

BIOPHYSICS

Cell dipoles feel their way

Biological cells respond actively to the physical properties of their surroundings as well as to external mechanical forces — a coupling that is captured in a model of a cell as a contractile dipole, and shown to drive cell re-orientation.

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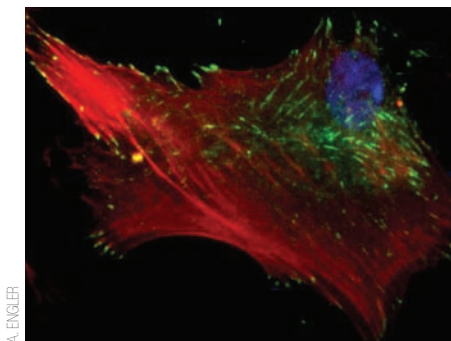
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How does one sense one's surroundings? Smell, taste, touch, hearing and sight are the five key senses that no doubt come to mind. How does an individual cell — of which the average person has about 10^{14} — sense its surroundings? Smell and taste perhaps capture a cell's sensitivity to many soluble chemical factors in the cell's environment (such as hormones). However, it is also increasingly clear that mammalian cells have an acute sense of touch. Individual cells of many types are capable of feeling and responding actively to mechanical aspects of the environment that range from static or dynamic external forces to the elasticity and shape of external substrates.

Understanding of these phenomena is rapidly emerging, not only through experiment, but also through the development of theoretical models that build on a number of condensed-matter topics involving asymmetric objects in symmetry-breaking fields. On page 655 of this issue, De *et al.*¹ model biological cells as uniaxial force-generating structures and calculate the cell's re-orientation in response to external oscillating force fields. Their results address a dynamical puzzle from past experiments, which showed that, in low-frequency strain fields, cells align roughly parallel to the direction of applied strain, whereas higher frequencies (above 1 Hz) drive a near-perpendicular orientation of the cells.

The rearrangement of tissue cells is known to be a very active, energy-consuming process, as all of our tissue cells are adherent and literally depend on 'anchorage' to a substrate for viability. Indeed, cells are not dense and cannot rely on gravity to hold them in place either in



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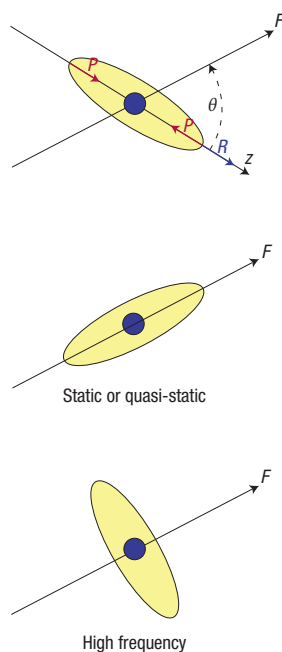


Figure 1 Stem cell and coarse-grain dipole model.

The fluorescence image shows the cytoskeletal actin fibres that generate stress (red), the sites of adhesion to the substrate (green) and the cell nucleus (blue). The model proposed by De *et al.*¹ consists of a contractile force dipole P along the z -axis oriented at an angle θ to the direction of an external force field F . R is the reaction stress in the adjacent elastic matrix due to the cell's contractility. In the static and low-frequency case, the cell aligns parallel to the strain; at higher frequencies, the cell orients nearly perpendicular to the oscillating stretch.

tissues or on a culture substrate; cells rely on adhesion. To re-orient or move, the cells must therefore physically break adhesions, and they must also — again for viability and further movement — re-establish adhesions. Think of someone climbing up a building with suction cups on their hands and knees, detaching and reattaching one suction cup at a time. Adhesion sites are needed for motion as they enable cells to transmit forces generated by their actin-based cytoskeleton — the cell's microscopic system of bones, tendons and muscle. Especially important for cell-detachment processes are contractile forces, which are similar in molecular origin to the forces exerted in your bicep when flexed: myosin ratcheting along actin filaments. Indeed, although we know a good bit from the 'bottom up' in terms of molecular explanations for the active and passive behaviour of the cell's actin cytoskeleton^{2,3}, with insights extending to the material properties of the whole cell⁴ and some ideas for the transduction of forces into chemical signals⁵, theoretical guidance for how a tissue cell will respond in unknown mechanical situations has been lacking.

De *et al.*¹ focus their study on cells that can be approximated to first order as contractile force dipoles in which the cell axis z is oriented at an angle θ with respect to the direction of an externally applied force F (Fig. 1). Such stresses are intended to mimic the dynamic forces in an organism as generated by other cells, fields or objects. The model seems appropriate to a wide range of cell types, such as various muscle cells and even some stem cells. The cell's contractile force dipole P generates a reaction stress R in the deformable matrix around the cell. Some experiments⁶ suggest that a cell attempts to achieve an optimal stress P^* in the matrix; De *et al.* suggest the deviation from this has an energetic cost scaled by a metric of cell activity, ξ , which indicates the tendency of the cell to reorganize its adhesions and its cytoskeleton. This factor combines with the elastic energy of the externally stressed matrix (having elastic constant E)

as well as the externally applied force and an unknown relaxation timescale for molecular reorganization to characterize the elastostatic and dynamic responses of the model cell.

Damped-dynamics solutions yield a two-state-like response for cell orientation versus forcing frequency. For low frequencies, which extrapolate to the static case, the cells align nearly parallel to the orientation of external strain, thus minimizing the total free energy. At high excitation frequencies, the cells orient their major axis nearly perpendicular to the oscillating force field in order to minimize the force acting on them. The physical origin of the latter effect is the frustration that occurs at high frequencies where the cell cannot instantaneously adjust to the

magnitude of the applied force for cells in the parallel orientation — analogous to the behaviour of an electric dipole in an oscillating electromagnetic field.

As the authors point out, the model addresses only the lowest-order force dipole effects in the complex mechanical interplay between cells and their surroundings. The optimal stress P^* and/or higher moments of the contractile stress distribution are influenced by matrix elasticity E , and already appear to couple into key biological pathways, including the differentiation of human stem cells into various types of tissue cells⁶. Dynamic stresses exerted by nearby cells generate dipolar couplings⁷ that might or might not be mimicked by a homogeneous external field. Experiments that vary E as well as externally applied

dynamical forces should provide further tests of the model, and perhaps reveal biological responses that are otherwise obscured in static cell cultures. Such effects seem critical to understanding and exploiting how our cells feel their way through life.

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COMPUTING

Quantum to classical and back

Quantum mechanics can simulate a classical system evolving in (and towards) thermal equilibrium. This finding adds a further ingredient to the story of what problems a computer — classical or quantum — could possibly master.

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A quantum-mechanical system in equilibrium can in many respects be thought of, and studied as, a classical system living in a world with one extra dimension — an ‘imaginary time’ variable. We owe that deep intuition to Richard Feynman, whose famous path-integral formulation of quantum mechanics is now a standard cornerstone of a physicist’s education. Much less known to the wide community of physicists is that the apparently opposite route is also possible: studying classical stochastic dynamics using quantum mechanics. This is the point from which Rolando Somma and colleagues move in an investigation reported in *Physical Review Letters*¹ that takes them to a quantum approach to solving classical statistical mechanics problems.

Not unknown to the experts^{2,3}, essentially any classical probabilistic

dynamics governed, at a finite temperature, by transitions between different energy states — technically, a classical Master equation — can be equivalently rewritten as the Schrödinger dynamics of an appropriate quantum hamiltonian. Contrary to the ordinary form of the Schrödinger equation, where the imaginary unit ‘ i ’ appears, there is no ‘ i ’ in the rewritten form; quantum dynamics now occurs in imaginary time. Ordinary and imaginary-time Schrödinger dynamics are different, of course. However, Somma *et al.*¹ observe that many known results of ordinary quantum mechanics still apply to the transformed classical problem. This is in particular true for the adiabatic theorem, which governs the behaviour of a quantum system when the parameters appearing in its hamiltonian change only slowly in time.

Through such a detour into the quantum world and imaginary time, predictions can be made, for example, on the behaviour of a classical system whose temperature is slowly decreased in time. This procedure is at the heart of the so-called simulated annealing approach⁴, a classical optimization technique where the problem of minimizing a complex cost (energy) function — typically with

many non-trivial local minima in a large configuration space — is tackled by introducing a temperature T and slowly ‘cooling’ the system (a process known as ‘annealing’ in metallurgy) down to $T = 0$. Now, as emphasized by Somma and colleagues, from the quantum-mapping point of view there is nothing unique in such a gradual decrease of T : other parameters in the quantum hamiltonian might be adiabatically changed — or even new terms added to it — with the goal of driving the system towards its absolute minimum energy state. Such an enlarged freedom in the quantum hamiltonian adiabatic dynamics leads to a minimization strategy called quantum annealing^{5,6}, also known as adiabatic quantum computation⁷ in the quantum-information community.

What relationship do these adiabatic strategies have with the standard paradigm of quantum computation (QC)? There is an interesting equivalence⁸, which guarantees that given any standard QC algorithm — like Shor’s famous algorithm⁹ for integer factorization — an adiabatic quantum algorithm can be constructed on the basis of a time-dependent hamiltonian $H(t)$ that performs the equivalent job. Standard QC and adiabatic QC are therefore entirely