Cell State Transitions and Fate (in)decisions Workshop

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Workshop Goals

The goal of the workshop was to bring together researchers from biology, mathematics, physics, and computation to discuss how cells transition between states and how those transitions ultimately become fate decisions. A central motivation was to create a setting in which experimental and empirical observations could be examined alongside theoretical descriptions of cell-state dynamics, with particular emphasis on identifying where mathematical and physical ideas can clarify biological questions and where current biological measurements challenge existing theory.

Major Themes and Discussions

Several themes emerged repeatedly throughout the workshop.

- **Single-cell preprocessing and normalization.** Some of the liveliest discussion concerned the preprocessing of single-cell gene-expression data. Participants discussed the advantages and limitations of commonly used normalization procedures, transformations, filtering choices, and feature-selection approaches. A recurring concern was that preprocessing is often treated as a purely technical step, even though it can substantially affect the quantities being compared across cells and the biological conclusions that follow. In particular, normalization can alter apparent correlations, relative expression patterns, and inferred cell-state geometry, while potentially removing biologically meaningful information associated with global changes in transcriptional activity. These discussions emphasized the importance of making the assumptions behind preprocessing more explicit and of understanding how they propagate into downstream dynamical or mechanistic interpretations.
- **Equilibrium and nonequilibrium statistical physics.** A second major theme was the role of ideas from statistical physics in describing cell-state transitions. Equilibrium concepts such as attractors, potential landscapes, and free-energy-like descriptions provide intuitive ways to think about stable cell states and transitions between them. At the same time, many biological systems are actively driven, transient, history-dependent, and maintained far from equilibrium. This led to substantial discussion about when equilibrium landscape descriptions are useful approximations, when nonequilibrium fluxes and irreversibility must be incorporated explicitly, and how the two perspectives might be related within a common framework.
- **Inferring dynamics from incomplete observations.** Participants repeatedly returned to the difficulty of reconstructing dynamics from static or sparsely sampled single-cell measurements. A snapshot of a heterogeneous population does not uniquely determine the trajectories that generated it. Discussions therefore focused on questions of

identifiability and uncertainty, as well as the value of lineage information, perturbation experiments, time-resolved measurements, and biological constraints for distinguishing among competing dynamical explanations.

- **Connecting theoretical models to biological observables.** Another recurring theme was the need to connect mathematical abstractions directly to quantities that can be experimentally measured. Concepts such as developmental landscapes, transition barriers, lineage structure, physiological constraints, and collective cell-state coordinates can be useful theoretical constructs, but their value ultimately depends on whether they generate experimentally interpretable and testable predictions. Participants discussed the advantages of simple models for revealing general principles while also emphasizing the importance of retaining sufficient biological detail.

Outcomes and General Observations

A major outcome of the workshop was not necessarily convergence on a single framework for describing cell-fate dynamics, but rather the identification of a shared set of questions and productive points of disagreement. In particular, discussions helped clarify how strongly interpretations of cell-state dynamics can depend on assumptions made during preprocessing and modeling, and highlighted the need to distinguish between convenient mathematical descriptions and mechanisms that can actually be inferred from available data.

The workshop also appears to have been successful in strengthening interdisciplinary communication. According to the participant evaluation, all survey respondents reported that the workshop helped them better understand terminology or language that had previously been unfamiliar to them. Ninety-one percent reported feeling better equipped to apply mathematical tools or concepts to biological questions, and 86% reported exposure to new mathematics or mathematical ideas that were new to them.

More broadly, the workshop was very positively received. All survey respondents indicated that the workshop was worth their time, that they would consider attending another NITMB workshop, and that they would recommend future NITMB events to colleagues. Eighty-six percent reported that they were more likely to invest time in NITMB activities following the workshop.

Opportunities for Future Workshops

Participant feedback also suggested several ways that future workshops could build on this format:

- Preserve more time for informal discussion, coffee breaks, and extended conversations following talks.
- Use focused breakout or working-group sessions organized around concrete open problems.
- Create more opportunities for trainees to ask questions and present their work.
- Encourage presentations of newer, unpublished, or less polished work when doing so can stimulate genuine discussion.

- Develop follow-up activities around particularly active topics, including principled single-cell preprocessing, inference of dynamics from lineage and perturbation data, and equilibrium versus nonequilibrium descriptions of cell-state transitions.

Closing Perspective

Overall, the workshop succeeded in creating a productive interface between biological questions and mathematical and physical theory. Experimental realities repeatedly challenged theoretical assumptions, while mathematical perspectives helped expose assumptions that are often hidden within standard analysis pipelines. The particularly lively discussions surrounding normalization, inference, and equilibrium versus nonequilibrium statistical physics suggest that these are not merely technical issues, but central conceptual questions for developing a quantitative theory of cell-state transitions.

The workshop therefore served both as a snapshot of an active interdisciplinary field and as a starting point for future collaborations, methodological comparisons, and theory–experiment interactions.