Numerical modelling of multicellular dynamics

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Resumen

En este trabajo se desarrollar un modelo computacional que permite simular y predecir las deformaciones sucesivas que tienen lugar durante fases de la embriogénesis que han sido biológicamente bien detalladas. Las simulaciones resultantes tienen como objetivo reproducir la sincronización en la dinámica celular, las fuerzas que la dirigen, y la regulación genética y química del desarrollo embrionario.

Los modelos numéricos tradicionales, basados mayoritariamente en elementos finitos, muestran dificultades en capturar tanto los cambios de geometría como las propiedades no lineales del material. El modelo propuesto hereda la partición física en células biológicas, y está consecuentemente basado en un medio discontinuo, en vez de un medio continuo. El modelo resuelve el equilibrio mecánico de las fuerzas intra- e inter-celulares, y para ello, combina estrategias de modelos centrados y de vértices, que a su vez son ampliados con ecuaciones de difusión/reacción que simulan y controlan la respuesta mecánica de la célula.

Palabras Clave: Modelización, mecánica celular, tejidos, embriogénesis, mecanobiología

Abstract

This work aims to develop a computational model that can simulate and predict those successive deformations that biologically well understood cell shape changes take place in embryogenesis. The resulting simulations aim to reproduce the synchronised cell dynamics, the mechanical forces that drive them, and also the chemical and genetic regulation of embryo development.

Traditional numerical models, which are mainly based on finite element techniques, are unable to capture the geometrical changes and the non-linear material properties. The proposed model inherits the physical partition in biological cells, and is thus based in a discontinuum rather than a continuum medium. The model aims to solve the mechanical equilibrium of intra- and inter-cellular forces, and in order to do so, it combines cell-centred and vertex strategies, which are in turn enhanced with diffusion-reaction equations that simulate and control the cell mechanical response.

Keywords: Modelling, cell mechanics, tissues, embryogenesis, mechanobiology

1. Introducton

Soft biological tissues such as embryonic tissue undergo dramatic structural, chemical and genetic transformations. From the mechanical standpoint, these changes may be classified as [6] growth (change of mass), remodelling (change of property or direction of structural elements), or morphogenesis (change of shape). These processes are not necessarily exclusive, and depending on their developing stage, organisms undergo one or more prominent processes.

Experimentally, the detailed micro-scale dynamic description of cell monolayers and general multicellular systems are mainly based on staining techniques that mark some of the components of cells such as the cytoskeleton elements, cell membranes, cell nuclei, or relevant proteins and genes. On the other hand, the forces that drive the observed cell kinematics may be computed by using mechanical tools for measuring forces at the molecular level (magnetic or optical tweezers, atomic force microscopy), at the cellular level (embedded magnetic beads in polyacrylamid (PA) gels, nano-pillars, or micropipette aspiration) or at the tissue level (embedded magnetic beads in

PA gels or nano-pillars). Although these techniques cannot be used as a predictive tool for simulating cell dynamics, they have demonstrated that mechanical forces, together with other chemical, genetic or electrical signalling, are permanently used for controlling multicellular dynamics [3].

This work aims to combine, modify and extend these techniques to model robust and reliable modelling of multicellular dynamics, not necessary of monolayer cells, able to also simulate epithelium to mesenchymal (loosely connected tissue) transitions. This changes in the cell-to-cell connectivity motivate the use of discontinuum modelling approaches. Previous models of embryogenesis developed by the principal investigator have resorted to continuum media and the decomposition of the deformation gradient into active and elastic part, and discretised with two- and three-dimensional finite elements [1, 2, 4], as shown in Figure 1. Despite the success of these models to reproduce some morphogenetic movements, they are limited to short periods of embryo development, and are unable to deal with cell topology changes, and track the cell boundaries. For these reasons, the proposed project will resort to a discontinuum approach that mixes cell centred and vertex models.
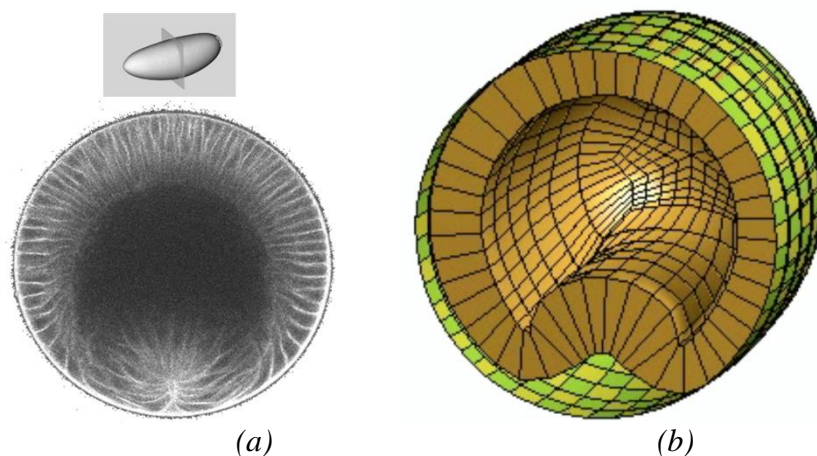

(a) *(b)*

Figure 1. a) Cross-section of Drosophila Melanogaster embryo showing ventral invagination.b)Finite element model using a purely hyperelastic material in Drosophila Melanogaster invaingation [2]

2. Methodology

2.1. Intra-cell interactions

The model solves the mechanical equilibrium of cell-to-cell interactions for an arbitrary constitutive law. Elastic interaction is described by defining a non-linear elastic potential that depends on the distance between the cell nuclei.

The model will also allow the update of the resting length between cells. This is equivalent to the decompostion of the total deformation in an elastic and an active component, in a similar manner as it has been employed in plasticity or growth in biomechanics [4,5].

Cell-to-cell interactions are only allowed between close cells. The closeness of cells is determined by using a Delaunay triangularisation (or "tetrahedrisation" in 3D). In this manner, we aim to simulate the cell reorganisation in the cell connectivity within a tissue. In order to ease the convergence, these topology changes are performed incrementally.

We also measure the cost of the cell connectivity. In the context of continuum mechanics, these discontinuous deformations do not induce elastic deformation in the bulk, but the reorganisation is not cost-free since new adherent junctions (cell-cell connections) are created while other are depolymerised.

Since the mechanical forces a transmitted through truss-like tractions, the stress state of the cells is performed by mapping these tractions on an equivalent continuous stres field which minimises the relation between stresses and tractions along the direction joining the nuclei, as expressed in the following equation:

$$\boldsymbol{\sigma} = \operatorname{argmin}_{\boldsymbol{\sigma}} \sum_i ||\boldsymbol{\sigma}\boldsymbol{n}_i - \boldsymbol{t}_i|| \tag{2}$$

where $\boldsymbol{n}_i$ is the unit vector joining two close cells, while $\boldsymbol{t}_i$ is the traction force along this direction.
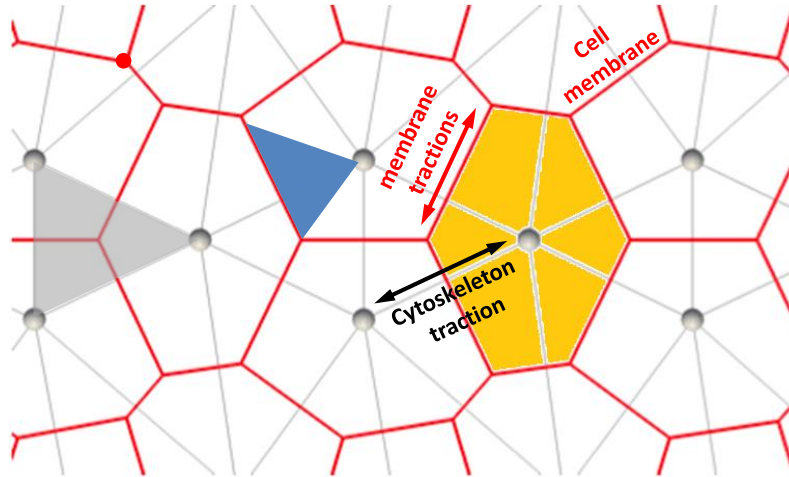

Figure 2. Schematic of the hybrid Vertex-centred model: Delaunay triangularisation (gray), Voronoi diagram (red), a finite element (blue) formed by nodes (cell nucleous and Voronoi vertices) onto which diffusion-reaction forces are solved, and mechanica forces involved.

2.2. Inter-cellular interactions

In order to mimic the adhesion forces at the cell membrane such as surface tension or bending stiffness, mechanical equilibrium equations at the Voronoi regions will be also computed. The vertex of the Voronoi regions will be interpolated using a finite element discretisation of the associated Delaunay regions (see Figure 2). By applying mechanical equilibrium at the Voronoi regions, we intend introduce cell polarity, and consequently simulate actin concentration, apical constriction, or activation of cadherins and integrins at the adherence junctions (cell-cell) and focal adhesions (cell-extra cellular matrix), respectively.

We aim to replicate the visco-elastic response of a cell by changing its reference configuration. Such approach is similar to the gradient decomposition in plasticity or growth. In the mechanical system considered here, where the constitutive law reduces to one dimension, the change in the reference configuration is equivalent to changing the reference length, as indicated in the following equation:

$$\dot{\varepsilon}^{active} = \gamma \varepsilon^{elastic} \tag{1}$$

In this equation, the active strains map the reference configuration onto a new resting position that is mediated through the genetic information, while the elastic strains accommodate the cell due to material continuity and equilibrium conditions.

2.3. Cell rheology

We add a rheological law that mimics the measured cell and tissue stiffness and viscosity. These quantities are in fact the result of mainly the following different contributions: (i) the remodelling of the cross-links, (ii) the (de)polymerisation process of the cytoskeleton and (iii) the reorganisation of the cell-to-cell connectivity at the adherent junctions. We aim to reproduce the measured

viscoelasticity [7] by implementing evolution laws for these processes, in a similar manner as described in [6].

3. Results

We have applied the model to the stretching of an active viscoelastic tissue. The measured averaged elastic strains and the reactions at one of the ends are plotted in Figure 3. The pltos show the effect of the cell-cell topology changes in the tissue.
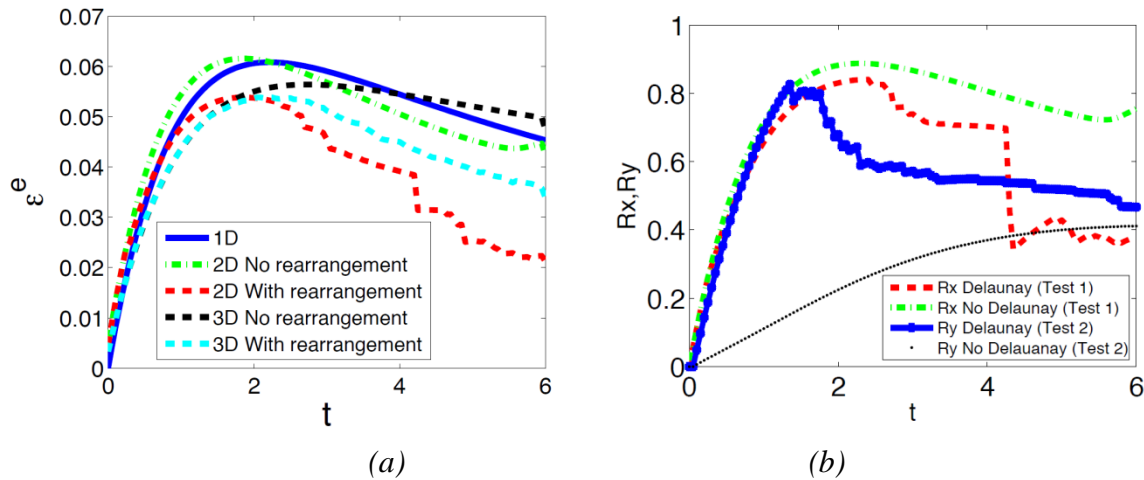

(a)   *(b)*

Figure 3. *Response of the elastic strain (a) and reaction (b) of a stretched tissue in 2 orthogonal directions.*

4. Conclusions

The results show that the developed numerical model allow scientists to simulate and predict significant morphogenetic movements in experiments "in vitro" and in embryo development. Indirectly, this numerical platform improves our understanding of the interactions between the regulatory capacities of the proteome and the mechanical response on embryo development. In this manner, we aim to contribute to enhance current knowledge of the human interactome, primarily during the early stages of its development.

3. References

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