Biophysical *Journal*
New and Notable

Biophysical Society

Watching the Internal Clock of Cells while They Move and Divide

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Cellular processes in which both cell division and cell motility occur are ubiquitous in multicellular animal life throughout embryonic development, normal and anomalous growth, and healing of damaged tissue. These processes arise in many contexts in clinical medicine, for which cell-level observation and experimentation on human subjects to understand mechanisms and explore therapies before clinical trials are often neither practical nor ethically acceptable. Of necessity, recourse is made to models. Animal models that mimic as closely as possible clinically serious conditions are not entirely immune to ethical considerations and are ill-suited to exploratory studies in which many experimental control parameters are to be varied or data are to be sourced at frequent intervals, requiring the sacrifice of large numbers of animal subjects. Of necessity, then, recourse is made to simpler models, which include ex vivo tissue cultures, in vitro studies, or in silico studies. These simpler models have proved helpful in such diverse contexts as early tumor growth (1,2), wound healing (3), and the development of the enteric nervous system (4).

A major challenge for in silico studies of motile proliferating cells is the correct identification of mathematical models adequate for the resolution of the required level of detail and the accurate determination of key parameters associated with the living cell. The scrape assay (or scratch assay) analog of a wound in tissue provides a perfect exemplar. In this experimental setup, a planar substrate is seeded with proliferative cells, which are permitted to proliferate in a monolayer until confluence (or to any desired lesser density). Then a strip is cleared of cells by scraping them away, and the recolonization of the scraped region is observed over time. Typical in silico modeling, whether partial differential equation based or agent based (5,6), matches average cell division rates and effective motility to experimental observations but totally ignores the reality of the cell cycle.

A recent work by Vittadello et al. (7) makes a major contribution to the modeling of motile reproducing cells. Although their in silico and in vitro studies are specifically of the scrape assay using melanoma cells, the methods developed should be more widely applicable. Their clever experimental design exploits a remarkable, relatively recent technology for exposing the time-evolving phase of the cell cycle of individual cells over time intervals that cover many mean cell cycle times. The technology, a fluorescent ubiquitination-based cell cycle indicator, also known by the acronym FUCCI (8,9), is embedded in a number of available cell lines and is preserved under cell division. The fluorescent ubiquitination-based cell cycle indicator causes cells to fluoresce red in the G1 phase of the cell cycle and to fluoresce green in the other three phases (S, G2, and M). This means it is now possible to incorporate phase within the cell cycle into computational models and benchmark results against laboratory experiments running over an extended period.

As part of their experimental validation of their partial differential equation model that disaggregates the cell population according to the fluorescing color, Vittadello et al. were able to check that the effective diffusion constant of cells is independent of the phase within the cell cycle.

Why does this work matter? As Zielke and Edgar (9) have noted, "in most situations in animals and plants, whether a cell proliferates, remains dormant, or exits the cell cycle to differentiate depends largely on its interactions with neighboring cells and physiological signals from elsewhere in the organism. Thus to tackle general problems in development, regeneration, and the transformation of normal cells into tumor cells, it is essential to understand how cell proliferation is regulated by a cell's context." The work of Vittadello et al. is a very useful contribution to this quest, but it remains to be seen how far these ideas can be taken into systems closer to living tissue,

Submitted January 18, 2018, and accepted for publication February 2, 2018.

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Editor: James Sneyd.
https://doi.org/10.1016/j.bpj.2018.02.001

where motile cells must traverse, and sometimes remodel, the extracellular matrix.

ACKNOWLEDGMENTS

The author acknowledges the support of the Australian Research Council (DP140100339).

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