BIOPHYSICS

Island hopping for cells

A two-state hopping experiment combined with a dynamical systems model reveals that cancer cells are deterministically driven across barriers, whereas normal cells cross only with the help of stochastic fluctuations.

Ulrich S. Schwarz

Migration is doubtless one of the most important features of living cells. There are around 3.7×10^{13} cells in our body[1] — a huge number that is made possible by exponential growth during the nine months of embryonic development. Although these cells are all mobile during development, once they differentiate into distinct cell types only a few retain a migratory lifestyle. But each and every one of our cells maintains the capacity to migrate, which is what saves us when we suffer a wound: non-migratory cells can switch to migration mode and close the wound. The flip side of this remarkable ability is that some cells can make the change without an external cue, and this is exactly what happens when we develop cancer metastases. Now, writing in *Nature Physics*, David Brückner and colleagues have used a clever combination of experiments and dynamical systems theory to reveal surprising differences in the way that these cells migrate[2].

Biological systems are based on the interaction of many biomolecules and are the most complex systems that physicists study. Therefore, it is always gratifying when a simple quantitative approach reveals novel insight without being burdened by molecular detail. Recently, such progress has been achieved repeatedly in the context of collective cell migration, in which new behaviours emerge from the interplay of many cells acting as an ensemble[3]. Brückner and co-workers focused instead on single-cell behaviour, designing a simple two-state pattern that induced motile cells to continuously switch between two adhesive islands. Because cell migration usually covers larger distances, most experiments in this area are designed to follow cells that move over a flat substrate or through some structured yet extended environment. Brückner and co-workers now studied an even simpler situation, namely how cells cope with a single geometrical constriction, which is a common challenge in their physiological environment.

Using standard tools from micropatterning adhesive environments for cells[4], they designed two islands connected by a thin bridge (Fig. 1a). When motile cells were plated onto these patterns, they started to hop from one island to the other — once they arrived on an island, their intrinsic activity eventually drove them back to the bridge and over to the other island. By using a fluorescent label for the cell nucleus, the authors were able to record a large number of two-state trajectories for position and velocity. Their sampling time of 10 min reflected the slow timescales of cell migration: a typical dwell time on one island was 3 h and a typical velocity was 1 μm min^{-1}.

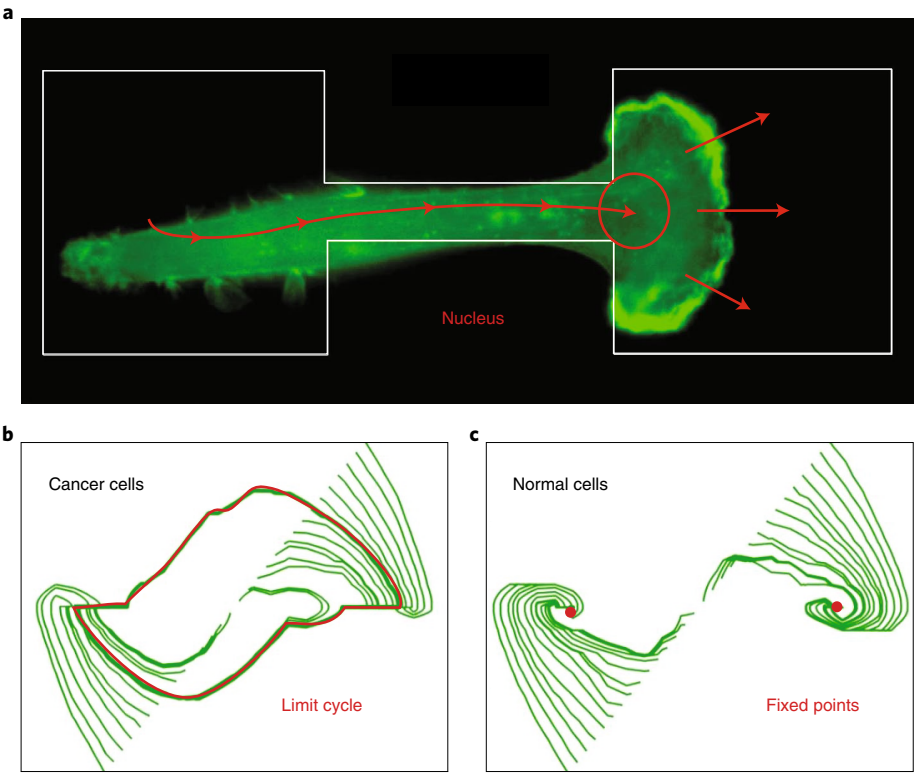

Fig. 1 | Cancer and normal cells show very different dynamical behaviours on two-state micropatterns. **a**, A cancer cell crossing over from one to the other island on a two-state micropattern (white outline, squares with 37 μm side lengths; cell image with fluorescent actin). The nucleus is tracked to obtain two-state trajectories (shown schematically as a circle). **b**, Phase plane analysis for the deterministic forces for the cancer cell. A closed limit cycle exists similar to the van der Pol oscillator (position on *x* axis and velocity on *y* axis, respectively). **c**, For the normal cell, the same analysis reveals two stable fixed points, thus this system is bistable. Figure adapted from ref. [2], Springer Nature Ltd.

The next challenge was then to come up with a theoretical framework to analyse these high-quality time-lapse data. Top-down approaches to cell migration usually start from the concept of persistent random motion[5,6], whereas bottom-up approaches focus largely on the role of polymerizing actin gels pushing the cell envelope forward[7]. In this study, the authors decided to go for a phenomenological top-down approach, but one that focused

on the oscillatory behaviour observed in the two-state system. They considered several options and found that the simplest successful description was a Langevin equation describing the velocity with deterministic forces and a (multiplicative) noise amplitude. Both functions can be inferred from the experimental data and thus one could theoretically analyse the relative contributions from deterministic and stochastic force.

Surprisingly, from the deterministic part they found completely different fixed-point structures for the two cell lines they analysed. The simulated phase portrait for cancer cells revealed a closed limit cycle similar to the van der Pol oscillator (Fig. 1b), but the phase portrait for the normal cells showed two stable fixed points and thus bistability (Fig. 1c). This implies that noise has a completely different function in the two systems. For the cancer cells, noise seems to only amplify the deterministic driving over the barrier, whereas for the normal cells, noise is essential to escape from the attractive fixed points to cross the barrier and to generate the observed oscillations.

This study shows the power of a top-down analysis firmly rooted in the concepts and methods provided by dynamical systems theory. Because it provides novel insight into the fundamentally different control structure in cancer versus normal cells, it also has medical relevance. However, it does not address the question of the underlying molecular mechanisms, in particular of differences in the control system for the polymerizing actin gels that push the cell envelope forward onto the bridge connecting the two islands.

The actin cytoskeleton can exist in many different self-organizing modes, and cells use a certain family of regulatory proteins (the small GTPases from the Rho family) to control how the actin cytoskeleton organizes itself in different situations. It is very likely that the two cell lines studied here show differences in this regard, and one way to probe these differences would be to use the new tool of optogenetics for the cytoskeleton[8]. Such attention to molecular detail is left for future biophysical studies, but the prospects look much more interesting in light of the success of this top-down analysis. Without the clever experimental set-up and the detailed quantitative analysis introduced here, these fundamental differences might have easily gone unnoticed. ❐

Ulrich S. Schwarz
Institute for Theoretical Physics, Heidelberg University, Heidelberg, Germany.
e-mail: schwarz@thphys.uni-heidelberg.de

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