# Modeling mammary gland from biological first principles.

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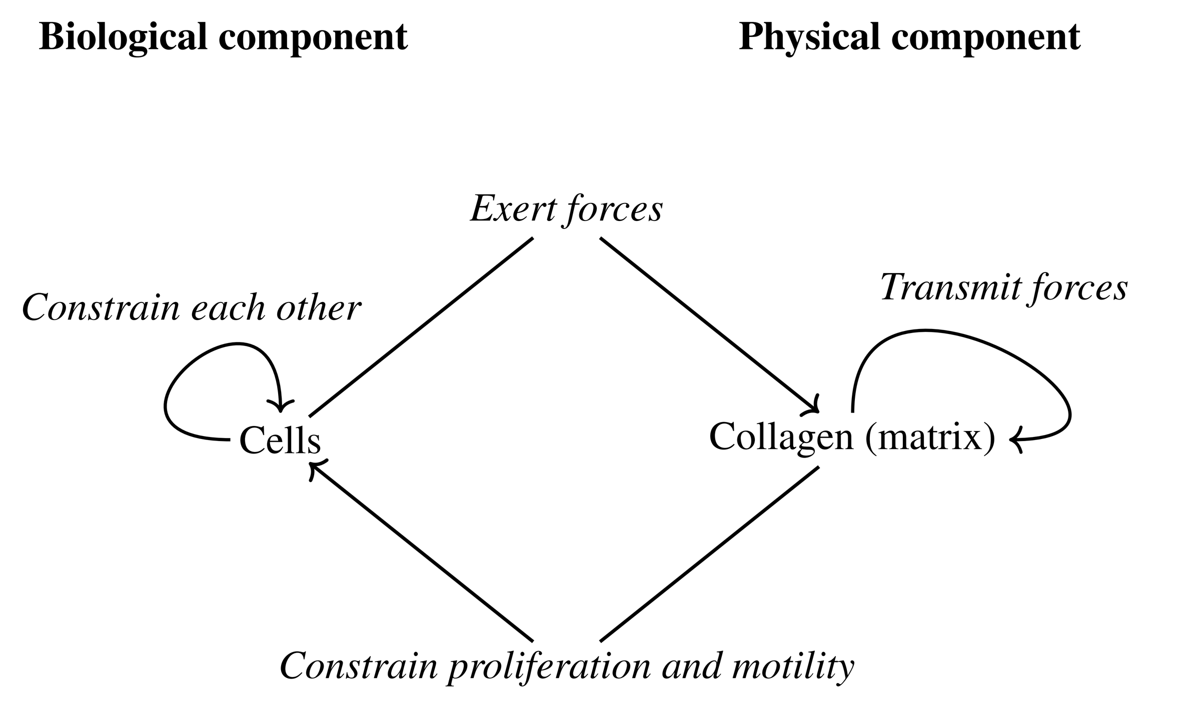
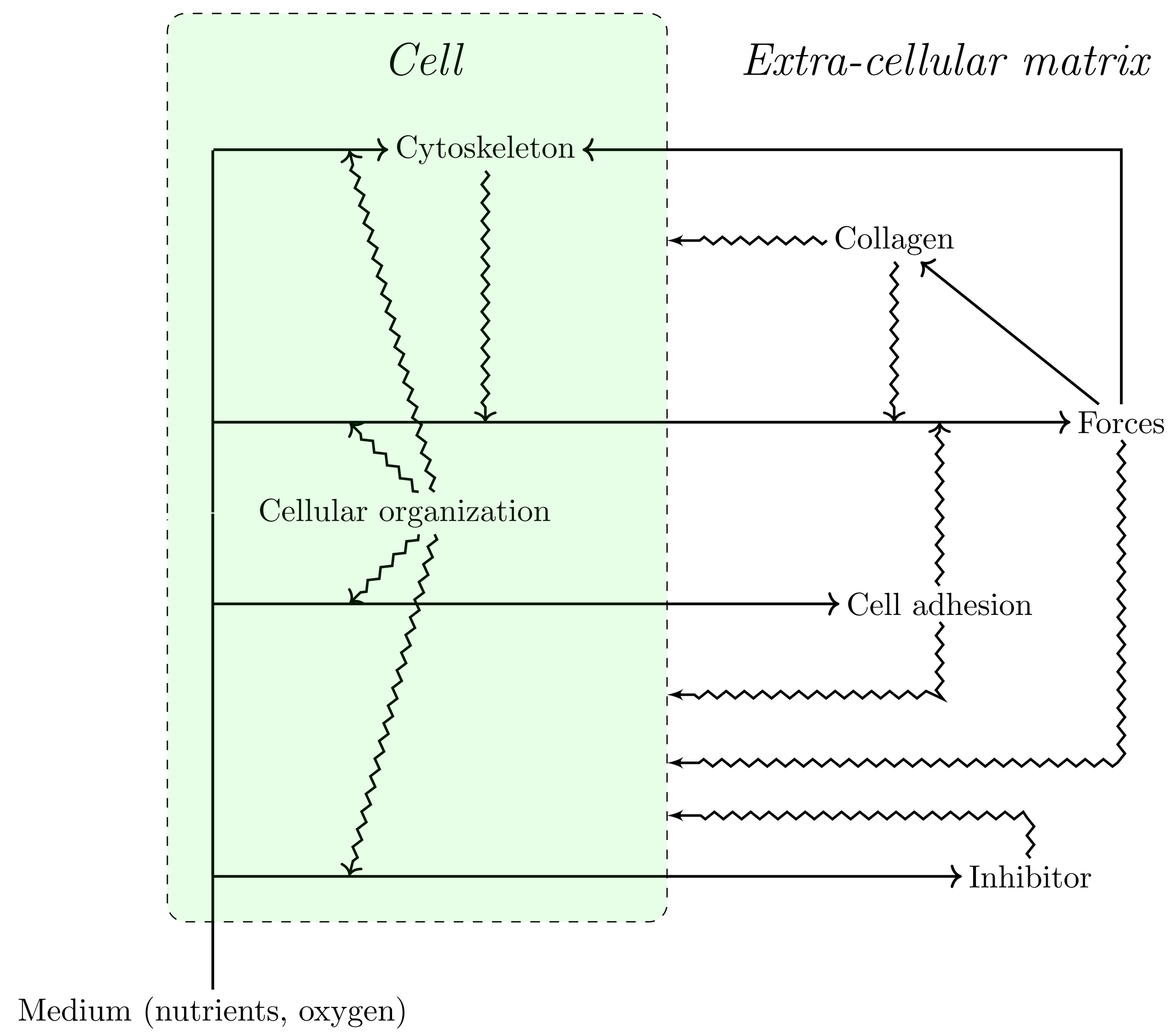
## Abstract

We study a 3D culture method that reproduces mammary gland ductal morphogenesis *in vitro*. We propose a conceptual framework to understand morphogenetic events based on epistemologically sound biological principles instead of the common practice of using only physical principles.
We emphasize the role played by the agency of cells embedded in a gel and the circularity that is relevant for the intended process, whereby cells act upon other cells and on matrix elements, and are subject to the agency of neighboring cells.

## Basic analysis



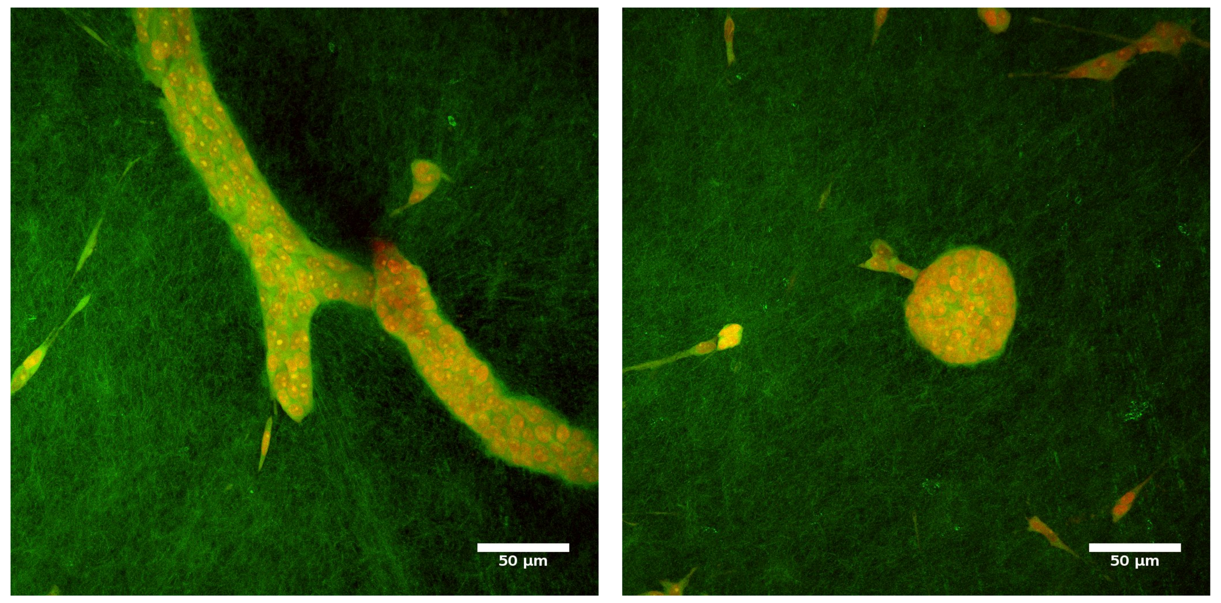

## Model




- *Constraints on proliferation.* Cells tend to proliferate along the direction of forces. Strong mechanical stress slows down proliferation. The inhibitory layer prevents proliferation. Proliferation is impossible if there is no space for a new cell.
- *Constraints on cell movement.* A strong mechanical stress slows down movement. Movement is facilitated when it occurs along collagen fibers. Movement is facilitated towards other cells, and cell adhesion prevents movement. The inhibitory layer prevents movement.
- *Motility.* Besides movement, cell motility leads cells to exert spontaneously forces on the ECM when possible.

## Experimental model

Collagen-I is the main protein of the stromal extracellular matrix of mammary gland. A 3D biological model of mammary gland morphogenesis consists of a collagen gel containing epithelial cells.




- Seeding cells of the breast epithelial cell line MCF10A in collagen gels leads to the formation of elongated epithelial structures which are similar to mammary ducts (LEFT).
- Globular matrices (such as matrigel based) lead to the formation of spherical structures, similar to acini (RIGHT).
- Intermediate matrices enable the formation of both structures.

## Theoretical principles

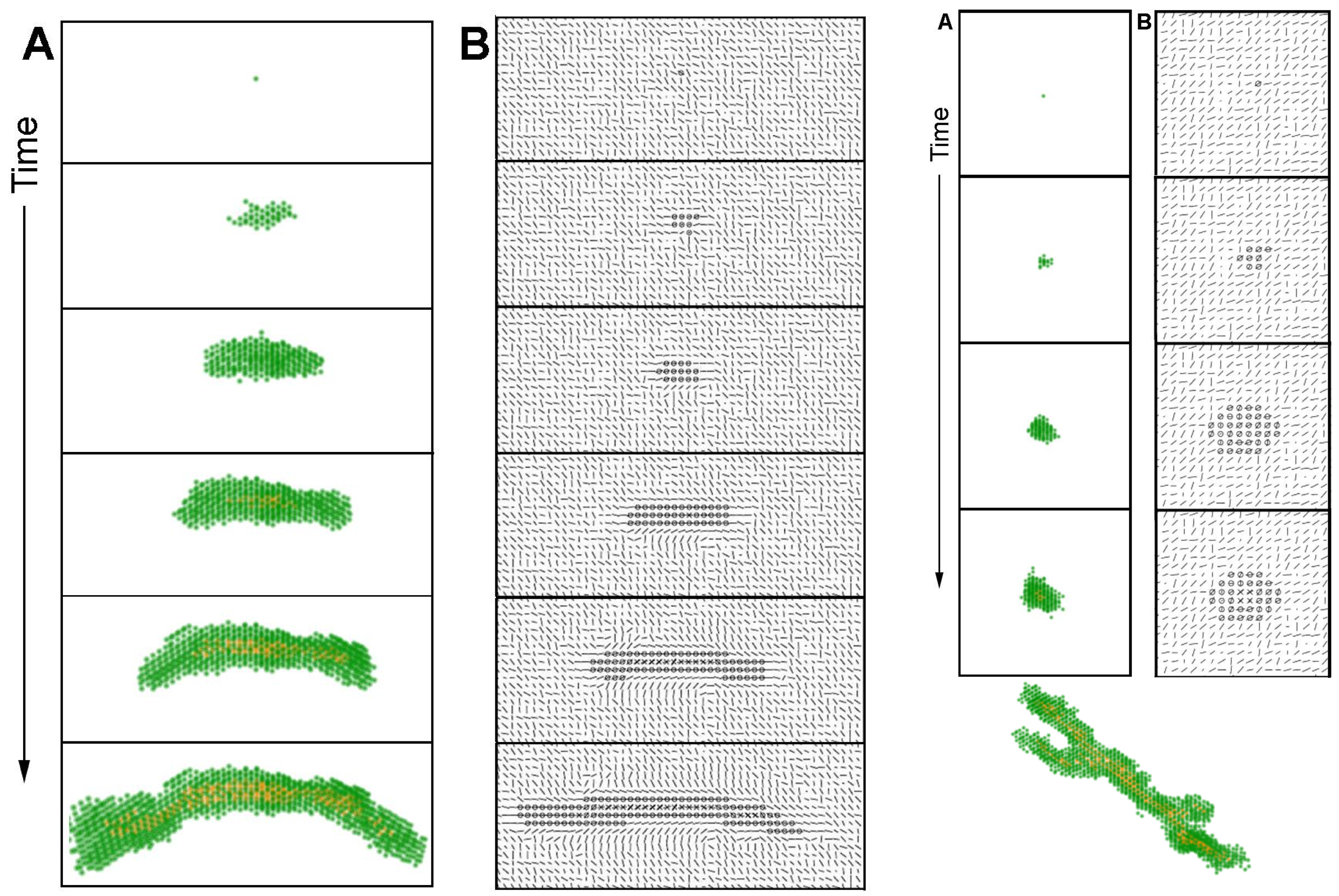
Fundamental principles for organismal biology:

- Principle of variation
- Principle of organization
- **Default state of cells: proliferation with variation and motility**

A default state is what happens when nothing is done to a system, like inertia in mechanics.
It specifies what causes are: they constrain the default state, i.e. prevent proliferation and motility.

| Object studied | Modeling cell proliferation | Modeling motility | Implicit default state | Reference |
|---|---|---|---|---|
| **Collagen network remodeling** | Not discussed | ECM constrains movement. | Motility | (Harjanto and Zaman 2013) |
| **Collagen and fibroblasts** | Not discussed | Cells spontaneously exert forces and move. Stress may prevent motion. | Motility | (Dallon et al. 2014) |
| **Acinus in 2D** | Limited space prevents proliferation. Although not included in the math model, it is stated that proliferation is regulated by signals/growth factors | Not discussed | Proliferation (quiescence is invoked the Discussion) | (Rejniak and Anderson 2008) |
| **Acinus in 3D** | Only cells adjacent to the basement membrane proliferate. Cells have a proliferative potential that decreases at each division. | Not discussed | Shifts from proliferation to quiescence as time elapses. Not discussed for inner cells | (Tang et al. 2011) |
| **Review on biophysical cell self-assembly** | No proliferation | Cells show trend to move modeled by a parameter formally similar to temperature. | If this "temperature parameter" is an intrinsic property of cells, the default state is motility, otherwise quiescence. | (Neagu 200) |
| **Terminal End Buds** | Not causal analysis (measured or assessed indirectly) | | NA | (Paine et al. 2016) |
| **Epithelial tree** | Components resulting from the action of matrix metalloproteinases are inferred to stimulate cell proliferation. | Not discussed | Quiescence | (Grant et al. 2004) |

## Results




LEFT: morphogenesis of a duct in the model. Cells reorganize the collagen and the collagen and others cells constrain cell proliferation and movement.
RIGHT: morphogenesis of an acinus, in a situation where the matrix is not fibrillar. Cells are unable to exert forces on the extracellular matrix, which prevents the formation of a dominant axis of tension. This leads to the formation of a spherical structure.

## References

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## Future Research

We aim to further develop the model and study its predictions. We will also extend it to analyze other biological situations. We are also interested in studying the destabilization of the morphogenetic process, with applications to cancer biology.

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