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***In vitro* evidence of the structural optimization of the human skeletal bones**

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1 **ABSTRACT**

2 Optimization can be seen in a number of human skeletal bones. While there is strong
3 evidence concerning the mechanism at the tissue-level for bone adaptation to the
4 applied loads, the structural optimization at the organ-level is somewhat less clear.
5 This paper reviews the evidence, mainly based on *in vitro* testing, but also from
6 anatomical and biomechanical considerations, concerning the shape-function
7 relationship in some exemplar cases. The proximal femur is robustly optimized to
8 resist a force applied in a range of directions during daily life, but also to absorb a
9 large amount of energy if an impact is delivered on the greater trochanter during a
10 sideways fall. The diaphysis of the tibia is shaped so as to act as a uniform-stress
11 structure (i.e. structurally efficient) when loaded by a bending moment in the sagittal
12 plane, such as during locomotion. The body of the thoraco-lumbar vertebrae is
13 optimized to resist to a load applied strictly in an axial direction. The result of this
14 review suggests that the structure of bones derives from a combination of local
15 stimulus-driven tissue-level adaptation within the subject, and organ-level generational
16 evolution.

17 **Keywords:**

18 Robust optimization; shape and function; evolution; bone strength; robustness;
19 functional adaptation

1. INTRODUCTION

The structure of skeletal bones has called the attention of scientist for centuries. In the nineteenth century, anatomy studies combined with modern mechanics provided the first evidence that the arrangement of the trabeculae of cancellous bone is strongly related to the biomechanical function. In 1856 Swiss engineer Karl Culmann remarked the similarity of the trabecular arrangement in the proximal femur, and that of the “Culmann crane” he had recently designed (Crystal, 1998). Few decades later Julius Wolff gave the first formal description of the optimization principle underlying the structure of bones (Wolff, 1892). While Wolff focussed on the mechanical description of such an optimized design, it was Wilhelm Roux who first introduced the concept of a quantitative self-regulatory mechanism as an explanation for such an optimal structure (Roux, 1881). Shortly later, John Koch provided a thorough theoretical analysis of the stress distribution in the proximal human femur, including a first estimate of the safety factor for the femoral neck (5.7, both for the maximum tensile and compressive stress) (Koch, 1917). With the advent of contemporary biology, a hundred years later it became possible to describe a cellular mechanism capable of managing bone adaptation (Carter, 1984; Roesler, 1987). Although the principles of bone adaptation (misleadingly known as “Wolff’s law”) have often been put under discussion (Bertram and Swartz, 1991; Huiskes, 1995), its general principles remain valid, and are the backbone of modern bone biomechanics (Cowin, 2001; Currey, 1982; Fung, 1980; Roesler, 1987).

It was Dennis Carter who provided a first description of the bone apposition/resorption balance in response to cyclic loading, in the form of an algorithm (Carter, 1984), which was soon converted into numerical models based on finite element (FE) analysis (Huiskes et al., 1987). The principles of bone adaptation were incorporated in FE

models initially to predict adaptation of bone to the presence of an implant (e.g. (Huiskes et al., 1989; Huiskes et al., 1992)). With the advancement of the understanding on the control mechanism of bone cells, FE models became capable of predicting trabecular morphology (i.e. sizes and branching of struts) in relation to the local loads (Huiskes et al., 2000; Mullender et al., 1994; Ruimerman et al., 2005b). Predictions of bone adaptation based on such local optimization criteria have been validated qualitatively (Huiskes, 1993). More recently, quantitative validation has become possible thanks to the advancement of high-resolution *in vivo* imaging (Lambers et al., 2011).

While local adaptation has extensively been explored at the tissue-level, its up-scaling to the organ-level has only partially been accomplished (e.g. (Kuiper et al., 1991)). Optimization of the shape of bones to achieve the maximum resistance with the minimum amount of material has been for long hypothesized (Roux, 1881). It has recently been stated that measuring bone strains can improve the understanding of bone shape-function relationships (Demes, 2007). Several studies suggest that bone geometry and density are adjusted by bone remodelling so as to attain a constant level of stress/strain (e.g.: (Lanyon, 1980)). A recent study when contralateral bones of the human lower limbs were compared (Cristofolini et al., 2014) showed that the differences in stiffness observed at the whole-bone level are mainly explained by bone segment geometry (i.e. global anatomical adaptation), rather than by differences in bone tissue properties (i.e. tissue-quality adaptation). A structure that is optimized for a given loading condition presents a uniform state of stress: this corresponds at the same time to a minimum amount of material (which translates into a minimal metabolic energy expenditure, both during growth and during locomotion), and a minimum risk of damage (Beer et al., 2006). However, the link between different

dimensional scales (from tissue-scale local adaptation to organ-level optimal structure)
is far from understood.

The problem should then be considered at different dimensional scales. Rather than sticking to the classic reductionist strategy, an integrative approach has recently been proposed, which is capable to provide a deeper understanding (Noble, 2006). It has been demonstrated that a synergic use of numerical models and *in vitro* simulations (Cristofolini et al., 2010b) can provide the most reliable and extensive understanding for such multiscale problems (Cristofolini et al., 2008; McDonald et al., 2010; Webster and Muller, 2011).

This paper will review the evidence coming from *in vitro* testing concerning the following questions:

- Are bones optimized in their multiscale structure?
- How does the structure of bones respond to the different “design specifications”?

2. “IF BONE IS THE ANSWER, THEN WHAT IS THE QUESTION?” (Huiskes, 2000)

Prof. Rik Huiskes certainly knew how to be provocative, and probably he actually enjoyed fierce debates with colleagues, both at conferences and in scientific papers (Huiskes, 1995, 2000). Myself, like many others who work in bone biomechanics, was inspired by the work of prof. Huiskes, and, like him, tried to understand better how and why bone adapts itself. Most of the work of prof. Huiskes and his co-workers in the Eighties and Nineties turned around total hip replacement, rather than focusing directly on bone. I suspect that he saw hip stems as a tool to “interrogate” the bone by

modifying the loading imposed to the proximal femur, so that the laws of bone adaptation could be investigated. In fact, in the last decade his activity was more characterized by investigation on the bone in itself, including ageing, osteoporosis, fatigue (Isaksson et al., 2006, 2008; Ruimerman et al., 2005a; van Oers et al., 2008; van Oers et al., 2011), and more in general on the mechano-biology of bone adaptation (van der Meulen and Huiskes, 2002).

3. OPTIMIZATION OF THE PROXIMAL HUMAN FEMUR

3.1 “Design requirements”

One frequently addressed example of structural optimization is the proximal human femur. If one had to describe it in engineering design terms, these are the main mechanical requirements:

- Provide a rigid structure for the attachment of muscles, ligaments and tendons, which enables enable body movements.
- Effectively respond to physiological loads: daily loads applied to the femoral head are cyclic by nature, and vary in direction (Bergmann, 2013). To resist them effectively, a combination of cortical and trabecular bone is arranged so as to provide the maximal fracture load with a minimal (but optimally arranged) amount of bone material. No sort of failure (other than bone-adaptation-inducing microcracks (Martin and Burr, 1982; Taylor and Prendergast, 1997)) is acceptable, due to the cyclic nature of such loads. The concept here is similar to the one that structural engineers apply to the design of strenuously loaded mechanical components such as a crankshaft.

- Safely resist to occasional trauma: a sideways fall is a common challenge to the proximal femur (Grisso et al., 1991; Hwang et al., 2011; Michelson et al., 1995; WHO, 1994, 2007). In this perspective, what really matters is toughness, i.e. the amount of energy absorbed prior to catastrophic failure. Sub-critical structural damage (partial bone fracture) is not desirable, but acceptable under these special circumstances. The concept here is similar to the principle that engineers apply to the design of car safety components such as the bumpers.
- Meet the requirements above with a minimal mass.

3.2 Response to loading in a physiological direction

As far as physiological loading of the femur is concerned, most of the published *in vitro* studies focussed on the effect of hip stems (Cristofolini, 1997). Failure of the proximal femoral metaphysis has often been investigated *in vitro* (e.g.: (Cristofolini et al., 2007; Lochmüller et al., 2002; Yang et al., 1996)), but the strain distribution has seldom been assessed. A theoretical study has shown that the shape and anteversion of the femoral neck provides an optimal response to physiological loads (Fabeck et al., 2002). The strain distribution in the intact and resurfaced femur has often been investigated for a single loading configuration (Crick et al., 1985; Field and Rushton, 1989). However, the directions of the hip joint resultant force during physiological and para-physiological motor tasks spans a cone of approximately 24° (Bergmann, 2013). This certainly results in a variety of loading conditions in the femur (Duda et al., 1998; Fabeck et al., 2002; Raftopoulos and Qassem, 1987; Rybicki et al., 1971). Recently, the strain distribution (magnitude and direction of principal strains) in the proximal femur has been measured by means of triaxial strain gauges at 12 locations

(Cristofolini et al., 2009), with a number of loading scenarios spanning such a cone of loading directions.

When physiological tasks are adequately simulated *in vitro*, the principal tensile strains are comparable to those recorded *in vivo* (Table 1). Such values are also comparable to the accepted threshold for physiological strain to prevent bone remodelling and resorption.

Where principal tensile strain predominates in the femoral neck (supero-lateral side during physiological loads), the cortical bone is thinner, whereas the cortex is thicker in the areas where compression predominates (medial side) (Cristofolini et al., 2009). This could be a strategy to minimize the risk of buckling.

When physiological loads are simulated *in vitro*, the direction of principal tensile strain is generally aligned with the axis of the neck/diaphysis on the lateral and medial sides (Cristofolini et al., 2009). This confirms the predominance of bending in the frontal plane. Conversely, the direction of principal strains is generally close to 45° from the axis of the neck/diaphysis on the anterior and posterior sides (Cristofolini et al., 2009), due to the presence of shear stress on the anterior and posterior sides, in agreement with previous theoretical considerations (Fabeck et al., 2002). Such an alignment of the principal strain directions is in agreement both with the reported trabecular arrangement (Ciarelli et al., 1991; Huiskes et al., 2000; Ruimerman et al., 2005b; Singh et al., 1970), and with the alignment of the osteons on the cortical surface (Baca et al., 2007).

Not surprisingly, the magnitude of the principal strains vary significantly between the different loading configurations within the 24° cone mentioned above (Cristofolini et al., 2009). However, the direction of principal strains in the cortical bone vary by a

162 remarkably narrow angle (less than $\pm 6^\circ$) when the hip joint force spans the 24° cone
163 covered by physiological loading (Cristofolini et al., 2009). Hence, the state of stress
164 in the proximal metaphysis allows structural optimization to face most physiological
165 tasks: in fact, at each point it is sufficient if the materials has a single strongest
166 direction, to resist a range of loading directions. This architecture provides the
167 maximal strength for a range of loading directions: therefore the structural
168 optimization is robust with respect to a range of loading conditions (Anonymous,
169 2013b). These findings are in agreement with a continuum-model study (Pidaparti and
170 Turner, 1997), which demonstrated that a non-strictly-orthogonal trabecular
171 arrangement provides a mechanical advantage for multidirectional loading. This effect
172 can be achieved by a multiscale arrangement of the anisotropic and inhomogeneous
173 properties of the proximal femur, which generates a sort of “funnel effect” (Fig. 1).

174 The proximal femur is structurally optimized to withstand daily loads to such an extent
175 that any artificial modification of its structure makes it weaker. Insertion of a metal
176 component such as a resurfacing or a minimally invasive hip stem (definitely stronger
177 than bone) in the best case does not affect bone strength, but in the worst case can
178 significantly weaken the structure (Cristofolini et al., 2011; Davis et al., 2007; Long et
179 al., 2009; Morlock et al., 2006; Murray et al., 2007; Schlegel et al., 2010).

180 The so-called spontaneous fractures (Jeffery, 1974; Michelson et al., 1995) can occur
181 in a specific type of subjects (Viceconti et al., 2012) when an excessive force is
182 applied to the proximal femur in a physiological direction (e.g. simulating stance). If
183 this scenario is replicated *in vitro*, the femur exhibits an almost-perfectly elastic
184 response (Juszczyk et al., 2011), with minimal delay between fracture onset and
185 catastrophic failure (Juszczyk et al., 2013) (Fig. 2). Such a brittle behaviour is typical
186 of materials and structures where the largest possible failure force is achieved, while

giving up ductility. Therefore the femur seems to be optimized to withstand the largest possible force peak (and hence the largest fatigue-inducing cyclic load) during physiological loading.

Recently, a study was carried out on the safety factor of the proximal femur of a diverse population (200 subjects, male and female, 23 to 84 years old (Taddei et al., IN PRESS)). Subject-specific FE models were built using a multi-scale approach that incorporated inhomogeneous tissue properties, and scaled musculo-skeletal loads. This study has shown that the proximal femur has a remarkably constant safety factor with respect to a wide range of loading directions experienced during physiological activities.

3.3 Response to loading in a non-physiological direction

Most fractures in the proximal femoral metaphysis are a consequence of accidental falls (Hayes et al., 1993; Parkkari et al., 1999). There is a general agreement on the mechanism leading to fractures in the proximal femur during falls: in most cases the subject falls on his/her side hitting the floor with the side of the hip (Nankaku et al., 2005; van den Kroonenberg et al., 1996). As a consequence, a force is delivered to the greater trochanter through the soft tissues, which is more or less perpendicular to the long axis of the femur (Hayes et al., 1993; Parkkari et al., 1999). At the same time, part of the load is transmitted from the pelvis to the femoral head. This scenario loads the proximal femur with a large bending moment in the frontal plane, having opposite direction to the physiological one (and possibly a torsional moment). No information is available about the exact direction of the forces applied during a sideways fall (in fact, falling itself is an unpredictable event).

The first *in vitro* simulation of sideways fall loading of the femur is due to Backman (Backman, 1957): the femur diaphysis (adducted by 10°, internally rotated by 15°) was held distally, free to rotate in the frontal plane, while a force was applied to the femoral head with the greater trochanter resting on a clay cushion.

The failure force of the proximal femur has often been measured under *in vitro* simulated sideways fall (Bauer et al., 2006; Bouxsein et al., 1999; Cheng et al., 1997; Courtney et al., 1994; Eckstein et al., 2002; Eckstein et al., 2004; Juszczuk et al., 2010). The strain distribution in the proximal femur has also been measured *in vitro* for a simulated fall (a sideways load was delivered to a femur adducted and internally rotated by 30°, while strain was measured at 9 locations (Lotz et al., 1991)). More recently, an *in vitro* test has been developed that enables measuring the strain distribution in the proximal femur for a simulated sideways fall where a wide range of loading adduction and internal rotation angles can be explored (Zani et al., 2014).

Also for this kind of loading, the magnitude of principal strains strongly depends on the direction of the applied force (Cristofolini, 2011; Zani et al., 2012; Zani et al., SUBMITTED). Increasing the internal rotation angle (and consequently, the bending moment in the neck and the torque delivered to the proximal diaphysis) a general increase of strains was observed. The largest compressive strain are found on the supero-lateral neck region, and are more than double of the largest tensile strain (on the medial side). This tends to crush the thin cortical shell and trabeculae that are present on the supero-lateral side (such a structure represents an optimum only for a physiological loading scenario, which generates tension in this region). For this reason, failure can initiate due to compression, in the supero-lateral neck region (Cristofolini, 2011; de Bakker et al., 2009; Zani et al., 2012; Zani et al., 2014; Zani et

al., SUBMITTED). Furthermore, fracture is not achieved as a single catastrophic event, but takes energy and time to occur (Fig. 2).

The force required to fracture a femur in a sideways fall is lower than for physiological loading directions by a factor that varies between 2.16 according to an *in vitro* study (Keyak, 2000), 2.85 according to a FE study (Keyak et al., 2001), 3.5 according to a different *in vitro* study (Duchemin et al., 2006), and 4.4 according to a more recent FE study (Bessho et al., 2009). Conversely, the energy required to fracture a femur in sideways fall is 1.4 times higher than for physiological loading directions (Duchemin et al., 2006).

For a simulated sideways fall, the direction of principal strains varied greatly (by up to 45°) when the loading direction was tilted within a 30° cone (Cristofolini, 2011; Zani et al., 2012). The largest variations in alignment were observed on the lateral side. This is quite different from what occurs for physiological loading, where the direction of the applied force has a minimal effect of the alignment of principal strains, and can be taken as an indicator of the fact that principal strains go “against” the strongest directions of the anisotropic bone tissue. For this reason, the “funnel effect” described above does not work when a force is applied laterally (Fig. 1).

3.4 The optimized femur

As previously reported, the need for optimizing the femur for cyclic daily loads requires a stiff structure, with spatial constraints that results in a vulnerable structure when a different load is applied, such as during a fall (Currey, 2003). However, evolution has lead to a structure that is optimized to different scenarios (Fig. 2): when daily loads are exerted, the proximal femur is rigid (providing maximal efficiency) and strong (preventing excessive propagation of fatigue cracks). If an occasional overload

is applied during a fall, the maximal force is lower, but the proximal femur undergoes a quite progressive failure, which enables absorbing a much higher energy before complete failure.

4. OPTIMIZATION OF THE DIAPHYSIS OF THE HUMAN TIBIA

4.1 Anatomical and biomechanical considerations

The human tibia shows a peculiar shape when observed from lateral, where its cross-section varies linearly along its axis (Fig. 3). This suggests that the shape of the tibia could be optimized to resist cantilever load acting in the sagittal plane. In fact, when a slender structure is loaded by a shear force, a compressive force, and a bending moment, the latter generates stress values that can be orders of magnitude higher (and at a higher risk of fracture) than the other load components (Beer et al., 2006).

There are some anatomical peculiarities that should be considered for the tibia: first of all, there is no major muscle insertion in a large portion of the diaphysis; the main proximal insertion is that of the patellar tendon. Furthermore, the two main joint complexes (i.e. knee and ankle) can be, as a first approximation, considered respectively as a cylindrical hinge and a saddle. From these considerations, it is likely that a compressive force is transmitted through the tibial plateau (which is relatively flat), while a moment is generated in the sagittal plane by the patellar tendon. Equilibrium is achieved by the ankle joint reaction. This consideration is confirmed by musculoskeletal models (Wehner et al., 2009), and by *in vivo* measurements of joint forces by means of knee prostheses for a number of physiological activities (gait, stair-climbing and –descending, jogging (Bergmann, 2013; Kutzner et al., 2010; Mundermann et al., 2008)):

281 • The largest component of force is directed axially, while the second largest
282 component of force is the antero-posterior one (one order of magnitude lower
283 than the axial one). The right-left force component is 2-10 times lower than the
284 antero-posterior one.

285 • When the force peak is reached, the moment in the sagittal plane is at least
286 twice as high as the moment in the frontal plane. The torsional moment about
287 the tibial axis is lower in magnitude than the other two moments.

288 Given this relatively simple loading condition, one could expect the anatomy of the
289 human tibia to generate a uniform state of stress, which would correspond to an
290 optimized organ-level structure (Beer et al., 2006). The geometric moments of area
291 (where the cross-section was modelled as a homogenous, hollow axisymmetric shaft)
292 exhibit an almost-linear variation along the tibia (Martens et al., 1981; Minns et al.,
293 1975).

294 A recent study where six cadaver tibias were CT scanned (Cristofolini et al., 2013a)
295 has shown that the diaphysis of the tibia is shaped so as to resist best to a linearly-
296 varying bending moment in the sagittal plane, such as for cantilever loading
297 (Cristofolini et al., 2013a):

298 • The moments of area and moments of inertia increased linearly from distal to
299 proximal.

300 • Linearity was stronger for the area and inertia properties corresponding to a
301 moment in the sagittal plane than in the frontal one.

302 • The section modules increased linearly from distal to proximal.

- Conversely, the variations of area and polar moments along the tibia did not seem to be optimized for the corresponding loading components (torsion and axial force).

4.2 Strain distribution

In vivo strain has been measured in the human tibia. However, such experiments are limited by the number of strain measurement locations (typically just one point) (Al Nazer et al., 2012). Therefore, the strain distribution *in vivo* is not known. *In vitro* strain measurements in the human tibia concentrated on four-point-bending, axial compression and torsion (Cristofolini et al., 2010a; Cristofolini and Viceconti, 2000; Gray et al., 2008; Gray et al., 2007; Heiner, 2008).

An *in vitro* study on six tibias, each with 28 triaxial strain gauges, investigated the hypothesis that the strain distribution in the human tibia is optimized for a cantilever loading in the sagittal plane (Cristofolini et al., 2013a). The strain distribution for the different loading configurations showed that the diaphysis of the tibia behaves as a uniform-stress structure (i.e. optimized (Beer et al., 2006)) for a cantilever loading in the sagittal plane and, to a lesser extent, in the frontal plane (Fig. 4). In fact, the strain distribution was remarkably uniform along the tibia for cantilever loading. For all the other loading configurations (including axial compression), the strain variations along the tibia were one order of magnitude larger than for cantilever.

4.3 The optimized tibia

In conclusion, the *in vitro* studies mentioned above support the idea that the human tibia is optimized to resist to the bending moment that is generated in the sagittal plane when a force is delivered to its distal extremity (with an antero-posterior

component). In fact, such a force generates a bending moment that varies linearly along the diaphysis. Such a linearly-varying bending moment is compensated by a linear variation of the cross-sectional properties along the tibia. This results in a remarkably uniform state of stress in the diaphysis, which is a highly efficient structural solution.

5. OPTIMIZATION OF THE BODY OF THE THORACOLUMBAR VERTEBRAE

5.1 Anatomical and biomechanical considerations

Daily activity induces complex loading scenarios on the human vertebrae. Information about spinal loads can be derived from a combination of *in vivo* measured kinematic parameters and mathematical models. A similar approach has been used to predict compressive forces and moments in the lumbar spine during lifting activities (Dolan et al., 1994). EMG-based techniques, along with intra-discal pressure measurements, have been used to validate biomechanical models for the prediction of spinal loads (Hansson et al., 1984; Schultz et al., 1982). While biomechanical simulations have the advantage of being non-invasive, more reliable loading data can only be obtained through direct *in vivo* measurement with telemeterized spinal implants (Ledet et al., 2012). An extensive amount of spinal load data is available for different motor tasks and postoperative periods (Bergmann, 2013). From the analysis above it is clear that only indicative estimates of the loads (and their direction) acting on the vertebrae *in vivo* is possible.

From the analysis of the spine models and *in vivo* data, one can conclude that (Brandolini et al., 2014):

- During physiological loading, the intervertebral disks in first approximation act ball-joint-like structures. Such a hypothesis underlies many numerical models of the spine (de Zee et al., 2007; Han et al., 2011).
- Therefore, the resultant loading delivered to the vertebral body by the disks consists of a force passing through the centre of such ball-joint-like disks, and therefore is roughly aligned with the vertebral body itself.
- When most daily motor tasks are considered, such a force spans a cone of approximately 30° (Fig. 5) (Bergmann, 2013).

The optimal structure to withstand a distributed force consists of a dense mesh of cancellous bone (with the trabeculae being aligned with the axial force itself), and an extremely thin cortical shell (Fields et al., 2011; Prakash et al., 2007).

5.2 Strain distribution

One of the first studies on the strain distribution in the vertebral body was carried out by means of brittle coating, photoelasticity (Shah et al., 1976) and 17 strain gauges (Shah et al., 1978), for different compressive loads. They reported strains of the order of 500-1500 microstrains for a 1470N compressive force. The effect of an inclined load (2800 N at 16°) has been investigated on functional spinal units using 3 to 4 strain gauges, where compressive strain of about 650 microstrain were measured (Lin et al., 1978). Strains induced by compression and shear loads were quantified with three triaxial strain gauges on the vertebral rim, and one on the endplate surface (Frei et al., 2002). Fracture risk was assessed by (Kayanja et al., 2004), but the most stressed region could not be identified as only one gauge was applied on each vertebral body. Axial compression is probably the most frequent *in vitro* loading condition (e.g.

(Bürklein et al., 2001; Fields et al., 2011; Jiang et al., 2010; Lochmüller et al., 2008; Luo et al., 2010)). In some cases also eccentric compression (Furtado et al., 2007; Teo et al., 2001) or anterior bending (Buckley et al., 2007; Granhed et al., 1989) were simulated. Recently, a study was published (Cristofolini et al., 2013b) where eight thoracolumbar vertebrae instrumented with eight triaxial strain gauges. The vertebrae were loaded through their disks and were subjected to a variety of loading conditions that included the cone spanned by the resultant force during physiological motor tasks, but also other load components such as torsion and traction (Bergmann, 2013). The principal strains were generally aligned as expected: axially/circumferentially for all loading configurations implying a compressive force, and roughly at 45° for torsion. The results from (Cristofolini et al., 2013b) indicate that the structure of the vertebral body is optimized for a compressive force aligned with the vertebral body. In fact:

- Strain was lower when the compressive force is perpendicular to the vertebral body, as opposed to all the configurations where the force was tilted by 15° in any direction within the 30° cone (Fig. 5).
- The strain distribution was significantly more uniform for axial-compression than for any other configuration (Fig. 5): uniform stress/strain is an optimization criterion in structural engineering (Beer et al., 2006).
- When the force was tilted by 15° in any direction, the direction of principal strains varies by a much wider angle (nearly 30°) compared to the axial-compression configuration (Fig. 6). As bone (especially trabecular bone) is known to be significantly weaker when loaded oblique to its structure (Fields et al., 2011; Öhman et al., 2007), this seems to suggest that the structure of the vertebra is optimized (in terms of local tissue arrangement, and anisotropy) for a single, specific, loading direction.

5.3 The optimized vertebral body

The studies above concur on the idea that the micro- and macro-structure of the vertebral body is optimized to withstand the daily loads: a distributed force strongly aligned with the vertebral body itself. Any other load, different from the ones for which the structure is optimized, is not resisted as effectively (Fig. 5,6): for instance, when a bending moment or an eccentric force are applied, the strength of the vertebra is significantly lower than for a purely axial force (Buckley et al., 2007; Bürklein et al., 2001; Fields et al., 2011; Kayanja et al., 2004; Teo et al., 2001). In fact, a modification to such an optimized structure may result in a weakening of the structure itself. This could be the reason for the contradictory results reported for prophylactic vertebroplasty (Cristofolini et al., 2013c; Cristofolini et al., SUBMITTED; Oakland et al., 2009).

It must be pointed out that such a structure of the vertebral body is optimal for biped locomotion, where the spine mainly works in compression (i.e. in humans and primates (Sheng et al., 2009)). Conversely, the spine in quadrupeds is mostly subjected to bending. The optimal structure in that case is more similar to that of the diaphysis of long bones: a hollow, thick cortical shell filled with a coarse trabecular structure (Boszczyk et al., 2001; Kandziora et al., 2001; Sheng et al., 2009).

6. CONCLUSIONS (“SURVIVAL” IS THE QUESTION)

The examples in the previous pages show how bones are optimized structures in a very complex way. In fact: (i) they are able to withstand daily loads with a rather uniform margin of safety; (ii) they are able to tolerate variations of direction of such daily loads, without losing such an optimal distribution of stress/strain; (iii) they do so with

a minimal mass; (iv) they are sufficiently tough to minimize damage when an occasional non-physiological load occurs. The first three criteria are rewarded in daily life (in terms of minimal expenditure of resources), and could be driven by a daily stimulus. Conversely, the fourth criterion becomes crucial only occasionally (in terms of survival to trauma), and cannot be based on a stimulus on a daily basis.

To make things more complex, one should not forget the additional challenge posed by growth: in fact, the structure needs to be optimized throughout increase in size. This is possibly accounted for by the fact that bones are not just “designed and built”, but they grow and adapt over an entire lifetime.

At the tissue-level, biological studies have uncontroversibly shown that bone tissue responds to mechanical loads with a local deposition/resorption balance in a way that tends to generate a uniform state of stress. This means that bone tissue is capable of adapting to the mechanical demand (and to changes of the mechanical demand) at each anatomical site of each individual. However, local optimization (at the tissue-level) does not automatically guarantee structural optimization (at the organ-level). The shape-function relationship of bones is a debated issue. No mechanism for an “active” global structural optimization has so far been identified within the bone metabolism.

The overall “engine” behind such efficient, safe and robust structural arrangement of skeletal bones is evolution. The best phenotype variations (either deriving from gene mutations, or from mutation-driven changes in gene regulation and expression) tend to procreate; sub-optimal variations tend to be lost (too heavy and slow to escape a predator, or whining in a ditch with a broken bone). This mechanism acts at (at least) two levels:

1. The overall optimal anatomy (e.g. number of bones, their mutual position, their gross geometry) has been selected through the generations. The recent evolutionary developmental biology approach (EVO-DEVO (Anonymous, 2013a)) suggests that modularity is a key pattern in the evolution process.
2. At the same time, a mechanism for on-the-fly adaptation has been selected and embedded in the form of mechanically-regulated deposition-resorption mechanisms, that is capable of adjusting the local structure in response to an altered mechanical environment. This is a necessary adaptation mechanism as there is no “optimal structure” that fits all individuals, all lifestyles, and all stages of life (Jepsen, 2011).

To describe it with a metaphor: in order to fly, an aircraft needs to have a suitable structure (wings, vertical stabilizer, rudder, flaps, etc), but also the ability to adjust dynamically its elements in order to remain stable.

To follow up Prof. Huiskes provocation (“If bone is the answer, then what is the question?” (Huiskes, 2000)), this review suggests that the question to which bone is the answer remains “how to best survive?”.

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CAPTIONS AND FIGURES

Range of physiological loading directions

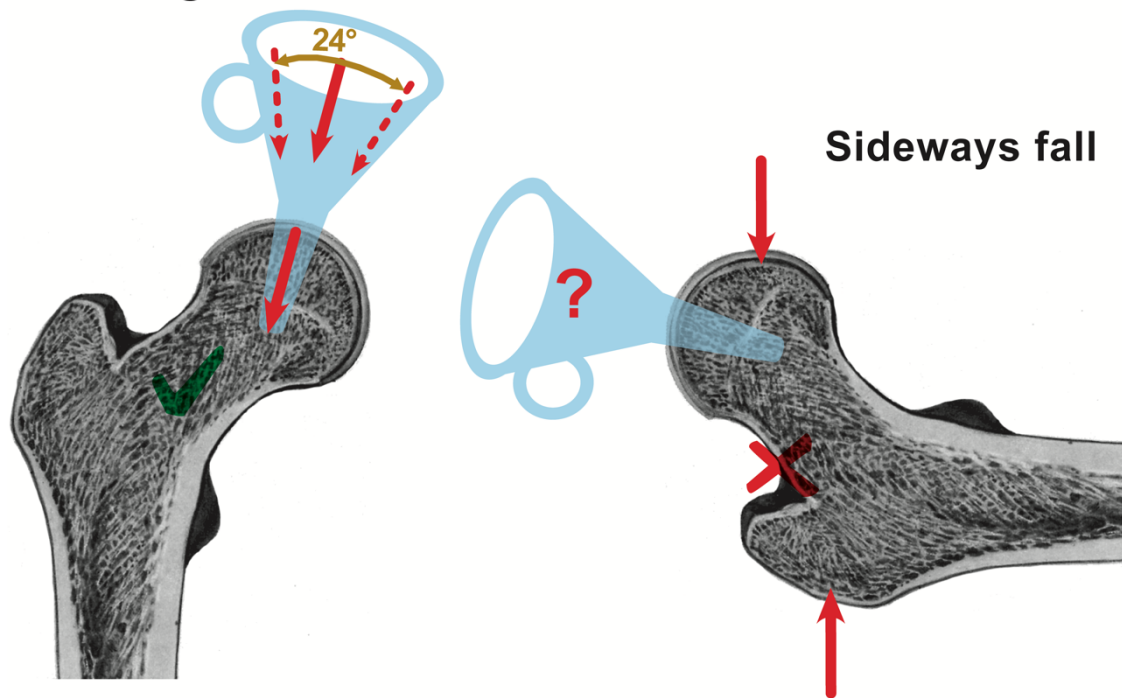


Fig. 1 – The multiscale arrangement of anisotropic and inhomogeneous properties of the proximal femur generates a sort of “funnel effect”. LEFT: when a force is applied to the femoral head within a range of directions (corresponding to the physiological range), this makes the directions of principal strain converge to well-defined directions (which correspond to the strongest directions of the anisotropic tissue at each point). RIGHT: Conversely, if a force is applied in a different direction (e.g. during a sideways fall) such an effect is not reached and the directions of principal strain can be quite different from the strongest structural directions.

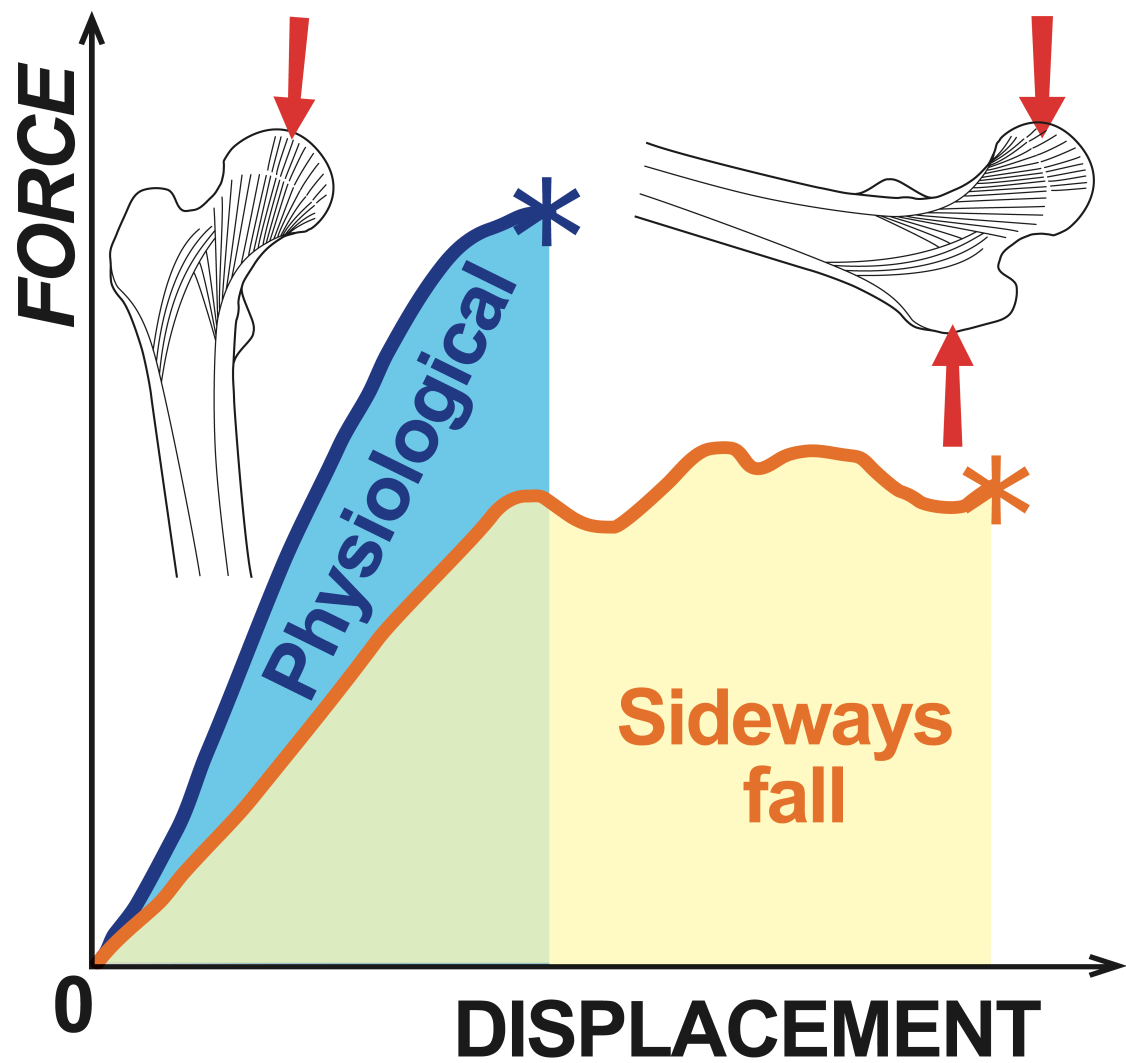


Fig. 2 – Qualitative force-displacement plot for a femur undergoing two different loading conditions: stiffness and high maximal force predominate for physiological loading, while a large energy is needed to cause a complete fracture during a sideways fall.

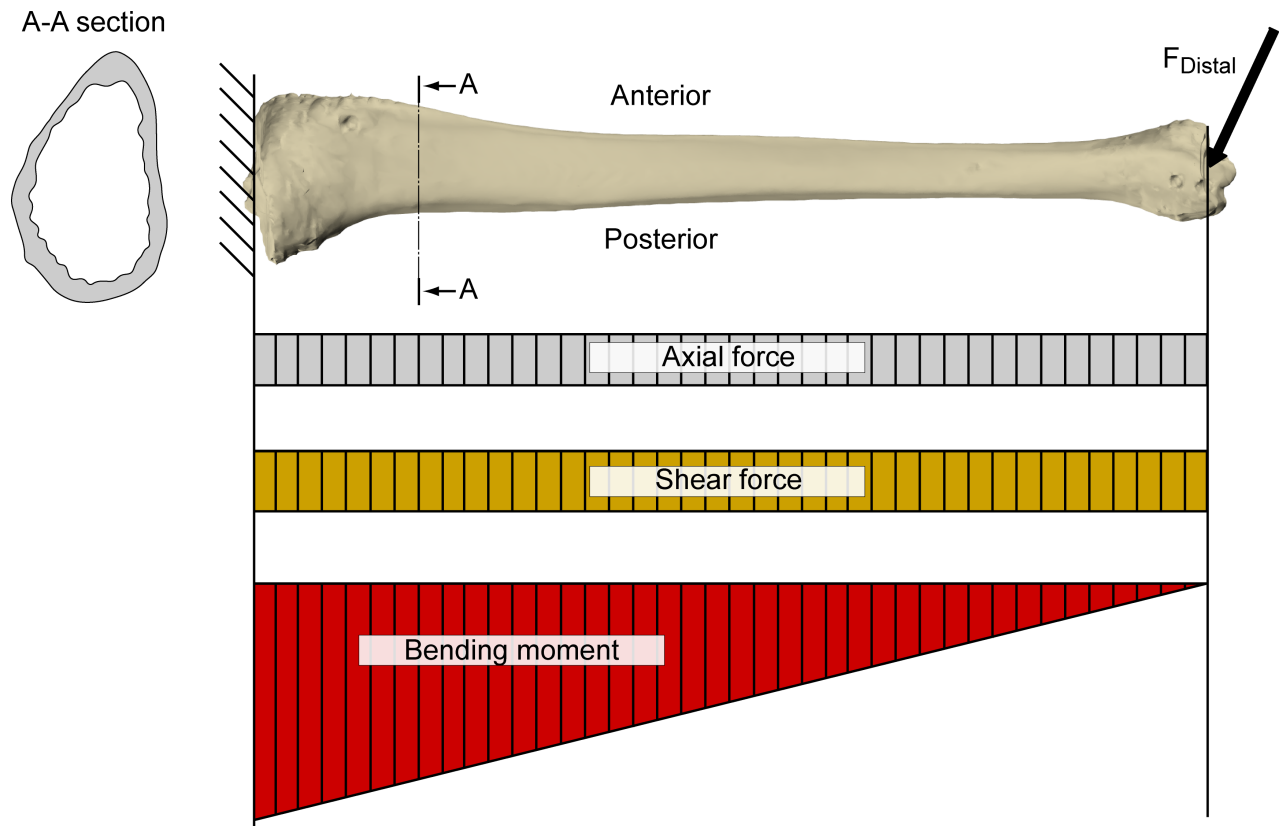


Fig. 3 – Lateral view of a human tibia: the variation of cross-section along its axis is visible. Also indicated is a schematization of the physiological loading condition: a force is applied at the distal end in the sagittal plane. The axial component of such a force generates compression. The antero-posterior component generates a cantilever condition, where the bending moment varies linearly along the tibial axis.

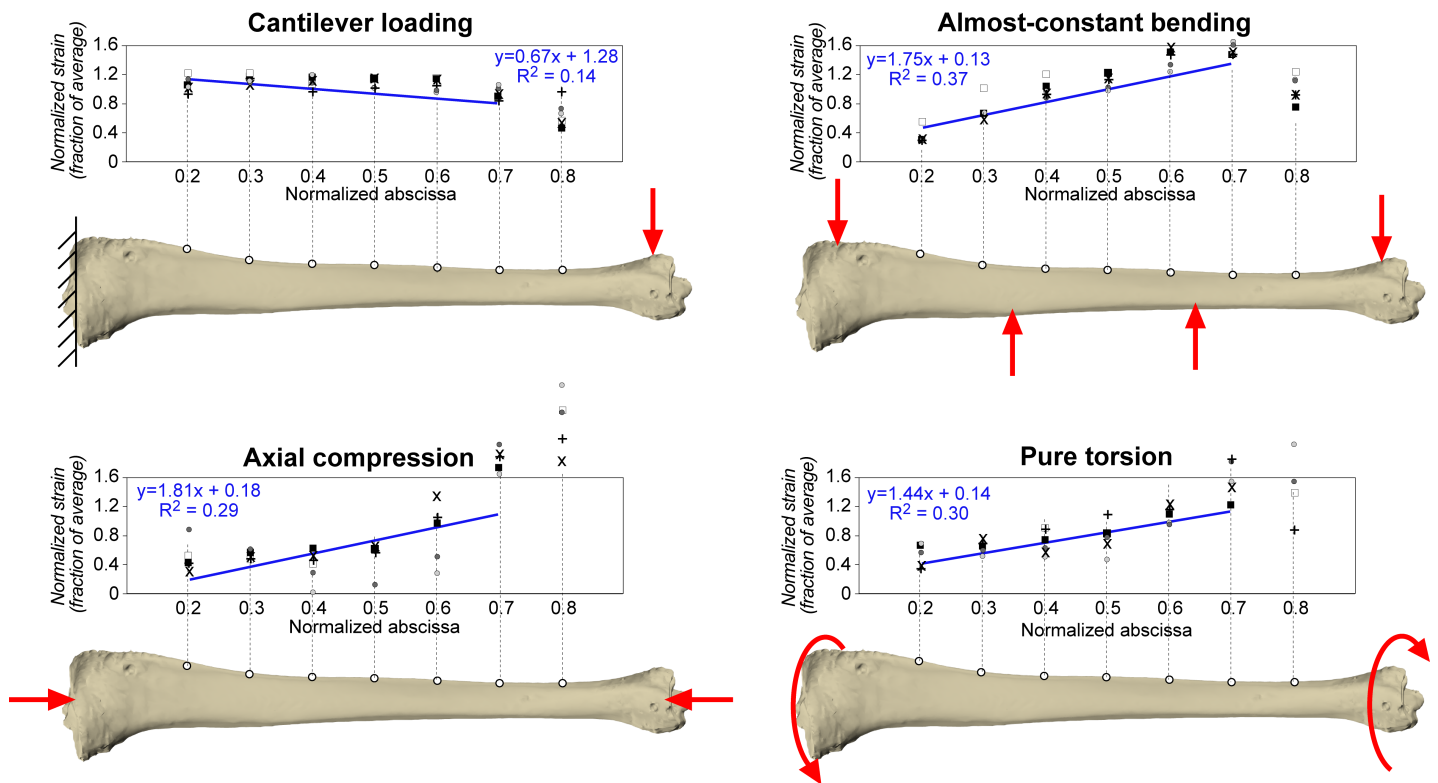


Fig. 4 – Strain distribution on the anterior side of the tibia for different loading conditions: cantilever loading (maximal bending moment proximally) in the sagittal plane; four-point-bending (almost-constant bending moment along the tibia) in the sagittal plane; axial compression; torsion. For each specimen (6 are plotted) principal strain at each strain gauge is reported as a fraction of the absolute value of the average between the 7 strain gauges. The strain distribution for the cantilever loading in the sagittal plane is far more uniform than for any other loading configuration. Adapted from (Cristofolini et al., 2013a).

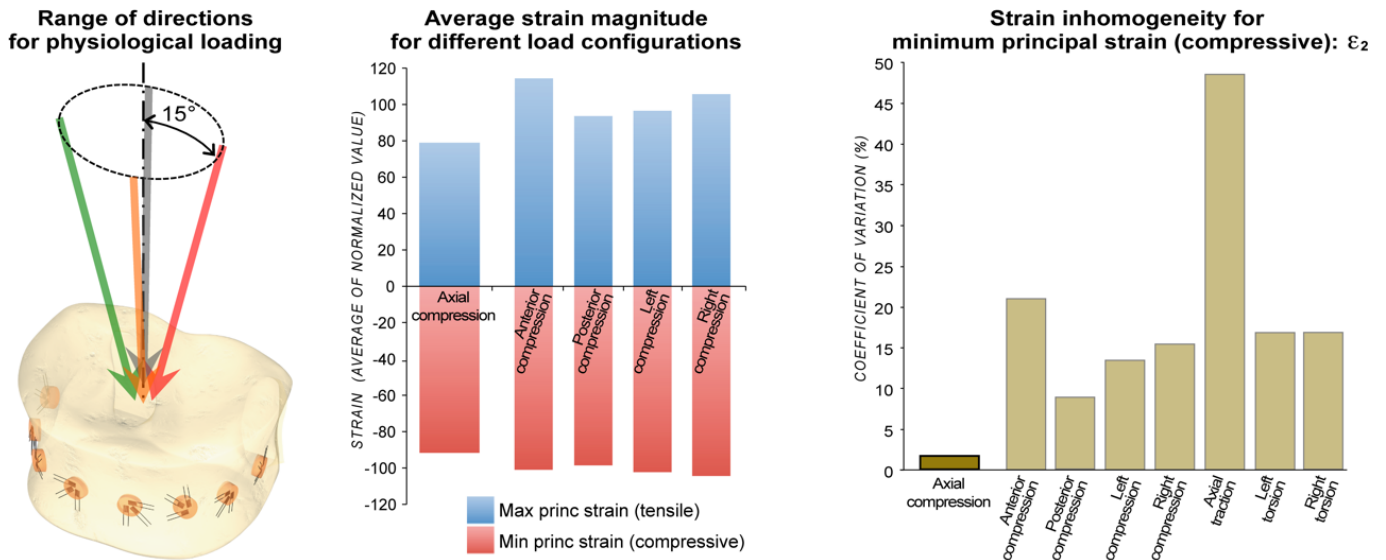


Fig. 5 – The vertebral body seems to be designed to withstand an axial force. LEFT: cone spanned by the resultant forces during daily activities (Bergmann, 2013). CENTRE: strain is lower when the compressive force is aligned with the vertebral body, compared to the cases where the force was tilted by 15° in any direction (to enable comparison between the different loading configurations, for each strain gauge, each strain component is normalized with respect to the average between the five loading configurations; the average between eight measurement locations on each vertebra is plotted; data adapted from (Cristofolini et al., 2013b)). RIGHT: when an axial force is applied strain gradients are much lower than for any other type of loading (the strain inhomogeneity for the different loading configurations is computed as standard deviation between strain measurement locations, for the compressive principal strain; data adapted from (Cristofolini et al., 2013b)).

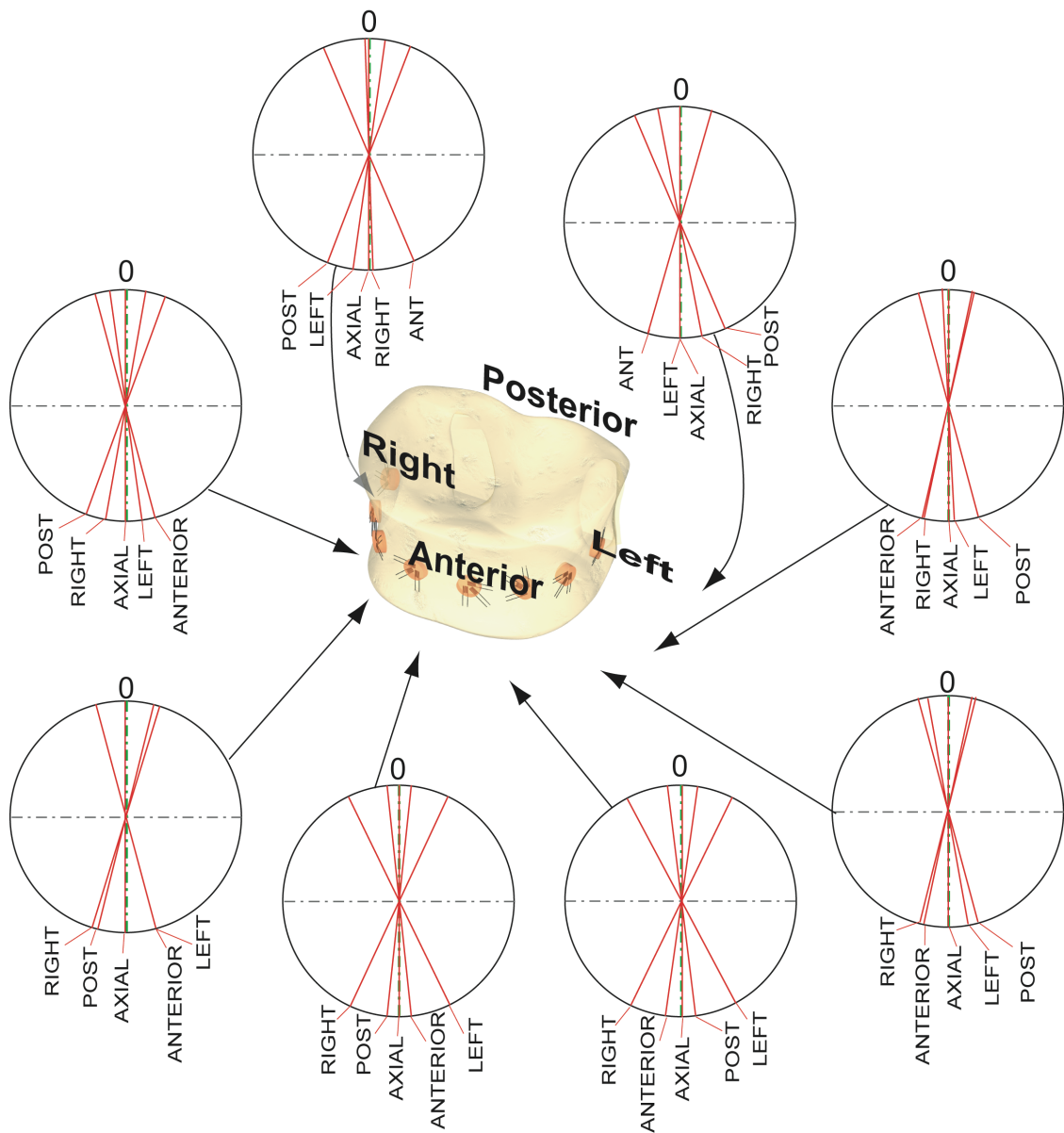


Fig. 6 – The vertebral body seems to be designed to withstand an axial force: when the force is tilted by 15° in any direction (anterior, posterior, right, left) within the 30° cone, the alignment of principal compressive strains becomes quite different from the alignment of the trabeculae (i.e. the strongest direction of the bone) (Cristofolini et al., 2013b).

TABLES

Table 1 – Strain values measured *in vitro* when physiological motor tasks are simulated. When available, forces are expressed in Body weight (BW).

	Motor task	Measured strain (microstrain)	Note
<i>In vitro experiment</i>			
(Field and Rushton, 1989)	F =1500 N at 16° in the frontal plane	Range: -1800 to +1200	Peak value out of 17 uniaxial strain gauges
(Cristofolini et al., 2009)	Single leg stance, walk (F = 2.5 BW) Stumbling (F = 8.7 BW)	Max tensile: +735, Max compressive: -1029 Max tensile: +5760 to 8468 Max compression: -11850	Average of 12 locations, 24 femurs Local peak
<i>In vivo measurements</i>			
(Aamodt et al., 1997)	One-leg stance Walking Stair Climbing	Range: -435 to +1463 Range: -393 to +1198 Range: -948 to +1454	One strain triaxial strain gauge on the lateral proximal part of the femur
<i>Physiological ranges</i>			
(Lanyon, 1980)	Bone resorption/formation	Approximately 1000	
(Bayraktar et al., 2004)	Bone tissue fracture	Tensile: +7300, Compressive: -10000	