Statistical mechanics of stem cells

SIDHARTHA GOYAL
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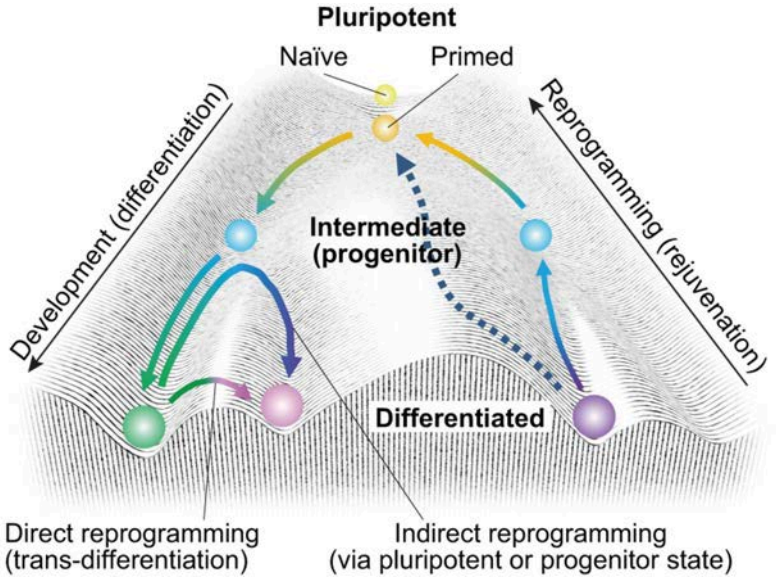

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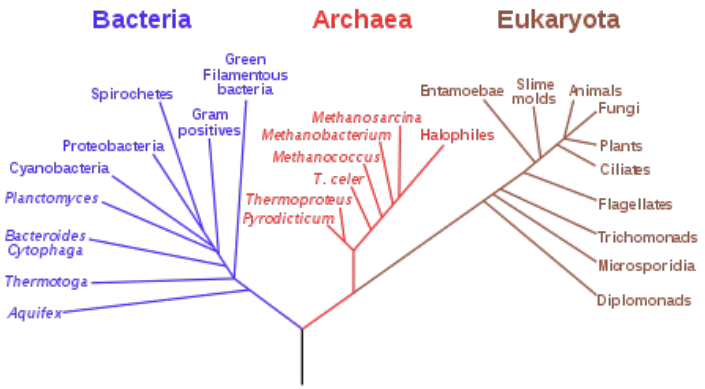
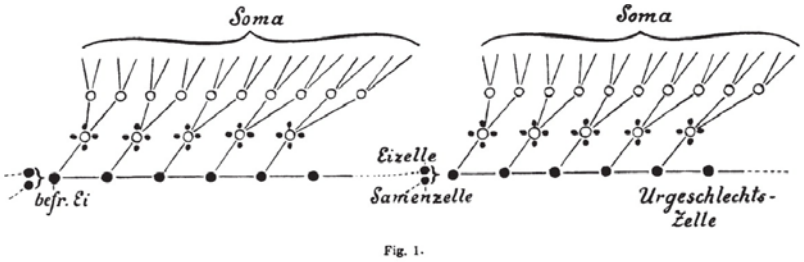
MEDICINE by DESIGN

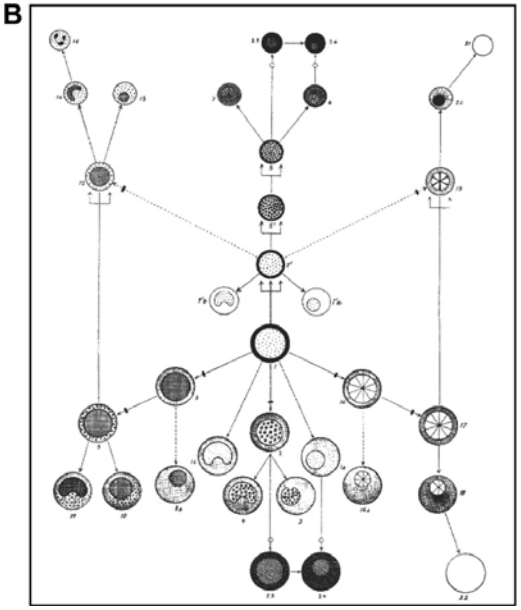
Origin of stem cells



Unicellular ancestor

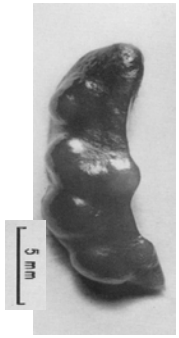


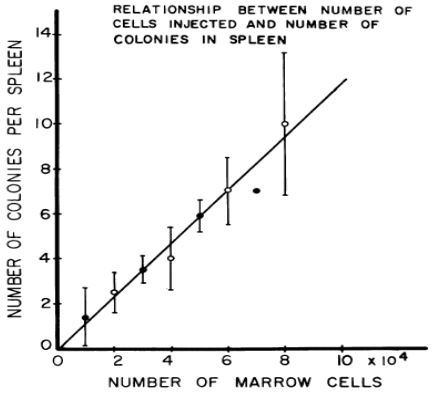
Fertilized egg (1870's)



Progenitor of blood cells (1905)

Precursor of tumors (1920's)

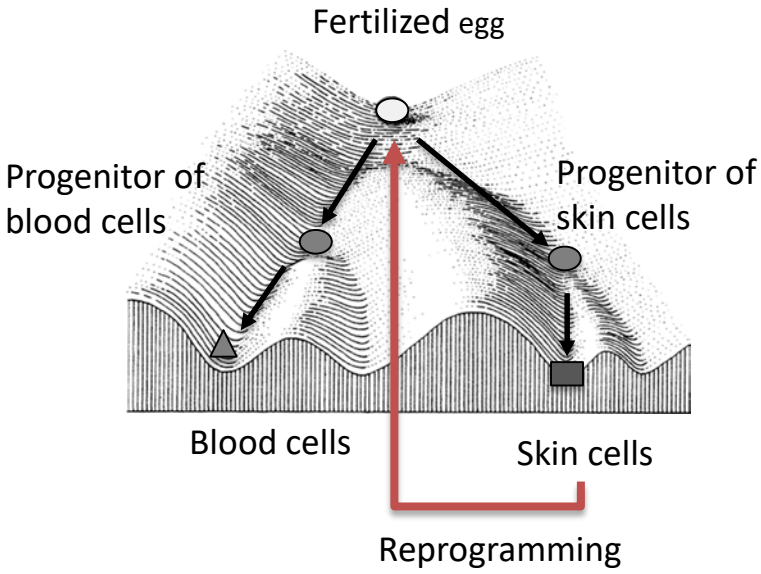




- Self-renew
- Generate other types of cells

Radiation Research, 1961
Till and McCulloch at University of Toronto

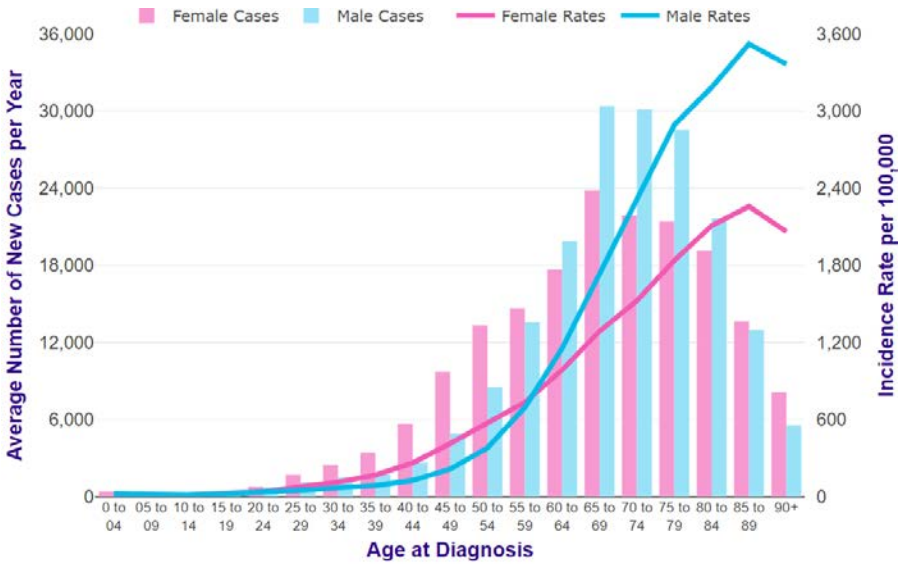
Evolution of stem cells



Non-genetic (epigenetic) inheritance (1930-40)

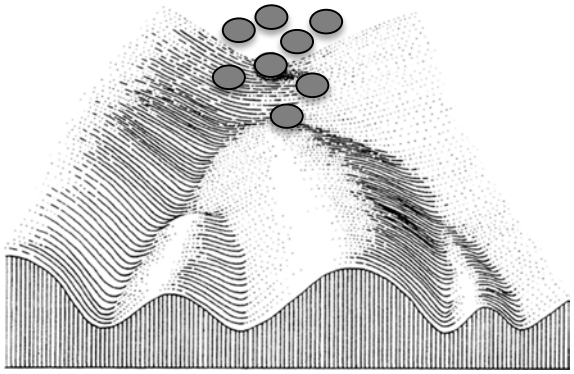
Robustness and response to environment

Genetic changes in stem cells



Population of stem cells

Stems cells



Does epigenetic variability affect stem cell evolution?

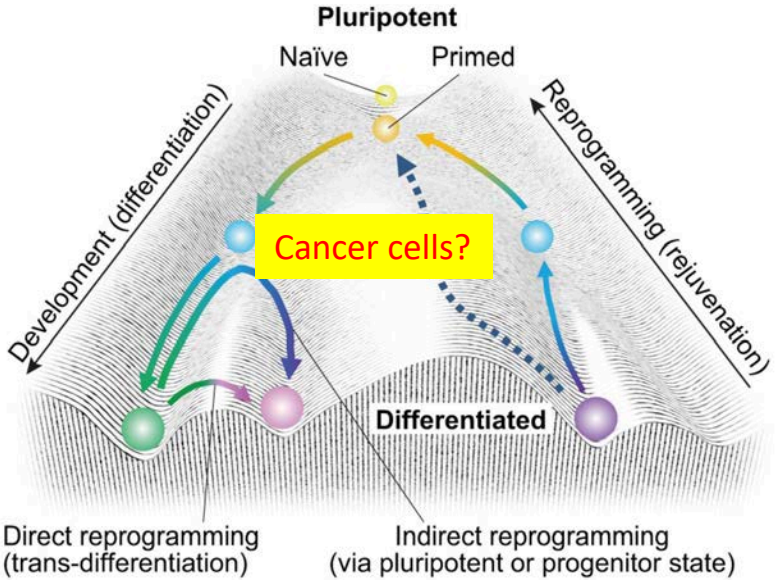
How does stem cell function evolve and diversify?

Can we predict stem cell fate, for example which stem cell may lead to a tumor?

Outline

Blood regeneration: homeostasis and clonality
Tom Chou
Sanggu Kim
UCLA

BMC Biology, 2015



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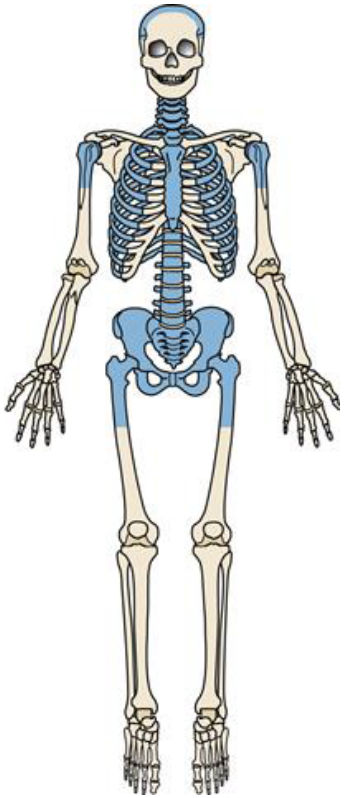
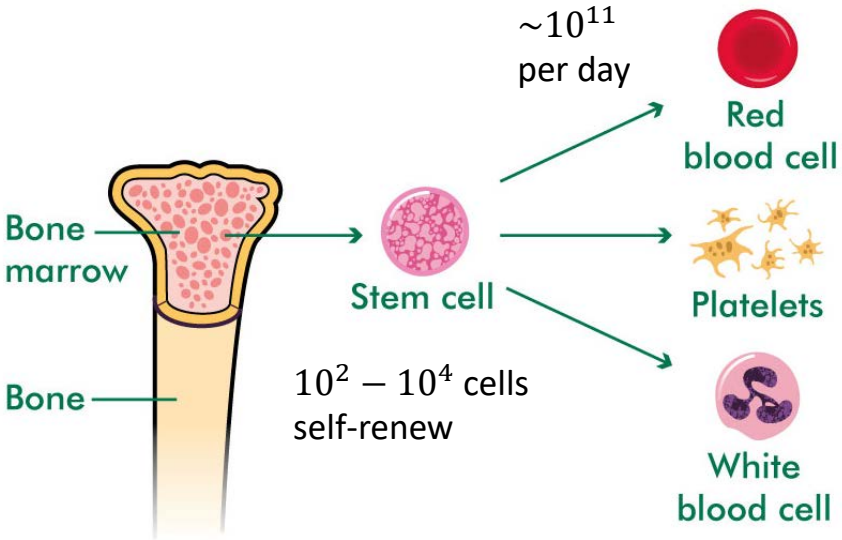
Blood production





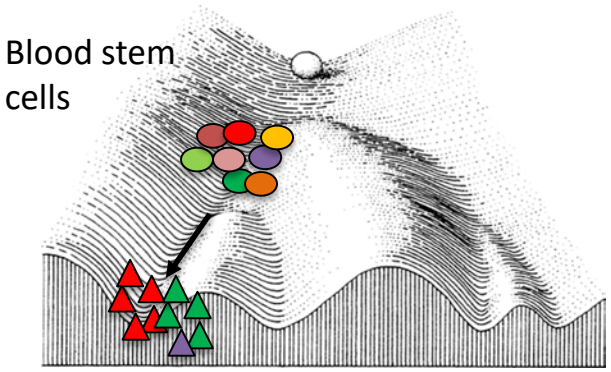
$\sim 10^{13}$ cells
don't replicate

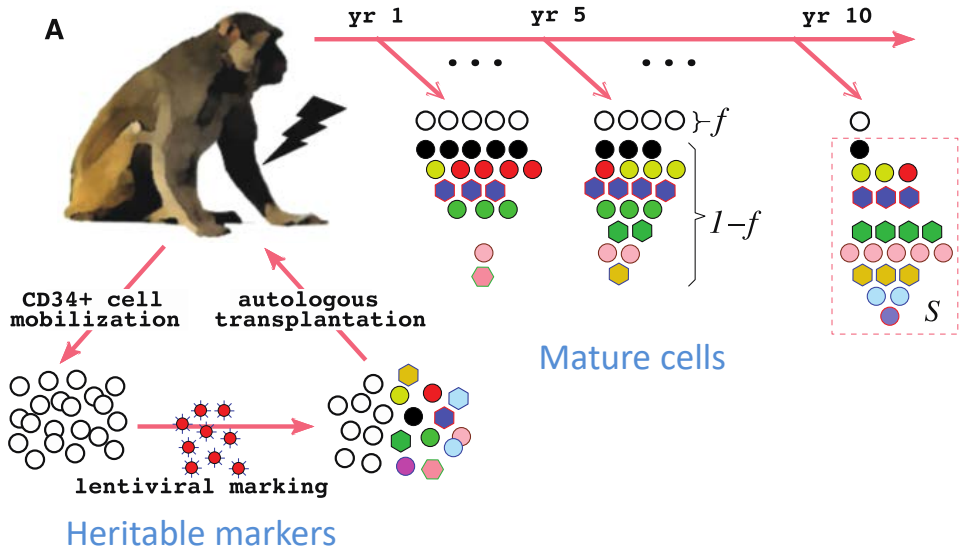
How many stem cells are producing blood?

Are some stem cells better than others?

Are stem cells biased in their output?

Tracking clonal output

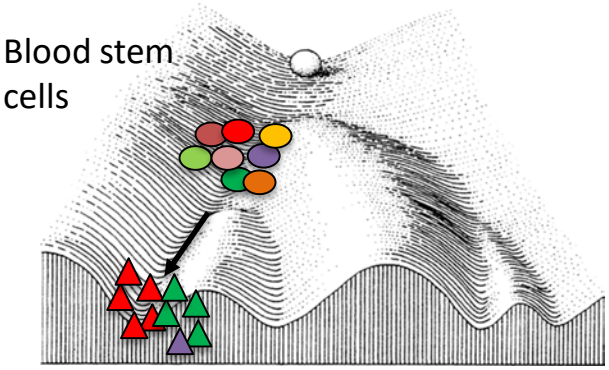


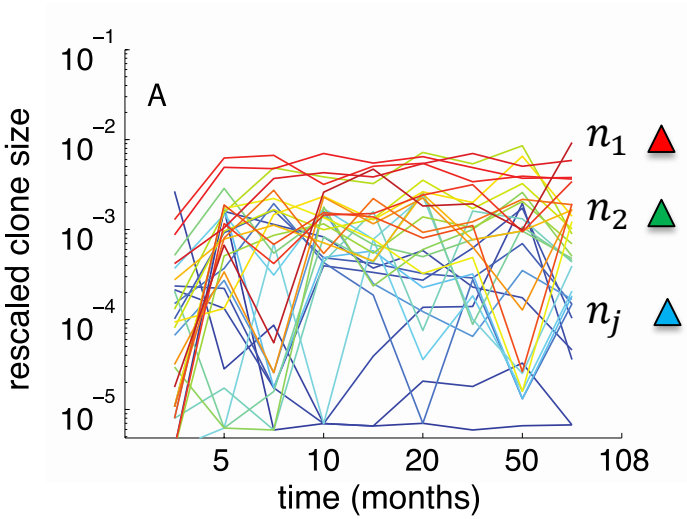


What are the features of long-term, animal-level blood production?

Phenomenology: data -> model -> predictions?

Tracking clonal output

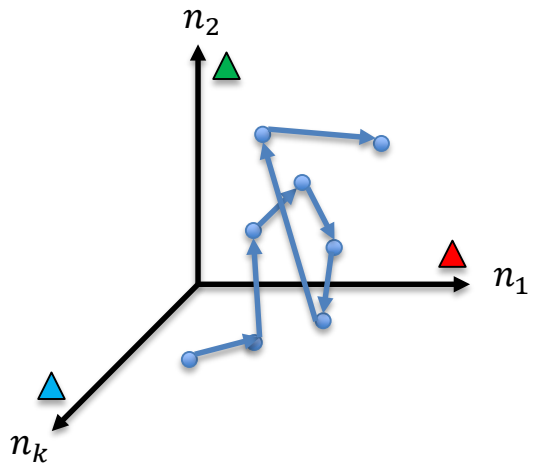




Large variability in stem cell output

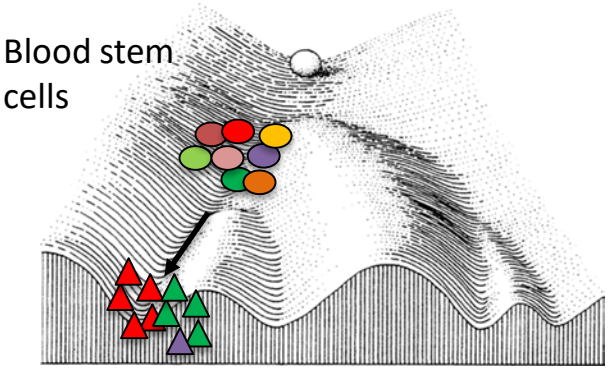
So, are some stem cells better than the others?

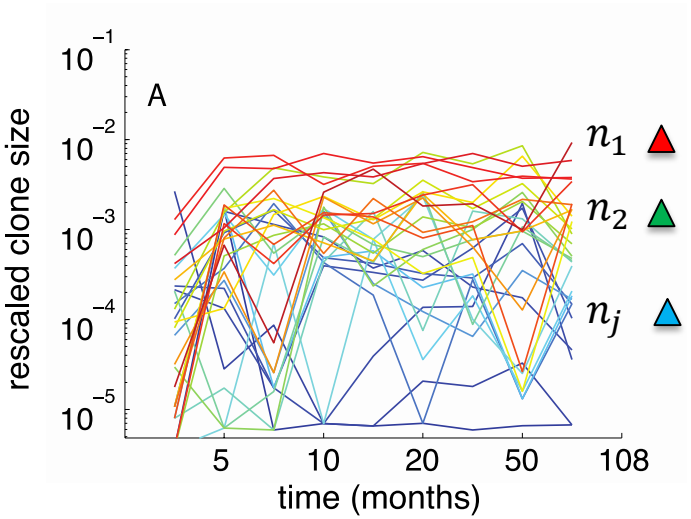
Need some “theory” or a model to compare against



Flow in high dimensions

Tracking clonal output



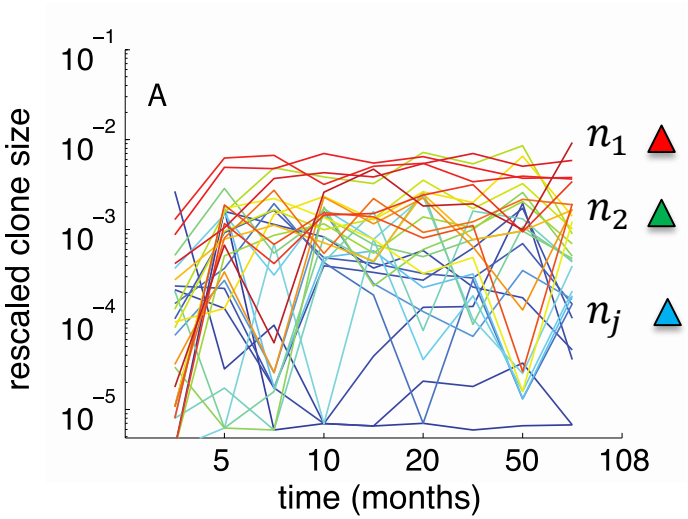


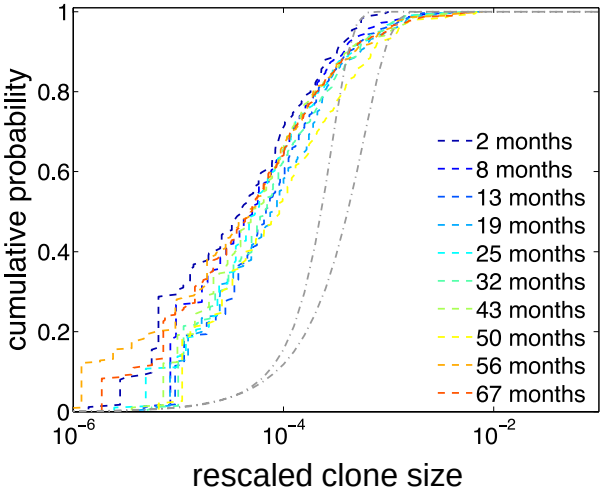
$$p(\{n_1(t), n_2(t), n_3(t), \ldots, n_j(t), \ldots\})$$

Under sampled distribution

Look for something *simpler*

Density of “states”





$$p(\{n_1(t), n_2(t), n_3(t), \ldots, n_j(t), \ldots\})$$

Under sampled distribution

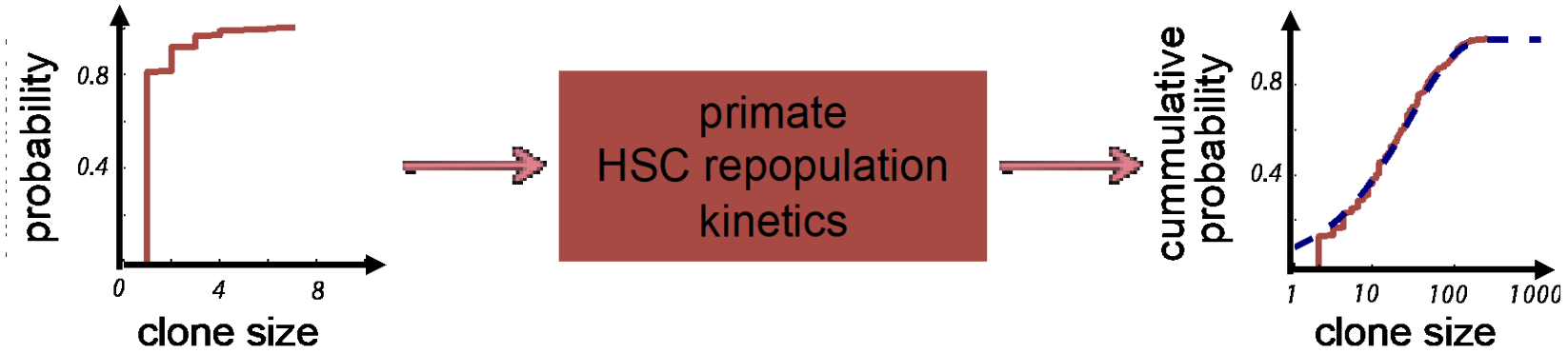
Look for something *simpler*

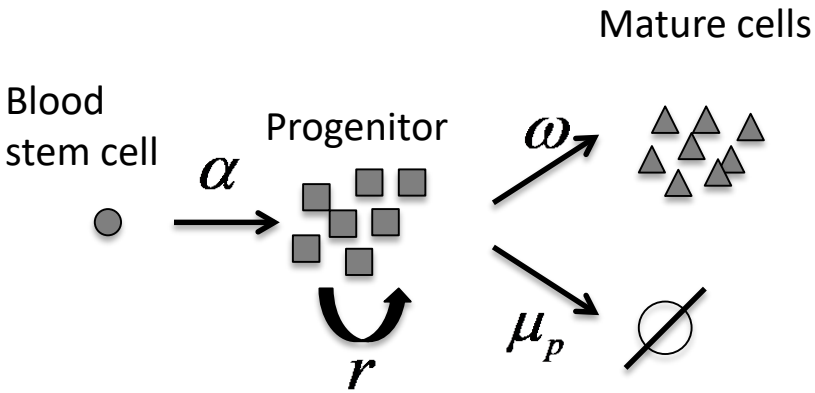
$$p(s,t) = \left\langle \sum_j \delta(n_k(t) - s) \right\rangle$$

Density of states

Time-invariant distribution
(conserved quantity)

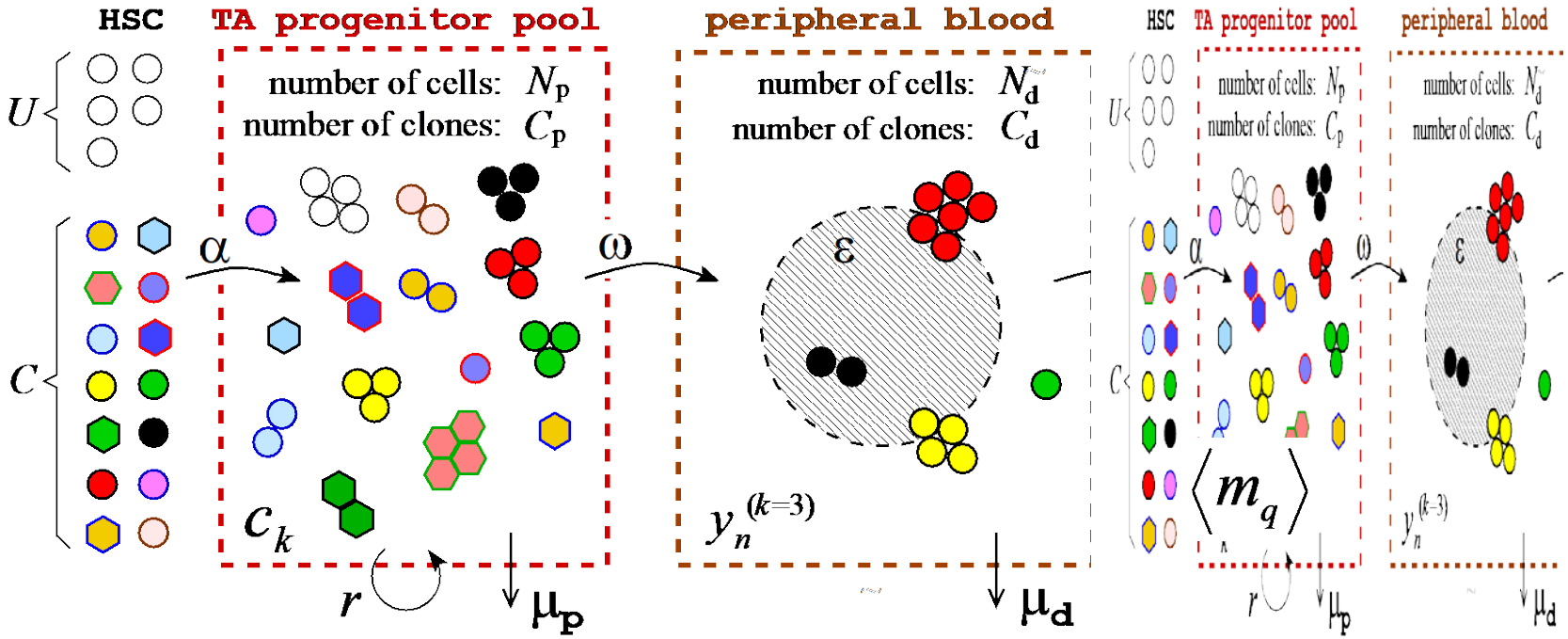
Reframing the problem





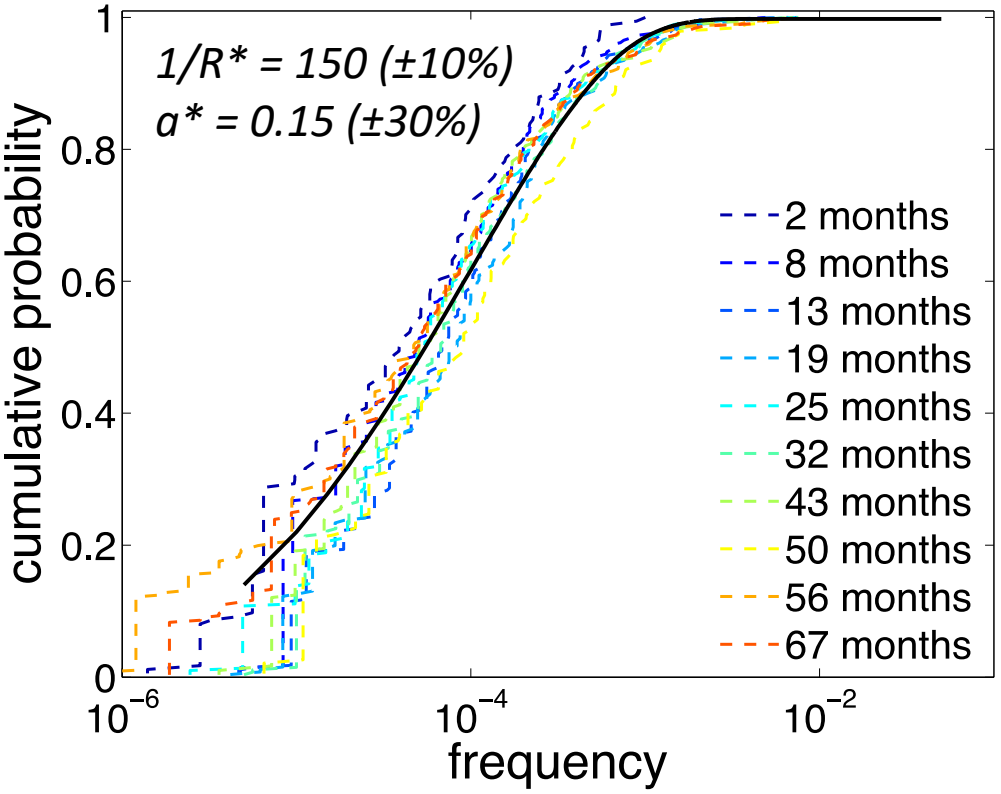
Global feedback on
progenitor growth

Model for tracking clones

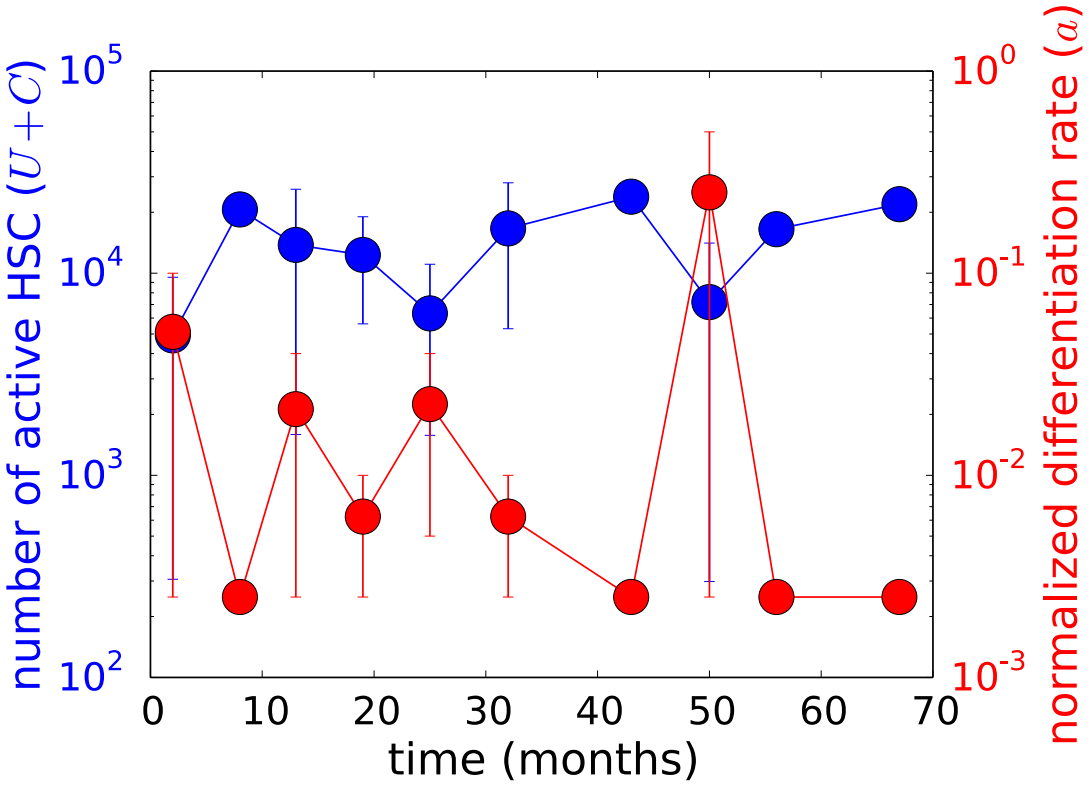


“Neutral” theory explains the data

$$m_{q>0} \approx A\left[\Gamma(a,(q+1)R)-\Gamma(a,qR)\right];\ R=-\frac{\varepsilon w}{\log \bar{r}},\ a=\frac{\alpha}{r}$$



Coming back to biology of blood regeneration

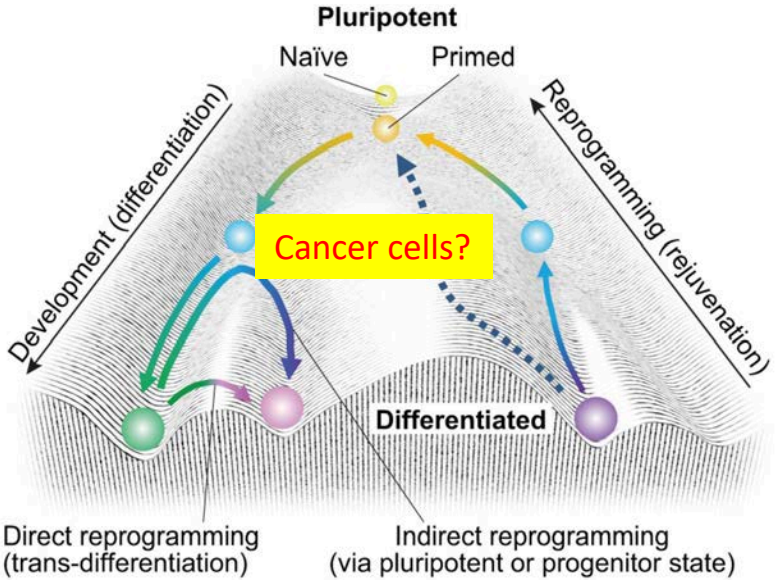


Number of active stem cells at any time is of the order 10K

Differentiation rate << progenitor replication rate

Blood regeneration: homeostasis and clonality
Tom Chou
Sanggu Kim
UCLA

BMC Biology, 2015



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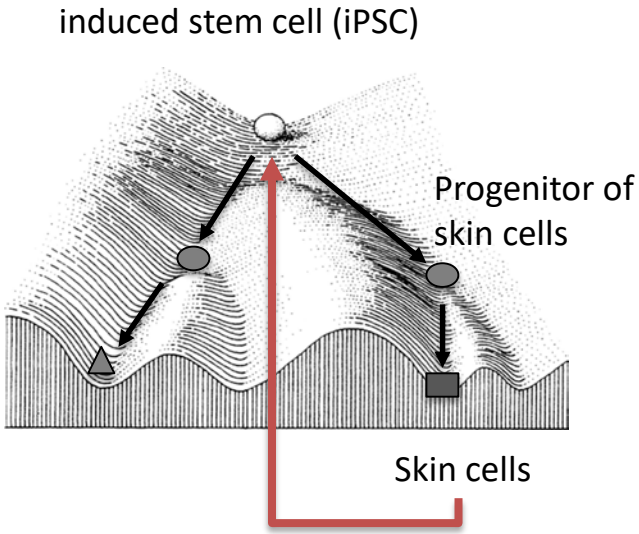
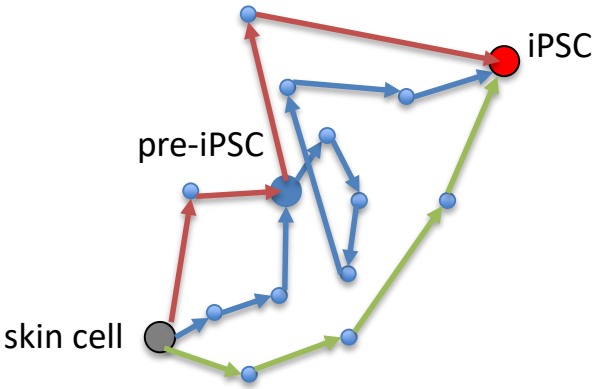
Cellular reprogramming



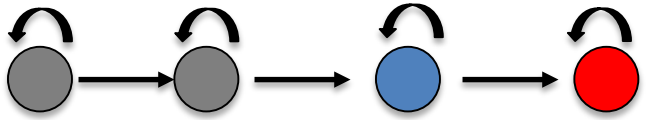


Gene expression space (high dimensional)

reprogramming landscape vs undirected search

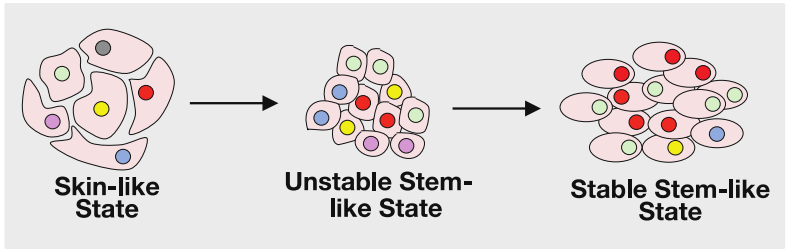
individual cells vs group of cells

four state model



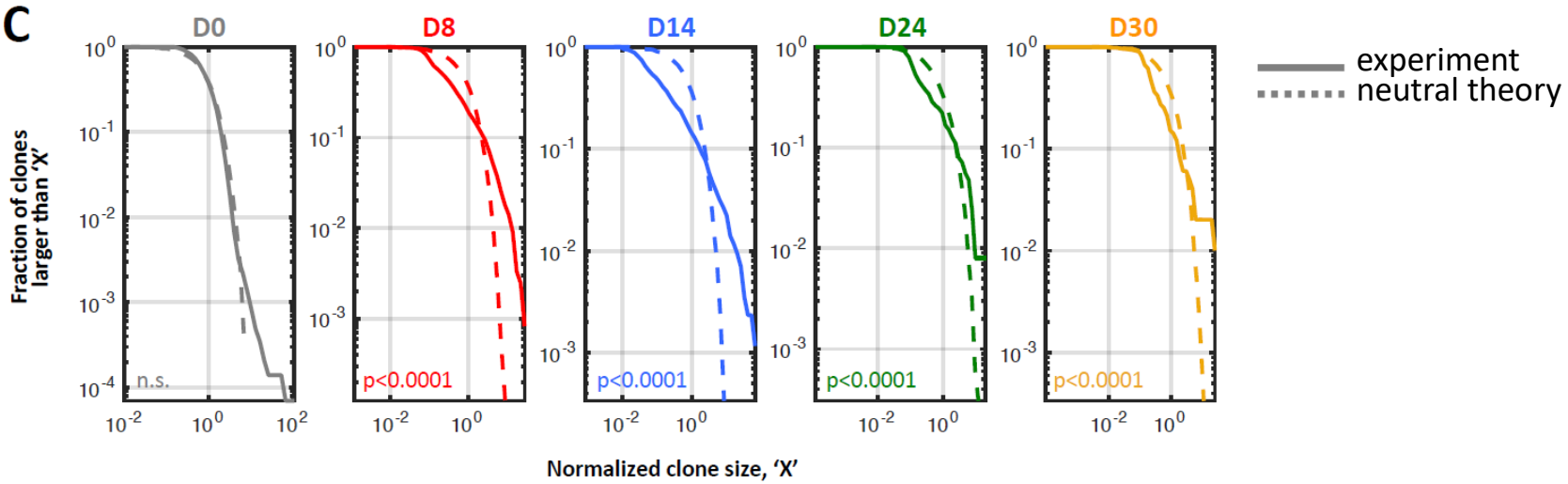
skin cell (MEF) pre-iPSC iPSC

Tracking reprogramming potential

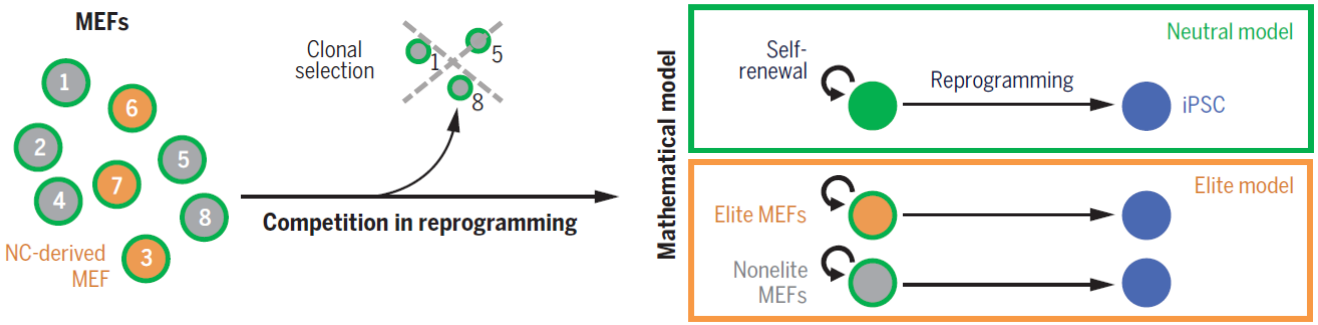


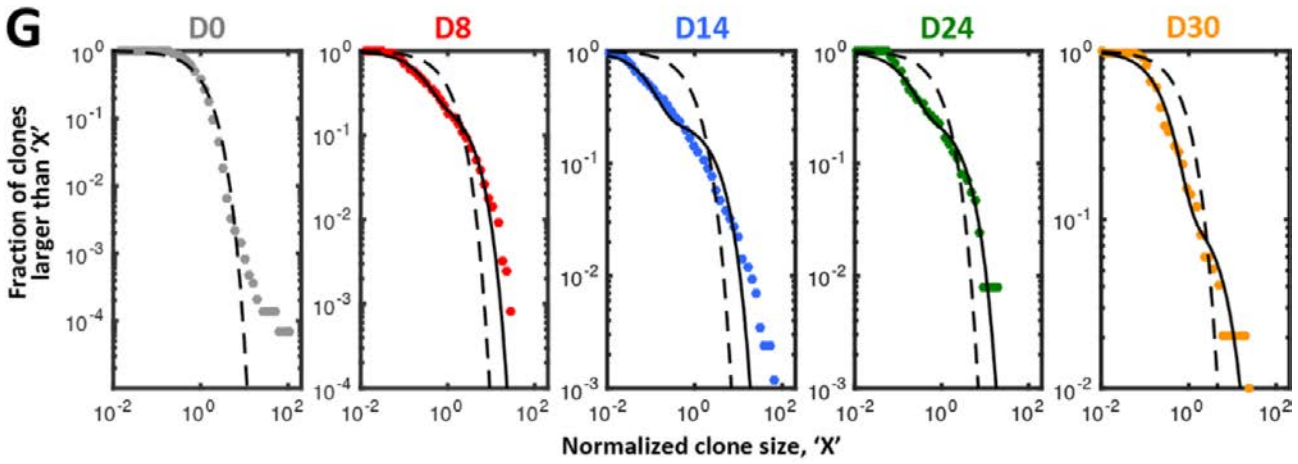
skin cell (MEF) pre-iPSC iPSC

D0 D8 D14 D24 D30

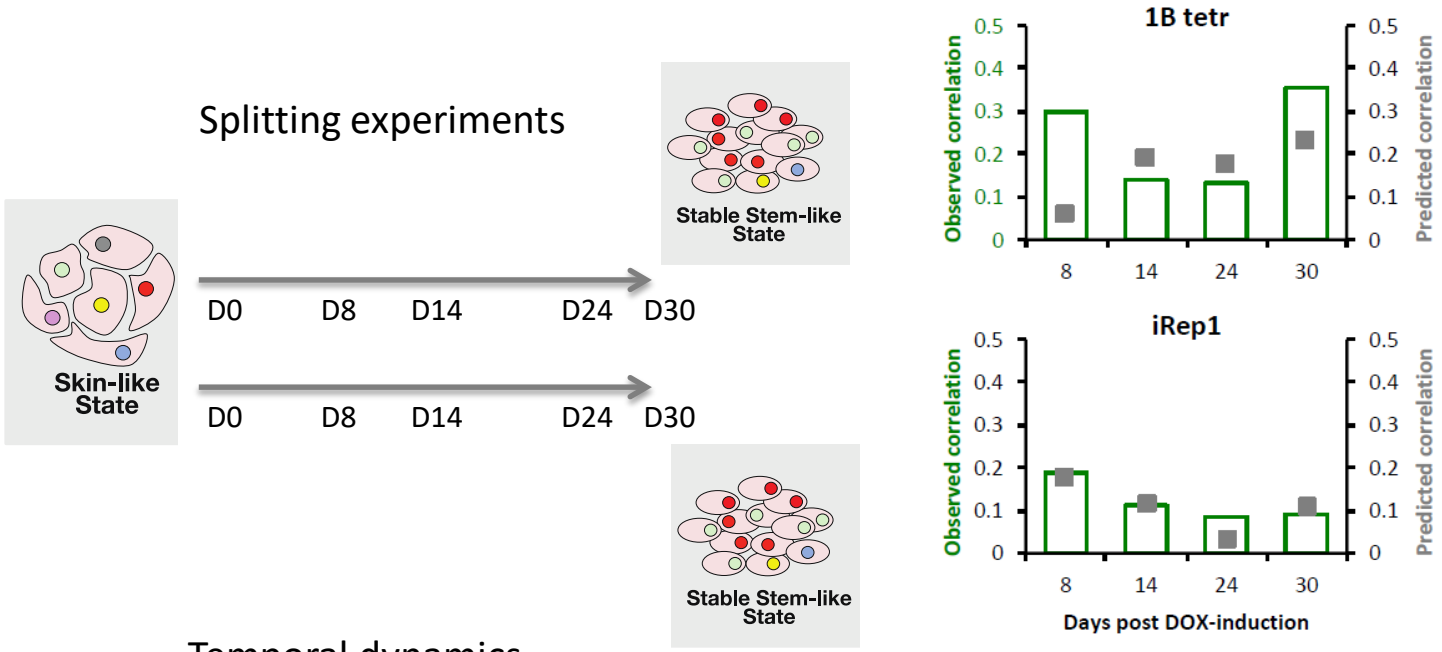


Competition model

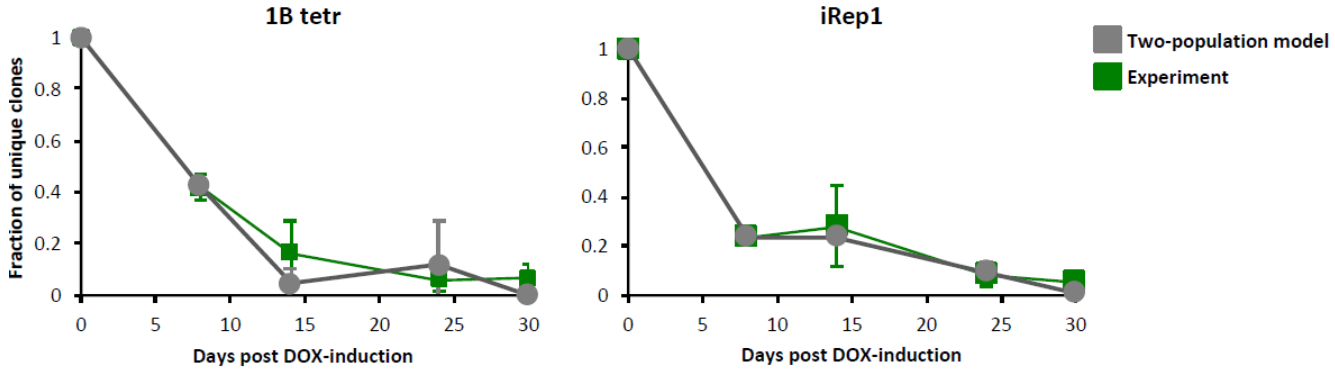




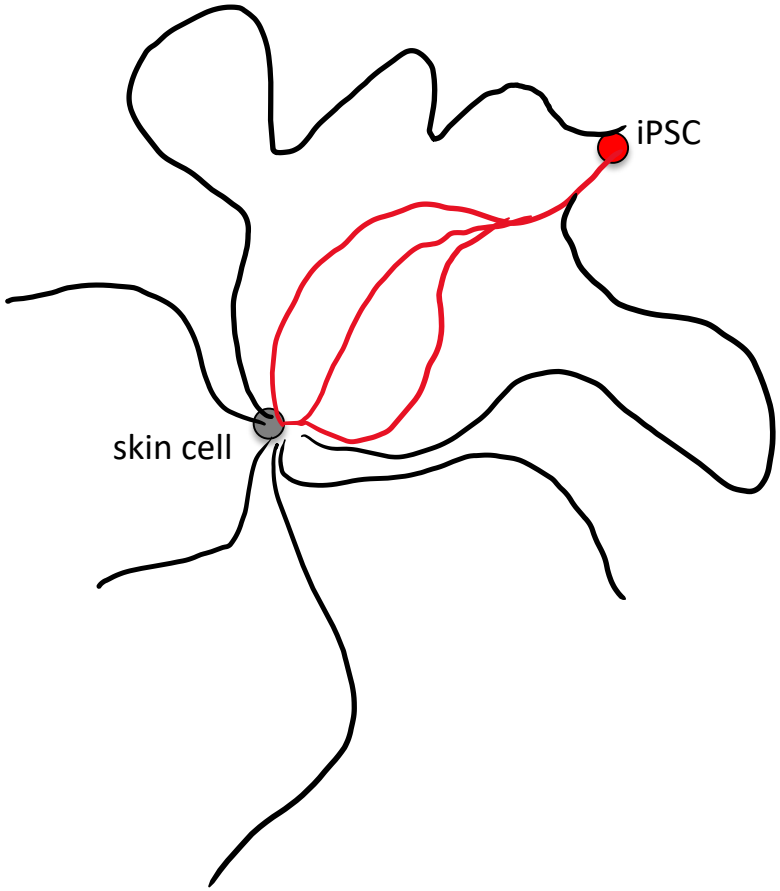
Testing the model



Temporal dynamics



Outlook: Track trajectories of reprogramming cells in gene expression space



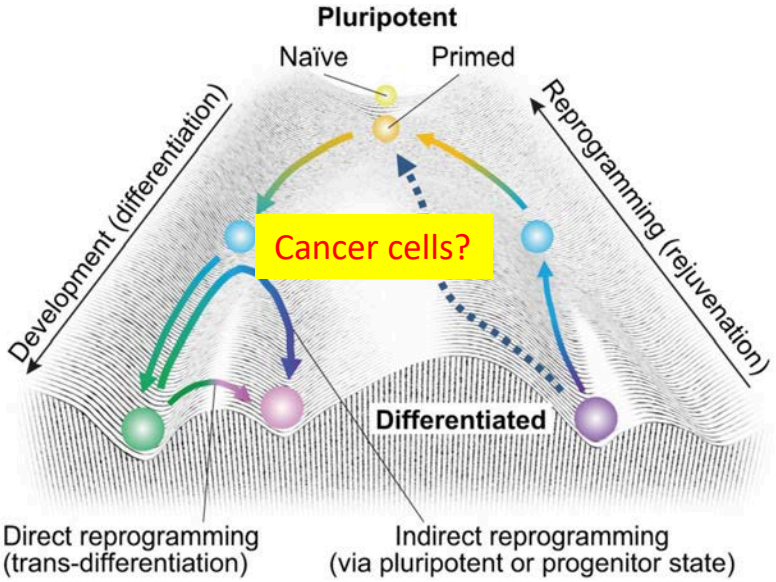
How do elite and non-elite trajectories differ?

Is their a reprogramming landscape that elite cells utilize?

Are non-elite cells solving a “search” problem

Blood regeneration: homeostasis and clonality
Tom Chou
Sanggu Kim
UCLA

BMC Biology, 2015



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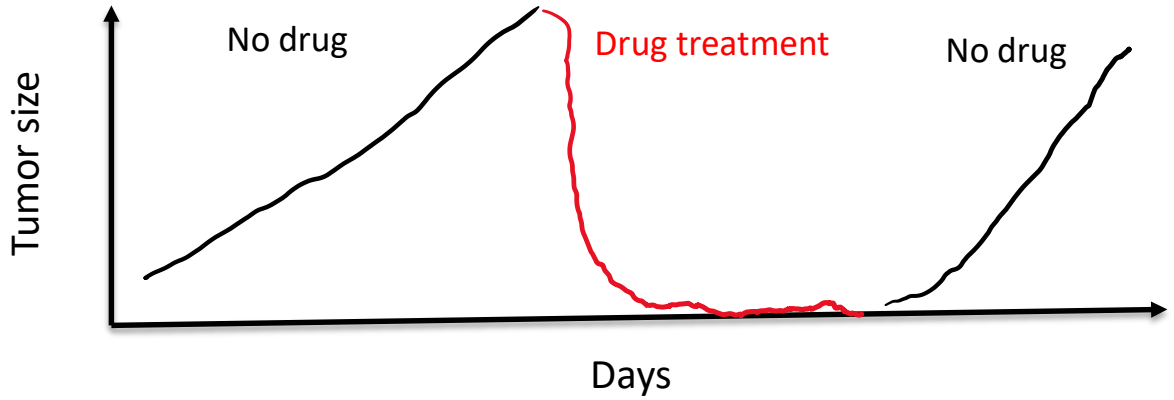
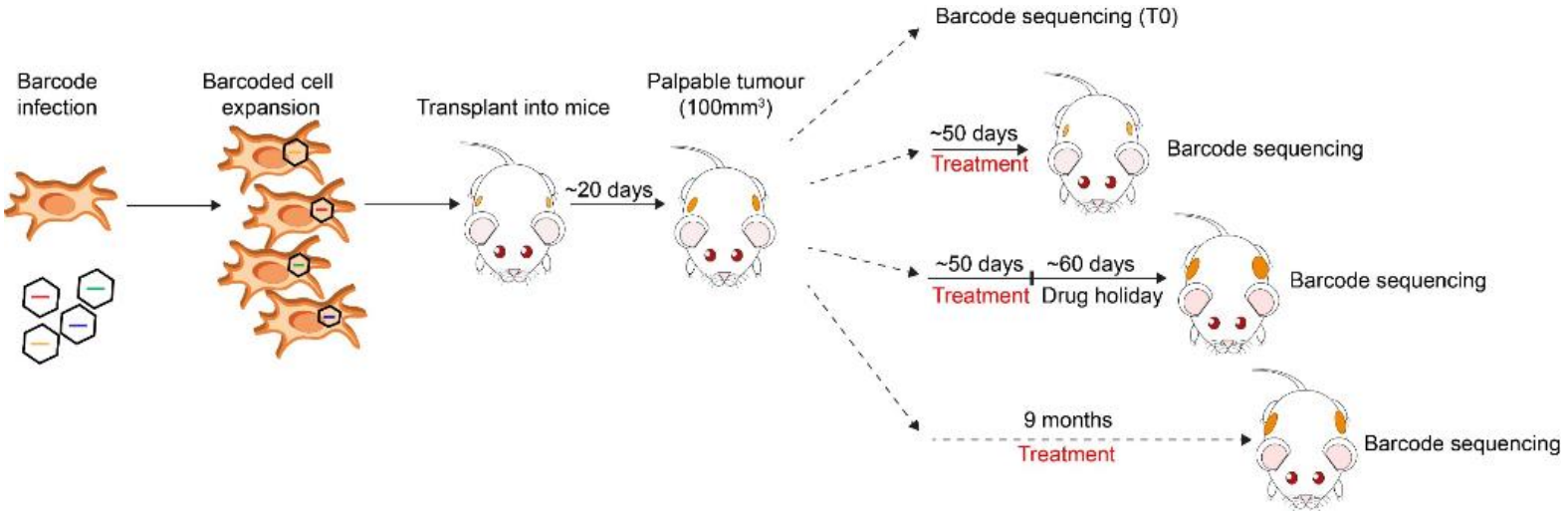
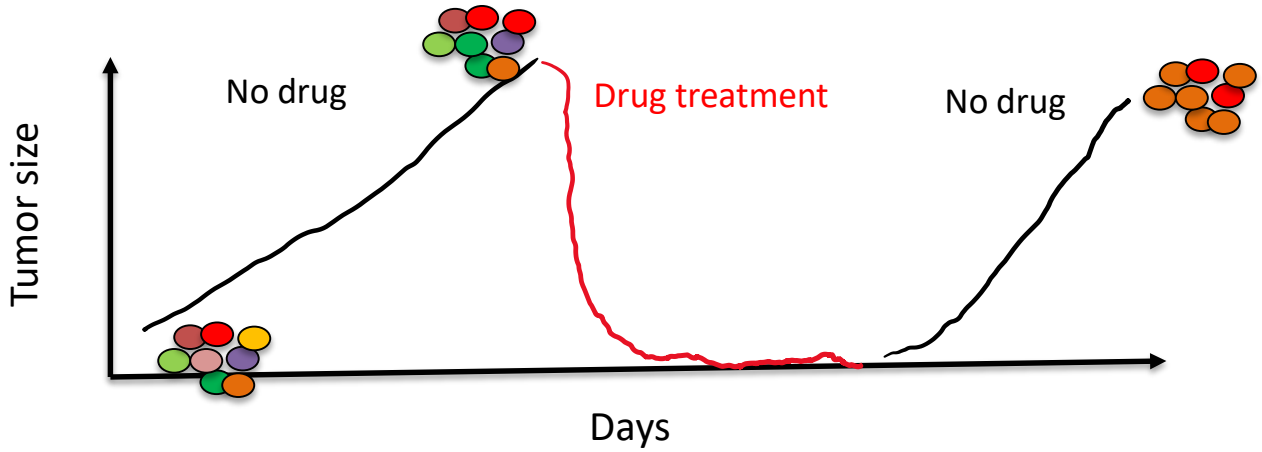
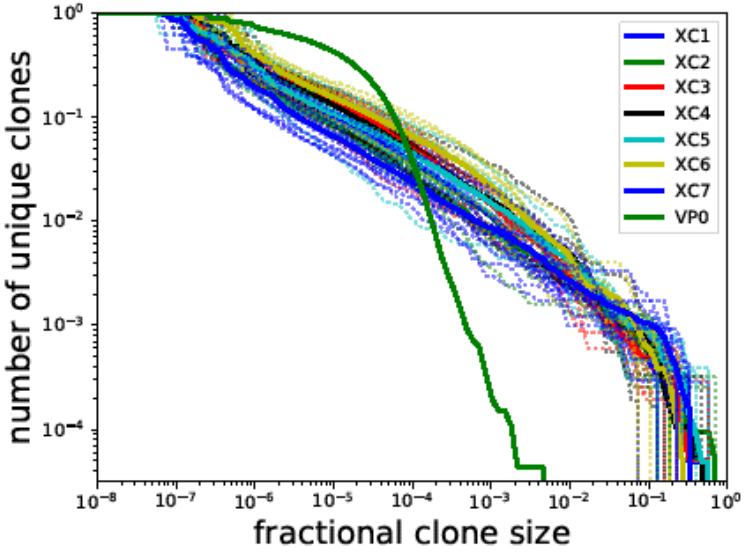
Complexity of tumors





Hint of equipotency in cancer





How do all clones survive drugs?

Epigenetic rather than genetic mechanisms?

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