Single-Cell Trajectory Detection Uncovers Progression and Regulatory Coordination in Human B cell Development

Sean C. Bendall, Kara L. Davis, El-ad David Amir, Michelle D. Tadmor, Erin F. Simonds, Tiffany J. Chen, Daniel K. Shenfeld, Garry P. Nolan, Dana Pe'er

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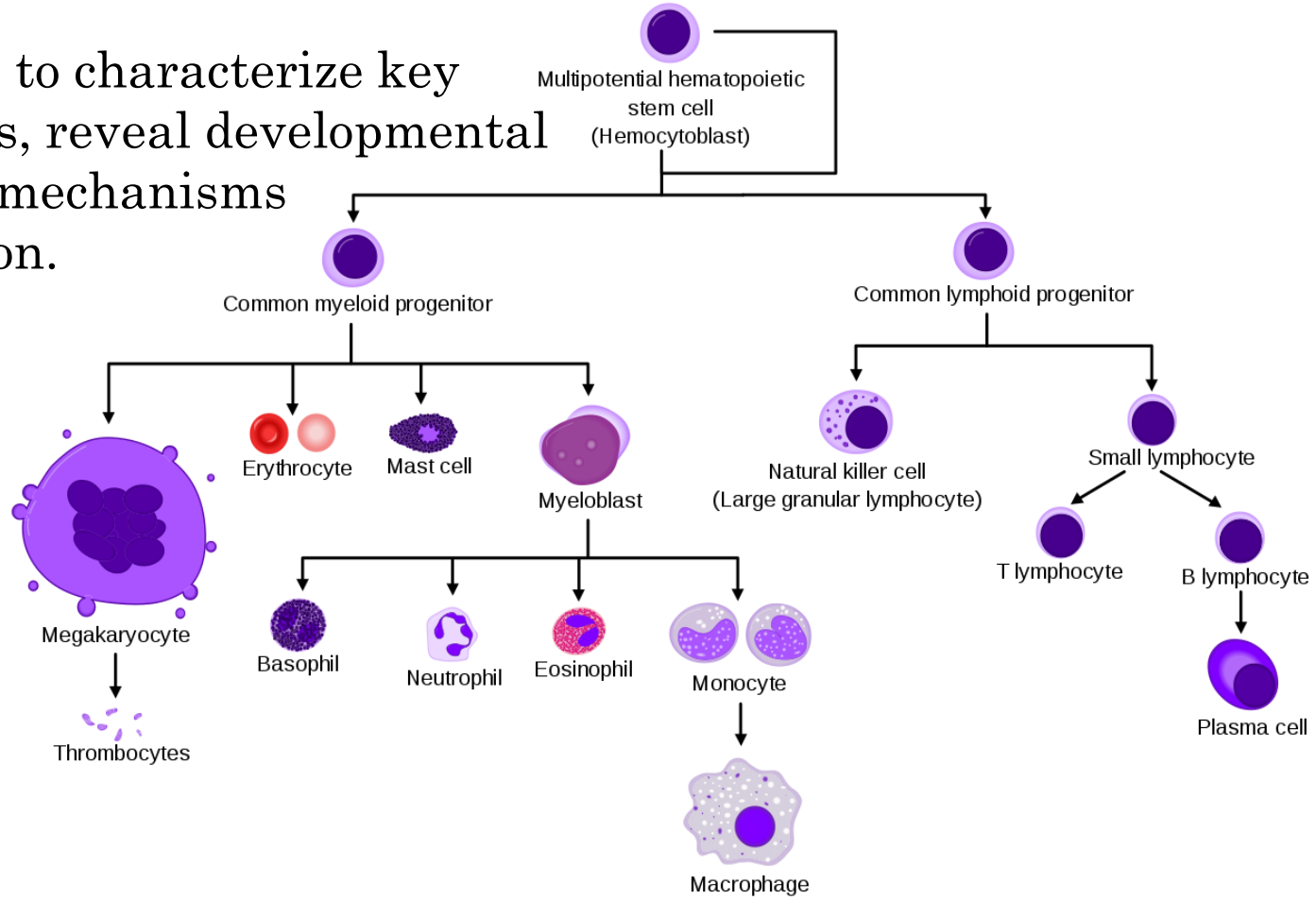
Goal

Generally - analyze and order cells on a developmental trajectory.

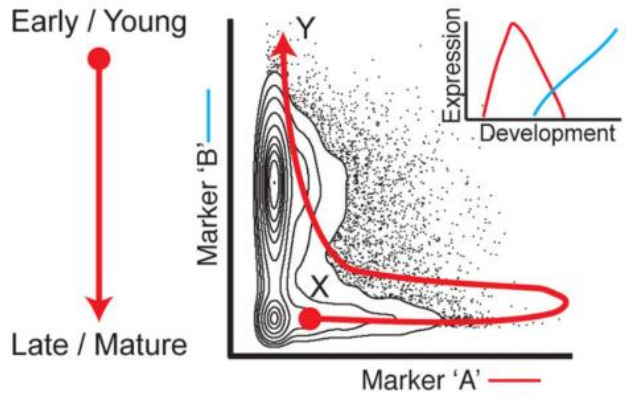
This trajectory could be used to characterize key molecular and cellular events, reveal developmental relationships, behavior, and mechanisms that govern cell differentiation.

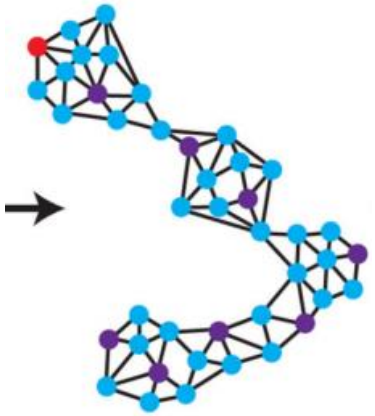


Approach

Using single-cell mass cytometry data, develop a graph-based trajectory detection algorithm that orders cells by the chronological order of development.

- Mass cytometry: a technique for measuring cellular features: proteins, enzymes, etc.
- Why a new graph-based algorithm?

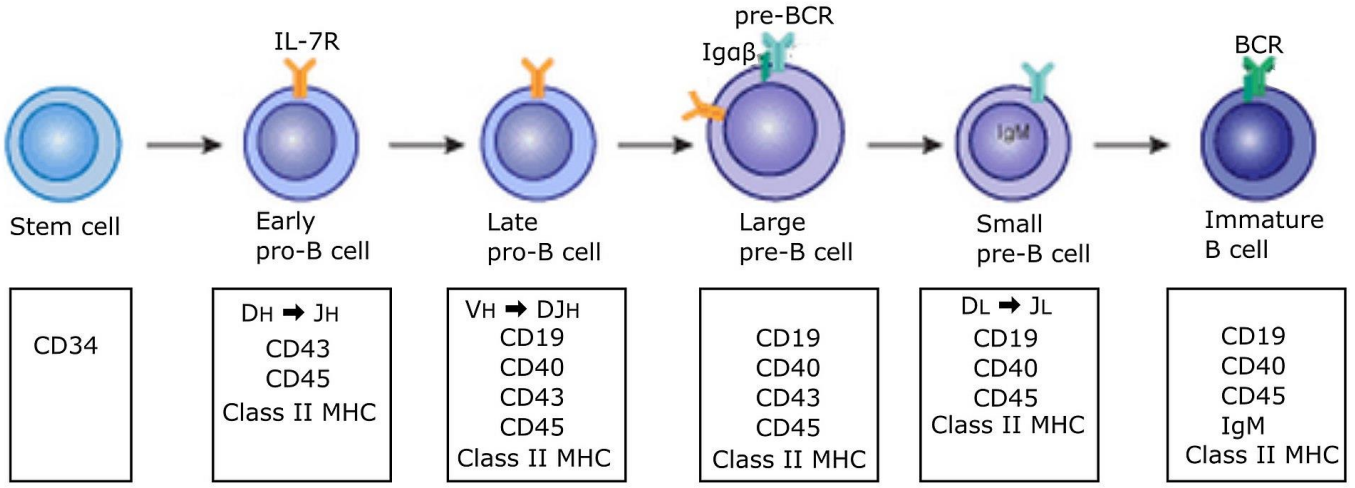




- B cell lymphopoiesis – the perfect test case.

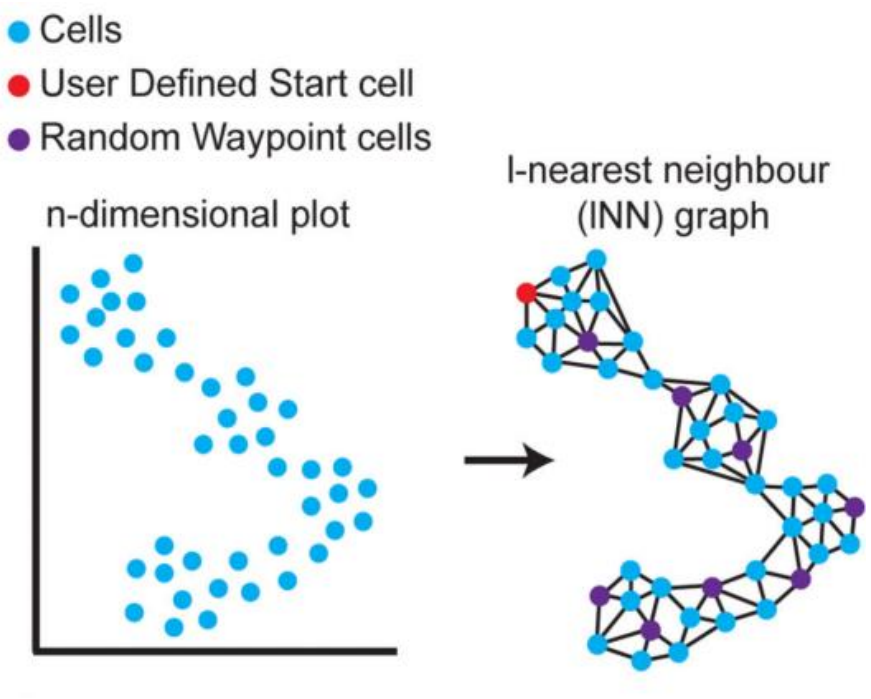
Human B lymphocytes

- Develops from hematopoietic stem cell (HSC) to immature B cell, which migrates out of the marrow.
- A non-branching process occurring entirely within bone marrow.
- Enables extracting a developmental trajectory from a snapshot of the system, rather than from time-series data.



Wanderlust Algorithm

- Input: single-cell measurements and a user-defined “early” cell.
- The data is converted into a i-nearest neighbor graph (I-NNG): the edges’ weights are set as the cosine distance between cells.



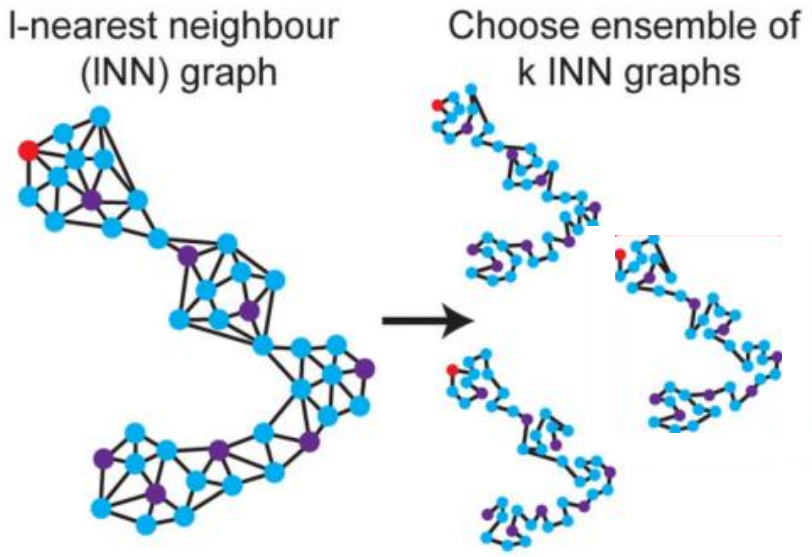
Wanderlust Algorithm

Problem: Short circuits

Edges between developmentally distant cells, which nevertheless have similar properties.

Solution: k-out-of-i-nearest neighbor graphs (k-i-NNG)

A short circuit will only appear in few graphs in the ensemble.



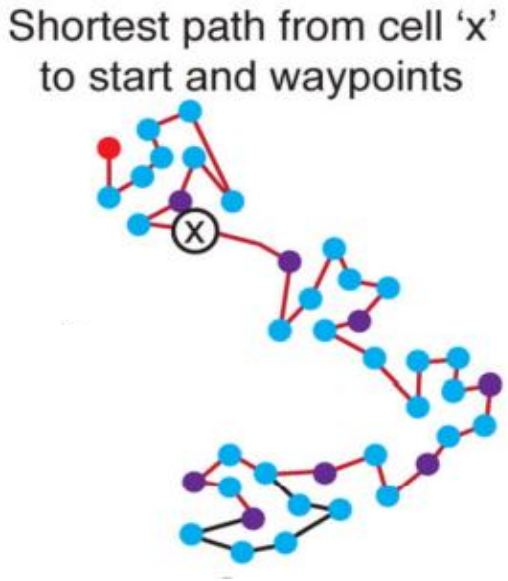
Wanderlust Algorithm

Problem: Noise

Noise accumulates with each step - longer paths are less reliable.

Solution:

Randomly assign “waypoint” cells to refine estimations of nearby cells.
Each waypoint is weighed so that closer waypoints contribute more to the calculation.



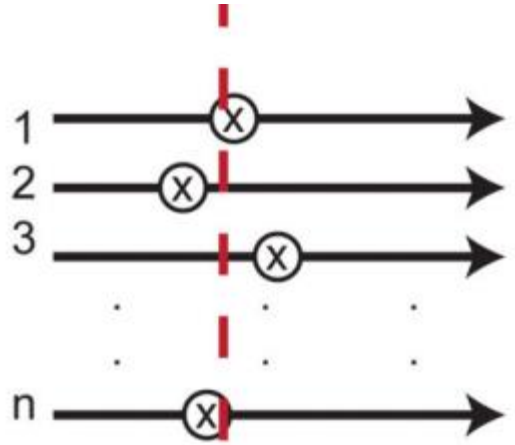
Wanderlust Algorithm

For each k-i-NNG:

1. Each cell's position is first set to the shortest-path from the initiator cell
2. Refine positions according to the distance from waypoints
3. Waypoints are themselves cells - their position changes based on the same calculation

Repeat until positions of all cells converge.

The final trajectory is the average over all graphs.



Performance Evaluation

- Initially tested with synthetic data
- Markers changes along the resulting trajectory matched prior knowledge of B cell development
- Correct trajectory even when using mature initiator cell
- Consistent trajectories when excluding any individual marker (16/17) except HLA-DR, or when removing all canonical markers
- Consistent trajectory over different samples
- Playing with free parameters (i, k, number of waypoints)

Results and following research

- Ordering of B cell precursors
- Examine trends by plotting the trace of each marker
- Functional characterization by manipulation of the cells
  - ✦ Signaling response to IL-7
  - ✦ Disruption of STAT5 regulation restricted further progression of cells from population II
- Enable to observe the rewiring of the regulatory signaling network in the rare, early B cell populations
- Discovery of ‘coordination points’ dictating cell fate decisions