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1 **The multiple influences of mechanical forces on cell competition**

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5 **Abstract**

6 Cell competition is a widespread process leading to the expansion of one cell population through
7 the elimination and replacement of another one. A large number of genetic alterations can lead
8 either to competitive elimination of the mutated population, or expansion of the mutated cells
9 through the elimination of the neighbouring cells. Several processes have been proposed to
10 participate to the preferential elimination of one cell population, including competition for limiting
11 extracellular pro-survival factors, communication through direct cell-cell contact, or through
12 differential sensitivity to mechanical stress. Recent quantitative studies of cell competition have
13 also demonstrated the strong impact of the shape of the interfaces between the two populations.
14 Here, we discuss the direct and indirect contribution of mechanical cues in cell competition, which
15 can act either as a modulator of competitive interactions or as a direct driver of cell elimination.
16 We first discuss how mechanics can modulate contact dependent and diffusion based competition
17 by modulating the shape of the interface between the two populations. We then describe the direct
18 contribution of mechanical stress to cell elimination and competition for space. Eventually, we
19 discuss how mechanical feedbacks also influence compensatory growth and trigger preferential
20 expansion of one population.

21 **Introduction**

22 The plasticity of adult and developing tissues is based on the capacity of every cell to adjust its
23 behaviour to the local environment. This includes the probability of one cell to die. While this
24 plasticity is absolutely required for the homeostasis of adult tissues undergoing constant cell
25 replacement (such as the gut), the modulation of cell death may also be co-opted to favor the
26 expansion of one cell population. This phenomenon is illustrated by the concept of cell
27 competition: the context dependent elimination of one cell population favoring the expansion of
28 another one. Cell competition was initially described more than forty years ago in the *Drosophila*
29 wing epithelium using Minute mutant clones which reduce the quantity of ribosomes [1] [2]. While
30 Minute mutant flies are viable and show minor developmental defects, Minute clones are
31 systematically eliminated from the developing wing when surrounded by wild type (WT) cells [2].
32 Alternatively, other mutations can promote the expansion of the clones at the expense of the WT

33 cells, a process named “supercompetition”. For instance, a relative increase of expression of the
34 proto-oncogene Myc in clones promotes their expansion through the elimination and replacement
35 of the neighbouring WT cells [3, 4]. Since then, a large number of genetic alterations have been
36 associated with a so-called “loser” status: viable cells that are eliminated in presence of WT cells
37 (here called the “winners”), or “supercompetitor” status: mutant cells (here the “winner”)
38 eliminating and replacing the WT cells (here the “losers”) [5, 6]. This conserved process [7] has
39 been associated with several physiological and pathological functions, including the enhancement
40 of developmental robustness [3, 8, 9], cancer progression [10] and delayed ageing [8].

41 So far, most of the studies of cell competition have been focusing on the mechanisms that will
42 enhance the elimination of the so-called “loser” cells. These include death induced by the
43 depletion of extracellular survival factors or the secretion of pro-apoptotic factors [11-13], death
44 induced by contact dependent mechanisms [14, 15] and death induced by mechanical stress [16,
45 17]. Interestingly, the interactions between loser and winner cells can also enhance the growth
46 rate of the winner population [3, 18, 19]. However the potential mechanisms that will bias cell
47 proliferation and their contribution to winner expansion have been much less studied so far.

48 Mechanical cues are now recognised as central regulators of cell signalling and cell fate [20-22].
49 Not so surprisingly, cell competition is not an exception and several recent studies have outlined
50 the strong impact of the mechanical environment on the regulation of competitive interactions.
51 This includes a direct role in cell elimination through a so-called mechanical based competition
52 [16, 17]. It also includes indirect contributions through the modulation of the shape of loser and
53 winner interfaces which can affect the probability of loser cell elimination [9, 23]. Here, we propose
54 to discuss how mechanical forces may modulate directly or indirectly every step of cell
55 competition, focusing mainly on competition occurring in epithelia. We will first describe the
56 biochemical basis of cell competition and the molecular cues driving cell death. We will then focus
57 on the indirect contribution of mechanical forces to loser cell elimination through the modulation
58 of cell shape and the geometry of the interface between loser and winner cells. We will then
59 discuss how mechanical forces can directly induce loser cell elimination during mechanical cell
60 competition. Eventually we will discuss the contribution of forces in the compensatory
61 mechanisms that will enhance winner growth.

62 **Indirect contribution of mechanical forces to loser cell elimination.**

63 *The molecular cues driving cell death in cell competition.*

64 Loser cell death may be mediated by biochemical or biomechanical cues. Mechanically induced
65 cell competition is further discussed in the next section of this review. We will discuss now briefly
66 the molecular cues driving loser cell elimination in order to introduce in the next section the
67 contribution of the loser-winner interface geometry. Molecular cues driving cell death include
68 diffusive factors or cell-cell contact dependent communication. Competition for extracellular
69 survival factors has long been thought to be involved in competitive cell interactions. The
70 neurotrophic theory already postulated that new born neurons death could be triggered by
71 competition for survival factors [24]. Similarly, Minute mutant elimination in the *Drosophila* wing
72 imaginal disc was initially proposed to be mediated by a reduced capacity to process Dpp, an
73 extracellular pro-survival signal [25]. Competition for interleukin 7 also triggers competitive
74 elimination of old progenitor cells in the thymus [13]. In these examples, winner cells behave like
75 a sink which locally reduces the concentration of pro-survival factors. Alternatively, winner cells
76 have been proposed to trigger directly loser cell death through the secretion of so-called “killing
77 factors”. This may explain the killing capacity of conditional media produced during Myc-
78 dependent competition in S2 cells [11]. More recently, the extracellular ligand Spätzle (Spz),
79 which binds Toll-related receptors and induces NF-κB dependent activation of proapoptotic
80 genes, has been implicated in Minute and low Myc cell elimination in the *Drosophila* wing imaginal
81 disc [26]. In this case, winner cells do not directly secrete the ligand that triggers death (Spz), but
82 rather produce secreted enzymes which enhance Spz activation and loser cell death [12]. In all
83 these examples, the pattern of cell death is closely related to the pattern of diffusion of survival or
84 killing factors.

85 Alternatively, loser cell death may also occur through cell-cell contact dependent signalling. The
86 initial observation of cell competition suggested that Minute mutant elimination was based on
87 short range signalling [2, 27]. Accordingly, low Myc expression cells elimination was shown to be
88 strictly contact dependent in the pupal notum [23] as well as in the mice epiblast [28]. Several
89 transmembrane proteins were involved in the process of loser cell elimination. This includes the
90 transmembrane protein Flower [14], which induces cell death in the loser cells (Minute, low Myc
91 and apico-basal polarity mutants) through the differential expression of loser specific isoforms
92 (*fwe^{lose}*). The elimination of clones mutant for genes of the apico-basal polarity pathway (*scribble*,
93 *disc large*, *lethal giant larvae*, *Mahjong*, *crumbs*) also relies on contact dependent signals which
94 triggers c-Jun N-terminal Kinase (JNK) signalling in the first row of loser cells in contact with
95 winners [15, 29-31]. Recently, Yamamoto and colleagues [15] found that the death signal is
96 transmitted at the interface between normal and *scribble* mutant cells through the ligand Sas and

97 the receptor-type tyrosine phosphatase PTP10D. This enables local JNK activation through the
98 downregulation of EGFR signalling in the first row of *scribble* mutants[15].

99 At first sight, these mechanisms of elimination seem unrelated to mechanical cues. Yet cell-cell
100 contact-dependent and diffusion-dependent signalling may strongly be influenced by the local
101 geometry of the interfaces between the two populations, which is eventually set by mechanics.
102 We will discuss now how the geometry of the interface between loser and winner cells may
103 influence signalling between them.

104 *Modulation of competition by the shape of the interface between loser and winner populations.*

105 Juxtacrine cell-cell signalling relies on the existence of an interface between the two
106 communicating cells. Intuitively, one would expect that the output of signalling will not only rely on
107 the membrane concentration of ligands and receptors, but also on the surface of contact between
108 the two cells and the duration of these contacts. Accordingly, cell shape, junctional length and
109 tissue topology have been shown to influence cell-cell signalling in different contexts. For
110 instance, the levels of Notch signalling between pairs of cells correlate with their contact area [32].
111 In ascidians, cell geometry and the number of neighbours of a given cell are central determinants
112 of cell fate specification [33]. Similarly, the propagation of planar cell polarity information in the
113 *Drosophila* wing epithelium is disrupted in clones with abnormal cell packing and cell shape [34].
114 Altogether, these studies suggest that cell shape and contact area can directly impact cell-cell
115 signalling. Not so surprisingly, the shape of the interface between loser and winner cells can also
116 influence cell competition. For instance, the probability of elimination of low Myc cells in the
117 *Drosophila* pupal notum (a single layer epithelium) and in wing imaginal discs correlates with the
118 surface of contact shared with high Myc cells[23] (**Figure 1A**). Interestingly, early reports of cell
119 competition have shown that winner clones have highly convoluted shape[27] and that Minute
120 clones were quite often fragmented[35]. These abnormal shapes should increase the surface of
121 contact between winner and loser and enhance loser cell elimination. Clone fragmentation was
122 later shown to be driven by reorientation of winner cell division[36] and biased cell-cell
123 intercalation events between low Myc and high Myc cells (**Box 1, Figure 1A**, see below)[23]. The
124 effect of clone shape on cell competition was confirmed by modulating loser clone shape. While
125 generating compact clones (hence reducing the surface of contact with winner) is sufficient to
126 slow down loser clone elimination, increasing cell mixing can accelerate cell elimination[23].
127 Interestingly, the effect of surface contact on cell competition may also explain the absence of cell
128 competition from either side of compartment boundaries[27, 37], borders that separate
129 populations with different fates[38]. The high tension at compartment boundaries[39] reduces the

130 surface of contact between the two cell populations (see below) which may prevent the induction
131 of loser cell death. Accordingly, decreasing the straightness of the anteroposterior compartment
132 boundary in the wing disc is sufficient to increase the surface of contact between the two
133 populations and allows cell competition to occur between compartments[23]. These results also
134 suggest that communication between cells should rely on receptors located on the apico-lateral
135 regions of cells (where the smoothness of compartment boundary is higher[39]). This could fit
136 with the role of the transmembrane protein Flower, a general fitness marker which is located on
137 the apico-lateral region of cells[14, 23]. We have discussed the influence of geometry in relatively
138 static epithelia with little cell movements and junction remodeling. The situation is slightly different
139 in cases where cells are more mobile. In mouse embryonic stem cells (ESC), cell to cell
140 heterogeneity in Myc expression leads to the competitive elimination of low Myc cells[9, 28]. Here
141 the probability of elimination seems to be set by the duration of random contacts between high
142 and low Myc cells since loser death occurs for contacts longer than 600-800 minutes[9]. Despite
143 the absence of biases in cell movements and contact stability driven by Myc levels[9], the
144 characteristic speed of displacement and the levels of mixing should also modulate the time of
145 contact between cells and may impact the efficiency of competition.

146 So far, we discussed the contribution of clone shape in contact dependent competition. However,
147 the shape of the interfaces between winner and loser cells might also influence the concentration
148 profile of diffusive molecules involved in competition. To illustrate this point, we simulated the
149 concentration profile of a hypothetical killing factor secreted by winner clones of various shape
150 (square, band and cross-like winner clone shape, **Figure 1B**). As shown in Figure 1B (middle
151 panels), the local concentration at which loser cells are exposed varies along clone boundaries
152 and differs between these three conditions. For instance, higher concentrations are reached in
153 the “pocket” region of the cross-like clones, while concentrations are higher in the center of the
154 edges for square-like clones and along the long edges of the band-like clones. This suggests that
155 clone shape could also influences the concentration profile of diffusive factors and may define the
156 location and local intensity of competition driven by diffusive factors.

157 To conclude, the shape of the boundaries between winner and loser cells can modulate the
158 intensity of the signal driving loser cell elimination, irrespective of its nature. It follows that the
159 description of the mechanical parameters regulating cell-cell contacts is relevant for the
160 understanding of the regulation of cell competition.

161 *Mechanical modulation of the surface of contact between loser and winner cells.*

162 The geometry of the interface between two epithelial cell populations is set by the size, the stability
163 and the distribution of cell-cell junctions at the interface. The size and the stability of cell-cell
164 junctions can be well predicted by the distribution of surface tension (**Box 1**), a mechanical
165 parameter known to regulate the shape of many materials including epithelial cells, bubbles in
166 soap foams or an oil droplet in water[40, 41]. Surface tension minimises the surface of contact
167 between two phases (e.g., air and liquid; cell type A and B). In the case of an epithelium, surface
168 tension is mostly regulated by the actomyosin cortex, which is counterbalanced by the strength
169 of cadherin mediated cell-cell adhesion at adherens junctions[40]. Hence the surface of contact
170 between two competing cell populations will be mostly regulated by the local distribution of
171 actomyosin and E-cadherin at the loser-loser, loser-winner and winner-winner interfaces. This
172 distribution will either lead to sorting of the two populations and minimisation of the surface of
173 contact (similar to oil and water), or to enhanced mixing (“salt and pepper” pattern) (**Figure 1A**).
174 Initially, cell sorting was mostly explained by intrinsic differences in adhesion (so called differential
175 adhesion hypothesis), or by intrinsic differences in tension (so called differential tension
176 hypothesis)[42]. However, modulation of tension and/or adhesion specifically at the interfaces
177 between the two populations can also drive sorting. This was shown for instance in the case of
178 compartment boundaries (reviewed in [38]) which prevents the mixing between cell lineages.
179 Studies in *Drosophila* have shown that compartment boundary formation is mostly mediated by a
180 local increase of actomyosin and tension[39, 43, 44]. These two models of sorting (bulk
181 differences versus boundary regulation) can be reconciled when considering the relative tension
182 at the homotypic junctions between cells of the first lineage, the homotypic junctions between
183 cells of the second lineage and the heterotypic junctions between the two cell types. This was
184 nicely illustrated by a recent study using genetics, laser ablations and simulations, which has
185 shown that clone roundness and cell mixing can be fully explained by the ratio between these
186 tensions[45]. For instance when tension at clone boundaries is higher than tension at interfaces
187 between clonal cells, clone roundness increases. Conversely, when tension at interfaces between
188 clonal cells is higher than tension at clone boundaries, the two populations tend to mix (**Figure**
189 **1A**). Interestingly, the distribution of tension during competition between high and low Myc cells
190 falls in the second category[23]. This is driven in this case by the low levels of PIP3 and actin at
191 the winner-loser and loser-loser interfaces[23]. Bosveld and colleagues also found that
192 overexpression of several oncogenes involved in competition (e.g.: Ras, Yki[6]) leads to a relative
193 increase of tension at clone boundaries which increases clone roundness[45]. This may reduce
194 the efficiency of cell elimination during contact based competition. However the molecular basis
195 of these changes of tension at the interfaces are not known. Changes of tension distribution also

196 occur during competition driven by mutations of apico-basal polarity genes. Local variations of
197 Crumbs (an apical protein) concentration trigger the formation of a supracellular actomyosin
198 cable[46] leading to cell sorting. Interestingly, the spatial pattern of different Toll receptors also
199 regulates the planar polarised distribution of Myosin II (Myo II) in *Drosophila* embryo[47], which
200 biases cell-cell intercalation and contributes to tissue extension[48]. Thus Toll receptors are also
201 both involved in cell competition[26] and in the modulation of junction tension[47]. Overall, several
202 genetic conditions triggering competition have been shown to modulate the distribution of tension.
203 The mechanisms that regulate the tension at the interface between loser and winner cells are not
204 well understood in most of the cases. They may rely on the juxtaposition of cells with different
205 concentration of apical markers (like Crumbs[46] or of differential expression of adhesive
206 molecules (such as differential N-cad expression[49] or Dachshous[45])). Further studies are
207 needed to understand the mechanisms regulating tension at clone interfaces.

208 So far, we described AJs in a rather static manner. However, a local increase of tension
209 can also lead to junction shrinkage and new junction formation perpendicular to the former one.
210 This so-called T1 transition (**Box 1, Figure 1A**) will lead to the swapping of cell position and cell-
211 cell intercalation (reviewed in [50]). As described above, cell-cell intercalation contributes to clone
212 fragmentation and mixing between loser and winner cells[23]. AJs remodelling can be controlled
213 by intrinsic forces and polarized distribution of MyoII such as the one observed during germ band
214 extension in the early *Drosophila* embryo[48, 51], or by random fluctuations of MyoII levels[52].
215 Alternatively, cell-cell intercalation can be driven by external forces and will dissipate in that case
216 large scale mechanical stress[50]. For instance, pulling forces generated by the folding of
217 neighbouring tissues contribute to the junction remodeling in the *Drosophila* germ band[53, 54].
218 Similarly, the contraction of the hinge region and the attachment of cells to the distal cuticle of the
219 pupal wing orient cell-cell intercalations during *Drosophila* pupal wing development[55-57].
220 Altogether, these studies suggest that both internal forces and anisotropic external constraints
221 impact the orientation of cell-cell intercalation which may modulate the surface of contacts
222 between loser and winner cells.

223 In summary, extrinsic mechanical constraints and local distributions of actomyosin are
224 central regulators of junction length and junction stability which will both impact sorting and/or
225 mixing of cell populations. This will modulate the surface of contact between loser and winner
226 populations and can significantly change the efficiency of loser cell elimination. Importantly, most
227 of the factors triggering cell competition (e.g., Ras, Yki, Myc, Toll, apico-basal polarity genes) can
228 also modulate junction tension which may either slow-down (if promoting sorting) or accelerate (if

229 promoting mixing) contact-dependent competition and alter the gradient profile of diffusive factors.
230 As we will see in the next section, the effect of these factors on junction tension may also directly
231 contribute to cell elimination through the generation of local mechanical stresses.

232 **Regulation of cell death by mechanical inputs and mechanical cell competition**

233 So far we have described how clone shape and mechanical forces may modulate the
234 communication between winner and loser cells. Recently, mechanical stress has also emerged
235 as an important driver of competitive interactions which can directly trigger loser cell
236 elimination[16, 17, 58]. This mechanical competition was described as a new and alternative
237 mode of cell competition and may be relevant in a wide range of genetic and tissue backgrounds.
238 Recent reviews have already discussed the process of mechanical based competition[59-61] and
239 the role of mechanical forces in death induction[62]. We will therefore give here a rather brief
240 overview of the concept of mechanical competition by describing first how cell deformation can
241 trigger cell elimination, then focusing on two alternative modes of compaction-driven elimination.

242 *Cell compaction can trigger cell death*

243 Cell survival is regulated by its microenvironment, including the mechanical state of the tissue/cell.
244 An overload of mechanical stress can trigger cell elimination either through excessive stretching
245 or through excessive compression. For instance, increasing hydrostatic pressure from 0.5 to 200
246 MPa (5 to 2000 time the atmospheric pressure) is sufficient to trigger apoptosis and/or
247 necrosis[63, 64]. However these pressures are 1 to 3 orders of magnitude higher than the pressure
248 experienced by cells *in vivo* (e.g.: 100 to 300 kPa for osteoblasts [65]). A milder and more relevant
249 increase of isotropic pressure (2-8 kPa) can also trigger apoptosis in 3D cancer cell
250 aggregates[66]. Similarly a 30% reduction of glioma cell volume is necessary and sufficient to
251 drive caspase 3 activation and apoptosis[67]. These studies suggest that high hydrostatic
252 pressure and volume reduction can trigger caspase activation most likely through the
253 mitochondrial pathway[66]. Since cell competition was mostly studied in epithelia, the behaviour
254 of epithelial cells upon lateral and/or apico-basal compaction is also highly relevant.

255 Cell spreading on the substrate can directly modify cell survival by modulating the pro-
256 survival signals associated with integrin activation[68]. In a seminal work, Chen and colleagues
257 used micro-patterned adhesive islands with various spreading to modify endothelial cell geometry
258 and could show that low cell area was sufficient to trigger apoptosis[69]. Similarly high cell density
259 can reduce the activity of the prosurvival kinase FAK (Focal Adhesion Kinase)[70] and can
260 decrease survival by activating the Hippo pathway through Lats1/2 kinases activation[71].

261 Alternatively, stretchable substrates have been used to increase transiently cell density by 30 %
262 [72]. This was sufficient to trigger massive cell extrusion (the concerted removal of an epithelial
263 cell from the tissue layer [73]) which eventually restored steady state tissue density. Cell extrusion
264 was triggered by the activation of Ca^{+2} stretch-activated channel Piezo independently of caspase
265 activation[72]. Similarly, local compaction of the *Drosophila* pupal notum (a monolayered
266 epithelium) can trigger cell extrusion[17, 74]. We recently showed that the pro-survival signal
267 EGFR/ERK could be activated by local stretching of the notum and that ectopic compaction can
268 trigger cell death through the inhibition of EGFR/ERK[58]. Alternatively, spontaneous
269 compression of MDCK cells can occur through aberrant alignment of cells during collective
270 migration and triggers caspase activation and cell extrusion through the exclusion of Yap/Taz
271 from the nucleus[75]. Altogether, these studies demonstrate that lateral compaction of an
272 epithelium or an increase of isotropic pressure can trigger cell extrusion and/or apoptosis through
273 various sensing pathways (see [62] for a more exhaustive discussion). How could then such
274 mechanical stresses arise during competition and induce preferential elimination of the loser
275 cells?

276 *Mechanical competition driven by differential sensitivity to mechanical stress*

277 In a seminal theoretical work, Boris Shraiman proposed that differential growth could lead to
278 mechanical stress accumulation in epithelial tissues[76]. Cells with faster growth/proliferation will
279 push on the neighbours which will eventually lead to a local increase of pressure. If in addition
280 the fast growing population is less sensitive to pressure than the neighbouring cells, this will lead
281 to preferential elimination of the slow proliferating cells (**Figure 2A**). This relatively simple
282 mechanism relies on three hypotheses: the epithelial tissue must behave like a solid (namely that
283 stress is not dissipated through cell movements and cell rearrangements); compaction must be
284 able to trigger cell death; and different cell types must have different sensitivity to compaction.
285 We will discuss below the relevance of these three hypotheses. Alternatively, competition could
286 also be explained by the concept of homeostatic pressure[77, 78]. Assuming that cell proliferation
287 and cell death can both be modulated by pressure (i.e., low pressure fueling proliferation and high
288 pressure triggering death), a cell population in a confined environment will grow until reaching a
289 stationary phase where cell proliferation is perfectly compensated by cell death. If now two
290 populations with different homeostatic pressures are mixed, the one with the higher homeostatic
291 pressure will always become winner and eventually fully replace the other population, even for
292 little differences of homeostatic pressure [77, 78] (**Figure 2B**). Interestingly, this framework was

293 rather developed in the context of a fluid-like tissue where elastic behaviours were neglected[77]
294 and would also be valid in very dynamic tissues.

295 These two frameworks rely on a certain number of hypotheses which have been validated
296 recently. As mentioned in the previous section, there is now a large number of evidences showing
297 that isotropic compaction or lateral compaction of an epithelium can induce cell extrusion and cell
298 death. Similarly, tissue compaction can also slow-down cell proliferation (see the next section for
299 more details). The framework of Boris Shraiman also relies on the solid-like behaviour of the
300 tissue: namely that the timescale of proliferation is faster than the characteristic time of stress
301 dissipation through junction remodelling and cell displacement[76]. This assumption is not
302 satisfied in most tissues, which behave like fluid on long time scales, with the notable exception
303 of the *Drosophila* wing imaginal disc, one of the main tissues used to study cell competition.
304 Indeed, the rate of junction remodelling is presumably low[79, 80], making the fluidity in this tissue
305 low enough to allow differential growth to induce compaction of the fast growing population and
306 tangential stretching of the neighbouring cells[79, 81-83]. Interestingly, overgrowth of a circular
307 clone has been mostly associated with two concomitant effects on the neighbouring cells: they
308 are stretched tangential to the clone border and compacted along the radial axis of the clone[79,
309 81-83]. This could either lead to a net increase of area (thus promoting growth) or a net decrease
310 of area (thus promoting death) of the surrounding cells. As such the effect of clone growth on the
311 compaction of the neighbouring cells is not intuitive and will probably rely on clone size, clone
312 shape and boundary conditions. However, to our knowledge these conditions were never
313 explored experimentally or theoretically.

314 Finally, it remains unclear whether different cell types would have differential sensitivity to
315 mechanical stress, a cornerstone hypothesis of the two frameworks described above. This was
316 particularly true in epithelia where the initial reports of compaction described caspases-
317 independent extrusion processes[72, 74] (see [61, 62] for more discussion).

318 Yet, several recent reports confirmed that cell compaction could drive cell competition in epithelial
319 cells[16, 17, 19]. Using MDCK cells, Wagstaff and colleagues have shown that the elimination of
320 Scribble mutant cells was driven by their active compaction[16]. Two components contribute to
321 the preferential elimination of the mutants: their active compaction driven by the collective
322 migration of the WT cells toward the mutants (see below), and their lower homeostatic
323 density/pressure. Their higher sensitivity to compaction is driven by their high basal levels of p53,
324 which is further upregulated by p38 and ROCK upon compaction. The differences in homeostatic
325 density and the high motility of MDCK cells fit well with the framework of competition driven by

326 differential homeostatic pressures as depicted above[77, 78]. Alternatively, differential growth was
327 shown to drive cell compaction and cell elimination in the *Drosophila* pupal notum[17].
328 Perturbations of caspase activation in clones and live tracking of caspase activity suggested first
329 that caspase activation was preceding and was necessary for cell extrusion in this tissue.
330 Therefore cells refractory for caspase activation should be resistant to compaction-driven
331 extrusion. Accordingly, induction of active Ras in clones (which promotes growth and inhibits
332 caspase activation [84-86]) was sufficient to compact and eliminate neighbouring WT cells.
333 Recently we showed that cell elimination was driven by the downregulation of the EGFR/ERK
334 pathway upon compaction, which leads to the activation of the pro-apoptotic gene *hid*[58].
335 Although not formally tested, a similar process was observed upon induction of active Yki in clones
336 in the pupal notum[83]. The deformation of cells neighbouring the fast growing clones and the
337 higher sensitivity to compaction of the WT cells is in good agreement with the framework
338 developed by Boris Shraiman[76].

339 *Mechanical competition driven by boundary constrictions*

340 We focused so far on situations where winners and losers are both exposed to the same
341 mechanical constraints and where competitive advantage is given by differential sensitivity to
342 mechanical stress. Alternatively, preferential elimination of one population could be achieved if
343 the compaction is restricted to one population. This was reported in several cases where
344 compaction is driven by specific properties of the boundaries between the two populations.
345 Collective migration can generate transient convergent flows of cells which locally increase
346 pressure and trigger apoptosis in the central cell[75]. Similar collective movements occur during
347 the compaction of Scribble mutant MDCK cells by WT cells and contribute to the higher
348 compaction and higher elimination of the mutants[16] (**Figure 3A**). Alternatively, cell
349 misspecification can increase the line tension at the boundary between the mutant and the WT
350 cells[46, 49, 87]. Accordingly, modification of morphogens readout in clones in the wing imaginal
351 disc (e.g., Dpp, Wg) generates local tissue bending in cysts[87-90] and can also lead to cell
352 death[87-89, 91]. This type of cell elimination was initially described by Adachi-Yamada and
353 colleagues using the concept of morphogenetic apoptosis[91, 92]. Tissue bending and clone
354 elimination are driven by an increase of the line tension at the clone border, caused by the
355 accumulation of actomyosin at clone boundaries[87] (**Figure 3B**). This local increase of line
356 tension generates an internal pressure in the clone, which is inversely proportional to the clone
357 radius (according to Laplace law, **Box1**). This is consistent with the fact that small clones are
358 preferentially eliminated [87]. However the role of cell compaction in cell elimination has not been

359 formally tested in this context. Importantly, the compressed population is always the population in
360 minority with concave boundaries, irrespective of its genetic background. As such, this
361 mechanism could equally eliminate WT cells if they are surrounded by a majority of misspecified
362 cells (including pretumoural cells such as Ras activation), or could eliminate misspecified cells if
363 they are in minority (including active Ras cells)[87]. Since modulation of adhesive molecules and
364 components of the apico-basal polarity in clones is sufficient to increase clone boundary
365 tension[46, 49], this mechanism may also be active in all the competition scenarios affecting
366 apico-basal polarity components (Crumbs[93], Scribble[15], Lgl[29], Dlg[31]). Interestingly,
367 modulation of the mechanical properties of cell boundaries also contributes to the extrusion of
368 isolated active Ras cells from MDCK epithelial layers[94, 95]. To conclude, the modulation of the
369 mechanical properties at the interface between loser and winner cells may be a general
370 mechanism of cell elimination. In this context, winner and loser status will be rather set by the
371 topology of the interface and the population in majority will always tend to be favored, irrespective
372 of the intrinsic cell properties (growth and survival rate).

373 **Regulation of compensatory growth and space occupation**

374 We focused so far on the processes that modulate and/or initiate the elimination of loser cells.
375 However the bias in cell death impacts the final occupancy of the tissue only if winner cells expand
376 to compensate for the loss of loser cells. Indeed, if loser cell elimination was fully compensated
377 by loser cell growth, their elimination would have no impact on winner relative expansion. Studying
378 compensatory growth/proliferation and its impact on the relative growth of the winner and the
379 loser cells is therefore essential for the understanding of competition. Yet, it has so far drawn
380 much less attention. We will give here a brief overview of the compensatory processes at play
381 during competition and discuss when and where mechanical inputs may also influence them.

382 *Compensatory growth driven by extracellular signals*

383 One striking feature of the classically studied competition contexts (Myc and Minute driven
384 competition) is the absence of visible defects in term of tissue size. This suggests that the
385 overgrowth of winner cells should perfectly compensate the loss of loser cells[2-4, 37]. What are
386 then the mechanisms that regulate the replacement of the dying cells? The first insights were
387 obtained by studying the behaviour of so-called “undead cells”, where completion of apoptosis is
388 prevented by overexpression of p35, an inhibitor of effector caspases. Neighbouring cell
389 proliferation is here driven by the secretion of multiple mitogenic factors by the undead cells,
390 including Dpp, Wg, and Hh, mostly driven by the Dronc dependent activation of JNK[96-100].

391 Similarly, compensatory proliferation in the adult *Drosophila* gut relies on the secretion of multiple
392 mitogenic ligands by the dying cells promoting stem cell proliferation, including EGF (Spitz), Wg
393 and Unpaired (the JAK/STAT ligand)[101-103]. However all these compensatory phenomena
394 were mostly studied in conditions of massive cell death/stress, and it remained unclear whether
395 they could participate to the normal homeostasis of tissue size. More recently, the elimination of
396 Minute mutant cells in the fly gut was shown to promote the expansion of the WT stem cell pool
397 through symmetric divisions[18]. This was driven by the secretion of the JAK/STAT ligand
398 Unpaired by the eliminated Minute cells. In physiological contexts, the spontaneous death of gut
399 enterocytes drives stem cell proliferation through the secretion of EGF/Spitz[104]. Alternatively
400 compensation for cell loss can also be driven by a net increase of neighbouring cell size/area
401 without proliferation [105]. Altogether, these studies suggest a framework in which the “sensing”
402 of cell loss is mediated by molecular signals secreted by the dying cells, and driving either cell
403 proliferation or cell volume expansion (**Figure 4A**).

404 How could such phenomena promote preferential expansion of the winner cells? Two hypotheses
405 may explain such a bias: winner and loser cells have a differential capacity to bind/access to
406 mitogenic factors, or/and the downstream response to pro-mitotic signalling inputs are different
407 between the two cell types. Consistent with the first hypothesis, Minute mutant cells have a
408 reduced capacity to bind/process Dpp[25]. Biased accessibility to the mitogenic factor may also
409 depend on the shape of the interface between loser and winner cells and on the location of the
410 dying cells. For instance, mitogenic factors secreted by a dying loser cell surrounded by winner
411 cells will mostly benefit to the winners irrespective of any bias in the capacity to bind the mitogenic
412 factors. This may be particularly relevant in the cases of competition associated with cell mixing
413 (see above)[23]. The second hypothesis assumes that loser cells have an intrinsic reduced
414 capacity to respond to promitotic signals. Following this line, Minute and *mahjong* mutant discs
415 display a chronic activation of the JNK pathway[106]. JNK activation was recently shown to block
416 progression of the cell cycle[107, 108] by maintaining cells in G2 phase[108]. Thus JNK activation
417 may prevent proliferation of the loser cells irrespective of the extracellular mitogenic factor levels.
418 Accordingly, inhibition of JNK in Minute cells could increase their growth rate independently of its
419 effects on loser cell apoptosis[106]. To conclude, quantitative evaluation of the compensatory
420 growth in winner and loser cells and its effect on the final tissue occupancy is essential to fully
421 describe competition. Along this line, the systematic tracking of Scribble mutants and WT MDCK
422 cells has recently revealed a significant stimulation of growth of the WT cells when surrounded
423 by Scribble mutant cells, which was more prominent than the bias for Scribble cell death near WT
424 cells[19].

425 *Compensatory growth driven by mechanical cues*

426 Compensatory mechanisms could also be driven by the space released by the dying cells and
427 consequent stretching of the neighbouring cells (**Figure 4B**). The removal of an epithelial cell
428 involves an active contraction of the dying cell and of the boundaries shared with its
429 neighbours[73, 109-111]. This leads to transient stretching of the neighbouring cells and to an
430 increase of their apical surface[112]. This local geometrical/mechanical effect may also be a driver
431 of compensatory growth. Indeed there is nowadays a growing body of evidences showing that
432 cell stretching is sufficient to promote cell proliferation. For instance, spacing of adhesive islands
433 and the spreading of endothelial cells is sufficient to promote their proliferation[69]. MCF10A cells
434 spreading and stretching also promote YAP/TAZ nuclear localization, which promotes cell survival
435 and cell proliferation[113, 114]. Contact inhibition also halts cell proliferation at high density
436 through the exclusion of YAP from the nucleus[115]. Similarly, constraining MDCK cells in 2D with
437 a physical barrier is sufficient to slow down the G1-S transition, while stretching the substrate is
438 sufficient to accelerate this transition[116]. Epithelial cell stretching also leads to a rapid increase
439 of cell proliferation driven by the opening of the Ca²⁺ stretch-activated channel Piezo and
440 activation of ERK[117]. Recently a systematic analysis of the dynamics of traction forces and
441 tension during the cell cycle of MDCK cells revealed that the product of cell tension and area
442 (homogeneous to an energy) was the best predictor of the duration of the G1-S transition[118].
443 Altogether, these studies demonstrate that lateral stretching of an epithelium promotes cell
444 proliferation, whereas its compaction inhibits growth. Similar effects were also observed upon 3D
445 compaction as nicely illustrated with tumour spheroids where the local rate of proliferation is
446 anticorrelated with pressure[66, 119, 120].

447 These studies demonstrate that cell deformation can affect cell proliferation. However they do not
448 prove that such mechanical feedbacks are at play in the neighbourhood of dying cells. Recent
449 work in the adult mice epidermis has shown that cell extrusion events (here leading to cell
450 differentiation) generate a transient and significant increase of the probability of neighbouring cell
451 division which is preceded by cell area expansion[121]. The same bias has been observed upon
452 laser induced-cell death or drug induced apoptosis[121]. This suggests that local cell removal
453 significantly affect the rate of proliferation in the neighbouring cells probably through
454 geometrical/mechanical feedback. While this was not formally tested, the same mechanical
455 compensation could affect the homeostasis of the adult fly gut where the death of enterocyte can
456 promote the division of the neighbouring stem cells through the secretion of Spitz/EGF[104]. Since
457 ERK is also sensitive to mechanical stretching[58, 122, 123], removal of enterocytes may also

458 promote stem cell proliferation through stretching/space release. Overall, it seems reasonable to
459 believe that such mechanical feedbacks affects neighbouring cells during loser cell elimination.

460 How mechanical-driven compensatory phenomena would then favour the expansion of the winner
461 cells? Here again, two layers of regulation could bias compensatory growth: 1. Winner cells are
462 more stretched than loser cells upon loser cell apoptosis, hence leading to higher winner
463 compensatory growth. 2. Winner and loser cells are equally stretched but proliferation stimulation
464 is higher in winner cells. First, how could loser cell death trigger preferential stretching of the
465 winner cells? In that regard, a recent study from Tsuboi and colleagues proposed a simple and
466 elegant model[83] (**Figure 4C**). By combining live imaging in the *Drosophila* pupal notum and a
467 vertex model, they have shown that the high proliferation rate of winner cells will increase the
468 anisotropy of loser cells at winner clone boundaries (elongated along clone boundaries, as
469 previously observed in the wing disc[79, 81]). This biases the orientation of junction remodellings
470 occurring during loser cell elimination, and statistically favours the area expansion of the
471 neighbouring winner cells, irrespective of their relative mechanical properties (**Figure 4C**). In their
472 simulations, this bias accelerates the expansion of the winner clones. Moreover, their model
473 suggests that loser cell death occurring right next to winner cells will have a stronger impact on
474 winner expansion. Alternatively, winner cells could be more stretched if loser cell elimination
475 occurs when they are surrounded by winner cells (see above). Finally, higher winner stretching
476 upon loser cell death may occur if winner cells have lower tension/contractility and/or higher
477 pressure than loser cells. In that case, winner and loser will experience the same force, but the
478 area of winner cells will expand more. Indeed, many genetic backgrounds associated with
479 competition can modulate junction tension[23, 45, 82] and may favour such bias. This hypothesis
480 requires that the parameter regulating cell cycle progression is the strain rate and/or the absolute
481 apical area of cells. However a recent study has shown that cell cycle progression rather
482 correlates with the product of tension by area [118]. This parameter would be equal for winner
483 and loser cells in the scenario depicted above and would not bias proliferation. Loser cells may
484 also have a reduced sensitivity to stretching, either because they are intrinsically unresponsive to
485 mitogenic signals (as depicted in the previous section) or because the relevant
486 mechanotransduction pathways are modulated in these cells. For instance, the stretch sensitive
487 channel Piezo may be differentially located in the two cell populations[117]. Alternatively, cells
488 may express different levels of EGFR hence affecting the responsiveness of ERK to
489 stretching[58]. Finally, winner cell proliferation could also be higher if winners have a higher
490 homeostatic density/pressure, hence proliferating more despite the same degree of stretching

491 [77]. The higher homeostatic pressure may actually be directly related to a higher sensitivity to
492 stretching or the responsiveness to mitogenic signals discussed above.

493 To conclude, local mechanical feedbacks may be important modulators of compensatory growth
494 and could modify the outcome of cell competition by promoting preferential winner cell division. A
495 better assessment of area compensation during loser cell elimination and its impact on cell
496 proliferation will allow to understand the contribution of local mechanical feedbacks to cell
497 competition.

498 **Conclusion and perspectives**

499 In this review, we have illustrated how mechanical cues may significantly change the outcome of
500 cell competition, by modulating the efficiency of cell signalling leading to loser cell elimination,
501 through direct death induction, or by stimulating the preferential expansion of winner cells. As
502 explained above, most of these effects are at play irrespective of the molecular effectors of loser
503 cell recognition and elimination. Resolving the exact contribution of these parameters in cell
504 competition will require a heavy investment in live imaging and quantitative analysis. This would
505 include a systematic quantification of the mechanical parameters of the loser and winner cells, a
506 better characterization of the geometry and dynamics of cell-cell contacts, as well as a systematic
507 characterization of potential biases in cell expansion and cell death. The recent development of
508 deep-learning approaches to enhance systematic cell segmentation and cell tracking[19] will
509 eventually allow such exhaustive characterization of the parameters associated with biased cell
510 elimination or biased cell proliferation. A better characterisation of the contribution of mechanical
511 cues to cell competition will also generate new general knowledge for the field of
512 mechanotransduction and a better understanding of the coupling between cell division and cell
513 elimination during tissue homeostasis.

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519 **Authors contribution**

520 AMV and RL discussed the topic and wrote the manuscript. AMV developed the diffusion model
521 shown in Figure 1.

522 **Declaration of interests**

523 The authors declare no competing interest

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820

821

822 **Figure legends**

823 **Figure 1: Influence of the shape of winner and loser cell interfaces on contact-**
824 **dependent communication and diffusion pattern.**

825 **A:** Influence of the level of winner-loser cells mixing on contact dependent death induction. Left:
826 high cell sorting (minimal mixing) and minimisation of the surface of contact. Centre: release of
827 tension at the winner-loser cell interfaces allows cell mixing by cell intercalations. Some loser cells
828 (marked with *) increase the number of contacts with winner cells. Right: further cell intercalation
829 events lead to complete isolation of some loser cells that become fully surrounded by winners
830 and undergo apoptosis. The inset shows a process of cell intercalation, consisting in cells
831 neighbour exchanges through junction remodelling. **B:** Influence of the shape of winner and loser
832 cell interfaces on diffusion pattern. In the initial conditions (left), the tissue is composed of a
833 winner cell population (purple) secreting a death factor that diffuses freely from cell to cell, and of
834 a loser cell population (green) initially devoid of the death factor. Three boundary topologies
835 between loser and winner cells were simulated: a square-like winner clone (top), a band-like
836 winner clone (middle) and a cross-like winner clone (bottom). After diffusion of the killing factor

837 (middle panels), the extracellular concentration profile (shown in pseudocolour) of the factor
 838 surrounding loser cells varies according to the shape of the winner/loser interface. The right
 839 panels show the expected localisation of loser cell deaths (red cells). The patterns of the killing
 840 factor diffusion were obtained by simulating a pulse of 5 arbitrary units (a.u.) of the killing factor
 841 emanating from the cells of the winner clone, and diffusing passively from cell to cell without any
 842 further production or degradation. The diffusion of the killing factor was only governed by the
 843 difference in concentration of the factor between a cell and its neighbours. Thus, the variation for
 844 cell i of the concentration $[F]$ of the killing factor was given by the equation:

845

$$846 \quad \frac{\partial [F]_i}{\partial t} = [F]_i + \left[\sum_{\text{neighbour cells}} ([F]_{\text{neighbour}} - [F]_i) \right]$$

847 Simulations were run for 15000 time steps.

848 **Figure 2: Different modes of mechanical cell competition based on differential**
 849 **sensitivity to mechanical stress**

850 **A:** Elimination of loser cells (green, red cells are apoptotic cells) by a clone of fast growing cells
 851 resistant for apoptosis (purple). The high growth rate of the purple cells generate compressive
 852 forces (orange arrows). The middle graph shows the profile of pressure along the clone (black
 853 dotted lines are at clone boundaries). The right graph shows the hypothetical probability of cell
 854 elimination for a given pressure for loser cells (green) and winner cells (purple). Grey dotted line
 855 is the pressure value at clone boundaries. **B:** Competition for space driven by different
 856 homeostatic pressures (**Box 1**). Purple cells (winner) and green cells (losers) are growing in a
 857 chamber with fix boundaries on the outside (black lines) and a sliding boundary at the interface
 858 (grey). When pressure (P) is equal to the homeostatic pressure of loser ($P_{h, \text{loser}}$), losers stop
 859 expanding while winners still expands (since $P < P_{h, \text{winner}}$). Pressure is therefore increasing, which
 860 starts to induce shrinkage of the loser population (middle panel). Eventually loser cells are
 861 completely eliminated and winner cells expand until reaching their homeostatic pressure.

862 **Figure 3: Cell compaction driven by boundary constraints**

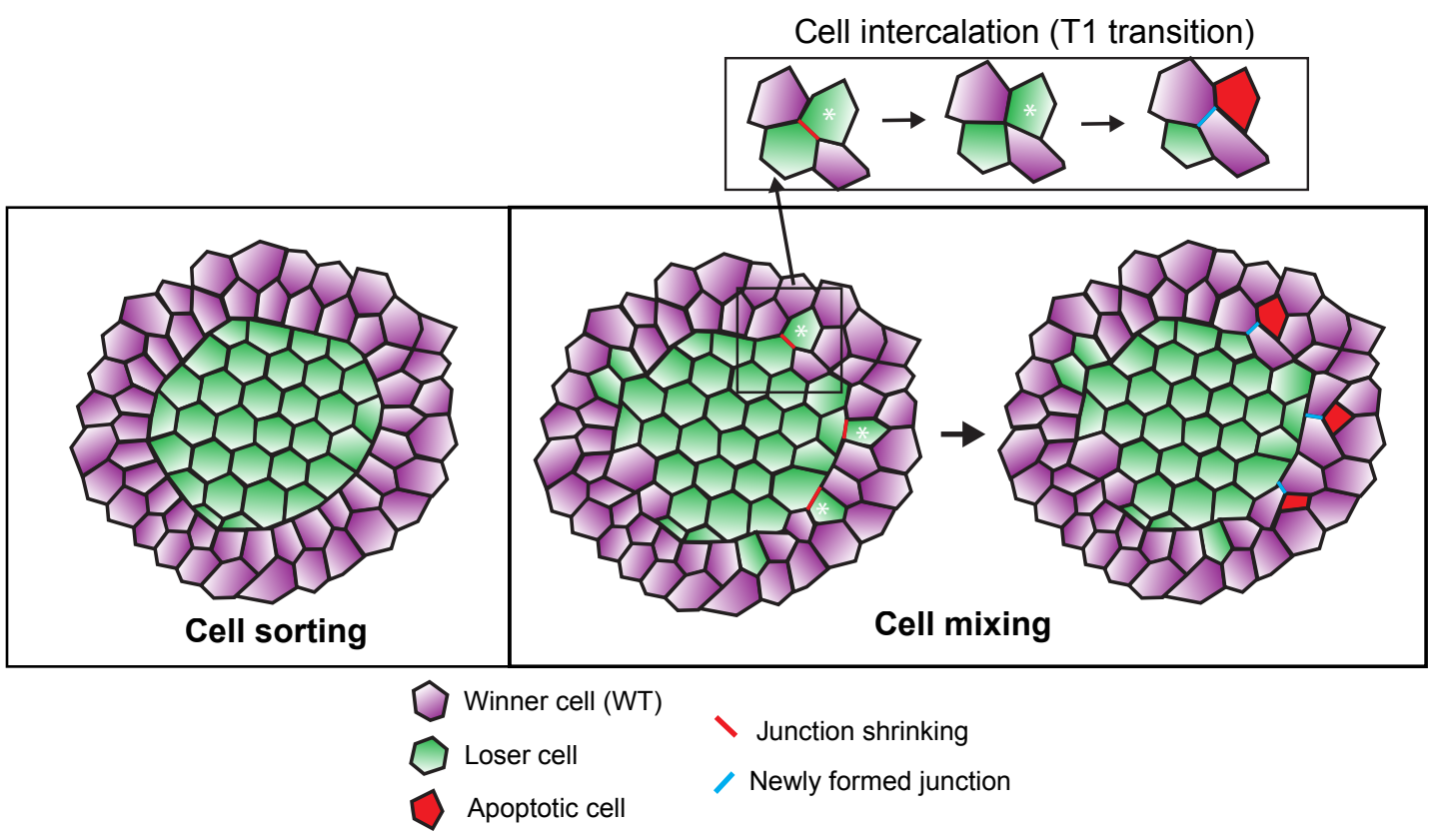
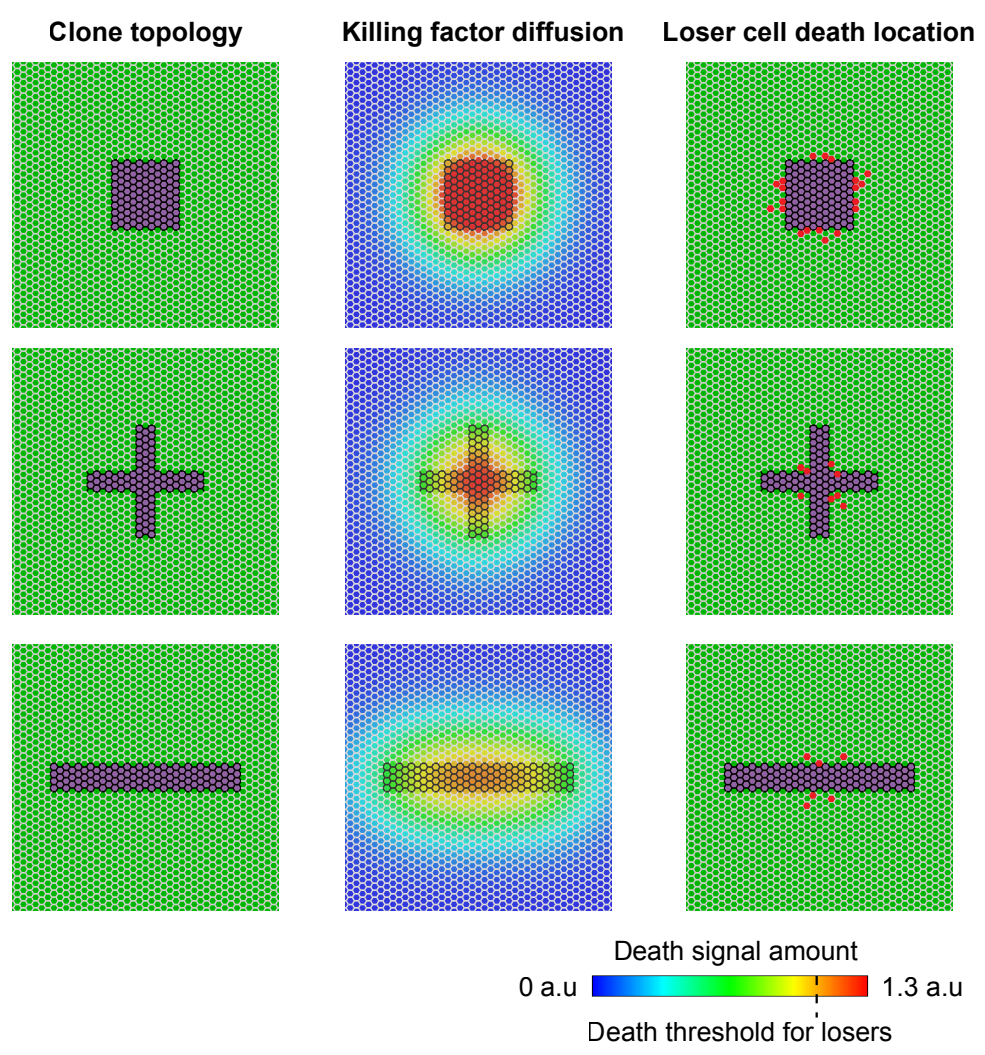
863 **A:** Compaction and elimination of the loser cells (green) is driven by the collective migration and
 864 the convergent movements of the winner cells (purple). **B:** Increase of line tension at the boundary
 865 between loser and winner cells. The consequences will depend on the size of the clone (which
 866 sets the pressure applied to the green cells according to Laplace law, **Box1**). The high pressure

867 will drive cell death and cell elimination in small clones (top right), the formation of folds and cysts
868 in intermediate clones (middle) and the sorting of the two population for large clones (bottom).

869 **Figure 4: Compensatory growth and biased cell expansion**

870 **A:** Compensatory growth driven by the secretion of mitogenic factors (orange dots) by the dying
871 cells. Purple: winner cells, green, loser cells. **B:** Compensatory growth driven by the stretching of
872 the neighbouring cells (red arrows=tension) which promotes cell proliferation. Purple: winner cells,
873 green, loser cells. **C:** Mechanism of biased area compensation (adapted from [83]). The fast
874 growth of winner cells (purple) induces the stretching of neighbouring loser cells (green) along
875 the clone boundaries (left). Upon loser cell death (red cells), the junction remodellings (orange:
876 shrinking junction, blue: new junctions) will increase the number of junctions in neighbouring
877 winner cells relative to loser cells (+: net gain of junction, -: net loss of junction, =: no change of
878 junction number), which will lead to a net relative increase of area. This could bias compensatory
879 proliferation for winner cells.

880

A**B****Figure 1**

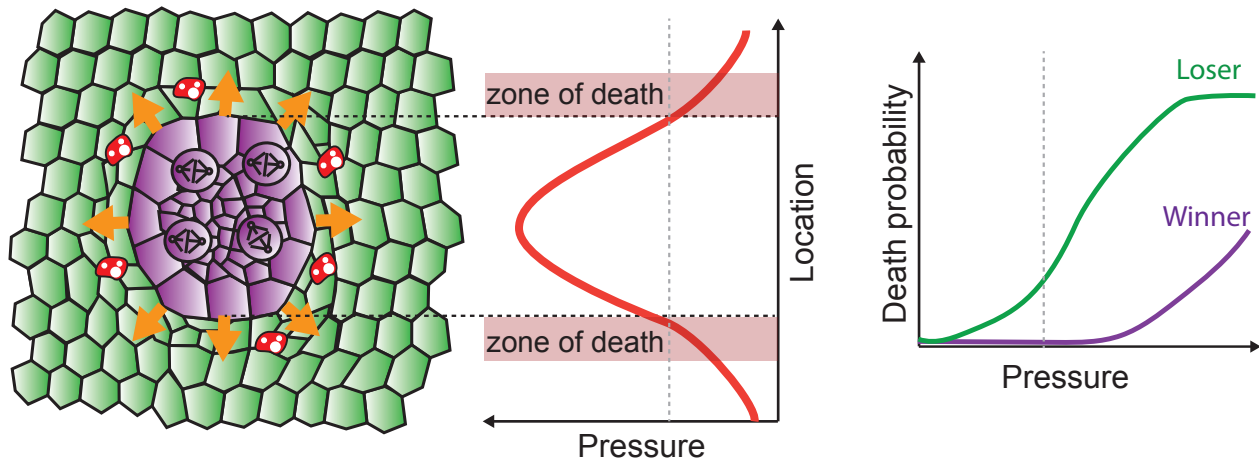
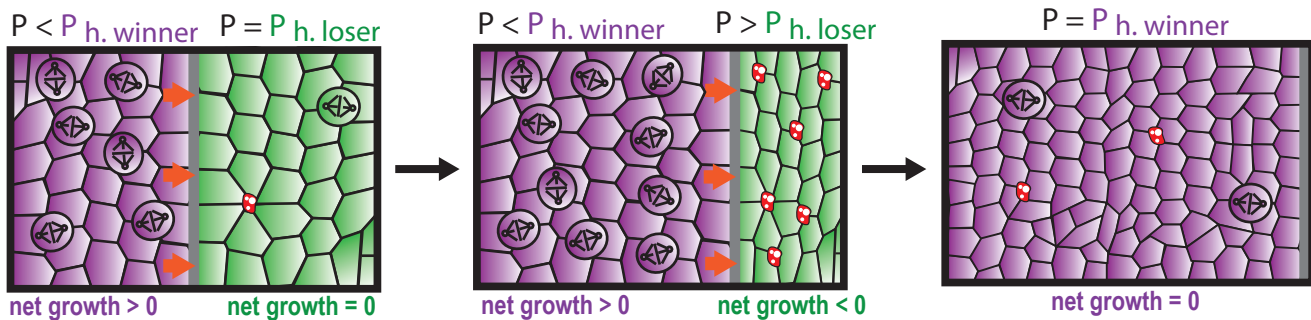
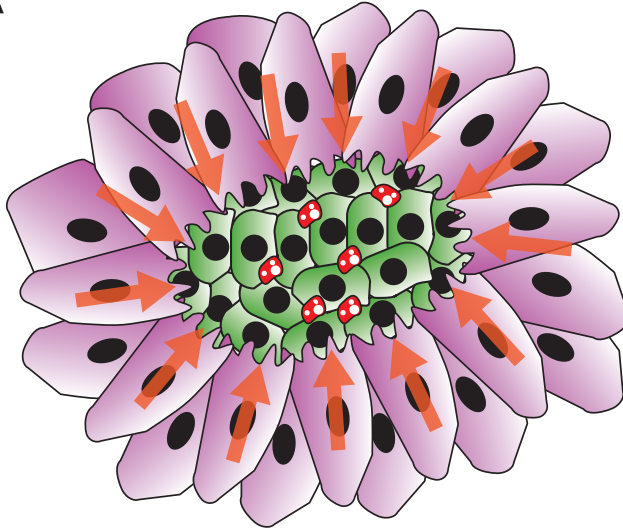
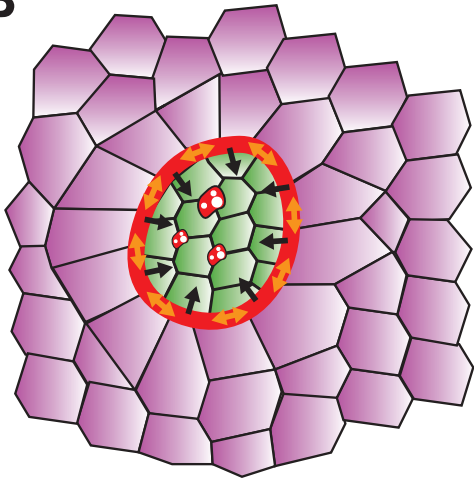
A**B**

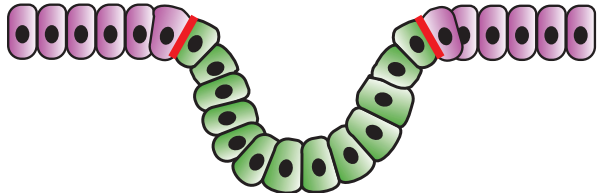
Figure 2

A**B**

Small clone: extrusion/death



Intermediate clone: cyst



Large clone: sorting

**Figure 3**

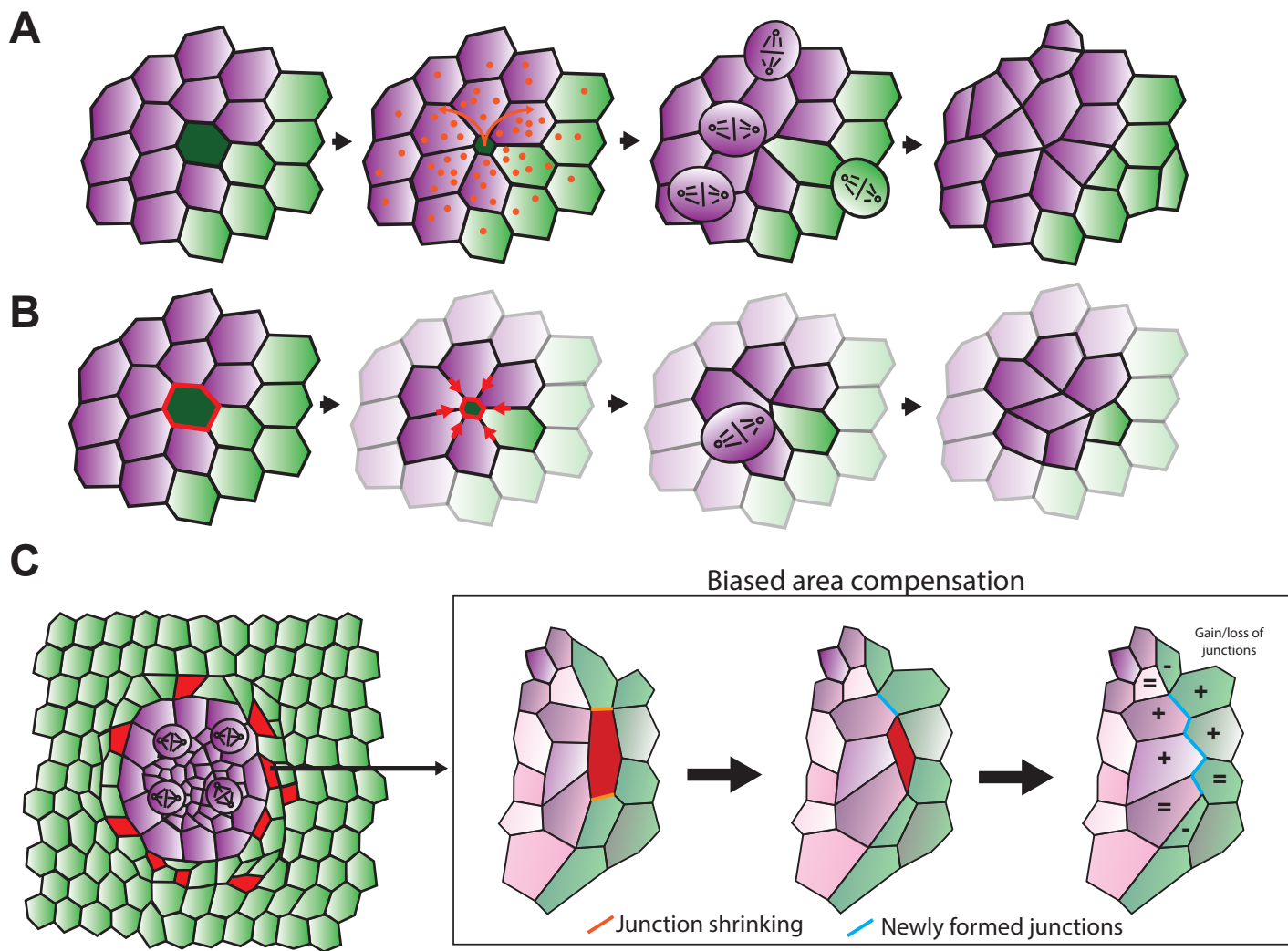


Figure 4

Box 1: Definition of terms describing epithelial mechanics

Cell intercalation (T1 transition): Topological rearrangement of epithelial cells during which cells exchange neighbours through cell-cell junctions shrinkage and elongation.

Compaction: A negative strain (relative reduction of area and/or volume irrespective of the mechanical cause)

Compression: Opposite of tension. Magnitude of a force pointing inside to the object experiencing the force.

Deformation (also called « Strain »): Relative change in size of an object in response to stress.

Homeostatic pressure: Pressure is a force applied per unit of area to the surface of an object orthogonally with respect to its boundaries (unit: Pascal). The homeostatic pressure is the pressure at which cell proliferation is perfectly compensated by cell death, hence leading to constant population size.

Laplace law (or Young-Laplace equation): Describes the relationship between the pressure differences between two phases, line tension and the curvature of the interface. For a liquid droplet, the expression is as followed: $\Delta P = \frac{2\gamma}{R}$, with P: pressure, γ : line tension, and R: radius of the droplet.

Shear: Deformation in which an object is compressed in one direction and extended in the orthogonal direction.

Stress: Internal force that a tissue is experiencing. When a tissue region (A) experiences a force from a neighbouring tissue region (B), the mechanical stress is defined as the ratio of the force to the area of contact between regions A and B. A stress is expressed in Newtons per square meter (or Pascals).

Surface tension: The energy required to increase the membrane surface by a unit area.

Tension: Magnitude of a force pointing outside from the object experiencing the force (i.e., pulling on the object).