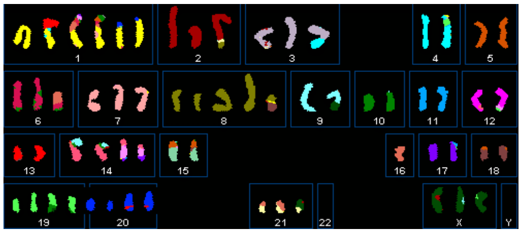
Mathematical Models of Cancer

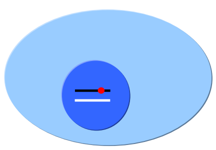


Franziska Michor
Harvard University

People

Martin Nowak (Princeton)
Yoh Iwasa (Kyushu)
Natalia Komarova (Princeton)
Steven Frank (Irvine)
Christoph Lengauer (Johns Hopkins)
Bert Vogelstein (Johns Hopkins)

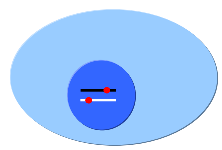
Oncogenes



one copy of the gene gets mutated in a specific way

→ **the cell has an increased reproductive rate**

Tumor suppressor genes

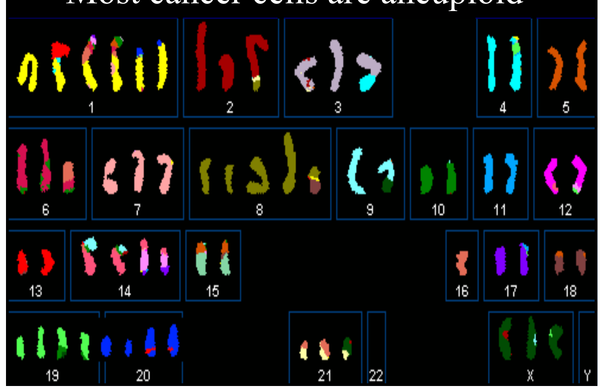


both copies of the gene must be inactivated

→ **the cell has an increased reproductive rate**

Normal cells are diploid

Most cancer cells are aneuploid



Genetic instability genes

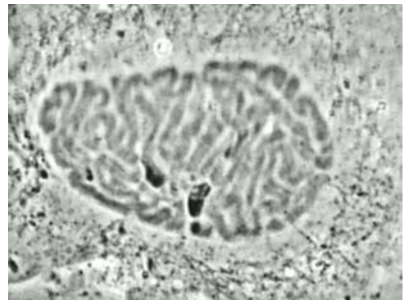
produce proteins that maintain the genomic material of a cell. If such genes are mutated, then the rate of accumulating further mutations can increase.

Chromosomal instability (CIN)

Increased rate of losing (arms of) chromosomes.

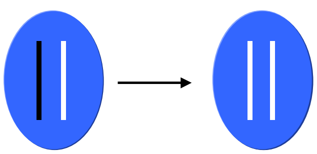
Mitosis

in the African blood lily Haemanthus katherinae



Loss of heterozygosity, LOH

Loss of the maternal or paternal copy of a gene.



Colon cancer

normal — adenoma — cancer — metastasis

→ time

APC RAS p53

Colon cancer

normal — adenoma — cancer — metastasis

→ time

APC RAS p53

↔ somewhere: CIN

Colon cancer

normal — adenoma — cancer — metastasis

→ time

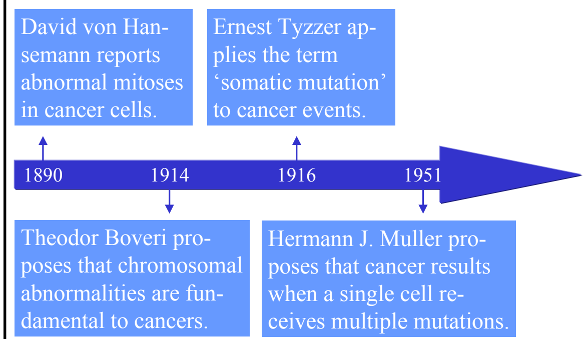
↑ APC RAS p53

Does CIN occur before APC ?

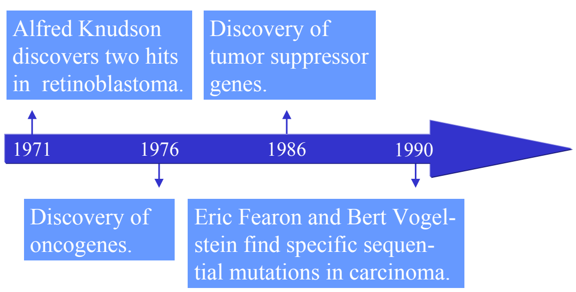
The biggest question

- Is genetic instability necessary for the somatic evolution of most cancers?
- Is genetic instability an early event, a driving force of cancer progression?

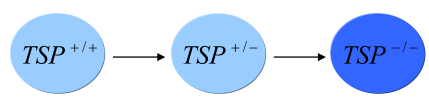
Mutation and Cancer



Mutation and Cancer

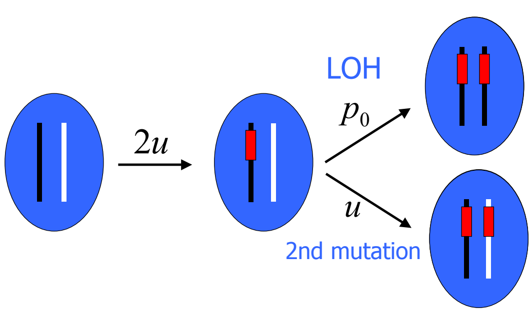


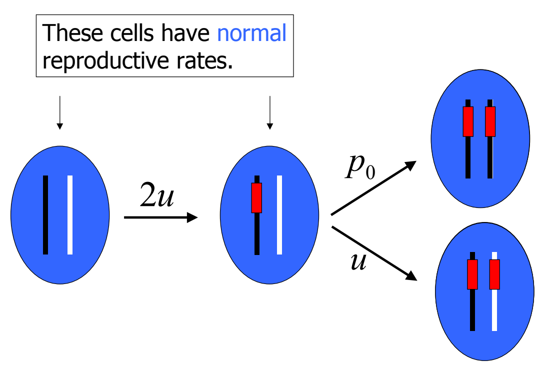
Knudson’s two hit hypothesis

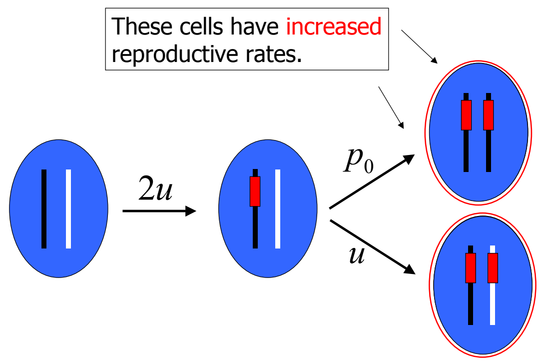


Tumor suppressor genes are inactivated by 2 hits

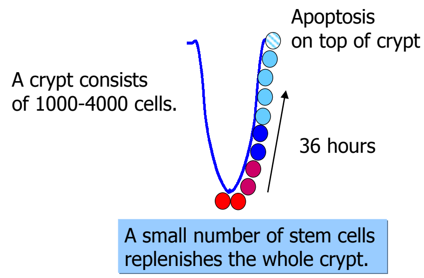
A tumor suppressor gene







Colon cancer arises in a crypt



The colon contains 10^7 crypts.

Colon cancer arises in a crypt

The effective population size of a single crypt is small.

$N \approx 1-100$

A stochastic description is necessary.

Approximation of homogeneous crypts

At any one time, all cells in a crypt have either 0, 1 or 2 inactivated copies of APC.

This is a good approximation, if $u << 1/N$.

$u \approx 10^{-7}$

$N \approx 10$

Rate of evolution

$TSP^{+/+} \xrightarrow{2u} TSP^{+/-} \xrightarrow{N\rho(u+p_0)} TSP^{-/-}$

u...mutation rate

p_0...rate of LOH

N...compartment size

ρ...probability of fixation

$TSP^{+/+} \xrightarrow{2u} TSP^{+/-} \xrightarrow{N(u+p_0)} TSP^{-/-}$

$\dot{X}_0 = -2uX_0$

$\dot{X}_1 = 2uX_0 - N(u+p_0)X_1$

$\dot{X}_2 = N(u+p_0)X_1$

Kolmogorov forward equation

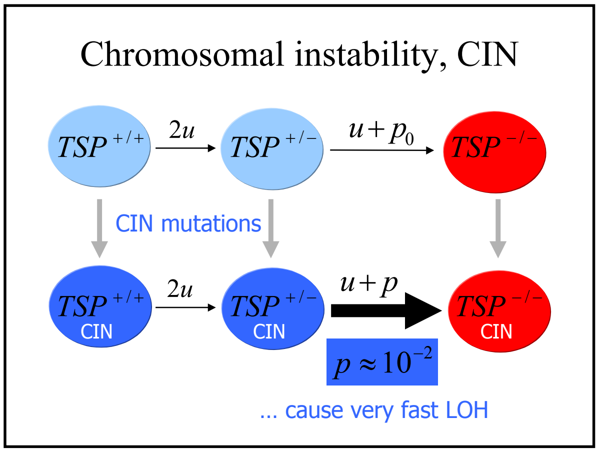
If $ut << 1$:

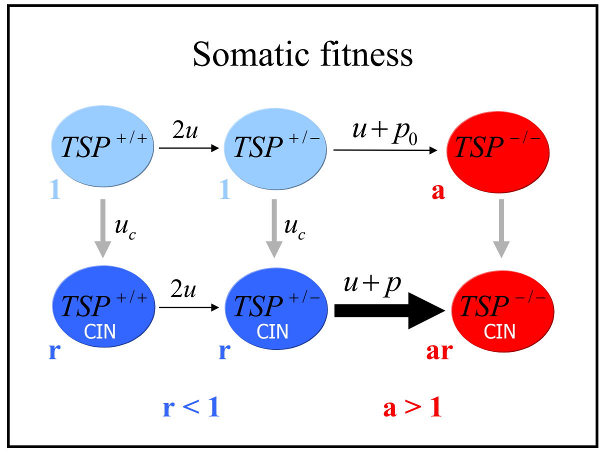
$X_0(t) \approx 1$

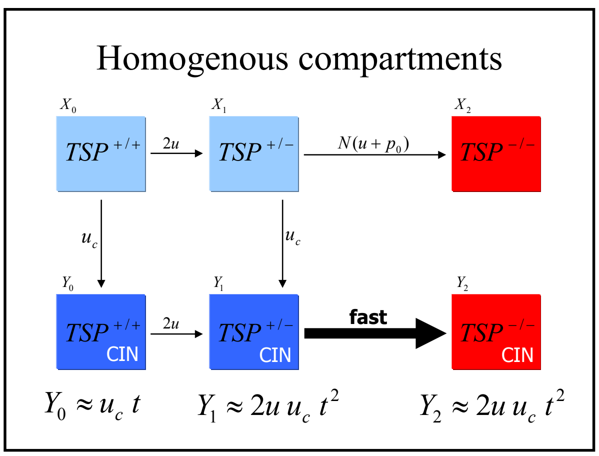
$X_1(t) \approx 2u\,t$

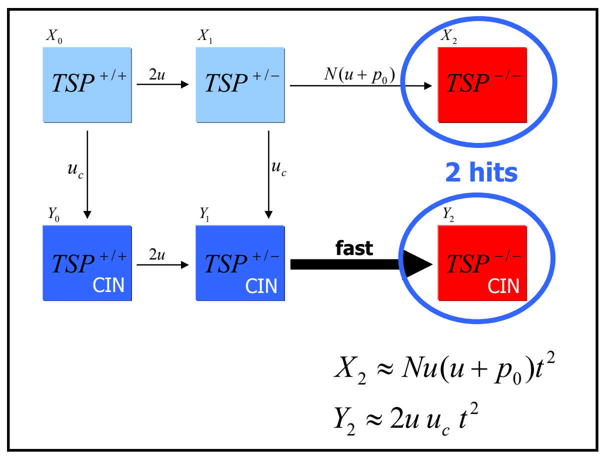
$X_2(t) \approx Nu(u+p_0)\ t^2$

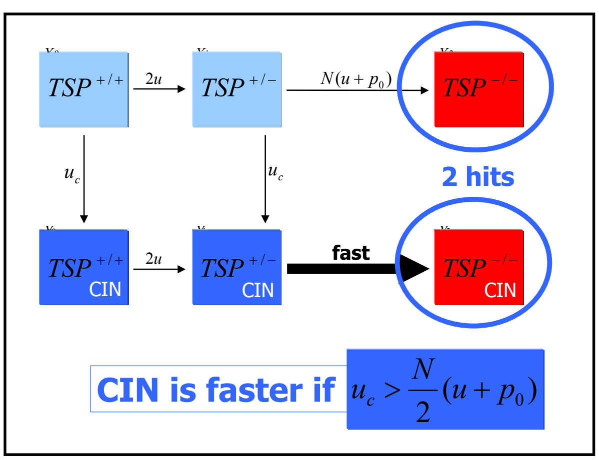
2 hits ... t^2

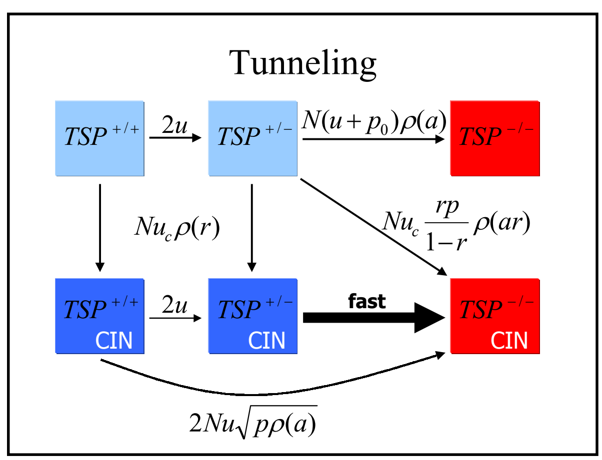

Chromosomal instability, CIN
TSP +/+
2u
TSP +/−
u + p0
TSP −/−
CIN mutations
TSP +/+ CIN
2u
TSP +/− CIN
u + p
TSP −/− CIN
p ≈ 10^−2
… cause very fast LOH

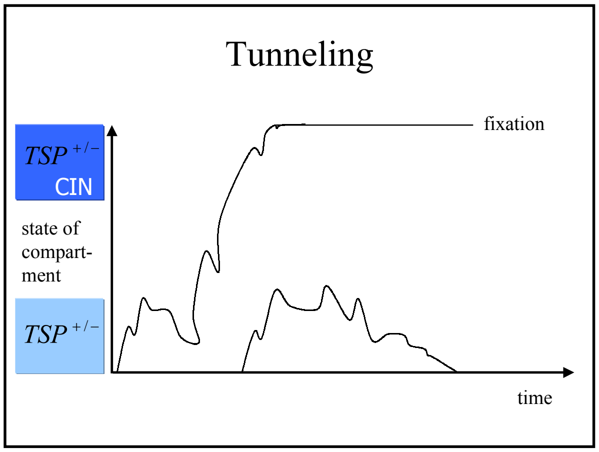

Somatic fitness
TSP +/+
2u
TSP +/−
u + p0
TSP −/−
1
1
a
uc
uc
TSP +/+ CIN
2u
TSP +/− CIN
u + p
TSP −/− CIN
r
r
ar
r < 1
a > 1

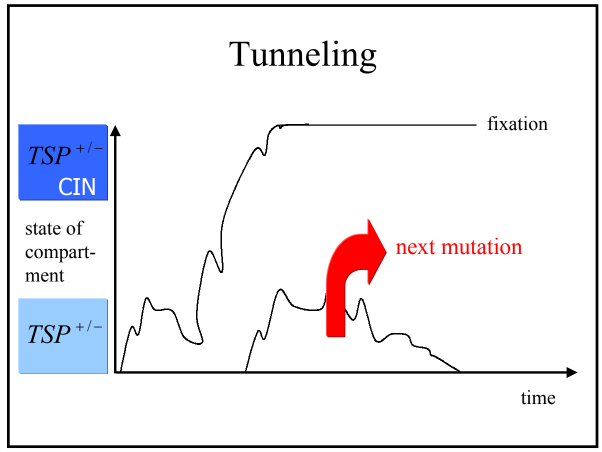

Homogenous compartments
X0
X1
X2
TSP +/+
2u
TSP +/−
N(u + p0)
TSP −/−
uc
uc
Y0
Y1
Y2
TSP +/+ CIN
2u
TSP +/− CIN
fast
TSP −/− CIN
Y0 ≈ uc t
Y1 ≈ 2u uc t^2
Y2 ≈ 2u uc t^2

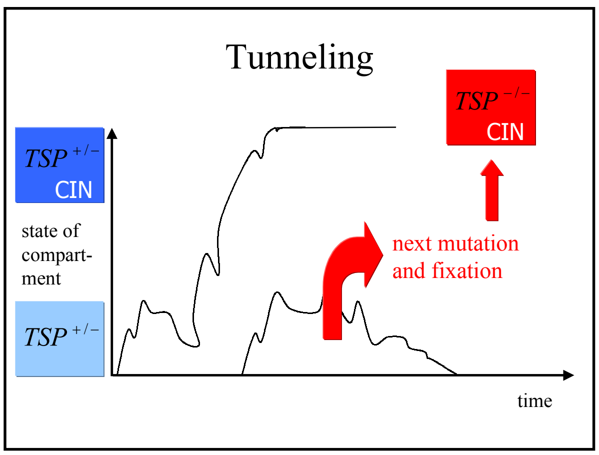

X0
X1
X2
TSP +/+
2u
TSP +/−
N(u + p0)
TSP −/−
uc
uc
2 hits
Y0
Y1
Y2
TSP +/+ CIN
2u
TSP +/− CIN
fast
TSP −/− CIN
X2 ≈ Nu(u + p0)t^2
Y2 ≈ 2u uc t^2

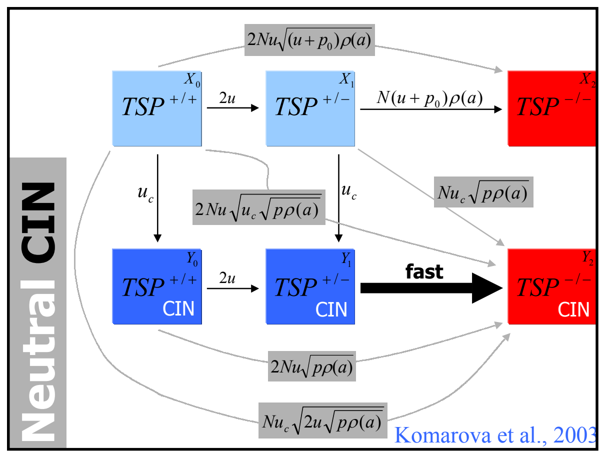

TSP +/+
2u
TSP +/−
N(u + p0)
TSP −/−
uc
uc
2 hits
TSP +/+ CIN
2u
TSP +/− CIN
fast
TSP −/− CIN
CIN is faster if uc > N/2 (u + p0)

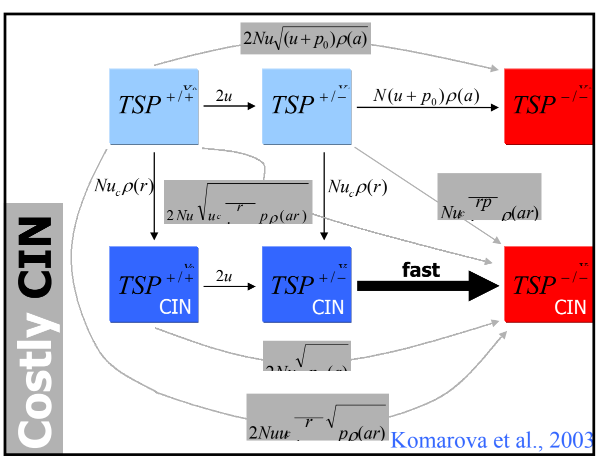

Tunneling
TSP +/+
2u
TSP +/−
N(u + p0)ρ(a)
TSP −/−
Nucρ(r)
Nuc rp/(1−r) ρ(ar)
TSP +/+ CIN
2u
TSP +/− CIN
fast
TSP −/− CIN
2Nu√(pρ(a))









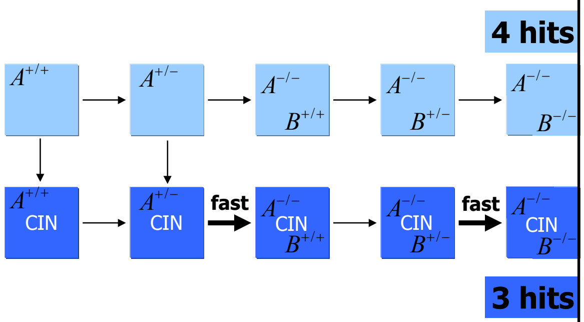


Timing

Whether a CIN mutation occurs before the inactivation of the first TSP depends on parameters.

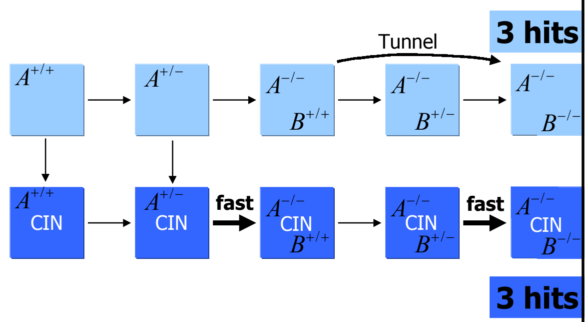
Natural choices of parameters suggest that CIN occurs before TSP.

Two tumor suppressor genes



CIN wins

Two tumor suppressor genes

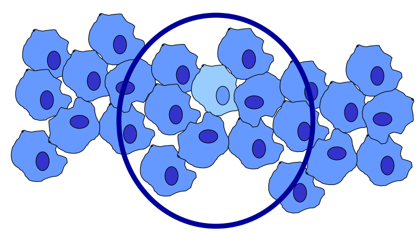


it depends on parameters

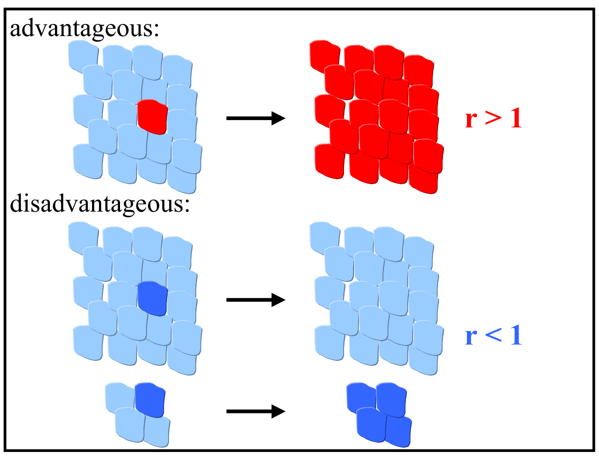
Many TSP genes

With the addition of each new TSP,
it is more likely that
CIN occurs before the
inactivation of the first TSP.

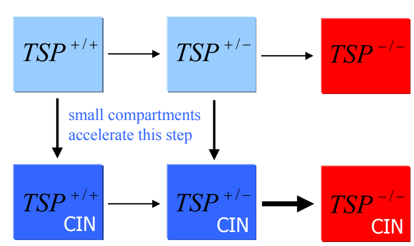
The effect of tissue architecture on cancer initiation



Somatic selection



Small compartments protect against tumor suppressor genes …



… but favor **CIN**.

Tissues evolved to minimize the risk of developing cancer

At the optimum compartment size, the contribution of CIN cells to the total risk can be substantial.

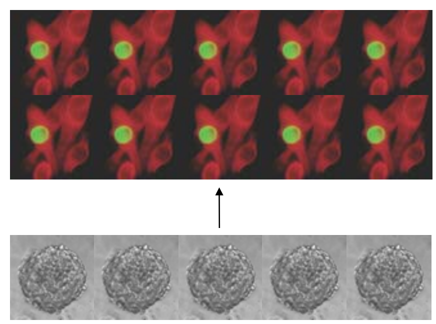
Summary-1

- In many cases of tumorigenesis, CIN mutations might precede the inactivation of the first TSP gene
- CIN is compatible with Knudson's two hit hypothesis

Summary-1

- Somatic selection works for and against cancer
- Small compartments protect against mutations in TSP genes and oncogenes
- … but favor CIN
- There is an optimum compartment size

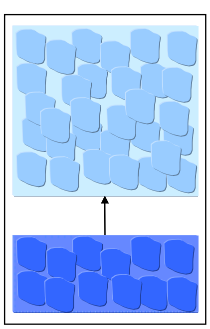
Stochastic elimination of cancer cells



diff. cells

stem cells

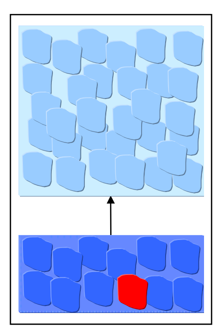
Stochastic elimination of cancer cells



diff. cells

stem cells

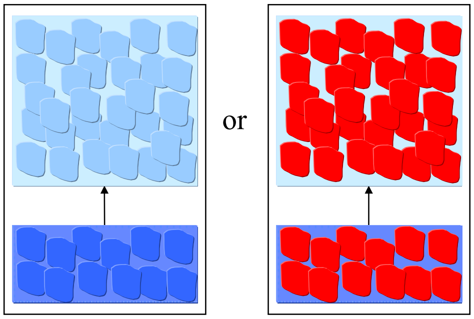
Transition dynamics



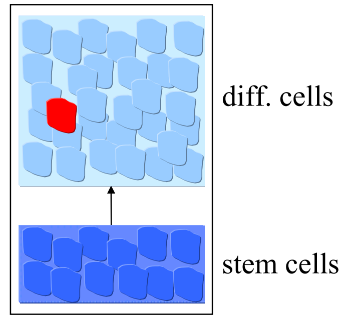
diff. cells

stem cells

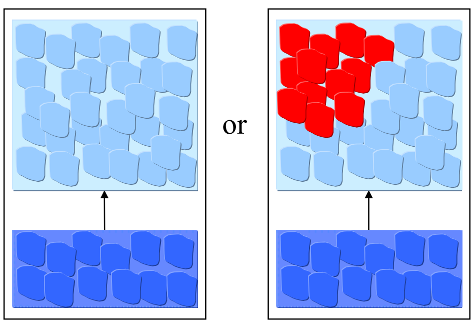
Transition dynamics



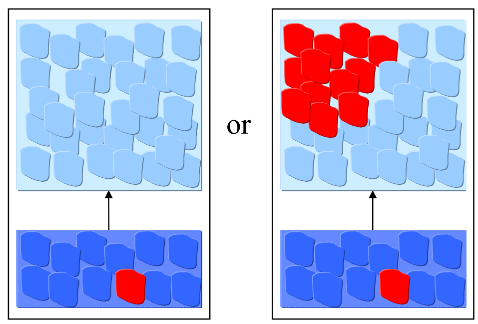
Transition dynamics



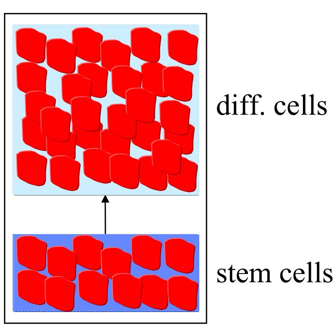
Transition dynamics



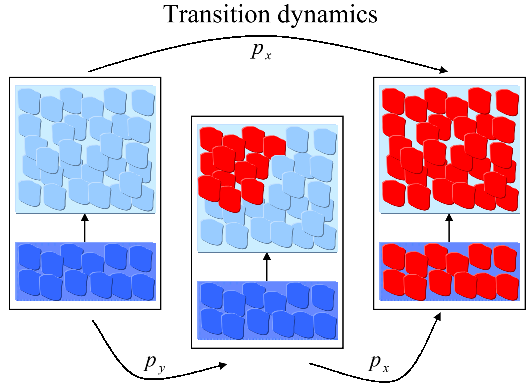
Transition dynamics



Transition dynamics



Transition dynamics



Optimum abundance of stem cells …

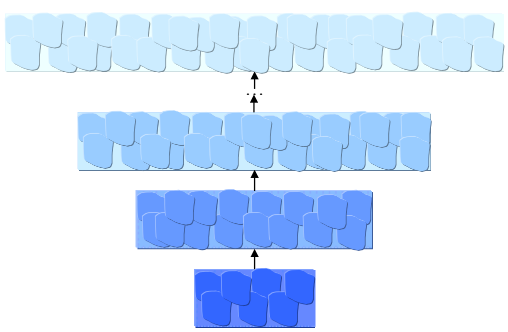
… depends on the somatic fitness of the mutated cells and the mutation rates in stem cells and differentiated cells.

Tissue architecture with stem cells evolved to wash out cells with advantageous mutations.

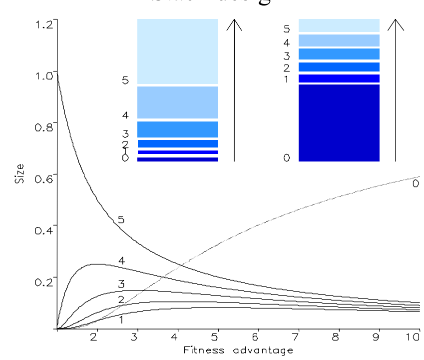
It has no consequence for neutral mutations.

The rate of neutral evolution is independent of the population size (Kimura 1968).

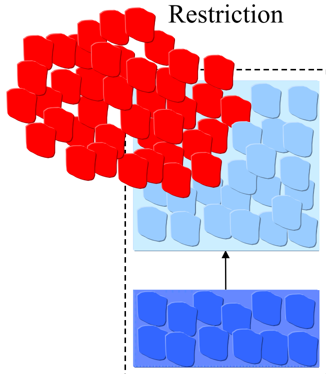
Stack design



Stack design



Restriction



Summary-2

- Tissue design can reduce the rate of somatic evolution that leads to cancer
- Stem cells can prevent the accumulation of mutations in differentiated cells (wash out)
- Stack design guaranteeing wash out can further reduce the risk of neoplastic growth

Summary-2

- Advantageous mutations are best contained in small compartments that allow wash out
- Neutral mutations are unaffected by tissue design

People

Martin Nowak (Princeton)
Yoh Iwasa (Kyushu)
Natalia Komarova (Princeton)
Steven Frank (Irvine)
Christoph Lengauer (Johns Hopkins)
Bert Vogelstein (Johns Hopkins)

Stochastic elimination of cancer cells

$$\dot{x}_0 = r(1-u)x_0 - dx_0 - \Psi x_0$$
$$\dot{x}_1 = rux_0 + r\alpha x_1 - dx_1 - \Psi x_1$$
$$\dot{y}_0 = dx_0 + s(1-v)y_0 - \Phi y_0$$
$$\dot{y}_1 = dx_1 + svy_0 + s\alpha y_1 - \Phi y_1$$

$$\Psi = (rx_0 + r\alpha x_1 - dx)/x \qquad x = x_0 + x_1$$
$$\Phi = (dx + sy_0 + s\alpha y_1)/y \qquad y = y_0 + y_1$$

Stochastic elimination of cancer cells

$$z = x_1/x \text{ and } w = y_1/y$$

$$\dot{z} = ru(1-z) + r(\alpha-1)(1-z) + A\xi_x(t)$$
$$\dot{w} = sv(1-w) + dx/y(z-w) + s(\alpha-1)w(1-w) + B\xi_y(t)$$

$$A = \sqrt{2rz(1-z)/x}$$
$$B = \sqrt{2sw(1-w)/y}$$

$\xi_x(t),\ \xi_y(t)$ ... white noise

Stochastic elimination of cancer cells

$$\text{wash out condition : } r_i x_i = \frac{1}{\alpha-1}\left(\frac{\alpha}{\alpha-1}\right)^{i-1} r_0 x_0 \quad \text{for } i = 1, 2, \ldots, n$$

$$\text{discarding rate : } c = \left(\frac{\alpha}{\alpha-1}\right)^{n} r_0 x_0$$

$$\text{optimal stack design : } r_0 x_0 = c\left(1-\frac{1}{\alpha}\right)^{n}$$

$$r_i x_i = \frac{c}{\alpha}\left(1-\frac{1}{\alpha}\right)^{n-i} \quad \text{for } i = 1, 2, \ldots, n$$