The law of adaptive bone remodeling : a case for crying Newton?

THE LAW OF ADAPTIVE BONE REMODELING: A CASE FOR CRYING NEWTON?

RIK HUISKES
Biomechanics Section, Orthopaedic Department
University of Nijmegen, 6500 HB, The Netherlands

ABSTRACT

The biological mechanisms of strain-adaptive bone remodeling are largely unknown. Yet, several authors published algorithms to mimic this process, without prior validation of its premises. Biologists are sometimes confused by this seemingly irresponsible behavior. However, this kind of inductive investigation has a long tradition in physics, inspired by Newton. Depending on its predictive capacity, an algorithm can reveal information about the process it simulates and generate fruitful hypotheses about underlying mechanisms. This obviously requires comparison of its results to an experimental reality at some point in time. But as the algorithms tend to be complicated, it is not unreasonable that they are discussed in the literature already in their developmental phases.

1. On Wolff and Wolves

"It is widely accepted in the Orthopaedic literature that bone mass adapts to loads in accordance with Wolff's Law". How often have we put this sentence on our hard disks? And yet, the authors whose article[1] I so frivolously paraphrased in the title of this chapter hold a mirror in front of us, asking if we really believe that (answer: no, but pretend for the sake of the kids). It is a scholarly article, well-researched and written. Its main point is that nobody has been able to show that trabecular architecture adapts to a change in load direction in normal mature bone, as it should according to Wolff's trajectorial theory. Growing bone, fine, fracture repair, OK, but no miraculous transformations associated with a shift in load alone in healthy, mature bone. Furthermore, the authors argue that phenomena commonly associated with adaptive remodeling of bone to mechanical stimuli, like atrophy and hypertrophy, might as well be explained by other causes. I am not being sarcastic, it is simply an excellent article, and all should read it.

Poor Wolff[2]; another pack at his throat. Roesler[3] told us that Wolff just used and misinterpreted the engineering analyses of Cullmann, but did not really understand its mechanics. Dibbits[4] even built a convincing case against his grasp of biology. Treharne[5], in another excellent historical review, showed that Wolff's thoughts were not very original and that the Law was in fact a Tropism. Hayes[6] argued that it is, rather, a Hypothesis. And now Bertram and Swartz[1] suggest it might even be the wrong one. If Wolff could hear us, he might linger at one of Jacques Brel's famous poems, 'La Statue', in translation from Rod McCuen: "I'd like to get my hands on he/who made a hero out of me". To his defense, however, must be that he provided Orthopaedics with the only Law it has in its scientific baggage, and that he left lots of funded research proposals in his wake. But maybe the gravest dishonor to his heritage is yet to come. A century after Wolff so aptly grasped the Law out of the hands of a civil engineer, a mechanist, a builder of mathematical models, a computer freak *avant la lettre*, these people strike back. They crunch bytes instead of cells and, oh blasphemy, have turned the Law into an Algorithm. Fortunately, however, Currey[7] has discovered that their Algorithms do not accord and found the seeds of disunity, ready to be exploited. Cleverly, he proposes the Algorithms to be benchmark tested, measured against a universal standard of realism, well aware that this will engage them in endless, if not deadly disputes.

Most biologists will accept that when one has a Law (a real one, that is), an Algorithm is readily composed. But to turn, conversely, an Algorithm into a Law, is apparently not fashionable, at least not for Currey. And is that not what the number crunchers are up to? Yes, we are; I am (exposed!). Our inspiration comes from the misty Angle-Saxon shores, where a magic cult emerged some three centuries ago.

2. On Inspiration

There is no use hiding that John Currey's chapter in this book[7] provided the inspiration for mine; not to say that he turned me on. In summary, he writes that there are now many different Algorithms (a 'plethora' of them) meant to explain bone remodeling. It is unclear how, precisely, they are different, and what their explanatory capacities are. He suggests that each new Algorithm should be benchmark tested against standard experimental data, before it is published. He proposes 7 questions that he believes to be the pertinent ones in bone-remodeling biomechanics, and wants us to at least answer some of them before our Algorithms can be exposed to the general readership of the Archive Literature. In short, he wants facts, not fiction, and certainly no computer games.

There is no plethora of different Algorithms. Other than that, I have no quarrel with Currey's questions. Although I do hope his suggestions are not implemented by the Editorial Boards of our Journals.

The scientific approach we use to unravel the process of adaptive bone remodeling has a long tradition in physics, inspired by Newton. One could say that his universal Law on gravitation originated from an Algorithm, which regulates the attraction of two objects in space by a force between their centers of gravity, proportional to the product of their masses divided by the square of their distance. A very simple Algorithm, which turned out to regulate the motions of objects in the entire universe, and the gravity forces on earth as well.

Three aspects of Newton's work are pertinent to our cause. First, evidently Newton did not develop this insight on the stroke of an apple. It took him many years of interpretation, integration, re-interpretation and re-integration of information and observations to get to this point; in fact a novel way to conduct research which, as said, inspired scientific methodology in physics ever since. Of course, he only published his Principia after he validated his Law with calculations based on motions of the planets and he had absolutely convinced himself to be right. Conversely, we seem to publish our work already when the apple still hangs in the tree and besides, we are no Newtons. The reason for this seemingly arrogant behavior is that science is now conducted in an open environment, as opposed to the seclusion in Newton's time. In our culture it is essential that we learn from each other while the science is in progress. Not to speak of our funding system, which requires us to report to our peers what we accomplish with taxpayers money.

The second aspect of relevance relates to the mechanistic basis of Newton's Law. He had no clue about what caused the attraction between two masses. This is one of the reasons why it took so many years before the Law was accepted by his peers. Christiaan Huygens, for example, refuted the idea simply because the origin of the attraction force was a mystery. The Law was immensely valuable for its predictive capacities, although the Algorithm on which it was based could not be explained. There is a similar example in history, which has inspired me particularly in my approach to bone-remodeling analysis. Hooke's Law of elasticity specifies that the stretch in metals and minerals is directly proportional to the force exerted upon it. The Algorithm now applied to represent this regulatory mechanism uses the modulus of elasticity as the proportionality constant. The value of this number obviously depends on the packing characteristics of the molecules in the material concerned. While the Algorithm provides for valuable predictive capacity, it has not been possible yet to derive the value for the elastic modulus of a material from its chemical constituents. I am in no way suggesting that we have developed an Algorithm for bone remodeling that even comes close to the predictive capacities of the above examples; remodeling is immensely more complex than the orbits of the planets or the deformation of elastic materials. But if our approach does, one day, produce such an Algorithm, it must be judged on its capacity to predict the regulation of bone mass as an effect of a mechanical input; it does not necessarily have to explain all the biological steps in the regulatory process, to become a useful addition to the scientific body of knowledge. I think here lies an important difference in the motivations of biology and mechanics.

The third aspect of Newton's Law that illustrates the scientific philosophy behind our approach relates to its validity. Newton's Law of universal gravitation invalidated Kepler's third Law on the orbits of planets in space. The ratio between the cubed average distance from sun to planet and its squared orbital period is not a constant, as Kepler had it, but depends on mass. Newton's Law, in its turn, was invalidated by Einstein, who showed that mass is not a constant, but depends on the speed of the object. Nevertheless, both Kepler's and Newton's Laws produce quite precise predictions within a wide margin of external conditions. While our methods of observation and scientific understanding of nature develop, our references for validity adapt as well. Validity of an Algorithm's premises is not the first issue, it is the precision of its predictions, relative to contemporary means of experimental assessment that counts. Sir Karl Popper, I believe, wrote extensively on these subjects. So Currey's benchmark test for bone-remodeling Algorithms could be adapted gradually by his own accomplishments in experimental bone mechanics, condemning us, like Tantalus, to chase him forever. A devilish proposal indeed!

In proposing Algorithms meant to explain bone remodeling, some tend to be careful and try to account for contemporary knowledge about biological factors, thought to play a role in the regulatory process. Others, in the best Medawarian tradition, are bolder, investigating hypotheses motivated by nothing more than their intuition. This is all irrelevant, the important part comes when they are applied. Some produce rubbish. Others produce something sensible relative to some sort of reality. Because these Algorithms and their behavior tend to be complicated, even the rubbish may contain important information; we learn from that, and progress, provided that it is published. I can understand that some get bored by these attempts, or even confused, particularly when solution methodology is discussed, rather than the process itself. But I have yet to meet a peer who seriously proposes, as Currey suggests they do, to have found the 'true' Algorithm, which is something different from defending ones hypothesis until proven useless.

Coming back to the scholarly work of Bertram and Swartz[1], I believe that the 'Newtonian' approach to the problem is a rewarding avenue to resolve the matter of mechanical versus other stimuli in the regulation of bone mass. It is simply impossible, in my mind, for practical reasons, to devise an experiment in which all factors but the mechanical are incapacitated. Only if an Algorithm which makes sense according to our contemporary scientific knowledge, directly relating bone load to the regulation of mass, can consistently predict the outcome of the biological process with a reasonable degree of accuracy, will I believe that Wolff may have been right. And then, finally, we will have a Law.

3. On Algorithms

There are only a few Algorithms meant to explain bone remodeling, and they are not all that different. First, we have to make a clear distinction between two kinds of computer procedures that have quite different objectives[8]. One is, indeed, the type intended to mimic bone remodeling. The second is a type of computer-optimization procedure meant to reproduce a bone based on some kind of overall mechanical objective. If the shape and the architecture of the model produced by the procedure mimic a real bone, then we know that the bone is an optimal construction according to the same objective. Such a procedure is not intended to investigate the *process* of remodeling, but only its product. In a way, bone is considered as the answer, the objective is to find the question. In fact, they re-enact the attack of Cullmann with bigger guns: the finite element method is just more powerful than Cullmann's method of 'graphic statics', it is not principally different in scope. Personally, I find these studies interesting, but of a rather academic nature, due to their teleological perspectives. They may once find useful applications in engineering design, however.

The Algorithms developed to mimic bone remodeling itself build on the ideas of Roux[9], who first hypothesized on the workings of a regulatory, cell-based process in adaptation of bone. They basically all use the same paradigm of Wolff's Law. There is a bone structure of some internal architecture and external shape which is externally loaded. The loads produce deformations and the deformations produce other mechanical variables, such as stresses of different types, elastic energy or others. One of these mechanical variables, or their temporal derivatives, like energy dissipation, fluid transport or damage accumulation, is thought to be a 'signal' for bone remodeling. This signal is appraised by some 'sensor' (or mechanoreceptor) in the bone and compared to a reference. This comparison produces a 'stimulus' for bone-mass regulation which stimulates formation or resorption by the 'actors', the osteoclasts and osteoblasts (finally something we know for sure!). The actors alter net bone mass, hence architecture and shape, hence mechanical properties, hence the distribution of the remodeling signal value, and the feed-back loop is closed.

To simulate (or analyze) a process like this requires two procedures, one to translate external loads to a distribution of the signal of choice, dependent on shape and internal architecture, and one to translate a local signal value to a local change in bone mass (hence a change in shape and architecture). For the first procedure one may use a closed-form mechanical theory, a finite-element model or, for those charmed by antiques, graphic statics. Evidently, FEA provides the best tool to represent structural behavior accurately, although only to a certain detail. Internal architecture may be represented, for example, by an apparent density distribution only, by additional parameters for bone directionality or even by the trabecular structure itself, but it is always schematized to some extent. This affects the structural level at which the strains and their associate variables are determined, and how accurately. But this is all just straightforward, albeit complicated, mechanics.

The second procedure required, the Algorithm for remodeling (or the remodeling rule), involves the biological factors. Although the above paradigm of Wolff's Law is probably broad enough not to cause dispute, a number of choices must be made. What is the signal? Which aspect of the signal is appraised (e.g. magnitude, rate, frequency, history)? What is the sensor or, maybe more pertinent for the Algorithm, *where* is the sensor? To what is the signal value compared, and how is the stimulus composed from the comparison? What is the (quantitative) relationship between stimulus and bone-mass regulation? These are all questions that relate directly to those asked by Currey[7], they are only posed in a different form. There is much dispute, not to say confusion, on how they are to be answered, and this often seems to divide biologists and mechanists. Biologists like to concentrate on the intrinsic validity of an assumed answer to questions like the above, whereas mechanists tend to emphasize what such an assumed answer produces. While there can be stimulating and fertile disputes on, for example, what the signal for adaptive remodeling might be, an equally rewarding subject is whether alternative choices produce substantially different results. The questions are complementary and the answers should eventually converge. But not necessarily now. Both approaches require experimentation, as Currey emphasizes[7], but not always as a prerequisite at the onset.

4. On Experimentation

A number of years ago we developed an algorithm to investigate bone resorption and formation around hip prostheses[10]. Our long-term goal was to be able to predict it, based on prosthetic characteristics, for the sake of pre-clinical testing. Our algorithm was based on the Wolff paradigm, discussed in the previous section, and we were largely inspired by the theory of adaptive elasticity of Cowin and associates[11]. For the signal we chose the strain energy per unit of mass (the first question). We also assumed (second question), that the *magnitude* of this variable was appraised by the bone. It is not that we actually believed this to be the case, they were just the simplest alternatives available. We assumed the sensors to be omnipotent in the bone and directly coupled to the actors, just as in adaptive elasticity. Hence, the Bone Multicellular Units[12] (BMU's) were simply assumed to be distributed over the bone as a continuum. The signal values were compared to the reference of a strain-energy distribution in the normal bone, i.e. without prosthesis, for the same loading conditions. Hence, the stimulus is basically the difference of what the bone locally experiences presently and what it experienced before the operation (a site-specific approach). The relationship between stimulus and resorption or formation was a tri-linear one, assuming a threshold level ('minimum effective strain'[12] or 'dead zone'[13,10]) on either side. The Algorithm was effected in 2-D and 3-D FE-models in which the signals were supposed to act at the apparent level; hence, trabecular architecture was represented by apparent density only.

We did not consider the intrinsic validity of all these assumptions *a priori*, but concentrated on the validity of the predictions. For that purpose we collaborated with a research group in Chicago to simulate canine experiments with hip replacement[14]. We simulated 6 series of experiments with prostheses of different coating and material specifications, predicting cortical morphology and trabecular apparent density after 6 months and 2 years postoperatively. The results were quite satisfactory to our taste. In a qualitative sense, the patterns of resorption and formation were very similar, even at a local level, while quantitatively the overall amounts of bone loss and gain predicted per cross-section were close to what were found as averages in the separate experimental series. The simulation of the first series, used to trigger the unknown model parameters, was published[15], and so was the simulation of the second one[16]. A publication of the other series is pending, but their results only confirmed the earlier trends. Recently, Weinans et al.[17] even succeeded in explaining the quantitative variations of the averages, in one of the canine series, from variations in the preoperative bone properties of the dogs.

We have also studied predictions for human cases of hip replacement in relation to measurements of bone density in retrieved post-mortem specimens[18]. In this case too, the overall similarities between predictions and experimental results were satisfactory[19,20]. Also in this case could we predict the effects of pre-operative bone density on long-term morphology. In summary, our simple algorithm is apparently capable of predicting the long-term net formation and resorption patterns around hip stems within a reasonable range of accuracy. Even more importantly, in all cases where this was studied, the model reacted to arthroplasty features like implant geometry and rigidity, but also bonding conditions and variations in pre-operative bone quality, as human or animal bones do. We now feel quite confident to use it for pre-clinical testing of implants in a generic sense. Not to replace animal or clinical trials, but rather to give these direction, explain their results and extrapolate them to general clinical conditions.

We learned much about remodeling Algorithms and how their predictions relate to the assumptions on which they are based. It seems that in the approach we used, the results are not very sensitive to the assumed loading conditions, as long as different loading components are represented (e.g. axial and transverse forces, bending and torsion). This is probably due to the site-specifity of the remodeling rule, in which the same loading conditions are applied in the pre and post-operative cases. For the same reason, the results are not very sensitive to the choice of signal, at least not at the structural level that we have studied and the details of the comparisons between predictions and reality that satisfied us. We believe that another signal can produce very similar results, as long as it provides for a reasonably complete representation of the stress (or strain) intensity, like strain energy does. As a matter of fact, Prendergast et al.[21] produced results similar to ours[10] when using accumulated damage as the stimulus. While we do not actually believe that the magnitude of the signal drives the remodeling process, rather than its rate, frequency or history, it seems that in the comparative, site-specific approach taken, it produces quite realistic predictions. This is not as strange as it seems, because the rate of a periodic signal is directly related to its amplitude. We are not sure yet to which level of accuracy the predictions are precise in individual cases, but we faithfully continue our validation studies. Although there is much left to be done, the Algorithm is already quite useful for pre-clinical testing and design-evaluation purposes of implants[20].

In the meantime, however, we have not learned very much about the process of bone remodeling itself, nor about the intrinsic validity of our assumptions. Certainly, our predictions are already so specific relative to different kinds of experiments, that we find it very unlikely that the remodeling patterns we see would not be caused by mechanical factors. In other words, we have enough material to reassure Bertram and Swartz[1] about the validity of the Wolff paradigm, at least where implants are concerned. In addition, our results give evidence to the nonlinearity of the relationship between stimulus and net remodeling, as suggested by Frost in his 'minimum effective strain' theory[12]. Without a 'dead zone', no realistic results could be produced. Our results also suggest that the threshold levels are lower for dogs than for humans, i.e. canine bone seems to be much more reactive than human bone.

We could not confirm, however, that these levels have a high intraspecies variability[12]; variations between individuals of the same species in post-operative morphology were largely explained by pre-operative bone density and shape. But other than that, the explanatory capacity of this Algorithm, relative to the bone-remodeling process, is limited; it is more 'Keplerian' than 'Newtonian' in scope. There have been recent developments in the use of Algorithms, however, which are much more exciting in this respect.

5. On Excitement

The explanatory capacity of an Algorithm obviously depends on the measurability of its parameters. The explanatory capacity of Hooke's Law is limited by the difficulty of relating elastic modulus to material chemistry. Kepler's Third Law did specify the distance between planets, but the constant in his formula did not relate to any identifiable physical quantity. The Algorithms for bone remodeling are still largely limited in the same way, but this is not a principle limitation.

Recently, we developed an Algorithm to simulate generation and adaptation of the trabecular structure itself[22], which is also reviewed in this book. It is based on the assumption that osteocytes are sensors[23] of mechanical signals (strain energy), who then mediate osteoclasts and osteoblasts in their environment to regulate bone mass. This model has a number of interesting features. The sensor and actor functions are associated with cells, rather than represented by abstract parameters. Furthermore, it no longer relies on an apparent parametric representation of trabecular architecture, but describes it directly. As a result, all parameters used in the Algorithm represent identifiable physical quantities, measurable in principle (although not all of them in practice, yet). This Algorithm produces trabecular architecture from any given initial configuration, aligning trabeculae with principle-stress orientations, just as Wolff hypothesized they would. This in no way proofs that this hypothesis is true, of course; there is no case here against Bertram and Swartz[1] and their doubts about the 'transformation' of mature, healthy bone, discussed at the start of this chapter, still stand. But it does show that it is *feasible* with a regulatory mechanism as proposed by Roux[9]. It proofs, for instance, that the osteocytes would not necessarily need information about local load directionality, in order to build, in concert, an anisotropic structure. The results also indicate that the morphological parameters of the emerging architecture (i.e. volume fraction, trabecular thickness, directionality) are all in some particular way associated with the identifiable physical quantities on which the model is based. Osteocyte density and range of influence are very prominent in this respect. Again, this is what the Algorithm predicts, it has no base in reality. But it does produce a testable hypothesis of grave potential consequences, namely that osteocyte density (which has not really been measured ever) is related to trabecular architecture; maybe even in pathology. Is that not exciting, even for a biologist?

6. Acknowledgements

I am grateful to Professor John Currey for sending me a preprint of his chapter in this book. Hopefully, he does not regret the consequences. I have great respect for his opinions and accomplishments in bone biomechanics. He is right in warning against negligence of experimentation. Surely, some of my peers at least give the impression of seeing no use for it, but not many. I felt that the tone of his text, however commendable in scope, does give fuel to an attitude that is counter-productive and does not serve our efforts right. My only goal was to restore the balance. As to the tone of *my* text, I rely on his sense of humor.

This was not meant as a review. I have been rather parochial in my discussion of examples, neglecting many of my 'Newtonian' partisans and their exciting work in 'Algorithism'. I expect to be forgiven; sometimes pride takes the better of you.

Finally, I do not really believe that 'Algorithm' should be capitalized all the time.

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