Tissue Adaptation as a Dynamical Process Far from Equilibrium

H. WEINANS1 and P. J. PRENDERGAST2

1 Biomechanics Section, Institute of Orthopaedics, University of Nijmegen, Nijmegen, the Netherlands and Rush Arthritis and Orthopaedic Research Institute, Rush-Presbyterian-St. Luke’s Medical Center, Chicago, IL, USA
2 Department of Mechanical Engineering, Trinity College, Dublin, Ireland

It is well established that tissue growth, maintenance, and degeneration are biochemically regulated processes influenced by mechanical function. Biomechanical models have been developed to predict adaptive processes; for example, computer simulation of bone remodeling around orthopaedic implants can accurately predict the effect of certain implant design variables. However, the same success remains to be achieved with other adaptive processes such as joint morphogenesis or osteoporosis. We propose that, to become capable of simulating such adaptive processes, biomechanical models should capture the inherently irreversible nature of tissue adaptation and therefore should not rely on the assumption of a “homeostatic” equilibrium. In this article, it is proposed that tissue adaptation is an unstable process of moving between three states that are far from the equilibrium state—and that to simulate it, independent sensors and positive feedback stimuli should be employed. (Bone 19:143–149; 1996)

Key Words: Tissue adaptation; Instability; Irreversibility; Feedback control; Bone adaptation.

Introduction

It seems that Roux60 was the first person to explore the relationship between mechanical stimuli on cells and tissue adaptation. He proposed that cells within tissues engage in “a competition for the functional stimulus” and that this competition determines cell survivorship and therefore, tissue phenotype. He hypothesized that the mechanical environment (or climate) bears the rules, and therefore he used the term selbst-gestaltung (self-organization) for the resulting process in the tissue. Similar to Darwinian competition, the concept of tissue-level competition implies a resource, which supports the cells within the organ. Only the favored cells, getting enough of the resource, will survive; or only the substance at favored locations will be maintained. Similarly to the way that individual organisms can influence their environment and thereby affect the evolutionary path of the species, so too can cells affect their extracellular matrix and thus affect their prospect of survival within the tissue. In summary, according to this view, the interaction between cells is one of a “struggle” for survival within the extracellular matrix.

Morphogenesis: Pattern Formation

Turing64 made his contribution to theoretical biology by showing, mathematically, that instabilities and subsequent pattern formation can arise in a medium containing chemicals (morphogens), which diffuse at different rates through the medium. For example, he showed that there are conditions under which a homogeneous tissue, perceived as being in equilibrium at some apparent level, could actually be in unstable equilibrium whereby the smallest perturbation of the mechanical environment would cause the homogeneous equilibrium to disappear and a spatial structure (pattern) to be generated (morphogenesis). In these systems, once any “homeostatic” equilibrium is lost, the tissue
adapts to another equilibrium and the previous "homeostatic" equilibrium cannot be regenerated—the change is irreversible. If the stimulus has sufficient spatial variation then tissue differentiation can occur and boundaries between different tissue phenotypes are generated. Cooke and Zeeman, for example, propose that repeated pattern formation (as in vertebrate somites) can be explained by a pulsating chemical process (clock) and a wavefront of rapid cellular change approaching a cusp catastrophe.

It may be said that the systems described by these models are "far from equilibrium" because they are very far from achieving stable homogenous equilibrium; and they exist in a state where an irreversible change would occur after a perturbation. The source of morphogenesis in Turing's system is the instability of the tissue whose parts react to diffusion of morphogens. On the other hand, Roux proposed that competition between cells causes self-organization of the tissue and hence morphogenesis. Many biomechanical models used to simulate adaptive processes have employed the self-organizational concept of Roux on the basis that the adapted state for the biological structure is a "homeostatic" equilibrium or reference state which is always returned to after a perturbation (see Taber for a review of biomechanical models in general). In the original Turing model, a diffusive morphogen is a stimulus, whereas tissue adaptation models use a mechanical stimulus. Hence morphogen and mechanical stimuli are analogous variables. This article attempts to further integrate the concepts of nonequilibrium systems with existing biomechanical models of tissue adaptation.

Adaptation Models and Equilibrium

Current Adaptation Theories

In many adaptation theories, it is assumed that the tissue is in equilibrium so that the mechanical stimulus received at all sites is equal to the homeostatic (or setpoint) stimulus at those sites. If the local mechanical stimulus changes, as it will on an alteration in the load, then the difference between the new stimulus and the homeostatic stimulus drives structural change to regain the objective at homeostatic equilibrium (the steady state reference value) at all sites in the tissue, see Fyhrie and Schaffler, for a review, and Turner for an inclusion of the role of biochemical agents. Adaptation theories have been put in the form of computer algorithms using the concept of a feedback loop. For describing bone adap-
tation around orthopaedic implants, these models are quite successful as preclinical testing tools.\textsuperscript{2,3,4,8,10,11,58,70,72} Huiskes and Hollister\textsuperscript{3,5} and Hart and Fritton\textsuperscript{31} present reviews of these and other computational implementations. These models are continuum models in the sense that they assume that activity at the sites can be spatially smoothed and the predictions for adaptation are presented on a continuum level. Some of these approaches exhibit convergence to homeostatic equilibrium at all remodeling points.\textsuperscript{18,20,21,25,28} However, they do implicitly place a constraint on the capability of the local cell systems to compete since individual cell response is smoothed out. In fact, a new, more global rule stipulating smooth transitions in cell behavior is imposed, and the individual cells are no longer free to act independently in response to the morphogenetic signals in the tissue.

Development to Include Competitive Self-Organization

It has been proposed that the mechanosensory system in bone consists of discrete sensors (perhaps osteocyte cells\textsuperscript{19,30}), therefore, the actual adaptive-elastic situation is controlled by many sensor cells within the tissue where the cells make decisions based on the morphogenetic signals they receive. Despite this apparent autonomy, cells are coupled both mechanically and chemically; mechanically since the load has to be transferred through the continuum, and chemically by the diffusion or flow of biochemical mediators through the cellular processes and the extracellular matrix, i.e., the sensors are coupled via signal flow in the cell processes and extracellular matrix but there is no constraint that the amount of morphogenetic signals they receive should be continuous from one sensor to its neighbor. Hence we say that sensor cells are signal coupled, but behavior independent. Figure 2 shows a schematic diagram of sensors, extracellular matrix, and signal transfer.

Finite element models offer the possibility of modeling independent behavior for the sensor cells, because a site (element) can be independently adapted based on the morphogenetic signal at that particular site. The coupling through the extracellular matrix can be calculated in the computer model. However, computerized contouring and nodal averaging techniques will deprive the sensors of a capability to take independent decisions by enforcing a continuity constraint for the sensor activity. This numerical "smoothing" allows the "homeostatic" equilibrium to be regained after a change of the load. Any approach that smooths out activity of the sensors, and thus inhibits them from operating individually, may prevent competition and therefore self-organization; the result could lead to loss of the morphology-generating mechanism.

Irreversibility

Turing,\textsuperscript{64} Thom,\textsuperscript{60} and Murray\textsuperscript{49} among others have shown in a mathematical sense that irreversibility, operating on a microscopic level, can be the actual cause of macroscopic pattern formation. A biomechanical model, in which return to a "homeostatic equilibrium" is assumed (i.e., where the stimulus has reached the setpoint), does not reflect the irreversible nature of tissue adaptations. In other words, the irreversible nature can only be captured if the tissue is allowed to abandon homeostatic equilibrium. If the tissue is allowed to enter an adaptation pathway toward a new state, driven by the independent behavior of its sensor cells, the process becomes irreversible and the instability or positive feedback moves the system to a boundary of its solution space far from the homeostatic configuration to a metastable state. Since there are many of those metastable configurations, a sufficiently big perturbation may force the tissue to another more stable state. In fact, the process is a search on a rugged landscape\textsuperscript{3} for its most stable (lowest energy) state, see Kaufman.\textsuperscript{37}

Adaptation Models: Relationship Between Mechanical Stimulus and Feedback

If tissue adaptation is a response to a mechanical stimulus, it seems a straightforward idea to assume that the sum of all these local stimuli is the total resource of mechanical stimulus available. If we assume that stress is the stimulus, it follows that the total resource in a cross section is determined by the external loading, since the sum of the stresses in a cross section, should balance the total available external load (i.e., the load of weight bearing). Hence, in each arbitrary chosen cross section, the sensors compete for the load resource. If a sensor does not get sufficient resource, then it cannot maintain its microenvironment and losos the struggle-for-survival and disappears. In other words, if appropriate stimuli cannot be transferred to the cell via extracellular matrix then the cell/extracellular matrix will be replaced by some other tissue; a perhaps related hypothesis is put forward by Brand.\textsuperscript{4} For example, a bone sensor site with a slightly higher density has a competitive advantage and will attract more of the stress resource resulting in a gain of bone mass relative to neighboring sites. The neighboring sites will then be even further under stressed and will tend to loose mass. Stress is, in this respect, a very competitive stimulus since the resource, the external load, is fixed. Stress stimuli therefore generate positive feedback. For strain as the mechanical stimulus this is entirely different. If a sensor site is deformed intensely, the neighboring sites will also deform since they are made of a substance that is bonded to the deformed site. No matter how this substance changes its material properties, it will still deform continuously. Therefore, a site will receive stimulus whenever its neighboring site receives stimulus. So, sites in a deformed field will "share" or "distribute" a strain stimulus because strain is not a fixed resource. If deformation is the stimulus, then the total amount of stimulus in the system will depend on the stiffness in the system. In fact, the system can, in such a case, generate as much stimulus as required by changing its elastic properties. This is a crucial difference between strain and stress as tissue stimuli.

Therefore, there is a relationship between the kind of stimulus and the nature of the feedback. In fact, this idea is inherent in the results of computer simulations carried out by Weinsans et al.\textsuperscript{71} Jacobs et al.,\textsuperscript{36} and Turner et al.\textsuperscript{66} They showed that the structure will only form a pattern under stress or energy stimuli, whereas a pure strain stimulus will not form a pattern. The competition analogy therefore contributes to the ongoing
discussion relative to stress, strain, or energy-based adaptation stimuli. Strain can be considered as a much more "neighbor-friendly" stimulus criterion. If energy is taken as the stimulus for bone adaptation, then competition is again evident in the adaptation process, but unlike stress the system can change its total amount of stimulus.

Positive Feedback, Competition, and Pattern Formation

If the amount of bone tissue (i.e., local density) increases at a particular site, the amount of stimulus will subsequently increase at the same location, if the feedback is positive. If the stimulus is considered as a resource that follows an equilibrium principle (stress) or conservation principle (energy) it means that the resource is limited at some point in time. Therefore an increase in stimulus at one position should lead to a decrease of this stimulus in a neighboring location; in effect the sites may be considered to compete with each other in the sense proposed by Roux. This relationship between positive feedback, competition, and pattern formation in adaptation can be conceptually explained by Figure 3. In a homogenous equilibrium, a small fluctuation in either the stimulus or the density will enhance itself under positive feedback. Hence the decrease in stimulus reduces the amount of bone formation at a location nearby such that a spatial wave or pattern arises in the structure. The consequence of this idea is that the setpoint stimulus of each site is not necessarily reached. In fact, the error signal (setpoint minus actual signal) is corrected during adaptation such that the sites are directed toward the overuse and disuse windows.

Independent Sensors and Positive Feedback for Bone Remodeling

Bone remodeling is an adaptive process involving the coupled action of osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells) during a remodeling cycle, see Eriksen and Langdhal for a review. These cells combine into units of a particular size called basic multicellular units (BMUs), which resorb and deposit bone in packets about 60 μm deep by 100 μm wide on bone surfaces, or 200 μm diameter "cutting cones" inside cortical bone. Internal control of the BMU is probably achieved by direct cell-to-cell coupling between osteoblasts and osteoclasts. The physiological pathways for BMU activation are hypothesized to involve retreat of lining cells to allow osteoclast resorption, stimulated by either osteocytes or microdamage. Mechanical and chemical coupling has been identified in bone tissue. BMUs can be regarded as discrete sites operating independent of central regulation, but coupled through the mechanical and chemical effects as discussed above.

Is there any evidence of positive feedback for the bone remodeling process carried out by BMUs? It has been shown that cell recruitment rates depend on the mechanical environment. For positive feedback to exist, the cells (osteoblast and osteoclast) which are in their physiological mechanical environment (or usage window) must compete better for the functional stimulus than cells in nonphysiologic or pathologic mechanical environments. Some evidence that this might be true comes from the fact that pathological mechanical environments have been shown to generate woven bone, which is indicative that the cells there are not able to generate a sustainable microenvironment compared with cells in physiological mechanical environments.

Discussion

We have argued that, to simulate the time course of irreversible tissue adaptation processes, spatial instability should be included in biomechanical models using sensors that are mechanically coupled with the capability for independent response and positive feedback. Models which use the instability as the drive for the development of a pattern can be considered as Turing models (also called reaction/diffusion models). Turing did explicitly mention the possibility of taking the mechanical aspects into account, though he did not work this out in his examples. Mechanochemical Turing models for morphogenesis were described by Oster et al. and various examples can be found in Murray. Carter et al. examined the development of trabecular bone density distribution in computer models of the femoral head and, based on the lack of convergence in their analyses, they remarked "one may argue that a unique equilibrium solution does not exist in bone biology." They recognized the positive feedback in the computer simulation and suggested that it might be a significant biological factor. However, the difficulty with their simulations was that the tissue structure immediately went to an unreasonable degenerated state. The question posed by this result is "what factors control how long the tissue will be maintained in the nonequilibrium state without complete degeneration?" Mullender et al. and Mullender and Huiskes have introduced an...
“Influence function” between the sensors (thereby adding direct sharing of the morphogenetic stimulus between the sensor sites in the medium) and found that the structure maintains a trabecular resemblance. With the influence function, they in effect introduced more coupling and made the system more spatially stable such that it could be trapped in metastable states. Therefore the answer to the above question seems to lie, at least in part, in the independence (capacity to compete) of the sensor and surrounding ECM and the degree of mechano-coupling between them. A similar conclusion has been reached in a different way by Harrigan and Hamilton

To illustrate the point of instability, consider the process of irreversible trabecular bone loss when an osteoclast does not deposit as much as an osteoblast has resorbed leading to eventual perforation of a trabeculae during life, resulting in irreversible deterioration from one trabecular structure to another. In that case, other trabeculae will take over the load and become slightly thicker as it is often observed in the vertebral body. This can be regarded as the loss of a metastable equilibrium, and it may happen so slowly as to appear continuous. It has been well documented that biochemical factors can control the rate of osteoporosis, and we might interpret this as that they can control the rate that the trabecular structure leaves its unstable or metastable equilibrium.

Instability and Maintenance of Structure

“What keeps bone in these metastable equilibria, and why is it moving so slowly to a degenerated state?” In a series of lectures delivered at Trinity College in Dublin in February 1943, Schrödinger explained this with the concept that “organization is maintained by extracting order from the environment.” As he put it, an organism attracts “negative entropy” upon itself to compensate for entropy production during living. This may be the reason why a disordered structure—which one might intuitively expect from a complex process driven by independent/coupled sensors—does not emerge. Tissues are therefore dissipative structures in the sense proposed by Nicolis and Prigogine. The term dissipation refers to the fact that a part of the morphogen resource is lost and cannot be used for generating or maintaining the structure. So apparently morphogen is wasted and it appears that there is less effective use of the resource within the whole structure. The competition causes poor sharing of the resource and a lower total effective resource could do the same task as well (maintain the same structure) if it could be distributed efficiently. For this reason the instability of such a process is linked with the non unique character of the solution and irreversibility. In bone remodeling computer models, the nonunique character of the solutions and the corresponding ineffective distribution of morphogen have been clearly shown. Martin has hypothesized that this can lead to chaotic remodeling behavior associated with diseased states of bone.

Instability and Symmetry Breaking

Another consequence of the instability is that, at all levels, the symmetry and homogeneity of the tissue is broken. “Symmetry break” can be considered as the result of competition, because in a system where small fluctuations or small advantages are the drivers of dynamical processes, every symmetry or homogeneity will break down; initially at the microscopic level but once this is accomplished, the macroscopic level will follow and hierarchical structures will develop as described for joints by Mow et al. Speaking in terms of osseous tissue: what one site gains in mass is linked to the loss of another site. The relative size of these sites does not matter in this respect. The breakdown of symmetry should appear within one trabeculae, among trabeculae, between medial and lateral sites within one bone, and finally between left and right. In the theoretical models of morphogenesis, this instability is considered to be the origin of asymmetry. Paraphrasing from Turing “an embryo in its basula stage has spherical symmetry but an organism such as a horse is not spherically symmetrical.” For the same reason as symmetry breaking is linked to morphogenesis (creating shapes), it is also linked with ageing and degeneration (breakdown of shapes).

A Possible Experiment?

One consequence of the instability is that small fluctuations in the system work up and play an important role in determining the final configuration. Therefore, although the theoretical design is deterministic, the outcome of the patterns appears in a stochastic manner. This is precisely one of the typical characteristics of trabecular bone and tissues in general. The irreversible character at the macroscopic level could be investigated in real bone from in vivo experiments which determine response to a sequence of loads rather than to one load as is done at present, e.g., hindlimb suspension experiments. Different loading pathways could be used leading to identical end loading conditions. Different pathways should have different outcomes and, if what is proposed in this article is correct, then the more fluctuations there have been, the less efficient the resource will be shared and therefore, less bone mass would survive.

Conclusion

In conclusion from the above, it would seem that, from a biophysical point of view, two attributes are required to simulate tissue adaptation as an irreversible process occurring far from equilibrium, giving tissue the vital capacity for self-organization: (i) discrete sites behaving independently of their neighboring sites, though coupled by morphogenetic stimulus transfer in the tissue; (ii) a positive feedback mechanism giving survival advantage for sensor sites closest to their preferred mechanical environment, thereby attracting as much of the resource as possible.

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