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Review

Phenomenological approaches to collective behavior in epithelial cell migration☆

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ABSTRACT

Collective cell migration in epithelial tissues resembles fluid-like behavior in time-lapse recordings. In the last years, hydrodynamic velocity fields in living matter have been studied intensely. The emergent properties were remarkably similar to phenomena known from active soft matter systems. Here, we review migration experiments of large cellular ensembles as well as of mesoscopic cohorts in micro-structured environments. Concepts such as diffusion, velocity correlations, swirl strength and polarization are metrics to quantify the cellular dynamics both in experiments as well as in computational simulations. We discuss challenges relating collective migration to single cell and oligocellular behavior as well as linking the phenotypic parameters to the underlying cytoskeleton dynamics and signaling networks. This article is part of a Special Issue entitled: Mechanobiology.

1. Introduction

During many physiologically relevant processes such as morphogenesis, wound healing and cancer invasion, cells migrate collectively in tightly connected groups. Epithelial cells are a prominent example of cells preferring not to migrate on their own. Instead, they are linked to their neighbors via various junctions, forming sheets, ducts, clusters or strands depending on the particular biological context they reside in [1–4]. Despite this, they still maintain the capability of remodeling their relative positions with time.

In this respect, the malleable epithelial cell sheets resemble two-dimensional complex fluids, which consist of interacting units that are not permanently linked and hence can be mutually displaced. The time scale for flow behavior in epithelial cell sheets is measured in hours or days. However, cellular matter differs from ordinary fluids in two important aspects. Each subunit consumes energy to propel itself and crucially, cells proliferate. In condensed matter theory such out-of-equilibrium systems are referred to as active matter and are known to exhibit unusual hydrodynamic properties and dynamic collective states such as swarming or turbulent swirling [5–10].

Collectively migrating cells indeed display intriguing features of soft active matter systems. In recent years, many efforts have been made to describe cellular motion in mathematical terms and to define rules that determine the apparent cellular flow behavior. This top-down approach is distinct from a cell-biological view on migration that accounts for molecular determinants of migration such as the cytoskeleton dynamics including actin polymerization and force generation via molecular motors, the molecular interaction with the substrate and extracellular matrix via the focal adhesion complex as well as extracellular stimuli via chemical signaling [11–15]. In a mechanistic biophysical view, the entire cell is modeled as an elastic body. Its shape is determined by cell substrate adhesion and the elasticity of the cellular cortex. In migrating epithelial monolayers, the cytoskeleton generates protrusions and exerts traction forces onto the substrate as well as onto adjacent cells via cadherins. Vast progress has been made on the mechanobiology of cells, cellular adhesion and migration in recent years [16–18]. Despite this, the relation of mechanical cell models to the observed motion in tissue at large scales is still challenging and subject of intense research. Collective migration can, to some extent, be analyzed and captured by mathematical equations parameterizing the underlying molecular and mechanical interactions in a coarse grained manner. The phenomenological description is obtained using image-based algorithms and the experimental sets of migration parameters can then be compared to parameter estimations in computational models.

In this review, we focus on the phenomenological analysis of cellular flow behavior, in particular in confining geometries of micro-structured surfaces. We address theoretical concepts capable of reproducing some of the generic properties of cellular matter and discuss the use of standardized micro-environments in cell migration experiments.

Much of this review will concentrate on experiments performed with layers of MDCK cells, as they represent a well-studied model

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system for epithelial sheets. Collective phenomena are also observed in other epithelial systems, such as the *Drosophila* wing disc, however, going into depth about complex biological phenomena like morphogenesis or tumor formation related to migration would go beyond the scope of this work.

2. A mechanical view on cell packing and growth

The outlines of epithelial cells in a sheet adhering to a surface show a striking resemblance to an accumulation of polygons (see Fig. 1). They appear to typically have either five or six corners and form a connected layer without gaps. In a first approximation, the contact lines between cells can be considered straight. In an early study, the average area of a cell in tissue was found to scale approximately linearly with the number of sides (and thus neighbors) it has [19], a relation known as Lewis's law. The pattern formed in experimentally observed cultured cell sheets or epithelial cells in the surface of tissues is captured well by a so called Voronoi construction that, starting from a set of cell center positions, divides the area into polygons corresponding to the regions closest to the cell centers [20] as illustrated in Fig. 1. Nowadays, this cell center is usually approximated from the position of the nucleus.

Voronoi constructions can also serve as a starting point for a theoretical approach to describing the packing geometry in epithelial monolayers. In the so-called vertex model the theory of foams, which assumes that the forces at each vertex have to vanish in the case of stable network configurations, is adapted. The theory introduces an energy function that needs to be minimized locally [21,22]. The energy function consists of three components describing the cells' elastic properties:

$$E(R_i) = \sum_{\alpha} \frac{K_{\alpha}}{2}\left(A_{\alpha} - A_{\alpha}^{0}\right)^2 + \sum_{\langle i,j \rangle} \Lambda_{i,j} l_{i,j} + \sum_{\alpha} \frac{\Gamma_{\alpha}}{2} L_{\alpha}^2. \quad (1)$$

The contributions are an area elasticity (K_α is the elastic constant, with A_α the area and A_α^0 the preferred area of cell α, respectively), the line tension at junctions between individual cells (Λ_{ij} is the line tension per unit length with l_{ij} the length of the junction between nodes i and j) and a term describing cell cortex contractility (L_α is the cell perimeter and Γ_α is a contractility-describing parameter).

The vertex model satisfactorily reproduces polygon class distribution, cell area variation and packing geometry found in the *Drosophila* wing disc, as well as its response to laser ablation [21]. In addition, it is capable of explaining how cell compartment boundaries can be maintained despite remodeling through cell division through increased tension along the boundaries [23].

While this mechanical cell model accounts for observed packing states, it still remains quasi-static, describing only the equilibrium states a system relaxes to after dynamic remodeling events such as cell divisions or disruption of cell-cell contacts. In order to study the perpetual remodeling of tissue as a function of time, Ranft et al. proposed a continuum description of tissue dynamics, showing that by inclusion of proliferation and apoptosis, cell sheets in essence behave like viscoelastic fluids [24]. One key point of this model is the existence of a homeostatic tissue pressure at which cell division and cell death are balanced. This state is reached autonomously if the growing tissue is confined to a fixed volume. If a pressure slightly larger or smaller than the homeostatic pressure is applied, the tissue will completely invade the surrounding area or vanish, respectively [24]. Experimentally, these fluid-like, out-of-equilibrium states are observed in wound healing assays [25–27], for migration on stripes or in channels [28,29], or for expanding patches and colonies of cells [30,31]. When cell density in such a colony is high enough to pose a mechanical constraint that causes following cell divisions to reduce the cell area, this initially leads to a drop in cell motility. Eventually, this “contact inhibition” leads to a static regime where a sharp transition in the rate of mitosis appears and cell rearrangement is completely limited to cell division [31].

In contrast to the compaction during growth in limited space, the average area of cells can also increase over time in the case of freely expanding cell groups. In previous work, we released small cohorts of MDCK cells by removing confining structures [30] created via a stencil-based technique similar to the one introduced by Poujade et al. [32]. Initially, cells are grown to high densities within the confinement.

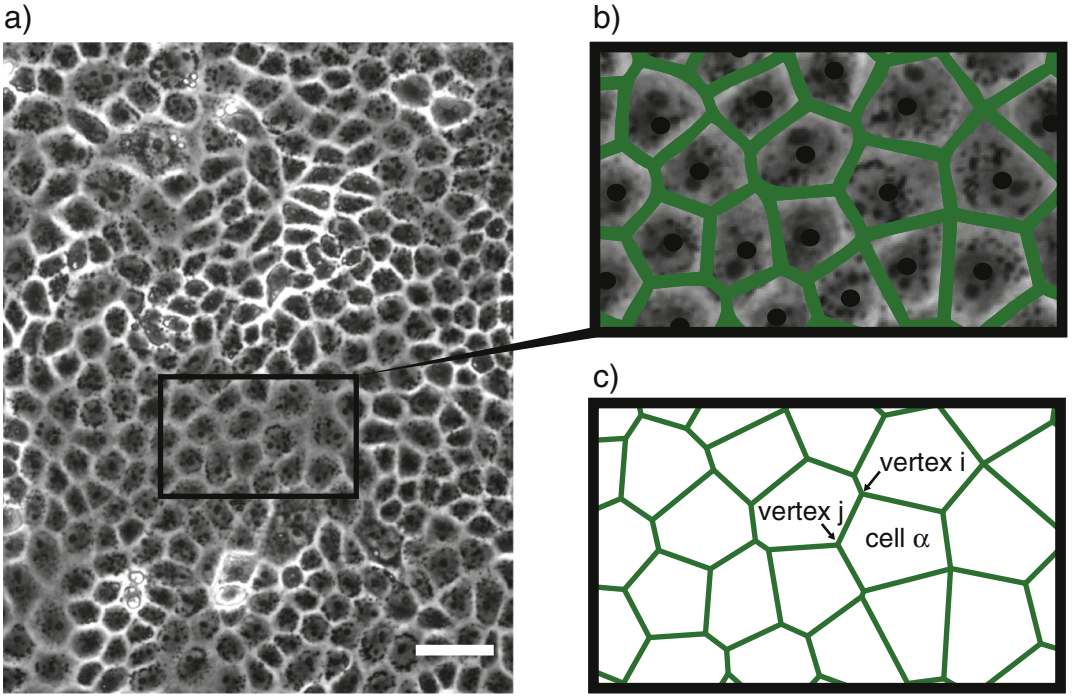

Fig. 1. Polygon-like cell shapes in an epithelial cell layer. a) Cells in an MDCK monolayer have nearly straight borders and close to 5 or 6 neighbors (scale bar corresponds to 50 μm). b) Subsection of the cell sheet with a polygonal meshwork resulting from a Voronoi construction overlain in green. Black dots mark the center points of the cells. c) Abstract vertex model of an epithelial cell layer.

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