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Dynamical Crossover of Clone Size Statistics in a Stochastic Model of Stem Cell Differentiation

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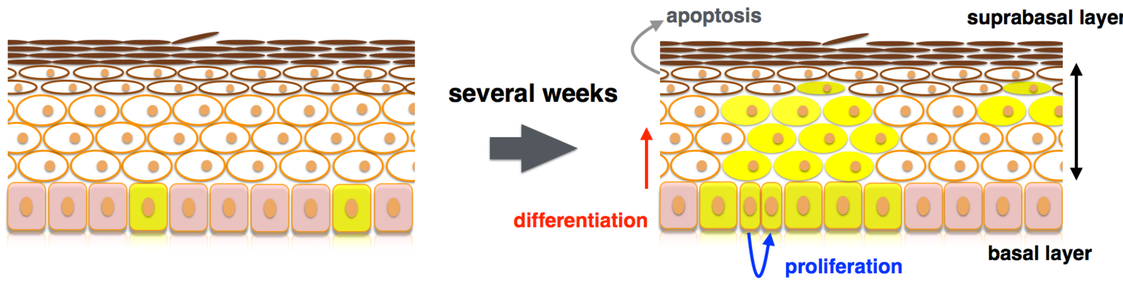
Critical Statistics of Clonal Population

Stem Cells (SCs) support tissue homeostasis



in vivo Lineage Tracing

Tracking the labeled population of progenies of single SCs
to unravel how cells choose their fate and maintain tissue

Clone Size Statistics

Universal scaling form of cumulative distribution

$$C_n(t) \simeq \Phi(n/n_{\rm surv}(t))$$

collapse onto a single scaling function $\Phi(X)$

Average clone size grows!! $n_{\rm surv}(t) \sim t^{\alpha}$

A.M.Klein and B. D. Simons, Development **138**, (2011).

Previous Models of Cell Fate Decision

Critical Birth-Death Process (CBD)

prob. 1/2
prob. 1/2

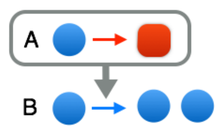
Proliferating Cell (PC)
Differentiated Cell

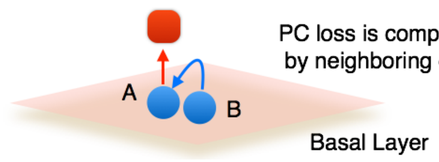
with **finely-tuned** probabilities

$\alpha = 1 \quad \Phi(X) = e^{-X}$

exp.: epithelial (sheet) tissues

Voter Model (VM)





PC loss is compensated by neighboring cells

$(d = 1)$
$\alpha = 1/2 \quad \Phi(X) = e^{-\pi X^2/4}$

exp.: intestinal crypts (ring) & seminiferous tubules

$(d \geq 2)$
$\alpha = 1 \quad \Phi(X) = e^{-X}$

exp.: epithelial (sheet) tissues

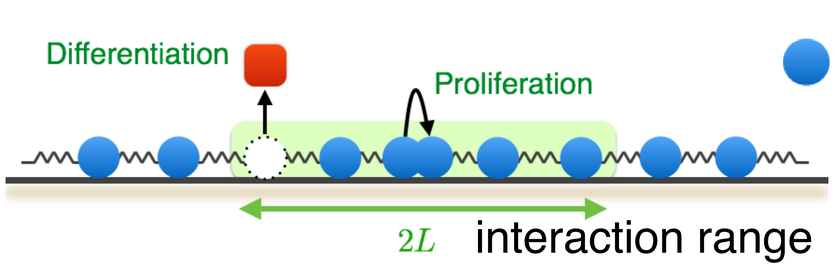
Problems & Research Questions

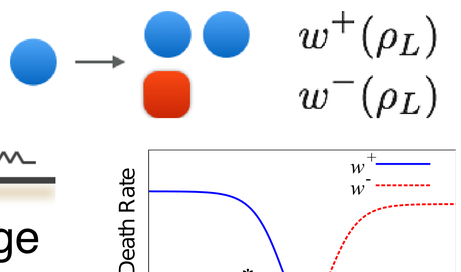
✓ Fine-tuning is required in the previous models.
→ A theoretical model without fine-tunings is desirable.

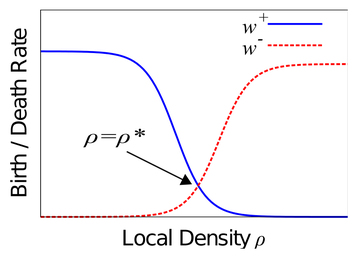
✓ CBD and VM are not discussed in the equal foot point.
→ Can we treat the two models in a unified framework?

Self-replicating Langevin System: Many-Body Langevin + Birth-Death Process

Self-replication Process : Local Density Dependent







Negative feedback via local density $\rho_L(\vec{r})$

$w^{\pm}(\rho)$ are **balanced** at an **attractive fixed point** $\rho = \rho^*$

Spatial cell-cell Interaction : Cell Adhesion

$$\frac{d}{dt}\vec{r}_j(t) = -\vec{\nabla}_j U\left(\{\vec{r}_i(t)\}\right) + \sqrt{2T}\vec{\xi}_j(t) \qquad j = 1, 2, ..., N(t)$$

$$U(\{\vec{r}_i\}) = \sum_{j=1}^{N}\sum_{k>j} u(\vec{r}_j - \vec{r}_k)$$

$$\langle \xi_j^{\mu}(t) \rangle = 0$$
$$\langle \xi_j^{\mu}(t)\xi_k^{\nu}(t') \rangle = \delta_{j,k}\delta^{\mu,\nu}\delta(t-t')$$

$d = 1$

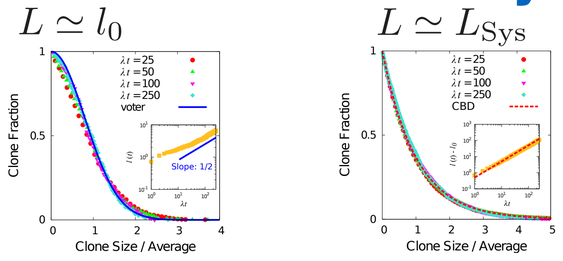
$$u(\vec{x} - \vec{y}) = \frac{1}{2}K(|\vec{x} - \vec{y}| - l_0)^2$$

for $\vec{x}, \vec{y}$: neighboring pairs

l_0 : typical length scale of a single cell

Main Results: Dynamical Crossover

$L \simeq l_0$ $\qquad$ $L \simeq L_{\rm Sys}$



interaction range L

$L \simeq l_0$ small **VM** $e^{-\pi x^2/4}$

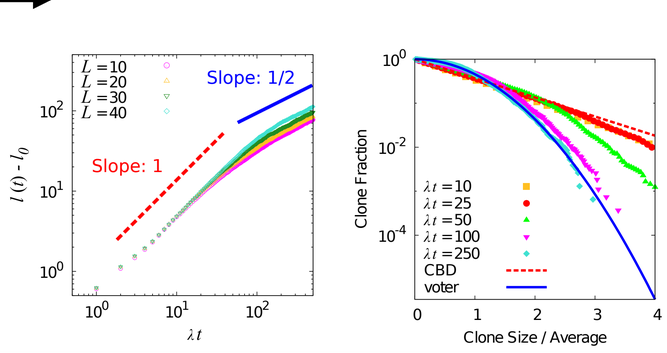
$L \simeq L_{\rm Sys}$ large **CBD** e^{-x}

unified by the interaction range!

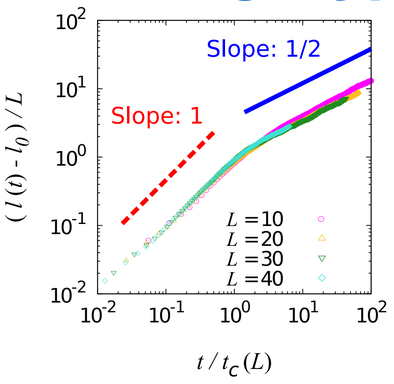
Dynamical Crossover

short time: CBD statistics

long time: VM statistics



Scaling Hypothesis



Scaling form

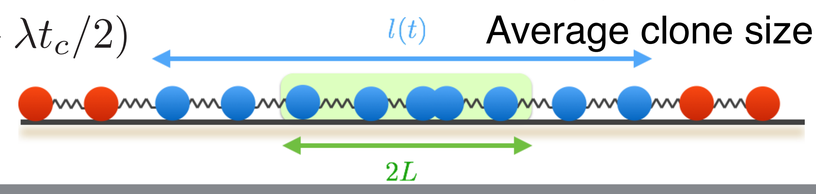
$$\frac{l(t)-1}{L} = f\left(\frac{t}{t_c(L)}\right) \begin{cases} \simeq \frac{t}{t_c(L)} & t \ll t_c(L), \\ \sim \left(\frac{t}{t_c(L)}\right)^{1/2} & t \gg t_c(L). \end{cases}$$

Crossover Time $t_c(L) = 2\lambda^{-1}(L-1)$

A simple scenario: competition between $l(t)$ and L

$L = l(t) \simeq (1 + \lambda t_c/2)$

with $l_0 = 1$



Remark: Clustering of Cells

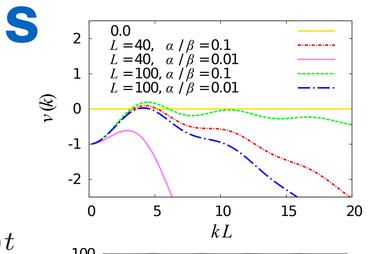
Large interaction range

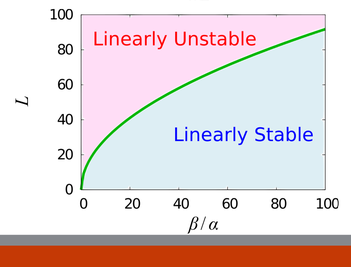
➡ Unphysical clustering of cells

Linear Stability Analysis $\rho(k;t) \sim e^{\nu(k)t}$

Uniform distribution is unstable if $\frac{\beta}{\alpha L^2} \lesssim 0.012$

$$\frac{\beta}{\alpha L^2} \sim \frac{K}{\lambda L^2} = \frac{\text{time scale of cell division}}{\text{time scale of spatial interaction}}$$





Summary of Current Study

In this study, we propose
a model of cell fate decision with cell-cell interaction

✓ Fine-tuning is avoided
✓ CBD and VM are unified by the interaction range
: A unified framework to study interacting cell population
✓ Dynamical crossover of clone size statistics for 1 dim