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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

20 **1. INTRODUCTION**

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

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

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

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

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

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

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

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

84 **2. “IF BONE IS THE ANSWER, THEN WHAT IS THE QUESTION?”** 85 **(Huiskes, 2000)**

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

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

99 **3. OPTIMIZATION OF THE PROXIMAL HUMAN FEMUR**

100 **3.1 “Design requirements”**

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

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

- 115 • Safely resist to occasional trauma: a sideways fall is a common challenge to the
116 proximal femur (Grisso et al., 1991; Hwang et al., 2011; Michelson et al.,
117 1995; WHO, 1994, 2007). In this perspective, what really matters is toughness,
118 i.e. the amount of energy absorbed prior to catastrophic failure. Sub-critical
119 structural damage (partial bone fracture) is not desirable, but acceptable under
120 these special circumstances. The concept here is similar to the principle that
121 engineers apply to the design of car safety components such as the bumpers.
- 122 • Meet the requirements above with a minimal mass.

123 **3.2 Response to loading in a physiological direction**

124 As far as physiological loading of the femur is concerned, most of the published *in*
125 *vitro* studies focussed on the effect of hip stems (Cristofolini, 1997). Failure of the
126 proximal femoral metaphysis has often been investigated *in vitro* (e.g.: (Cristofolini et
127 al., 2007; Lochmüller et al., 2002; Yang et al., 1996)), but the strain distribution has
128 seldom been assessed. A theoretical study has shown that the shape and anteversion of
129 the femoral neck provides an optimal response to physiological loads (Fabeck et al.,
130 2002). The strain distribution in the intact and resurfaced femur has often been
131 investigated for a single loading configuration (Crick et al., 1985; Field and Rushton,
132 1989). However, the directions of the hip joint resultant force during physiological
133 and para-physiological motor tasks spans a cone of approximately 24° (Bergmann,
134 2013). This certainly results in a variety of loading conditions in the femur (Duda et
135 al., 1998; Fabeck et al., 2002; Raftopoulos and Qassem, 1987; Rybicki et al., 1971).
136 Recently, the strain distribution (magnitude and direction of principal strains) in the
137 proximal femur has been measured by means of triaxial strain gauges at 12 locations

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

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

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

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

159 Not surprisingly, the magnitude of the principal strains vary significantly between the
160 different loading configurations within the 24° cone mentioned above (Cristofolini et
161 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

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

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

197 **3.3 Response to loading in a non-physiological direction**

198 Most fractures in the proximal femoral metaphysis are a consequence of accidental
199 falls (Hayes et al., 1993; Parkkari et al., 1999). There is a general agreement on the
200 mechanism leading to fractures in the proximal femur during falls: in most cases the
201 subject falls on his/her side hitting the floor with the side of the hip (Nankaku et al.,
202 2005; van den Kroonenberg et al., 1996). As a consequence, a force is delivered to the
203 greater trochanter through the soft tissues, which is more or less perpendicular to the
204 long axis of the femur (Hayes et al., 1993; Parkkari et al., 1999). At the same time,
205 part of the load is transmitted from the pelvis to the femoral head. This scenario loads
206 the proximal femur with a large bending moment in the frontal plane, having opposite
207 direction to the physiological one (and possibly a torsional moment). No information
208 is available about the exact direction of the forces applied during a sideways fall (in
209 fact, falling itself is an unpredictable event).

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

214 The failure force of the proximal femur has often been measured under *in vitro*
215 simulated sideways fall (Bauer et al., 2006; Bouxsein et al., 1999; Cheng et al., 1997;
216 Courtney et al., 1994; Eckstein et al., 2002; Eckstein et al., 2004; Juszczuk et al.,
217 2010). The strain distribution in the proximal femur has also been measured *in vitro*
218 for a simulated fall (a sideways load was delivered to a femur adducted and internally
219 rotated by 30°, while strain was measured at 9 locations (Lotz et al., 1991)). More
220 recently, an *in vitro* test has been developed that enables measuring the strain
221 distribution in the proximal femur for a simulated sideways fall where a wide range of
222 loading adduction and internal rotation angles can be explored (Zani et al., 2014).

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

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

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

243 For a simulated sideways fall, the direction of principal strains varied greatly (by up to
244 45°) when the loading direction was tilted within a 30° cone (Cristofolini, 2011; Zani
245 et al., 2012). The largest variations in alignment were observed on the lateral side.
246 This is quite different from what occurs for physiological loading, where the direction
247 of the applied force has a minimal effect of the alignment of principal strains, and can
248 be taken as an indicator of the fact that principal strains go “against” the strongest
249 directions of the anisotropic bone tissue. For this reason, the “funnel effect” described
250 above does not work when a force is applied laterally (Fig. 1).

251 **3.4 The optimized femur**

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

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

261 **4. OPTIMIZATION OF THE DIAPHYSIS OF THE HUMAN TIBIA**

262 **4.1 Anatomical and biomechanical considerations**

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

269 There are some anatomical peculiarities that should be considered for the tibia: first of
270 all, there is no major muscle insertion in a large portion of the diaphysis; the main
271 proximal insertion is that of the patellar tendon. Furthermore, the two main joint
272 complexes (i.e. knee and ankle) can be, as a first approximation, considered
273 respectively as a cylindrical hinge and a saddle. From these considerations, it is likely
274 that a compressive force is transmitted through the tibial plateau (which is relatively
275 flat), while a moment is generated in the sagittal plane by the patellar tendon.
276 Equilibrium is achieved by the ankle joint reaction. This consideration is confirmed by
277 musculoskeletal models (Wehner et al., 2009), and by *in vivo* measurements of joint
278 forces by means of knee prostheses for a number of physiological activities (gait, stair-
279 climbing and –descending, jogging (Bergmann, 2013; Kutzner et al., 2010;
280 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.

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

306 **4.2 Strain distribution**

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

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

322 **4.3 The optimized tibia**

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

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

331 **5. OPTIMIZATION OF THE BODY OF THE THORACOLUMBAR** 332 **VERTEBRAE**

333 **5.1 Anatomical and biomechanical considerations**

334 Daily activity induces complex loading scenarios on the human vertebrae. Information
335 about spinal loads can be derived from a combination of *in vivo* measured kinematic
336 parameters and mathematical models. A similar approach has been used to predict
337 compressive forces and moments in the lumbar spine during lifting activities (Dolan et
338 al., 1994). EMG-based techniques, along with intra-discal pressure measurements,
339 have been used to validate biomechanical models for the prediction of spinal loads
340 (Hansson et al., 1984; Schultz et al., 1982). While biomechanical simulations have the
341 advantage of being non-invasive, more reliable loading data can only be obtained
342 through direct *in vivo* measurement with telemeterized spinal implants (Ledet et al.,
343 2012). An extensive amount of spinal load data is available for different motor tasks
344 and postoperative periods (Bergmann, 2013). From the analysis above it is clear that
345 only indicative estimates of the loads (and their direction) acting on the vertebrae *in*
346 *vivo* is possible.

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

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

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

360 **5.2 Strain distribution**

361 One of the first studies on the strain distribution in the vertebral body was carried out
362 by means of brittle coating, photoelasticity (Shah et al., 1976) and 17 strain gauges
363 (Shah et al., 1978), for different compressive loads. They reported strains of the order
364 of 500-1500 microstrains for a 1470N compressive force. The effect of an inclined
365 load (2800 N at 16°) has been investigated on functional spinal units using 3 to 4 strain
366 gauges, where compressive strain of about 650 microstrain were measured (Lin et al.,
367 1978). Strains induced by compression and shear loads were quantified with three
368 triaxial strain gauges on the vertebral rim, and one on the endplate surface (Frei et al.,
369 2002). Fracture risk was assessed by (Kayanja et al., 2004), but the most stressed
370 region could not be identified as only one gauge was applied on each vertebral body.
371 Axial compression is probably the most frequent *in vitro* loading condition (e.g.

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

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

397 **5.3 The optimized vertebral body**

398 The studies above concur on the idea that the micro- and macro-structure of the
399 vertebral body is optimized to withstand the daily loads: a distributed force strongly
400 aligned with the vertebral body itself. Any other load, different from the ones for
401 which the structure is optimized, is not resisted as effectively (Fig. 5,6): for instance,
402 when a bending moment or an eccentric force are applied, the strength of the vertebra
403 is significantly lower than for a purely axial force (Buckley et al., 2007; Bürklein et al.,
404 2001; Fields et al., 2011; Kayanja et al., 2004; Teo et al., 2001). In fact, a
405 modification to such an optimized structure may results in a weakening of the structure
406 itself. This could be the reason for the contradictory results reported for prophylactic
407 vertebroplasty (Cristofolini et al., 2013c; Cristofolini et al., SUBMITTED; Oakland et
408 al., 2009).

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

415 **6. CONCLUSIONS (“SURVIVAL” IS THE QUESTION)**

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

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

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

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

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

- 443 1. The overall optimal anatomy (e.g. number of bones, their mutual position, their
444 gross geometry) has been selected through the generations. The recent
445 evolutionary developmental biology approach (EVO-DEVO (Anonymous,
446 2013a)) suggests that modularity is a key pattern in the evolution process.
- 447 2. At the same time, a mechanism for on-the-fly adaptation has been selected and
448 embedded in the form of mechanically-regulated deposition-resorption
449 mechanisms, that is capable of adjusting the local structure in response to an
450 altered mechanical environment. This is a necessary adaptation mechanism as
451 there is no “optimal structure” that fits all individuals, all lifestyles, and all
452 stages of life (Jepsen, 2011).

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

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

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CAPTIONS AND FIGURES

Range of physiological loading directions

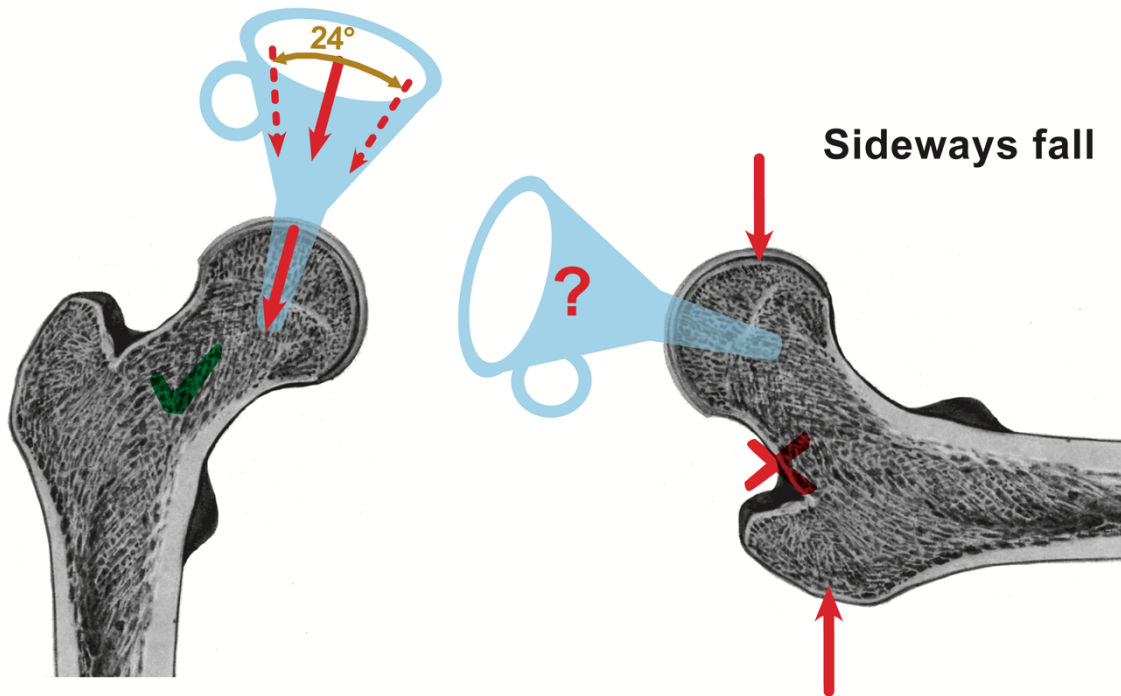


Fig. 1 – The multiscale arrangement of anisotropic and inhomogeneous properties of the proximal femur generates a sort of “funnel effect”. LEFT: when a force is applied to the femoral head within a range of directions (corresponding to the physiological range), this makes the directions of principal 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.

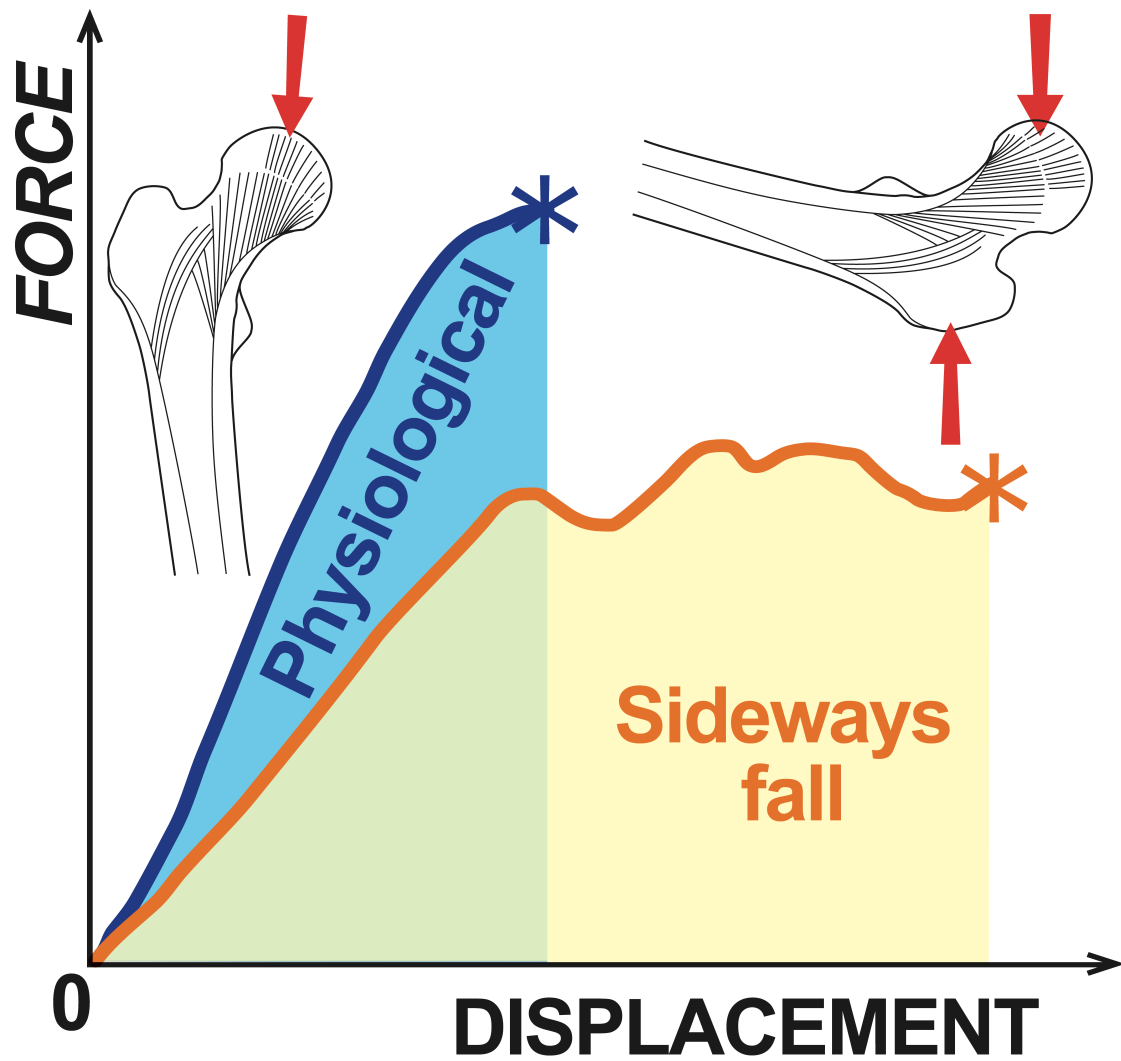


Fig. 2 – Qualitative force-displacement plot for a femur undergoing two different loading conditions: stiffness and high maximal force predominate for physiological loading, while a large energy is needed to cause a complete fracture during a sideways fall.

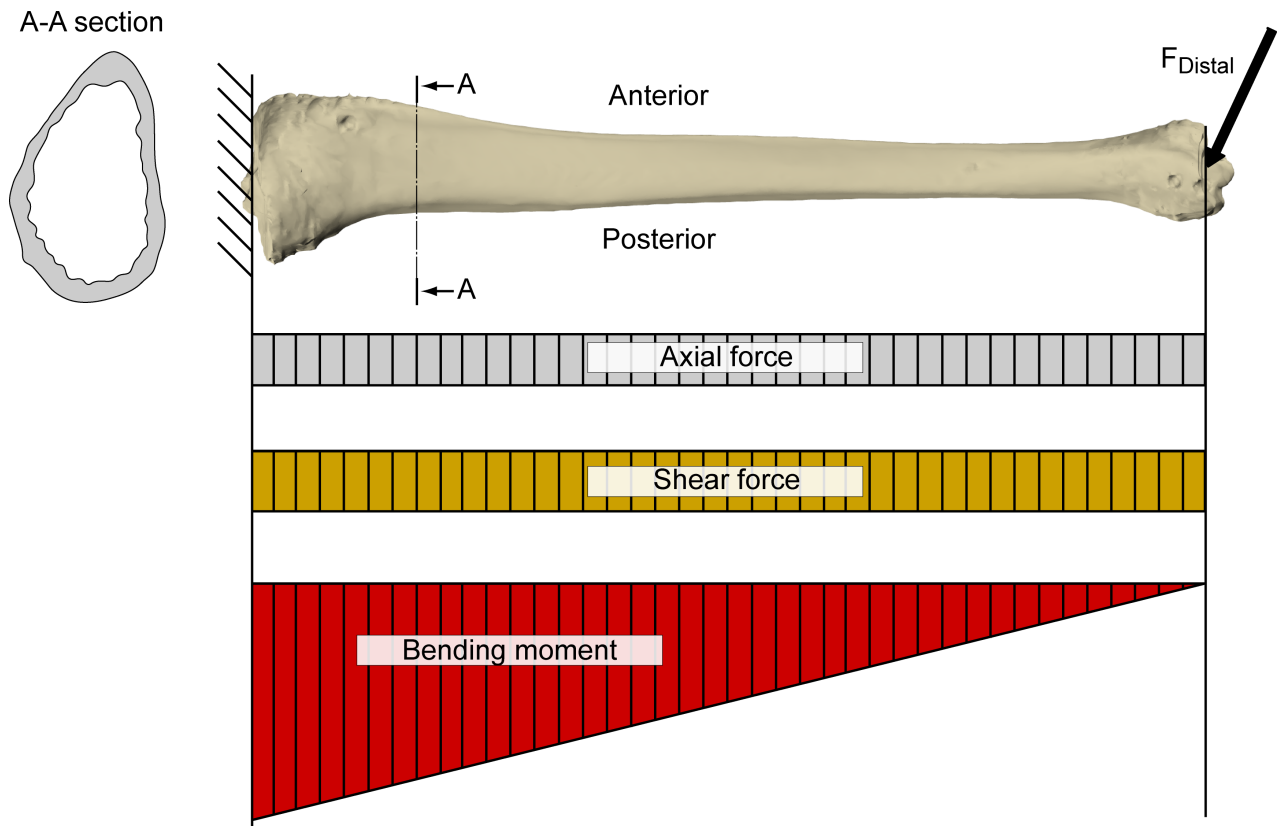


Fig. 3 – Lateral view of a human tibia: the variation of cross-section along its axis is visible. Also indicated is a schematization of the physiological loading condition: a force is applied at the distal end in the sagittal plane. The axial component of such a force generates compression. The antero-posterior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

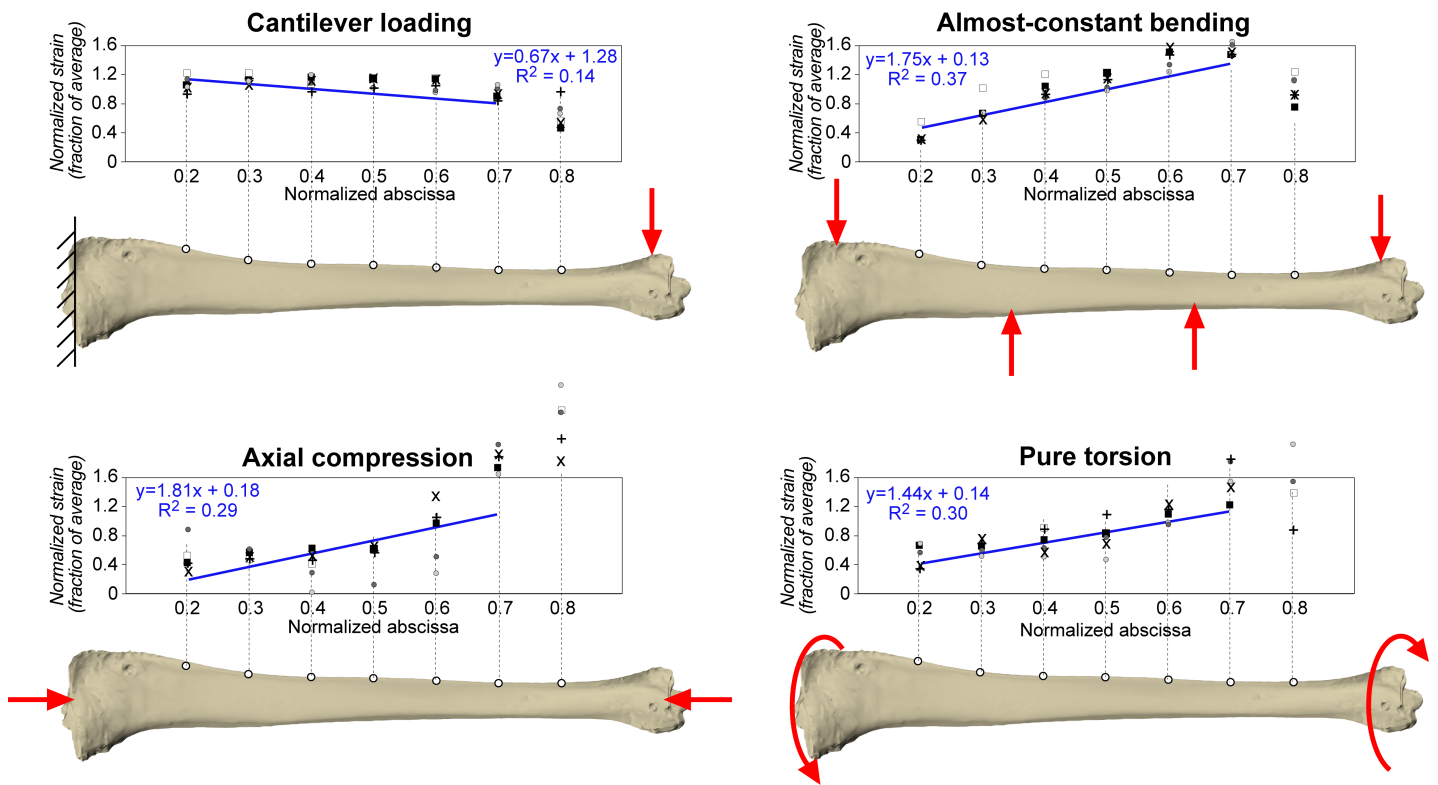


Fig. 4 – Strain distribution on the anterior side of the tibia for different loading conditions: cantilever loading (maximal bending moment proximally) in the sagittal plane; four-point-bending (almost-constant bending moment along the tibia) in the sagittal plane; axial compression; torsion. For each 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).

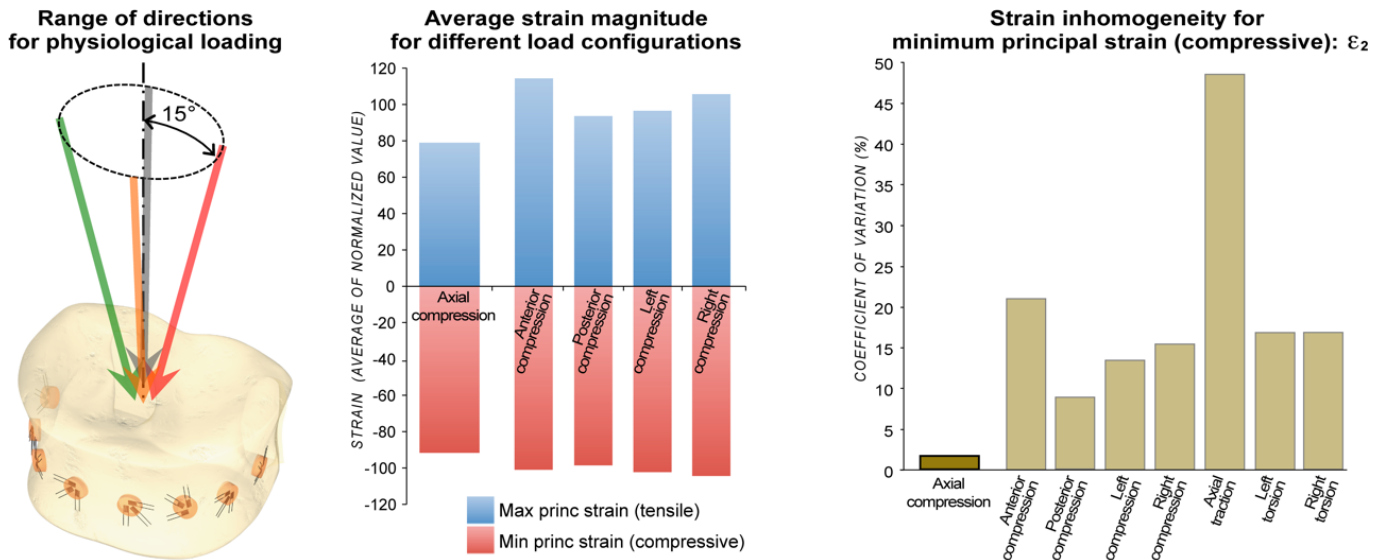


Fig. 5 – The vertebral body seems to be designed to withstand an axial force. LEFT: cone spanned by the resultant forces during daily activities (Bergmann, 2013). CENTRE: strain is lower when the compressive force is aligned with the vertebral body, compared to the cases where the force was tilted by 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)).

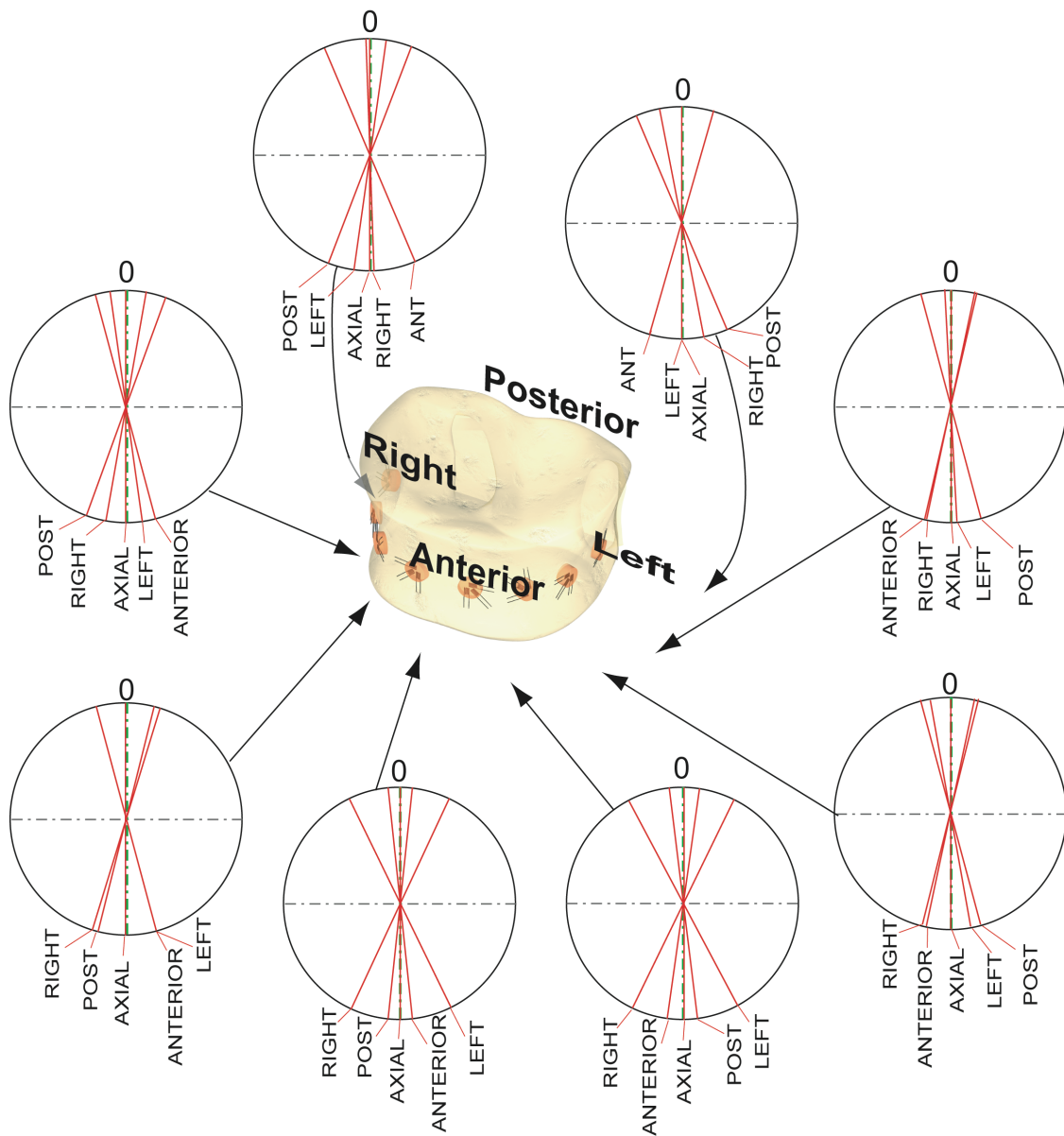


Fig. 6 – The vertebral body seems to be designed to withstand an axial force: when the force is tilted by 15° in any direction (anterior, posterior, right, left) within the 30° cone, the alignment of principal compressive strains becomes quite different from the alignment of the trabeculae (i.e. the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