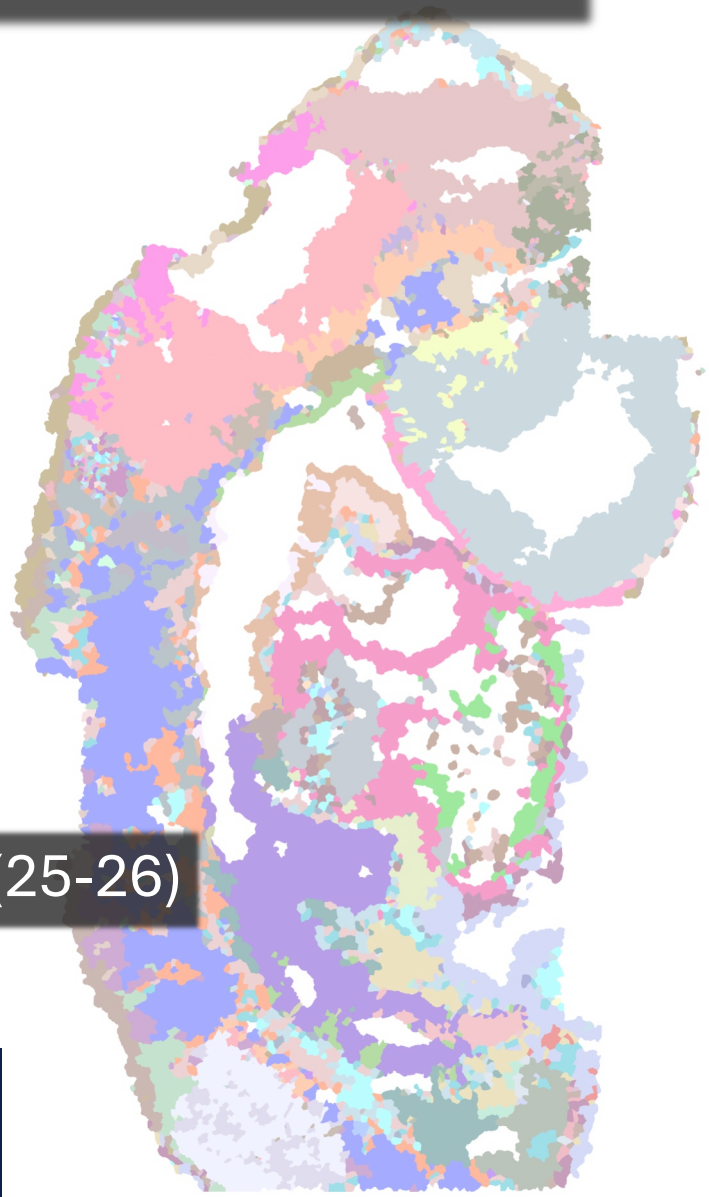
Pattern formation in tissues: from development to pathology

Adrien Hallou

adrien.hallou@kennedy.ox.ac.uk



Case Studies in Mathematical Modelling (25-26)

KENNEDY

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Tissue level pattern formation through mechanical instabilities

Villification: How the Gut Gets Its Villi

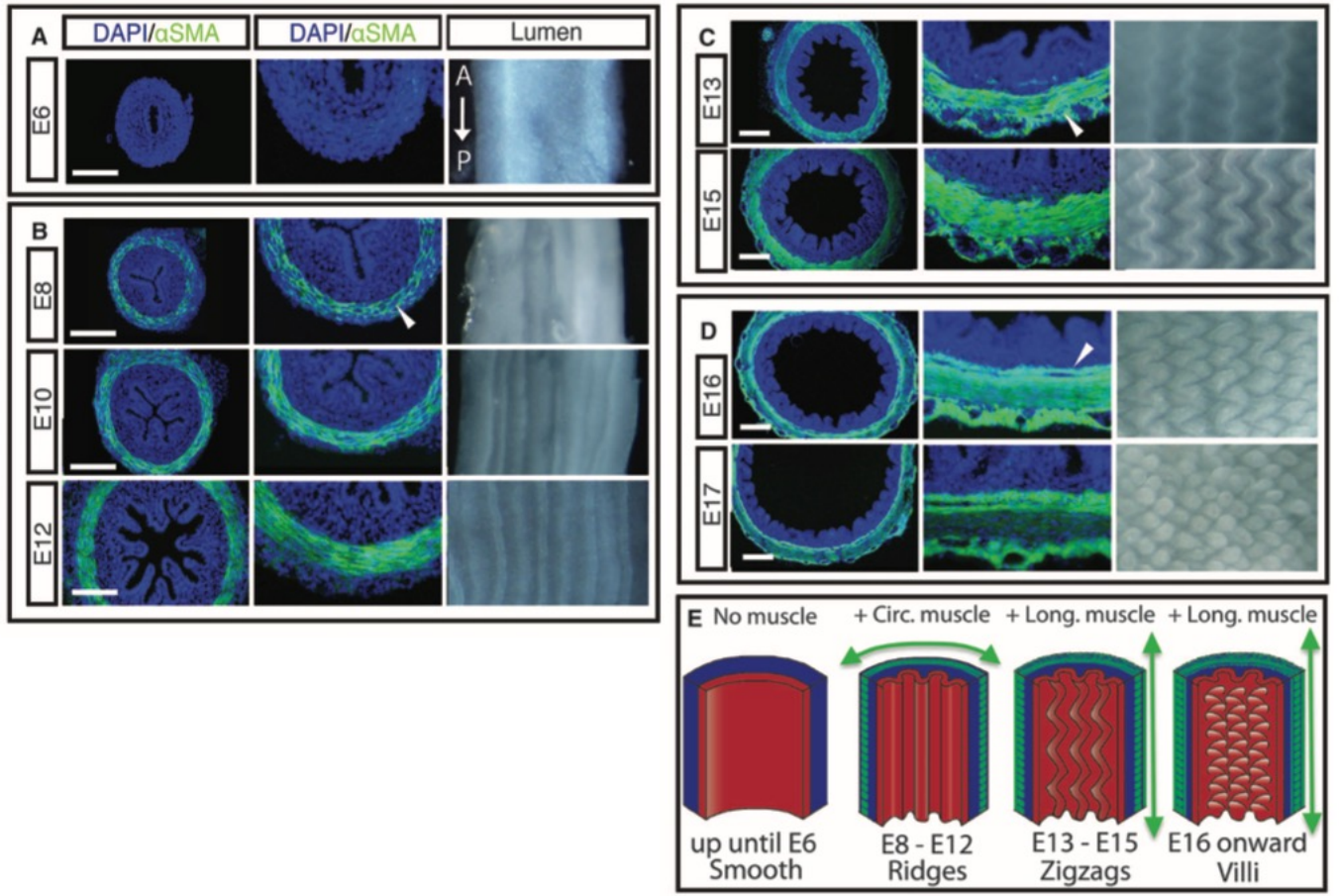
Amy E. Shyer,[1]* Tuomas Tallinen,[2,3]* Nandan L. Nerurkar,[1] Zhiyan Wei,[2] Eun Seok Gil,[4] David L. Kaplan,[4] Clifford J. Tabin,[1]† L. Mahadevan[2,5,6,7,8]†

The villi of the human and chick gut are formed in similar stepwise progressions, wherein the mesenchyme and attached epithelium first fold into longitudinal ridges, then a zigzag pattern, and lastly individual villi. We find that these steps of villification depend on the sequential differentiation of the distinct smooth muscle layers of the gut, which restrict the expansion of the growing endoderm and mesenchyme, generating compressive stresses that lead to their buckling and folding. A quantitative computational model, incorporating measured properties of the developing gut, recapitulates the morphological patterns seen during villification in a variety of species. These results provide a mechanistic understanding of the formation of these elaborations of the lining of the gut, essential for providing sufficient surface area for nutrient absorption.

In amniotes, the primitive midgut is established as a cylinder with an outer mesenchymal layer and an inner, luminal endoderm. As development proceeds, distinct radial layers of smooth muscle differentiate. In parallel, the luminal surface of the gut transforms from a smooth surface to a convoluted morphology. In humans, as well as in mice and birds, this leads to an organized array of fingerlike projections termed intestinal villi (*1*, *2*) although a variety of morphologies such as ridges, zigzags, and honeycombs occur in other species (*3*–*5*). Early work suggested a mechanical basis for villus formation (*6*); however, systematic biological or physical studies of this hypothesis are lacking.

Morphogenesis and Differentiation of the Chick Midgut

Until embryonic day 7 (E7), the gut tube, with its inner endodermally derived epithelium and outer



Tissue level pattern formation through mechanical instabilities

PNAS RESEARCH ARTICLE | DEVELOPMENTAL BIOLOGY
BIOPHYSICS AND COMPUTATIONAL BIOLOGY

The developmental mechanics of divergent buckling patterns in the chick gut

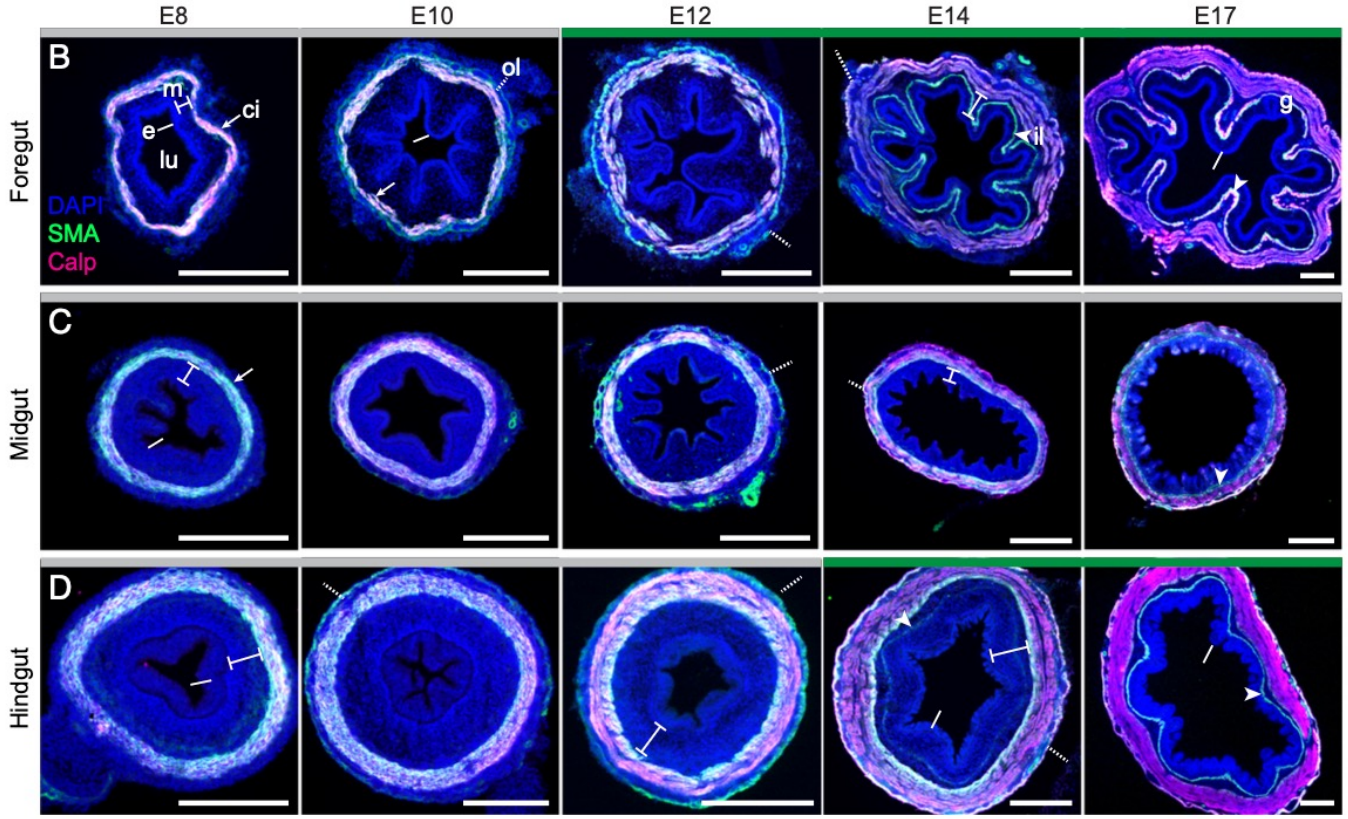
Hasreet K. Gill[a,1], Sifan Yin[b,1], John C. Lawlor[a], Tyler R. Huycke[a,c], Nandan L. Nerurkar[d], Clifford J. Tabin[a,2], and L. Mahadevan[b,e,f,2]

Affiliations are included on p. 11.

Edited by Marianne Bronner, California Institute of Technology, Pasadena, CA; received June 30, 2023; accepted May 6, 2024

Tissue buckling is an increasingly appreciated mode of morphogenesis in the embryo, but it is often unclear how geometric and material parameters are molecularly determined in native developmental contexts to generate diverse functional patterns. Here, we study the link between differential mechanical properties and the morphogenesis of distinct anteroposterior compartments in the intestinal tract—the esophagus, small intestine, and large intestine. These regions originate from a simple, common tube but adopt unique forms. Using measured data from the developing chick gut coupled with a minimal theory and simulations of differential growth, we investigate divergent lumen morphologies along the entire early gut and demonstrate that spatiotemporal geometries, moduli, and growth rates control the segment-specific patterns of mucosal buckling. Primary buckling into wrinkles, folds, and creases along the gut, as well as secondary buckling phenomena, including period-doubling in the foregut and multiscale creasing-wrinkling in the hindgut, are captured and well explained by mechanical models. This study advances our existing knowledge of how identity leads to form in these regions, laying the foundation for future work uncovering the relationship between molecules and mechanics in gut morphological regionalization.

gut | morphogenesis | modeling | mechanics



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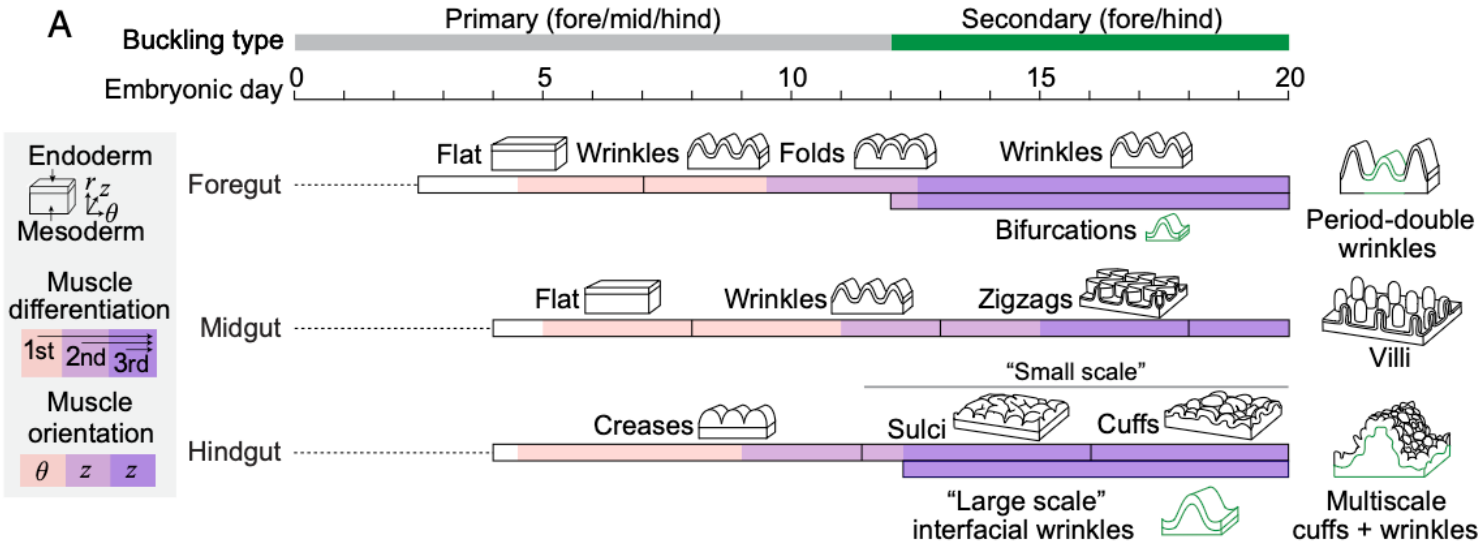
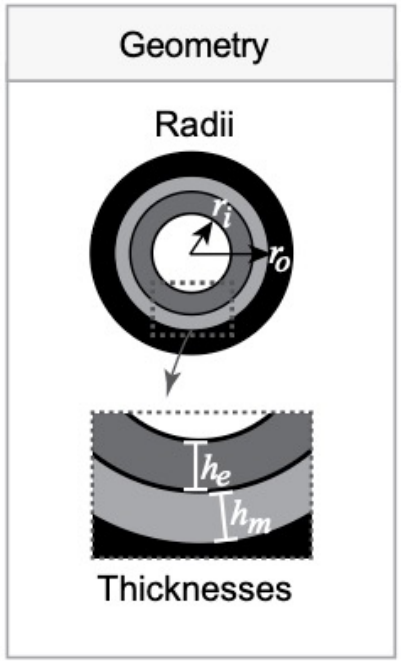


A growth-driven buckling instability (1)



Hypothesis of the model

- **The Multilayered Cylinder:** The gut is modeled as a concentric elastic bilayer.
- **Inner Layer (h_e):** The mucosa (epithelium and mesenchyme), which undergoes volumetric growth.
- **Outer Layer (h_m):** The smooth muscle layers, which act as a restrictive elastic foundation.
- **The Driving Force:** Differential growth. The inner layer expands at a rate faster than the outer constraint, accumulating compressive stress σ that eventually triggers a buckling instability.

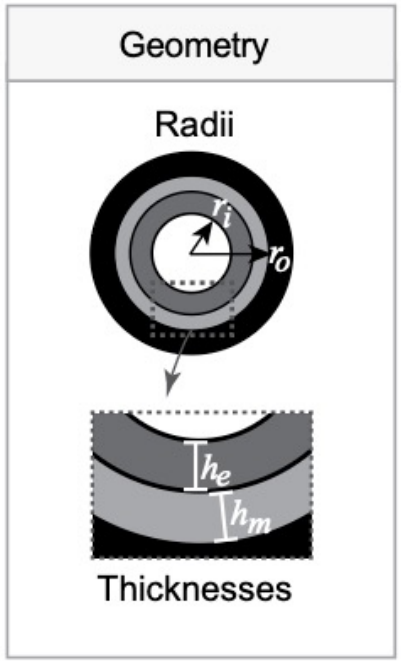
Energy of the system

$$U = \int \left[\frac{B}{2} \left(\frac{d^2 w}{dx^2} \right)^2 + \frac{K}{2} w^2 \right] dx$$

Where:

- B **(Bending Stiffness):** $B = \frac{E_e h_e^3}{12(1-\nu_e^2)}$
- K **(Foundation Stiffness):** $K \approx \frac{\bar{E}_m}{\lambda}$ (representing the elastic resistance of the muscle layer h_m).
- $w(x)$**:** The radial displacement of the mucosa.

A growth-driven buckling instability (2)



Critical wavelength

By assuming a sinusoidal perturbation $w(x) = A\cos(kx)$ where $k = 2\pi/\lambda$, we minimize the energy functional with respect to the wavenumber k. Solving $\frac{\partial U}{\partial k} = 0$ yields the characteristic wavelength that minimizes the cost of deformation:

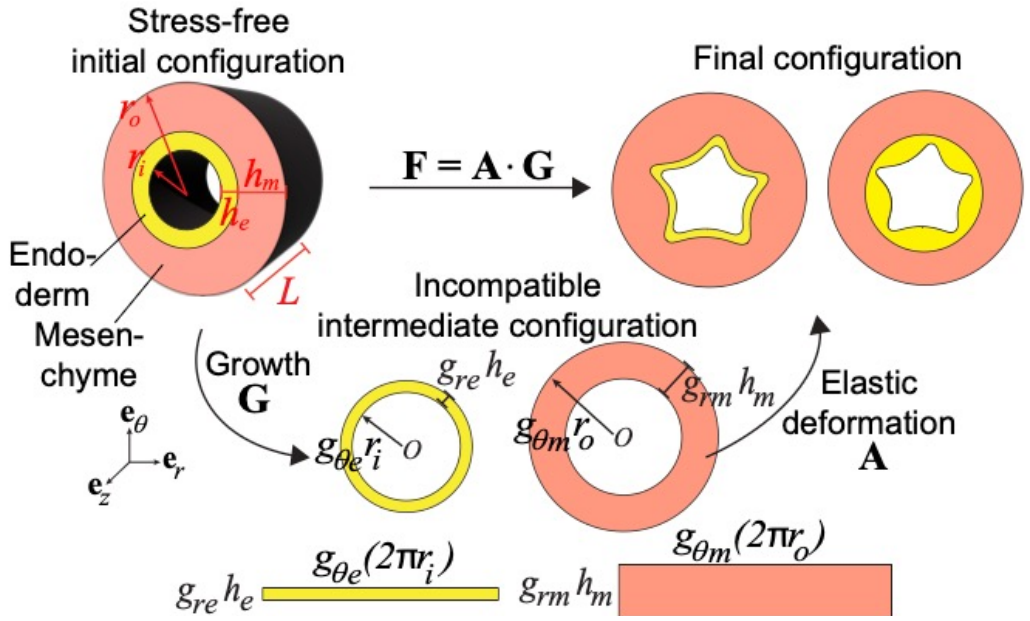
$$\lambda \approx 2\pi h_e \left(\frac{\bar{E}_e}{3\bar{E}_m}\right)^{1/3}$$

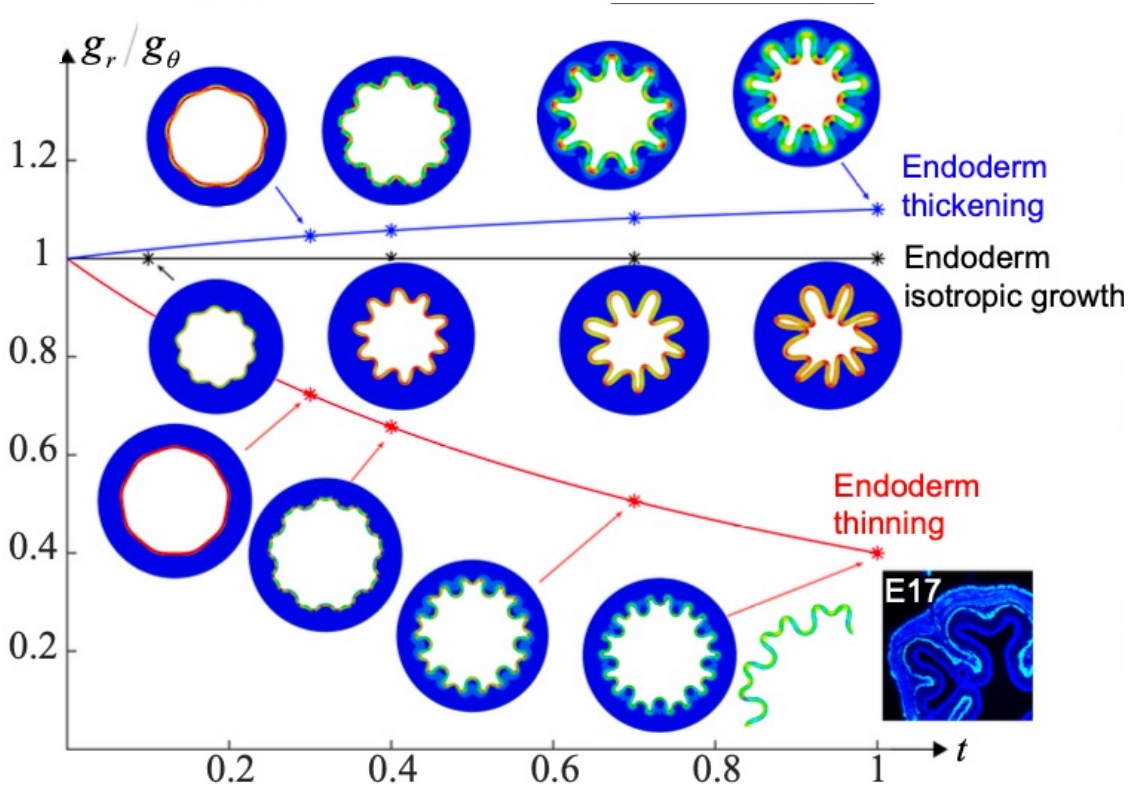
Number of folds

In the cylindrical geometry of the gut, the pattern must satisfy the periodic boundary condition around the circumference ($2\pi R$). The number of folds N is thus:

$$N = \frac{2\pi R}{\lambda} \approx \frac{R}{h_e}\left(\frac{3\bar{E}_m}{\bar{E}_e}\right)^{1/3}$$

A finite element model of differential growth

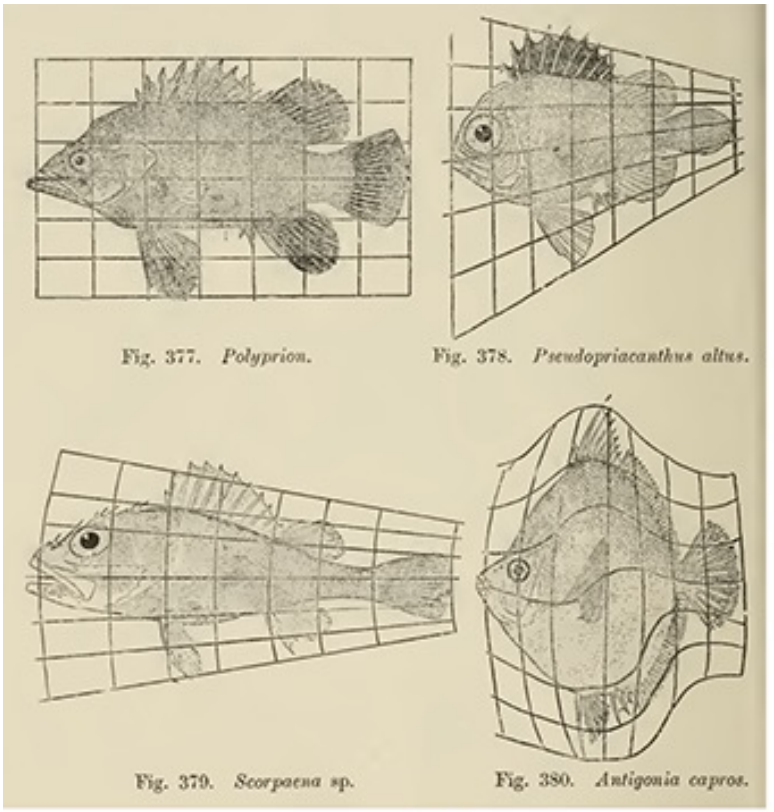
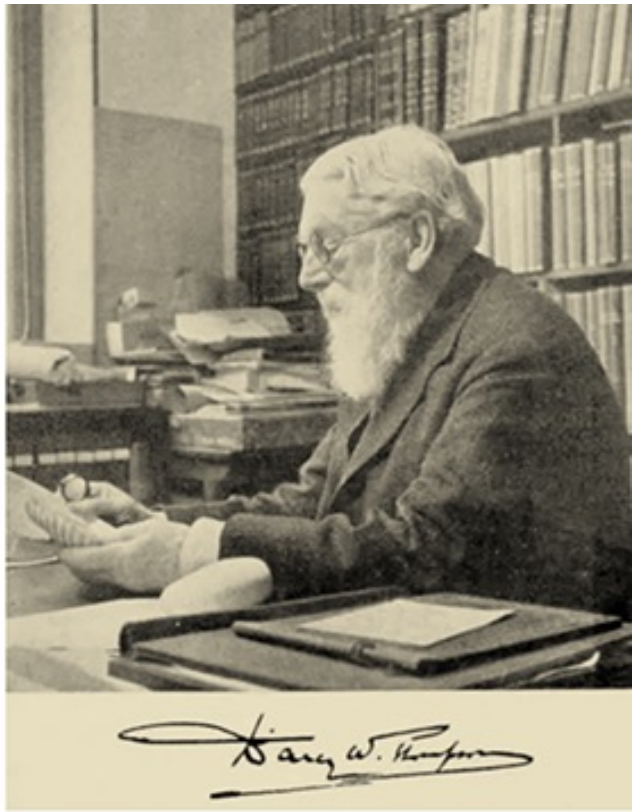




Aims of the project

- **Biological and biophysical context.**
- **Establishment of a mechanical model for a bi- and multi-layer elastic system.**
- **Analytical solutions and scaling behaviour.**
- **Finite element modelling and simulations.**
- **Application to a pathological system – the inflamed colon in ulcerative colitis.**

The “form of living matter” as a “diagram of force”

The form, then, of any portion of matter, whether it be living or dead, and the changes of form that are apparent in its growth, may in all cases alike be described as due to the action of force. In short, the form of an object is a “diagram of forces”.

D'Arcy Wentworth Thompson,
On Growth and Form, 1917.