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High-pressure Adaptation of Extremophiles and Biotechnological Applications

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19 High-pressure Adaptation of Extremophiles and Biotechnological

20 Applications

21 Abstract (about 150 words)

22 During the last decades, high pressure has been an important physical parameter not
23 only to study biomolecules, but also for its biotechnological applications. High pressure
24 affects organism's ability to survive by altering most of cell's macromolecules. These
25 effects can be used, for example, to inactivate microorganisms, enhance enzymatic
26 reactions or to modulate cell activities. Moreover, some organisms are capable to
27 growth under high pressures thanks to their adaptation at all cellular levels. Such
28 adaptation confers a wide range of potentially interesting macromolecules still to be
29 discovered. In this chapter, we firstly present the different effects of pressure on cells
30 and the diverse strategies used to cope against this harsh environment. Secondly, we
31 explored the pressure biotechnological applications on pressure-sensitive and adapted-
32 pressure organisms.

33
34 Keywords: high pressure, deep biosphere, stress, piezophile, adaptation

36 Introduction

37 High pressure (HP) characterizes many habitats on Earth, such as deep sea, sub sea floor
38 and continental subsurface. Ocean covers approximately 70% of world's surface and its
39 average pressure is 38 MPa (1 MPa = 10 bar). This hydrostatic pressure originates from
40 the weight of the water column and corresponds to 10 MPa/km[1]. Part of the oceans
41 are defined as "deep sea", which encompasses the entire biosphere below 1000 m from

42 the water surface and consequently with pressure higher than 10 MPa. The highest
43 hydrostatic pressure detected in the ocean is approximately 110 MPa at 11,000 m depth
44 at the Challenger Deep of Mariana Trench in the Pacific Ocean. Though, pressures
45 above 110 MPa have been found at the sub sea floor. In this case, pressure is caused by
46 hydrostatic pressure but also by the weight of material (lithostatic pressure) and it
47 increases roughly by 15 MPa/km in sediments and by about 28 MPa/km in oceanic
48 rocks. Sub sea floor contains a substantial part of the Earth biomass and can potentially
49 influence global biochemistry [2–4].

50 All high-pressure habitats are occupied by microorganisms and other complex
51 organisms and they highly contribute to the Earth's biomass [5,6]. Pressure impact on
52 organisms' growth allow to divide them in different categories. Organisms that cannot
53 tolerate ambient pressure are designed as strict or obligate piezophiles, inversely,
54 facultative piezophiles or just piezophiles are organism that tolerates ambient pressure,
55 but their optimal growth pressures are higher than 10 MPa (figure 1). On the other side,
56 organism that withstand optimal pressures lower than 10 MPa are called piezotolerants
57 and, finally, organisms which their growth is inhibited by pressure are designed as
58 piezosensitive [7].

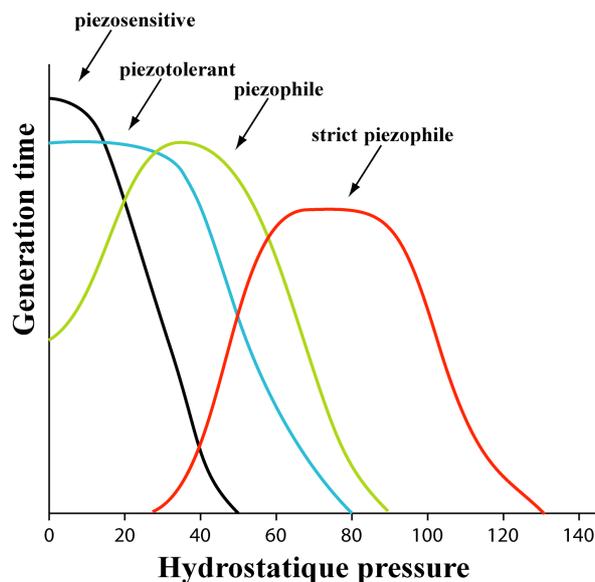


Figure 1. Schematic growth curves of microorganisms according to pressure (MPa) [7].

59

60

61 The interest in piezophiles has begun more than a century ago[8,9], but the
 62 technological difficulties and the need of specialized equipment have done that high-
 63 pressure studies are not, currently, developed in most laboratories. However, the interest
 64 and the applications of the pressure biotechnological applications have been growing
 65 during last decades.

66 Bacteria and Archaea domains contain facultative and obligate piezophiles. Examples of
 67 obligate piezophiles are the bacteria *Shewanella benthica* and *Colwellia marinimaniae*,
 68 with their optimal pressure at 70 MPa and 120 MPa respectively [10,11], and the
 69 archaeon *Pyrococcus yayanossi*, withstanding an optimal pressure of 50 MPa [12]. The
 70 technical constraints to isolate obligate piezophiles may provoke their underestimation.
 71 Obviously, piezophiles excel in sustaining pressure conditions beyond the usual limits
 72 for humans; however, the reasons for that adaptation are still debated.

73 1. Effects of Pressure on Macromolecules and Cells

74 Pressure alters the biomolecules by changing their volume. Thermodynamically, the
 75 variation in Gibbs free energy (G) is defined by the equation 1

76
$$d \Delta G = -\Delta S dT + \Delta V dP, \quad (1)$$

77 where ΔS is the difference in entropy, ΔV the change in volume and T and P represent
78 temperature and pressure, respectively. At constant temperature, $dT = 0$ and thus

79
$$\left(\frac{\partial G}{\partial P}\right)_T = \Delta V. \quad (2)$$

80 This equation, according to the Le Châtelier principle [13], states that an increase in
81 pressure will cause a shift to the state that occupies the smallest volume, meaning, for
82 example, to the unfolded state for most globular proteins, where $\Delta G < 0$. As a result,
83 pressure modifies the volume of the system but not its internal energy (as temperature
84 does). Water with its low compressibility is a crucial partner for pressure action.
85 Notably hydration water (water bound at the surface of macromolecules) is very
86 sensitive to pressure and it can reorganize its network under pressure implying an effect
87 on the macromolecule[14]. Moreover, macromolecules present an extraordinary
88 stability against pressure under low hydration conditions [15,16].

89 Relatively low pressures affect the interatomic molecular bindings (such as Van der
90 Waals, hydrogen bonding and hydrophobic interactions) altering conformations and
91 structures of biomolecules and therefore, their physical properties (solubility, melting
92 point, density), equilibrium states and processes' rate [17]. Electrostatic and
93 hydrophobic interactions are specifically affected by pressure. In contrast, pressures
94 above 2 GPa are needed to impact non-covalent interactions [18,19].

95 **1.1. Nucleic acids**

96 Although the unfolding volume of DNA duplexes is small, pressures up to 1 GPa have,
97 in general, a stabilizing effect on canonical DNA (e.g. with common pair bases). This
98 stabilizing effect may be explained by the decrease of hydrogen bonds' distance.

99 Consequently, pressure increases the duplex-single-strand transition temperature[20].
100 Only in specific cases of synthetic polymers (e.g adenine – thiamine copolymer) and
101 salt concentrations, pressure can lead to double-stranded melting [21]. Regardless, the
102 mechanism is not the same as the heat-induced DNA melting, as under pressure, water
103 molecules penetrate DNA base pairs destabilizing their interactions [22,23].

104 There is a lack of information about the effect of pressure on RNA but, generally, it has
105 been observed that RNA is more pressure sensitive than DNA. For example, pressure
106 induces a structure reorganization of tRNA [24,25] and it destabilizes small RNA
107 oligomers [26].

108 Non-canonical pair structures (different from the usual Watson-Crick pair bases), such
109 as G-quadruplexes or stem-loops, are less stable under pressure than canonical
110 structures by a factor of 10 [22,27].

111 Although canonical DNA duplexes are stabilized by pressure, DNA—protein
112 interactions may be perturbed due to changes in the electrostatic and hydrophobic
113 interactions. Accordingly, pressure affects negatively all molecular reactions where
114 DNA is involved, such as replication, transcription and recombination [28,29].

115 **1.2. Proteins**

116 Most of the knowledge about pressure effects on proteins is based on studies on
117 globular proteins[30–32]. Some of these studies reveal that structural transitions of
118 globular protein due to pressure are based on a hydration mechanism that accompanies
119 protein conformational changes. At higher pressure the hydration degree is increased by
120 the penetration of water into the protein cavities causing the increase of the surface area
121 in contact with the solvents thus contributing to the volume change[33]. Pressure mainly
122 alters tertiary and quaternary structures of proteins but secondary structures (α -helices,

123 β -sheets, and turns) are much less sensitive to water penetration and to destabilization
124 by pressure. For this reason, the state unfolded by pressure may be a hydrated globular
125 structure with large amounts of folded structure[17,34]. It is important to note again the
126 role of water on pressure denaturation, since this volume change can only be observed
127 for proteins in solution. Dry proteins are highly stable against pressure[18,35,36].

128 The unfolding of many monomeric proteins begins above 200 MPa [4], however
129 enzymatic activities are usually modified at lower pressures. In fact, the application of
130 pressures < 200 MPa confers higher thermostability to most proteins [35,37].
131 Consequently, superposing pressure and temperature usually accelerates most of
132 enzymatic reactions, such as hydrolases and transferases reactions [36]. Moreover, few
133 reactions can be enhanced by pressure even at low temperatures [36]. For example, the
134 efficiency of coconut husk hydrolysis by cellulases from *Penicillium variable* is
135 increased at 300 MPa [38].

136 Pressure generally changes the equilibrium between oligomers and their subunits or
137 between two different proteins and this even at relative low pressures (about 50 MPa)
138 [39]. At this pressure, for example, ribosomes' subunits are dissociated [29] and larger
139 protein assemblies as cytoskeletal proteins are disturbed resulting in reversible
140 morphological changes [40]. However, other oligomers are more resistant to pressures
141 as the tetrameric urate oxidase, which dissociates at about 150-175 MPa [41].

142 Actually, a protein in its native state possesses distinct, nearly isoenergetic
143 conformational substates, which may have similar or dissimilar functions or the same
144 function with different rates (statistical substates). As pressure can decrease the folding
145 rate and increase the unfolding one, it can shift the population of different protein
146 substates on the basis of their volumetric differences [42–44]. This capability allows the
147 characterization of various intermediate substates by pressure, which may act in the

148 folding process [45]. Moreover, pressure can change the reaction rates, providing new
149 information about the dynamics and reactions of proteins [34]. This was confirmed, for
150 example, by a dynamic study of myoglobin, where it has been shown that pressure
151 reduces protein motions and facilitates access to different substates [44].

152 Few studies have been done on pressure effects of non-globular proteins, as fibrous,
153 disordered and membrane proteins. Examples are the studies on the collagen structure
154 [46], the intrinsically disordered protein alpha synuclein [47] and on the Lmr
155 transmembrane protein [48] or the ion channel MscS [49]. An important point is that the
156 behaviour of transmembrane proteins against environmental stresses is affected by the
157 protein structure but also by its lipids surrounding [50].

158 Membrane proteins and membrane lipids form an ensemble; they influence each other
159 as a result of biochemical or environmental changes which can compromise membrane
160 process as energy production or ion flux. For example, the transporter efficiency of the
161 tryptophan permease Tat2 from yeast cells is affected due to a membrane fluidity
162 modification at HP[51]. Therefore, membrane integrative studies are necessary to better
163 describe the membrane protein behaviour. Its influence of the lipid matrix on the protein
164 response to pressure have been studied for few proteins [52–54].

165 **1.3. Phospholipids**

166 Lipids, and specially their hydrocarbon chains, possess a highly compressible potential,
167 which makes them very sensitive to pressure [55]. When pressure is applied on a
168 phospholipid bilayer, the acyl chains from phospholipids get straighten resulting in a
169 thicker and higher ordered bilayer. Due to this higher acyl chains' order, pressure
170 promotes the lipid phase transition from liquid-crystallin (phase essential for the
171 biological function of the membrane) to a more rigid phase called the gel phase.

172 Additionally, pressure can also promote the apparition of new phases, such as
173 interdigitated phases or non-lamellar phases (i.e., cubic or hexagonal)[55–59].
174 Nevertheless, not all lipids have the same sensitivity to pressure, for example, lipids
175 with longer hydrophobic chains are more responsive to pressure. This may result in a
176 phase separation in domains on model membranes from a mixture of lipids[60].

177 Pressure may have also an impact on more complex macromolecules, as lipoproteins.
178 Recent studies on human plasma lipoproteins under HHP revealed a reduced flexibility
179 and higher compressibility of its triglyceride rich form, the form associated to
180 pathological health conditions [61,62].

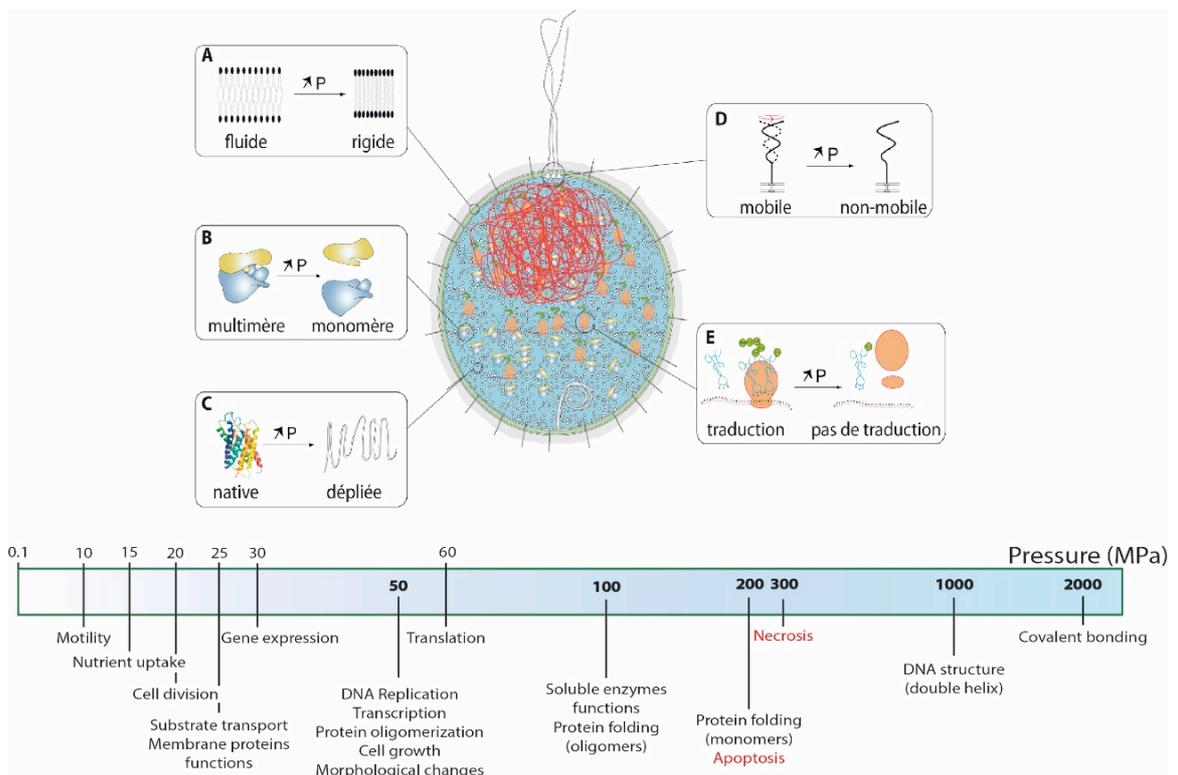
181 **1.4. Cells**

182 Surprisingly, pressure is the unique physical parameter capable of inducing heat-shock
183 and cold-shock proteins' as a cell response to a same stress. *Escherichia coli* (*E. coli*)
184 exposed to 53 MPa induces 55 proteins, 11 heat-shock and 4 cold-shock proteins among
185 them. *E. coli* may try to counteract the damage produced by pressure at different cell
186 levels, such as stability of macromolecules and membrane functionality[63].

187 As mentioned, pressures up to 100 MPa affects most of the cellular functions as
188 enzymatic reactions, gene expression, cell motility and morphology, and cell membrane
189 (figure 2). Since pressure is transmitted through a fluid, it will be transmitted uniformly
190 (Pascal's law) over the whole cell and therefore, it makes difficult to identify, if it
191 exists, the main cause of the cell death. Moreover, pressure-induced cell inactivation
192 relies on the type of microorganism and its physiological conditions, such as water
193 content and salt presence.

194 Overall, eukayotes are more pressure-sensitive than prokaryotes and piezosensitive
195 bacilli and spiral-shaped bacteria are inactivated at lower pressures than cocci [39,64].

196 For instance, pressures above 150 MPa usually reduces the viability of mammalian cells
197 and may induce cell death by apoptosis from 200 MPa or through a necrotic-like
198 pathway at 300 MPa [65]. On the other hand, bacteria cocci may resist much higher
199 pressure variations, for example, *Staphylococcus aureus* cell inactivation begins at 350
200 MPa [64].



202

203

Figure 2. General effects of pressure on cellular macromolecules (black) and cells (red). Adapted from [66]

204

In addition, most gram-negative bacteria seem to be less resistant to pressure than gram-

205

positive [67]. Gram-negative bacteria possess a much more complex membrane which

206

makes it a target for pressure damage [68]. Finally, microorganisms on the exponential

207 growth phase present lower pressure-tolerance than on their stationary growth
208 phase[69,70], for example, exponential-cells may present filamentous shape under
209 pressure which can disrupt membrane functions [29,71]. Moreover, stationary-cells
210 have the capability to synthesize stress-response proteins to adapt and, therefore, better
211 resist to different harsh conditions[72].

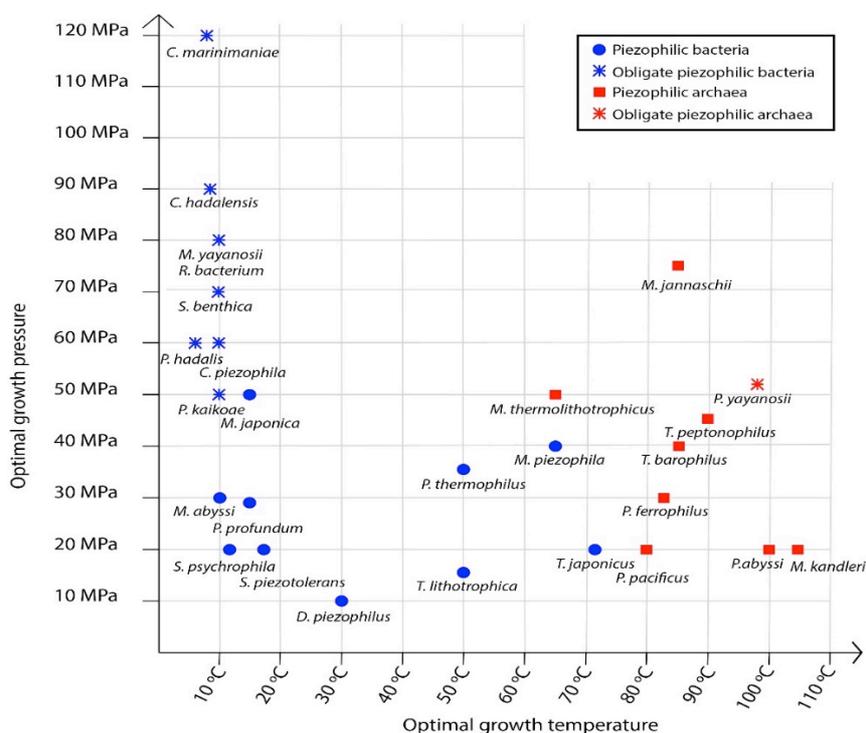
212 Spores present formidable high resistivity to harsh environments, likely due to their
213 structure with numerous protective layers and their low water content [73].
214 Interestingly, relative moderate pressures (50 to 300 MPa) cause the germination of a
215 dormant spore. Though, higher pressures are often less effective to induce
216 germination[74]. Pressure alone is not very effective to inactivate bacterial spores and a
217 treatment with temperature is necessary[75].

218

219 **2. Pressure Adaptation in Piezophiles**

220 The biodiversity of piezophiles is huge [5,76–78]. Organisms adapted to pressure
221 include unicellular bacteria, archaea, eukaryotes as invertebrates and fishes and even
222 deep diving marine mammals [79–81]. For example, in several hydrothermal vents have
223 been found large invertebrates like mussels, crabs and shrimps and some marine
224 mammals can dive exposed to almost 20 MPa without any negative symptom [82,83].
225 There are differences in the microorganisms adapted to HP, as some are also adapted to
226 low temperatures (psychrophiles) and others to high temperatures (hyperthermophiles),
227 which increases the piezophilic diversity. Hyperthermophilic and piezophilic organisms
228 are found near vent sites, where temperatures can go from 350 °C to 2°C in only few cm
229 distances. Altogether, this represents a source of microorganisms with great potential

230 for technological and pharmaceutical applications, such as new enzymes, antibiotics or
 231 cancer cell line active derivatives.



232

233 *Figure 3. Optimal growth temperature and pressure for some piezophilic bacteria (blue) and archaea (red).*

234 Most piezophiles identified in the deep sea are bacteria, they are psychrophiles and
 235 piezophiles, but in the niche of hydrothermal vents, most microorganisms are archaea,
 236 they are thermophiles and piezophiles [84] (figure 3). This indicates that piezophiles
 237 may follow a different adaptation to temperature and makes it difficult to separate the
 238 adaptation to pressure from other stress adaptation since microorganisms may adopted a
 239 common strategy to cope with various environmental stresses [85]. High pressure has a
 240 close relation with other stresses as temperature, pH and salt. Moreover, there are
 241 relatively few studies on adaptation mechanisms to pressure and not all adaptations are
 242 equally used by the different piezophiles studied. Additionally, not all necessary
 243 pressure adaptation mechanisms are deleted at ambient pressure, and therefore the
 244 homologue enzymes may use the same mechanism [66]. Finally, piezophilic biospheres

245 are closely related to nutrient limitation and most piezophiles must also be oligotrophes
246 [4].

247 Extremophiles have developed great capabilities to adapt to harsh and even fluctuating
248 conditions (e.g. temperature, pressure, composition of the host rocks...) thanks to their
249 own unique macromolecules, such as polysaccharides, lipids or enzymes and even
250 specialized organs[86]. These macromolecules adapted to HP present a high potential to
251 develop new biotechnological applications.

252 **2.1. Genomes**

253 Marine biosphere contains mobile genetic elements, such as plasmids, bacteriophages,
254 transposons, integrons, integrative conjugative elements and genomic islands [87]. All
255 of them are essential to understand the high marine microbial diversification and
256 thereby their adaptation [88,89]. Consequently, horizontal gene transfer of these mobile
257 genetic elements may play an essential role in the microbial adaptation to pressure and
258 other extreme conditions [90].

259 Recently, it has been described that the gene Ypr153w is possibly responsible for the
260 tryptophan permease's Tat2 stability in *Saccharomyces cerevisiae* under pressure. It is a
261 gene which has also been identified in other related species as *Debaryomyces* and
262 *Candida* strains which have been isolated from sediment samples of deep sea floors
263 [91]. Another possible HP adaptation could be the 16s rRNA longer stems found in
264 strains from *Photobacterium*, *Colwellia* and *Shewanella* [92].

265 The high genetic tractability and hyper-responsiveness to pressure of the piezophile
266 *Photobacterium profundum* strain SS9 has made it a reference for studies on piezophile
267 adaptation. It has been discovered a pressure-sensitive mutant of SS9 that lacks the recD
268 gene, responsible for a DNA-binding protein. Besides, the transfer of the recD gene

269 from SS9 to *E.coli* enabled the latter one to divide normally under HP. This indicates
270 that RecD may have an important role for piezoadaptation together with a role of DNA
271 metabolism and cell division[93,94].

272 To date, it has not been possible to detect any piezospecific gene. Consequently, it is not
273 possible to determine if an organism is piezophile by molecular approaches, it is
274 necessary to do cultivation approaches and to determine the growth rates at different
275 pressures. However, it has been found that the pressure regulated operons ORFs 1–3 are
276 distributed among different piezophilic *Shewanella* species[95].

277 **2.2. Proteins**

278 Relatively few enzymes from piezophiles have been studied under pressure. Although
279 there are no apparent differences between the crystal structure of an enzyme from a
280 piezophile and its piezosensitive homologue, there is a variation in the stability between
281 both enzymes caused by a difference in flexibility and hydration of the proteins[96].
282 Most molecular motion studies about pressure adaptation have been done *in vitro*, or
283 investigating, for example, molecular dynamics[97]. Nevertheless, nowadays *in vivo*
284 studies have gained importance thanks to, for example, neutron scattering and NMR
285 experiments that can examine timescales from few nanoseconds to hundreds of
286 milliseconds[98–100].

287 It has been shown that some proteins are involved in HP adaptation as well as in
288 adaptation to other stresses (Hsp60, Hsp70, OmpH, RecA, F1F0 ATPases, Cct and
289 Tat2)[101]. A system highly studied under pressure is the Omp/Tox system. The
290 proteins ToxS and ToxR from *P. profundum* SS9 are responsible for regulating the
291 genes that encode the membrane proteins OmpH, OmpL and OmpI. Pressure reduces
292 the abundance and the activity of ToxR, which therefore upregulates the protein OmpH

293 among others, the system acts as a piezometer. Regardless, the systems ToxS and ToxR
294 do not confer HP adaptation and their role under pressure is not clear [8,102].

295 The protein adaptation to extreme conditions is a balance between the imperative
296 stability (higher number of bounds) to be functional and the flexibility (lower number of
297 bounds) to be capable to adapt to different conditions [103]. One of the most studied
298 enzymes is dihydrofolate reductase (DHFR). Studies comparing DHFR from the
299 piezosensitive *E. coli* and from the facultative psychro-piezophile bacteria *Moritella*
300 *profunda* reveals that applying pressure decreases EcDHFR activity and increases
301 MpDHFR activity up to 50 MPa before diminishing its activity at higher HP. MpDHFR
302 seems to have higher sensitivity to pressure due to its higher flexibility [104]. A more
303 flexible protein may explain the higher absolute activity of piezophile proteins [105].

304 However, most of studies are done in protein-isolated solutions, which differs from their
305 native state. An innovative quasi-elastic neutron scattering study examined the
306 dynamics from whole cells of the piezophile *Thermococcus barophilus* and the
307 piezosensitive *Thermococcus kodakarensis* microorganism under atmospheric pressure
308 and 40 MPa. This study revealed that the HP adaptation on whole cells is based on an
309 overall higher proteins' flexibility and, in addition, on the modification of their
310 hydration layers [99].

311 Proteins from piezophiles may have a larger total volume of small internal cavities,
312 which makes the protein more compressible and less sensitive to distortion caused by
313 pressure [105]. Moreover, the presence of small cavities allows water penetration at HP
314 and consequently increases the hydration but, as seen in MpDHFR, cavities are not big
315 enough to cause the protein denaturation but allow the protein to be more flexible. The
316 presence of more small cavities could decrease the amount of water molecules
317 contained in each cavity (a volume of 15\AA^3 is necessary for a single water molecule and

318 an increase of approximately 45\AA^3 is required for each extra molecule [106]). It is
319 important to consider that cavities are not mere “packing defects” but that they play a
320 role in conformational changes and in controlling binding and catalysis of the proteins
321 [106,107].

322 Generally, monomeric proteins are more resistant to pressure than oligomeric proteins.
323 However, it has been shown that multimeric proteins may be adapted to resist to
324 pressure. For example, studies on the hyperthermophile and piezophile TET3 peptidase
325 from *Pyrococcus horikoshii* indicate that the protein multimerizes into a dodecamer
326 structure instead of conserving its classical barrel-shape multimer conformation.
327 Dodecamer multimerization protects the hydrogen bonding between the different
328 subunits and increases its stability against temperature and pressure up to 300 MPa
329 [108].

330 A general extrinsic cell response to pressure-stress is the presence of piezolytes and
331 other low weight organic compounds called osmolytes (e.g., sugars and amino acids) to
332 protect the cell macromolecules, such as proteins, from pressure modification [109] and
333 therefore adapt its dynamics. Some piezophiles accumulate these low-weight molecules
334 in response to an increase on pressure and others to a decrease, indicating in the latter
335 case that the growth at lower pressure than optimal is perceived as a stress for these
336 piezophiles. For example, trimethylamine oxide (TMAO) is a pressure co-solute that
337 helps proteins to remain active under HP in certain fishes and crustaceans [80,110]. On
338 the other hand, the hyperthermophilic and piezophilic *Thermococcus barophilus*
339 accumulates mannosyl-glycerate when it is grown in non-optimal conditions (ambient
340 pressure) [111]. This indicates that this archaeon perceives the lack of pressure as a
341 stressful condition.

342 Few studies have been done on pressure adaptation of higher complex pluricellular
343 organisms. For example, it is thought that the regulation of N-methyl-D-aspartate
344 receptor (NMDR), a cell membrane protein found in nerve cells, is responsible for the
345 absence of the high-pressure nervous syndrome (HPNS) on deep dive mammals
346 [83,112]. The regulation of this protein may be done by modulating its interaction with
347 lipids, for example by the presence of cholesterol, and thanks to protein's particular
348 tertiary structure in piezo-tolerant organisms.

349 **2.3. Membrane lipids**

350 Cells have the capability to modify their cell membrane lipid composition metabolically
351 to maintain it in a functional liquid crystalline phase with specific functional
352 physicochemical properties, such as fluidity, permeability and membrane curvature in
353 spite of environmental stresses. This process is known as homeoviscous adaptation
354 [113].

355 Eukarya and bacteria possess lipids different from those in archaea but their
356 homeoviscous adaptations have similarities. Eukaryal and bacterial lipids are composed
357 by straight hydrocarbon chains linked by ester bonds on 1,2 *-sn-* glycerol and a
358 phosphodiester-linked polar group or sugar. On the other hand, archaeal lipids have
359 isoprenoid hydrocarbon chains bounded by ether bonds on 2,3-*sn-*glycerol. Partly, the
360 adaptation of archaea to extreme conditions may thus rise from their particular lipid
361 structure [114].

362 The common routes of lipid adaptation of bacterial and archaeal membranes are the
363 change of the acyl chain length, the addition or removal of mono-unsaturated lipids and
364 the change in the polar headgroups [115,116]. Longer acyl chains are translated into
365 more rigid membranes, in contrary adding just one unsaturation to lipid chains makes

366 the membrane more permeable and larger headgroups increase the disruption of the
367 membrane packing by increasing the membrane fluidity. Furthermore, archaea possess
368 tetraether lipids, which may form a monolayer instead of the common bilayer. In
369 addition, some archaeal species comprise lipids with cyclopentane rings and isoprenoid
370 chains that are crosslinked. The change in the different ratios from di- and tetra-ether
371 lipids and the presence of cyclopentanes and crosslinked chains modifies as well the
372 properties of the cell membrane. Finally, psychrophilic bacteria present polyunsaturated
373 fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid
374 (DHA), which, just as lipids with one unsaturation, increase the permeability of the
375 membrane under low temperatures[117]. The function of PUFAs is not clear, one of the
376 hypotheses is that requires less carbon and energy to obtain the same effect than the
377 mono-unsaturated lipids [8,117,118]. Another hypothesis is that they may play a role in
378 cell division under HP, as demonstrated for bacteria *Shewanella violacea*[119].

379 Only two studies have been done to examine the lipid composition under pressure: one
380 on *Methanocaldococcus jannaschii* and another on *T. barophilus*[120,121]. Both
381 present an increase in the diether : tetraether lipid ratio to counteract the increase in
382 rigidity provoked by pressure on the cell membrane.

383

384 **3. Pressure Biotechnological Applications**

385 HP application is mostly used in food processing since it does not affect non-covalent
386 interactions (at least up to 2 GPa) and it can inactivate bacteria and viruses without
387 changing markedly nutrients and flavours of food. Furthermore, pressure can change the
388 reaction rates, which may favour the extraction of the required product[19].

389 Besides, pressure may be used for diverse biotechnological and biopharmaceutical
390 applications, for example to explore new therapies [122,123] and conserve vaccines
391 [123], improve cryopreservation [125] or for orthopaedics' surgery [126].

392 **3.1. Food Industry**

393 HP (400 — 600 MPa) inactivates microorganisms, like yeast, molds and viruses. It
394 affects the cell at different levels, such as nutrient transport and cell reproduction,
395 reaching to the cell death [75,127]. Moreover, HP hardly affects low-molecular weight
396 compounds (ex: vitamins, amino acids, flavour molecules) so, organoleptic and
397 nutritional properties are only slightly modified [128]. On the other hand, HP alone
398 cannot inactivate bacterial spores and thus a combination with other variations of pH,
399 chemicals or thermal processes maybe needed. Nevertheless, pressure reduces
400 considerably the working temperature, as 70 °C instead of 180 °C is enough to
401 inactivate spores if it is combined with 600 MPa [75]. Such decrease in temperature can
402 help to preserve quality and minimise off-flavour generations. Therefore, HP techniques
403 are useful as a complement on thermal process but also to inactivate microorganisms on
404 products where temperature cannot be applied. As an illustration, high pressure
405 pasteurization of cold-pressed juices eliminate pathogens of juices without impairment
406 of its fresh-like qualities and increasing the shelf life of the product [129,130].

407 HP extends shelf life of a high variety of food products. For example, fresh shrimp
408 treated at 435 MPa has a shelf life of 15 days, three times longer than the shelf life of
409 the untreated shrimp[131]. Fresh cheese treated at 300–400 MPa has a shelf life at 4 °C
410 of 14–21 days, which is greatly higher than the 7 days for the untreated cheese[132].

411 Food is a complex matrix and inactivation efficiency depends on different factors as
412 treatment conditions, microorganisms to inactivate and its food matrix characteristics.
413 For example, meat treated at 300 MPa has a cooked like appearance but if it is
414 processed at 100–200 MPa and 60 °C, it is more tender than the untreated meat[133].
415 Consequently, inactivation conditions must be defined for every food product. HP is not
416 efficient for low water content food (such as flour) or food with high content of air
417 bubbles and if the food needs to be wrapped before treatment only plastic packaging is
418 acceptable, as packaging material needs a compressibility of at least 15% [127].

419 Finally, HP may also be applied as a pre-treatment. On the one hand, it has been
420 demonstrated that the application of sublethal HP on cells gives them cross-resistance to
421 other stresses. For example, the most studied probiotic, *Lactobacillus rhamnosus*, is
422 more resistant to heat after an application of 100 MPa for 10 min[134]. This opens the
423 possibility to inactivate the pathogens on probiotic products, conferring a health benefit.

424 On the other hand, pre-treatment can be useful to facilitate the extraction of internal
425 nutritional components. HP makes the cells more permeable, increasing the mass
426 transfer rate and as a result increasing the release of extracts. It has been shown that the
427 time extraction of caffeine from green tea leaves is reduced from 20h to 1 min if a
428 pressure of 500 MPa is applied; extraction of anthocyanin red grape skin is increased by
429 23% by applying 600 MPa of pressure and the extraction yield of ginsenosides from
430 *Panax quinquefolium* root increases linearly between 100 MPa and 500 MPa [135].

431 **3.2. Allergenicity and digestibility**

432 Several proteins can provoke allergic reactions caused by an immune disorder on the
433 IgE binding. Because HP tend to denature proteins and as a result, it has been shown to
434 induce a modification of their allergenicity[136], both on protein solutions and on food
435 systems. For example, pressures of 300–700 MPa reduce the allergenicity of a ginkgo
436 seed protein and of soybean allergens[137]. Another interesting example is the use of
437 HP together with proteases to obtain hypoallergenic rice[138,139]. However, the effect
438 of HP on allergenicity is not universal. There is no allergenicity change caused by
439 pressure on almonds, or on the protein Mald1 from apples[140,141]. Mald1 native state
440 possess a high internal cavity occupied by water [142] and therefore, pressure may not
441 be able to conform significant hydration changes since the protein is already highly
442 hydrated.

443 HP may have not only an effect on the allergenicity of the food products but can help to
444 increase its digestibility by exposing inaccessible sites of proteins and, thereby,
445 enhancing the efficiency of protein hydrolysis. For example, the time required for
446 proteolysis of β -lactoglobulin, the major allergen in cow's milk, is reduced from 48h to
447 20 min at 200 MPa [143].

448

449 **3.3. Antiviral vaccines**

450 Several viruses are inactivated or dissociated by pressure. Under pressure, the atomic
451 contacts between subunits are replaced by interactions with the solvent and therefore
452 once pressure is released, viruses cannot come back to their native form. For example,
453 pressure inactivates picornaviruses by causing the lack of VP4 from the intern capsid
454 [144]. Both viruses with polyhedral and helicoidal symmetry are sensitive to pressure.

455 Even so, not all viruses are equally reactive to pressure, for example, the foot-and-
456 mouth-disease picornavirus is highly sensitive and poliovirus is much higher resistant
457 against HP[144].

458 Interestingly, virus re-associate under their fusogenic state under pressure, a less
459 infectious and highly immunogenic form[144–146]. This is why high pressure has been
460 suggested for antiviral vaccine development. It has been demonstrated that
461 immunization against HP-inactivated virus is equally effective as against intact virus
462 and have higher immunity response than isolated viral subunits [42,147].

463 **3.4. Bio-purification**

464 An antigen may be purified from its medium by affinity chromatography due to a steric
465 recognition with an antibody linked to a matrix. The recognition causes an increase in
466 molecular volume and, as pressure causes a volume decrease, it could be useful to apply
467 pressures to dissociate the product of interest without using drastic elution process
468 which reduce the lifetime of matrices [148]. This has been demonstrated for the
469 recovery of β -galactosidase: four 15 min cycles of 150 MPa at 4°C recovers 32% of *E.*
470 *coli* β -galactosidase compared with the 46% recovered by adding a solution of pH=11
471 [149]. Although the product yield is lower when using HP, the method is simpler and
472 have a lower impact on matrices than the current elution process.

473 HP ability to disrupt immune complexes has been proved on anti-prostate specific
474 antibody from its antigen [149,150], its dissociation was increased by 22-37% when
475 pressures from 140 to 550 MPa were applied. Pressure may also optimize the
476 dissociation of amphiphilic biomolecules from a fixed adsorbent: 80% of Triton-X can
477 be recovered form a bed absorption if a pressure of 250 MPa is applied on the system
478 [151].

479 Finally, as pressure can dissociate aggregates, it may be used for the recovery of
480 proteins from inclusion bodies, i.e. aggregates of incomplete folded proteins.
481 Traditionally, to separate proteins from inclusion bodies is necessary to use high
482 concentrations of agents that destroy the spatial structure of proteins with a necessary
483 subsequent difficult refolding. However, a pressure of 240 MPa is effective to dissociate
484 the inclusion bodies of endostatins and a subsequent application of 40 MPa induces the
485 refolding of 78% of the protein [152].

486

487 **3.5. Modulation of Cell Activity**

488 Already relative low applied pressures can enhance the cell activity to our profit, as for
489 example observed at 10 MPa for ethanol production by *Saccharomyces cerevisiae* [153]
490 which occurs 3 times faster than at atmospheric pressure. Another example is on the
491 fermentation by *Clostridium thermocellum* [154], this *Clostridium* converts cellobiose
492 to biofuels and other chemicals but also synthesizes other non-desired products (acetate,
493 H₂, CO₂). When the fermentation happens under pressure of 7 or 17 MPa, the
494 microorganism modifies the metabolic pathways and shifts the production to desired
495 metabolites, reaching an increase of 60-fold.

496 However, as HP is considered a stress for most cells, it will translate into the expense of
497 additional energy for cell maintenance and growth, reducing the product yield. For
498 example, HP reduces the fermentation rate of lactic acid fermentation due to the
499 inhibitory effect on the growth of *Streptococcus thermophilus*, *Lactobacillus bulgaricus*
500 and *Bifidobacterium lactis* [155]. To avoid the loss of efficiency rates under HP, efforts
501 are made to enhance the resistance to HP of mesophilic microorganisms, leading to HP
502 resistant organisms with higher performance under HP [156].

503

504

505 **4. Biotechnological Applications of Piezophiles**

506 There are more than 3000 enzymes identified to date and most of them are used for
507 biotechnological applications. Nevertheless, these enzymes are not enough to respond to
508 the new technological challenges that appear each day [157]. One of the problems is the
509 stability of the enzymes under industrial conditions, so it is necessary to find enzymes
510 which are highly resistant to harsh conditions and here deep-sea enzymes may play a
511 major role. Pressure-stable enzymes are capable of sustaining biocatalysis under HP,
512 modifying therefore specific enzymatic reactions, and have even higher thermostability.
513 For example, Biolabs[®] has already commercialized a DNA polymerase from a
514 hyperthermophile and piezophile *Pyrococcus*, which presents a half-life of 23 hours at
515 95 °C. Moreover, piezophilic enzymes may possess different properties than their
516 surface homologues, which may open new possibilities for industry[158]. The market
517 for industrial enzymes is growing every year and the exploitation of extremozymes is a
518 huge and mostly unexplored resource[159].

519 As we have seen, lipids from extremophiles are unique. Archaea in particular contain
520 lipids which confer to the cell a highly stable and impermeable membrane. The unique
521 stability may be used in biotechnological or pharmaceutical applications, for example to
522 protect therapeutic peptides from the harsh environment of the gastrointestinal
523 tract[160,161]. Additionally, many piezophilic bacteria contain omega 3-PUFAs
524 associated with their cell membrane, which are precursors to hormones and hormone-
525 like molecules in many animals. Consequently, it could be used for
526 hypertriglyceridemia diseases and clinical studies for this purpose have already been
527 approved[158].

528 The high marine biodiversity has woken up the interest to search new compounds with
529 biopharmaceutical potential[162]. It has been discovered marine derived molecules

530 with, for example, antitumor potential, for the treatment of pain or antimicrobial
531 activities [158,161,162]. For example, studies have identified some bioactive
532 compounds from marine echinoderms (such as the piezotolerant *Cucumaria frondosa*)
533 with antiproliferative, antimetastatic and immunomodulatory activities[163].

534

535

536 All pressure-specific impacts allow to modify macromolecules and cells in unique ways.
537 Food industry was pioneer in using pressure to inactivate microorganisms and as a
538 pretreatment, but pressure capability does not stop here. Promising applications, such as
539 antiviral vaccines, the use of pressure for bio-purification or to vary cell activities has
540 led to a greater interest on this physical parameter. In addition, piezophile organisms
541 opens a range of possibilities to use pressure-adapted molecules, and to increase, for
542 example, the reaction rates, or to find new active macromolecules.

543

544

545 **EXTRA**

546 **Biopharmaceutical**

547 **Bacterial ghosts as delivery systems**

548 *Bacterial ghosts are usually obtained by the expression of a lyses gene that leads to the*
549 *formation of a transmembrane tunnel with its consequent cell material leakage. These*
550 *products retains their immunogenic properties as their cell surface is not affected.*
551 *Bacterial ghosts obtained by the expression of lysis gene does not retain their cellular*
552 *structure and are permeabilized and therefore lose their immunogenic properties. HP is*
553 *capable to prepare bacterial ghosts without the disadvantages of lysis gene, which*
554 *make them a good option to use as delivery systems for subunit or DNA vaccines. For*
555 *example, HP bacterial ghosts have been obtained applying a pressure of 100 MPa for*
556 *15 min to E.coli.*

557

558 **Cryopreservation**

559 *Oocyte cryopreservation by vitrification is one technique used to maintain women's*
560 *fertility but blastocyst formation rate after this process is still low. This low formation*
561 *rate is caused by the production of ROS components. As remarked above, sublethal HP*
562 *stress makes the cells more resistant to thermal treatments and oocytes are not an*
563 *exception. For example, pig oocytes, mouse and bovine blastocysts show a higher*
564 *resilience against cryopreservation after being subjected to sublethal hp treatment.*
565 *Moreover, It has been demonstrated that HP (20-40 MPa for 90-120 min) treated bull*
566 *and boar spermatozoa before cryopreservation preserve the viability, motility and*
567 *fertility after thawing.*

568

569 **Vaccines preservation**

570 *HP can be also considered as a stabilizing method for vaccine preservations. It has*
571 *been demonstrated that high pressure stabilizes attenuated poliovirus against*
572 *temperatures of 37°C, giving a higher thermal resistance to this virus. Actual trivalent*
573 *oral polio vaccine (OPV), as most live vaccines, is heat labile, particularly OPV is*
574 *between the most heat labile vaccines and it needs to be stored frozen and used*

575 *immediately after thawing. HP treatment may solve the problems of refrigeration*
576 *guarantying a higher stabilised and effective poliovirus vaccine.*

577

578 **Oncology**

579 ***Dendritic cell based vaccines***

580 *Shinitzky and colleagues have been explored the use of HP killed tumor cells as a whole*
581 *cell vaccine, they have demonstrated that a pressure of 100-200 MPa increases the cell*
582 *immunogenicity. However, since their phase I study in 2000, there are no more clinical*
583 *studies using this approach.*

584 *Recently, dendritic cell (DC, antigen presenting cells from the mammalian immune*
585 *system) based vaccines have been studied to obtain a vaccine for tumours. This*
586 *approach uses pressures of 200 – 300 MPa to kill cancer cell lines, pressure will reveal*
587 *immunogenic sites on the killed cancer cell surface. Then, these molecules interacts*
588 *with the specific receptors presents on the surface of DC and activates the phagocytosis*
589 *of killed cells by DC. Finally, mature DC will activate tumour cell specific immune*
590 *responses and therefore it could modify the clinical response of the patient with cancer.*
591 *Moreover, HP killed cells have easy cryopreservation without affecting their*
592 *immunogenicity.*

593 *This technique is still under development; nevertheless, it is under clinical testings for*
594 *several cancers indications, such as lung, prostate and ovarian cancers.*

595

596 ***Orthopaedics surgery***

597 *The actual treatments for exvivo devitalization of infected or tumour affected bone*
598 *segments are based on irradiation, autoclaving, thermal treatment or use of chemicals.*
599 *Even if the devitalization is total using these techniques, they reduce the biomechanical*
600 *and biological integrity of the bone. The procedure is based on the resection, the*
601 *extracorporeal disinfection and finally the devitalization before its reimplantation.*

602 *High pressure can also be used to exvivo devitalization of bone segments without*
603 *altering the main proteins present in bone tissue (fibronectine, vitronectine and type I*

604 collagen). HP inactivates several bacteria, fungi and virus, however it is necessary to
605 take into account that bacteria in bones are less sensitive to HP than in solution.

606 For example, HP treatment of 300 MPa for 10 min of a cancerous bone segment is
607 sufficient to inactivate all bone cells, including the bone tumour cells. This possible
608 treatment mainly concerns bone segments and tendons. It has been demonstrated that
609 HP treated Achilles tendons and trabecular bones does not loss their properties after a
610 pressure treatment at 600 MPa. Finally, the revitalization of high pressure treated bone
611 segments has been demonstrated indicating that a successful implementation of HP
612 treated bone segments may be possible.

613 Moreover, HP may be useful to disinfect biomaterials as prosthesis or bone plates and
614 surgical equipment as screws. It has been demonstrated that a pressure of 300 MPa
615 and 40°C for 30 min disinfect screws contaminated with *Staphylococcus aureus*.

616 **Cartilage stimulus**

617 With the development of tissue engineering, engineered meniscus have been a new
618 option to combat knee cartilage diseases. However, engineered meniscus constructs,
619 without the correct stimulation, possess a lower organization and mechanical
620 properties than the native meniscus.

621 Cartilage is an avascular and aneural tissue that detects HP, with an adequate
622 stimulation, as a mechanical sign to increase its regeneration. In a normal activity,
623 knee cartilage and synovial joint are hydrostatically pressurized reaching pressures up
624 to 10 MPa. For example, it has been demonstrated that static pressure of 5 MPa for
625 1.5h increases the glycosaminoglycan incorporation in explants cultures. Interestingly,
626 the effect of pressure on cartilage differs if the study is done on a chondrocytes
627 monolayer or on a three dimensional matrix, which indicates that the interaction cell –
628 extracellular matrix may play a role in HP regulation.

629

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