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Supervisor Expression of Interest
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Department Name: Research topic: (https://www.polimi.it/en/scientific-research/research-at-the-politecnico/departments/)	MOX, Dipartimento di Matematica, Politecnico di Milano Applied Mathematics, Theoretical mechanics, Morphogenesis, Mechano-Biology
MSCA-IF Research Area Panels	• ENG_Information Science and Engineering • MAT_Mathematics
Politecnico di Milano Areas:	• Health • Industry 4.0
Brief description of the Department and Research Group (including URL if applicable):	The MOX Laboratory@Polimi (mox.polimi.it) was founded in 2002 and its activity has broadened to a vast range of applications, establishing strong collaboration with industries and research centres all over the world. MOX is currently hosting an advanced ERC grant in PE1, awarded to prof. Quarteroni. It has been established precisely with the scope of promoting research advances in field of mathematical modelling and scientific computing for Science and Engineering, which is the strategic objective of this project. MOX has a large activity in dissemination and technology transfer and takes an active part in the education system of PoliMi. The research activity at the MOX in cardiac mechanics, nanomedicine, tumour growth, etc. Specific outstanding expertise at the MOX is in the numerical simulations and biomechanical modelling of living systems. Professor Pasquale Ciarletta is leading expert in mathematical modelling of growth and remodelling in living matter.

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The mechanical basis of morphogenetic size control and growth termination: translating design schemes from Nature to digital factory

How does a cell in an organ know what overall size the organ has? How does the cell decide when to stop dividing once the organ has the right size? This classical mystery [1] of developmental biology has been revived in recent decades through progress in plant morphogenesis and especially with the Drosophila wing disc. Recently, in the wing imaginal disc of the fruit fly *Drosophila*, a signalling network called the Hippo pathway was shown to respond to mechanical forces and integrate them with biochemical signals. In the *Arabidopsis* plant root, it was proposed that a change in the growth pattern reorients microtubules, serving as a proprioception mechanism determining the final size [2]. These and other findings raise the challenging mathematical and physical question how the size of an organ can be deduced from the local information (such as mechanical stress) available to the cell, a question which received considerable attention and creativity but remains elusive. I plan to work on the two physical/mechanical questions: **(1) Identifying the role of mechanics in the regulation of growth that achieves size control and growth termination and (2) explaining how among many spatiotemporal patterns of growth that arrive at the same geometric shape the right morphogenetic sequence is chosen?**

Living systems tend to voluntarily accumulate internal mechanical stresses during their development, and I think this is in part to enable size control. For instance, the Drosophila wing disc builds compressive stress in its centre, and for the same reason arteries open when radially cut, and killer trees (‘arbres tueurs’) can explode when logged. Internal stress can be built through differential growth, which means that some patches of tissue grow faster than others, causing a mechanical ‘conflict’ between locally overgrowing or undergrowing patches. This conflict is called ‘incompatibility’ and causes internal stresses [3]. Internal stress does not necessarily lead to structural improvement, sometimes it makes things worse (buckling), and its purpose is generally not clear. Also, it can be avoided: Growth that follows a “harmonic” profile accumulates no stress, which is for instance how tobacco plants grow. The downside is that it provides cells with no information on the tissue size. There appears to be a tradeoff between building some internal stress through differential growth to allow size control, but not too much to avoid undesired effects (buckling, distortion of cell shape). Intriguingly, stress gradients are compatible with size control [4], so is mean stress [5,6], both of which are non-local quantities [7]. I want to investigate the relationship between non-locality, harmonicity and size control to understand how developmental systems such as the Drosophila wing disc follow not quite harmonic growth profiles to build a controlled amount of internal stress to achieve size control but avoid negative side effects like buckling.

The Drosophila wing disc system poses a fascinating paradox: The growth rate (cell division rate) during development is practically constant throughout the disc, but the accumulated internal stress is not. The most widespread model of growth-mechanical feedback (growth rate proportional to stress) fails spectacularly here, because it permits neither size control nor a spatially constant growth rate. I adapted the model to remove such restrictions [5], highlighting another crucial point: Even when endowed with size control, our current paradigm of modeling growth-mechanical feedback allows multiple final sizes, i.e. growth termination works but is ambivalent. How is the right size chosen during morphogenesis? My second goal is to classify different growth strategies and see how they can be plausibly encoded in cell behaviour to yield a reproducible size.

This seminal understanding of morphogenetic processes in Nature will be used to translate new paradigms of material design and fabrication in digital factory, e.g. 4d printing.

[1] Travis, *Science* (2013). **[2]** Hervieux, N. *et al. Curr. Biol.* (2016) **[3]** Zurlo, G. & Truskinovsky, L. *Phys. Rev. Lett.* (2017). **[4]** Ambrosi, D., Pettinati, V. & Ciarletta, P. *Int. J. Non Linear Mech.* (2015). **[5]** Erlich, A., Moulton, D. E. & Goriely, *Bull. Math. Biol.* (2019). **[6]** Hufnagel, L. *et al*. *Proc. Natl. Acad. Sci. U. S. A.* (2007). **[7]** Haas, P. A. & Goldstein, R. E. *Phys Rev E* (2019). **[8]** Ishihara, S. & Sugimura, K. *J. Theor. Biol.* (2012). **[9]** Wartlick, O. *et al. Science* (2011). **[10]** Irvine, K. D. & Shraiman, B. I. *Development* (2017). **[11]** Alim, K *et al. Phys. Biol.* (2016)