EDITORIAL

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EDITORIAL

The diverse landscape of modeling in single-cell biology

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Single-cell biology is computational by necessity. The size and complexity of the datasets involved demand it. To meet the need, a broad and ever-expanding range of computational methods and models are being developed (figure 1). In this special issue, we present a collection of research papers and reviews that offer an overview of the current landscape of quantitative methods and physical modeling in single-cell biology.

Studies of single cells are as old as the microscopes under which we first visualized them. However, in the last decade or so, our ability to make quantitative measurements of single cells has undergone a revolution. Led by advances in sequencing technologies, we can now characterize properties of single cells in unprecedented resolution, including measurements of the genome, transcriptome, proteome, epigenetic states, and spatial properties of cells from surface polarity to chemotaxis. Not only can we assay these states individually, but we are able to combine multiple assays in 'multi-omic' datasets, as well as combine genomic measurements with functional assays, such as live imaging or clonal tracking.

The rate of growth of the size of single-cell RNA sequencing datasets far exceeds Moore's law [1]. This leads to a curse of dimensionality, solutions to which rely on computational methods for data processing. Typical pipelines for computational data analysis of such datasets begin with data normalization, visualization, cell clustering, and differential gene expression. Yet, far greater insight can remain in these data untapped. To harness the full capacity of single-cell genomics datasets, not only do we need new methods to infer biological properties from data [2, 3], but we need to integrate physical and dynamical systems perspectives to build predictive models of individual cells, e.g. as they transition through intermediate states [4] towards commitment.

To address gaps in our ability to infer important features from genomic data, Ruske *et al* [2] develop new computational methods to infer cell division/differentiation rates from snapshot data, and Elyanow *et al* [3] develop a new method to infer copy number variation in cells using spatial transcriptomics data, explicitly making use of cell–cell neighbor information that these data provide. The heterogeneity of cancers provides ample motivation for the use of single-cell approaches to study them. Zhang and Campbell [5] provide an overview of state-of-the-art methods with which to analyze single-cell cancer genomics data, encompassing a broad range of data types from DNA to protein and epigenetic assays.

Towards the challenge of integrating dynamical systems perspectives with genomic data, Guillemin and Stumpf [6] develop a model to characterize cell fate decision-making, taking into consideration gene expression, chromatic organization, and cellular signaling pathways, all of which are under the influence of various sources of biological noise. Sharing a focus on cell fate decision-making, Stumpf *et al* [7] present a model of memory in stem cell proliferation, and show that the resulting heterogeneity goes some way to explain aging-related stem cell phenotypes.

A focus on biochemical reaction networks in light of the properties of single cells enables the characterization of new out-of-equilibrium biological phenomena. KhudaBukhsh *et al* [8] develop a model of stochastic biochemical processes that permits the incorporation of molecular ages into biochemical reaction models. Laghmach and Potoyan [9] build upon the physical theory of phase separation to study non-equilibrium biochemical dynamics in the nucleoplasm and the heterogeneous gene expression distributions that result.

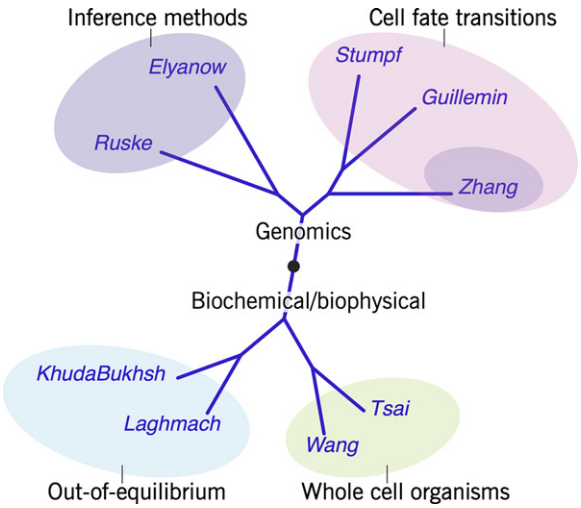

Figure 1. Hierarchical clustering of papers appearing in this special issue by keyword.

By crossing scales from the molecular to the cellular, we arrive at studies of whole-cell phenotypes. Single-celled organisms offer useful test cases of such phenotypes, as well as the cell fate decisions that underlie them. Wang and Wu [10] develop a reaction–diffusion–convection model to describe the swimming dynamics of *Dictyostelium discoideum* under the influence of chemotaxis. Tsai *et al* [11] develop a three-dimensional particle-based model of the cell surface of *Saccharomyces cerevisiae*, used to explain the roles of mechanical and cell polarization properties during bud formation.

As we look forward, we have no doubt that the pace of development of new quantitative and biophysical methods will continue unabated. New technologies demand it ([12, 13], to give just two of many examples). Still, the challenges associated with single-cell data analysis extend well beyond the development of tools for inference from data. Fundamental new mathematical approaches are required to build models of multiscale out-of-equilibrium biological systems, and, eventually, to scale these models up to the size of whole cells, and fit them to data via statistical inference [14]. The rapid emergence of single-cell measurement technologies has led to the generation of large, diverse multi-modal datasets. These data will continue to offer great potential for the development of new mathematics and biophysical models, in turn enabling expansive opportunities for biological discovery.

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Data availability statement

No new data were created or analysed in this study.

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