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Beyond mechanosensing: How cells sense and shape their physical environment during development

Matyas Bubna-Litic and Roberto Mayor

The role of mechanics as a regulator of cell behaviour and embryo development has been widely recognised. However, much of the focus in mechanobiology during embryo development has been on how the mechanical properties of a cell affect its behaviour and fate determination. We discuss the role of mechanosignalling in development and propose that an equally important aspect of embryo mechanobiology is understanding how dynamic changes in tissue mechanics are regulated. Comparably to how chemical signals influence the fate of responding tissues during embryonic induction, we suggest that embryonic cell populations can alter the mechanical properties of adjacent tissues in a process we name 'actuation'. Several examples of embryonic actuation and mechanical feedback are discussed.

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Information flows in living systems and the role of mechanochemical feedback

Cells sense chemical and mechanical cues from their environments, which affects their behaviour and fate choices. Much less is known about how cells dynamically modify their physical environment to promote tissue formation. In this review, we focus on recent examples of this interaction between tissues that are affected by their environment but ultimately go on to regulate the mechanical properties of their surroundings to allow for the emergence of patterns and complex collective behaviours. The relationship between genes and biological function is not as linear as often conceptualised [1]. Stable biochemical and physical states in cells can be achieved without activation of a genetic response, instead relying on protein modifications or alterations of the cell's physical properties. While biochemical processes can regulate emergent mechanical and geometrical changes in cells and tissues, biologically relevant information arises from dynamical feedback among chemical, mechanical and geometrical properties [2]. Recently, such mechanical feedback loops have been demonstrated in chicken gastrulation as contractility reinforces itself through actomyosin cable alignment [3] and contributes to a long-range tension gradient [4]. Tissue geometry can also provide boundaries that trigger patterning event [5,6]. It is clear then that changes to tissue mechanics should be considered when attempting to understand the flow of information on both cell and tissue levels [7,8]. Importantly, embryonic tissues undergo dynamic changes to their physical properties across multiple levels of organisation, further complicating models of signalling in development [9–11].

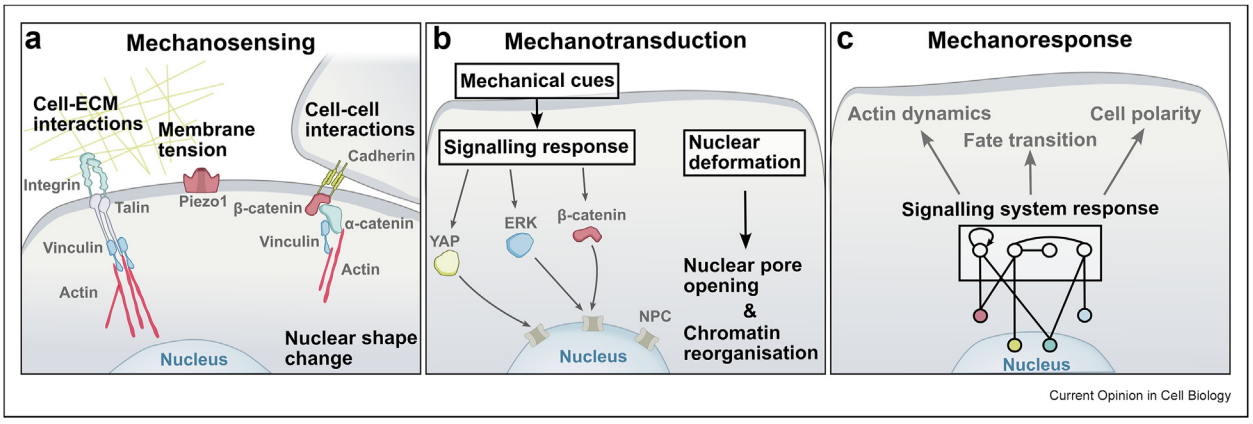
Beyond embryonic development, considering tissue mechanics is key in clinical studies as, for example, tumour growth can lead to local tissue stiffening that promotes cell migration and metastasis [12,13,14]. Here we present recent work that illustrates the interplay between signalling and tissue mechanics and discuss the role of embryonic cell populations in modifying the mechanical properties of tissues that then feed back through mechanochemical signalling.

Role of mechanics in signal sensing, transduction and response

In the past decade, a large body of evidence has emerged reinforcing the notion that cells integrate and respond to stimuli from sources beyond classical molecular signalling [7,15]. One example, and the focus of this review, is the ability of cells and cell collectives to respond to their physical interactions with other cells or the extracellular matrix. Detecting (mechanosensing, Figure 1a), relaying (mechanotransduction, Figure 1b) and responding to (mechanoresponse, Figure 1c) physical stimuli are now well described processes with a variety of examples of cell behaviours during embryonic development.

Mechanical forces resulting in cell deformations lead to the activation of pathways downstream of cadherins and integrins, which are both directly linked to the actin cytoskeleton [16,17]. For example, β-catenin, which

Figure 1



Mechanics-dependent signal sensing, transduction and response.
(a) Mechanosensing involves the detection of mechanical properties and forces that includes a large variety of mechanisms. Cell-ECM interactions are largely detected through parts of the integrin–talin–vinculin complex, cell–cell interactions through cadherins and associated α-catenin, β-catenin and vinculin, mechanosensitive ion channels such as Piezo1 and changes to nuclear shape. **(b)** Mechanics-dependent signals are then transduced through a signalling response that typically depends on a network of kinases and transcription factors or direct effects of nuclear deformation such as increased nuclear pore permeability and chromatin organisation. **(c)** The resulting mechanoresponse is a complex interaction of many systems including transcriptional regulation and posttranslational modifications that can affect various processes including actin dynamics, fate transitions or regulation of cell polarity.

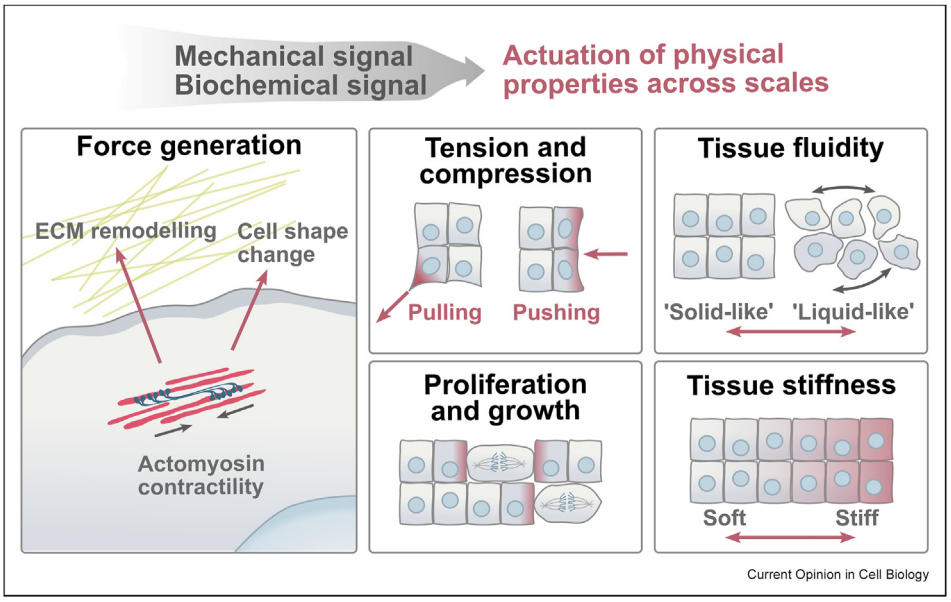
forms a structural part of adherens junctions, has been reported to directly respond to mechanical stimulation by acting as a transcription factor [18,19,20] which is a key feature of mechanics-dependent mesoderm induction in zebrafish and *Drosophila* [21]. Other key transcription factors, such as Yes-associated protein (YAP) [22,23] and Extracellular signal-regulated kinase (ERK) [24,25] are parts of networks that process downstream of mechanical stimulation. Additionally, deformation of the cell membrane is detected by mechanically stimulated ion channels like Piezo1 [26] that release Ca^{2+} ions when under tension to trigger intracellular responses, ranging from migrating cell polarity [27] to neuron depolarisation [28]. Finally, nuclear shape is also affected by external forces [29]. Deformation of the nucleus has been shown to change the permeability of the nuclear pore complex allowing a different range of molecules (e.g. YAP) to enter the nucleus [22]. Nuclear deformation can further lead to chromatin reorganisation and therefore affect its accessibility [29,30,31]. Interestingly, heterochromatin deformation can feed back to soften chromatin reducing damage from mechanical stress [32].

Inputs from mechanical stimuli feed into decision making processes that happen at multiple scales, and the emerging cellular response results from complex molecular interactions, whether in the nucleus or cytoplasm [1,2,33]. The response to mechanical stimuli (Figure 1c) may involve changes to actin dynamics [34,35], regulation of cell polarity [36] or cell fate transitions [21,37]. Recently, a stiffness gradient in the embryonic brain has been described to promote axon outgrowth towards stiffer regions through activation of Ephrin signalling [38].

Embryonic cell populations can modify the mechanical properties of cells and tissues through 'actuation'

Embryonic cell populations undergo major transitions in their physical properties. In terms of deformability, tissues can differ in elastic modulus and transition between softer and stiffer material properties. Tissues are active materials and can be classified into separate phases, where solid-like tissues have few cell rearrangements and fluid-like tissues can efficiently adapt to deformation with high levels of neighbour exchanges [8,39,40]. On the level of individual cells, properties such as surface tension [41] or cell–cell adhesion [42] can change significantly and rapidly during development. Recently, the idea that tissue mechanical properties arise from self-organised processes with a limited ability to assign causality has gained traction [2,33,43,44]. However, we propose that a specific class of processes exist that are instructive and share some features support their explicit description as a unique developmental process. We suggest the term *embryonic actuation* for processes where tissue mechanics are modified directly by the mechanical or biochemical activity of adjacent embryonic cell populations (Figure 2). *Actuation* acts in parallel with *embryonic induction*, in which a cell population generates a signal that instructs adjacent tissues and leads to a transition in cell fate [45].

Figure 2



Modifications of biophysical properties through 'actuation' at different scales. Properties of cells and tissues, as well as the extracellular matrix, can be modified by adjacent cells acting through biochemical or mechanical signalling to actuate a change in the mechanical properties of the responding tissue. These processes are labelled using red arrows and often require a mechanical force to be generated in the actuating tissue through actomyosin contractility. On a tissue level, the proliferation, growth, fluidity and stiffness can all directly affect the mechanical properties of adjacent tissues.

However, actuation specifically refers to changes in physical properties.

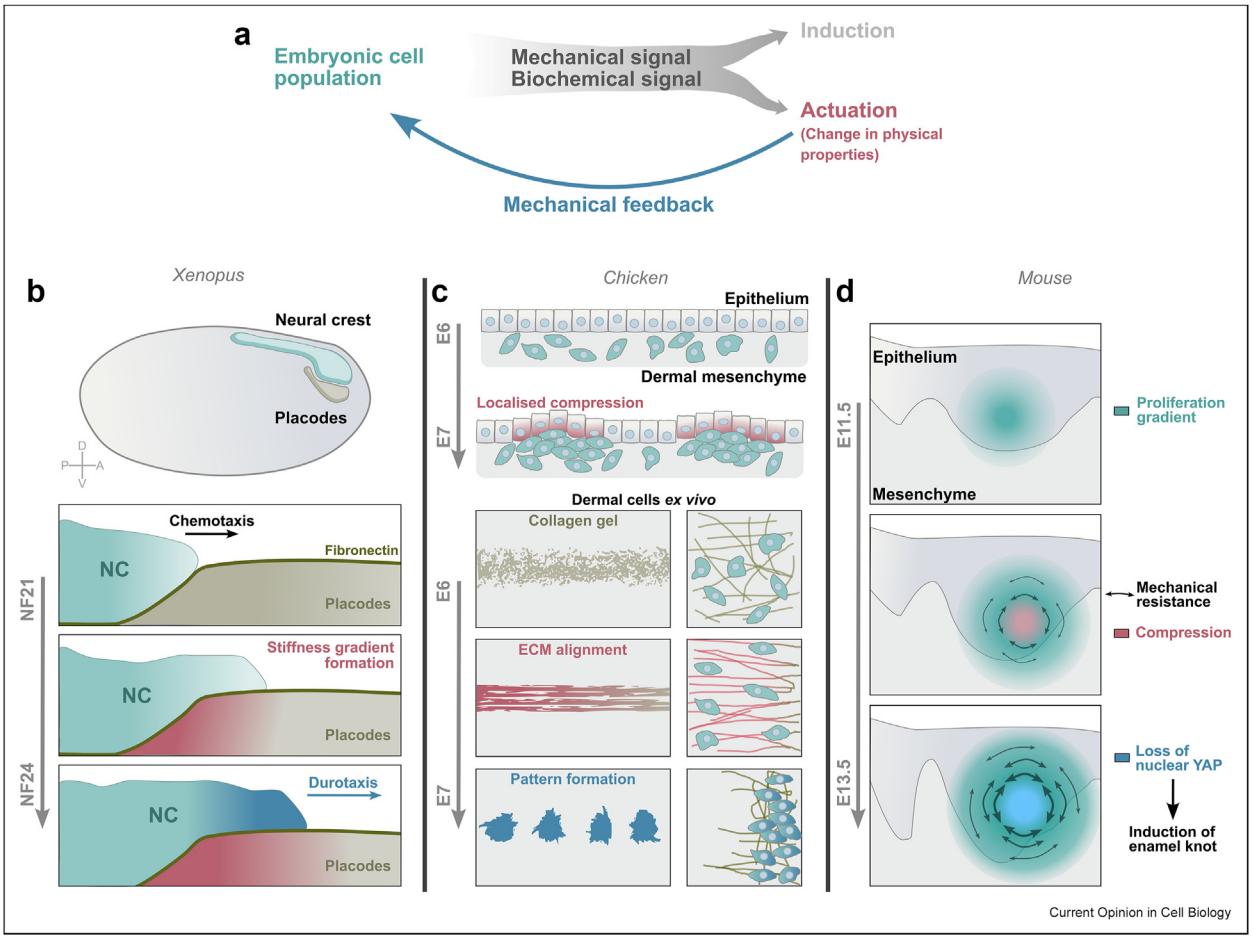
Examples of actuation include processes where a force is generated to change cell shape or remodel the extracellular matrix [46,47]. A pulling or pushing force may also be applied through actomyosin contractility or cell proliferation [48,49], resulting in increased mechanical stress. An interesting example, where force generation works in an actuation feedback loop, is the early migration of prechordal plate (PPL) mesendoderm cells during zebrafish gastrulation [50]. PPL cells push interstitial fluid by moving towards the animal pole causing it to accumulate. This in turn mechanically opens up the space in front of PPL cells allowing them to migrate and accumulate more interstitial fluid that helps form the animal-vegetal embryonic axis. Finally, tissue fluidity and stiffness can also be externally regulated through signalling [36,51].

Note that actuation is separate to mechanics-mediated induction of fate. Recently, it has been shown that mechanical stimulation through tissue compression activates head organiser genes through β-catenin in *Xenopus* gastruloid-like activin-induced explants [52]. In the embryo, the build up of hydrostatic pressure in the blastocoel limits the window of competence for neural crest induction [53]. Finally, confinement of mouse placodes that directly stimulates Sox9 through YAP nuclear exclusion would also not be considered actuation [54]. Conversely, both embryonic induction and actuation can be the consequence of biochemical signals not just mechanical interactions [55]. For example, morphogen signalling can affect mechanics at the supracellular scale in the chicken dermis [56] or fluidise the zebrafish mesendoderm [57]. Epidermal growth factor (EGF) signalling leading the formation of an adhesion gradient required for ventral cell flow during *Drosophila* gastrulation would both be examples of biochemically mediated actuation [58]. Note that actuation and induction do not have to be strictly orthogonal and can act through the same pathways to change either mechanical or fate outcomes. We describe the following recent examples in detail as they illustrate the instructive role of actuation and mechanical feedback, which makes it distinct from self-organised transitions of mechanical properties (Figure 3).

Mechanics-mediated feedback emerging from a changing biophysical state can alter the dynamics of signalling during development

Recent work illustrates the important role of mechanical actuation in embryonic development and its effect on information flow through feedback (Figure 3a). Actuation, the alteration of physical properties of another

Figure 3



Embryonic tissues capable of altering the mechanical state of adjacent tissues or ECM receive self-generated mechanical cues that reinforce their development. (a) Actuation (red), the alteration of physical properties of another tissue or ECM, can mechanically feed back (blue) to the cell population (green) responsible for generating the initial mechanochemical signals. Examples of this process include the following: **(b)** The cranial neural crest (NC) in *Xenopus laevis* migrates in a directional manner that is mediated through Sdf1-dependent chemotaxis. The emergence of a self-generated stiffness gradient results in durotaxis-dependent mechanical feedback. **(c)** In skin hair follicle development of the chick embryo, a pattern in the epithelial layer is generated through spontaneous aggregation of dermal mesenchyme cells that leads to localised compression and ECM alignment. This alignment mechanically aids the formation of dermal cell aggregates. **(d)** In mouse incisor development, the enamel knot (EK) is a key organising centre. A proliferation gradient forms that leads to compression within less mechanically resistant cells in the centre of the proliferating tissue. This in turn leads to the loss of nuclear YAP signalling that induces Shh expression and the formation of the EK.

tissue or extracellular matrix (ECM), can feed back to the cell population responsible for generating the initial mechanochemical signals and allow for progression of migration or the establishment of new signalling centres.

During *Xenopus laevis* development, cranial neural crest cells (NCCs) migrate dorsolaterally and ventrally in a directional manner following a gradient of Sdf1 generated by placodal cells (Figure 3b). NCCs interact with adjacent ectodermal cells called placodes through N-cadherin that is sufficient to disrupt the cortical actin cytoskeleton and soften the placodes closest to the NCCs [36]. The emergent stiffness gradient then mechanically feeds back to the NCCs to direct migration via durotaxis.

Two cases of mechanical actuation have been described during the development of skin hair follicles in the chicken embryo (Figure 3c). A periodic pattern in the superficial epithelial cell layer is generated through the spontaneous aggregation of dermal mesenchyme cells [44,59]. The self-organised dermal cell aggregation actuates nearby epithelial cells through mechanical compression, which leads to the activation of β-catenin and a gene expression profile favouring the formation of hair follicles [59]. More recently, the ability of dermal cells to aggregate has

been shown *ex vivo* without the necessity for any signals controlling this process [44]. In this case, dermal cells directly actuate the extracellular matrix *in vitro* by mechanically aligning collagen through actomyosin-dependent force generation. The collagen alignment reinforces the aggregation through mechanical feedback acting on the dermal cell population responsible for actuation.

As a final example, we highlight the enamel knot (EK) organising centre formation in mouse incisor development [49]. Initially, a proliferation gradient forms in the presumptive incisor tissue composed of both epithelial and mesenchymal cells. Mechanical stress, which builds up due to increasing cell density, is resisted by the tissue surrounding the presumptive EK leading to compressive actuation of the cells in the central region. This compression affects Hippo/YAP signalling by shuttling YAP into the cytoplasm allowing for the induction of *Shh* expression and EK formation, which then feeds back through chemical signalling to pattern the surrounding tissues.

Conclusion

In recent years, much attention has been given to mechanisms where morphogenetic and fate transitions in development are downstream of mechanical stimuli and mechanosignalling. Here, we propose that *actuation* is a special case of a developmental process, where changes in the mechanical properties of a tissue are the result of direct modifications by an adjacent embryonic cell population. We described some of the many examples of actuation that have been recently published.

We believe developing a better understanding of the role of mechanics in dynamic embryonic processes will rely on our ability to distinguish between instructed and self-organised processes. We also currently lack characterisation of how developmental systems change over time in a way that integrates information about gene expression and biophysical states [44]. Finally, mechanical memory, or the ability of cells to be affected by mechanical stimuli after the initial source is lost, should be more broadly considered in our models of development.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Gallo E, Renzis SD, Sharpe J, Mayor R, Hartmann J: **Versatile system cores as a conceptual basis for generality in cell and developmental biology**. *Cell Syst* 2024, **15**:790–807, https://doi.org/10.1016/j.cels.2024.08.001.

2. Collinet C, Lecuit T: **Programmed and self-organized flow of information during morphogenesis**. *Nat Rev Mol Cell Biol* 2021, **22**:245–265, https://doi.org/10.1038/s41580-020-00318-6.

3. Nájera GS, Plum AM, Steventon B, Weijer CJ, Serra M: ***Control of modular tissue flows shaping the embryo in Avian gastrulation***. https://doi.org/10.1101/2024.07.04.601785.

4. Caldarelli P, Chamolly A, Villedieu A, Alegria-Prévot O, Phan C, Gros J, Corson F: **Self-organized tissue mechanics underlie embryonic regulation**. *Nature* 2024, **633**:887–894, https://doi.org/10.1038/s41586-024-07934-8.

5. McNamara HM, Solley SC, Adamson B, Chan MM, Toettcher JE: **Recording morphogen signals reveals mechanisms underlying gastruloid symmetry breaking**. *Nat Cell Biol* 2024, **26**:1832–1844, https://doi.org/10.1038/s41556-024-01521-9.

6. Muncie JM, Ayad NME, Lakins JN, Xue X, Fu J, Weaver VM: **Mechanical tension promotes formation of gastrulation-like Nodes and patterns mesoderm specification in human embryonic stem cells**. *Dev Cell* 2020, **55**:679–694.e11, https://doi.org/10.1016/j.devcel.2020.10.015.

7. De Belly H, Paluch EK, Chalut KJ: **Interplay between mechanics and signalling in regulating cell fate**. *Nat Rev Mol Cell Biol* 2022, **23**:465–480, https://doi.org/10.1038/s41580-022-00472-z.

8. Mao Y, Wickström SA: **Mechanical state transitions in the regulation of tissue form and function**. *Nat Rev Mol Cell Biol* 2024, **25**:654–670, https://doi.org/10.1038/s41580-024-00719-x.

9. Busby L, Steventon B: **Tissue tectonics and the multi-scale regulation of developmental timing**. *Interface Focus* 2021, **11**, 20200057, https://doi.org/10.1098/rsfs.2020.0057.

10. Ebisuya M, Briscoe J: **Timing and Tempo in development**. *Curr Opin Genet Dev* 2024, **86**, 102202, https://doi.org/10.1016/j.gde.2024.102202.

11. Newman SA, Bhat R: **Dynamical patterning modules: physico-genetic determinants of morphological development and evolution**. *Phys Biol* 2008, **5**, 015008, https://doi.org/10.1088/1478-3975/5/1/015008.

12. Crosas-Molist E, Graziani V, Maiques O, Pandya P, Monger J, Samain R, George SL, Malik S, Salise J, Morales V, Le Guennec A, Atkinson RA, Marti RM, Matias-Guiu X, Charras G, Conte MR, Elosegui-Artola A, Holt M, Sanz-Moreno V: **AMPK is a mechano-metabolic sensor linking cell adhesion and mitochondrial dynamics to Myosin-dependent cell migration**. *Nat Commun* 2023, **14**:2740, https://doi.org/10.1038/s41467-023-38292-0.

13. Deng B, Zhao Z, Kong W, Han C, Shen X, Zhou C: **Biological role of matrix stiffness in tumor growth and treatment**. *J Transl Med* 2022, **20**, https://doi.org/10.1186/s12967-022-03768-y.

14. Graziani V, Crosas-Molist E, George SL, Sanz-Moreno V: **Organelle adaptations in response to mechanical forces during tumour dissemination**. *Curr Opin Cell Biol* 2024, **88**, 102345, https://doi.org/10.1016/j.ceb.2024.102345.

15. Valet M, Siggia ED, Brivanlou AH: **Mechanical regulation of early vertebrate embryogenesis**. *Nat Rev Mol Cell Biol* 2022, **23**:169–184, https://doi.org/10.1038/s41580-021-00424-z.

16. Clarke DN, Martin AC: **Roles of the actin cytoskeleton and cell adhesion in tissue morphogenesis**. *Curr Biol CB* 2021, **31**: R667–R680, https://doi.org/10.1016/j.cub.2021.03.031.

17. Kelkar M, Bohec P, Charras G: **Mechanics of the cellular actin cortex: from signalling to shape change**. *Curr Opin Cell Biol* 2020, **66**:69–78, https://doi.org/10.1016/j.ceb.2020.05.008.

18. Ayad NME, Lakins JN, Ghagre A, Ehrlicher AJ, Weaver VM: ***Tissue tension permits β-catenin phosphorylation to drive mesoderm specification in human embryonic stem cells***. https://doi.org/10.1101/2023.07.14.549074.

19. Pukhlyakova E, Aman AJ, Elsayad K, Technau U: **β-Catenin-dependent mechanotransduction dates back to the common ancestor of Cnidaria and Bilateria**. *Proc Natl Acad Sci USA* 2018, **115**:6231–6236, https://doi.org/10.1073/pnas.1713682115.

20. Röper J-C, Mitrossilis D, Stirnemann G, Waharte F, Brito I, Fernandez-Sanchez M-E, Baaden M, Salamero J, Farge E: **The major β-catenin/E-cadherin junctional binding site is a primary molecular mechano-transductor of differentiation in vivo**. *Elife* 2018, **7**, e33381, https://doi.org/10.7554/eLife.33381.

21. Brunet T, Bouclet A, Ahmadi P, Mitrossilis D, Driquez B, Brunet A-C, Henry L, Serman F, Béalle G, Ménager C, Dumas-Bouchiat F, Givord D, Yanicostas C, Le-Roy D, Dempsey NM, Plessis A, Farge E: **Evolutionary conservation of early mesoderm specification by mechanotransduction in Bilateria**. *Nat Commun* 2013, **4**:2821, https://doi.org/10.1038/ncomms3821.

22. Elosegui-Artola A, Andreu I, Beedle AEM, Lezamiz A, Uroz M, Kosmalska AJ, Oria R, Kechagia JZ, Rico-Lastres P, Roux A-LL, Shanahan CM, Trepat X, Navajas D, Garcia-Manyes S, Roca-Cusachs P: **Force triggers YAP nuclear Entry by regulating Transport across nuclear pores**. *Cell* 2017, **171**: 1397–1410.e14, https://doi.org/10.1016/j.cell.2017.10.008.

23. Piccolo S, Sladitschek-Martens HL, Cordenonsi M: **Mechano-signaling in vertebrate development**. *Dev Biol* 2022, **488**: 54–67, https://doi.org/10.1016/j.ydbio.2022.05.005.

24. De Belly H, Stubb A, Yanagida A, Labouesse C, Jones PH, Paluch EK, Chalut KJ: **Membrane tension Gates ERK-mediated regulation of pluripotent cell fate**. *Cell Stem Cell* 2021, **28**: 273–284.e6, https://doi.org/10.1016/j.stem.2020.10.018.

25. Kinoshita N, Hashimoto Y, Yasue N, Suzuki M, Cristea IM, Ueno N: **Mechanical stress regulates epithelial tissue integrity and stiffness through the FGFR/Erk2 signaling pathway during embryogenesis**. *Cell Rep* 2020, **30**:3875–3888.e3, https://doi.org/10.1016/j.celrep.2020.02.074.

26. Lin Y-C, Guo YR, Miyagi A, Levring J, MacKinnon R, Scheuring S: **Force-induced conformational changes in PIEZO1**. *Nature* 2019, **573**:230–234, https://doi.org/10.1038/s41586-019-1499-2.

27. Canales Coutiño B, Mayor R: **The mechanosensitive channel Piezo1 cooperates with semaphorins to control neural crest migration**. *Development* 2021, **148**, dev200001, https://doi.org/10.1242/dev.200001.

28. Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ, Dubin AE, Patapoutian A: **Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels**. *Science* 2010, **330**:55–60, https://doi.org/10.1126/science.1193270.

29. Kalukula Y, Stephens AD, Lammerding J, Gabriele S: **Mechanics and functional consequences of nuclear deformations**. *Nat Rev Mol Cell Biol* 2022, **23**:583–602, https://doi.org/10.1038/s41580-022-00480-z.

30. Bergamaschi G, Biebricher AS, Witt H, Byfield FJ, Seymonson XMR, Storm C, Janmey PA, Wuite GJL: **Heterogeneous force response of chromatin in isolated nuclei**. *Cell Rep* 2024, **43**, https://doi.org/10.1016/j.celrep.2024.114852.

31. McCreery KP, Stubb A, Stephens R, Fursova NA, Cook A, Kruse K, Michelbach A, Biggs LC, Keikhosravi A, Nykänen S, Hydén-Granskog C, Zou J, Lackmann J-W, Niessen CM, Vuoristo S, Miroshnikova YA, Wickström SA: ***Mechano-osmotic signals control chromatin state and fate transitions in pluripotent stem cells***. https://doi.org/10.1101/2024.09.07.611779.

32. Nava MM, Miroshnikova YA, Biggs LC, Whitefield DB, Metge F, Boucas J, Vihinen H, Jokitalo E, Li X, García Arcos JM, Hoffmann B, Merkel R, Niessen CM, Dahl KN, Wickström SA: **Heterochromatin-Driven nuclear softening protects the genome against mechanical stress-induced damage**. *Cell* 2020, **181**:800–817.e22, https://doi.org/10.1016/j.cell.2020.03.052.

33. Pfeifer CR, Shyer AE, Rodrigues AR: **Creative processes during vertebrate organ morphogenesis: biophysical self-organization at the supracellular scale**. *Curr Opin Cell Biol* 2024, **86**, 102305, https://doi.org/10.1016/j.ceb.2023.102305.

34. Bieling P, Li T-D, Weichsel J, McGorty R, Jreij P, Huang B, Fletcher DA, Mullins RD: **Force feedback controls motor activity and mechanical properties of self-assembling branched actin networks**. *Cell* 2016, **164**:115–127, https://doi.org/10.1016/j.cell.2015.11.057.

35. Mehidi A, Kage F, Karatas Z, Cercy M, Schaks M, Polesskaya A, Sainlos M, Gautreau AM, Rossier O, Rottner K, Giannone G: **Forces generated by lamellipodial actin filament elongation regulate the WAVE complex during cell migration**. *Nat Cell Biol* 2021, **23**:1148–1162, https://doi.org/10.1038/s41556-021-00786-8.

36. ** Shellard A, Mayor R: **Collective durotaxis along a self-generated stiffness gradient in vivo**. *Nature* 2021, **600**: 690–694, https://doi.org/10.1038/s41586-021-04210-x.
The core idea reviewed here is exemplified in the case of the ability of neural crest cells to modify the stiffness of adjacent placodal cells to generate a stiffness gradient *in vivo* that guides further neural crest migration.

37. Engler AJ, Sen S, Sweeney HL, Discher DE: **Matrix elasticity directs stem cell lineage specification**. *Cell* 2006, **126**: 677–689, https://doi.org/10.1016/j.cell.2006.06.044.

38. Sipkova J, Franze K: ***Eph/ephrin signalling in the developing brain is regulated by tissue stiffness***. https://doi.org/10.1101/2024.02.15.580461.

39. Mongera A, Rowghanian P, Gustafson HJ, Shelton E, Kealhofer DA, Carn EK, Serwane F, Lucio AA, Giammona J, Campàs O: **A fluid-to-solid jamming transition underlies vertebrate body axis elongation**. *Nature* 2018, **561**:401–405, https://doi.org/10.1038/s41586-018-0479-2.

40. Petridou NI, Grigolon S, Salbreux G, Hannezo E, Heisenberg C-P: **Fluidization-mediated tissue spreading by mitotic cell rounding and non-canonical Wnt signalling**. *Nat Cell Biol* 2019, **21**:169–178, https://doi.org/10.1038/s41556-018-0247-4.

41. Lecuit T, Lenne P-F: **Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis**. *Nat Rev Mol Cell Biol* 2007, **8**:633–644, https://doi.org/10.1038/nrm2222.

42. Plater de L, Firmin J, Maître J-L: **Mechanical strengthening of cell-cell adhesion during mouse embryo compaction**. *Biophys J* 2024, https://doi.org/10.1016/j.bpj.2024.03.028. 0.

43. Hartmann J, Mayor R: **Self-organized collective cell behaviors as design principles for synthetic developmental biology**. *Semin Cell Dev Biol, Special Issue: Synth Develop Biol* 2023, **141**:63–73, https://doi.org/10.1016/j.semcdb.2022.04.009.

44. Palmquist KH, Ko CS, Shyer AE, Rodrigues AR: **Biological theories of morphogenesis based on holistic biophysical thinking**. *Biol Theory* 2024, https://doi.org/10.1007/s13752-024-00477-1.

45. Niehrs C: **Regionally specific induction by the Spemann–Mangold organizer**. *Nat Rev Genet* 2004, **5**: 425–434, https://doi.org/10.1038/nrg1347.

46. Ly M, Schimmer C, Hawkins R, E. Rothenberg K, Fernandez-Gonzalez R: **Integrin-based adhesions promote cell–cell junction and cytoskeletal remodelling to drive embryonic**

wound healing. *J Cell Sci* 2023, **137**, jcs261138, https://doi.org/10.1242/jcs.261138.

47. Palmquist KH, Tiemann SF, Ezzeddine FL, Yang S, Pfeifer CR, ** Erzberger A, Rodrigues AR, Shyer AE: **Reciprocal cell-ECM dynamics generate supracellular fluidity underlying spontaneous follicle patterning**. *Cell* 2022, **185**:1960–1973.e11, https://doi.org/10.1016/j.cell.2022.04.023.
The authors were able to recapitulate aspects of a self-organising pattern using an *ex vivo* approach demonstrating the ability of cells to mechanically modify and align extracellular matrix that promotes further organisation through mechanical feedback.

48. Bocanegra-Moreno L, Singh A, Hannezo E, Zagorski M, * Kicheva A: **Cell cycle dynamics control fluidity of the developing mouse neuroepithelium**. *Nat Phys* 2023, **19**:1050–1058, https://doi.org/10.1038/s41567-023-01977-w.
In the mouse neural tube a decrease in cell proliferation leads to increased tissue solidity linking division dynamics to tissue mechanical state *in vivo*.

49. Shroff NP, Xu P, Kim S, Shelton ER, Gross BJ, Liu Y, Gomez CO, ** Ye Q, Drennon TY, Hu JK, Green JBA, Campàs O, Klein OD: **Proliferation-driven mechanical compression induces signalling centre formation during mammalian organ development**. *Nat Cell Biol* 2024, **26**:519–529, https://doi.org/10.1038/s41556-024-01380-4.
The authors have used mouse incisor development as a powerful system to link cell proliferation dynamics with build-up of stresses resulting in the induction of the enamel knot organising centre.

50. Huljev K, Shamipour S, Pinheiro D, Preusser F, Steccari I, * Sommer CM, Naik S, Heisenberg C-P: **A hydraulic feedback loop between mesendoderm cell migration and interstitial fluid relocalization promotes embryonic axis formation in zebrafish**. *Dev Cell* 2023, **58**:582–596.e7, https://doi.org/10.1016/j.devcel.2023.02.016.
This study is an example of the dynamic nature of physical changes during development as interstitial fluid is pushed by prechordal plate mesendoderm and in turn this accumulation promotes migration and the establishment of the animal to vegetal embryonic axis.

51. Parada C, Banavar SP, Khalilian P, Rigaud S, Michaut A, Liu Y, * Joshy DM, Campàs O, Gros J: **Mechanical feedback defines organizing centers to drive digit emergence**. *Dev Cell* 2022, **57**:854–866.e6, https://doi.org/10.1016/j.devcel.2022.03.004.
Here authors show that a mechanical state fluid to solid transition can dynamically affect morphogen production in mouse digit patterning as an example of mechanical feedback *in vivo*.

52. Bubna-Litic M, Charras G, Mayor R: **Tissue mechanics modulate morphogen signalling to induce the head organiser**. *Cells Dev* 2024, 203984, https://doi.org/10.1016/j.cdev.2024.203984.

53. Alasaadi DN, Alvizi L, Hartmann J, Stillman N, Moghe P, Hiiragi T, Mayor R: **Competence for neural crest induction is controlled by hydrostatic pressure through Yap**. *Nat Cell Biol* 2024, **26**:530–541, https://doi.org/10.1038/s41556-024-01378-y.

54. Villeneuve C, Hashmi A, Ylivinkka I, Lawson-Keister E, * Miroshnikova YA, Pérez-González C, Myllymäki S-M, Bertillot F, Yadav B, Zhang T, Matic Vignjevic D, Mikkola ML, Manning ML, Wickström SA: **Mechanical forces across compartments coordinate cell shape and fate transitions to generate tissue architecture**. *Nat Cell Biol* 2024, **26**:207–218, https://doi.org/10.1038/s41556-023-01332-4.
By combining detailed *in vivo* observations and mathematical modelling the authors describe the importance of contractility of adjacent tissues in placode fate determination.

55. Villedieu A, Bosveld F, Bellaïche Y: **Mechanical induction and competence in epithelial morphogenesis**. *Curr Opin Genet Dev, Development Mech Patter Evol* 2020, **63**:36–44, https://doi.org/10.1016/j.gde.2020.03.003.

56. Yang S, Palmquist KH, Nathan L, Pfeifer CR, Schultheiss PJ, Sharma A, Kam LC, Miller PW, Shyer AE, Rodrigues AR: **Morphogens enable interacting supracellular phases that generate organ architecture**. *Science* 2023, **382**, eadg5579, https://doi.org/10.1126/science.adg5579.

57. Pinheiro D, Kardos R, Hannezo É, Heisenberg C-P: **Morphogen gradient orchestrates pattern-preserving tissue morphogenesis via motility-driven unjamming**. *Nat Phys* 2022, **18**:1482–1493, https://doi.org/10.1038/s41567-022-01787-6.

58. Clarke DN, Miller PW, Martin AC: **EGFR-dependent actomyosin patterning coordinates morphogenetic movements between tissues in *Drosophila melanogaster***. *Dev Cell* 2025, **60**:270–287.e6, https://doi.org/10.1016/j.devcel.2024.10.002.

59. Shyer AE, Rodrigues AR, Schroeder GG, Kassianidou E, Kumar S, Harland RM: **Emergent cellular self-organization and mechanosensation initiate follicle pattern in the avian skin**. *Science* 2017, **357**:811, https://doi.org/10.1126/science.aai7868.