Multiple States in Cancer Cell Population

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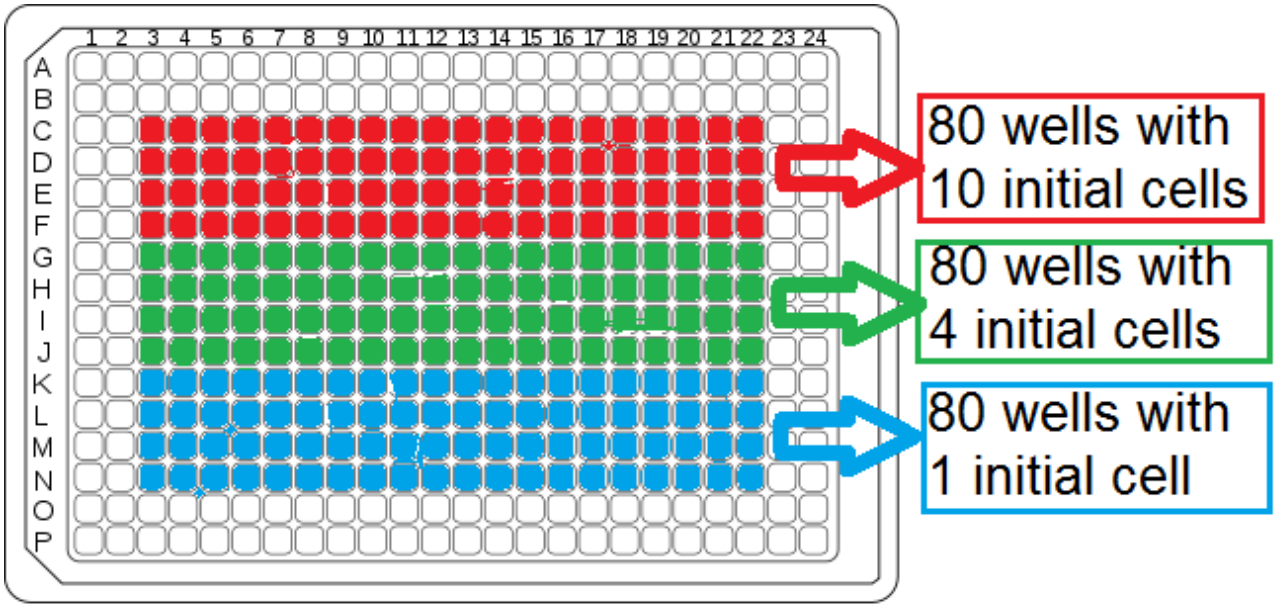
Outline

- Cancer cell population is often thought to be homogeneous.
- Analyze experimental data to reveal the existence of multiple cell states.
- Theoretical explanations of related new phenomena.

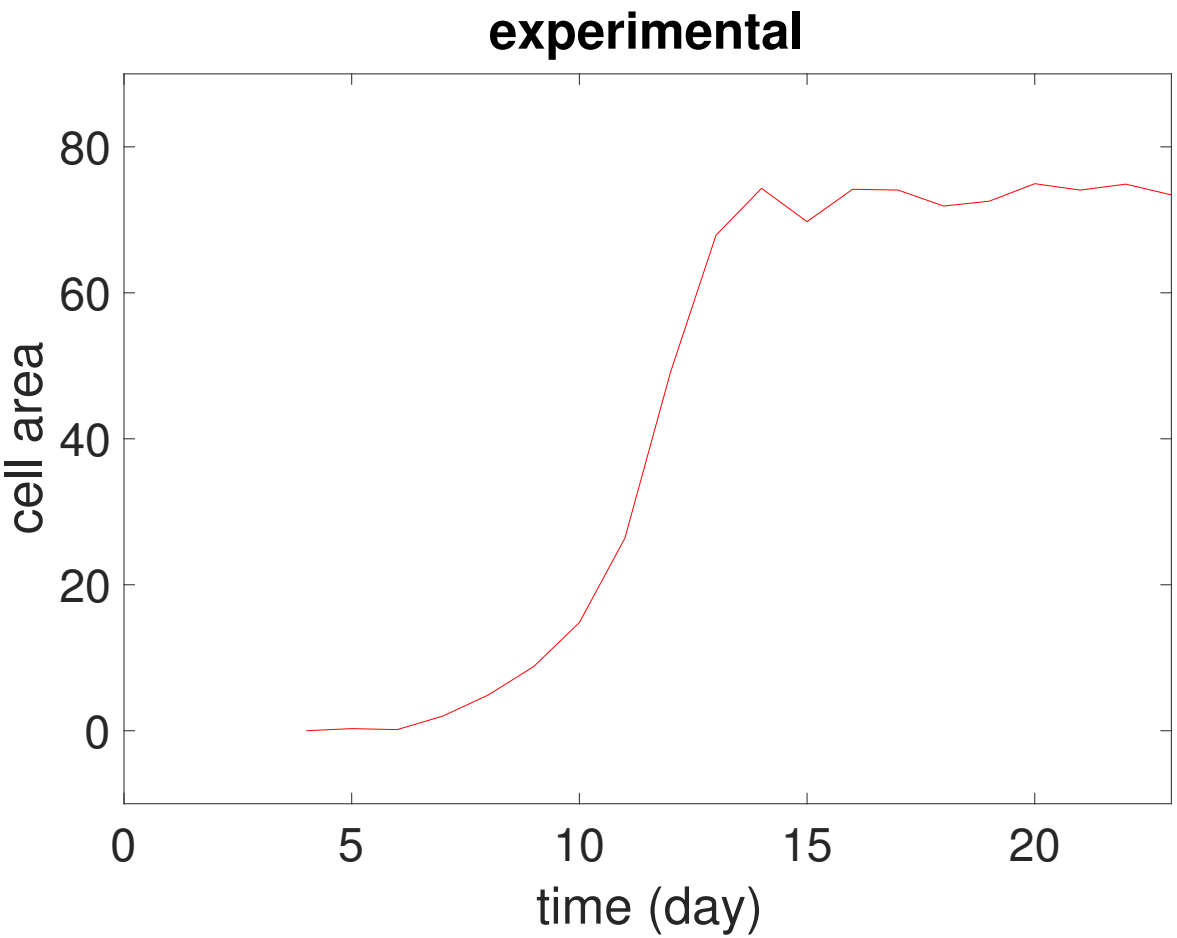
Experiments

- Cultivate HL60 leukemia cells *in vitro*.



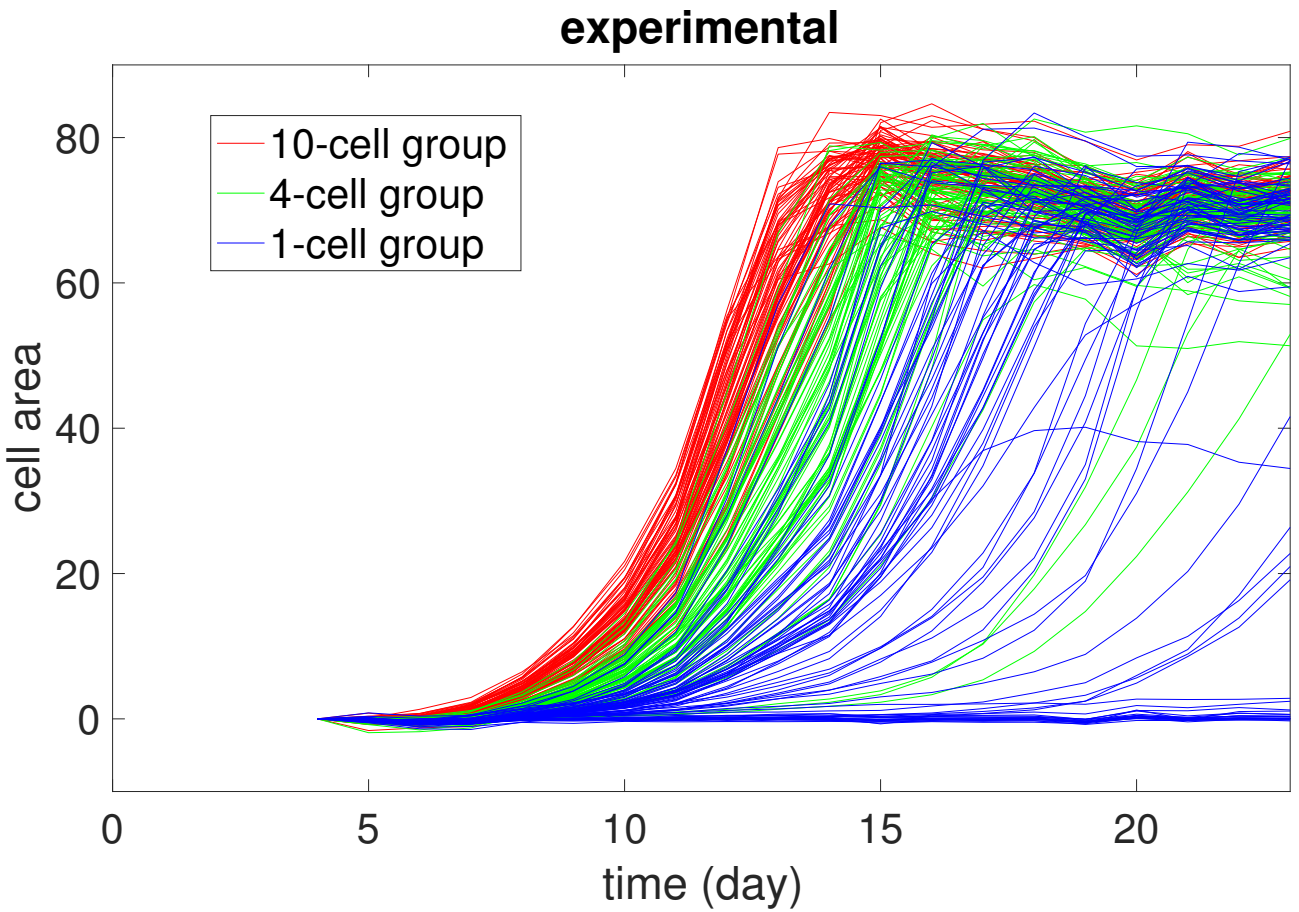
- Initial cells are sampled randomly from a large population.
- For each well, the cell area (proportional to cell number) is measured everyday.

Growth curves



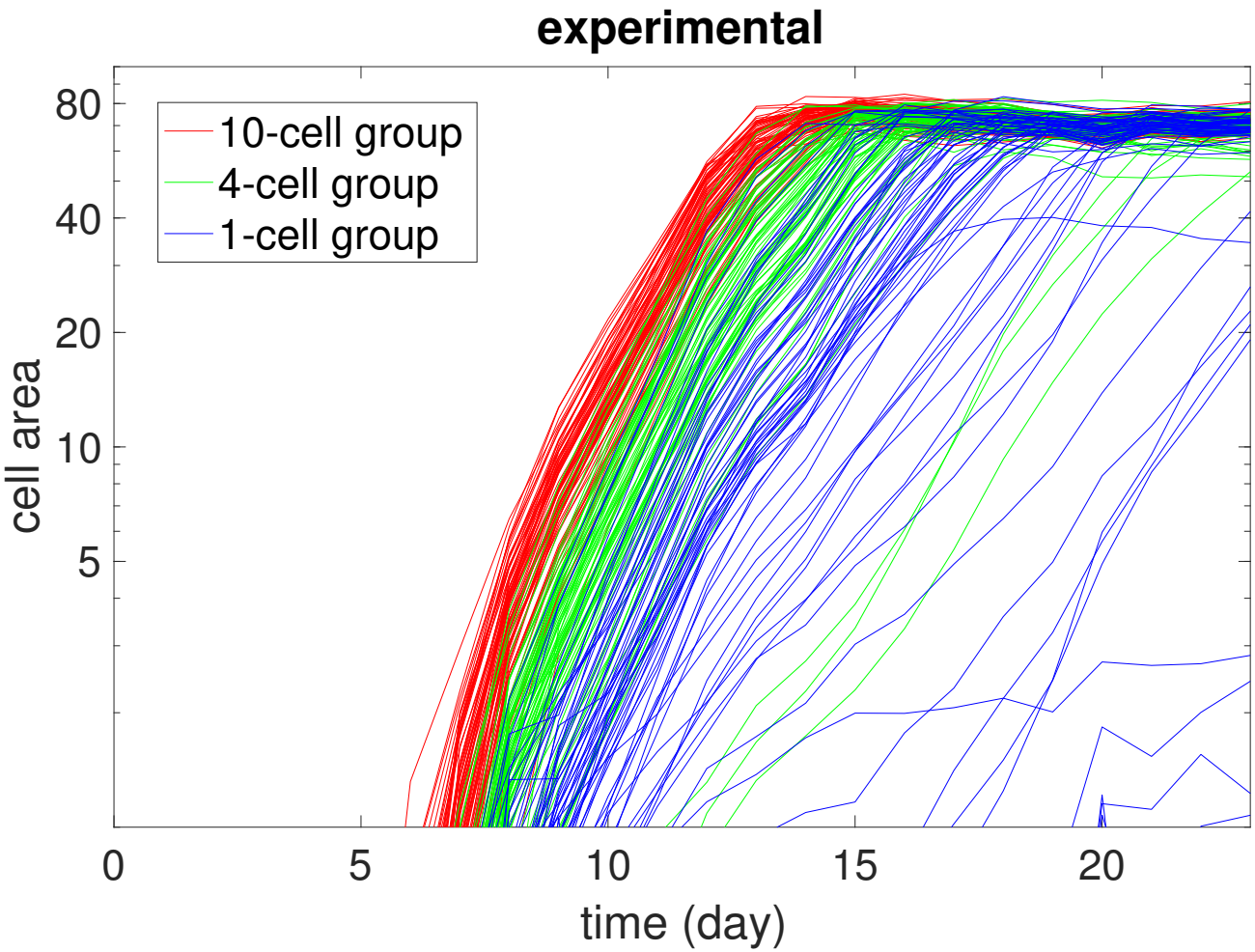
Growth curve of one well, describing how the population changes along time. In general, the population grows exponentially until saturation.

Growth curves



Each growth curve corresponds to one well. Red: 10 initial cells; green: 4 initial cells; blue: 1 initial cell.

Growth curves



Growth curves with y-axis in log scale. Red: 10 initial cells; green: 4 initial cells; blue: 1 initial cell.

Growth curves

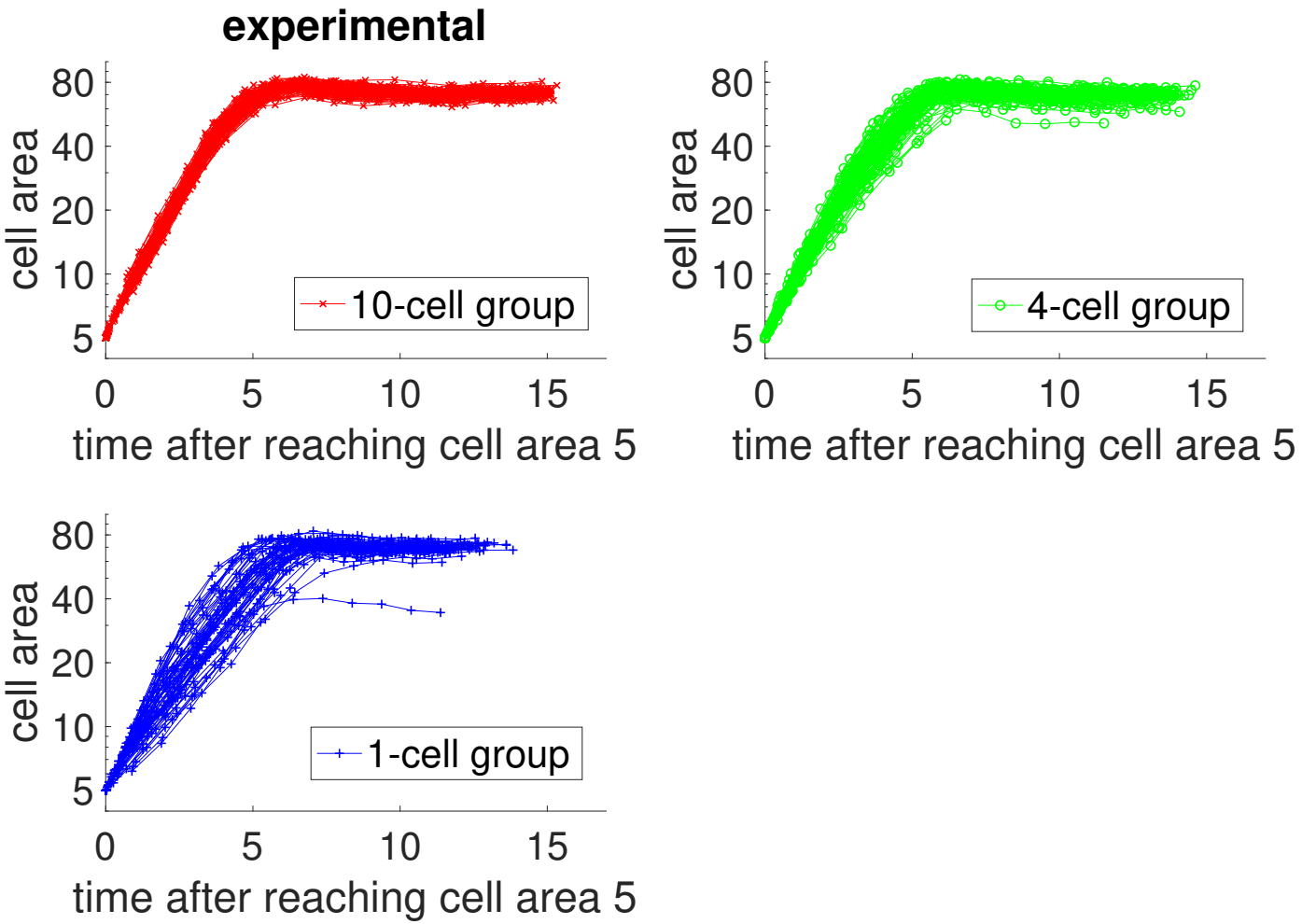
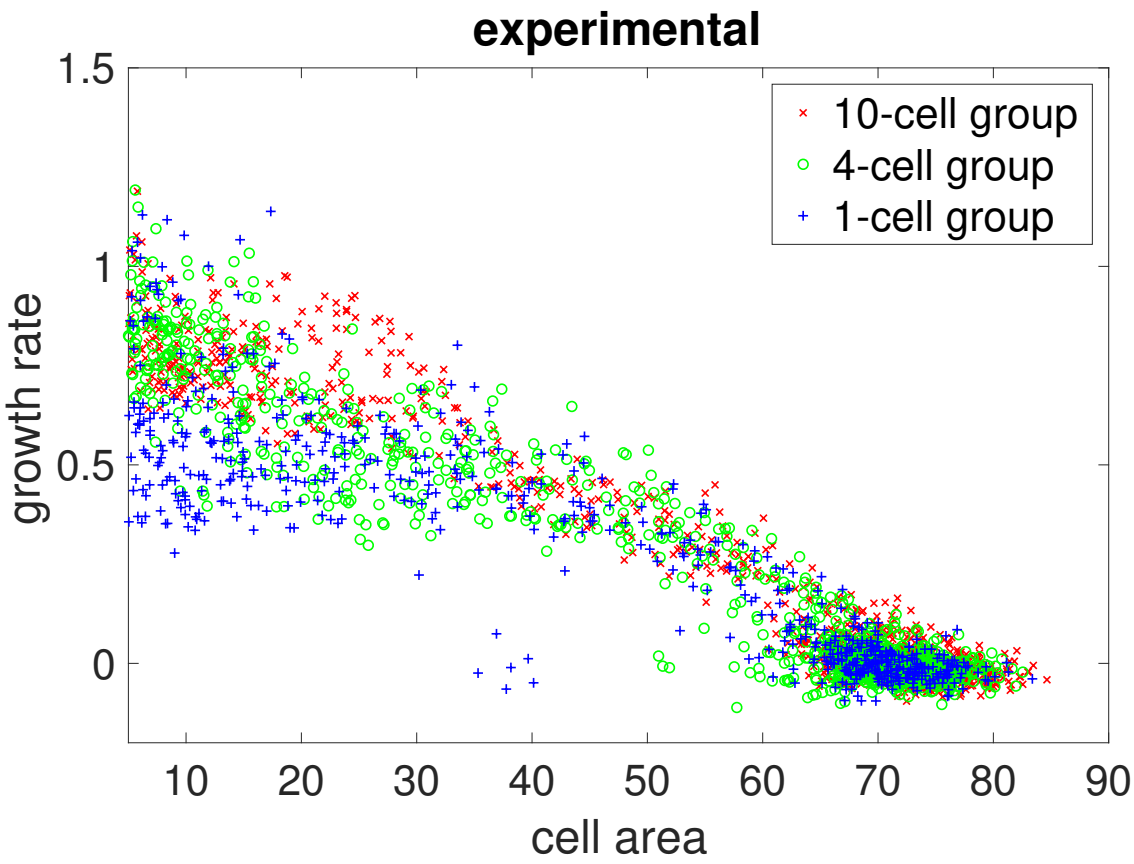


Figure: Translated population curves, starting from cell area 5. Y-axis is in log scale. Some 1-cell-wells never reach cell area 5, thus are not shown.

Growth rates

For one well, denote the population at day n as c_n, and the population at day $n+1$ as c_{n+1}. Then the growth rate is $g_n = (c_{n+1} - c_n)/c_n$. For each well in each day, draw the growth rate g_n versus the population c_n. The point cloud near $(75, 0)$ corresponds to saturated wells.

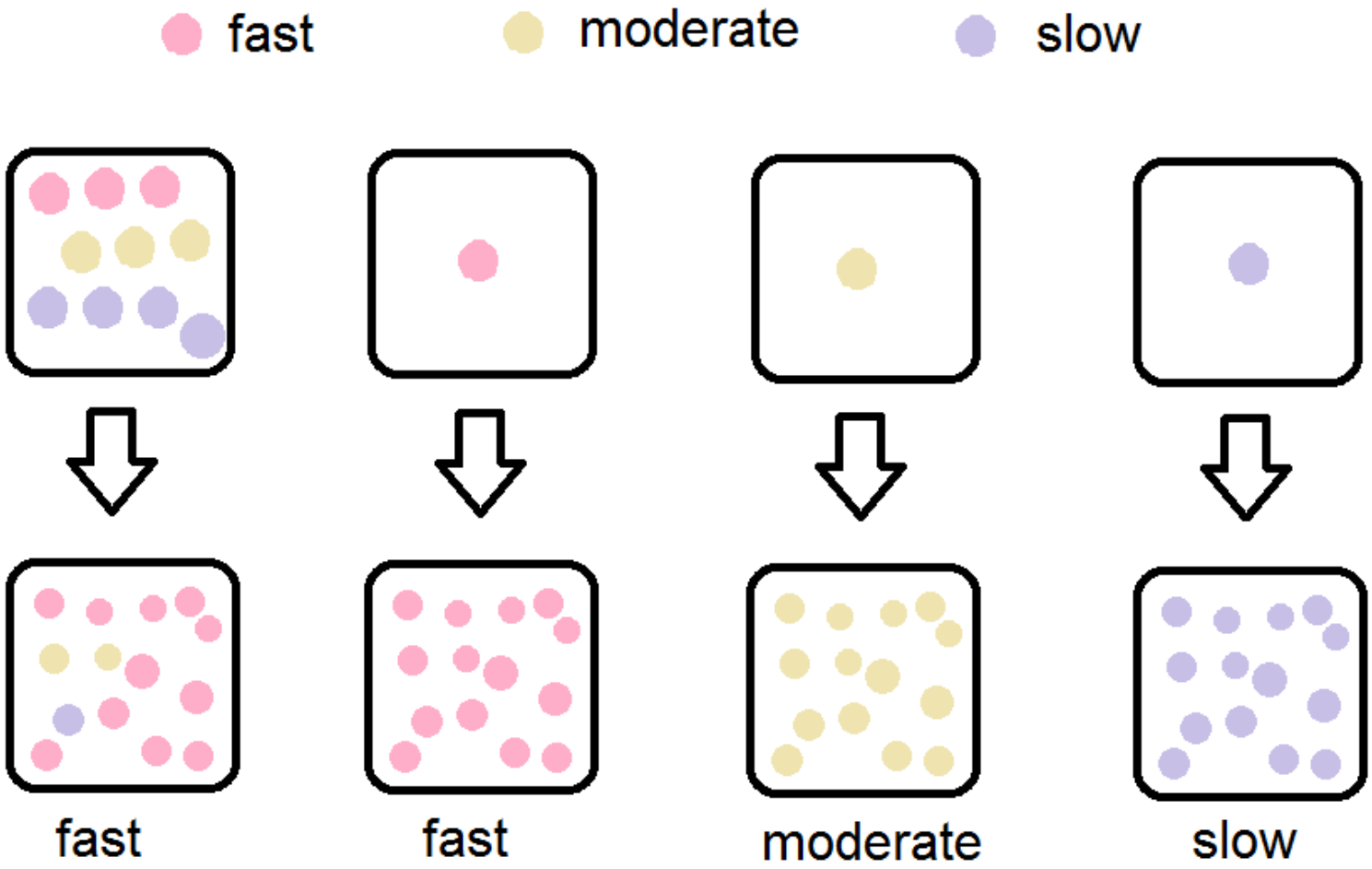


Experimental phenomena

- After reaching the same population, all 10-cell-wells grow fast; some 1-cell-wells grow much slower.
- Some 1-cell-wells keep at low population levels for a long time.
- When a 1-cell-well grows to have 10 cells, it is different from a 10-cell-well.
- Cells cannot be homogeneous.

Analysis

We assume that there are at least three cell states with different growth rates: fast, moderate, and slow.



Model

- Build a multi-type branching process model.
- Initial cells have three possible states, determining the growth rate. Growth rate is inheritable, and decreases as total population increases.
- For each time period, each cell has a probability to divide, and a probability to die.
- In simulation, this model can reproduce most experimental phenomena within a wide range of parameters.

Model

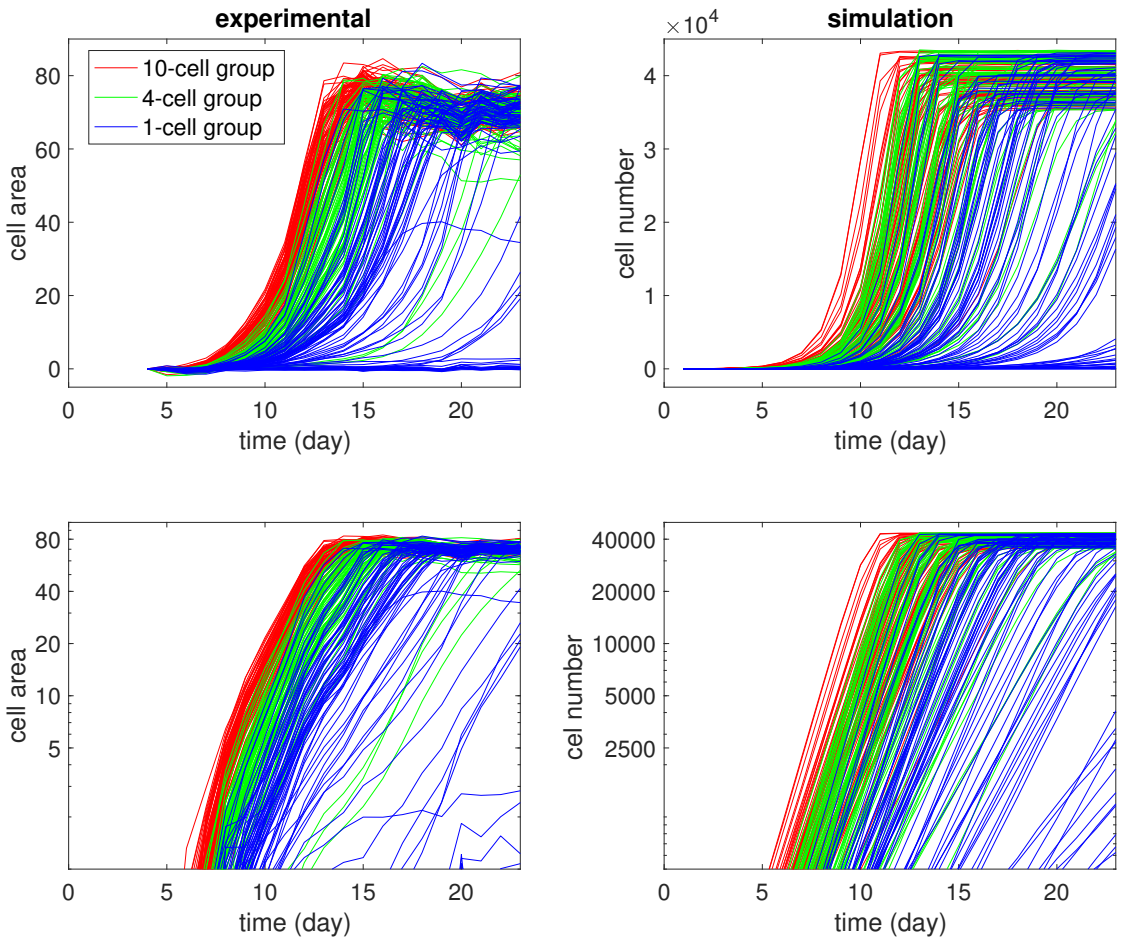


Figure: Population growth curves.

Model

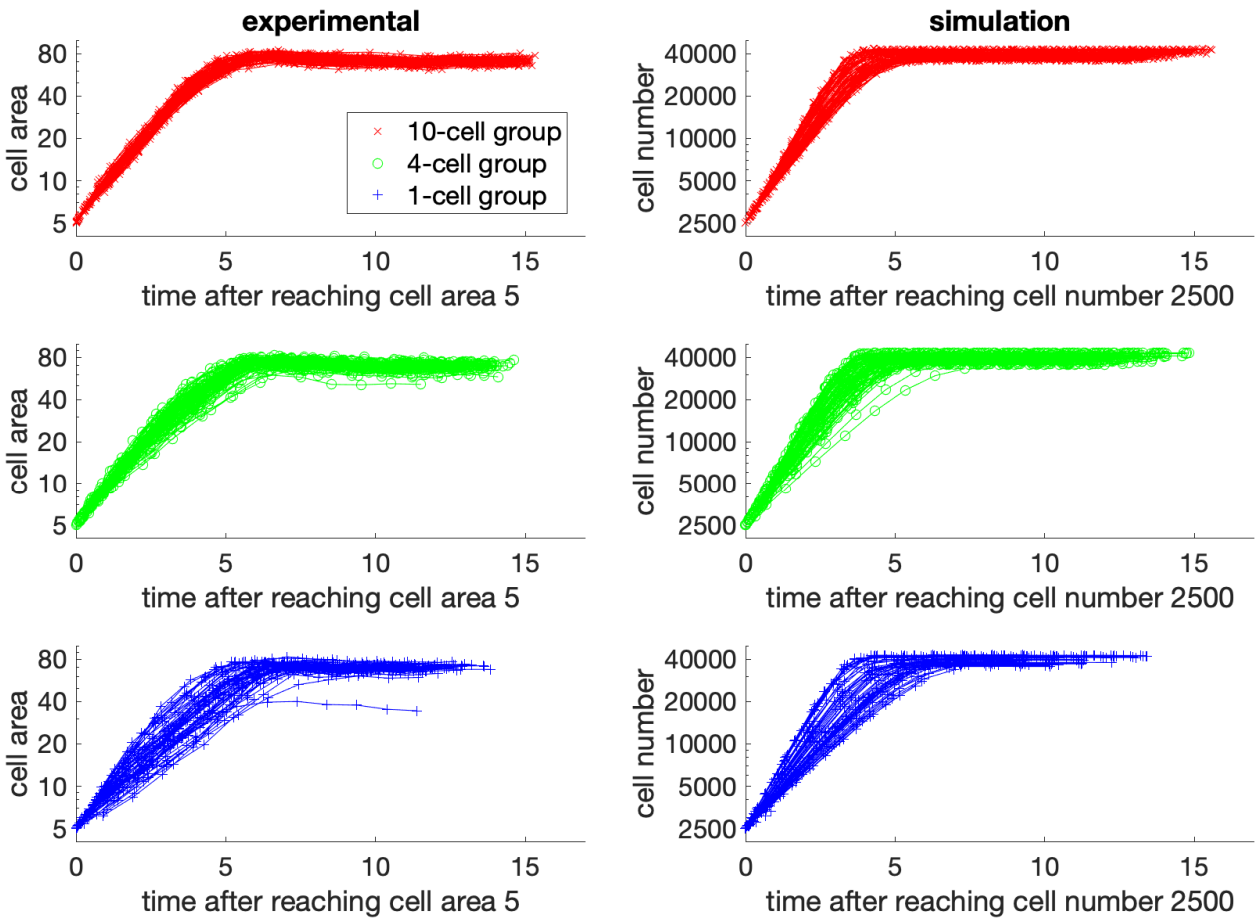


Figure: Translated population curves, starting from cell area 5 or cell number 2500. *Y*-axis is in log scale.

Model

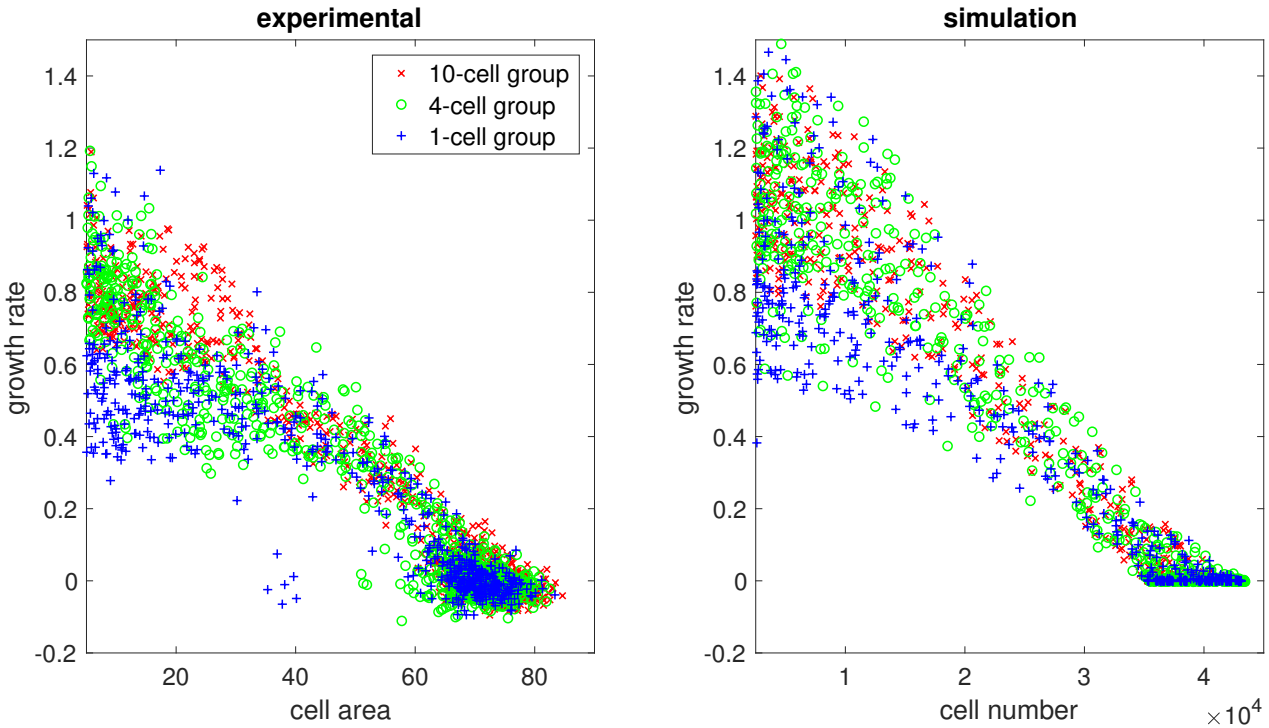


Figure: Growth rate versus population size.

Summary

- Experimental data reveal the existence of multiple states in cancer cell population.
- Corresponding model can reproduce experimental phenomena.

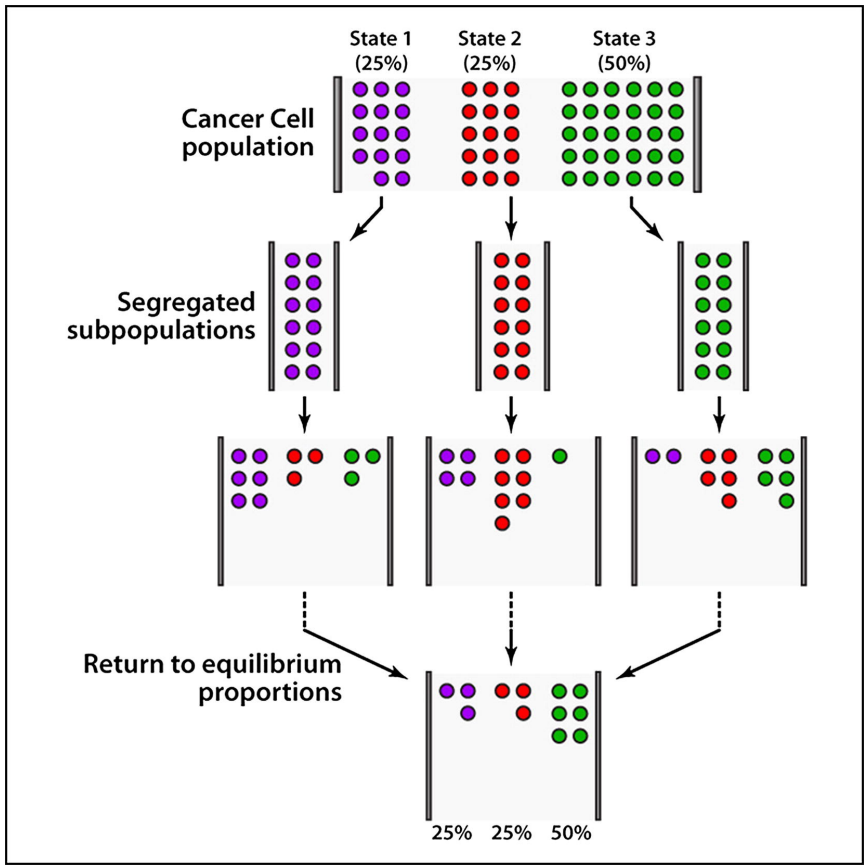
- Questions?

Multiple states

- The existence of multiple states has been verified in some other cancers.
- SUM159 breast cancer cell population has three states: stem, luminal, basal (distinguished by cell-surface markers).
- Why could multiple states (possibly with different growth rates) survive simultaneously?
- There exist epigenetic transitions between different states. Such change of state is inheritable.

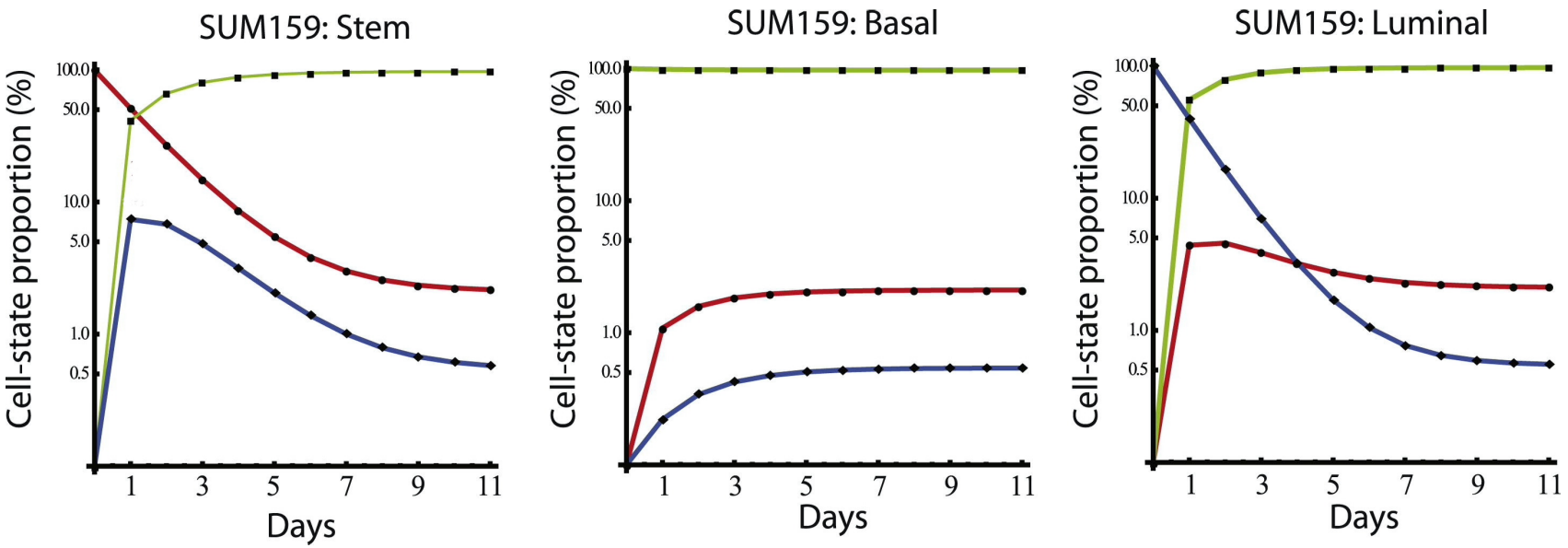
Multiple states

- Starting from any one state, other states will emerge, and the population gradually recovers the equilibrium proportions.
- It is called the “state equilibrium phenomenon”.



Experiments

How to explain such state equilibrium phenomenon?



Deterministic model

- Cells can divide, die or transform into other states. Assume cells do not interact, and there is no carrying capacity.
- The population vector $\vec{x}$ of different states satisfies a linear ODE system:

$$\mathrm{d}\vec{x}/\mathrm{d}t = \vec{x}\mathbf{A},$$

  where $\mathbf{A} = \{a_{ij}\}$, the matrix of transition rates.
- The population proportion vector $\vec{w} = \vec{x}/||\vec{x}||_1$ satisfies a quadratic system:

$$\frac{\mathrm{d}\vec{w}}{\mathrm{d}t} = \vec{w}[\mathbf{A} - (\vec{w}\vec{b}')\mathbf{I}],$$

  where $\vec{b} = \vec{1}\mathbf{A}'$.

Deterministic model

Perron-Frobenius Theorem states that **A** has a real eigenvalue λ_1, which is larger than the real parts of any other eigenvalues. Its normalized eigenvector is denoted by $\vec{u}_1$.

Theorem

If λ_1 is a simple root of the characteristic polynomial (in reality, this holds in general), the system $\mathrm{d}\vec{w}/\mathrm{d}t = \vec{w}[\boldsymbol{A} - (\vec{w}\vec{b}')\boldsymbol{I}]$ has a unique stationary fixed point $\vec{u}_1$.

Therefore the proportion vector $\vec{w}$ always converges to $\vec{u}_1$.

Stochastic model

- We can describe this population with a branching process.
- One cell of state i, Y_i, can branch into a (stochastic) combination of cells with different states: $Y_i \xrightarrow{\alpha_i} d_{i1} Y_1 + d_{i2} Y_2 + \cdots + d_{in} Y_n$. The waiting time is exponential with rate α_i.
- Here d_{ij} are random variables. For example,
  $d_{11} = 2$, $d_{12} = 0$ means division $Y_1 \to 2Y_1$;
  $d_{11} = d_{12} = 0$ means death $Y_1 \to \emptyset$;
  $d_{11} = 0$, $d_{12} = 1$ means transition $Y_1 \to Y_2$.
- If we take expectations for population, the branching process model returns to the ODE model.

Stochastic model

- Due to stochasticity, it is possible that all cells die out, and the proportions cannot be defined.
- We focus on the stochastic trajectories that no state dies out forever (called "non-extinction").
- If $\lambda_1 > 0$, as the initial cell number increases, the probability of non-extinction tends to 1.

Theorem

Assume that $\lambda_1 > 0$ and λ_1 is a simple root of the characteristic polynomial. Conditioned on non-extinction, the proportion vector $\vec{w}$ converges to $\vec{u}_1$ with probability 1.

- This is a strong law of large numbers for branching processes. It improves a result by Svante Janson in 2004.
- It provides a stochastic explanation for the state equilibrium phenomenon.

Summary

- We have explained the state equilibrium phenomenon in ODE model and branching process model.
- Questions?

References

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