulin subunit availability appears to be sufficient to regulate the growth of axons and dendrites (23). Therefore the concentration of tubulin subunits in a growing neuron has to be precisely controlled for correct growth.

Indeed, model neurons sharing the same channel densities and anatomical size can derive functional differentiation from their dendritic topology (24) which is dependent on the cytoskeleton. The differential growth of neurites in a single cell can be modeled as the outcome of competition between the neurites for tubulin subunits (25). This competition explains how cessation of growth in one neurite can promote growth in other neurites, resulting in dormant growth cones (25). The concentration of tubulin subunits in a particular neurite is therefore a major determinant of that neurite's growth. It follows that the microtubule thermal ratchet, which depends upon the local concentration of tubulin subunits, may thus be a major determinant of neuronal topology and hence brain development and function.

Another important property of microtubules is their tendency to undergo catastrophic depolymerisation. This may in fact be necessary to restrain microtubule growth by thermal ratchet mechanisms. If there is a large amount of free tubulin, for example in SCG10-deficient neurons, this promotes microtubule growth but also promotes microtubule catastrophe (26). Indeed mechanical forces, such as tension, in the microtubule cytoskeleton act to destabilize microtubules at low tubulin concentrations (27), possibly providing a necessary brake on thermal-ratchet microtubule-dependent growth of neurons.

Actin thermal ratchet activity appears to be suppressed by the cross-linking of actin filaments by various proteins. Artemin, a member of the glial cell line-derived neurotrophic factor family that supports sensory neuron survival, down regulates a number of genes involved in the regulation of actin dynamics and causes an increase in neurite length and branching (28). In addition, actin is more easily extracted by detergent from the growth cone of the axon than from the growth cones of other neurites, indicating that here, where maximal growth is required, the actin thermal ratchet is relatively unencumbered by interaction with other proteins (29). Presumably, when a neuron undergoes growth, the actin cytoskeleton is in effect deregulated, thus allowing the thermal ratchet properties of the molecule to take over and hence promote elongation of actin filaments and growth. This model is supported by a study using knockout of the actin cross-linking protein Neurabinl, which caused dendritic spine outgrowth (30). Cross linking of actin fibres would be expected to limit the ability of individual actin filaments to polymerise in response to tension. Removing this cross linking would allow individual actin fibres to respond to tensional forces, thus increasing the effectiveness of their thermal ratchet properties in increasing growth. Indeed, in Drosophila bristle cells, non-crosslinked actin turns over more quickly while crosslinked actin turns over more slowly but persists (31).

4. TENSEGRITY AND BRAIN SYMMETRY

4.1. The role of tensegrity in coupling small-scale asymmetry in the cytoskeleton to cellular symmetry

Symmetry-breaking requires that the cytoskeletal elements in question are held together by weak non-covalent bonds so that there is a significant off-rate of subunits (2). Efficient symmetry-breaking also requires that there is significant tensional load on the cytoskeletal elements. The fact that actin polymerization is sensitive to mechanical force enables small-scale biochemical interactions to generate large-scale cellular reorganisation (2). The same probably applies to tubulin and microtubules since they are also a thermal ratchet.

Tensional integrity, or tensegrity, is a model that has been able to explain complex mechanical behaviours in viruses, nuclei, cells, tissues and organs in animals, insects, and plants (32). This model states that biological structures gain their shape stability and ability to exhibit integrated mechanical behaviour through use of the structural principles of tensegrity architecture (32). In the simplest terms, tensegral structures maintain shape stability within a tensed network of structural members by incorporating other support elements that resist compression (32). One of the major predictions of the tensegrity model is that long-distance force transfer should be observed in a tensegral structure. The model also predicts that pre-stress of the

structural components is a critical determinant of the stability of the structure's shape. Tensegral structures tend to be symmetrical, indeed this property can be used to discover new tensegral structures for a given connectivity (33).

It has been suggested that the cytoskeleton may form a tensegral structure that regulates the response of the cell to mechanical forces (34). In this model cytoskeletal elements act with nuclei, extracellular matrix (ECM) components, membranes, cell-ECM adhesions, cell-cell adhesions and surface processes to transmit mechanical signals across cells or tissues (34). For example, mutations in actin-binding protein myosin VIIa, harmonin, cadherin 23, protocadherin 15, and scaffolding protein sterile α motif (SAM) underlie Usher syndrome I (USH1), the most frequent cause of hereditary deafness-blindness in humans (35). This is probably due to a defect in the hair-bundle of the mechanosensitive structure that is receptive to sound stimulation, suggesting that hair-bundle-mediated adhesion forces may be required to transmit sound (35). Thus tensegrity provides an interesting theoretical framework in which to interpret cell biological processes. A number of organs in the animal body have been postulated to represent tensegral constructs. These include the respiratory system of birds (36), the human spine, limbs, and visceral system (37), and embryos (38). Here we propose that the brain also represents a form of tensegral construction.

4.2. The brain as a tensegral structure

The brain is an unusual organ in that it is made up mostly of neurons and associated cells. Neurons are connected to one another via axons and synapses, creating an interconnected whole. It has been suggested that tension-based morphogenesis might underlie the compactness of neural circuitry in the adult brain (39). This envisages that during cerebral growth interconnected regions should pull together while weakly connected regions drift apart. While this model has merit, it envisages tension acting through viscoelasticity plus active growth and retraction. This is at variance with a tensegrity model of the brain in that it does not provide a key role for compression-resistant elements which enable mechanical forces to be transduced across tissues without the need for active growth and retraction.

The brain undergoes pulsatile movements (40). If the simple viscoelasticity model were fully correct, it would be expected that the brain would show uniform motion across its tissue. In fact the basal ganglia and the brain stem move in opposite directions (40). In addition the entire brain does not move simultaneously since a second, slower, movement takes place after the initial movement. The movement of tensegrity “modules” or joints in opposite directions is typical of a tensegral system, unlike what is seen in elastic structures (41). Also suggesting that the brain is a tensegral structure is the “dimpling” observed when electrodes are inserted into brain tissue (43). This “dimpling” typically occurs when a concentrated load is applied (towards the centre) of any vertex of any triangulated system (43). Indeed the brain is often modeled as a tetrahedral mesh (44). This is appropriate for a tensegral structure, but not a viscoelastic one.

4.3. Action at a distance

One of the predictions of the tensegrity model of the brain is that there will be reorganisation of brain tissue at a distance from any perturbation in another region. In fact the theory that damage to one part of the nervous system can have effects at a distance was popular during the 19th century (45). Following brain injury to rats, astrocytes proliferate not only at the site of injury but also at a distance from the wound (46). Moreover, damage to one hemisphere of the brain can also depress metabolism in the other hemisphere (47), and ischemic cortical lesion can lead to changes in neurons in uninjured distant areas of the brain (48). While it is possible that these changes may be due to other forms of intercellular communication, it is plausible that they may be due to changes in the overall structure of the brain and forces experienced by individual neurons as a result of altered mechanotransduction across tissue.

4.4. Integration of mechanotransduction with cell biology

If the brain truly works on the principles of tensegrity, then we would expect that the cell biology of its function would reflect this, and even use this property to actively modulate brain function. There is some evidence that this may indeed take place. Axons are made up of three types of cytoskeletal elements: intermediate filaments (neurofilaments), actin, and microtubules. In the traditional cell biological tensegrity model, actin provides the tension while microtubules provide the compression element (32). It appears likely that actin does play a major role in the maintenance of tension throughout neural tissue. For this to occur there must be a continuous physical connection between actin filaments across synapses. Here the actin filaments connect with the synapse plasma membrane, which is then linked to the opposing synapse with adhesion molecules.

One of the main compression elements in neurons appears likely to be the intermediate filaments (neurofilaments). The intermediate filament peripherin is a critical determinant of the overall shape of neurons (49), and heavy neurofilament subunits are required in axons with large calibres (50). In addition, neurofilaments undergo strain-stiffening which indicates a role in bearing compression loads (16). Thus intermediate filaments may bear a considerable part of the compression load in an axon. It appears that spectrin is the main protein linker between the compression and tension elements in the axon since spectrin binds both actin and neurofilaments (51). A recent study shows what happens to neurons when the tension element (actin) is not connected to the compression element (intermediate filaments). In *Caenorhabditis elegans* lacking beta-spectrin, axons spontaneously break from acute strain generated by movement (52).

Interestingly, it appears that the brain may actually target this link between compression and tension elements in axons to cause apoptosis in certain cells. This

may play a role during brain development and learning, where connections that come under great strain may be broken. This may then cause the cell with the broken axon to undergo apoptosis. This form of apoptosis is known as Wallerian degeneration (53). N-methyl-D-aspartate (NMDA) receptor channels are modulated by membrane stretch (54), and in turn activate calpain protease that cleaves spectrin (55). This mechanism may be used to "prune" unwanted axons and neurons. In this model, stretch caused by brain movements activates NMDA receptors, which then cause protease degradation of spectrin and thus leads to axon breakage and apoptosis. On the other hand, percussion injury of the brain causes breakdown of spectrin at a distance from the injury (56). Here it may be a case of a mechanism that normally operates to prune individual axons and neurons that become pathogenic when large parts of the brain experience high mechanical stress.

Microtubules also play a major role as compression-resistant elements in cells. They act to decrease cellular elasticity (57), which has the effect of reducing tension on actin filaments and thus reducing actin polymerisation via the thermal ratchet mechanism.

4.5. Tensegrity in disease

Another study also indicates that distribution of mechanical force through the brain may play a fundamental role in its function (58). This study examined the expression of genes involved in cell death and survival following mechanical stretching of organotypic brain slice cultures. The authors found that a subset of these genes was differentially regulated by mechanical stretching and that the expression of these genes was correlated with the mechanical parameters of the stretch. This again suggests that mechanical forces are crucial in regulating brain function.

Among the genes investigated was the Alzheimers' gene amyloid precursor protein 695 (APP695) (58). Expression of this gene was negatively correlated with strain rate, indicating that mechanical tension and compression may play a role in neurological disease. Here a lack of tension in the parts of the brain affected by Alzheimer's disease could lead to upregulation of APP751 (the disease-causing variant protein) and hence increased amyloid deposits and disease. This study also found that neurotrophic factors increased in response to mechanical stretching. Indeed brain-derived neurotrophic factor (BDNF) plays a role in mechanosensation (59), suggesting the presence of a positive feedback loop between mechanosensation and neurotrophic support. Neurotrophic factors regulate survival of neurons and have been implicated in many neurological diseases. Therefore the upregulation of neurotrophic factors by mechanical stretch, or down regulation by a lack of tension, may also play a role in various neurological disorders.

4.6. Tensegrity and consciousness

While the study of artificial intelligence is still in its infancy, the research of Mark Tilden is of particular interest. He has designed robots that are autonomous by mimicking designs seen in nature. Apparently, triangular and hexagonal circuits using a 60 degree angle allowed the development of emergent behaviours, in contrast to circuits built using "Manhattan logic" with 90 degree angles. Calvin makes an interesting proposal as to how this may work in the brain (60,61,62). In this model memories are evoked by cortical neurons, each neuron helping to implement other memories as well.

Given standard excitatory axon length, recurrent excitation between some cell pairs produces entrained firing patterns (60). Indeed cells in cortical minicolumns often reacted to the same kind of stimuli and fire in synchrony. If an entrained pair tends to recruit additional cells that are equidistant, the most efficient anatomy would be six equally-spaced axon branches from the same cell (60), or a triangular mosaic. Because simultaneous arrivals at the outlying neuron are important rather than equal length, the axonal length can vary so long as conduction velocity or synaptic delay can be varied. Interestingly, these triangular mosaics of entrained points will give rise to a hexagonal mosaic of spatiotemporal patterns.

Incredibly, in the dorsocaudal region of medial entorhinal cortex cells, spatial firing fields show a hexagonal grid pattern (63,64), and this pattern also occurs spontaneously in a two-dimensional spin glass model (65). This provides direct confirmation of Calvin's model and supports the idea that neurons are arranged, at least in this part of the brain, in triangular fashion. This also agrees with our tensegrity model that predicts the underlying shape of neuronal connections in the brain to be triangular. Indeed if rubber bands are strung in a triangular-shaped frame from equally spaced points with three-way crossings, they will form a hexagonal tessellation (Fuller 1975). This might be the way in which neurons are organised in the cortex, with cell bodies at the crossings and six axons radiating from each in a plane. Here the axons are the elastic (tensional) elements while the supporting triangular frame is the compression-resistant element. Other tensegral arrangements can also give rise to hexagonal shapes, for example, joining three-strut tensegral octahedron can form a geodesic sphere with hexagons separated by equilateral triangles (43).

Thus the structure and function of the brain can be seen as a dynamic interplay between the asymmetry introduced by the thermal ratchets of the cytoskeleton and the symmetry-seeking properties of tensegrity.

4. BRAIN SYMMETRY AND ASYMMETRY AND HIGHER COGNITIVE FUNCTIONS

It has been suggested that brain asymmetry may be necessary for some higher cognitive functions. For example, musicians with perfect pitch show stronger leftward asymmetry in the planum temporale than those without perfect pitch (66). However, brain symmetry and bilateral representation appears to increase language skills (67). Thus both symmetry and asymmetry may play a role in higher cognitive functions.

5. PERSPECTIVE

The dynamic interplay between symmetry-breaking by thermal ratchets and the inherent tendency of physical systems to maintain symmetry is seen in the coupling of symmetry-breaking by cytoskeletal elements to the cellular tensegral framework. This might help to explain the function of the brain, which also appears to be a tensegral structure with properties reflecting the properties of the constituent cytoskeletal elements.

6. ACKNOWLEDGEMENTS

JG is the recipient of an Australian Research Council postdoctoral fellowship. Work in RO's and JM's laboratories is funded by the Australian Research Council.

7. REFERENCES

1. MO Magnasco: Forced thermal ratchets. *Phys Rev Lett* 71, 1477-1481 (1993)
2. A Van Oudenaarden, JA Theriot: Cooperative symmetry-breaking by actin polymerization in a model for cell motility. *Nat Cell Biol* 1, 493-49 (1999)
3. ME Janson, M Dogterom: Scaling on microtubule force-velocity curve obtained at different tubulin concentrations. *Phys Rev Lett* 92 (2004)
4. MW Rochlin, ME Dailey, PC Bridgman: Polymerizing microtubules activate site-directed F-actin assembly in nerve growth cones. *Mol Biol Cell* 10, 2309-2327 (1999)
5. C Alexander: The Nature of Order. Book Two, The Process of Creating Life. *The Centre for Environmental Structure*. Berkeley, California, (2001)
6. S Jesuthasan, U Stahle: Dynamic microtubules and specification of the zebrafish embryonic axis. *Curr Biol* 7, 31-42 (1997)
7. BA Hyatt, JL Lohr, HJ Yost: Initiation of vertebrate left-right axis formation by maternal Vg1. *Nature* 384, 62-65 (1996)
8. Z Elisha, L Havin, I Ringel, JK Yisraeli: Vg1 RNA binding protein mediates the association of Vg1 RNA with microtubules in Xenopus oocytes. *EMBO J* 14, 5109-5114 (1995)
9. MV Danilchik, EE Brown, K Riegert: Intrinsic chiral properties of the Xenopus egg cortex: an early indicator of left-right asymmetry? *Development* 133, 4517-4526 (2006)
10. Y Shibazaki, M Shimizu, R Kuroda: Body handedness is directed by genetically determined cytoskeletal dynamics in the early embryo. *Curr Biol* 14, 1462-1467 (2004)
11. S Hozumi, R Maeda, K Taniguchi, M Kanai, S Shirakabe, T Sasamura, P Speder, S Noselli, T Aigaki, R Murakami, K Matsuno: An unconventional myosin in Drosophila reverses the default handedness in visceral organs. *Nature* 440, 798-802 (2006)
12. PT Yam, CA Wilson, L Ji, B Hebert, EL Barnhart, NA Dye, PW Wiseman, G Danuser, JA Theriot: Actin-myosin network reorganization breaks symmetry at the cell rear to spontaneously initiate polarized cell motility. *J Cell Biol* 178, 1207-1221 (2007)
13. AR Palmer: Symmetry breaking and the evolution of development. *Science* 306, 828-833 (2004)
14. F Lafont, M Rouget, A Rousselet, C Valenza, A Prochiantz: Specific responses of axons and dendrites to cytoskeleton perturbations: an in vitro study. *J Cell Sci* 104, 433-443 (1993)
15. KB Buck, JQ Zheng: Growth cone turning induced by direct local modification of microtubule dynamics. *J Neurosci* 22, 9358-9367 (2002)
16. C Storm, JJ Pastore, FC MacKintosh, TC Lubensky, PA Janmey: Nonlinear elasticity in biological gels. *Nature* 435, 191-194 (2005)
17. J Berro, A Michelot, L Blanchoin , DR Kovar, JL Martiel: Attachment conditions control actin filament buckling and the production of forces. *Biophys J* 92, 2546-2558 (2007)
18. RM Hochmuth, J-Y Shao, J Du, MP Sheetz: Deformation and flow of membranes into tethers extracted from neuronal growth cones. *Biophys J* 70, 358-369 (1996)
19. PC Bridgman, ME Dailey ME: The organization of myosin and actin in rapid frozen nerve growth cones. *J Cell Biol* 108, 95-109 (1989)
20. PC Letourneau: Differences in the organization of actin in the growth cones compared with the neuritis of cultured neurons from chick embryos. *J Cell Biol* 97, 963-973 (1983)
21. JS Da Silva, CG Dotti: Breaking the neuronal sphere: regulation of the actin cytoskeleton in neuritogenesis. *Nat Rev Neurosci* 3, 694-704 (2002)
22. P Forscher, SJ Smith: Actions of cytochalasins on the organization of actin filaments and microtubules in a neuronal growth cone. *J Cell Biol* 107, 1505-1516 (1988)
23. T Tararuk, N Ostman, W Li, B Bjorkblom, A Padzik, J Zdrojewska, V Hongisto, T Herdegen, W Konopka, MJ Courtney, ET Coffey: JNK phosphorylation of SCG10 determines microtubule dynamics and axodendritic length. *J Cell Biol* 173, 265-277 (2006)
24. J Duijnhouwer, MWH Remme, A van Ooyen, J van Pelt: Influence of dendritic topology on firing patterns in model neurons. *Neurocomputing* 38-40, 183-189 (2001)
25. A van Ooyen, BP Graham, GJA Ramakers: Competition for tubulin between growing neurites during development. *Neurocomputing* 38-40, 73-78 (2001)
26. H Morii, Y Shirashi-Yamaguchi, N Mori: SCG10, a microtubule destabilizing factor, stimulates neurite outgrowth by modulating microtubule dynamics in rat hippocampal primary cultured neurons. *J Neurobiol* 66, 1101-1114 (2006)
27. V Hunyadi, D Chretien, IM Janosi: Mechanical stress induced mechanism of microtubule catastrophes. *J Mol Biol* 348, 927-938 (2005)
28. S Park, YW Hong: Transcriptional regulation of artemin is related to neurite outgrowth and actin polymerization in mature DRG neurons. *Neurosci Lett* 404, 61-66 (2006)
29. F Bradke, CG Dotti: The role of local actin instability in axon formation. *Science* 283, 1931-1934 (1999)
30. K Zito, G Knott,GMG Shepherd, S Shenolikar, K Svoboda: Induction of spine growth and synapse formation by regulation of the spine actin cytoskeleton. *Neuron* 44, 321-334 (2004)

31. LG Tilney, PS Connelly, L Ruggiero, KA Vranich, GM Guild: Actin filament turnover regulated by cross-linking accounts for the size, shape, location, and a number of actin bundles in Drosophila bristles. *Mol Biol Cell* 14, 3953-3966 (2003)
32. DE Ingber, SR Heidemann, RE Lamoureux, RE Buxbaum: Opposing views on tensegrity as a structural framework for understanding cell mechanics. *J Appl Physiol* 89, 1663-1678 (2000)
33. R Pandia Raj, SD Guest: Using symmetry for tensegrity formfinding. Presented at IASS-2006, Beijing, China (2006)
34. DE Ingber: Cellular mechanotransduction: putting all the pieces together again. *FASEB J* 20, 811-827 (2006)
35. El-Amraoui Aziz, Christine Petit: Usher I syndrome: unravelling the mechanisms that underlie the cohesion of the growing hair bundle in inner ear sensory cells. *J Cell Sci* 118, 4593-4603 (2005)
36. JN Maina: Spectacularly robust! Tensegrity principle explains the mechanical strength of the avian lung. *Respir Physiol Neurobiol* 155, 1-10 (2007)
37. SM Levin: The tensegrity-truss as a model for spine mechanics: biotensegrity. *J Mech Med Biol* 2, 375-388 (2002)
38. DE Ingber: Mechanical control of tissue morphogenesis during embryological development. *Int J Dev Biol* 50, 255-266 (2006)
39. DC Van Essen: A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 385, 313-318 (1997)
40. D Greitz, R Wirestam, A Franck, B Nordell, C Thomsen, F Stahlberg: Pulsatile brain movement and associated hydrodynamics studied by magnetic resonance phase imaging. *Neuroradiol* 34, 370-380 (1992)
41. E Fest, K Shea, B Domer, IFC Smith: Adjustable tensegrity structures. *J Struct Engin* 129, 515-526 (2003)
42. W Jensen, K Yoshida, UG Hofmann: In-vivo implant mechanics of flexible, silicon-based ACREO microelectrode arrays in rat cerebral cortex. *IEEE Trans Biomed Eng* 53, 934-940 (2006)
43. RB Fuller: Synergetics. *Macmillan*, New York (1975)
44. I Bloch, J Pescatore, L Garnero: A new characterization of simple elements in a tetrahedral mesh. *Graphical Models* 67, 260-284 (2003)
45. S Finger, PJ Koehler, C Jagella: The Monakow Concept of Diaschisis. *Arch Neurol* 61, 283-288 (2004)
46. D Schiffer, MT Giordana, P Cavalla, MC Vigliani, A Attanasio: Immunohistochemistry of glial reaction after injury in the rat: double stainings and markers of cell proliferation. *Int J Dev Neurosci* 11, 269-280 (1993)
47. K Hoedt-Rasmussen, E Skinhoj:. Transneural depression of the cerebral hemispheric metabolism in man. *Acta Neurol Scand* 40, 41-46 (1964)
48. RG Robinson, FE Bloom, EL Battenberg: A fluorescent histochemical study of changes in noradrenergic neurons following experimental cerebral infarction in the rat. *Brain Res* 132, 259-272 (1977)
49. BT Helfand, MG Mendez, J Pugh, C Delsert, RD Goldman: A role for intermediate filaments in determining and maintaining the shape of nerve cells. *Mol Biol Cell* 14, 5069-5081 (2003)
50. GA Elder, VL Friedrich Jr., C Kang, P Bosco, A Gourov, P-H Tu, B Zhang, V M-Y Lee, RA Lazzarini; Requirement of heavy neurofilament subunit in the development of axons with large calibres. *J Cell Biol* 143, 195-205 (1998)
51. T Frappier, J Derancourt, LA Pradel: Actin and neurofilament binding domain of brain spectrin beta subunit. *Eur J Biochem* 205, 85-91 (1992)
52. M Hammarlund, EM Jorgensen, MJ Bastiani: Axons break in animals lacking beta-spectrin. *J Cell Biol* 176, 269-275 (2007)
53. MC Raff, AV Whitmore, JT Finn: Axonal self-destruction and neurodegeneration. *Science* 296, 868-871 (2002)
54. A Kloda, L Lua, R Hall, DJ Adams, B Martinac: Liposome reconstitution and modulation of recombinant N-methyl_D-aspartate receptor channels by membrane stretch. *Proc Natl Acad Sci USA* 104, 1540-1545 (2007)
55. E Bednarski, P Vanderklish , C Gall, TC Saido, BA Bahr, G Lynch: Translational suppression of calpain I reduces NMDA-induced spectrin proteolysis and pathophysiology in cultured hippocampal slices. *Brain Res* 694, 147-157 (1995)
56. E Park, E Liu, M Shek, A Park, AJ Baker: Heavy neurofilament accumulation and alpha-spectrin degradation accompany cerebellar white matter functional deficits following forebrain fluid percussion injury. *Exp Neurol* 204, 49-57 (2007)
57. I Karl, J Bereiter-Hahn: Cell contraction caused by microtubule disruption is accompanied by shape changes and a increased elasticity measured by scanning acoustic microscopy. *Cell Biochem Biophys* 29, 225-241 (1998)
58. B Morrison, DF Meaney, SS Margulies, TK McIntosh: Dynamic mechanical stretch of organotypic brain slice cultures induces differential genomic expression: relationship to mechanical parameters. *Trans of the ASME* 122, 224-230 (2000)
59. P Carroll P, GR Lewin, M Koltzenburg, KV Toyka, H Thoenen: A role for BDNF in mechanosensation. *Nat Neurosci* 1, 42-46 (1998)
60. WH Calvin: Error-correcting codes: coherent hexagonal copying from fuzzy neuroanatomy. *World Congress on Neural Networks* 1, 101-104 (1993)
61. WH Calvin: Cortical columns, modules and Hebbian cell assemblies. In: The Handbook of Brain Theory and Neural Networks. Ed: Michael A Arbib , *Bradford Books/MIT Press*, Cambridge Massachusetts (1995)
62. WH Calvin: The Cerebral Code. *Bradford Books/MIT Press.* Cambridge Massachusetts (1996)
63. M Fyhn, S Molden, MP Witter, EI Moser, MB Moser: Spatial representation in the entorhinal cortex. *Science* 305, 1258-1265 (2004)
64. T Hafting, M Fyhn, S Molden, MB Moser, EI Moser: Microstructure of a spatial map in the entorhinal cortex. *Nature* 436, 801-806 (2005)
65. MC Fuhs, DS Touretzky: A spin glass model of path integration in rat medial entorhinal cortex. *J Neurosci* 26, 4266-4276 (2006)
66. G Schlaug, L Jancke, Y Huang, H Steinmetz: In vivo evidence of structural brain asymmetry in musicians. *Science* 267, 699-701 (1995)

67. M Catani, MP Allin, M Husain, L Pugliese, MM Mesulam, RM Murray, DK Jones: Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci USA* 104, 17163-17168 (2007)

Abbreviations: APP: amyloid precursor protein, BDNF: brain derived neurotrophic factor, ECM: extracellular matrix, JNK: C-Jun N-terminal kinase, NMDA: N-methyl-D-aspartate, SAM: sterile α motif, SCG10: superior cervical ganglia, neural specific 10 protein, USH: Usher syndrome protein, Vg1: vegetal 1.

Key words: Actin, Microtubule, Cytoskeleton, Thermal ratchet, Tensegrity, Brain, Calvin's Theory of Consciousness, Symmetry, Asymmetry, Review

Send correspondence to: John Gardiner, The School of Biological Sciences, The University of Sydney, Camperdown 2006, Australia, Tel: 61293512384, Fax: 61293514771, E-mail: jgardiner@mail.usyd.edu.au

http://www.bioscience.org/current/vol13.htm