JOURNAL OF THE ROYAL SOCIETY Interface

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J. R. Soc. Interface 2008 **5**, S111-S112
doi: 10.1098/rsif.2008.0279.focus

Interface focus

J. R. Soc. Interface (2008) **5**, S111–S112
doi:10.1098/rsif.2008.0279.focus
Published online 29 July 2008

New frontiers in single-cell analysis

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For this special issue of *J. R. Soc. Interface* we present an overview of the driving forces behind technological advances in the field of single-cell analysis. These range from increasing our understanding of cellular heterogeneity through to the study of rare cells, areas of research that cannot be tackled effectively using current high-throughput population-based averaging techniques.

Keywords: single-cell analysis; systems biology; cellular complexity

1. INTRODUCTION

Since the advent of proteomics in the 1970–1980s and genomics in the 1990s, these disciplines have developed in ways that emphasize the rate and volume of data acquisition and analysis. They have, by necessity, worked on large populations of cells and thereby reported on population averages rather than their distributions, missed rare (but important) events and been unable to analyse cells that are only produced in small numbers. This is of course not by choice but owing to a paucity of techniques that allow experimentalists to measure protein levels at the single-cell level. In addition, genome sequence information provides powerful insights into cellular complexity but limited information pertaining to how individual parts of a cell are integrated in time and space to form dynamic cellular processes and how cellular interactions consequently translate to create higher order functions. This currently hampers an understanding of the mechanisms underpinning the morphological design of organisms that depends on programmes of cellular division and apoptosis that are closely linked to these spatially and temporally dependent signals.

Parameters based upon averages of large populations are often misleading. Cellular heterogeneity is widespread (Ferrell & Machleder 1998; Huang *et al.* 2000; Teruel & Meyer 2002; Marcus *et al.* 2006) in bacteria and increasingly apparent in eukaryotic cells. The complex and highly interconnected network of signalling pathways, their spatially dependent nature and reliance upon low-abundance molecules produces stochastic behaviour that subsequently underpins heterogeneity in cellular systems (Di Carlo *et al.* 2003). The noise in biological function subsequently expresses itself in many different forms, from noise-driven divergence of cell fates through to noise-induced amplification of signals (Rao *et al.* 2002). An understanding of the relationship between biological heterogeneity and signalling pathway regulation that may result in disease states is therefore critical and offers the potential to drive novel therapeutic interventions developed in response to single-cell behaviours.

In parallel, the study of rare cells such as stem cells and progenitor cells does not lend itself to high-throughput population-based protocols. In these cases, the development of single-cell analysis techniques that allow multiple measurements to be conducted on the same cell as a function of time is vital if we are to unravel the inner workings of these extraordinary systems.

This special issue brings together an exciting and diverse collection of pioneering technologies that address many of the current bottlenecks in single-cell analysis. Both Lai *et al.* (2008) and Sedgwick *et al.* (2008) present microfluidic platforms that can perform high-speed full cell lysis. Lai *et al.* describe the use of a pulsed laser microbeam for cell lysis on a microsecond time scale followed by electrophoretic separation of cellular analytes. By contrast, Sedgwick *et al.* present on-chip dielectrophoretic trapping of human epithelial carcinoma cells followed by electroporation using the same electrode framework leading to cell lysis. In their review, Brown & Audet (2008) expand upon these methodologies and also present an overview of the advantages offered by acoustic, mechanical and chemical technologies. In a similar vein, Chao & Ros (2008) review further exciting developments in the application of microfluidic devices to the analysis of intracellular compounds in single cells, ranging from cutting-edge proof of concept devices all the way through to applied systems currently being employed to tackle cutting-edge biological questions. Dragavon *et al.* (2008) introduce a cellular isolation system that allows the user to monitor single-cell oxygen consumption rates in real time, while Lanigan *et al.* (2008) introduce a new process termed *nanodigestion* in which microdroplets controlled using optical traps are used to effect spatially selective sampling of the plasma membrane of single cells without solubilizing the entire cell.

In commissioning this issue, *J. R. Soc. Interface* has recognized that the development of techniques of single-cell analysis requires multidisciplinary approaches that bridge the physical and life sciences divide. This falls

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One contribution of 7 to a Theme Supplement 'Single-cell analysis'.

Received 3 July 2008
Accepted 3 July 2008

within the heart of the journal's stated purpose. *J. R. Soc. Interface* will continue to highlight new and exciting advances in the area of single-cell analysis and we hope you will join us in promoting this interface by considering this journal as a platform for publishing your future research.

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