**SMART TIPPING**

The first atomic-resolution images of carbon nanotubes taken by a scanning probe microscope caused great excitement. Here at last was a direct view of what electron diffraction had previously disclosed: the hexagonal carbon framework. Or was it? Some experiments seemed to reveal the chicken-wire mesh of graphitic carbon\(^1,2\), but other experiments showed not a hexagonal honeycomb but a trigonal array of bright spots\(^3\). It might depend on the type of microscope used — the scanning tunnelling microscope (STM), say, which images electronic structure, or the atomic force microscope (AFM) and its variants, in which contrast depends on tip–sample forces. Or it might depend on the nature of the tip, or the separation between tip and sample.

This was no surprise. Ever since the earliest days of the STM and AFM in the 1980s, the issue of what was being imaged was hotly debated. The temptation to regard these regular arrays of bright blobs as atoms on a crystal surface was, for the most part, assiduously resisted in the knowledge that, especially for the STM, the imaging mechanism did not by any means guarantee a simple topographic map.

Indeed, graphite itself supplied a cautionary tale. It was used as a substrate for some of the earliest STM images, which showed the trigonal rather than honeycomb pattern\(^4\).

The standard interpretation invoked differences between two types of carbon atom in the surface layer: some \((\text{C}_\alpha)\) have a near neighbour in the second layer directly below, whereas others \((\text{C}_\beta)\) sit directly above the central void of a six-membered ring. Only the latter were predicted to register as bright spots at low bias voltages between tip and sample. Yet experimentally the trigonal pattern predominates for high bias too, though the honeycomb was occasionally seen even for low biases.

To add to the puzzle, AFM images might be expected to show a honeycomb because they supposedly report more directly on the arrangement of atoms — but the trigonal pattern is often seen here too\(^5\). So what is governing these images of graphitic carbon?

That’s what Ondráček et al. have set out to clarify\(^6\). Using first-principles calculations to predict both tip–surface forces and electronic tunnelling currents between graphite or single-walled carbon nanotubes and a variety of scanning probe tips, they rationalize the diverse results found in experiments.

The outcome depends on the tip–sample distance, the bias (for STM) and the chemical nature of the tip. For example, a pure silicon \((111)\) tip has an atom at its apex with a dangling bond, making it capable of changing the hybridization of a carbon atom and forming a chemical bond, changing the contrast mechanism for force microscopy. That effect is even more pronounced for a tungsten tip. But at greater separations, Pauli repulsion dominates the interaction, as it does with more inert tips even close up — and then the force maxima occur over the hexagonal ring centres, giving the trigonal pattern.

For the STM, the \(\text{C}_\beta\) sites do give larger currents for typical separations, but the ring centres produce the bright spots in near-contact mode, reversing the contrast. Thus, inert tips are generally the safest option for imaging carbon nanostructures.

**References**


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**CELL MECHANICS**

**Moving under peer pressure**

Collective cell motion in a continuous tissue is found to be guided by cooperative intercellular forces.

*Nir Gov*

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ells in the tissues of our bodies, thankfully, do not move much. The collective motion of cells in a multicellular tissue is of great interest, however, because it occurs during embryo morphogenesis and in unhealthy circumstances such as wound healing and cancer metastasis\(^7\). Although it is known that there are biochemical signals that guide the direction of motion — a process called chemotaxis — it is less clear what role mechanical forces play in organizing collective cellular motion. Writing in *Nature Materials*, Tambe *et al.* report an analysis of the coupling between cellular motion and mechanical forces in a continuous two-dimensional cell culture *in vitro*\(^8\). They generate high-resolution...
maps for the measurement of the local stress field that the moving cells exert on the underlying elastic substrate. By correlating the stress field with the cellular motion, the dominant mechanism for intercellular mechanical communication is concluded to be through direct cell–cell adhesion contacts. Furthermore, it is found that cells tend to move collectively in the direction of the maximal local stress, calling this form of guided motion ‘plithotaxis’, from the Greek plithos meaning a crowd or swarm.

Cells in a continuous tissue maintain the overall structural integrity through cell–cell adhesion contacts and through adhesion to the underlying supporting substrate (Fig. 1a). Adhesion requires the production of internal contractile forces, as the adhesion molecules become sticky only when stressed. The contractile forces are mainly produced by the actin–myosin network of the cytoskeleton, which is a miniature version of our muscles. A mechanochemical positive feedback between the adhesion contacts and the formation of the actin–myosin network enhances both processes. Under normal conditions the result is a cellular layer where the cytoskeleton of each cell is self-organized to maintain strong adhesions with its neighbouring cells. The pulling forces between the cells balance each other on average, in a form of tug-of-war, as police who lock arms during crowd control, thus maintaining a global contractile tension in the tissue that is balanced by the underlying substrate.

The symmetry breaking that selects the direction in which cells move is driven by the polarization of their cytoskeleton, which produces anisotropic and unbalanced traction forces on the underlying substrate. Even in the continuous layer, cells can produce net traction forces by extending polarized ‘feet’ (lamellipodia), below the edges of their neighbours (Fig. 1a), leading to limited motion. When the continuous cellular tissue is broken, transient chemical signals are released that enhance cellular motility near the wound edge. Cells at the wound edge extend large polarized lamellipodia towards the free surface, producing an overall traction force that is directed towards the wound (Fig. 1b). Some edge cells can become highly efficient ‘leaders’ and pull a row of cells behind them, in the form of flowing cellular ‘fingers’. In such fingers, cells move collectively together. But the mechanism that organizes cells to move together in the same direction remains poorly understood.

Tambe et al. have found that collective cellular motion is directed along the maximal principal stress, whenever the local stress field is polarized (Fig. 1b). In other words, regions where the traction forces produced by the cells are highly anisotropic are also areas where the cells tend to move along the direction of maximal stress. This is clear for a single ‘self-polarized’ cell, but not for a dense collection of adhered cells in a tissue. The directional ordering of local stress anisotropy is found to extend over tens of cell lengths (~100 micrometres). Cells are found to minimize the local shear between neighbours, thereby moving in large isotropic clusters. This finding agrees with previous observations of directional ordering of cellular velocity on similar length scales. For wound healing, plithotaxis is therefore an efficient way to transmit the information regarding the location of the wound over long distances, and induce cooperative cellular motion that closes the lesion. Note that cells are not simply pushed by their neighbours, but rather they respond to the external forces as a cue that guides their internal cytoskeletal ‘motor’. Cells have been shown to be highly sensitive to relatively small external forces during motility.

Tambe et al. also find that the long-range ordering in the cellular traction forces and motion is communicated by strong cell–cell adhesions; cancer cells that move independently do not exhibit plithotaxis.

These observations raise a number of questions — for example, what determines the length scale of stress and motion correlations in the cell layer? Also, how does plithotaxis emerge from the dynamics of the cytoskeleton in individual cells? These questions are important to complete our understanding of the mechanical guidance of cells, which can now be addressed experimentally. There is a large gap in our understanding between the complexity of the cytoskeleton and the collective dynamics observed on the scale of many cells. Controlling plithotaxis could potentially allow us to induce faster wound healing or impede metastasis.

The observed behaviour of a dense layer of cells, with its highly anisotropic field of intercellular forces and cell motion, resembles the dynamics observed

**Figure 1** Schematics of the forces inside a cellular layer. a, A schematic side-view of the forces produced in the two-dimensional cell layer. Cell–cell adhesions (blue) are pulled inwards by the actin–myosin cytoskeleton (black arrows). Cell–substrate adhesions (green) allow the cells to exert traction forces on the elastic substrate, which are then measured. Each cell is also shown to extend a small lamellipodia beneath its right-side neighbour, exerting a pushing force (red arrows). The overall polarization of the forces, and of cellular motion, is towards the right (dashed black arrow). b, A schematic top-view of the edge of the cell culture, moving to close the open wound at the top of the image. Local stress is denoted by the red ovals, where the eccentricity signifies more polarized forces. Tambe et al. have found that anisotropic stresses are highly correlated with cell motion (black arrows). Regions of low polarization (red circles) correspond to more random motion. Two cells at the edge are shown to develop large lamellipodia (grey) and may initiate the growth of cellular ‘fingers’.
in amorphous systems such as colloids, glasses and granular materials. The sources of the forces in the cellular case are the cytoskeletons of the cells themselves, as opposed to the external forcing or quenched stresses in the dead systems. The similarities include the observation of non-Gaussian stress fluctuations\(^5\), and increasingly collective and slow modes of structural reorganization as the density increases\(^6\). The detailed understanding of the dynamics in amorphous systems is an open question in materials science. Cellular layers present a new type of active amorphous material, whose study is beginning only now. It is yet another example where biology motivates and opens a new frontier in physics, as both fields enrich each other.

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\section*{ACTIVE GELS}

\textbf{Motors keep dynamics steady}

Steady-state remodelling in model cytoskeletal networks results from the combination of marginal stability and molecular-motor activity.

\textbf{Fred C. MacKintosh}

An intriguing mystery of living cells is their ability to simultaneously have mechanical integrity while demonstrating the seemingly contradictory ability to remodel, for instance, as they move. Cellular rigidity and shape depend largely on the cytoskeleton, which consists of networks of stiff protein filaments spanning the cytoplasm. Cytoskeletal networks self-organize in highly dynamic and heterogeneous patterns as a result of the interplay between active force generation by molecular motors and passive dissipation in the crowded cell environment. However, the dynamics of pattern formation and their underlying mechanisms are not well understood. Writing in Nature Materials, Andreas Bausch and co-workers describe a minimal model system of dynamical cytoskeletal networks that exhibits an active regime that is very reminiscent of the dynamics in living cells\(^1\): a dynamic steady state, with constant formation and restructuring. Their experiments and computer simulations reveal the microscopic mechanisms behind the formation of a broad distribution of cluster sizes, and suggest an interesting, non-equilibrium twist on the familiar processes of nucleation and growth.

Bottom-up model systems of the cytoskeleton usually consist of just a few components reconstituted from living cells\(^2\), and have been shown to display rich dynamical and mechanical behaviour that is often in stark contrast to the passive, equilibrium nature of most man-made materials. Indeed, living cells are kept far from equilibrium largely by energy-consuming molecular motors that generate forces to drive the machinery behind various cellular processes. Molecular motors — which are also the basis of skeletal muscle action at larger scales — have been shown to induce the formation of dynamic patterns in gel networks, such as vortices or asters, in which stiff filaments radiate out from a common centre\(^4\) (see Fig. 1a). These structures are analogous to the ordered mitotic spindles of stiff biopolymers in dividing cells. In addition to non-equilibrium pattern formation, motors can also cause dramatic changes in mechanical properties. On the one hand, they can enhance fluidization of gels by increasing filament motion, thereby speeding up the rate of stress relaxation\(^5\). On the other hand, when the gels are stabilized by permanent crosslinks, the build-up of motor stresses can dramatically stiffen networks by orders of magnitude\(^6\), and even lead to large-scale contraction\(^7\). This suggests new mechanisms for active control of material properties mediated by enzymatic activity.

The simplified model system of Bausch and colleagues, which consists of filamentous actin, crosslinking proteins and molecular motors (specifically, myosin-II motor filaments), is only marginally stable\(^1\): it strikes a delicate balance between a fluid and a permanent network of crosslinked actin filaments. The result of motor activity in this system is a rich, dynamical regime in which clusters of filaments constantly form, grow and dissolve, as shown in Fig. 2 (see also supplementary movies of ref. 1). Although this bears some resemblance to processes of nucleation and growth, in that small clusters merge to form larger ones, the authors find that constant rupture of large

\begin{figure}[h]
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\caption{Microscopy images of cytoskeletal meshworks. \textbf{a}, A mesh of asters in a minimal system composed solely of microtubules and the motor protein kinesin. Image reproduced from ref. 3, © 1997 NPG. \textbf{b}, Heterogeneous and transient cluster structures observed in the actin-myosin networks of \textit{C. elegans} embryos. Image reproduced with permission from ref. 9, © 2004 Elsevier. \textbf{c}, The reconstituted minimal \textit{in vitro} network model of Bausch and co-workers exhibits structures that bear a striking resemblance to those \textit{in vivo} (\textbf{b}), both in the disorder and transience of the clusters. Image courtesy of S. Köhler, V. Schaller and A. R. Bausch.}
\end{figure}

\section*{References}